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Organic Solid-State Reactions with 100% Yield

Gerd Kaupp

University of Oldenburg, Organic Chemistry 1, P.O. Box 2503, D-26111 Oldenburg, Germany

kaupp@kaupp.chemie.uni-oldenburg.de

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Abstract

Environmentally benign gas-solid, solid-solid and intracrystalline (thermal and photochemical) reactions that give 100% yield of only one product are summarized for almost all important reaction types. Their mechanistic background is evaluated on the basis of supermicroscopic studies and crystal packing analyses which helps in predicting good solid-state performance on the basis of phase rebuilding, phase transformation and crystal disintegration and in engineering solid-state reactions in the case of difficulties, in order to profit from the bargain of the crystal packing for reactions with unsurpassed atom economy, in most cases without any auxiliary or purifying workup necessity, mostly close to r.t. and with short reaction times. The experimental techniques are described in some detail including the scale-up. Preparative use is made with known and new reactions and many products cannot be prepared by any other technique or they are only stable in the solid state but they are quantitatively obtained and ready for further syntheses due to their very high reactivity. It is tried to exclude “solvent-free” reactions that pass through a liquid phase, but some comparisons with important quantitative stoichiometric melt reactions are made. Numerous new solid-state reactions are described here for the first time.

Keywords

Gas-solid reaction; solid-solid reaction; intracrystalline reaction; phase rebuilding mechanism; solid-state cascade reaction; 100% yield

List of Abbreviations and Symbols

AFM: atomic force microscopy

B3LYP:

DDQ: dichloro-dicyano-parabenzoquinone

DFT: density functional theory

DSC: differential scanning calorimetry

GID: grazing incidence diffraction

i.d.: internal diameter

rpm: revolutions per minute

r.t.: room temperature

SNOM: scanning near-field optical microscopy

TADDOL: tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol

TBAB: tetrabutylammonium bromide

TEMPO: tetramethylpiperidiny-N-oxyl

THF: tetrahydrofuran

1 INTRODUCTION

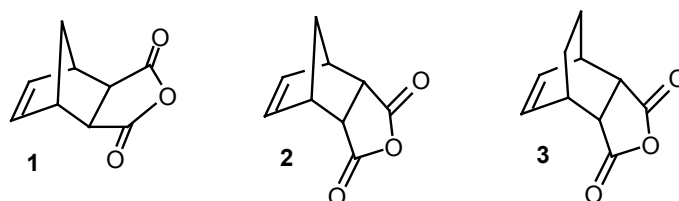
Waste-free environmentally benign solid-state reactions mean 100% yield of one product without any necessity for purifying workup by recrystallization, chromatography, etc. They have therefore the highest possible atom economy. This does not exclude gas-solid reactions, which frequently use excess reactive gas that is removed at the end of reaction by its collection in a cold trap, or which require a solid catalyst or a drying agent that has to be removed by a simple quantitative extraction procedure. Even quantitative protonic salt formation is covered. Essentially quantitative liberation of the organic acid or the organic base

therefrom may require treatment with water. Furthermore, quantitative stoichiometric reactions involving salts with the necessity to remove the simple stoichiometric coproduct salt (e. g. NaCl, etc. that can be simply washed out) remain environmentally benign and are not excluded. Not relevant, however, are so-called “quantitative reactions” at less than any specified conversion below 100% or non-stoichiometric solid-solid reactions that may provide quantitative conversion (100% yield with respect to the minor component) but require removal of the excess reagent using solvent. Polymerizations that require removal of residual monomers or oligomers are excluded. At present there are no microwave accelerated reactions known that would meet the selection criteria.

Solid-state reactions are known from thermal intracrystalline conversions (isomerizations or loss of volatile fragments), photoreactions, gas-solid reactions, and solid-solid reactions. As all of these relate strictly to the crystal packing (unifying solid-state mechanism) they are not separated in the various sections. Also, non-topotactic (normal) and topotactic (very rare) reactions are not separated in different chapters.

Pure solid-state reactions are more frequently waste-free than melt-reactions with increased risk of incompleteness or side reactions. We select here only quantitative examples of gas-solid reactions, stoichiometric solid-solid reactions, and intracrystalline reactions as these are particularly typical and we are well aware, that many previously non-quantitative solid-state reactions might be transformed to 100%-yield-reactions by application of the suitable techniques that derive from the mechanistic knowledge gained from submicroscopic AFM studies. These investigations show strict correlation with the crystal packing, because molecular movements within the crystal (along easy paths!) are required for all reactions with significant change in the molecular shape upon reaction. The geometrical change upon chemical reaction or conformational change creates so much internal pressure that the molecules have to move out of the lattice (very rarely to a suitable crystallographic void or channel [but not “reaction cavity”] in the lattice) directly upon the event. Such molecular migrations rely on the presence of cleavage planes or channels or free cages in the crystal lattice. The migrations are easily traced at the crystal surface with the AFM or in suitable cases with depth-dependent GID. The types of surface features have been exhaustively imaged in [1]. The three step solid-state mechanism of 1) phase rebuilding, 2) phase transformation and 3) crystal disintegration is amply demonstrated. It becomes multi step in reaction cascades, of course. That means, one observes at first gradually growing characteristic features, then abruptly enormous changes of surface features, and shortly thereafter disintegration of the original crystal with creation of fresh surface. This ingenious mechanism has been repeatedly termed “the phase rebuilding mechanism”.

The interplay of crystal packing, migrational aptitudes and solid-state reactivity may be demonstrated with reactivities of the Diels-Alder cycloadducts of maleic anhydride and cyclopentadiene (**1** and **2**) or cyclohexadiene (**3**) (Scheme 1). Figs. 1-3 show stereoscopic views of their crystal packing. It is clearly seen: the *exo*-bicyclo[2.2.1]anhydride **1** has a hardly interlocked monolayer structure and so does the *endo*-isomer **2** except for slight interpenetrations. These structural features facilitate molecular migrations upon chemical reactions, whereas the bicyclo[2.2.2] anhydride **3** exhibits strong interlocking preventing molecular migrations.



Scheme 1

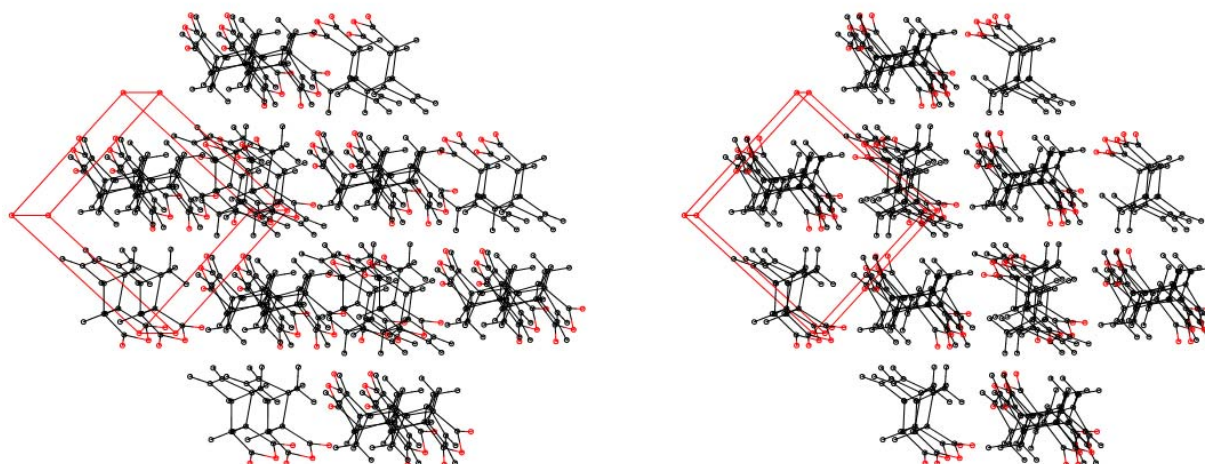


Fig. 1. Stereoscopic representation of the molecular packing of *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxyanhydride (**1**) on its (001)-face (rotated around y by 5° for a better view) showing the hardly interpenetrated monolayered structure.

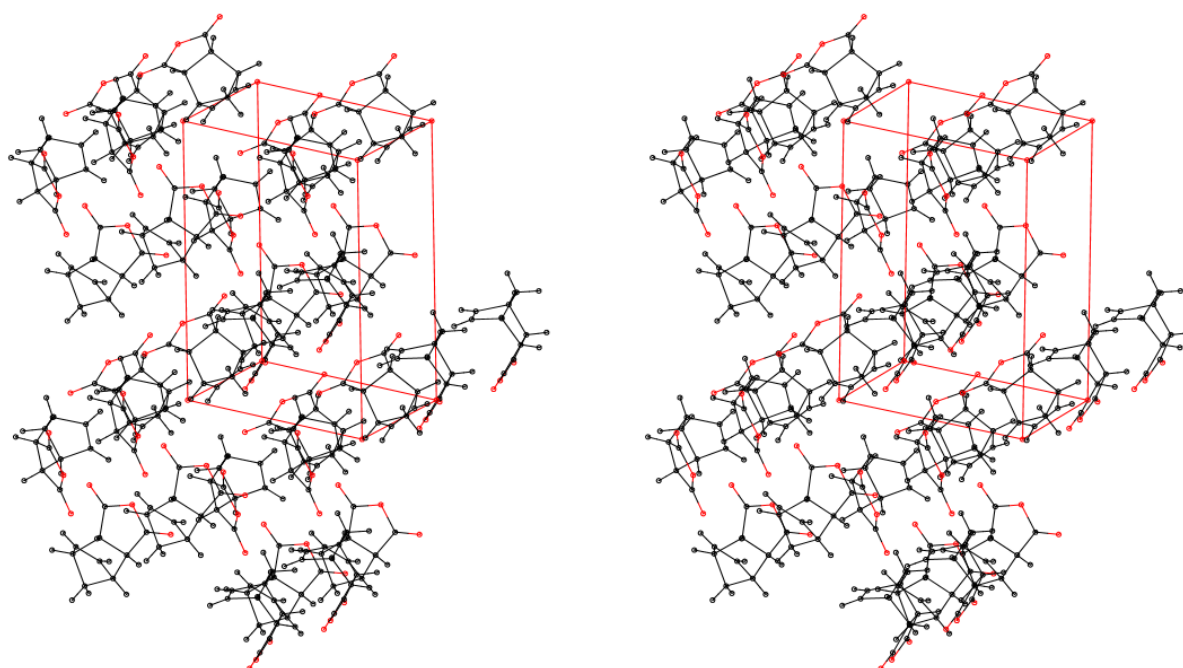


Fig. 2. Stereoscopic representation of the molecular packing of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxyanhydride (**2**) on its (111)-face showing the slightly interpenetrating monolayered structure.

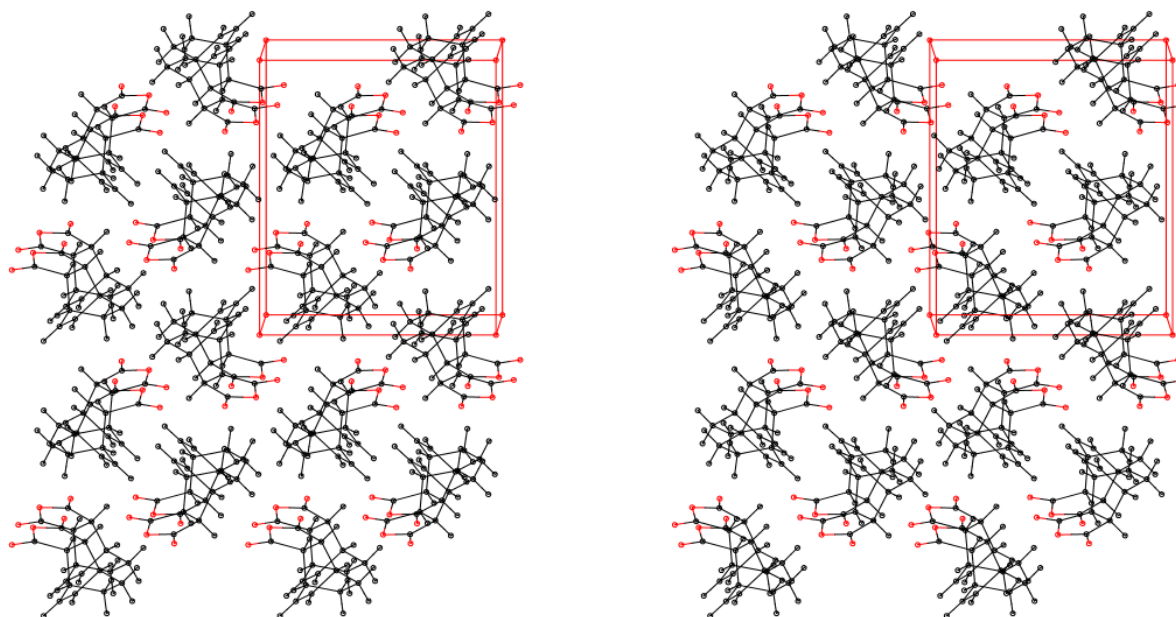


Fig. 3. Stereoscopic representation of the molecular packing of *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxyanhydride (**3**) on its (100)-face showing interpenetrating strongly interlocked layers.

If the crystals of **1** are exposed to bromine vapor, addition to the C=C-double bond occurs without difficulty as the molecules can anisotropically migrate along the cleavage plane and the quantitatively obtained *trans*-adduct does not include large amounts of bromine. The gas-solid addition of **2** is more complicated. The initially formed crystalline adduct keeps large quantities of additional bromine and eliminates HBr upon standing and in solution by forming lactones. Thus, mixtures of products arise because consecutive reactions prevent a clean result in that case. As expected, the behavior of **3** is totally different. If crystals of **3** experience diluted bromine vapor, no addition to the C=C-double bond occurs at 22°C (and upon removal of included Br₂ at 22-50°C in a vacuum) as long as the crystals do not melt by the uptake of excessive Br₂. The solid includes the bromine up to about 0.4 equivalents without melting. The lattice of **3** opens at best the possibility to form minor internal channels or cages for the inclusion of some bromine, but not for the accommodation of a possible dibromide in the absence of possibilities for migration. Therefore, no addition occurs in the solid state of **3** even though some bromine is accommodated by inclusion.

It is tried to exclude melt or intermediate melt reactions in this review as good as possible because these do not (fully) profit from the initial crystal packing. They can nevertheless be of preparative importance or be preferable in particular instances and if the products crystallize directly from the melt during reaction and thus produce a quantitative yield [2]. Nevertheless, these different types of solvent-free reactions should be sharply separated for the sake of a consisting wording. Solid-solid should not only mean that the reactants were solids but also that a profit was made from the crystal packing which is only possible if there were no liquids upon mixture and during the reaction period.

2 EXPERIMENTAL TECHNIQUES

Solid-state reactions may be very efficient as they avoid solvents or liquid phases and profit from crystal structure. In most cases of gas-solid-reactions the crystals must not be finely

ground or milled and the gas must be gradually added in order to calm down the reaction at r.t. or below. Solid-solid-reactions require repeated contacts over and over again. Milling rather than grinding or sonication or resting more easily and thoroughly obtains this. Liquids or intermediate liquids are observed or excluded by visual, microscopic or supermicroscopic inspection. It may be necessary to cool down or (rarely) to slightly heat in order to avoid liquid phases. There are, of course, limits to the cooling down, as the reactions will freeze out at too low temperatures and not all of them can be executed at -80°C , for example. The possibility to "solidify" liquid reagents by salt formation and complexation are far from being exhausted. However, these techniques introduce auxiliaries that slightly detract from atom economy even though a 100% yield may be valuable and worth the effort.

Gas-solid reactions that run to completion require vacuum-tight glassware. In lab-scale syntheses the flask containing the crystals is evacuated and the reactive gases are let in at the desired pressure or speed or amount at r.t. or with cooling or heating of the flask. Stirring or shaking is necessary if a product gas is liberated in order to mix the gases. Vapors of volatile liquids should be applied at a stoichiometric ratio, as there may be the risk of liquefaction if excess vapor dissolves the solid. Ultrasound application (from a cooled cleaning bath) may overcome rare problems with product disintegration (e.g. **177**). If this does not help in very rare cases of persistent product layers (e.g. **104b**) milling and cautious application of the reacting gas at low pressure and low temperature cannot be avoided for a quantitative conversion. These engineering techniques overcome problems with step 3 of the solid-state mechanism but they are rarely required. Larger scale gas-solid reactions use loosely packed columns and gas flow. Heat is removed or added by admixed air or inert gas at the appropriate ratio while increasing the reacting gas proportion towards the end. However, highly diluted reactive gases may create a sharp reaction front through the column. Both stream bed and suspension or fluidized beds are to be chosen from. Volume increase during reaction has to be taken into account [3-5].

For complete solid-solid reactions with 100% yield in stoichiometric mixtures, ball-milling is the first choice [3, 6-9]. If double-walled milling chambers are used the possibility of cooling/heating can be used which appears quite important. Continuous cogrinding and a final sonication for solid-solid reactions should only be used if milling is not possible. As ball milling of molecular crystals or salts [9-11] does not induce "mechanochemistry" (breaking of regular molecular bonds cannot occur, with the exception of weak bonds of explosives, but intermolecular interactions and van-der-Waals attractions or H-bonds can be broken, and the surface is increased by crystal disintegration) the moderate efficiency of swing-mills with cooling/heating device is sufficient [3, 12]. High milling efficiency in rotor-mills for larger-scale milling (up to the kg scale and beyond) [6-8] increases the contact rate. It is also essential for tribochemistry (mechanochemistry if strong σ -bonds in polymers or infinite covalent crystals are broken with formation of local plasma at the freshly broken crystal surfaces, for example at silica or silicon) with totally different reactivities in plasma chemistry with virtually all kinds of organic additives [6, 8], which, however, is not the subject of this review.

Mechanistic investigations of gas-solid and solid-solid reactions as well as their proper engineering require identifiable crystal surfaces for atomic force microscopy (AFM) and scanning near-field optical microscopy (SNOM) [1, 3, 13-15] in combination with X-ray diffraction data, which are the basis of crystal packing analyses [1, 3, 16-18].

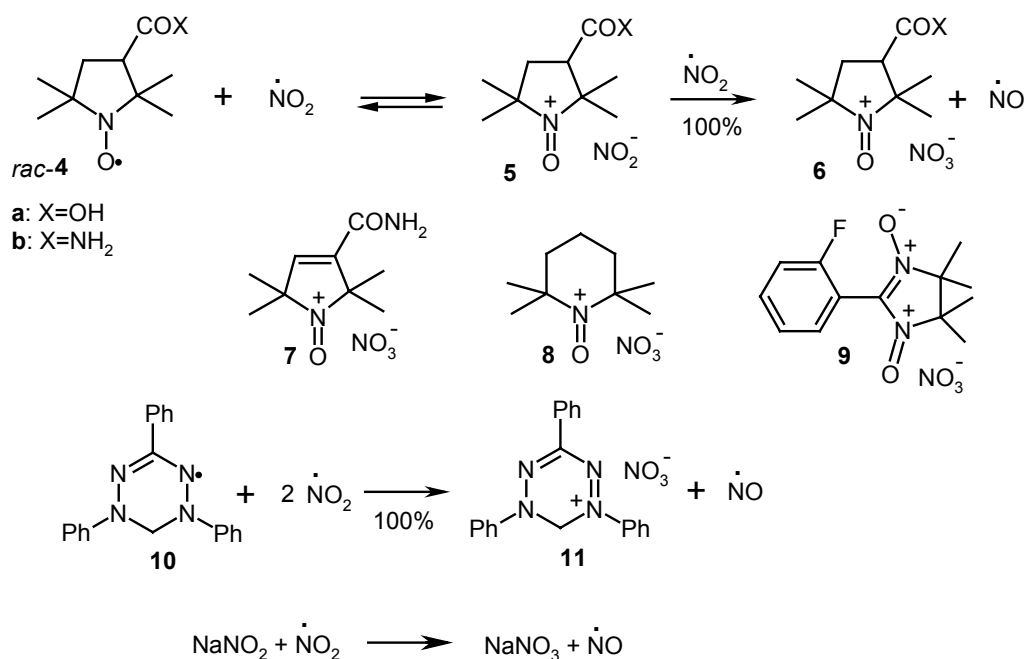
Spectroscopic analyses of solid-state reactions must first use solid-state techniques (IR, UV/Vis, Raman, Luminescence, NMR, ESR, CD, X-ray powder diffraction, DSC, etc.) in order to secure the solid-state conversion, before the solution techniques (detection of minor side products, specific rotation, etc.) are applied.

Environmentally friendly sustainable gas-solid and solid-solid or intra-solid thermal reactions proceed with 100% yield without side products. Simple couple products such as H_2O , or gases

or inorganic salts can be removed without application of solvents (salts may alternatively be washed out with water). In all of these cases genuine solvent free reactions or syntheses are achieved with unsurpassed atom economy, as these do not require purifying workup (such as crystallization, chromatography, etc.). It is therefore most important to run solid-state reactions to total conversion and starting with stoichiometric mixtures of reactants in the solid-solid version. Hard to remove catalysts are rarely required and should be avoided, if possible.

3 SINGLE ELECTRON AND OXYGEN ATOM TRANSFER

Probably the most simple, although hardly recognized, chemical processes are single electron transfer reactions that lead to stable products, for example **6-8** [19], **9** [20], and **11** [19]. The oxidations of stable nitroxyl or verdazyl radicals by NO_2 are of that type by necessity and they lead to quantitative yields of the cation nitrates [19]. Clearly, a second reaction type, the exchange of an oxygen atom between nitrite anion and nitrogen dioxide is coupled in all cases. This latter reaction type can be separately studied by the interaction of NO_2 -gas with sodium nitrite crystals [19]. Even the nitrogen monoxide formed in the single electron transfer reactions can be purified from nitrogen dioxide by storing over solid sodium nitrite. For large-scale production of NO by this technique, milling of the NaNO_2 is essential due to some difficulties with the crystal disintegration step [6].



Scheme 2

Also, the tribromides or fluorides of **6-9** and **11** can be quantitatively synthesized by similar one-electron transfer to bromine [20] or xenon difluoride in the solid state [1]. Further inorganic solid-state one-electron redox reactions have also been reported [6].

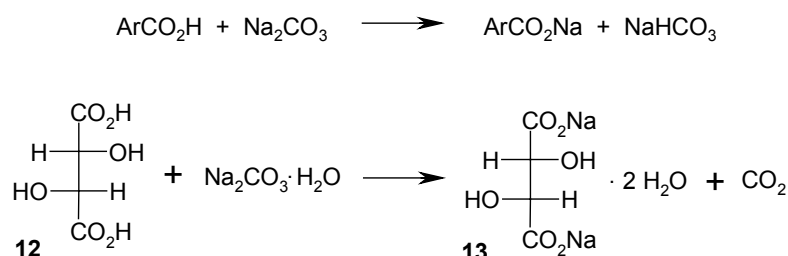
The ease of the synthesis may be disclosed by the experimental procedure:

An evacuated 100 mL flask was filled with $\text{N}_2\text{O}_4/\text{NO}_2$ to a pressure of ca. 650 mbar (296 mg, 6.4 mmol NO_2). The sampling flask was connected to an evacuated 1 L flask, which was then connected to an evacuated 10 mL flask that was cooled to 5°C and contained the nitroxyl **4a**, or **4b**, or the nitroxyl precursor to **7** (500 mg, 2.70 mmol). After 1 h, the cooling bath was

removed and excess NO₂ and NO were condensed to a cold trap at 77 K for further use. The yield was 665 mg (100%) of pure **6a**, or **6b**, or **7** [19]. Similarly, 2 g quantities of tetramethylpiperidine-N-oxyl (TEMPO) or 0.2 g of the ferromagnetic 2-fluorophenyl-tetramethylnitronyl nitroxide stable radical [21] were reacted at -10°C (initial pressure of NO₂ 0.03 bar) or 5°C (0.3 bar NO₂) in 12 h with a quantitative yield of pure **8** or **9**, respectively [19].

4 SALT FORMATIONS

Salt formations in the solid state may be achieved by solid-solid or gas-solid neutralization. The preparation of sodium or potassium salts of carboxylic acids by grinding or milling them with NaOH or KOH is not very practical due to the enormous heat development. The use of Na₂CO₃ or K₂CO₃ is helpful in this respect. However, it is hard to get complete reaction with benzoic acid or salicylic acid to the neat sodium salt upon co-milling at a 2:1 ratio, as the solid-state reaction of sodium hydrogencarbonate with these aromatic acids is uncomfortably slow (hours) [22]. There is, however, a claim of “rapid and complete neutralization” in a planetary ball mill at 60 g acceleration. [23]. The technical importance of solid-state neutralizations derives from the energy savings by avoiding large amounts of water. Such processes can be executed in large horizontal ball-mills. For example, 200 g batches have been executed in the neutralization of (*L*)-(+)-tartaric acid (**12**) with sodium carbonate monohydrate in a 2 L ball-mill under near ambient conditions and the disodium tartrate dihydrate (**13**), a food additive, is directly obtained in quantitative yield. If sodium hydrogencarbonate is stoichiometrically used the sodium hydrogentartrate hydrate for the preparation of carbonated lemonades is quantitatively obtained [6].

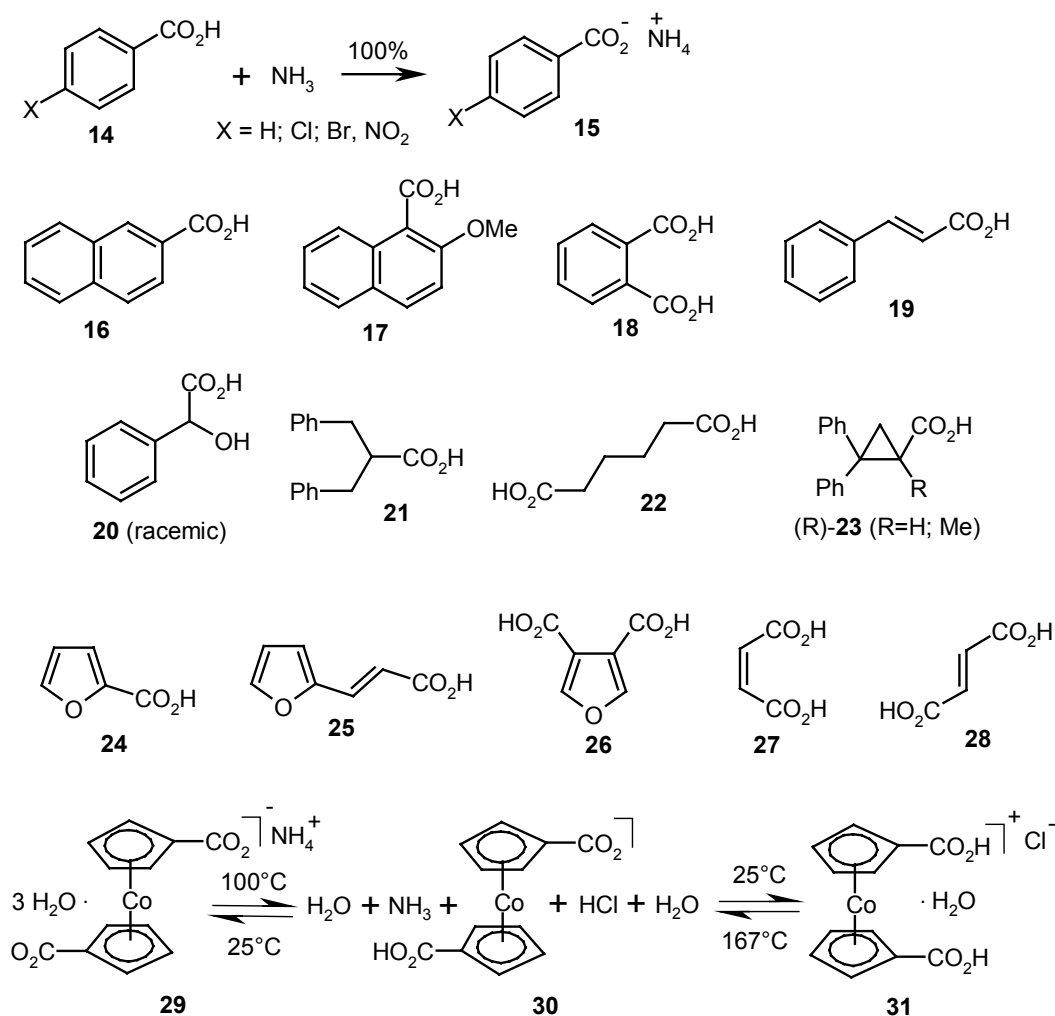


Scheme 3

The preparation in 200 g batches works as follows [6]: A horizontal water-cooled 2 L high-grade steel ball-mill (Simoloyer® CM01) is charged with 2 kg of steel balls (0.5 g), 200 g of (*L*)-(+)-tartaric acid and precisely the stoichiometric amount of sodium carbonate monohydrate taking into account its actual water content. The carbon dioxide that is formed during milling at 1300 rpm is released through a pressure valve and if gas production ceases the outmilling is started intermittingly at 300 and 800 rpm under gravity or in an autobatch arrangement by an internal air cycle through a cyclone of a connected separation/classification system (Simoloyer® VS01a). The latter equipment is particularly advantageous as it allows for automatic reloading for the next batches prior to complete powder collection. The yield of the solid powder **13** is quantitative.

The gas-solid neutralizations found more interest than the solid-solid variant. The quantitative reactions of gaseous ammonia with solid benzoic and related acids were interpreted by a concept of “gas permeability of the crystal” in order to explain anisotropic reaction fronts in

single crystals [24]. Also, the ammonium salts of the aromatic or aliphatic mono- and dicarboxylic acids **16-21** formed the corresponding salts with 100% yield. The need for molecular migrations immediately upon reaction was not considered at that time and indeed unexplainable anisotropies emerged with the acids **22** and **23** and **14**(X=Br) [25, 26] that can only be understood on the basis of the experimentally supported three-step solid-state mechanism including far-reaching molecular migrations [Section 1; 1, 3]. For example, AFM measurements have clarified the anisotropies in the reactions of **22** with ammonia and have pointed out the differences to the behavior of **24** also with respect to the migrational aptitudes in the crystals [1, 27].



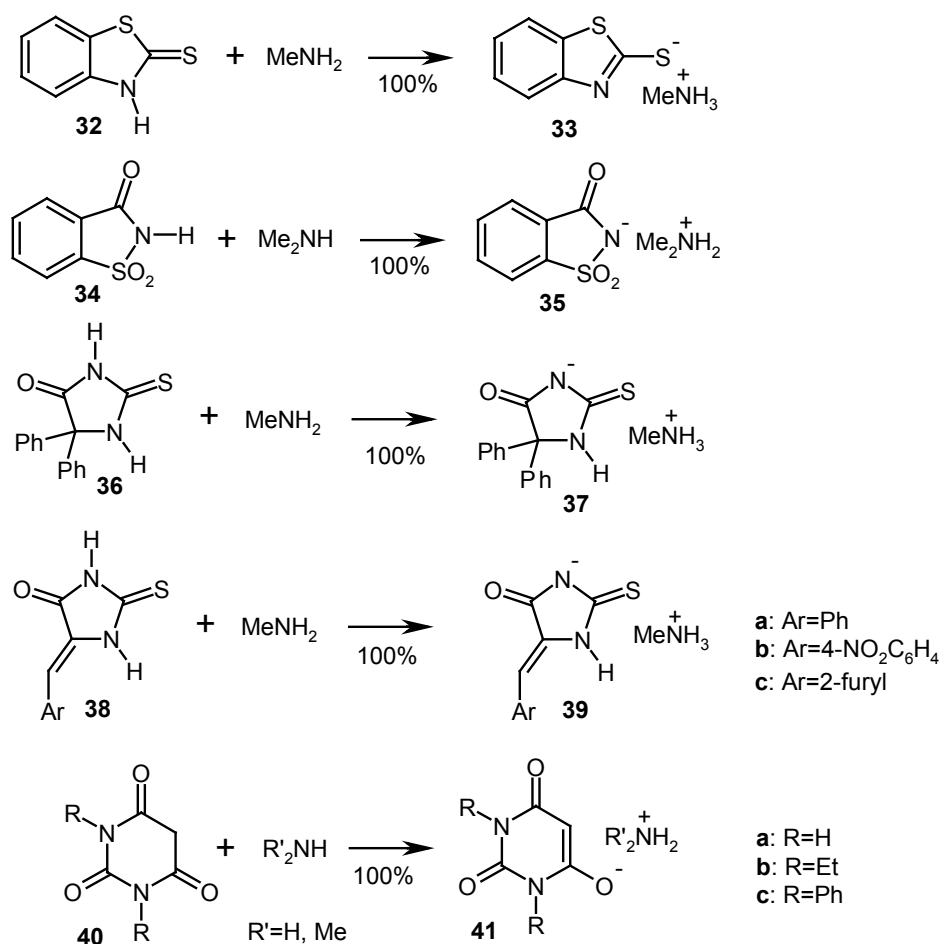
Scheme 4

Particularly rapid are the quantitative salt formations of gaseous ammonia with 2-furanocarboxylic (**24**) or 2-furylacrylic (**25**) and 3,4-furanedicarboxylic acid (**26**), maleic (**27**) or fumaric acid (**28**) (bis-ammonium salts). Applications in removal of ammonia from atmospheric gases appear promising [22, 28].

The solid amphoteric Co(III) complex **30**, that crystallizes in hydrogen bridged chains with the *transoid* arrangement of the ligands, protonates moist ammonia gas and quantitatively forms the hydrated salt **29** which keeps the *transoid* ligands' conformation. If, however, **30** is protonated with gaseous moist HCl the crystalline hydrated salt **31** is quantitatively formed. The *cisoid* conformation of the ligands in crystalline **31** enforces a new hydrogen bridged chain structure. This is shown by the X-ray crystal-structures of **29**, **30** and **31** and powder

diffraction data. The effects of the chain structure for the stereospecific gas-solid reactions have been elucidated with AFM. The clearcut results correlate the surface features formed with the crystal structures. The single crystals heavily disintegrate upon reaction and the neutral product **30** is reformed upon heating of **29** or **31** [29]. Clearly, the conformational reversal of **30** \rightarrow **31** or of **31** \rightarrow **30** is the result of chemical reactions combined with particular crystal properties. This is to be distinguished from crystal phase transitions that are not within the scope of this article. Similarly, protonation of **30** with the vapor of trifluoroacetic acid enforces the *cisoid* conformation in the salt though without additional water. On the other hand, the vapor of tetrafluoroboric acid forms a salt with **30** in which an again different chain structure in the *transoid* conformation is obtained [30].

Very weak acids, such as 2-mercapto benzothiazole (**32**) [27], saccharine (**34**), 5,5-diphenylthiohydantoin (**36**) [31] or 5-ylidene-thiohydantoin (**38**) [32], form salts with methylamine gas. Such quantitatively formed salts **33**, **35**, **37**, **39** cannot be obtained in solution. This new possibility of reaction was studied and interpreted with the AFM [1, 27].



Scheme 5

Even C-H acids such as barbituric acids **40**, which crystallize as the triketo tautomers, form the ammonium barbiturates **41** with gaseous bases such as ammonia or dimethylamine with great ease [32].

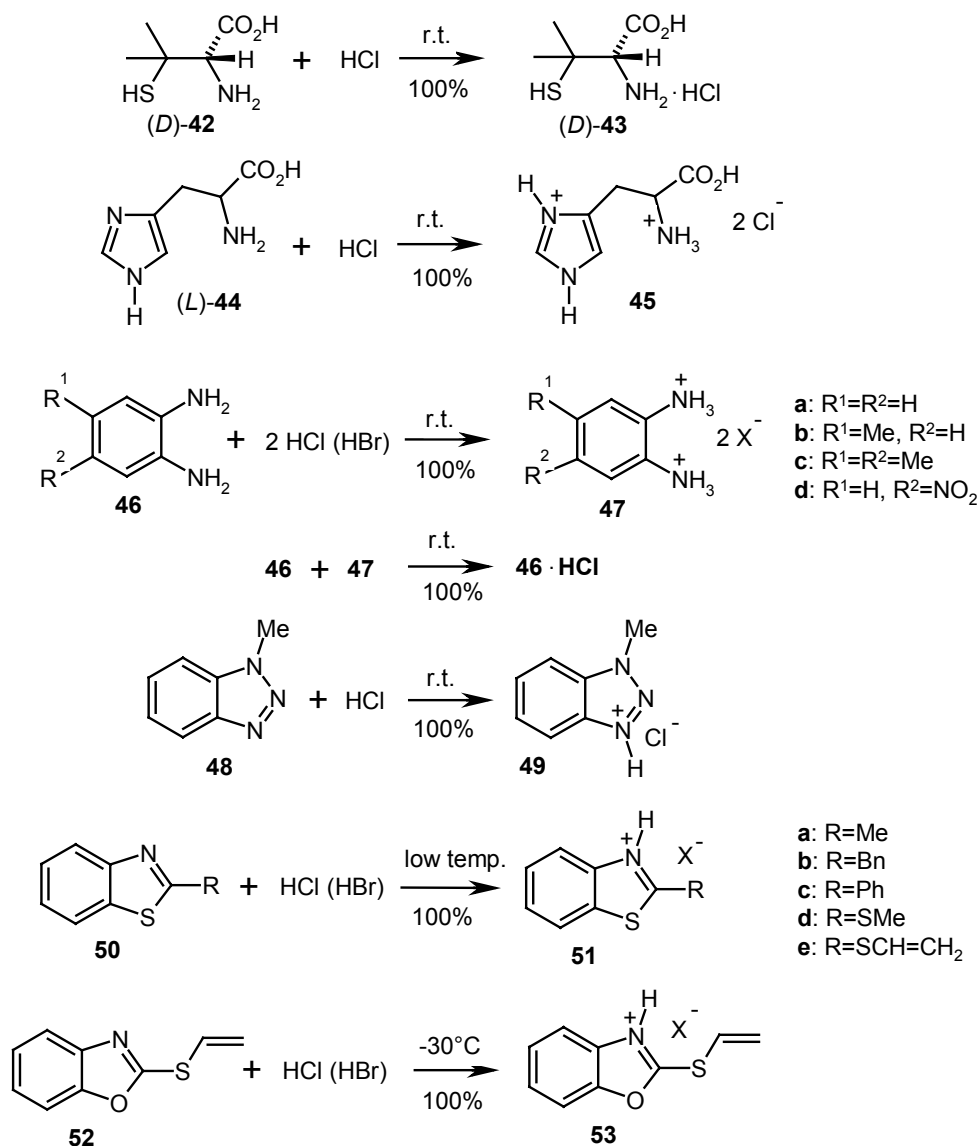
Equally important is the salt formation of solid bases with gaseous acids. An example has been cited above (**30** \rightarrow **31**). This type of reaction is quite general. Strong and very weak

bases react quantitatively and the gas-solid technique does not have problems with moisture. Amino acids such as (*L*)-phenylalanine, (*D*)-penicillamine (**42**), (*D/L*)-penicillamine, (*L*)-cysteine, (*L*)-leucine, (*L*)-proline, (*D/L*)-tyrosine (Pna2₁, layered structure with hydrogen bonded polar regions as well as channels along [100] with inside hydrogen bonds and channels along [001]) and others are quantitatively converted into their hydrohalides with gaseous HCl or HBr in preparative runs. Several of these amino acids react thoroughly without pregrinding. However, there may be surface passivation effects if the amino acids (in particular glycine and alanine) were previously exposed to ambient air. In those cases anhydrous premilling will enable the slightly exothermic complete salt formation [22]. It is remarkable that the usually three dimensional hydrogen bond networks (except α - and β -polymorphs of glycine) are broken up by the protonations so that molecular movements become possible and disintegration of the crystals ensues.

A bis-hydrochloride is obtained if solid (*L*)-histidine (**44**) reacts with HCl gas. Anisotropic molecular migrations that relate to the crystal packing have been shown with the AFM [1, 27]. Preparative applications have been found with the anhydrous bis-hydrochlorides of various *o*-phenylenediamines **46**. These were produced at the 50 g scale and all of these were required for enabling gas-solid condensation reactions with acetone [5]. If the monohydrochlorides of the *o*-phenylenediamines are required, the dihydrochlorides **47** are simply milled with a stoichiometric amount of the corresponding free solid diamine **46** in order to get a pure product with quantitative yield. The benzotriazole **48** gives a quantitative yield of the hydrochloride **49**, which on heating to 210°C provides a liquid mixture of **48** and 2-methyl-2*H*-benzotriazole in a 87:13 ratio. Similarly, solid 1-phenyl-1*H*-benzotriazole quantitatively adds HCl. On the other hand, solid 2-phenyl-2*H*-benzotriazole does not form a salt with gaseous HCl [22].

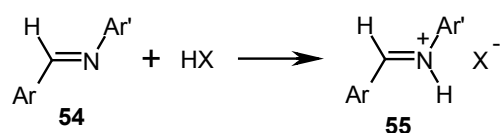
Liquid bases may be solidified at low temperatures prior to being exposed to gaseous HCl, HBr, or HI. Once quantitatively formed the solid salts are surprisingly stable under ambient conditions [5]. The benzothiazoles **50** (with the exception of **50c**) are liquids and require cooling down to -10, -30 or -45°C for solidification prior to the application of the reactive gases. Interestingly, *S*-vinyl-benzothiazole (**50e**) and -benzoxazole (**52**) form the salts with HCl and HBr but do not undergo addition to the double bond [33].

Furthermore, creatinine hydrochloride and hydrobromide are quantitatively obtained by gas-solid reaction and have much better quality than samples from solution reactions [28].



Scheme 6

The gas-solid technique is particularly attractive in the synthesis of extremely sensitive hydrohalogenides of Schiff-bases (e. g. **54**) as the exclusion of moisture is automatically achieved. Some of these salts include additional HX that cannot be completely removed by evacuation, and the phenolic compounds keep a second mole of HX that cannot be evaporated (Table 1) [9].



Scheme 7

Table 1. Iminiumhydrohalogenides (**55**), their m.p., C=N⁺ vibrational frequency, and titrated HX content

| | Ar | Ar' | X | m.p. | ν (cm ⁻¹) | HX-ratio |
|-----------|---|-----------------------------------|----|---------|---------------------------|----------|
| a | C ₆ H ₅ | C ₆ H ₅ | Cl | 189-190 | 1662 | 1.14 |
| b | 4-ClC ₆ H ₄ | 4-MeC ₆ H ₄ | Cl | 219-223 | 1659 | 1.26 |
| b' | 4-ClC ₆ H ₄ | 4-MeC ₆ H ₄ | Br | 248-249 | 1655 | 1.09 |
| c | 4-NO ₂ C ₆ H ₄ | 4-MeC ₆ H ₄ | Cl | 212-214 | 1670 | 1.00 |
| c' | 4-NO ₂ C ₆ H ₄ | 4-MeC ₆ H ₄ | Br | 241-243 | 1663 | 0.98 |
| d | 4-HOC ₆ H ₄ | 4-MeC ₆ H ₄ | Cl | 252-253 | 1659 | 1.93 |
| d' | 4-HOC ₆ H ₄ | 4-MeC ₆ H ₄ | Br | 280-281 | 1658 | 1.94 |
| e | 3-MeO,4-HOC ₆ H ₄ | 4-ClC ₆ H ₄ | Cl | 205-207 | 1652 | 2.04 |
| e' | 3-MeO,4-HOC ₆ H ₄ | 4-ClC ₆ H ₄ | Br | 239-239 | 1650 | 2.05 |

The characteristic melting points and IR-frequencies of **55** indicate well-defined compounds. The second molecule HX in the salts **d**, **d'**, **e**, **e'** is probably firmly included forming hydrogen bonds to the available oxygen atoms. These salts are easily obtained and should be versatile building blocks in solid-state reactions or reactions in dry aprotic solvents [9].

While the stoichiometric salt formations with HX are clearcut if the acid cannot be removed simply by evacuation there may be questions of salt formation versus complexation in solid-solid reactions between acids and bases. This point has been suitably addressed with IR-spectroscopy and X-ray powder diffraction studies of solid carboxylic acids and amine bases of varying strengths that were ground or milled together [34]. Yields are not given, but it may be assumed that quantitative reactions occurred in all stoichiometric mixtures. Unfortunately the authors argue that they were performing „mechanochemical“ reactions with mechanical energy input for the salt formations or complexations to occur rather than just creating the required contacts between reacting crystals. Furthermore, they did not exclude moisture, reported intermediate liquid phases in various cases and did not separate out any real solid-state reactions that might have been achieved. It is therefore not possible to discuss the results in more detail here.

5 COMPLEXATION

Solid-state complexations occur both as imbibition of gases into crystals of hosts or by comilling of the solid partners. In both cases, the host lattice will be changed unless the original host lattice exhibits large and accessible (via channels) cages such as in zeolites. This has been repeatedly shown by the detection of long-range anisotropic molecular migrations with the sensitivity of the AFM. Unlike crystallization of molecular complexes from solvents, the solid state technique may lead to higher loaded complexes that cannot be obtained from solution. A large number of gas-solid complexations have been observed in the research groups of Kaupp [28], Nassimbeni [35], Toda [36] and Weber [37]. Numerous host types are reported in [38], but their potential imbibition properties still await exploration as all inclusion experiments were executed from solutions. However, gas-solid imbibitions have particular advantages and applications.

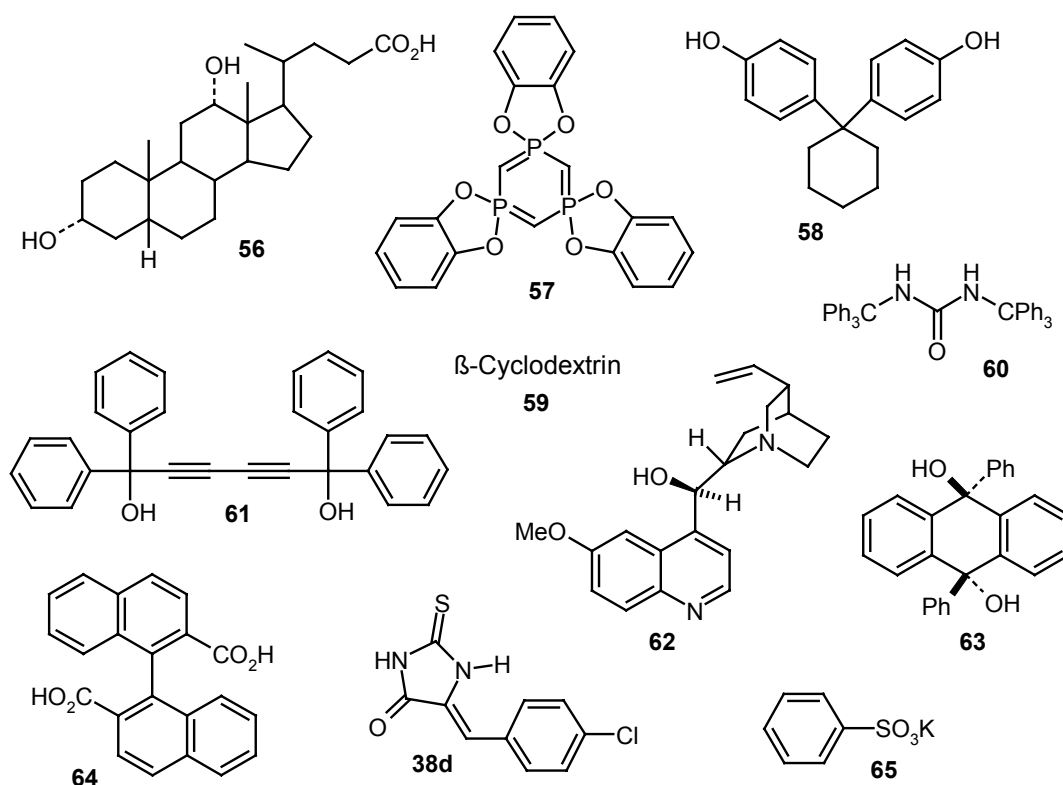
Of particular interest are exceedingly efficient imbibitions of acetone vapor into solid hosts at very low partial pressures (down to the detection limit) so that these reactions may be used for atmospheric detoxifications [5, 28].

Solid-state complexes are not always composed at simple ratios of the components if crystallized from solution. Such composition may change further upon gas imbibition into

crystals with usually higher uptake of the volatile component. On the other hand, as the crystal packing changes upon imbibition the three steps of phase rebuilding, phase transformation and crystal disintegration are a prerequisite and if one of these fail there will be no reaction. This has been nicely shown by AFM studies, which correlate the surface features with the initial crystal structure and by crystal structure investigations after complex formation [5]. Some typical examples of acetone vapor imbibition are listed in Table 2 together with the carbonyl frequencies ($\nu_{C=O}$) of the included acetone, which indicate the degree of polar interaction. Various host crystals with guest/host ratios that considerably exceed the values from the crystallized inclusion complexes take up the guest acetone. However, desoxycholic acid (**56**) does not include from the gas phase [5]. The inclusion ratios are stable upon completion of the reactions. The desorption temperatures under atmospheric pressure are high enough and in a comfortable range for collecting very diluted acetone gas in columns of host crystals and for recovering of the acetone by heating. A number of coexisting imbibitions of volatile solvents as ambient vapor mixtures (e.g. acetone, *t*-Bu₂O, THF, dioxane, cyclohexane, etc.) or separations of volatile liquids via the gas phase are known or can be developed [5, 28]. Host **61** imbibes acetone to a 1:2 host/guest ratio [36], but the rapid decay occurs below 60°C. Interestingly, host **63** imbibes two acetone molecules per diol host molecule. However, in that case a threshold pressure, which increases with increasing temperature, was found [35]. This disqualifies system **63** for the collection of minute quantities of acetone. Conversely, hosts **57-60** appear suitable for applications in the field of gas sensors, which are very promising [28].

Table 2. Some results with gas-solid imbibitions of acetone [28].

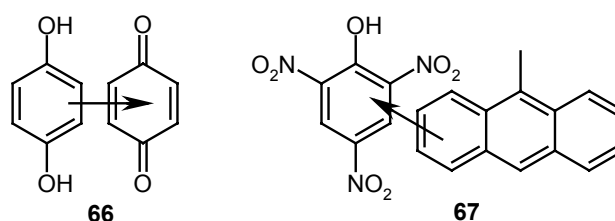
| Host | Acetone/Host (imbibed) | $\nu_{C=O}$ [cm ⁻¹] | Desorption Temperature [°C] | Acetone/Host (crystallized) |
|---------------------------|---------------------------|---------------------------------|--------------------------------|--------------------------------|
| 56 | – | – | – | 0.58 ^[37] |
| 57 | 0.48 | 1716 | 146 | 0.20 |
| 58 | 0.61 | 1701 | 63 | 0.58 |
| 59 | 2.56 | 1705 | 143 | 1.55 |
| 60 | 0.97 | 1711 | 121 | 0.76 |
| 61 ^[36] | 2.0 ^[39] | 1702 | 70 | 2.0 |



Scheme 8

Numerous gas-solid imbibitions are known (molar ratio; desorption temperature): Vapors of hexane are taken up by **57** (0.15; 175°C) and **62** (0.13), not by **56**, **59** or **60**; heptane by **57** (0.20); cyclohexane by **57** (0.29; 128°C), **62** (0.19), not by **56**, **59** or **60**; methylcyclohexane by **57** (0.26); benzene by **56** (0.31; 98 and 148°C), **57** (0.23; 107°C), **59** (1.59; 110°C), **60** (1.19; 104°C), **62** (0.49; 75°C), **64** (0.92; 110 and 154°C); toluene by **56** (0.38; 160°C), **57** (0.27; 155°C), **59** (0.72; 100°C), **60** (0.14; 93°C), **62** (0.52; 77°C), **64** (0.50; 92°C); dichloromethane by **57** (0.44; 147°C), **59** (1.43; 125°C), **60** (0.93; 117°C), **61** (2.0) [39] not by **56**; furane by **57** (0.21; 131°C), **59** (1.48; 120°C), **62** (0.25; 75°C), not by **56** or **60**; tetrahydrofuran by **56** (0.39; 162°C), **57** (1.40), **58** (0.40), **59** (1.70; 129°C), **64** (0.95; 115°C); dioxane by **38d** (34; 123°C); methyl-*t*-butylether by **57** (1.00 at flow; 106°C), **58** (0.20; 70°C); ethylacetate by **57** (0.40; 145°C); methanol by **59** (4.11; 130°C), **60** (1.14; 116°C), **64** (0.56; 126 and 140°C), not by **56**; ethanol by **56** (0.80; 132°C), **59** (2.76; 132°C), **60** (1.50; 123°C), **64** (1.80; 90 and 135°C); dinitrogen tetroxide by **65** (0.33; 80 and 160°C). All data are for r.t. [28]. The inclusion efficiencies differ from those found by clathration in solutions but are frequently higher or comparable. Sometimes inclusion is not reported from solution and there are only three cases of liquid-state inclusion, which do not occur by the gas-solid technique (**56** and dichloromethane, acetone and methanol) probably due to the low inclusion rate of that host. The stable compounds have reproducible composition, are not covalently bound and liberate the gases sharply upon heating to the desorption temperatures. The selectivities are remarkable and if the amount of vapor component stays below the capacity of the host all of it is included down to the detection limit. Actually, the mentioned gases can be eliminated from ambient atmosphere. Only host **56** is too slow for that purpose and only host **38d** requires removing of moisture prior to inclusion [28]. Importantly, the data offer the separation of vapors by gas-solid imbibition and there are also coexisting inclusion mixtures of compounds obtained [28].

Solid-solid complex formations are usually easily and quantitatively obtained upon grinding or better milling. This has been shown with the formation of numerous charge transfer sandwich complexes such as quinhydrones (**66**) or picrates (**67**) [22]. Numerous one by one combinations of essentially planar donors and acceptors provide the homogeneous complexes most easily upon milling. Two examples are depicted (milling of picrates should be preceded by a negative explosion test of a small sample with a hammer on an anvil). On the other hand, the combination anthracene and anthraquinone did not form the charge transfer complex upon milling or from solution but only from the rapidly cooled melt [15]. This brown complex separates slowly (several months) into anthracene and anthraquinone upon standing at r.t. in a complete solid-state reaction.



Scheme 9

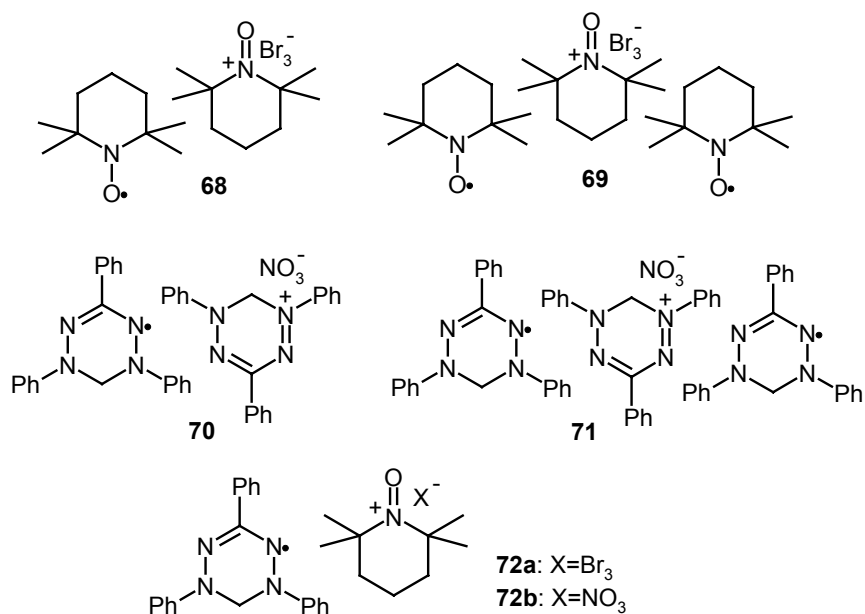
A big advantage of the solid-solid technique is the possibility for obtaining complexes that are not obtainable from solution. It must however be shown that uniform complexes rather than microcrystalline mixtures occur. Apart from X-ray powder diffraction (that does not properly account for very small crystallites), proof is obtained by solid-state spectroscopy (IR, UV, luminescence) or in the case of stable radicals by magnetic susceptibility measurements. The 1:1 and 2:1 complexes **68**–**72** were prepared by stoichiometric milling and relevant physical properties are collected in Table 3 [20].

Table 3. Physical constants of the radicals TEMPO (tetramethylpiperidinyl-N-oxyl), 1,3,5-triphenylverdazyl (**10**) and their complexes with the oxidized cation salts

| Compound | m.p. (DSC endotherms) (°C) | C (emu K mol ⁻¹) | Θ (K) | Magnetic Interaction |
|--------------------|----------------------------|------------------------------|-------|----------------------|
| TEMPO | 36-38 | 0.38 | -5.9 | antiferromagnetic |
| verdazyl 10 | 142-143 | 0.38 | -9.9 | antiferromagnetic |
| 68 | 115/161 | 0.0034 | -0.21 | antiferromagnetic |
| 69 | 114/150 | 0.60 | -5.7 | antiferromagnetic |
| 70 | 174 | 0.094 | -0.12 | antiferromagnetic |
| 71 | 139 | 0.20 | -3.3 | antiferromagnetic |
| 72a | 158 | 0.0079 | -0.25 | antiferromagnetic |
| 72b | 146/150 | 0.071 | -0.09 | antiferromagnetic |

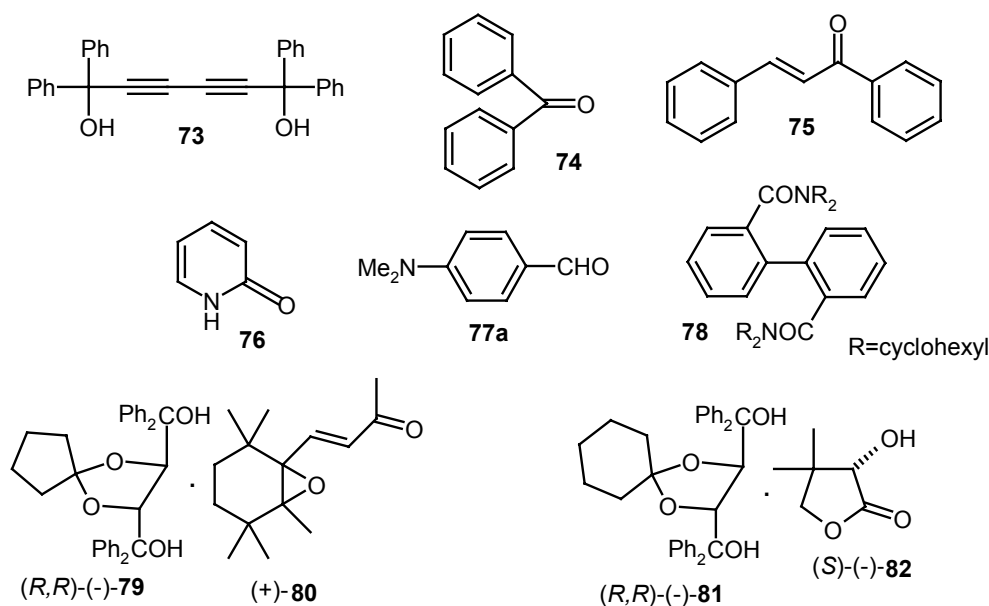
It is seen from Table 3 that **68**, **69** and **72b** have two DSC endotherms, the first without melting, the second with melting and decomposition. Interestingly, the Curie constants (2–300K range) differ markedly and are much larger in the 2:1 complexes **69** and **71** with considerable short-range order as compared to all of the 1:1 complexes, which exhibit only weak antiferromagnetic interactions between the spins. The large decrease of the magnetic susceptibility in all 1:1 complexes suggests a near-resonant charge-transfer from stable radical to cation with equal distribution of the spin over both partners that become chemically

identical if the anion is symmetrically located. There is also a marked influence of the anion in **72**. Evidently, the interactions of the resonant complexes with the additional radicals do not prevent short-range spin alignment. All Weiss constants in Table 3 are negative.



Scheme 10

Solid-solid inclusions of tetraarylhexadienediols (e. g. **73**) and TADDOLS (e. g. **79**, **81**) have been summarized in [40-42]. Most of these authors used crystallizations from solution or slurry techniques also for chiral resolutions. Less studied are solid-solid techniques in the preparation of these and related inclusion reactions. Benzophenone (**74**, 1 mole), or chalcone (**75**, 2mole), or 2-pyridone (**76**, 2 mole), or *p*-dimethylaminobenzaldehyde (**77a**, 2 mole) [43], or the bisamide **78** (1 mole) [40] are included by the diacetylene upon grinding. Furthermore, (+)- β -ionone oxide [(+)-**80**] has been quantitatively included by (*R,R*)-(-)-**79** upon grinding at r.t.. The quantitative inclusion of (*S*)-(-)-**82** by (*R,R*)-(-)-**81** required heating of coground solid mixtures to 80° C [44] or comilling at 25-30°C [22]. For the latter case and in the solid-state inclusion of (*S*)-(-)-**82** by (*R,R*)-(-)-**79**, AFM investigations [44] indicated low-distance solid-to-solid sublimation on the double layers with surface passivation that has to be broken for quantitative conversions in both cases by the above means or by addition of water which partly dissolves the guest, a slurry technique that was also used to separate the racemate of pantolactone **82** by enantioselective inclusion [45]. But only the AFM experiments and the milling experiments deal with true solid-state reactions. Further solid-solid complexation occurs if cholesterol and oxalic acid is comilled in a 1:1 ratio at r.t. as is clearly indicated by characteristic changes in the IR spectra and the uniformity of the obtained crystals [22]. The first gas-solid imbibitions of chiral molecules by the host (*S*)-1,2-dihydroxy-1,1-diphenylpropane were not highly enantioselective [46] and can therefore not be discussed here.



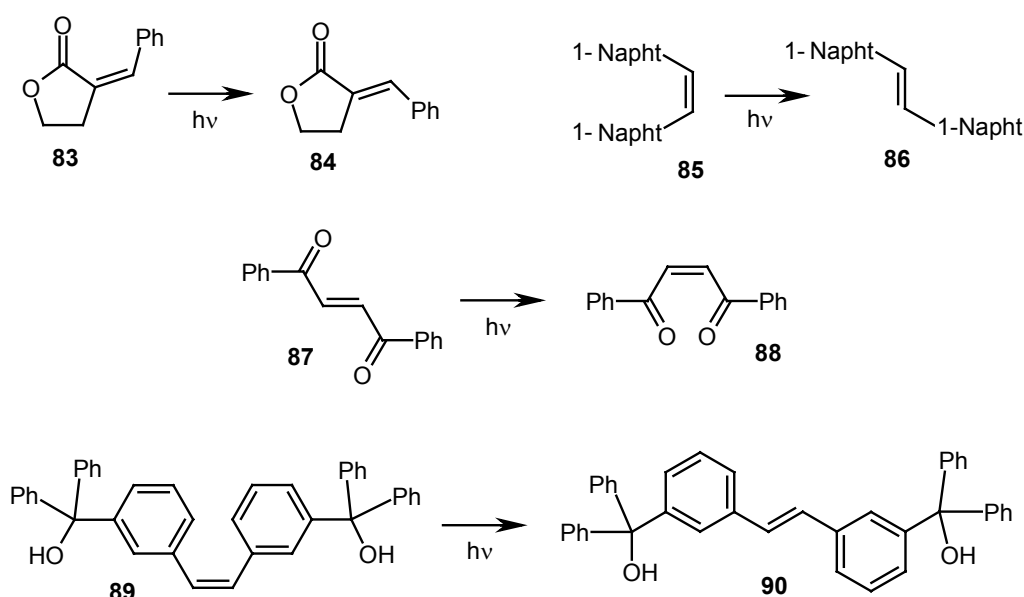
Scheme 11

6 GEOMETRICAL ISOMERIZATION

E/Z-isomerizations are usually not expected in the solid state. They have been widely studied in solutions or in liquids. This includes thermal, catalytic, photolytic processes and *E/Z*-isomerization was also observed in competition with biphotonic excimer laser photodecompositions [47]. Most of the *E/Z*-isomerizations in the solid state have been photochemically observed [48], but mostly not as uniform quantitative reactions. If these isomerizations cannot be performed under selective conditions of irradiation (an exception is **83/84**) [49] the only chance to have these reactions uniform with 100% yield is a very efficient isomerization (according to the phase rebuilding mechanism) that leads to an isomeric product with heavily interlocked crystal lattice. Under such circumstances side reactions of the substrate and photoconversions of the product are prohibited (including the back reaction, of course). Four favorable cases are known with the reactions of **83** to give **84** (selective irradiation at 365 nm; photodimers of **84** occur at $\lambda > 300$ nm irradiation [49]), **85** to give **86** [50] (the product lattice is interlocked [1]), **87** ($P2_1/c$) to give **88** ($P2_1$) ($E \rightarrow Z$; the bent product molecules **88** pack in crossing mono- and bi-layers with interlocked stacks [51]), and **89** to give **90** (neat or acetone complex; $T < -15^\circ\text{C}$; colloidal particles formed in a macroscopically unchanged crystal [52]).

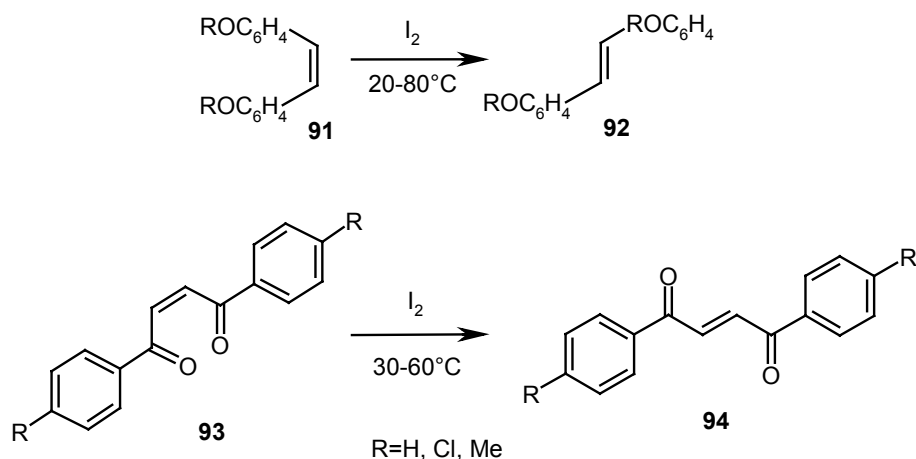
The reactions of **83**, **87** and **89** have been studied by AFM. The first two of them showed the common long-range anisotropic molecular migrations but not the third one with the extremely large substituents. The question of the chemical mechanism, i. e. the decision between space-intensive internal rotation and volume-conserving hula-twist mechanism [53] (which keeps the substituents in their planes while only one C-H unit translocates) could not be experimentally decided. While it might be possible to envisage a cooperative counterclockwise half-rotation on both sides of the double bond in **83** and **85**, these possibilities are to be excluded for **87** and **89** [48]. Hula-twist expects different initial product conformers, but their distinction was hampered by the molecular migrations and in **89/90** by the lack of X-ray diffraction signal [52] despite retention of the single-crystal shape. The latter case profited from void space in the structure, ready to accommodate the very large geometric

change. It should be noted, that completion of these *E/Z*-isomerizations may require many photons if internal filtering becomes more and more prominent towards the end while the yield approaches the 100% margin.



Scheme 12

The enormous amount of overactivation in photochemistry is not always required for solid-state *cis-trans* isomerizations. There are also some thermal *E/Z* isomerizations of crystalline olefins that are catalyzed by iodine. For example, crystalline *cis*-stilbenes **91** can be isomerized to give *trans*-stilbenes **92** without intervening liquid phases. The isomerizations follow first order kinetics with various rate constants for 4-MeO, two modifications of 2-MeO, 2-EtO, 2-*n*-PrO and 2-*i*-PrO substitution. The activation energies vary from 20 to 32 kcal mol⁻¹ but could not be interpreted [54]. Similarly, *cis*-1,2-dibenzoyl ethylene **88** (**93**, R=H) and its substitution products **93** give **87** and **94**, respectively, when gently heated with iodine vapor [55]. After apparent induction periods as evidenced by S-shaped conversion curves (the induction periods were not appreciated in the text of the publication) first order

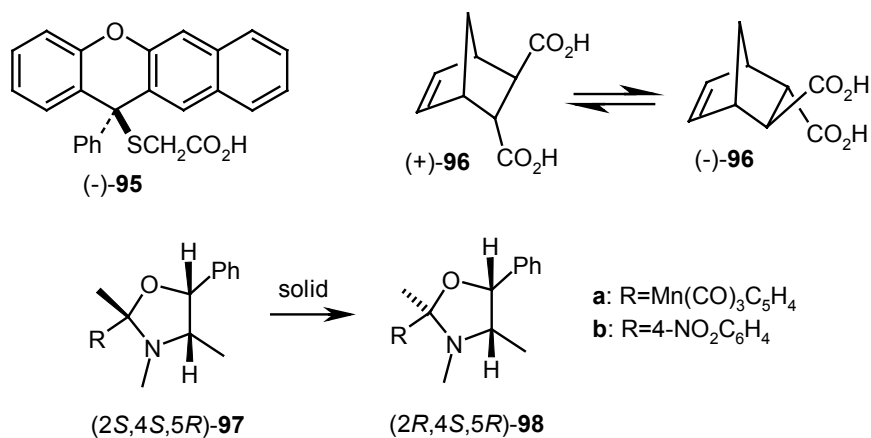


Scheme 13

rate constants and activation energies between 17 and 21 kcal mol⁻¹ were listed [55]. Mechanistic interpretation was not possible. Unlike the reported dibenzoylethenes, an *E/Z*-isomerization of *cis*-chalcone could not be catalyzed by iodine vapors in the solid-state [56]. Furthermore, the conclusion that the formation of the *meso*-dibromide upon gas-solid addition of bromine to *cis*-stilbene “is due to *cis-trans* isomerization prior to or during addition” [54, 56] cannot be accepted without further proof, as there is also the possibility for *cis*-addition [58-61].

Racemizations in the crystalline state have a long history. It is known, that (*L*)- α -amino acids slowly racemize in the solid-state [62]. As this also happens in solid proteins the implications are manifold not only in pure chemistry but also in biochemistry, nutrition, food technology and geology. Therefore, techniques have been developed to determine the *D/L*-ratio of amino acids down to 0.1% and inversion rate constants have been determined under acid hydrolysis conditions [63]. One could think of very slow de-amination and re-addition of the amine or an enolization mechanism. However, such reactions can also be induced by photolysis or radiolysis from natural sources [64].

Significantly faster is the solid-state racemization of the thioglycolic acid derivative **95**. A solid sample lost its specific rotation upon standing from -42.3° to -36.9° in two months and to -13.9° after 14 months. It is noted that such racemization was more rapid when the acid was exposed to light [57]. A heterolytic dissociation/recombination mechanism appears suitable.



Scheme 14

The racemization of Diels-Alder adducts in the solid-state appears to proceed via diradical or complete cycloreversion. For example, (+)-**96** racemizes in the solid state from 130-155°C ($\Delta H^\ddagger = 40.0$ kcal mol⁻¹; $\Delta S^\ddagger = 14$ cal mol⁻¹ K⁻¹) to give (-)-**96**, whereas the melt reaction (eutectic temperature is 165°C) from 176°C to 194°C has much lower activation parameters ($\Delta H^\ddagger = 29.7$ kcal mol⁻¹, $\Delta S^\ddagger = -6.9$ cal mol⁻¹ K⁻¹) [65]. Both the racemizations in the solid and in the melt follow strictly first order kinetics [65]. The extrapolated rate in the melt state is about ten times higher than the one in the solid state in this unimolecular reaction.

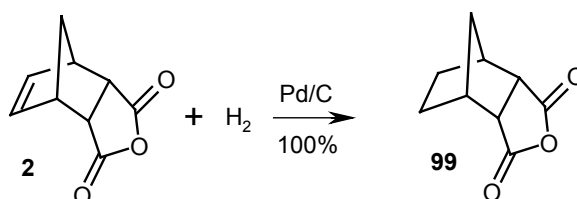
Chiral N/O-acetals may racemize in the solid state when water of crystallization is present. Examples are the epimerizations of the oxazolidines **97** that contain water from their preparation by stereoselective condensation. Thus, the kinetically preferred products **97a, b** (which are admixed to the thermodynamically more stable products **98a, b**) epimerize within

some weeks in the solid state to give enantiopure **98a, b** [66]. It appears that the N/O-acetal hydrolyses and recloses.

Solid-state racemizations are quantitative if the 1:1-equilibrium between the enantiomers is obtained. Therefore they do not really fulfill the criterion of only one product. Numerous examples in the organometallic field are listed in [67] and [68].

7 HYDROGENATION

Solid-state catalytic hydrogenations in the absence of any solvent can be easily and quantitatively performed in ball-mills that allow for evaporation and filling with gases. For example the Diels-Alder adduct of maleic anhydride and cyclopentadiene **2** hydrogenates readily upon milling with palladium on charcoal in an atmosphere of hydrogen in 200 g batches to give **99**, which is easily sublimed off from the catalyst [22].

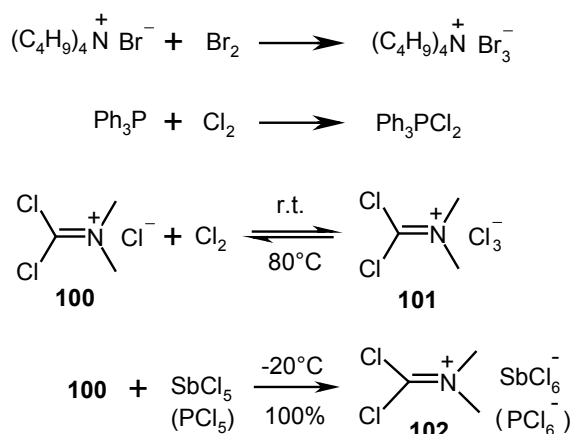


Scheme 15

These hydrogenations are rapid and quantitative. Conversely, the gas-solid hydrogenations of alkenes that were doped by platinum metal compounds on their recrystallization may be incomplete as, for example, the hydrogenation of *trans*-cinnamic acid or N-vinylisatin [58, 61], which should be milled for completion. Furthermore, the “spillover technique” by mixing powders of substrate and catalyst followed by application of hydrogen and several hours or days rest [69, 70] appears inappropriate for quantitative conversions. Milling is, however not applicable if volatile liquids have to be constantly pumped off [69] or if the products become liquid or sticky [70].

8 ADDITION OF HALOGENS

The addition of bromine to quaternary ammonium bromides to provide the tribromides is most easily obtained in a reaction column with the solid while a stream of air carries the required amount of bromine. Thus, in the case of tetrabutylammonium bromide (TBAB) a sharp yellow reaction front is obtained while bromine is quantitatively added and the pure bromination agent TBABr_3 is obtained. Small runs can be quantitatively performed with 0.5 bar bromine vapor and the unground crystals of TBAB [28] Equally simple is the gas-solid addition of chlorine to triphenylphosphane to give triphenylphosphane dichloride [28].



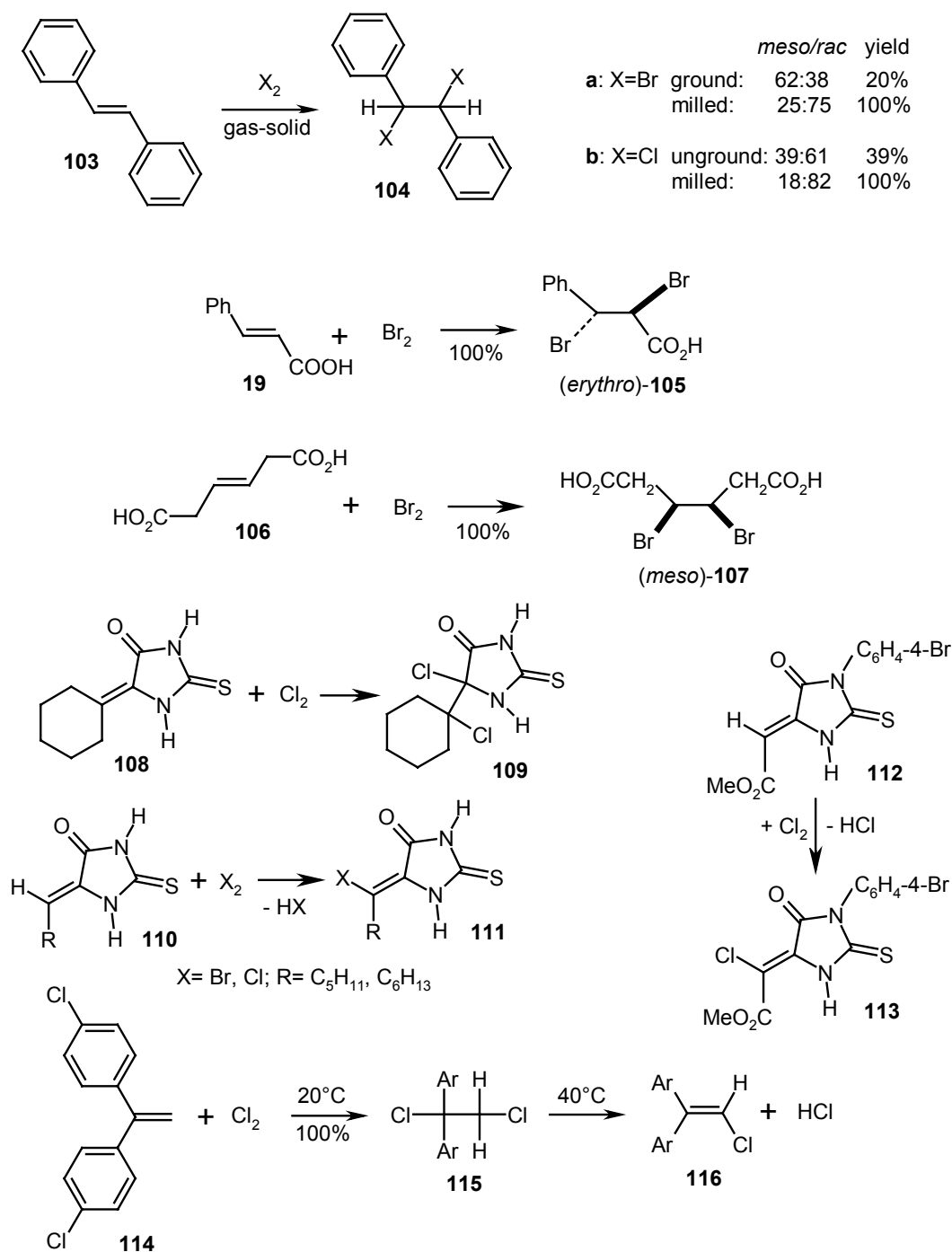
Scheme 16

Also the extremely labile trichloride **101** of Viehe salt **100** is reversibly and quantitatively obtained in the solid-state [9]. This latter reaction is related to the solid-solid syntheses of the extremely reactive hexachloro-antimonates or -phosphates (**102**) of the Viehe salt by its milling with antimony pentachloride or phosphorus pentachloride [9]. Also the labile adduct of chlorine to benzylideneaniline is obtained at -20°C and then stable in the solid state at r.t. [22].

The claims of exclusive formation of *rac*-stilbene dichloride upon gas-solid addition of chlorine to *trans*-stilbene (**103**) [71] and of *meso*-stilbene dibromide in the gas-solid addition of bromine to *trans*- or *cis*-stilbene [54] could not be verified. Scheme 17 shows the results of more detailed studies indicating the *meso/rac*-ratios at the solid-state chlorination and bromination of *trans*-stilbene (**103**) and some variations when the crystal size was changed [58, 60-61]. There is a risk of partial transient liquefaction if the chlorine is added too rapidly, due to initially heavy reaction. But even at the start with a stoichiometric amount of chlorine at 0.1 bar and 0°C a persistent product layer forms on the unground crystal powder of **103** that cannot be disintegrated by the ultrasound of a cleaning bath at 20°C for 60 h (only 7% conversion with *meso/rac*-ratio of 11:89 under these conditions) [22]. It is therefore unavoidable to mill the crystals of **103** to sizes $< 1\mu\text{m}$ in order to overcome these rare difficulties in the disintegration step. Anisotropic molecular migrations within the crystal of **103** upon halogen addition have been recorded by AFM [59].

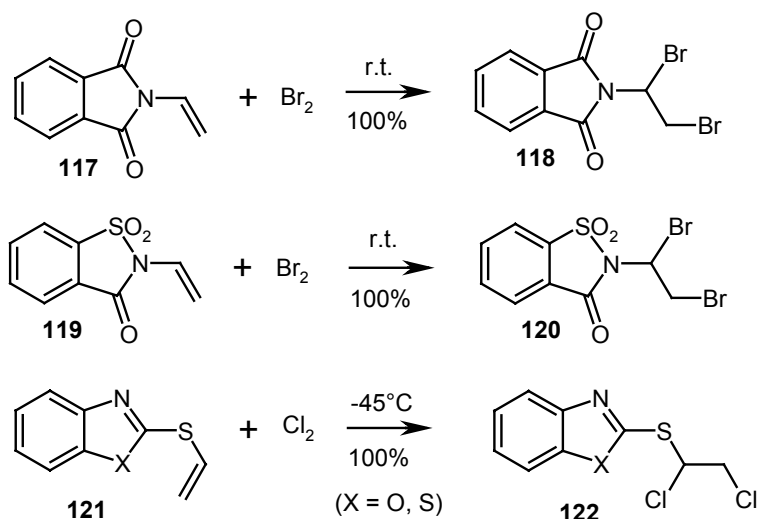
The early solid-state addition of bromine to *trans*-cinnamic acid [72] was revisited and provided a quantitative yield of the *erythro*-dibromide **105** both with the α - and β -modifications of **19** [59, 73]. The anisotropic molecular migrations within the crystals have been explored by AFM [59, 73]. Various substituted cinnamic acids (*m*-NO₂; *m*-Cl, α -Phenyl) in different crystal modifications were reported to yield quantitatively the corresponding *trans*-adducts, as detected by the weight increase of 20 mg samples [54]. No NMR spectra were reported. A large scale quantitative yield of the *meso*-dibromide **107** was also reported [54].

The chlorine adduct to the tetrasubstituted exocyclic double bond in **108** is quantitatively obtained by gas-solid reaction [27]. Conversely, related trisubstituted double bonds lose HX after the gas-solid halogen addition such as in the reactions of **110** and **112** that give **111** and **113**, respectively [28]. The completion of these solid-state eliminations is faster at 100°C . The product **113** is an interesting substrate for the synthesis of orotic acids. Furthermore, the production of **116** from solid **114** and chlorine gas proceeds with 100% yield via the intermediate adduct **115** [58, 60-61].



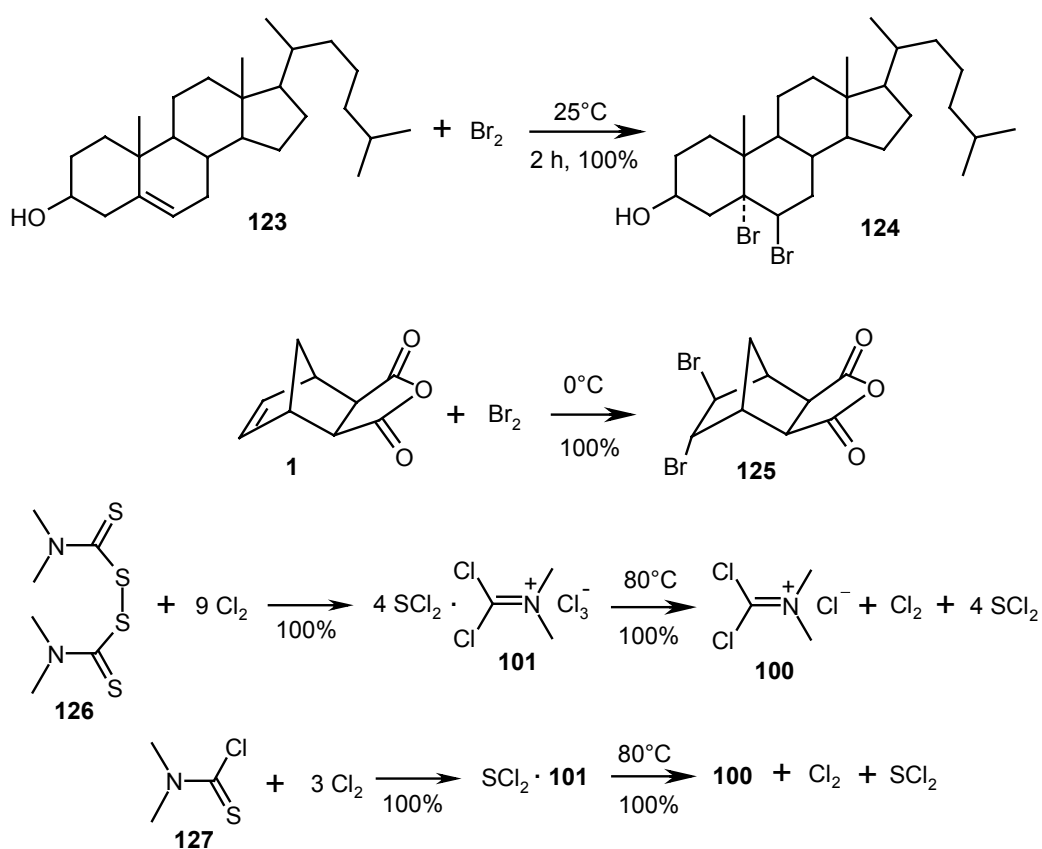
Scheme 17

A number of highly reactive dihalogenides **118**, **120** and **122**, far too reactive for being synthesized by conventional techniques, have been quantitatively obtained in pure form by halogen gas addition to solid N-vinyl and S-vinyl compounds at the appropriate temperatures [33, 61, 74].



Scheme 18

Unsubstituted solid alicyclic alkenes have also been exposed to bromine vapor and gave 100% of pure *trans*-dibromides as in the case of cholesterol (**123**) (channels along [001]) [75] and the (milled) *exo*-adduct **1** [22]. The products **124** and **125** cannot be obtained with the same good quality from solution reactions.



Scheme 19

Interestingly, the chlorination of dimethylthiocarbamoyl compounds such as **126** and **127** to give the trichloride of Viehe salt (**101**) can be performed as a quantitative gas-solid reaction as the volatile sulfur dichloride is included in the solid product [9]. Both SCl_2 and excess Cl_2 can be removed at 80°C in a vacuum. We have thus the easiest access to pure Viehe salt by the gas-solid technique:

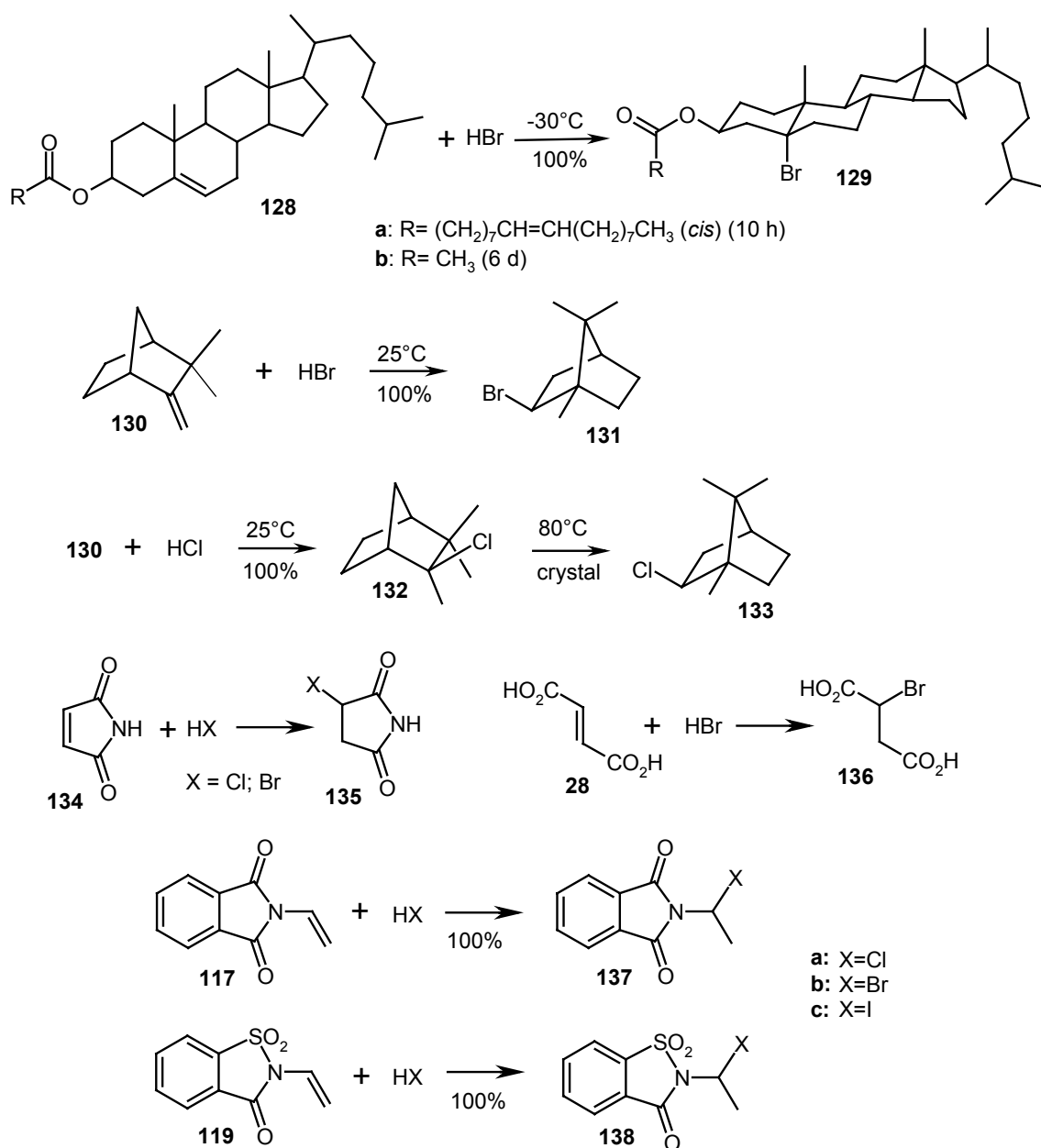
Tetramethylthiocarbamoyl disulfide (**126**) (1.20 g, 5.00 mmol) or dimethylthiocarbamoylchloride (**127**; 1.24 g, 10.0 mmol) were reacted in an evacuated 1 L flask with Cl_2 (1 bar, 45 mmol). After 10 h, all Cl_2 was consumed to form solid **101** with included SCl_2 . This product was heated to 80°C for 2 h in a vacuum with a cold trap (77 K) condensing the liberated Cl_2 and SCl_2 . The yield of pure **100** was 1.62 g (100%) in both cases.

9 ADDITIONS OF HYDROGEN HALIDES

Various unsubstituted solid alkenes are able to quantitatively add gaseous halogenohydrides. Prominent examples are the cholesterol esters **128** that give stereospecifically the bromides **129** at -30°C [75], [75a] and camphene (**130**) that gives stereospecifically the rearranged bromide **131** or the elusive camphene hydrochloride (**132**) with 100% yield [11]. The solid-state [1,2/2,1]-rearrangement [76] (Wagner Meerwein rearrangement) of **132** to give **133** is obtained at 80°C (6 h) or at r.t. (3 years). The same rearrangement in solutions is rapid, but it is possible to secure the purity of solid **132** by extrapolation back to time zero with ^1H NMR measurements.

Gaseous HCl adds to maleimide (**134**). Even more general are quantitative additions of HBr which succeed with maleimide (**134**), maleic anhydride, fumaric acid (**28**), and maleic acid [28].

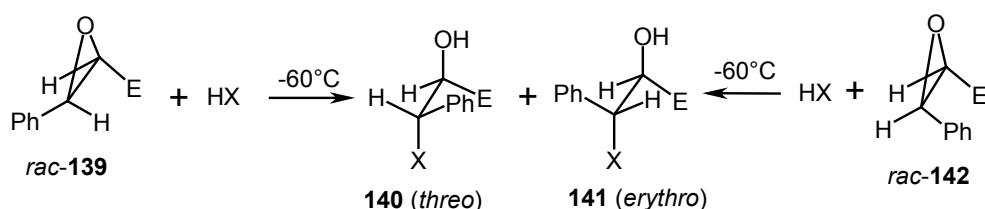
Very reactive (and probably not accessible from solution reactions) are the quantitatively obtained products **137** and **138** by the addition of gaseous HX to the N-vinyl compounds **117** and **119** [33, 61, 74]. Also N-vinylpyrrolidinone adds HBr probably quantitatively as a solid at -40°C in the Markovnikov orientation. However, the product is too labile for storage at r.t. and must be reacted further at the low temperature (examples are substitutions with methylthiol that work also with **137** and **138** [33]). Upon warming to r.t. the product N-(1-bromoethyl)pyrrolidinone releases HBr and forms the linear dimer (E)-1,1'-(3-methyl-1-propene-1,3-diyl)bis(2-pyrrolidinone) that is most easily obtained by this technique [58].



Scheme 20

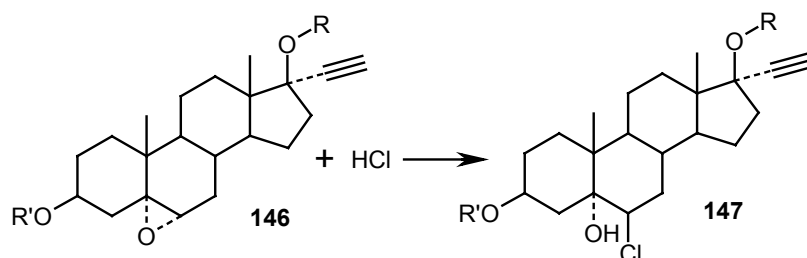
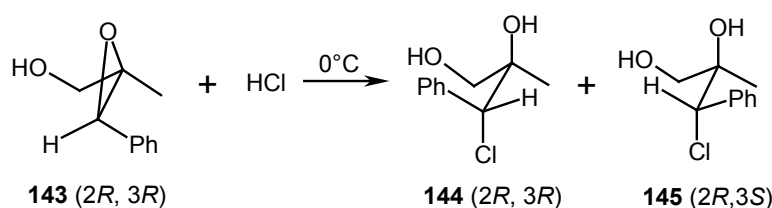
Numerous solid oxiranes add quantitatively gaseous HCl or HBr even at low temperatures. These reactions are stereoselective, the ratio of front to back side reaction of the protonated oxirane certainly depends on the stabilization of the intended carbocation [77]. This is worked out by the data in Scheme 21 for *rac*-**139** and *rac*-**142** that give the products **140** and **141** in the given proportions. Similarly, the epimer ratio **144**:**145** upon reaction of (*2R,3R*)-**143** is 74:26 and the configuration at the 2-position is conserved. The experimental procedure for *rac*-**139** is as follows: Liquid *rac*-**139** (500 mg, 2.80 mmol) was crystallized by cooling to -60°C in a 100 mL flask under vacuum. HCl gas (1 bar, 4.5 mmol) was let in through a vacuum line. After 15 h at -60°C the excess gas was pumped off and 600 mg (100%) yellow crystals (73: 27 mixture of **140a** and **141a**) were obtained that melted at r.t.. **140a** (m.p. $65-67^{\circ}\text{C}$) was obtained pure by crystallization from *n*-hexane, though involving heavy losses.

The marked stereoselectivities and clean solid-state reactions of oxiranes were used for synthetic purposes in the steroid field. The stereospecifically obtained *trans*-chlorohydrines **147** ensue quantitatively from the crystalline *5\alpha,6\alpha*-epoxides **146** with gaseous HCl [77]. Similarly, the crystalline *16\alpha,17\alpha*-epoxide **148** reacts with gaseous HCl to yield exclusively the *trans*-chlorohydrine **149** which easily loses HCl to reform the starting epoxide **148**. Therefore, an equilibrium situation is reached in that case [77].

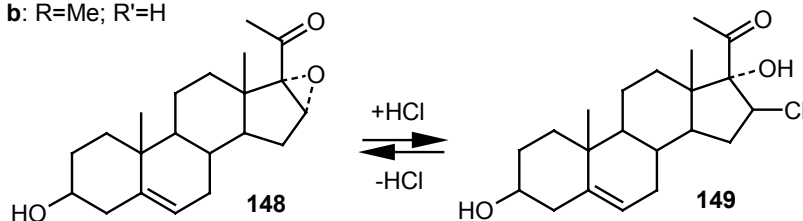


E=CO₂CH₃ a: X=Cl
 b: X=Br

| | front side | backside |
|-------------|------------------|------------------|
| 139a | 140a (73) | 141a (27) |
| 139b | 140b (74) | 141b (26) |
| 142a | 141a (71) | 140a (29) |
| 142b | 141b (65) | 140b (35) |
| 143 | 144 (74) | 145 (26) |



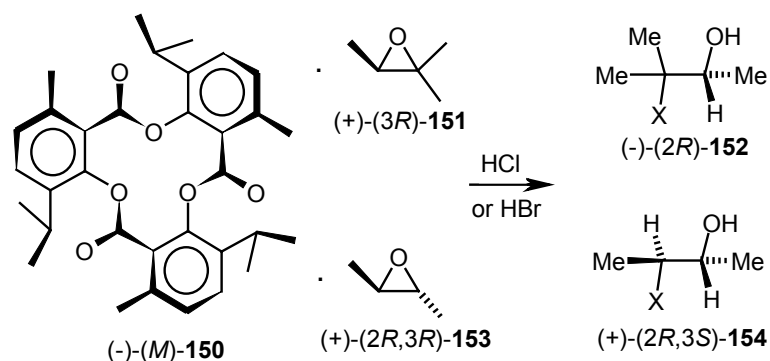
a: R=H; R'=COMe
 b: R=Me; R'=H



Scheme 21

The gas-solid addition of HCl or HBr to simple alkylated oxiranes requires their inclusion. (-)-(*M*)-tri-*o*-thymotide (**150**) (*P*3₁21) selectively enclathrates the oxiranes **151** or **153** with 13-14% ee for (+)-(3*R*)-**151** or 51-55% ee for (+)-(2*R*,3*R*)-**153**. Isolated molecules in the chiral cages of **150** react stereoselectively with HCl or HBr gas to give the products **152** and **154**, respectively, in almost stereopure form according to the optical rotations after quantitative

reaction under the influence of the chiral environment [78]. The host lattice is preserved during the reactions, but destroyed during liberation of the product molecules.

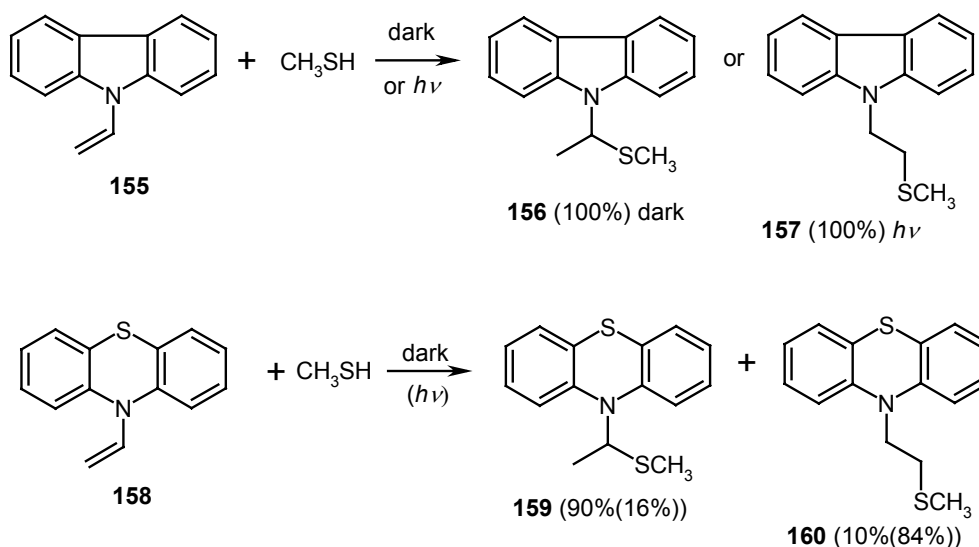


Scheme 22

The hydrohalogenide additions to oxiranes are ether cleavages, of course. A further example for this reaction type is the quantitative reaction of solid 2,4,6-trimethoxy-*s*-triazine with HCl gas at 100°C to give cyanuric acid and methylchloride [22].

10 ADDITION OF NUCLEOPHILES

Neutral gaseous nucleophiles such as water vapor are attacking hydrolyzable polar double bonds of all kinds (e. g. cyanates, isocyanates, iminium salts, etc.), however, these reactions tend to remain located at the surface due to its passivation (which allows the handling of such compounds in ambient air) or they form liquid layers. No quantitative reaction of the gas-solid type that may occur in a reasonable time (weeks) can be cited. More successful are solid-state addition reactions of thiols and amines. Methylthiol has been added to various N-vinyl compounds in the gas-solid variant, both thermally and photochemically, and the change in orientation has been studied [33]. The reactions of **155** are fully specific. Quantitative yields of **156** (Markovnikov orientation) were obtained in the dark and of **157** (*anti*-Markovnikov orientation) under irradiation. Similar reactions of **158** exhibit considerable selectivities for the orientation in the dark or under irradiation and mixtures of regioisomers are obtained, the yields of which add up to 100% as indicated in Scheme 23. The experimental procedures were

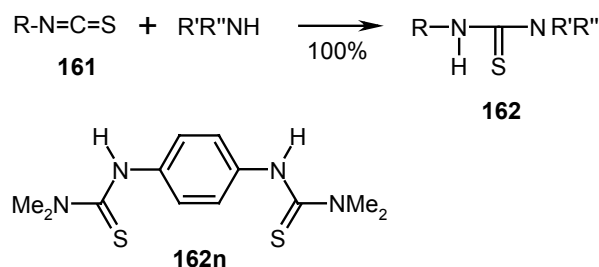


Scheme 23

as follows: Crystalline N-vinylcarbazole (**155**, 5.2 mmol, 0°C) or N-vinylphenothiazine (**158**, 1.8 mmol, r.t.) were exposed to 20 mmol or 10 mmol CH_3SH (0.9 bar) for 18 h or 2 d in the dark. Irradiations were similarly performed in a 250 mL round bottomed flask under 0.9 bar CH_3SH with a 500 W water-cooled tungsten lamp (**155**: 5.2 mmol, 2 h, 0°C ; **158**: 1.8 mmol, 11 h, r.t.). The purity of the products was determined by ^1H NMR spectroscopy.

Numerous further synthetic applications are to be envisaged.

Amines add to heterocumulenes. For example, the isothiocyanates **161** give a great number of thioureas in quantitative yield with gaseous or solid primary and secondary amines that are listed in Table 4 [12]. All thioureas are obtained with 100% yield directly in pure form.



Scheme 24

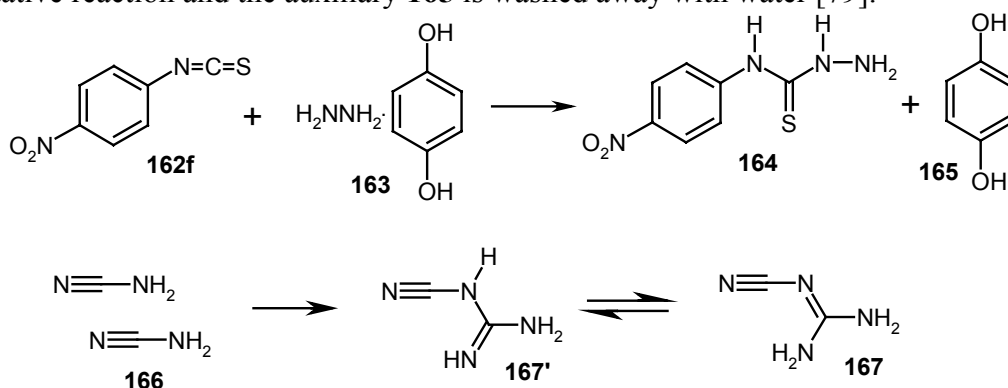
Table 4. Variations in the synthesis of **162**

| | R | R'/R'' | T ($^\circ\text{C}$) | Type[a] |
|-----------|----------------------|--------|------------------------|---------|
| a: | Ph | H/H | -30 | gs |
| b: | 4-BrPh | Me/H | r.t. | gs |
| c: | 4-BrPh | Me/Me | r.t. | gs |
| d: | 1-Naph | Me/H | r.t. | gs |
| e: | 1-Naph | Me/Me | r.t. | gs |
| f: | 4-NO ₂ Ph | Me/H | r.t. | gs |
| g: | 4-NO ₂ Ph | Me/Me | r.t. | gs |
| h: | Me | H/H | 0 | gs |
| i: | Me | Me/H | 0 | gs |
| j: | Me | Me/Me | 0 | gs |

| | | | | |
|-----------|------------|-----------|------|----|
| k: | Me | 4-MeOPh/H | r.t. | mo |
| l: | Me | 4-BrPh/H | r.t. | mo |
| m: | Me | 4-ClPh/H | r.t. | mo |
| n: | 4-S=C=N-Ph | Me/Me | r.t. | gs |

[a] gs: gas-solid; mo: ground in a mortar

A further variation is the reaction of isothiocyanates (e.g. **162f**) with hydrazine that has been “solidified by inclusion into the host hydroquinone (**163**). Ball-milling of the solids leads to a quantitative reaction and the auxiliary **165** is washed away with water [79].

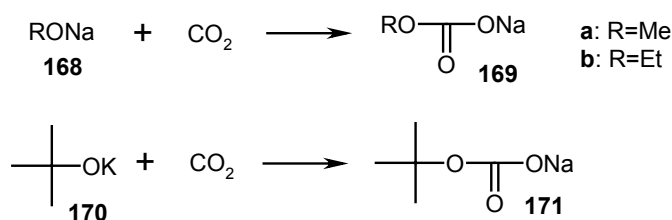


Scheme 25

The solid-state dimerization of cyanamide (**166**; m.p. 46°C) to give cyanoguanidine (**167**; m.p. 205°C) upon storage at r.t. represents an addition of the amino group to the triple bond. Thus, it happened in the author’s lab that a 1 kg supply of dry crystalline **166** was unwillingly stored at ambient temperature for more than one year and was thereafter completely transformed to crystalline **167**. However, 25 g of crystalline **166** in a sealed bottle were also completely transformed to **167** after 5 years in a refrigerator at 4°C. The corresponding melt-reaction of **166** in a DSC scan at a 5°C min⁻¹ rate was completed in the range of 125-155°C with an exothermic peak at 146°C, following the melting endotherm of **166** and followed by the melting endotherm of **167**. The tautomerism has been decided in favor of **167** as ab initio DFT calculations at the B3LYP/6-31G*- level predict the best possible rotamer of **167'** to be higher in energy by 13.2 kcal mol⁻¹ [22].

A great multitude of quantitative solid-state additions between anionic nucleophiles and appropriate double bonds can be envisaged, but the field is not explored. The potential may be demonstrated with larger scale additions of alkoxides (**168**, **170**) to carbon dioxide gas. Versatile carbonic acid half ester salts (**169**, **171**) ensue for diverse preparative applications in alkylations, carboxylations and acylations [4, 80]. The experimental technique may be cited: A chromatography column (diameter 4 cm, height 60 cm) with a D3-frit and gas outlet through a drying tube was charged upon glass wool with commercial 97.5% **168a** (250 g, 4.63 mol) or 95% **168b** (250 g, 3.68 mol) or 95% **170** (250 g, 2.23 mol) and covered with glass wool. Initially a mixture of CO₂ (250 mL min⁻¹) and N₂ (2.25 L min⁻¹) was applied from the bottom. It created a warm zone of about 50°C that passed the column in about 1 h. After that, the N₂-stream was halved and the reaction continued until the heat production ceased and such halving was repeated twice again. Finally the N₂-flow was removed and the now cold column left closed with pure CO₂ overnight. The weight increase (without correction for losses due to initially present ROH contents) was 191 g (97%), 154 g (95%) and 90 g (92%), and the fill volume increase 29, 45 and 56%, respectively. The pH values of aqueous solutions

of the products varied from 8.5 to 9. Titration after decomposition with aqueous H_2SO_4 gave content values between 97 and 102% of the versatile reagents **169a**, **169b** or **171**.



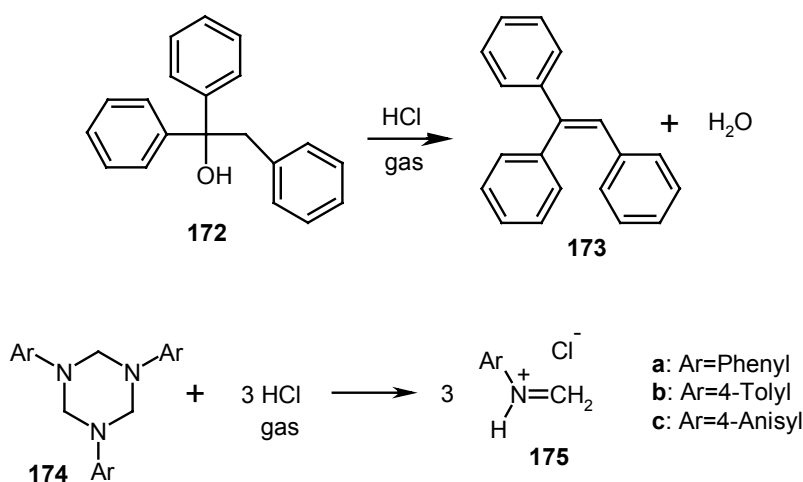
Scheme 26

Michael additions to electron poor alkenes are treated separately in Section 20.

11 ELIMINATION

Eliminations belong to one of the most diverse reaction types [76] and numerous solvent-free pyrolyses (sometimes quantitative melt reactions) provided useful syntheses [58, 81-87]. However, quantitative solid-state eliminations are rare (examples are found in the halogenations of 110, 112, and 114 (Scheme 17)). If an elimination reaction cannot be performed purely thermally or photochemically usually a catalyst or other auxiliary has to be added and it is no longer waste-free then.

The dehydration of solid alcohol **172** provides a 100% yield of solid triphenylethylene **173** upon the catalytic action of HCl gas in a desiccator [88]. Further examples of that type may have provided liquefied product.



Scheme 27

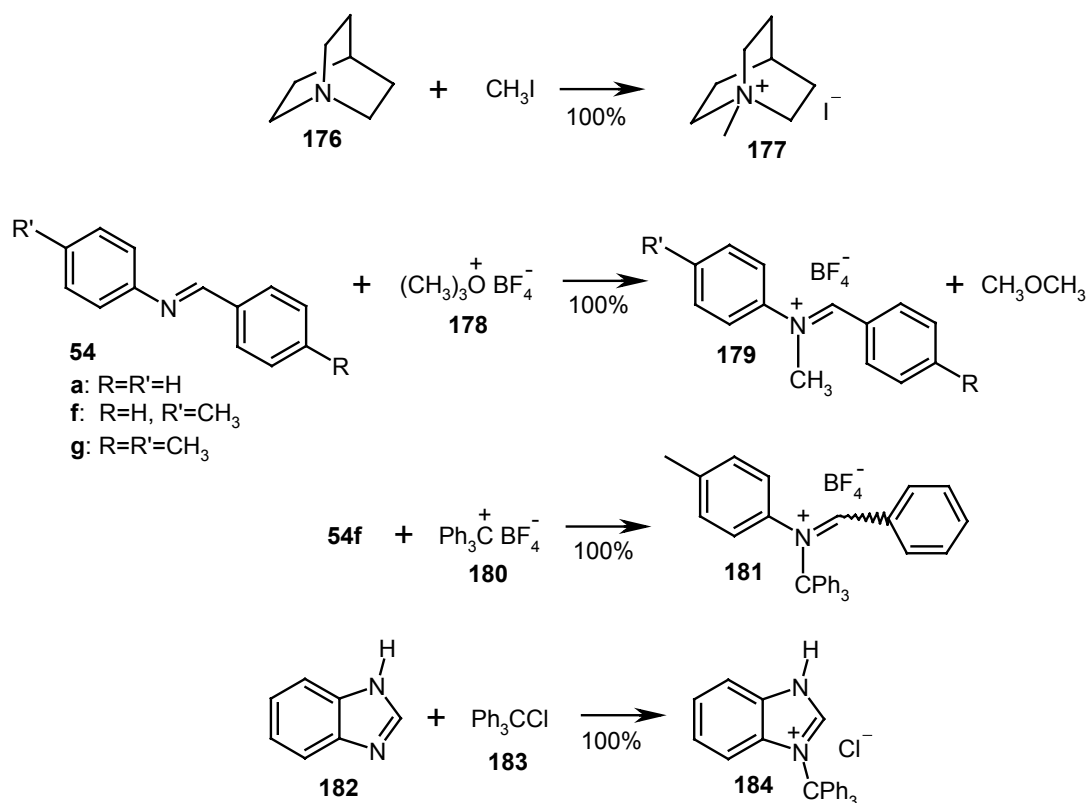
N-arylmethylenimine hydrochlorides are new highly reactive reagents that only exist in the solid state. They are easily and quantitatively obtained by *cyclo*-[1,2,(3)4,(5)6]-elimination [76] (also termed [2+2+2]-cycloreversion) of the hexahydrotriazine under the action of gaseous HCl at low temperature [10]: The hexahydrotriazines **174a-c** (3.00 mmol) were cooled to -18°C , -10°C and -10°C , respectively, in an evacuated 500 mL flask. HCl gas (500 mL, 1 bar) was let in through a vacuum line in 6 portions during 2 h or continuously through a

stopcock in 3 h. Excess gas was evaporated after thawing to 4°C and 8 h rest. A yellow **175a**, orange **175b**, and brown **175c** solid was obtained with quantitative yield. The versatile iminium salts **175** are only stable in the solid state and should be used for aminomethylations soon after their preparation. Gas-solid or solid-solid hydrolysis produces the corresponding Troeger's bases [10, 89].

A cyclizing elimination of water is described in Section 13.2 below: heating **220** gives quantitatively **221** in the solid-state.

12 ALKYLATION

Solid tertiary amines and imines may be quantitatively alkylated by gas-solid and solid-solid techniques. Methylation of quinuclidine (**176**) to give the methoiodide **177** is waste-free obtained by exposure to a stoichiometric amount of methyl iodide vapor. Difficulties with the disintegration of the crystals of **177** from those of **176** (reaction-step 3) are overcome by ultrasound treatment from a cleaning bath at 20°C [22]. Numerous applications of this technique to tertiary amines can be envisaged. However, solid Troeger's base (with interlocked layers, i.e. no possibility for molecular migrations) is not alkylated by methyl iodide vapor unless an excess of the vapor is applied to induce intermediate (partial) liquefying of the solid [22].



Scheme 28

Of particular interest are quantitative syntheses of extremely deliquescent and reactive alkyliminium salts by milling of solid imines with oxonium salts (**178**) or triphenylmethyl tetrafluoroborate (**180**) or triphenylmethyl chloride (**183**) (dry atmosphere in these cases). The sensitive salts **179**, **181** and **184** are formed in pure form without any waste by an easy

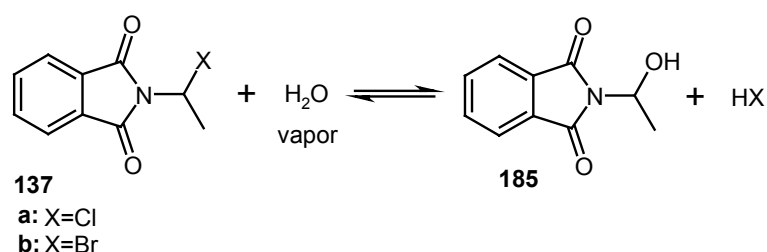
experimental technique [10]: Precisely weighed samples of **178** (ca. 2 mmol), or **180** (ca. 1 mmol), or **183** (1.00 mmol) were placed in a ball mill under argon together with the precise equivalent of **54a, f, g**, or **54f**, or **182**, respectively. The Teflon gasket was closed with a torque of 15-20 Nm and ball milling started for 1 h. The deliquescent salts **179**, **181**, **184** were quantitatively obtained and collected and stored under dry argon.

13 ALIPHATIC SUBSTITUTIONS

A large number of quantitative substitution reactions in the solid state are known. Typical examples will be arranged according to the entering reagent, but ring-opening substitutions of acid derivatives will be treated separately. Most substitutions are displacement reactions. But there may be also addition/elimination substitutions of vinylic substituents or vinylic hydrogen. A prominent example is the quantitative formation of 1-bromotriphenylethene from triphenylethene (**173**) and bromine vapor [22, 61]. Further examples can be found in [60].

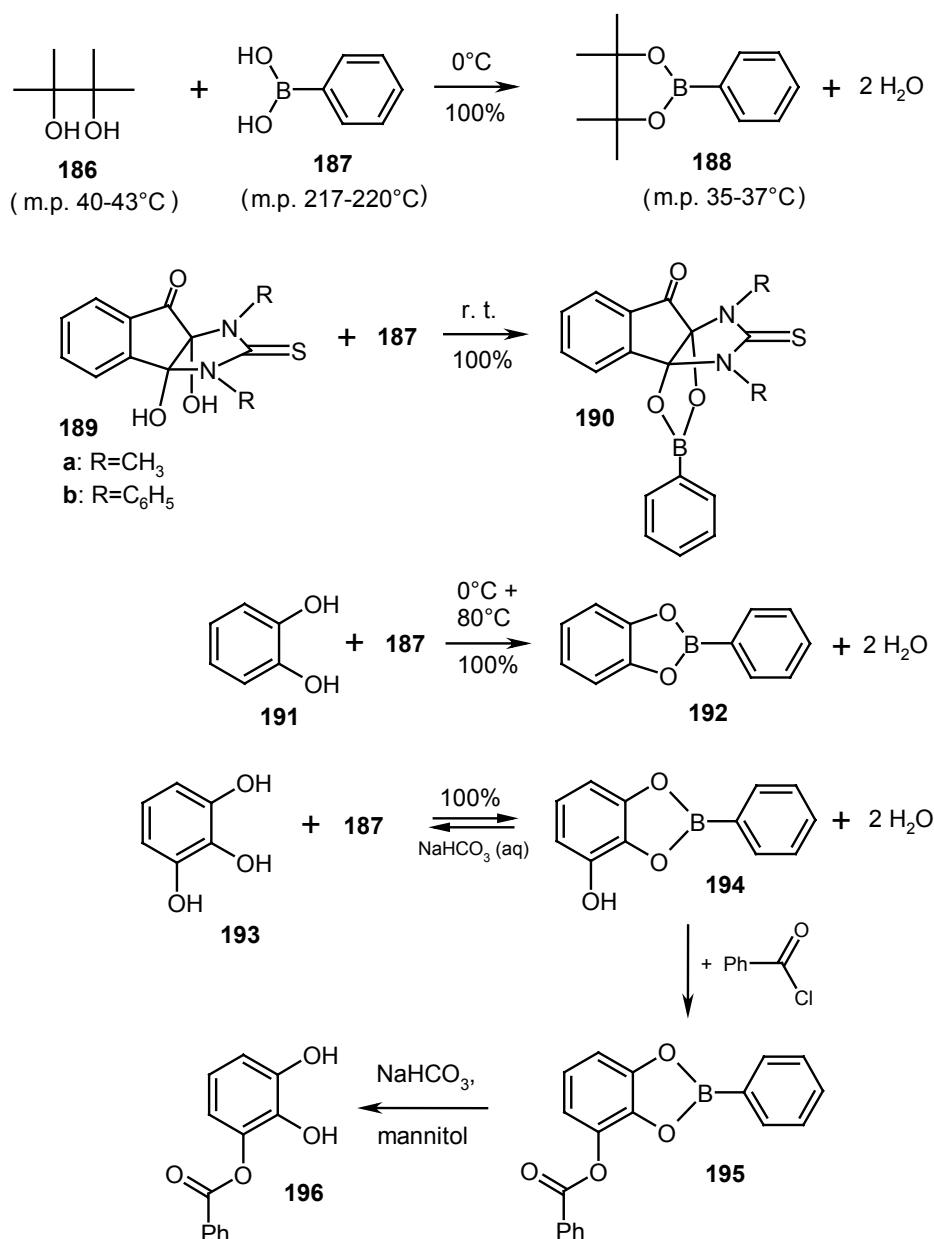
13.1 Hydroxyls and phenoxides

Water is a frequent reagent in substitution reactions. A surprisingly clean and complete synthesis of the elusive semi-N/O-acetal **185** is reversible if it is exposed to excess HX gas. No passivation of the crystal surface occurs even though the crystals become slightly wettish [74]: Compound **137a** (100 mg, 0.47 mmol) or **137b** (100 mg, 0.39 mmol) was placed on a glass frit and an aspirator for 2 h sucked through moist air. The slightly wettish crystals were dried in a high vacuum and consisted of pure **185** according to ¹H-NMR analysis. The reaction is reversible. If an excess of HX gas was applied to **185** the pure compound **137a** or **137b** was obtained.



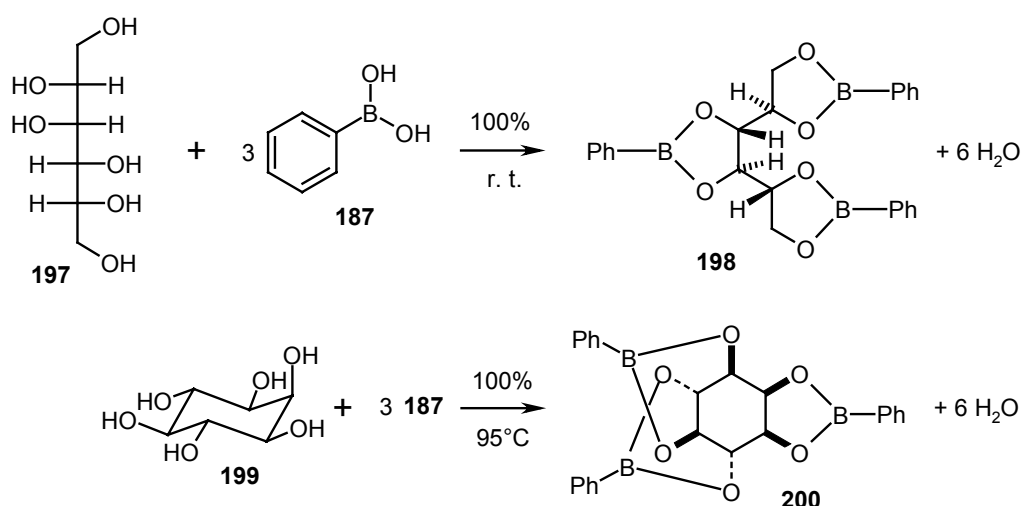
Scheme 29

Solid (*cis*-)1,2-diols and pyrocatechols react quantitatively with phenylboronic acid to form the phenylboronic esters upon stoichiometric milling. The water of reaction is taken up by the crystals and can be removed in a vacuum [90]. Thus, the aliphatic diols **186** and **189** give the boronic esters **188** and **190** with 100% yield. Equally successful is the reaction of pyrocatechol (**191**) and **187**. The reaction mixture is heated to 80°C after the milling at 0°C. These are powerful protection reactions. An example is given for the synthesis of 1-benzoyl-pyrogallol (**196**) starting with pyrogallol (**193**) that is quantitatively converted to its boronic ester (**194**) by stoichiometric milling with **187**. The free hydroxy group in **194** is benzoylated to give the derivatized boronic ester **195** which is finally deprotected by treatment with mannitol in aqueous sodium hydrogencarbonate [90]. Generally, the deprotection of boronic esters succeeds under very mild conditions.



Scheme 30

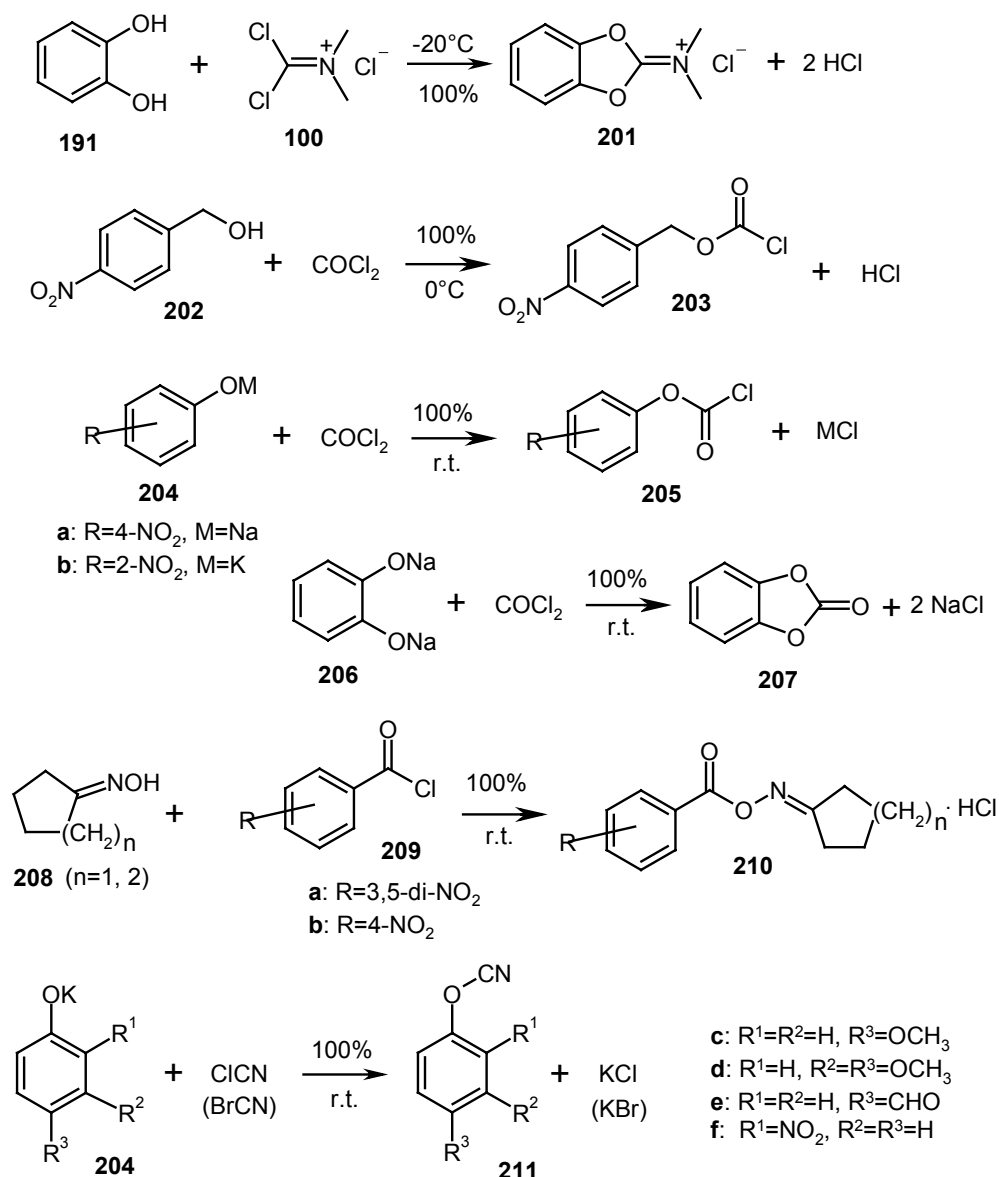
Very profitable are solid-state reactions of polyols. (*D*)-Mannitol (**197**) reacts quantitatively at r.t. with three molecules of phenylboronic acid (**187**) in the ball-mill to give the 1:2,3:4,5:6-product **198** with *2R,3R,4R,5R*-configuration as a non-sticky powder [90]. This fully protected mannitol is now available with great ease as the water can be removed by drying in a vacuum at 80°C. The same is true for the stoichiometric synthesis of the fully protected *myo*-inositol *rac*-**200**. It is obtained by milling of **199** with three molecules **187** at 95°C. The *meso*-compound **199** provides specifically the racemate of **200** with one five-membered and two six-membered rings. In both syntheses the six equivalents of the couple product water are taken up by the crystal lattice of the tris-boronic esters [90]. These fully specific reactions in highly complicated lattices with multiple hydrogen bonds are highly remarkable.



Scheme 31

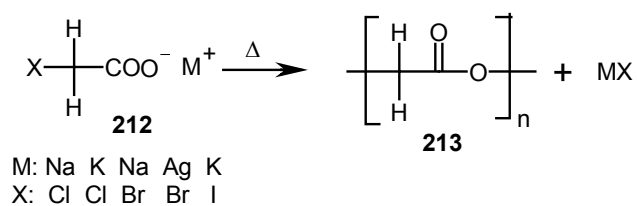
Highly reactive ketene iminium salts such as **201** are easily accessible, for example, by stoichiometric milling of **191** with **100** [9]. Also the quantitative gas-solid reactions of benzylic alcohols (**202**) or alicyclic alcohols like (1*S*)-(-)-borneol and phenolates (**204**) with phosgene are of high preparative importance [91]. If the disodium salt of pyrocatechol (**206**) is reacted with phosgene the carbonate **207** arises. Reactions with the poisonous phosgene are particularly safely handled if solvents are avoided. The quantitative esterifications of high melting alcohols or phenolates are attractive examples as only HCl or sodium (potassium) chloride are formed as easily removable stoichiometric coproducts. It is even possible to directly esterify crystalline alcohols with crystalline carboxylic acids. For example cholesterol (**123**), the crystals of which exhibit channels along [001], quantitatively forms the diester with oxalic acid when comilled in a 2:1 ratio at 90°C for one hour without intermediate melting. It is also possible to briefly (10 min) comill the components at r.t. and then heat the mixture for 1 h at 100°C for a quantitative solid state di-esterification. Interestingly, even the milled 1:1 ratio provides only the diester and unreacted oxalic acid. Therefore the intermediate monoester must be much more reactive in the solid state than the initial cholesterol [22]. On the other hand, the complex of cholesterol and benzoic acid does not esterify in the solid (90°C) or in the melt (2h 100°C). Versatile oxime esters **210** are obtained by milling of oximes (**208**) and acid chlorides (**209**) [91].

Also the hard to get in pure form cyanates (**211**) have been quantitatively obtained by reacting cyanogen chloride (gas-solid) or cyanogen bromide (solid-solid) with phenolates, washing away the salts and drying [92].



Scheme 32

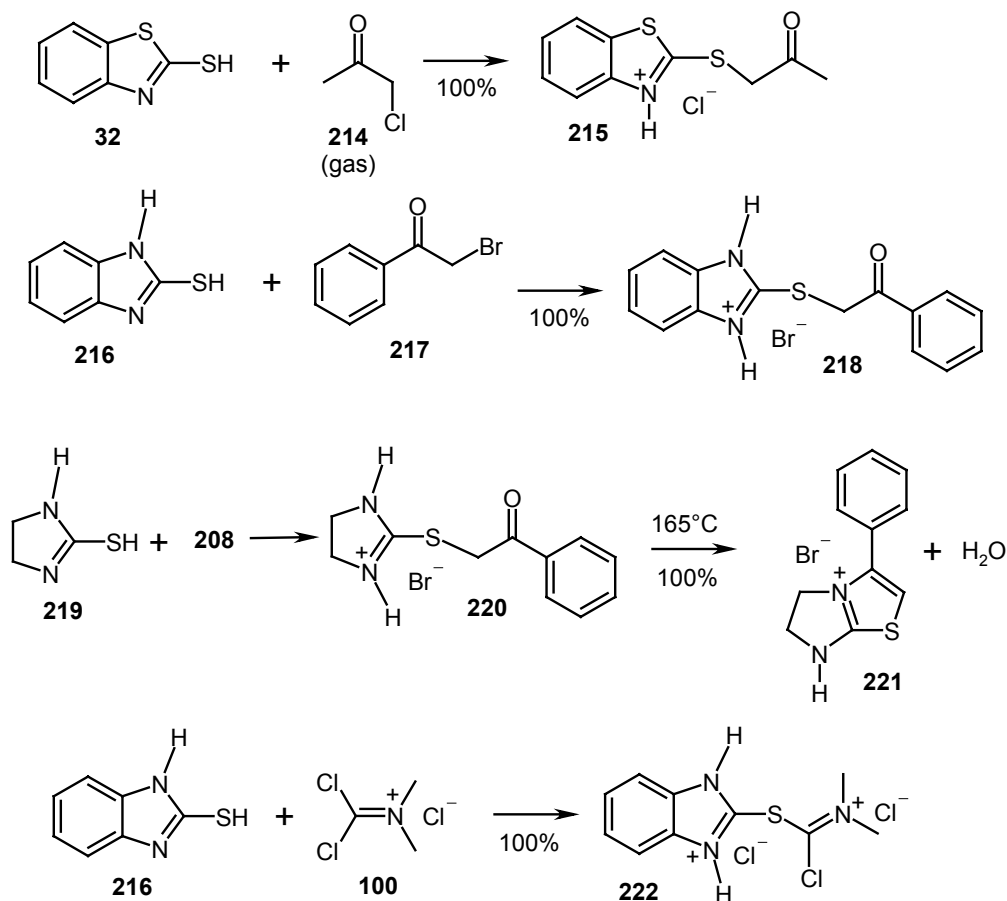
True solid-state reactions without liquids are exothermically obtained upon heating of halogenoacetate salts (**212**) to 100-200°C. Quantitative yields of polyglycolide matrices (**213**) with cubic holes after washing with water (when the MX dissolved away) were obtained [93].



Scheme 33

13.2 Thiols and thiolates

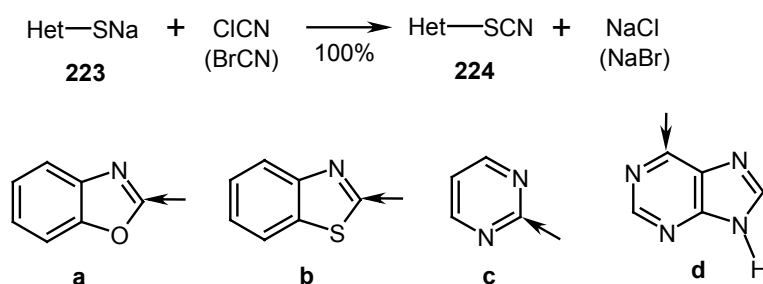
Thiols and thiolates are particularly versatile in quantitative solid-state substitutions. Thus, the solid heterocyclic thiols **32**, **216** and **219** react with gaseous (**214**) and solid (**217**) acylhalides to give the thiuronium salts **215**, **218** and **220** [10]. The thiuronium salt **220** undergoes an interesting cyclization reaction with loss of water upon heating to 165°C for 1 h. A quantitative yield of **221** is obtained without melting [10].



Scheme 34

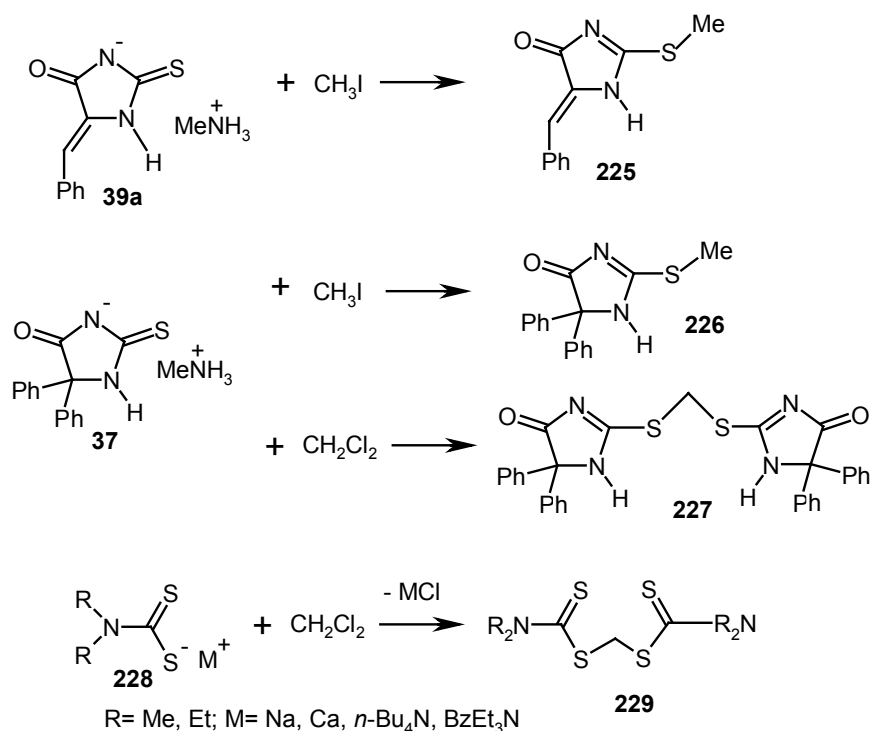
The solid-solid reaction (milling) of Viehe salt (**100**) with **216** gives the highly substituted doubly charged thiuronium salt **222** at r.t. again waste-free [10].

For the quantitative synthesis of thiocyanates by reaction with cyanogen chloride or cyanogen bromide it is essential to start with thiolates instead of thiols. The product salts are then removed by washing of the products with water. Thus, the various heterocyclic thiocyanates **224a-d** are easily obtained in pure form by either gas-solid (ClCN) or solid-solid (BrCN) reaction [92].



Scheme 35

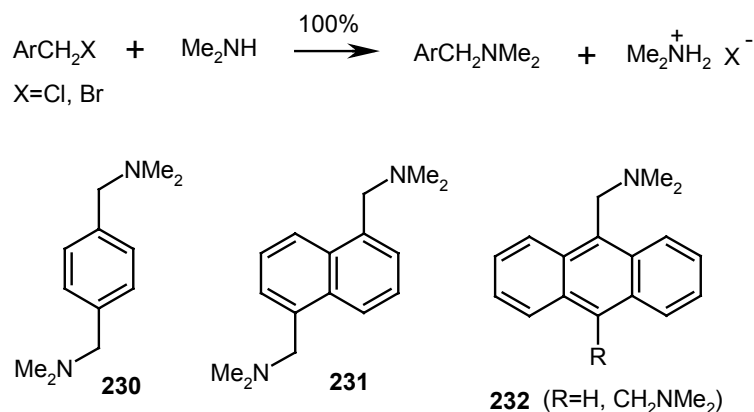
Volatile alkyl halogenides such as methyl iodide, methylene chloride, etc. react quantitatively with the solid methylamine salt of 5-benzylidene- (**39a**) [32] and 5,5-diphenyl-thiohydantoin (**37**) to form the anticonvulsive solids **225** and **226** in quantitative yield [28]. Unlike the solution reaction, only the S-alkylation occurs under gas-solid conditions. Furthermore, various dialkylamidodithiolate salts **228** react readily with dichloromethane at 80°C. The salts with the quaternary cations react at r.t. and it is also possible to catalyze the reaction of the sodium salt by admixture of 10% of the corresponding “phase transfer bromides” [28]. These reactions have been tuned for removal of dichloromethane from loaded air streams [28].



Scheme 36

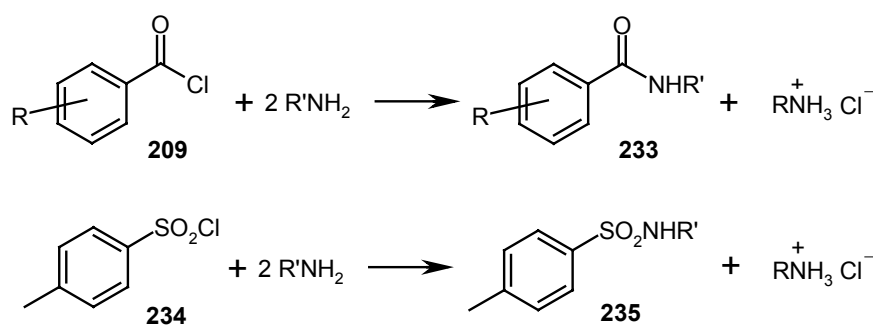
13.3 Amines and amide anions

Solid benzylic halogens are easily substituted with gaseous dialkylamines. Monoalkylamines are less suitable for uniform reactions due to secondary substitution of the initial product by the benzylic halide present. Some characteristic 100% yield conversions are listed in Scheme 37. The benzene (**230**) and naphthalene derivatives (**231**) started from the solid bromides, the anthracene derivatives (**232**) from the solid chlorides [22].



Scheme 37

Quantitative stoichiometric gas-solid or solid-solid (these at 0°C) acylations of amines with acid chlorides are varied. However, for a clean reaction the liberated hydrochloric acid has to be neutralized by an additional gaseous or solid base that may be also a second mole of the amine. The reactions are performed in an evacuated flask or in a ball-mill, respectively. There are only minimal losses of the amides or sulfonamides upon removal of the stoichiometric coproduct with water [91]. The solid-solid reactions can be turned into sustainable 100% yield processes with optimal atom efficiency by milling stoichiometric 1:1:1-mixtures of acid chloride, aniline derivative and K₂CO₃, followed by aqueous washings [22]. The quantitatively obtained amides **233** or **235** are listed in Table 5 [91].



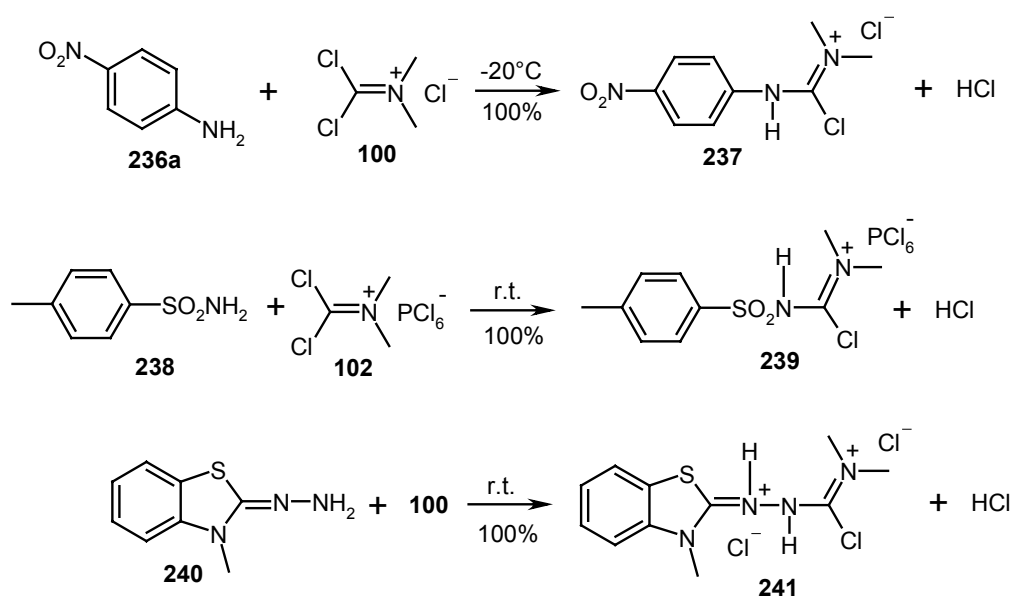
Scheme 38

Table 5. Quantitative acylations of amines by gas-solid and solid-solid reactions

| Acid chloride | Amine | m.p. (°C) | Amide | m.p. (°C) |
|--------------------------------|--|-----------|-------------|-----------|
| 209a : R = 3,5-di-Nitro | NH ₃ | gas | 233a | 175 |
| 209a : R = 3,5-di-Nitro | MeNH ₂ | gas | 233b | 145 |
| 209a : R = 3,5-di-Nitro | EtNH ₂ | gas | 233c | 123 |
| 209b : R = 4-Nitro | NH ₃ | gas | 233d | 140 |
| 209b : R = 4-Nitro | MeNH ₂ | gas | 233e | 214 |
| 209b : R = 4-Nitro | EtNH ₂ | gas | 233f | 149 |
| 209a : R = 3,5-di-Nitro | 4-MeC ₆ H ₄ NH ₂ | 41-46 | 233g | 283 |
| 209a : R = 3,5-di-Nitro | 4-MeOC ₆ H ₄ NH ₂ | 57-60 | 233h | 237 |

| | | | | |
|-------------------------------|--|-------|-------------|-----|
| 209a: R = 3,5-di-Nitro | 4-ClC ₆ H ₄ NH ₂ | 68-71 | 233i | 235 |
| 209a: R = 3,5-di-Nitro | 4-BrC ₆ H ₄ NH ₂ | 62-64 | 233j | 249 |
| 209a: R = 3,5-di-Nitro | 1-NaphNH ₂ | 48-50 | 233k | 270 |
| 209b: R = 4-Nitro | 4-MeC ₆ H ₄ NH ₂ | 41-46 | 233l | 200 |
| 209b: R = 4-Nitro | 4-MeOC ₆ H ₄ NH ₂ | 57-60 | 233m | 195 |
| 209b: R = 4-Nitro | 4-ClC ₆ H ₄ NH ₂ | 68 | 233n | 229 |
| | | -71 | | |
| 209b: R = 4-Nitro | 4-BrC ₆ H ₄ NH ₂ | 62-64 | 233o | 245 |
| 209b: R = 4-Nitro | 1-NaphNH ₂ | 48-50 | 233p | 173 |
| 234 | NH ₃ | gas | 235a | 137 |
| 234 | MeNH ₂ | gas | 235b | 77 |
| 234 | EtNH ₂ | gas | 235c | 63 |

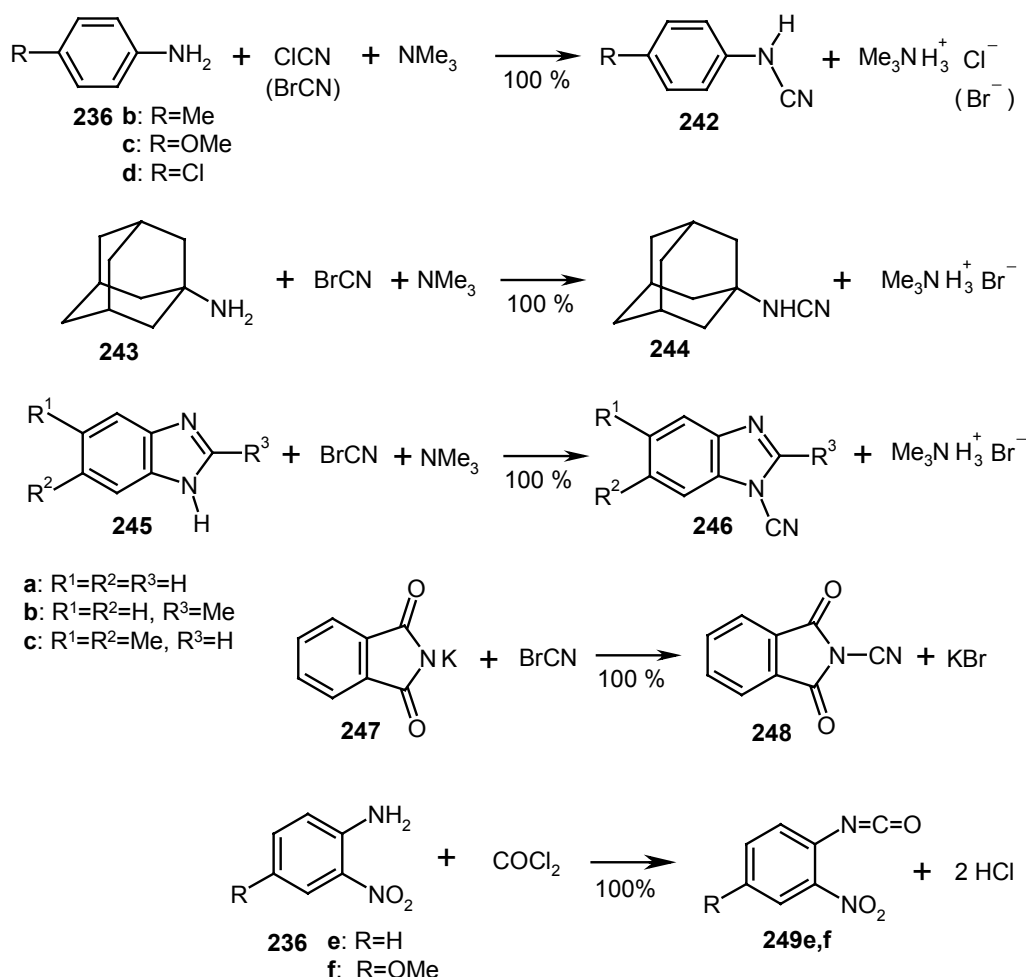
The solid-state reactions of Viehe salt (**100**) with primary amine functionalities (**236**, **238**, **240**) leads to highly substituted iminium salts in quantitative yield without wastes. Thus, compounds **237**, **239**, **241** are easily prepared. The mill is charged under dry atmosphere [9].



Scheme 39

The solid-state reactions of cyanogen chloride or cyanogen bromide with the primary and secondary amines **236**, **243** and **245** require the addition of an inert base such as trimethylamine if quantitative reactions are desired. Solid volatile BrCN may be reacted via the gas phase in the chosen setup that gives quantitative yields of the cyanamides **242**, **244** and **246** after removal of the amine salts [92]: The crystalline substrate **236a-c**, or **243**, or **245a-c** (10 mmol) was placed in a 500 mL flask which was evacuated and filled with a 1:1-mixture of ClCN and trimethylamine (11.7 mmol, each), or it was placed in an evacuated 250 mL wide neck flask connected to a 250 mL wide neck flask with freshly sublimed BrCN (1.17 g, 11.0 mmol). Trimethylamine (0.5 bar, 11.7 mmol) was added through a vacuum line. A magnetic spin bar was rotated in the flask in order to mix the gases and the system was left

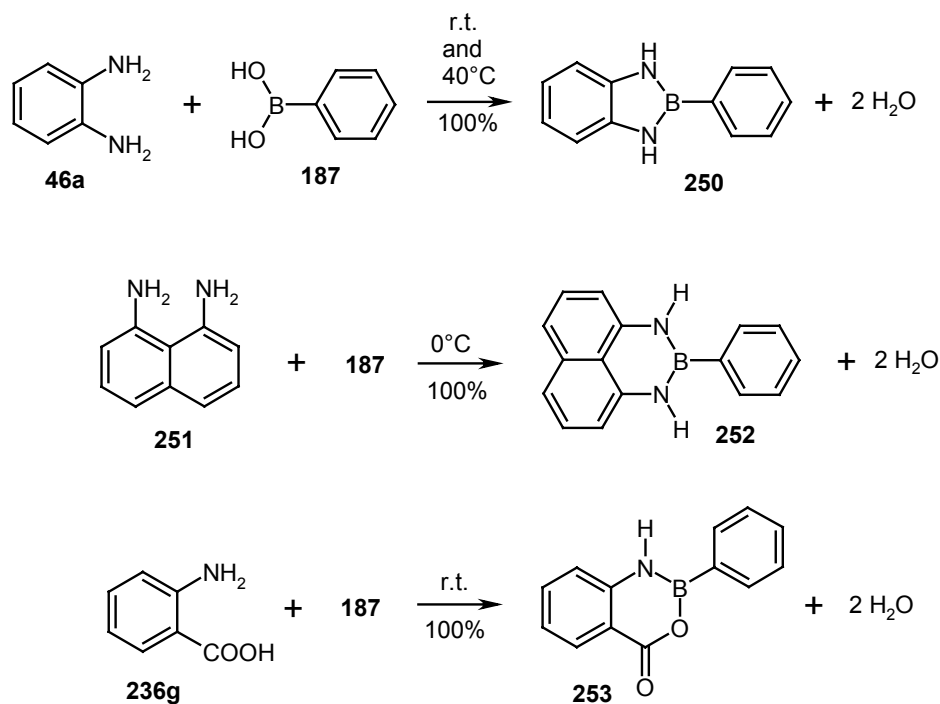
overnight at r.t.. Excess gas was pumped to a cold trap at 77 K. Washings with water removed the trimethylammonium chloride (bromide). The yield of **242** or **244** or **246** was quantitative in all cases. Furthermore, the reaction of ball-milled potassium phthalimide (**247**) with BrCN gas in a vacuum provides a quantitative yield of the cyanimide **248** [92]. These appear to be the best and the most convenient procedures for the preparation of these pure compounds.



Scheme 40

The gas-solid reactions of anilines with phosgene experience similar difficulties as the corresponding solution reactions giving product mixtures of carbamoyl chlorides, isocyanates, diarylureas. It was however possible to get product specificity by reacting *o*-nitroanilines with gaseous phosgene. Thus, **236e, f** provides quantitative yields of the isocyanates **249e, f** without producing wastes as the couple product HCl can be collected for further use [91].

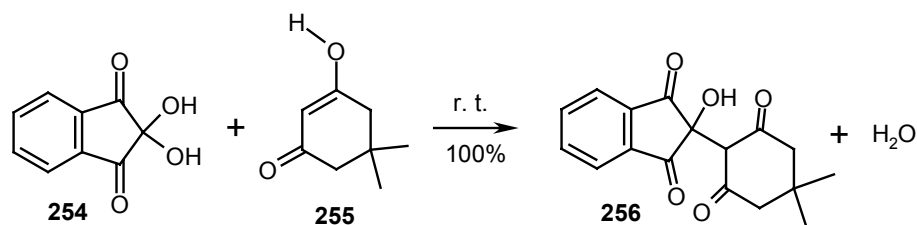
Interestingly, primary aromatic amino groups substitute the hydroxyl groups of phenylboronic acid with great ease in the solid state. Cogrinding of **46a** and **187** followed by heating to 40°C leads to a quantitative yield of **250**. The compounds **252** and **253** are quantitatively obtained by ball milling of **251** (0°C) or **236g** (r.t.) with **187** [90]. Both the amino and the carboxyl group participate in the reaction of anthranilic acid. The products lose the water of reaction at 80, 50, and 80°C, respectively, in a vacuum without melting. These are protection reactions. The diamines or anthranilic acid can be recovered by mild hydrolysis.



Scheme 41

13.4 Enols

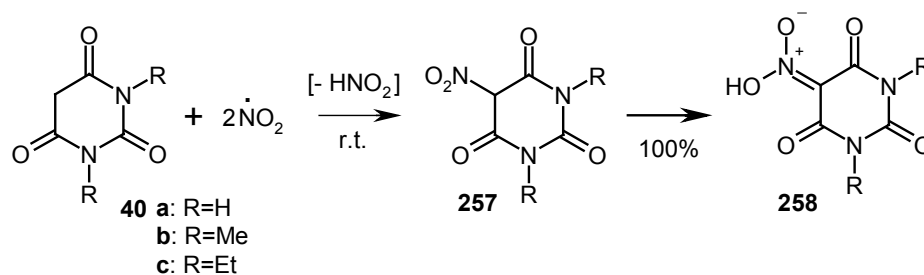
Solid enols such as dimedone (255) are able to substitute one of the hydroxyl groups of ninhydrin (254) upon milling and give a quantitative yield of the tertiary alcohol 256 [94]. This appears to be a rare reaction type, which merits further exploration.



Scheme 42

13.5 Radicals

Free radicals may substitute C-H bonds. Gaseous NO₂ (0.3 bar) has been tested with solid barbituric acids (40a-c). 100% yield reactions arise after 4 h exposure and the dried products (80°C) assume the *aci*-nitro forms 258a-c [19]. A very large field for preparative use appears to be opened with these and related waste-free reactions. The couple product N₂O₃ can be collected for further use.

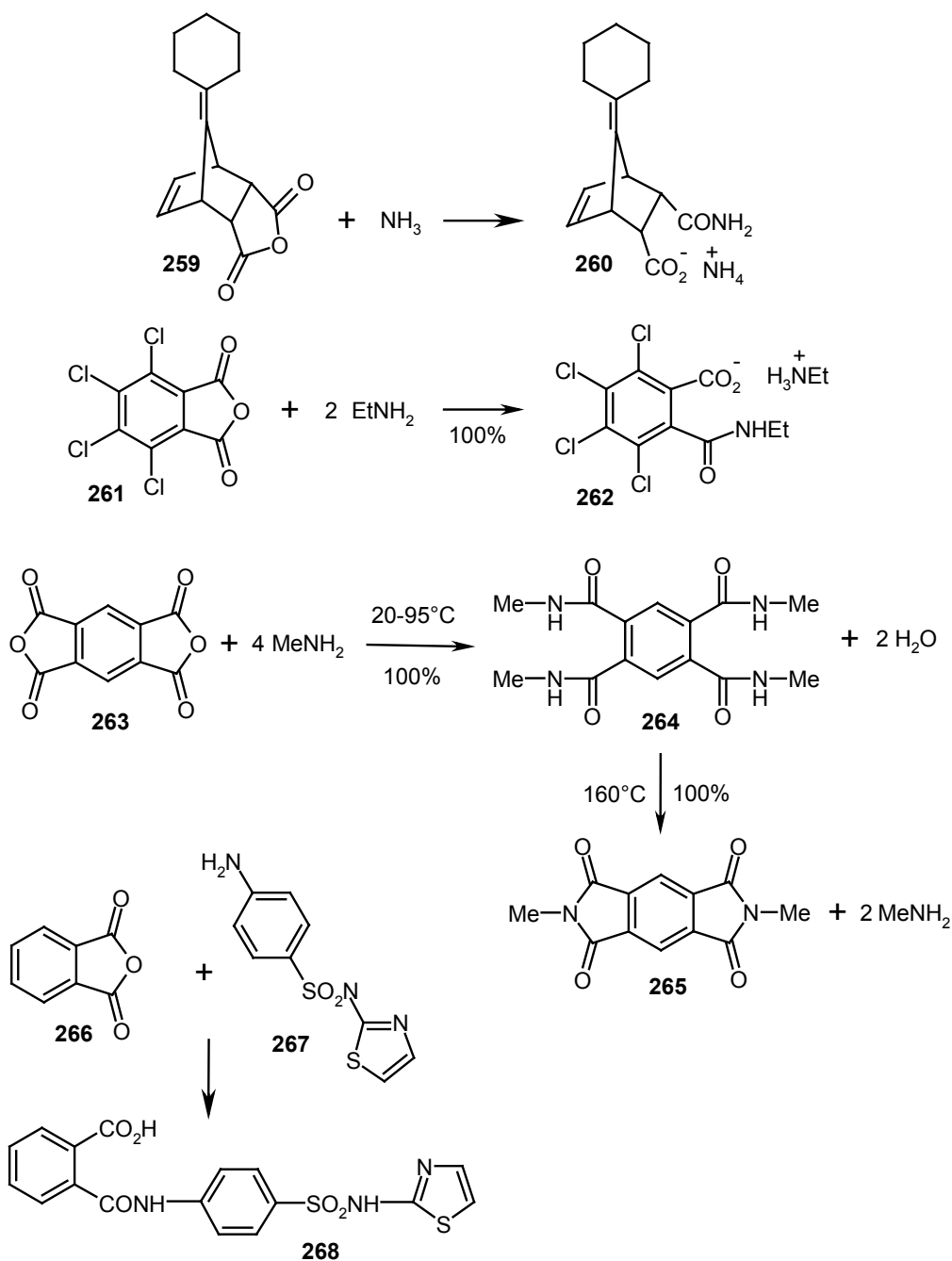


Scheme 43

13.6 Ring opening substitution of acid derivatives

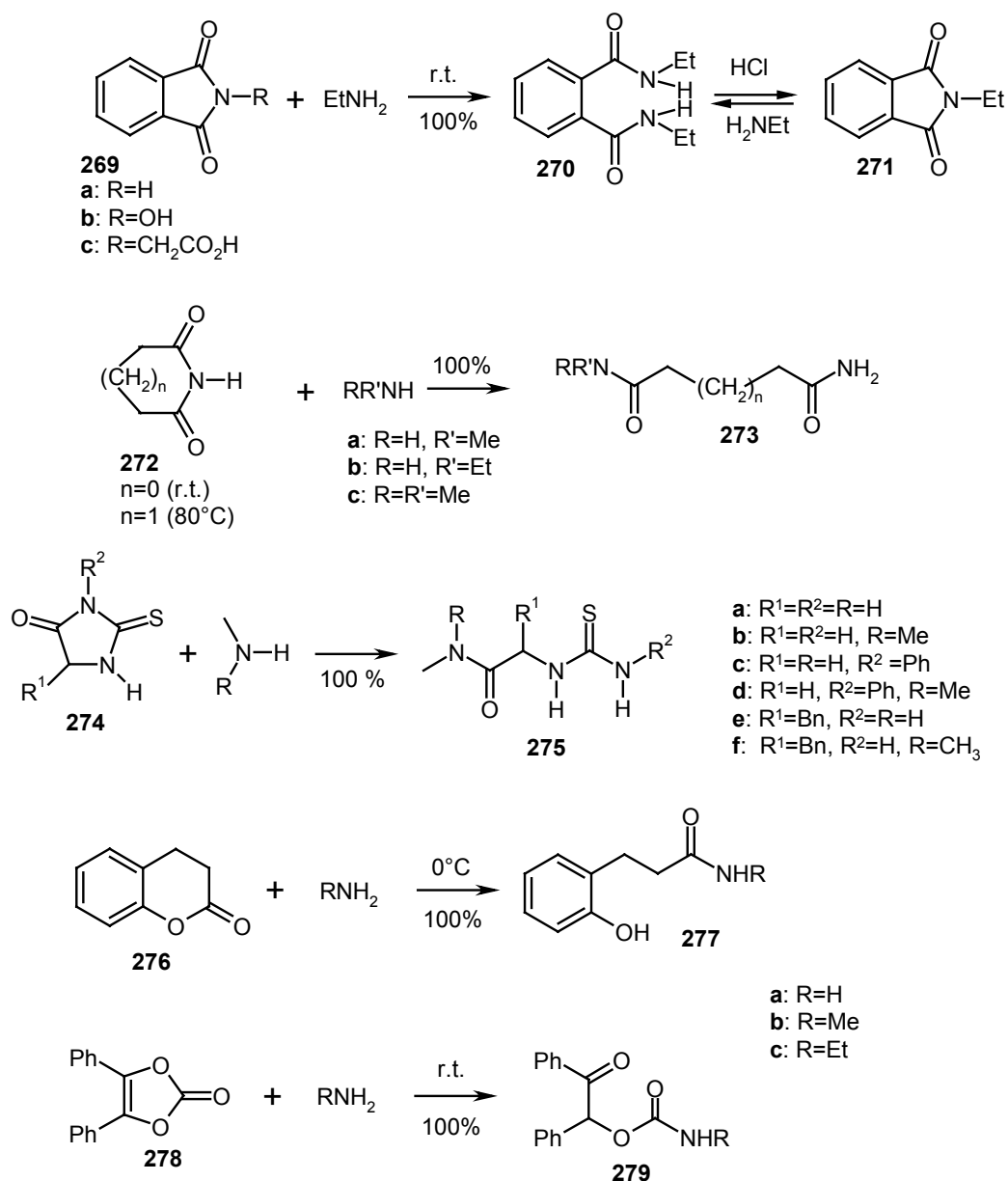
Most important are quantitative solid-state reactions of cyclic carbonic acid derivatives with gaseous or solid amines. These give open chain amides that can be recycled in various cases to new products of preparative interest.

Solid cyclic carboxylic anhydrides react with gaseous ammonia to give amide ammonium salts with quantitative yield. This has been observed with the labile Diels Alder adduct **259** [25]. Aliphatic amine vapors are equally able to open anhydride rings to form the amide salts from where the free amide acids can be obtained in 100% yield. The reaction of **261** with ethylamine to give **262** is an example for a large-scale preparative application [11-12]. Conversely, solid pyromellitic bis-anhydride (**263**) and methylamine vapor react exothermally (rise to 95°C) and quantitatively to yield the tetraamide **264**. Interestingly **264** cyclizes in a thermal solid-state reaction at 160°C to give the bis-imide **265** also with 100% yield [12].



Scheme 44

The antibacterial sulfonamide phthalazole **268** is obtained free of imide and bisamide side products (that occur upon reaction in solution or in the melt) if stoichiometric solid-state milling of the reactants **266** and **267** is performed for the acylation [95]. Numerous solid arylamines and heterocyclic amines react correspondingly with phthalic anhydride upon stoichiometric milling and provide 100% yield without any workup requirement [22]. Similarly, solid cyclic imides are attacked by gaseous aliphatic amines and lead to open chain diamides. For example, **269a-c** react with ethylamine gas to give a 100% yield of the diamide **270**, which can be quantitatively cyclized to the *N*-ethylimide **271** by the action of gaseous HCl [12]. As expected, the solid alicyclic imides **272** behave correspondingly and yield the bis-amides **273** in an easy waste-free procedure [12].



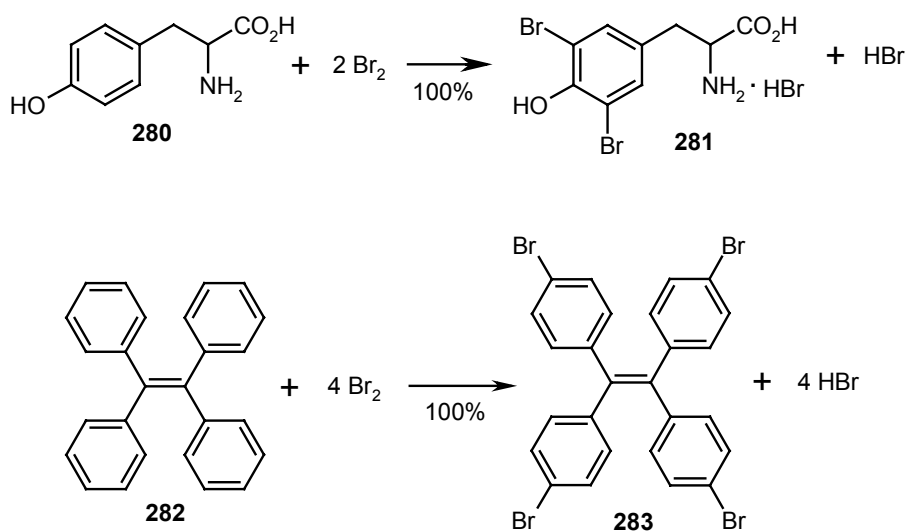
Scheme 45

A number of solid thiohydantoin **274** react quantitatively and specifically at the C(=O)-N bond with gaseous aliphatic amines to give the versatile [96] thioureido-acetamides **275** [31]. These reactions proceed equally well with secondary and allyl or propargyl amines and 29 preparative 100% yield gas solid conversions have been realized [32].

Solid lactones or cyclic carbonates form linear hydroxy amides upon reaction with gaseous ammonia, or methylamine, or ethylamine. For example, the compounds **277a-c** and (ketonized) **279a-c** are quantitatively formed at 0°C and r.t., respectively, without melting [12].

14 AROMATIC SUBSTITUTION

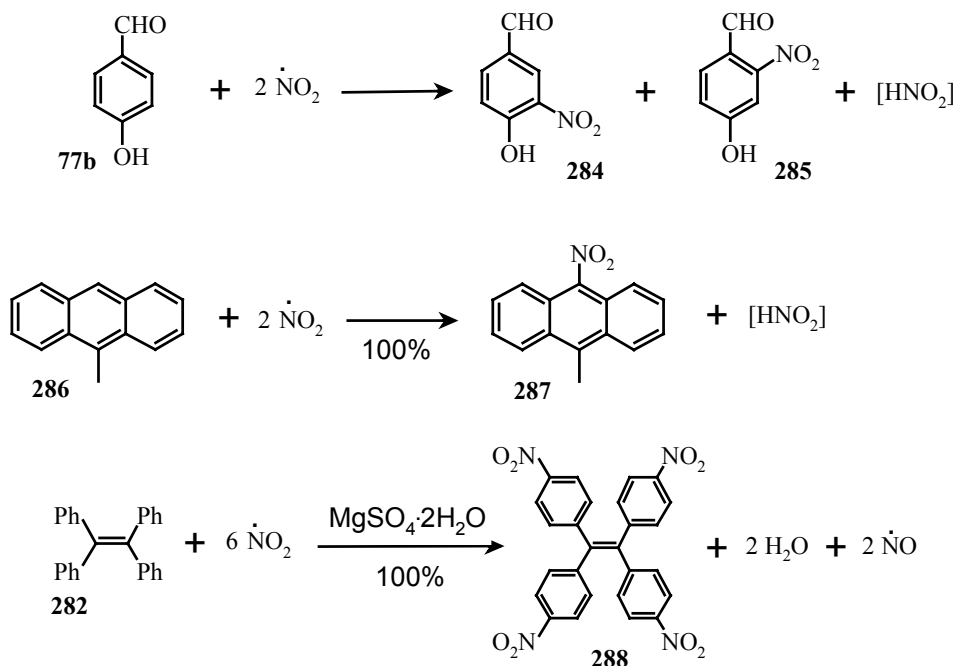
A very old gas-solid bromination of tyrosine (**280**) [97] has been revisited and it gave a quantitative yield for the reaction of *rac*-**280** [22]. The doubly brominated hydrobromide *rac*-**281** is spectroscopically pure after removal of included gases at 50°C in a vacuum. Quite spectacular is the specific and quantitative waste-free gas-solid tetrabromination of tetraphenylethylene (**282**), which shows some signs of autocatalysis and requires rotation of the flask around a horizontal axis at r.t. for 12 h as the reactant and product gases require mixing [60]. The isomer-free tetrabromide **283** is an attractive starting point for dendrimer syntheses and inclusion studies.



Scheme 46

Similarly, the crystalline heterocycle antipyrin (C2/c with channels along [001]) forms quantitatively 4-bromoantipyrin hydrobromide after removal of included gases when exposed to bromine vapors at r.t. [22]. Also antipyrin hydrobromide is quantitatively brominated with gaseous bromine.

Aromatic gas-solid nitrations with NO₂ gas are not always regiospecific. The reaction of 4-hydroxybenzaldehyde (**77b**) at 0.3 bar of reacting gas gave a 100% yield of a 82/18 mixture of **284** and **285** [19]. On the other hand, 9-methylanthracene (**286**) provides a quantitative yield of compound **287**. Highly spectacular is the quantitative yield of the pure tetra-*p*-nitro derivative **288** upon application of gaseous NO₂ in the presence of the drying agent MgSO₄·2H₂O for removal of the water of reaction that cannot be accommodated by the crystal in this case [19]. The yield is 100% if the magnesium salt is dissolved away with water after reaction. The couple product NO can be used in further reactions after reduction of excessive NO₂ by NaNO₂ (cf. Section 2). For larger scale runs the use of a flow apparatus is advisable, which allows for circulating of the gas and admixing of the calculated amount of oxygen to oxidize the NO formed for use in the running reaction.



Scheme 47

Azo couplings in the solid state are treated in Section 17.

15 DIAZOTIZATION

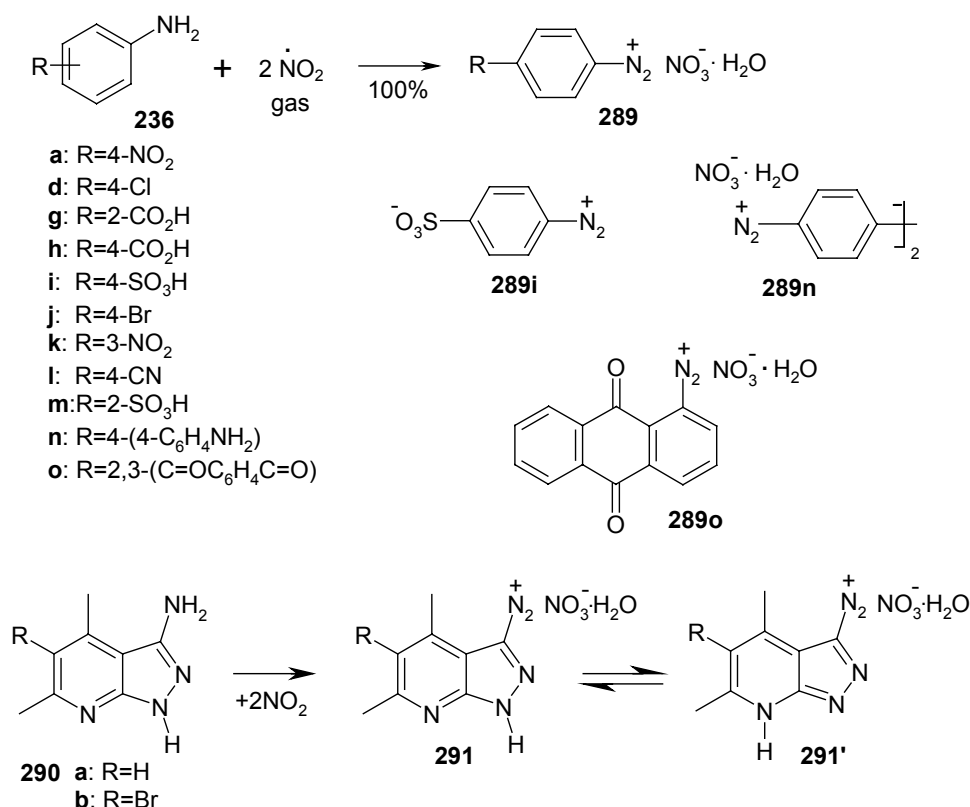
Solid diazonium salts are explosive upon heating (at least at their melting point) and upon shock (hammer on anvil, grinding over sharp edges or milling) and should be handled with great care. The most easy way to obtain diazonium nitrates in hydrated form is the action of gaseous NO₂ on solid aniline derivatives. These exothermic diazotizations are waste-free by avoiding strong acid solutions and by 100% yield throughout despite the multistep processes within the crystals [98-100]. A great variety of diazonium nitrates have been prepared. Even very highly substituted heterocycles such as **290** give a quantitative yield of the diazonium salt without nitrosation at one of the other nitrogen atoms (Scheme 48). The prescription should be closely followed for safety reasons:

Caution: solid diazonium salts explode upon heating to the melting point and upon shock or upon grinding at sharp edges. Do not ball-mill!

The solid aniline derivatives **236** (2.0 mmol; 1.0 mmol of **236n**) were treated with NO₂ gas in an evacuated 50 mL flask at 0°C (**236h, o** at r.t.). NO₂ (460 mg, 10 mmol) from a 250 mL flask was applied through a stopcock in 5 small portions, each after the brown color of the previous portion had disappeared. Finally, the excess gas was let in and the reaction completed by 6 h rest. Excess gas was recovered by cooling the 250 mL flask to 77 K.

Quantitative conversion to the diazonium nitrate hydrates **289/291** (except with **298a** where not all of the water could be accommodated by the crystal: 92 %) was secured by weight, spectroscopy, and quantitative coupling with β -naphthol. **289i, m** were freed from HNO₃ and water at 5·10⁻⁴ Torr (12 h) and were obtained as zwitterions. **289a** was purified by washings with ethylacetate in order to remove unreacted **236a**, a technique that should be applied in all cases where the aniline derivative **236** contained unpolar impurities that are most easily removed at that stage. Thus, the synthesis of **289o** started with **236o** of 97% purity. **289o** was

obtained in pure form by two washings with ethyl acetate. Density functional theory calculations (DFT) at the B3LYP/6-31G* level predict **291a** to be more stable than **291a'** by the minute amount of 0.53 kcal·mol⁻¹. Therefore, equilibrium is assumed but the crystal might prefer one of these tautomers [100].



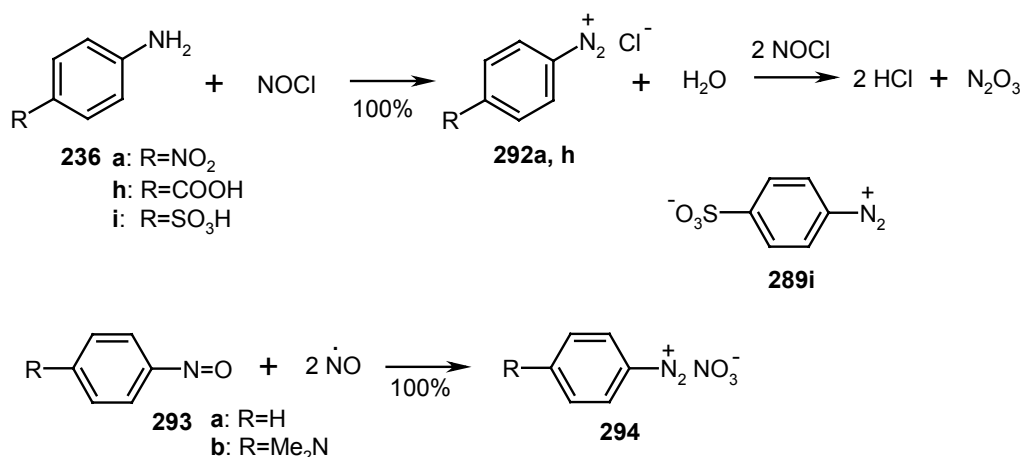
Scheme 48

The need for solid anhydrous diazonium chlorides can be complied with gas-solid reactions using NOCl as the reactive gas and anhydrous diazonium nitrates are obtained by reacting solid aromatic nitroso compounds with nitrogen monoxide gas. The alternative by reacting solid arylidene anilines with gaseous nitrogen monoxide to give diazonium nitrates and arylaldehydes did not give quantitative but only good yields [99]. Again, the prescriptions should be closely followed for safety reasons:

Caution: solid diazonium salts explode upon heating, upon shock and upon grinding at sharp edges!

The solid aniline **236** (1.00 mmol) in an evacuated 250 mL flask was connected via vacuum line to a 250 mL flask that was filled with NOCl (1 bar, 11 mmol). After 24 h, the gases were condensed back into the gas reservoir at 77 K, absorbed in water and neutralized with NaOH for disposal. The yellow-orange crystals **292a, h or 289i** were quantitatively obtained.

The nitrosobenzenes **293a, b** (2.00 mmol) in an evacuated 250 mL flask were connected via vacuum line with a 250 mL flask containing NO (1 bar, 11 mmol) that had been freed from traces of NO₂ by storing over 4-chloroaniline. After 24 or 48 h rest in a refrigerator at 4°C excess gas was recovered in a cold trap at 77 K. Pure **294** was quantitatively obtained.



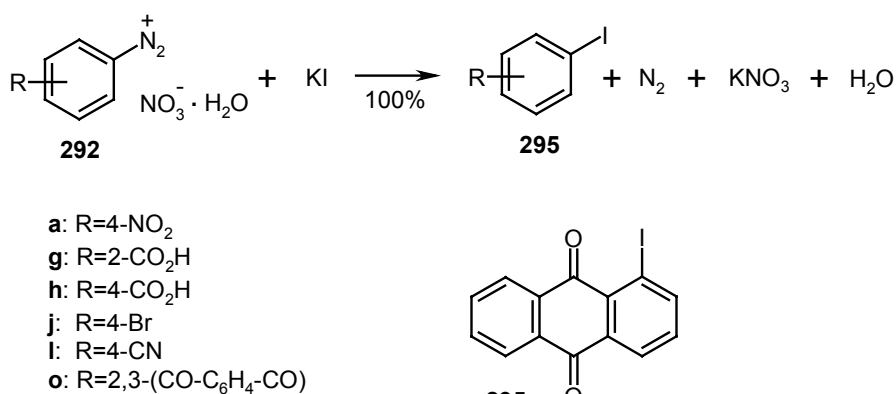
Scheme 49

16 SANDMEYER REACTION

Solid diazonium salts are well suited for reactions in the solid state. They rapidly react with potassium iodide when coground in an agate mortar (without sharp edges!) and give a quantitative yield of the solid aryl iodide after removal of the potassium salt by washing with water [99]. This is well superior to the normal Sandmeyer technique in solution that provides side products and requires purifying workup of the product mixtures. For safety reasons the prescription should be carefully followed:

Caution: solid diazonium salts are heat and shock sensitive; do not ball-mill!

Potassium iodide (830 mg, 5.0 mmol) was finely ground in an agate mortar and the diazonium salt **292** (0.50 mmol) added in five portions and co-ground for 5 min, each. After a 24 h rest with occasional grinding, the diazonium band in the IR spectrum had completely disappeared. Washings with cold water removed the potassium salts. The yield of pure aryl iodide **295** was 100% throughout.



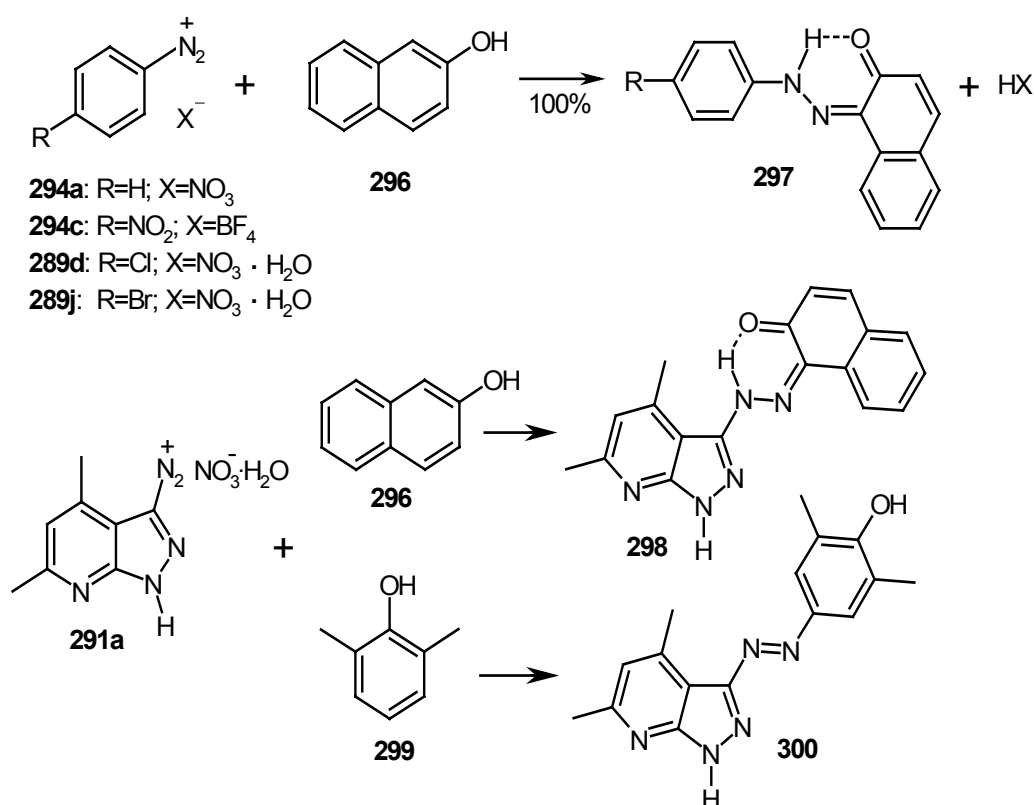
Scheme 50

17 AZO COUPLING

Equally popular are azo couplings of diazonium salts that keep the nitrogen atoms in the product. The solid-solid version is very suitable with appropriate phenols such as **296** and **299**. The waste-free and quantitatively obtained “azo-dye” salts can be neutralized. The free dyes have the hydrazono structure (**297**, **298**) or the azo structure (**300**) [99-100]. The prescription should be carefully followed for safety reasons:

Caution: these reactions might occur violently; use smooth agate mortar and do not ball-mill!

Solid diazonium salt **294** or **289** (0.50 mmol) and β -naphthol (**296**; 0.60 mmol) were separately ground in agate mortars and cautiously mixed. In the case of **289j** the drying agent $\text{MgSO}_4 \cdot 2\text{H}_2\text{O}$ (0.50 mmol) was added to the mixture. The mixtures rested for 24 h in test tubes and were then exposed to ultrasound for 24 h in a cleaning bath at 20°C. The quantitatively obtained “azo-dye” salts **297**·HX were neutralized and freed from excess **296** by washings with 0.5 *n*-NaOH (20 mL) and water (20 mL). The yields of the neutral dyes with the hydrazono structure **297** were 100%, 98%, 99% and 99%, respectively. The analogous procedure was applied for the syntheses of **298** and **300**, giving 100% and 98% yield, respectively, after the washings [100].



Scheme 51

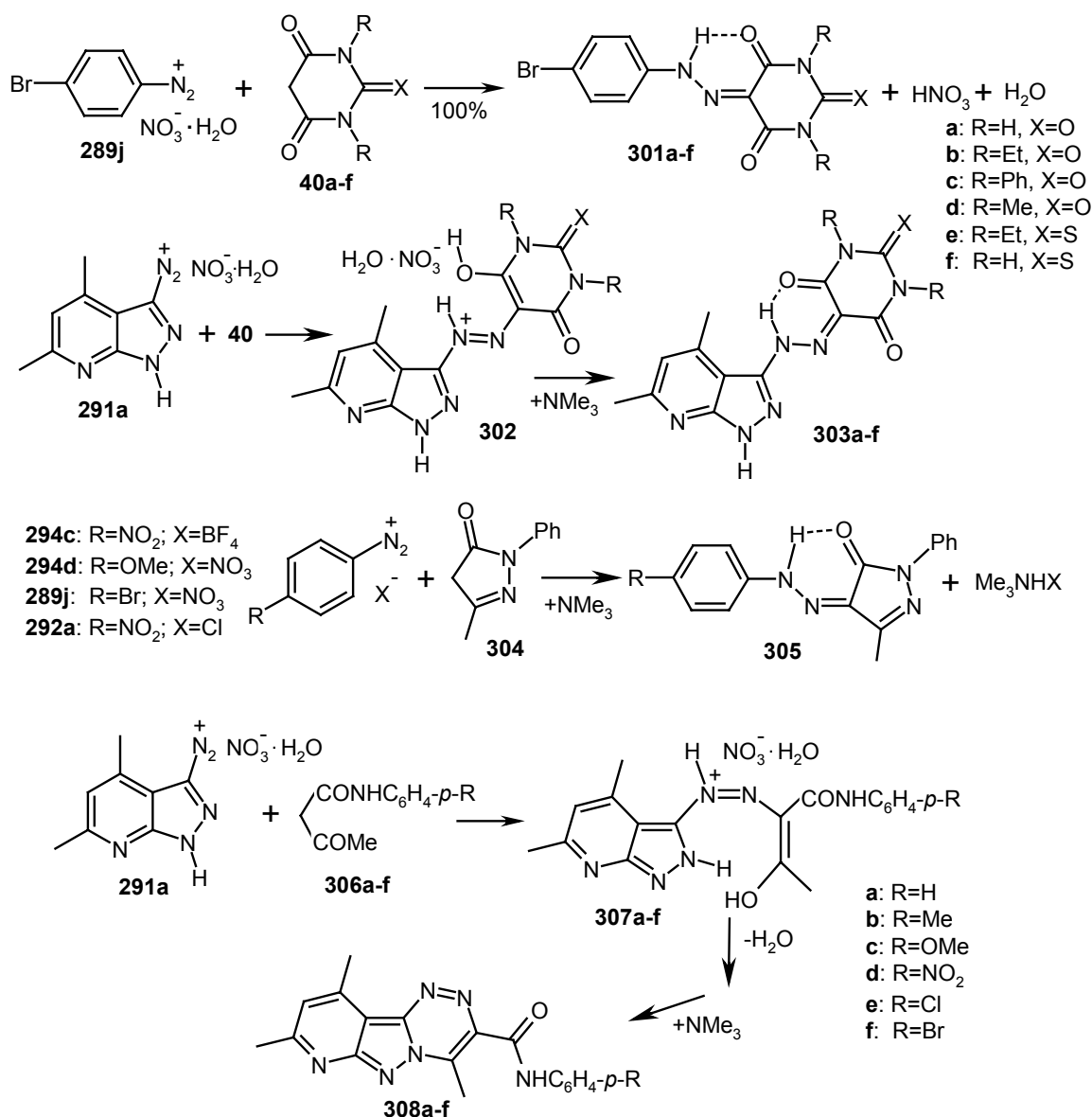
Azo couplings with C-H acidic compounds such as barbituric acids (**40**) or pyrazolones (**304**) proceed equally quantitative in the solid state. However, in some combinations a basic catalyst has to be added in the form of gaseous trimethylamine in order to speed up the reaction. The free “azo-dyes” occur in the hydrazono form after washing away the unavoidable stoichiometric salts [99-100]. The prescription should be carefully followed for safety reasons:

Caution: solid diazonium salts are heat- and shock-sensitive; do not ball-mill!

The barbituric acid derivative **40a-f** (0.50 mmol) was ground in an agate mortar. Solid diazonium salt **289j** (0.50 mmol) was added and co-ground in 5 portions for 5 min, each. Most of the diazonium band at 2280 cm^{-1} had disappeared, but completion of the reaction was achieved by 24 h ultrasound application in a test tube. After neutralization (0.5 *n*-NaOH, 20 mL), washings (H_2O), and drying, the quantitatively obtained products **301a-f** assume the hydrazono structure.

Similarly, the barbituric acids **40a-f** (1.00 mmol) were coground with five portions of **291a** (1.00 mmol in total). The mixture was transferred to a 100 mL flask, which was then evacuated. Me_3N (0.5 bar) was let in. After 12 h at r.t., excess gas was recovered in a remote trap at 77 K. The salt was washed away with water (20 mL) and the residual solid dried. The yields were 100%, 100%, 100%, 100%, 98% and 99%, respectively.

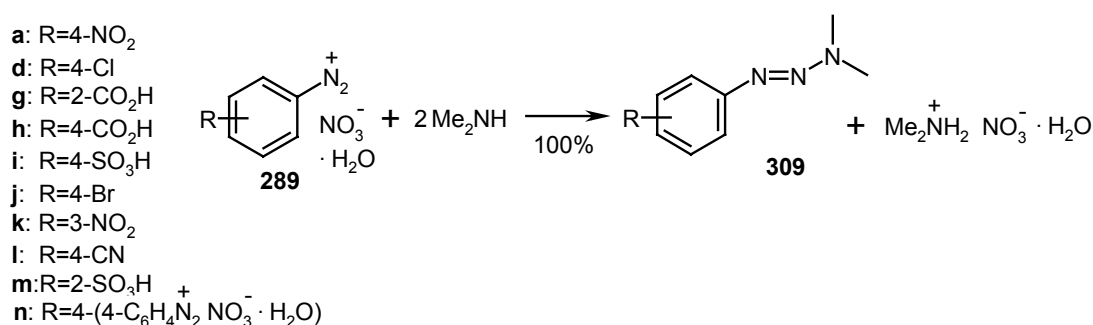
The pyrazolone **304** (1.00 mmol) and the solid diazonium salt **294c, d, 289j, or 292a** (1.00 mmol) were cautiously co-ground in an agate mortar for 5 min. The mixture was transferred to a 100 mL flask, which was then evacuated. Me_3N (0.5 bar) was let in. After 12 h at r.t., excess gas was recovered in a remote trap at 77 K. The salt was washed away with water (20 mL) and the residual solid dried. The yield was 98-99% of pure **305** with the hydrazono structure in all cases.



Scheme 52

An interesting cyclization reaction has been observed after the solid-state coupling of diazonium salt **291a** with the acetoacetanilides **306a-f**. Thus, quantitative yields of the pyridopyrazolotriazines **308a-f** occur with 100% yield (except **308b, c** where there is a loss of 1% by the washings) upon the action of trimethylamine on the intermediate **307a-f** [100]. The experimental technique (2.00 mmol runs) is the same as with the syntheses of **303a-f**.

Azo couplings of diazonium salts with primary or secondary amines give triazenes, which are normally hard to get in pure form. It is, however, quite easy to get triazenes with aliphatic or aromatic amines if solid-state techniques are applied that give rise to pure products in quantitative yield [98-100]. The dimethyltriazenes **309** have been quantitatively obtained by very cautious addition of gaseous dimethylamine (exothermic!) [98]. Extreme care has to be taken for safety reasons:

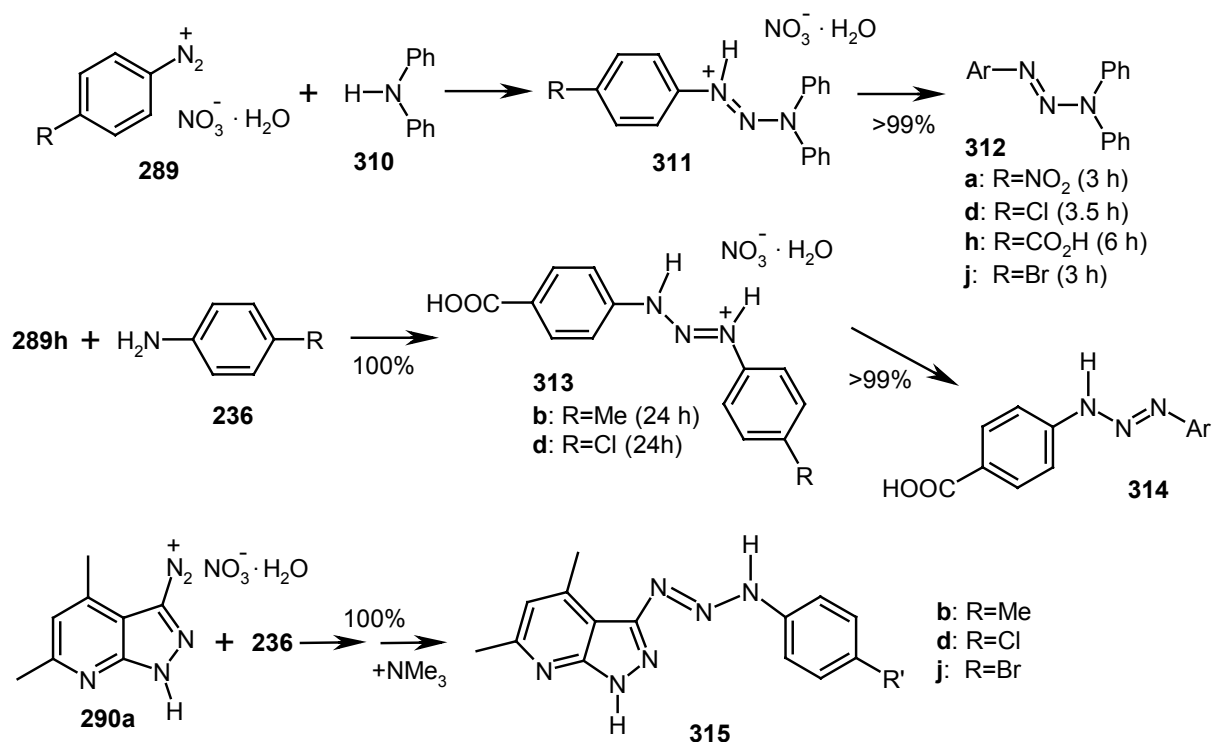


Scheme 53

Caution: these reactions may occur violently, use protecting shield!

The diazonium nitrate (**289** 0.70 mmol; **289n**, 0.35 mmol) or the zwitterion (**289i, m**, 0.70 mmol) or 4-nitrophenyldiazonium tetrafluoroborate (**294c**·BF₄; 0.70 mmol) in an evacuated 250 mL flask was cautiously treated with dimethylamine (**289g, h, i, m** and **294c**·BF₄ at r.t.; **1a, d, e, j, k, n** at 0°C): slow application was obtained by connecting to an evacuated flask with 70 mg (1.56 mmol) Me₂NH cooled to 77 K and then removing the liquid nitrogen bath, for security reasons behind a protecting shield. After the consumption of the amine, the slight excess of gas was condensed back to the other flask and a quantitative reaction was secured by weighing. The triazenes **309** were extracted from the dimethylammonium salts with dry EtOAc and evaporated. The purity was checked with m.p. and by spectroscopic techniques.

The reactions of solid diazonium salts with solid aromatic amines are less violent and the aryldiphenyltriazenium salts **311** or the 1,3-bis-aryltriazenuim salts **313** and **315**·HNO₃ are quantitatively obtained upon cautious cogrinding. From there, neutralization leads to the free triazenes **312, 314** and **315** with insignificant losses (<1%) [99-100]. The compounds **315** are almost isoenergetic with their tautomers as formed by 1,3-H-shift to the other N-atom according to DTF calculations at the B3LYP/6-31G* level [100]. The precautions during the grinding should be followed for safety reasons:



Scheme 54

Caution: solid diazonium salts are heat and shock sensitive; do not ball-mill solid diazonium salts!

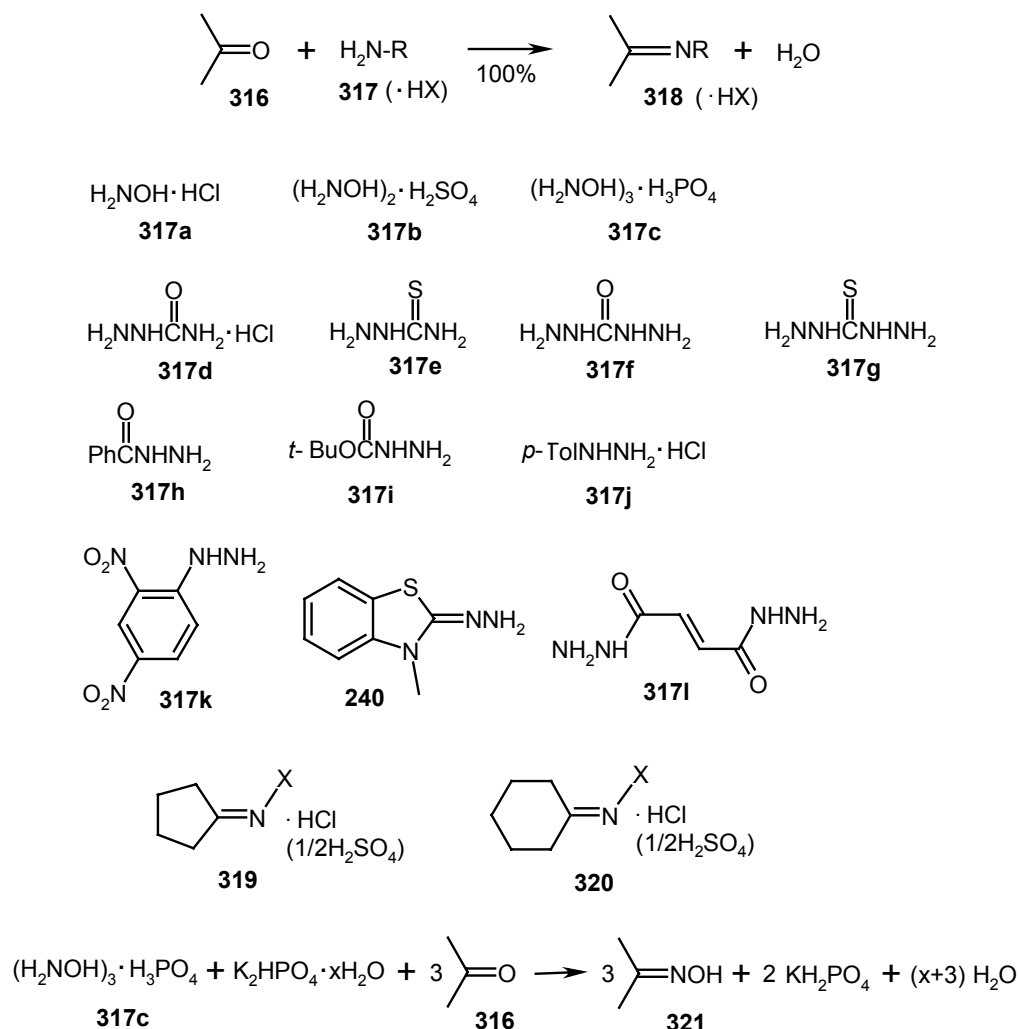
Diphenylamine (**310**, 1.00 mmol) or substituted aniline (**236b, d**; 1.00 mmol) was ground in an agate mortar. The diazonium salt (**289a, d, h, j**; 1.00 mmol) was added in five portions and co-ground for 5 min. To complete the reaction, the solid mixture was transferred to a test tube and then exposed to ultrasound in a cleaning bath, the temperature of which was maintained at 20–25°C for the time given, when the entire diazonium band in the IR had disappeared. The triazene salts **311** or **313** were obtained quantitatively. The free triazene bases **312** or **314** were obtained by trituration of their salts with 0.1 *n*-NaOH (20 mL), followed by filtering, washing (H₂O), and drying. The yield was >99% in all cases. Compound **315** was quantitatively obtained by the corresponding procedure.

18 AMINE CONDENSATIONS

18.1 Imine formation

Previously, the derivatization of primary amine functions by their reaction with carbonyl compounds in solution required strong acid catalysis and removal of the water of reaction from the equilibrium with production of much dangerous wastes. It is therefore of high interest that many of these reactions can be performed wasteless by the gas-solid or solid-solid technology which provides 100% yield of the product. This was exemplified with a great number of condensations using gaseous acetone (Scheme 55) [5, 28]. In some cases (**317a, b, c, d, j**) solid salts of the liquid free bases had to be used, but all of the solid hydrazine derivatives did not require any catalyst and formed the free imine compounds **318** directly.

The acetone gas is applied to an evacuated flask containing the solid carbonyl reagent **317** ($\cdot\text{HX}$) with an over night rest. Similarly, the oxime, cabodihydrazone, semicarbazone, and thiosemicarbazone salts of cyclopentanone or cyclohexanone (**319** and **320**) can be quantitatively obtained as monohydrates by the gas-solid technique [28].

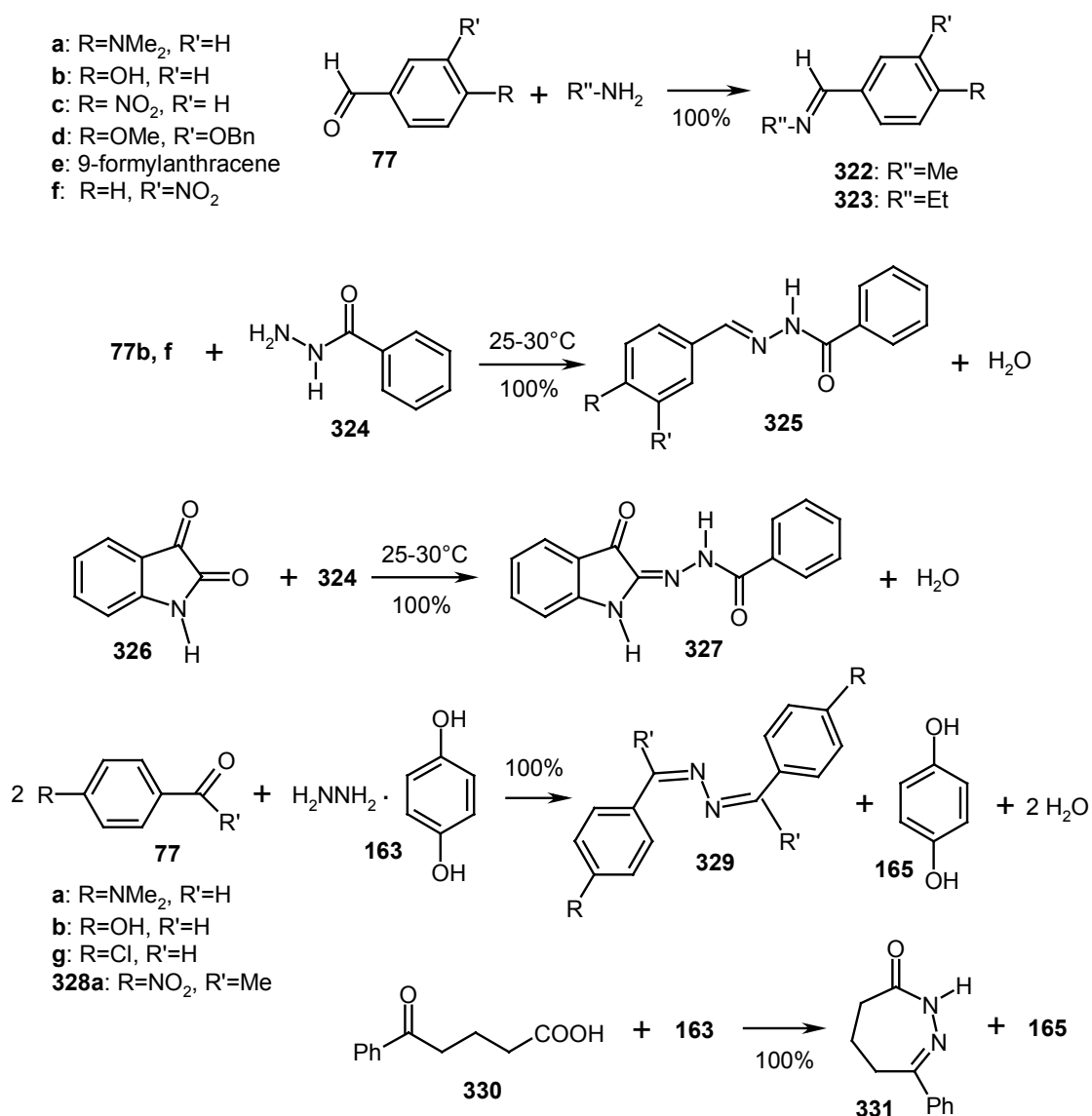


Scheme 55

Importantly, the volatile carbonyl compounds are consumed down to the detection limit by most of the solid reagents **317** from gas mixtures in dynamic systems. Therefore, volatile carbonyl compounds can be removed if they are present in spoiled atmosphere. A larger scale process has been devised for the rapid removal of acetone down to the detection limit using columns charged with hydroxylamine phosphate (**317c**) and pH adjusted such that free acetone oxime product is directly expelled together with the water at 80°C and high flow rates [5, 28]. Apart from the quantitative synthesis of **321**, that is also the easiest way to synthesize pure free acetone oxime (**321**), this experiment simulates exhaust gas purification down to zero emission. The experimental procedure describes the process: Two heatable glass tubes (l = 50 cm, i.d. = 2 cm) fitted with glass frits were each loaded with 53.1 g (0.269 mol) of ground (0.14 m² g⁻¹) hydroxylaminium phosphate (**317c**) and 51.9 g (0.269 mol) of unground (0.10 m² g⁻¹) K₂HPO₄·H₂O. Both tubes were externally heated to 80°C. Air (1 L min⁻¹) was passed through 46.9 g (0.807 mol) of acetone (**316**) and then over the solids from the top of the tubes. All of the acetone (at a load of ca. 78 g m⁻³) had reacted within 10 h. Behind the

second column was a condenser flask in an ice bath and a filter of activated carbon (5 g; $645 \text{ m}^2 \text{ g}^{-1}$) to catch the last traces of free acetone oxime (**321**) which escaped condensation. The product **321** and the water of reaction and crystal water were continuously expelled in gaseous form from the columns and condensed out at 0°C . Only after $>75\%$ conversion, acetone started to escape from the first column and the second column started to react (at $<50 \text{ g m}^{-3}$ acetone load, such escape started at $>90\%$ conversion). After passing all of the acetone, column 1 had reacted to 94% and column 2 to 6%. The condensate consisted of water (18.5 g, 96%) and of crystalline acetone oxime **321** (58.7 g, 99.3%). The missing 400 mg (0.7%) of uncondensed **321** were efficiently and completely absorbed by the activated carbon at the exhaust (400 mg of **321** are absorbed by 3 g of activated carbon). The acetone oxime (**321**) was separated from water by continuous azeotropic removal with *t*-butyl methyl ether. The reacted column was contracted by less than 10% and contained crystalline KH_2PO_4 in analytically pure form as a useful couple product.

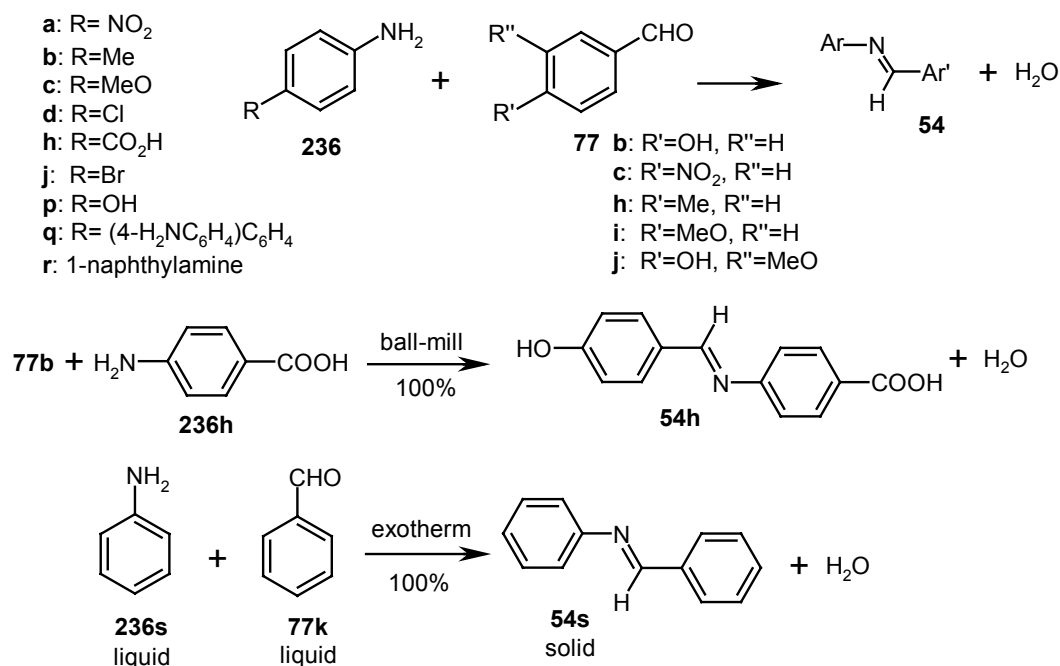
Solid aromatic aldehydes (**77a-e, j**) react quantitatively with aliphatic amines (0.25 bar) at r.t. (**77b** at 0°C) to give the solid *N*-alkyl-azomethines **322** and **323** without melting that are dried at 80°C in a vacuum. The yield is 100% throughout [12].



Scheme 56

Similarly, benzhydrazide (**324**) and “solidified” hydrazine (**163**) react quantitatively in the solid state with aldehydes, ketones and other carbonyl compounds. Thus, quantitative yields of the hydrazones **325** and fully specifically **327** are obtained upon stoichiometric milling of the components [10]. This works also with the “solid” hydrazine and **77**, **328a** and **330**. The azines **329** and the cyclic hydrazone (**331**) (by reaction of both the carbonyl and the carboxyl group) are obtained in pure form after aqueous washings to remove the auxiliary **165**, which is recycled [79].

Solid anilines (**236**) and solid aromatic aldehydes (**77**) give the benzylidene anilines **54** upon grinding with 100% yield after drying at 80°C. 20 combinations were performed [101-102]. A semibatch large-scale experiment of **236h** with **77b** yields quantitatively the hydrated imine **54h** that can be dried as well [7]. The reaction of aniline (**236s**) with benzaldehyde (**77k**) cannot be run as solid-state reaction. However, it should be mentioned that the stoichiometric liquid-liquid reaction proceeds with 100% yield because it profits from direct crystallization of the product **54s** upon reaction. This technique can be used large-scale and it so extremely supersedes all waste producing previous techniques (including 900 W microwave activation of 106 + 93 mg of the adsorbed reagents) in all respects that it must be shown here [2].



Scheme 57

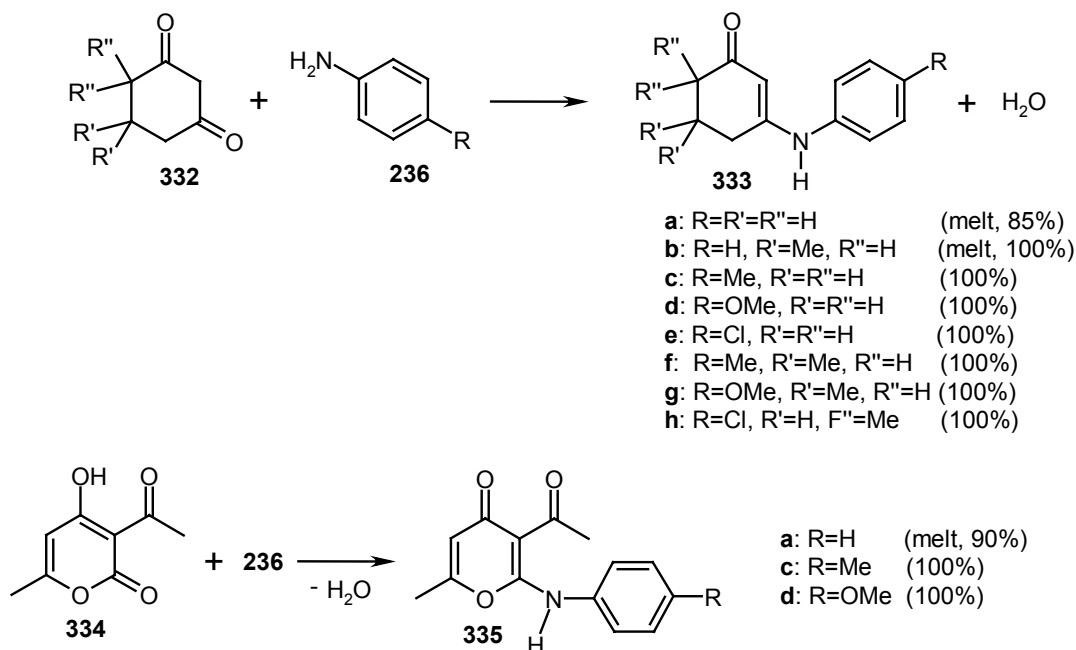
The experimental procedures are not complicated: All small-scale reactions were performed by grinding together 10 mmol of the pure aniline derivative **236** with 10 mmol of the pure aldehyde **77** in a mortar and keeping the mixture at r.t.. Some mixtures liquefied intermediately at r.t., but most of these could be run without melting at lower temperatures. It should be noted that the liquid-state synthesis of some of the products **54** starting with low-melting reagents might be more practical as the yield is also quantitative in these exceptional cases. The completion of the reactions was checked by IR spectroscopy in KBr. The water produced in the reaction was removed at 80°C in a vacuum. The yield of **54** was 100% at 100% conversion in the 20 studied combinations of **236** and **77**. Chemical analysis was carried out by IR and NMR spectroscopy, which gave the expected peaks and signals. Thin

layer chromatography and comparison of melting points with literature data confirmed the purity of the products **54**.

200 g quantities of a stoichiometric 1:1-mixture of the loosely premixed commercial crystals of **236h** and **77b**, both at >99% purity, were fed to a stainless-steel 2 L horizontal ball-mill (Simoloyer^R) equipped with a hard-metal rotor, steel balls (2 kg; 100Cr6; 5 mm diameter) and water cooling. The temperature was 15°C at the walls with a maximum of 19°C in the center of the mill. The rotor was run at 900 rpm (the power was 610 W) for 15 min for quantitative reaction. 100% conversion and 100% yield was indicated by m.p., IR spectrum, chemical analyses and DSC experiments. The product **54h**·H₂O was milled out for 10 min leaving some holdup, but a quantitative recovery was obtained from the second batch and so on. For quantitative recovery of the powdered material in the last batch, an internal air cycle for deposition through a cyclone should be used. The hydrate water was removed from **54h**·H₂O by heating to 80°C in a vacuum. A melt reaction is not possible in this case due to the high melting points involved and severe decomposition above 180°C.

For the stoichiometric liquid-liquid synthesis a flat steel pan (31 · 44 cm²) was charged with benzaldehyde (**77k**) (99.5%; 848 g, 7.95 mol) and aniline (**236s**) (99.5%; 744 g, 7.95 mol). The liquids were mixed at 18°C. The temperature rose to a maximum of 32°C and fell back to 24°C when crystallization started with another increase in temperature to a maximum of 35°C within 12 min when crystallization was virtually complete and water of reaction separated. Next day, the wet crystal cake was crunched with an ordinary household grain-mill and dried in a vacuum at r.t. to give 1.438 kg (100%) of pure benzylidene-aniline (**54s**).

An interesting synthetic approach to cyclic enamine ketones is provided by waste-free and quantitative solid-state reaction of the anilines **236** with cyclic 1,3-diketones such as **332** or enolized **334** (Scheme 58). The solid enamine ketones **333c-h** are quantitatively obtained in the solid-state by milling at r.t.. The melt reaction (80°C) for **333a** is not quantitative, but **333b** arises with 100% yield from the melt reaction [10]. All of the solid-state reactions give 100% yield, as usual.

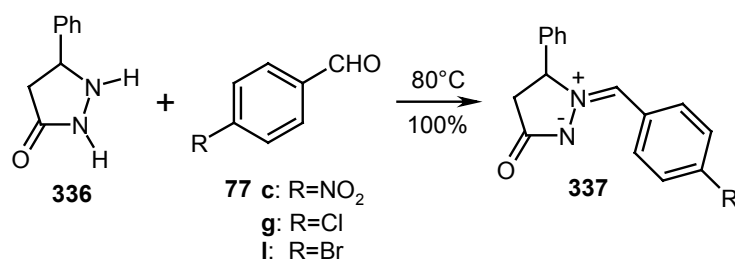


Scheme 58

Very exciting is the reaction specificity with dehydracetic acid **334** in the stoichiometric milling reaction. Only **335c, d** is obtained. Also, a rather good selectivity is observed in the (by necessity) melt reaction (80°C) with aniline (**236s**) giving a 90% yield of **335a** [10].

18.2 Secondary amines

Solid-state condensation reactions of secondary amines are not yet well developed. However, an interesting condensation of the pyrazolidinone (**336**) with aromatic aldehydes **77** gives a quantitative access to the azomethinimines **337** by cogrinding and heating to 80°C [103].



Scheme 59

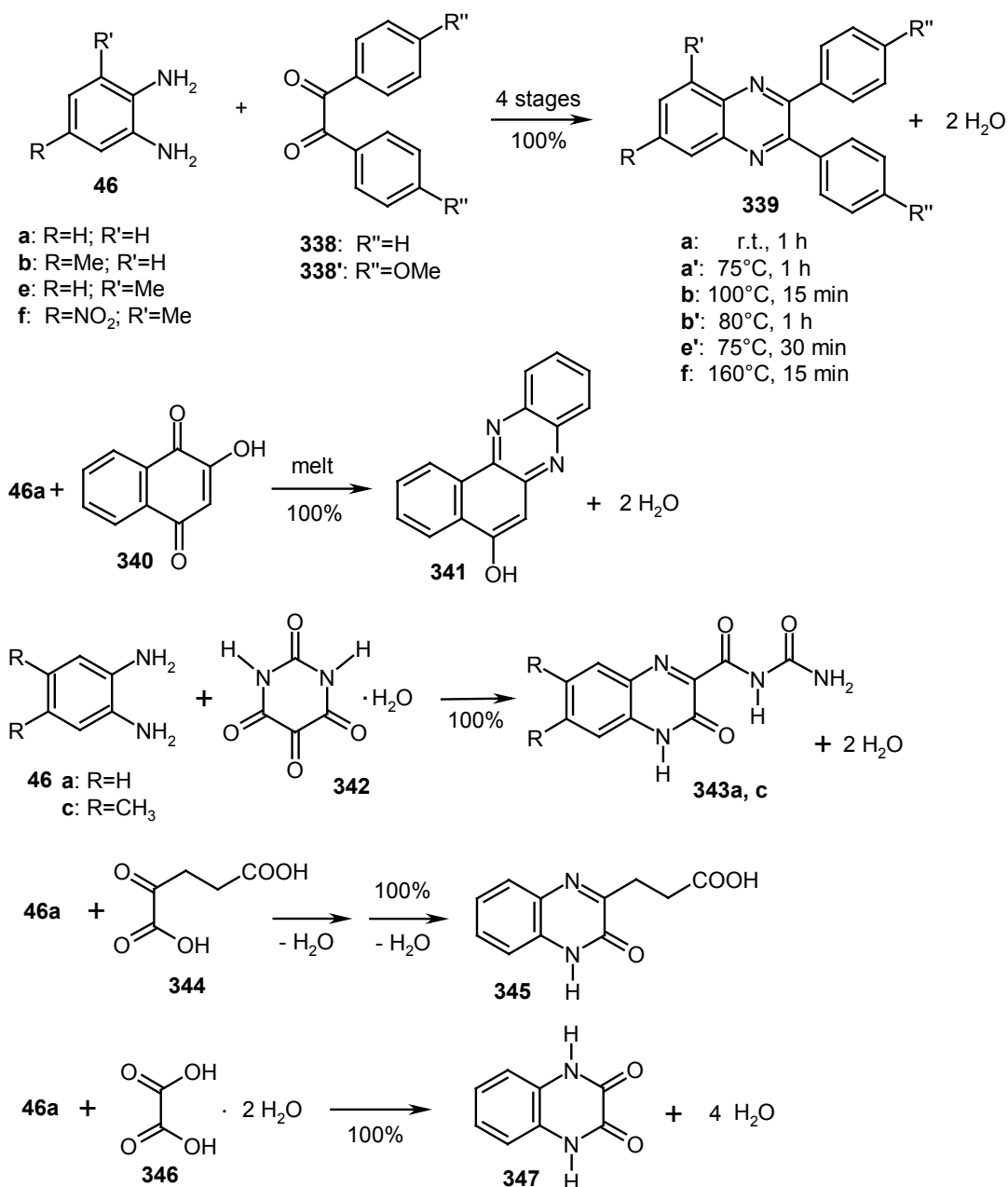
Furthermore, (*L*)-proline and paraformaldehyde give (*L*)-*N*-hydroxymethylproline (as the iminium carboxylate + H₂O) upon large-scale milling and stoichiometric millings of imidazole (0°C) or benzimidazole (r.t.) with (HCHO)_n quantitatively provide the corresponding solid 1-imidazolylmethanols [22].

18.3 Diamines

Aromatic 1,2-diamines (**46**) condense readily with 1,2-diketones, α -keto amides, α -keto acids, or oxalic acid and provide quantitative yields in the solid state. For example, benzils (**338**) react with *o*-phenylenediamines (**46**) at r.t. upon milling and drying. All products **339** are also obtained with 100% yield by heating to the temperatures given after initial stoichiometric cogrinding. Similarly **340** and **46a** (70°C, 15 min) give quantitatively compound **341** [104]. The reaction of alloxane hydrate (**342**) and **46a, c** give 100% yield of the products **343a, c** upon milling at r.t. [104].

The solid-state reaction of 2-oxoglutaric acid (**344**) and **46a** similarly gives a quantitative yield of the quinoxalinone **345** in the solid state upon heating of coground mixtures for 30 min to 120-125°C [104].

The solid-state reactivity of the carboxylic function was demonstrated with oxalic acid dihydrate (**346**) and *o*-phenylenediamine (**46a**). A 100% yield of quinoxalinedione (**347**) is easily obtained upon cogrinding of the components and heating of the high melting salt thus formed in a vacuum to 150°C for 8 h, or to 180°C for 30 min, or to 210-220°C for 10 min [104]. Compound **347** is ready for further interesting condensation reactions.

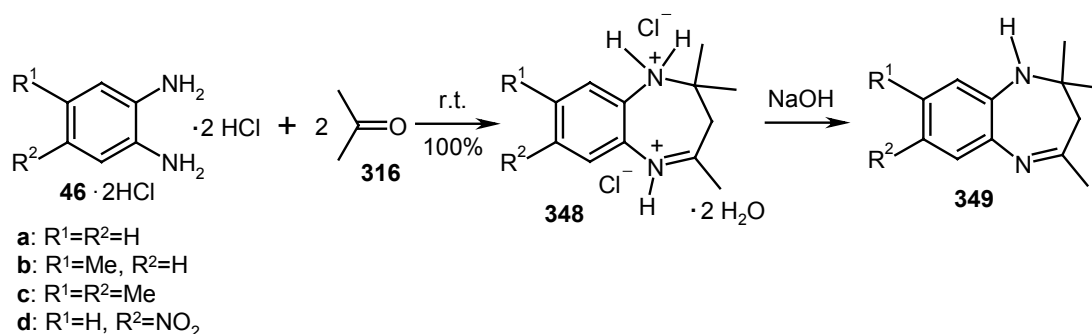


Scheme 60

18.4 Cyclizing condensation

1,2-diamines, aminothiols and aminoalcohols are well suited for quantitative solid-state cyclizing condensations with simple aldehydes and ketones. As yet only quantitative gas-solid reactions with acetone and solid-solid reactions with paraformaldehyde (that will monomerize upon the milling) have been profited from. An early remarkable reaction type involving two molecules of acetone (**316**) and one molecule of *o*-phenylenediamine dihydrochlorides (**46**) has been found to produce 1,4-benzodiazepine derivatives **349** in quantitative yield (except the synthesis of **349d**; 71%) upon gas-solid interaction of the reactants and neutralization of the salts **348** [5]. This cascade reaction (cf. Section 25) is treated here as no other quantitative cyclizing condensations of 1,2-diamines with ketones are known to date and all condensations

of **46** with acids in melts at 220°C to give benzimidazoles [105, 106] ended up with medium to good yields at best.



Scheme 61

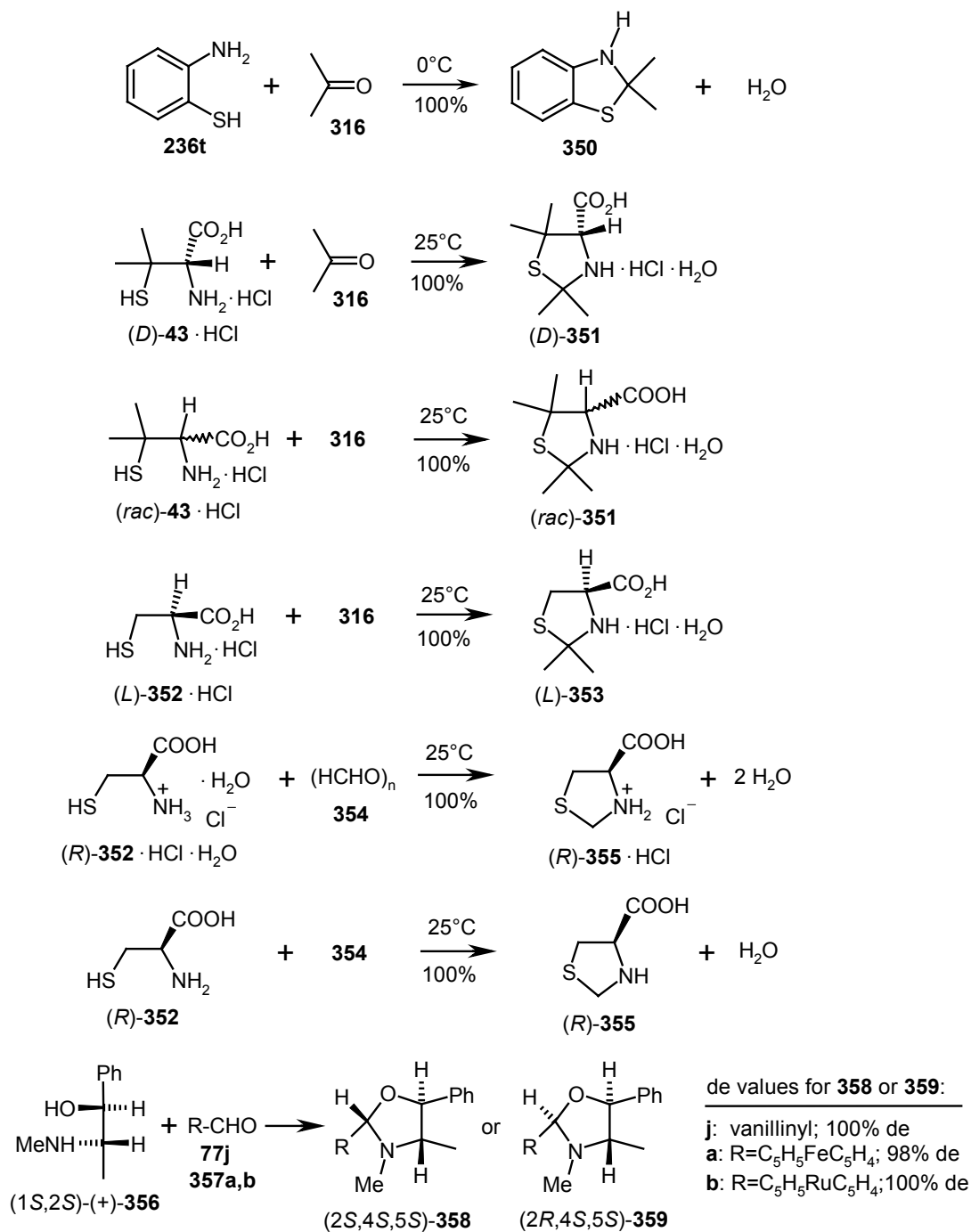
A larger scale synthesis of compound **349a** has been published [5]: The salt **46** · 2HCl (20 g, 80 mmol) was placed in a 10 L desiccator and after evacuation it was connected to a 100 mL flask containing 9.3–11.6 g (160–200 mmol) of acetone which had previously been degassed in a vacuum and cooled with liquid nitrogen. Upon removal of the cooling bath the acetone evaporated slowly into the desiccator. After 12 h, excess gas was condensed back to the flask (77 K) and a 100% yield of **348a** · 2H₂O was obtained. The free base **349a** was liberated with NaOH in water.

2-Aminothiophenol (**236t**) reacts quantitatively to give the five-membered compound **350** [5]. On the other hand, (*D*)- and *rac*-penicillamine hydrochloride (**43** · HCl) (but not the free bases) give the (*D*)- and *rac*-thiazolidine hydrochloride hydrates (**351**) with 100% yield if acetone (**316**) vapors are applied to them. The same is true for (*L*)-cysteine hydrochloride (**352** · HCl) giving the thiazolidine (*L*)-**353** · HCl · H₂O [5].

Various crystalline states of cysteine, cysteine hydrochloride and cysteine hydrochloride hydrate have been tested for solid-state reactivity. Thus, (*R*)-**352** and (*R*)-**352** · HCl · H₂O were also reactive in the solid-state. This was verified by quantitative solid-solid reactions with paraformaldehyde (**354**) in stoichiometric ball-milling experiments at r.t. giving 100% yield of (*R*)-**355** [12] or (*R*)-**355** · HCl [10] after drying.

Similarly, quantitative yields are obtained when solid (1*S*,2*S*)-(+)-pseudoephedrine (**356**) is reacted with prochiral organic and organometallic solid aldehydes **77j** or **357a, b** to give one of the epimeric oxazolidines **358** or **359** as a consequence of true solid-state reactions upon milling. The epimer configurations have not been assigned.

If (1*R*,2*S*)-(-)-ephedrine is similarly reacted with **357b**, a 1:1 mixture of (2*S*,4*S*,5*R*)-**97** (R=C₅H₅RuC₅H₄) and (2*R*,4*S*,5*R*)-**98** (R=C₅H₅RuC₅H₄) ensues with 100% yield in a solid-state reaction [66].



Scheme 62

19 KNOEVENAGEL CONDENSATION

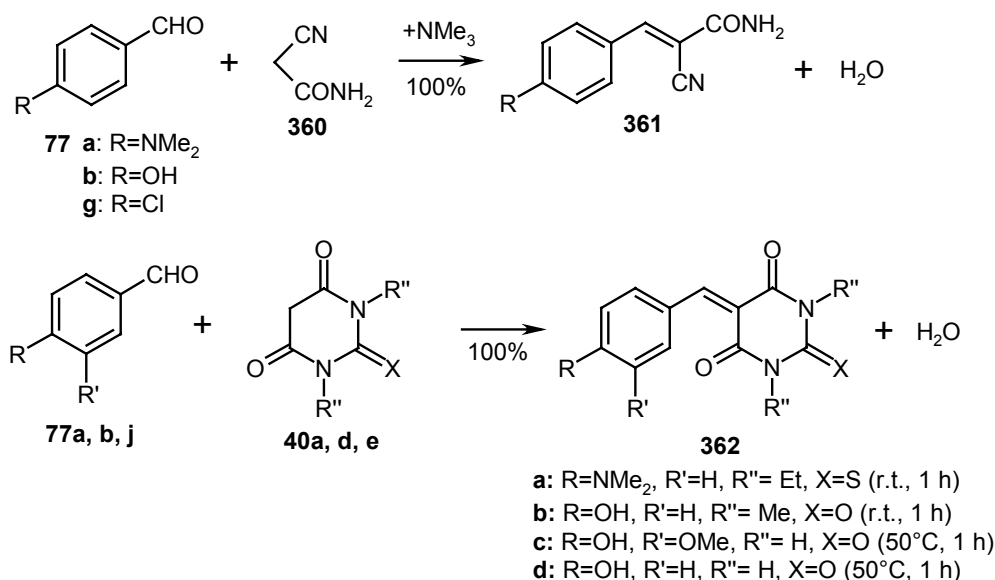
Quantitative Knoevenagel condensations of aldehydes with active methylene compounds are most desirable due to the frequent use of the electron poor alkenes that arise [107]. But previous techniques use catalysts and produce dangerous wastes even if highly energy consuming microwave irradiation upon polar solid supports is additionally used.

The solid-state reaction of **77a, b, g** with cyanoacetamide (**360**) is too slow at r.t. even upon ball milling. It is therefore best choice to put shortly milled stoichiometric mixtures in a vacuum and apply the easily removable gaseous catalyst trimethylamine for completion of the

condensation in the solid state and obtain a 100% yield of **361a, b, g** after evaporation of the catalyst [107]. Melt reactions of these reactants perform less efficiently due to inferior yield. The reason for the low reactivity is not elucidated but it is not encountered in the solid-state condensations by milling of **77a, b** with various (thio)barbituric acids **40** at 20-50°C to give quantitative yields of the products **362a-d** after drying (80°C in a vacuum) [107]. Two large-scale procedures show the synthetic potentials:

A stoichiometric mixture of **77b** and **40d** (200 g per batch) was milled in a water-cooled (14°C) horizontal ball-mill (2 L Simoloyer[®], Zoz GmbH) with 2 kg steel balls (5 mm diameter) for 1 h at 1000 rpm. The product **362b** was milled out at 600-1000 rpm. 100% yield (recovery) was obtained in the second batch etc. The purity of **362b** was checked by IR, ¹H-, ¹³C-NMR, and m.p. (297°C) after drying in a vacuum at 80°C.

Similarly, **77b** and **40a** reacted with quantitative yield in the 2 L ball-mill that was not water cooled while care was taken that the interior temperature did not rise above 50°C (1 h per 200 g batch) to quantitatively yield **362d**, m.p. 299-301°C.

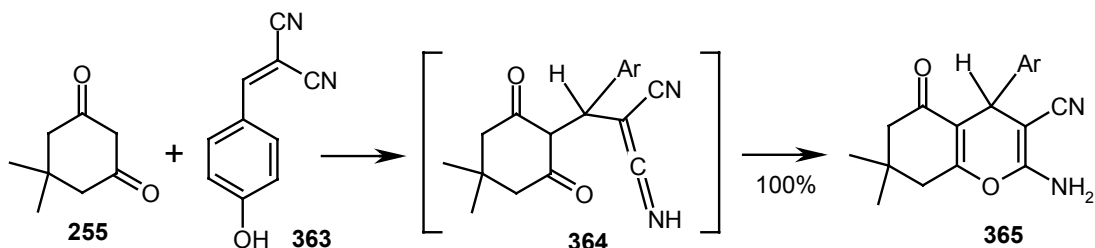


Scheme 63

Numerous solvent-free Knoevenagel condensations with malodinitrile, methylcyanoacetate, dimedone (**255**) and Meldrum acid proceeded with high to quantitative result with intermediate melt or full melt at higher temperatures but with direct crystallization [107].

20 ADDITION

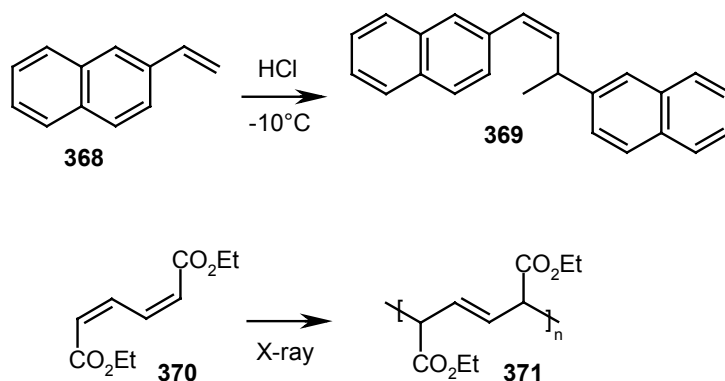
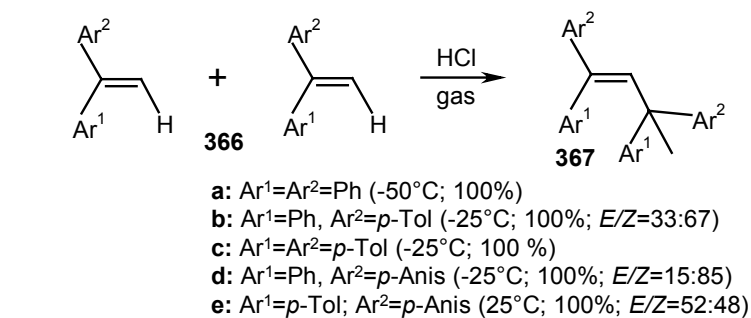
Electron poor alkenes are suitable starting points for Michael additions. For example the arylidene malodinitrile **363** adds quantitatively to solid dimedone (**255**) upon milling at 80°C followed by heating of the yellow powder to 100°C. The initial Michael adduct **364** is not isolated as it cyclizes in the solid state to give the pyrone **365** with 100% yield [107]. The potentials for waste-free solid-state chemistry are manifold indeed and deserve further exploration.



Scheme 64

21 LINEAR DIMERIZATION

The first solid-state linear dimerization was observed with N-vinylpyrrolidinone. It was first quantitatively converted to its Markovnikov HBr-addition product (by application of HBr gas at -40°C) which upon warming to r.t. lost HBr and formed (*E*)-1,1'-(3-methyl-1-propene-1,3-diyl)bis(2-pyrrolidinone, but the yield was less than 100% [58]. Interestingly, such head-to-tail dimerizations of alkenes lead to shrinking and that may create reactivity even if the crystal lattice does not allow for molecular migrations due to 3D-interlocked packing. Such a situation is encountered with solid 1,1-diarylethenes (**366**) that crystallize in 3D-interlocked structures and therefore do not add HCl or HBr gas. However, they dimerize linearly head-to-tail and the concomitant shrinking has been nicely shown with AFM measurements [3, 60]. Some of the preparative important quantitative linear dimerizations of solid **366** to give **367** are collected in Scheme 65. Similarly, the gas-solid catalyzed dimerization of 2-vinylnaphthalene (**368**) gives a 100% yield of **369** with *cis*-double bond [22]. The *cis*-arrangement of the hydrogen atoms is secured by the ^1H NMR coupling constant (6.8 Hz) of the neighboring hydrogen atoms. The linear dimerizations can also be catalyzed by HBr or BF_3 gas.



Scheme 65

There may be situations in the crystal packing of alkenes or dienes in which the spacing and period are the same for monomer and intended polymer so that no molecular migrations would be necessary upon reaction. That is the criterion for topotactic processes. Such a situation is encountered in specially selected single crystals of *cis-cis*-diethylmuconate (**370**). When a qualified single crystal of **370** was exposed to slow X-ray irradiation a single crystal of the polymer **371** was obtained almost free of monomer impurities. Topotacticity is assured by the crystal packing in monomer and polymer, both with spacing and period of 3.8 Å. The effective cross-sectional area was decreased by only 3% and the crystal structure did not change by the radiolysis. Therefore, no molecular movements were required and the linear polymerization proceeded smoothly [108].

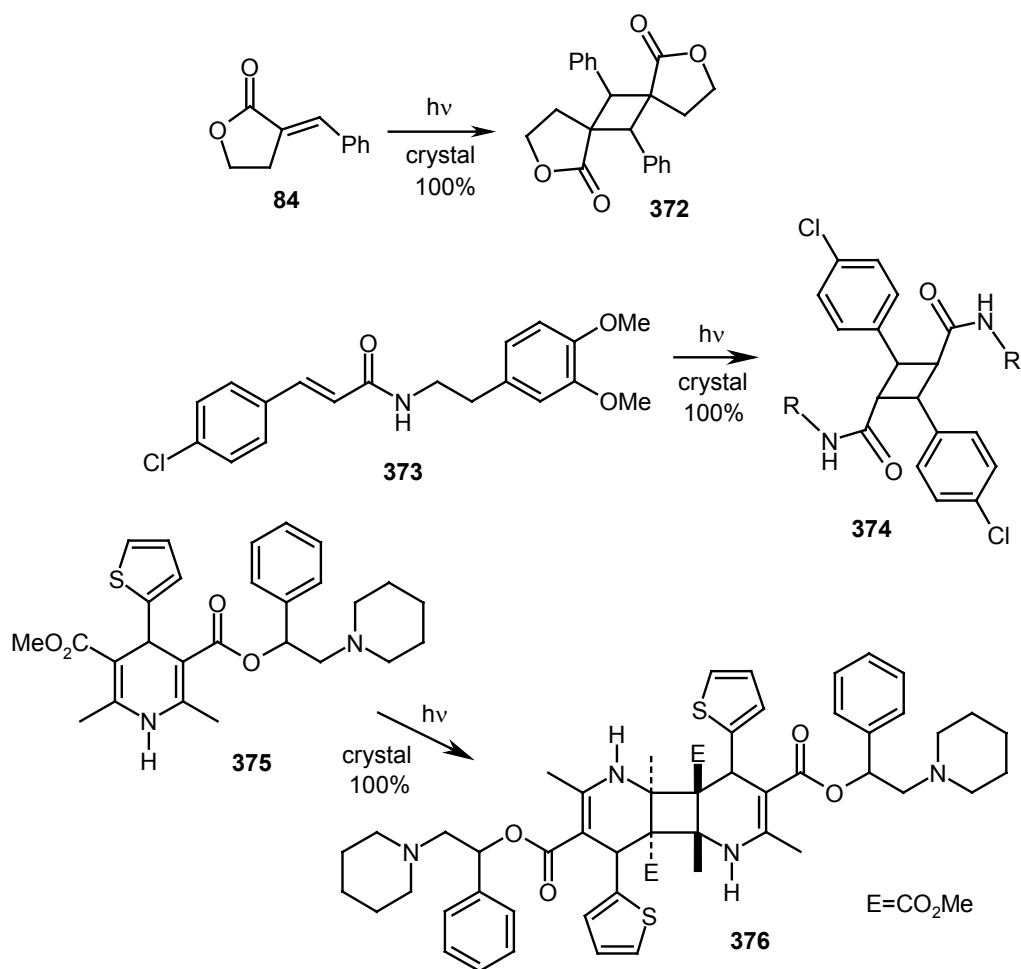
22 CYCLOADDITION

Most solid-state cycloadditions are photochemical and of the [2+2] type. Numerous early solid-state photodimerizations are listed in [109]. More recent examples are listed in [110]. Important polar effects engineer the crystal packing [111], but the yields are at best close to quantitative. Even the selectivities may be poor and interesting product mixtures may arise [112-114]. However, there are some quantitative photochemical cyclobutane syntheses. The quantitative head-to-tail photodimerization of the benzylidenelactone **84** to give **372** [115] exhibits the anisotropic molecular migrations as has been shown by AFM scrutiny [113]. The conversion of **373** to **374** was described as a quantitative single-crystal-to-single-crystal reaction [116]. Interestingly, while the photolysis of **375** in solution gives only dehydrogenation, irradiation of the crystals provides a 100% yield of **376** [117].

The photolytical synthesis of **372** proceeds as follows: α -Benzylidene- γ -butyrolactone (1.0 g, m.p. 115-117°C) was evenly spread on the inner wall of a mirrored Dewar vessel (diameter 14 cm, height 20 cm) with some dichloromethane. After heating to 80°C for 1 h the dry crystalline film was irradiated from within for 5 h with a Hg-high-pressure lamp (Hanovia 450 W) through a 5% solution of benzophenone in benzene (5 mm; $\lambda > 380$ nm) under cooling with running water at 30-35°C. The yield of the *head-to-tail-anti*-dimer **372** was 100% (m.p. 242°C).

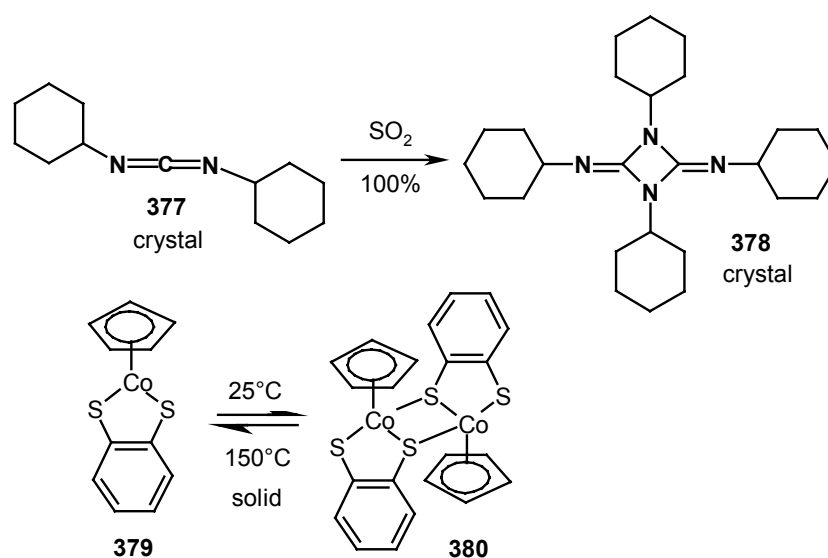
It may be suspected that the genuinely topotactic (as secured by the molecular precision of the AFM [18]) photodimerization of 2-benzyl-5-benzylidenecyclopentanone [118] might be a good candidate for a quantitative preparative photodimerization to give the *head-to-tail-anti*-[2+2]-dimer.

Early quantitative solid-state [2+2]-photodimerizations (most of the published mechanistic interpretations of which can no longer be accepted) are listed in [110]. These deal with the *anti*-dimerization of acenaphthylene-1,2-dicarboxylic anhydride, the *head-to-head-syn*-dimerization of acenaphthylene-1-carboxylic acid, the *syn*-dimerization of 5,6-dichloroacenaphthylene, and the thermally reversible *head-to-tail-anti*-dimerization of seven (*E*)-2,6-di-*t*-butyl-4-(2-arylethenyl)pyrylium-trifluoromethanesulfonates. All of these reactions proceed fully specific. On the other hand, quantitative photoconversions of a 1:1-mixed crystal of ethyl and propyl α -cyano-4-[2-(4-pyridyl)ethenyl]cinnamates gives mixtures of diesters with one ($\lambda > 410$ nm) or two cyclobutane rings (no cutoff filter).



Scheme 66

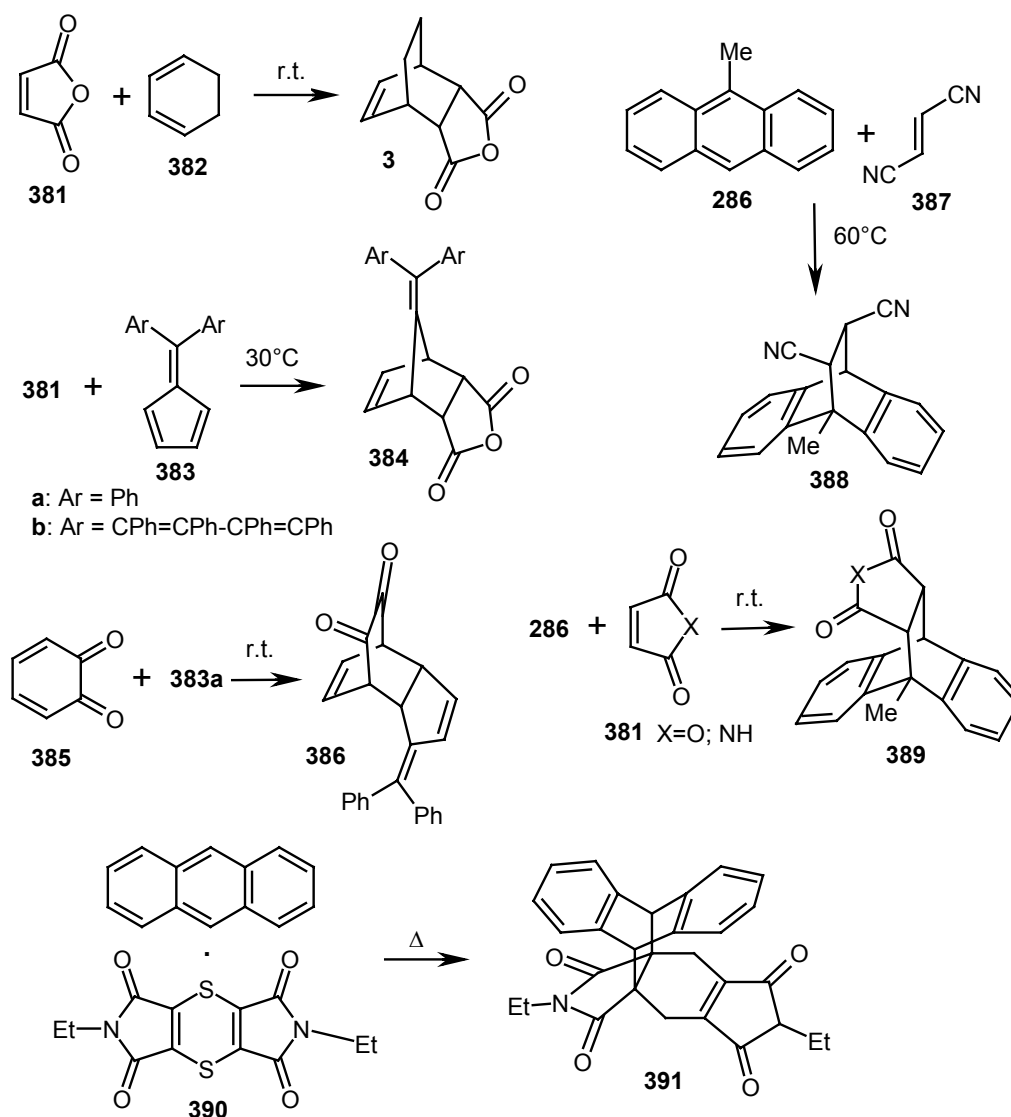
The thermal [2+2]-dimerization of solid dicyclohexylcarbodiimide **377** requires the action of gaseous sulfur dioxide at 0°C as an easily removable catalyst. The interesting heterocyclic compound **378** is quantitatively obtained [33].



Scheme 67

A reversible thermal solid-state [2+2]-cycloaddition which is stereospecific and proceeds in single crystals has been found with $(\eta^5\text{-C}_5\text{H}_5)\text{Co}(\text{S}_2\text{C}_6\text{H}_4)$ (**379**). The dimer **380** forms with major conformational changes in the crystal. The reaction is not topotactic, but the crystal shape remains unchanged both upon the dimerization at 25°C and at the cycloreversion at 150°C. The $\text{Co}\cdots\text{S}$ interaction distances in the monomer crystal are 4.702 and 4.325 Å, the corresponding bond lengths in the dimer 2.246 and 2.230 Å. The reversible dimerization (ΔH for **380** \rightarrow **379** at 150–160°C is 4.5 kcal mol⁻¹) profits from favorable differences in the crystal energies of **380** and **379**. The dimer **380** is only stable in the solid state. It dissociates in organic solvents at 25°C to give monomer **379** [119].

Endo-selectivity in some simple quantitative gas-solid Diels-Alder reactions has been secured [120]. However, there was not much motivation to repeat more well-known Diels-Alder reactions in the solid-state. For example, maleic anhydride (**381**) and vapors of cyclohexadiene (**382**) give a quantitative yield of the *endo*-adduct **3** [120]. Also the solid-solid stoichiometric additions of **381** with the fulvenes **383a, b** provide quantitatively and exclusively the *endo*-adducts (**384**) by milling at 30°C [120]. Similarly, the *endo*-adduct **386** is obtained by milling of *o*-benzoquinone **385** (prepared in situ according to Scheme 81) and



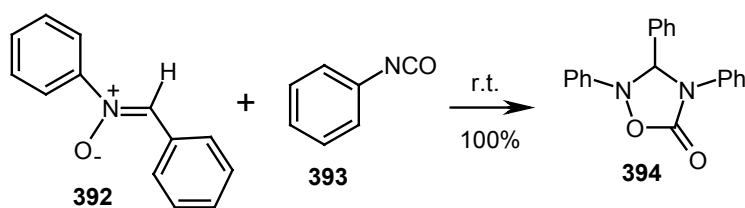
Scheme 68

the fulvene **383a** [22]. Further quantitative solid-state Diels-Alder additions occur with 9-methylanthracene **286** (favorable layered structure) and fumarodinitrile (**387**) [22]. This addition to give **388** is incomplete below 60°C due to softening in the ball-mill probably due to slow phase transformation resulting in an undercooled microliquid. At 60°C (not at 50°C) the solid-state reaction is complete giving the product as a powder in 100% yield. The *trans*-arrangement of the cyano groups is secured by the ¹H NMR coupling constant (4.9 Hz) of the neighboring hydrogen atoms. While this thermal behavior is certainly of mechanistic importance, from a preparative point of view it is easier to perform the quantitative melt reaction at 80°C or above also with 100% yield in this case.

No problems are encountered if 9-methylanthracene (**286**) is milled with maleic anhydride (**381**, X=O) or maleimide (**381**, X=NH) at r.t.. The solid adducts **389** form quantitatively [120]. Interestingly, anthracene does not undergo the corresponding solid-state Diels-Alder additions under these conditions. The reason must be sought in the crystal packing. 9-Methylanthracene crystallizes in double layers with well-developed cleavage planes, whereas anthracene exhibits scaly molecular arrangement with interlocked monolayers but not well-behaved cleavage planes. However, anthracene undergoes Diels-Alder reactions in preformed charge-transfer complex crystals such as **390**. The adduct **391** forms quantitatively upon heating single crystals of the complex **390** [121]. But the authors' claim of first order kinetics that was invoked in order to "substantiate" an assumed topotactic reaction is completely unjustified (obvious data mistreatment). The reported data clearly indicate zero order kinetics and there are also obvious signs of crystal disintegration. No AFM study has been tried that would have given the answer to the mechanistic question with molecular precision (cf. Section 1).

1,3-D

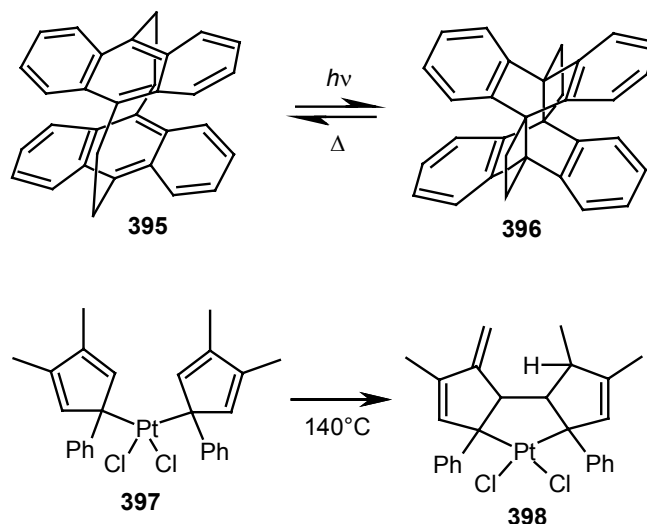
ipolar additions are a fertile field in quantitative solid-state chemistry. For example solid diphenylnitron (**392**) adds phenylisocyanate vapors (**393**) at r.t. to give a 100% yield of the interesting heterocyclic compound **394** [22].



Scheme 69

Quantitative [4+4]-additions and quantitative ene-additions in the solid state are still rare. Useful models are the very first example of a photo/thermochemical cycle photochrome [122], which is fully topotactic as proven by AFM with molecular precision [13]. The golden yellow crystals of **395** were exposed to glass-filtered daylight and thus formed the colorless "dimer" structure **396** with quantitative yield. If **396** was heated to 30°C in the dark for 5 h compound **395** was quantitatively formed back in a topotactic manner without change of the crystal shape even on the nanoscopic scale as shown by AFM [13]. Numerous cycles were performed without loss using single crystals of **395/396**.

A quantitative solid-state ene-addition between two ligands of the platinum complex **397** gives the rearranged platinum complex **398** upon extensive heating to 140°C [123]. This rearrangement reaction (cf. Section 24) is treated here, as it is the only known quantitative solid-state “ene-addition” to date. Further quantitative solid-state [4+4]-additions and higher vinylogs as well as ene-additions also of the intermolecular type await detection both as thermal and photochemical reactions.

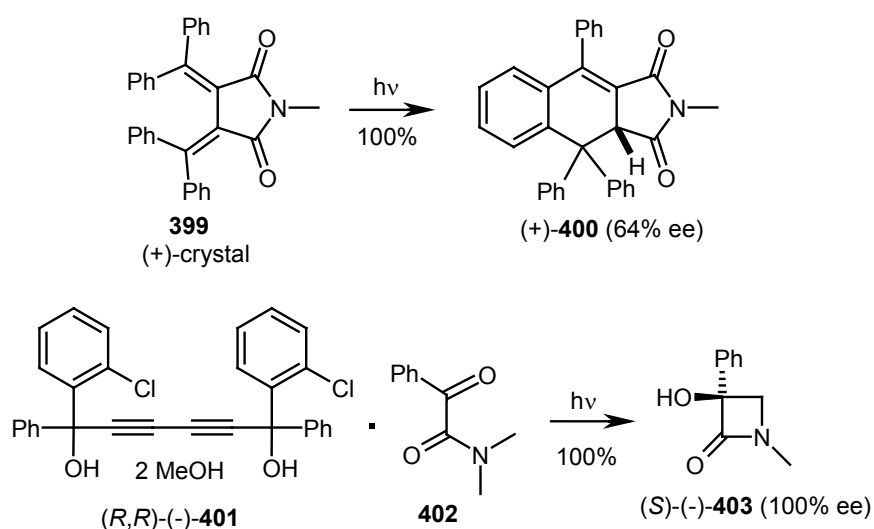


Scheme 70

23 CYCLIZATION

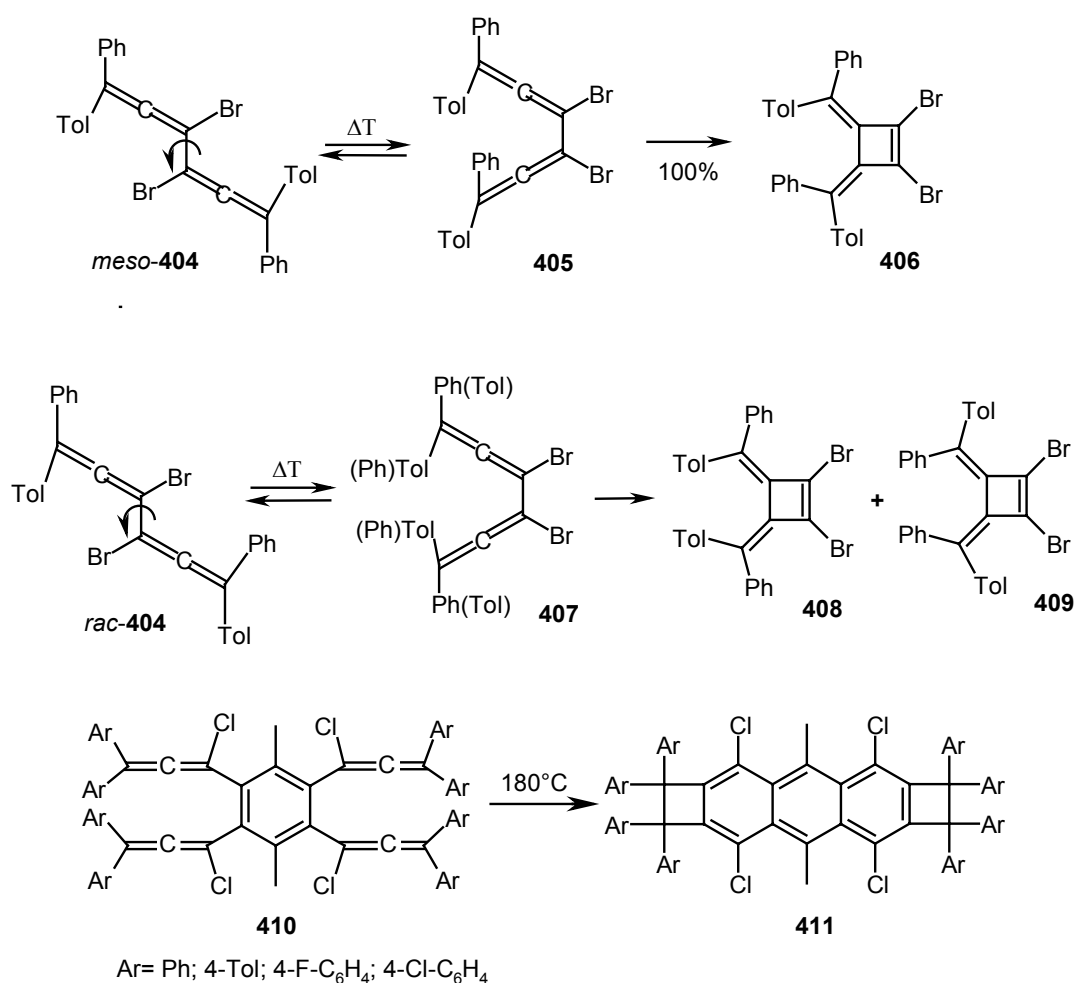
Several intramolecular eliminative cyclizations have been noted in previous Sections (**149** → **148**; **220** → **221**; **264** → **265**; **270** → **271**; **307** → **308**). The following cyclizations occur without elimination.

Chiral (+)-crystals of the *s-cis*-enforced tetraphenylbutadiene **399** photocyclize with 100% yield to give (+)-**400**. The (+)-enantiomer prevails with 64% ee. The corresponding (-)-crystal of **399** prefers (-)-**400**, correspondingly [124]. Clearly, this is a fine example of an absolute asymmetric synthesis [125]. Chiral hosts may also induce enantioselectivity. Thus, the guest **402** photocyclizes to give enantiospecifically the β-lactone (*S*)-(-)-**403** with 100% yield when included in the host (*R,R*)-(-)-**401** [126].



Scheme 71

Various bisallenes have been quantitatively cyclized by heating in the solid state. The space demand is extremely high for *s-trans*-configured samples within crystals and not all reactions proceed with quantitative yield, as is also rationalized by AFM studies [127]. Both *meso*-**404** and *rac*-**404** cyclize stereospecifically upon heating to 135 or 125°C for 90 min to give the bismethylene-cyclobutenes **406** or **408** + **409** (1:1-ratio) with 100% yield [128]. There cannot be any doubt that the *s-cis*-conformers **405** and **407** are intermediates. The space conserving hula-twist like mechanism for the formation of these *s-cis*-bisallenes is more plausible than internal rotation mechanisms around the single bond within the crystal [48]. However, there is also the necessity for molecular migration as the geometric change is considerable. These points have been clarified by detailed crystal packing analyses on the basis of X-ray crystal structural and AFM data, which detected anisotropic molecular migrations [129].



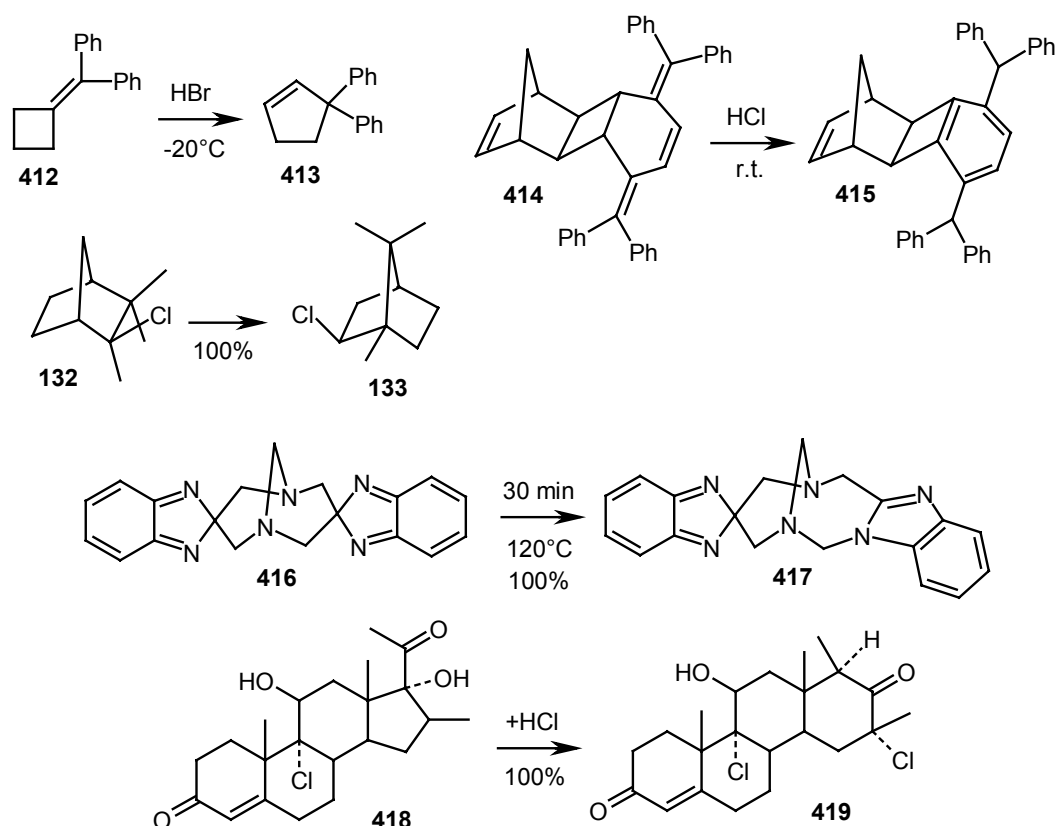
Scheme 72

The even more involved quantitative transformation of **410** to give **411** requires four cyclization steps within the crystal. These cyclizations can be performed on a hot stage at 180°C for 30 min and the macroscopic shape of the crystals does not change at least for the octaphenyl case [130]. Importantly, the tetraphenylsubstituted benzocyclobutene bonds of **411** exhibit the extraordinary length of 1.726 \AA [130], which is the world record for genuine single bonds [131].

24 REARRANGEMENTS

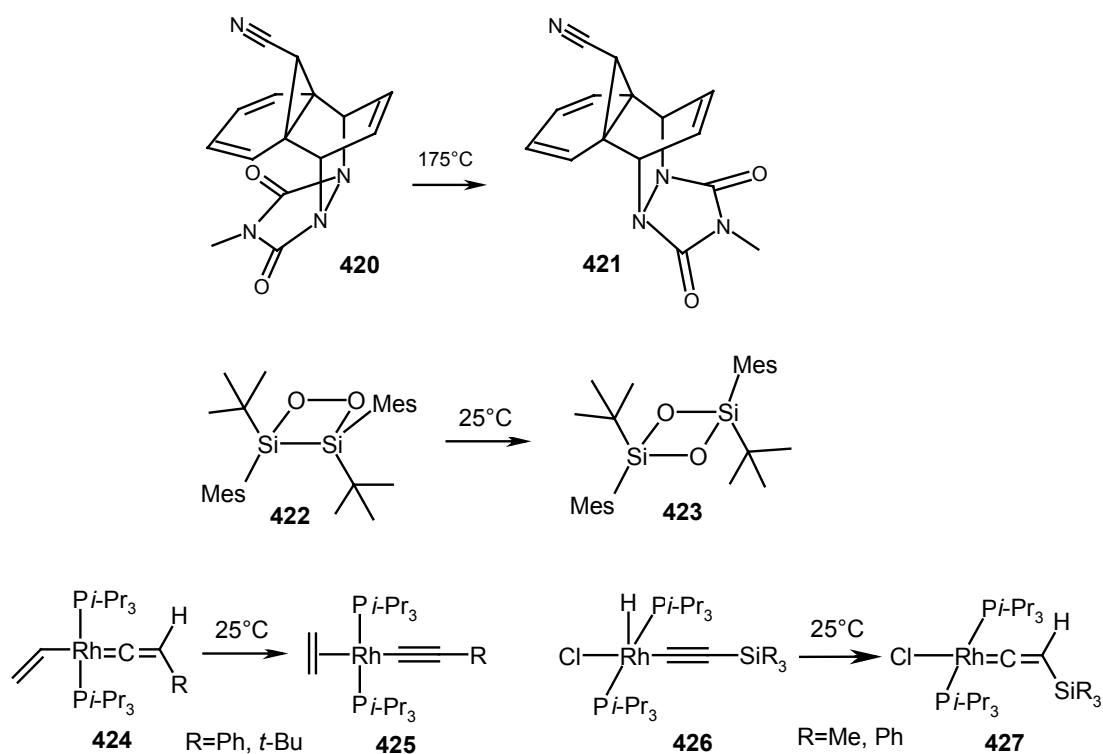
Acid catalyzed [1,3]-hydrogen shifts may occur quantitatively in the solid state. Thus, the conversions of **412** to give **413** (this requires [1,3]-H-shift and additional [1,2/2,1] rearrangement) and **414** to give **415** (two [1,3]-H-shifts) have been realized under HBr and HCl catalysis as gas-solid reactions [120]. Thermal rearrangements in crystals are comparatively rare. The crystalline camphene hydrochloride (**132**) rearranges slowly upon standing (quantitative after <3 years at r.t. or 6 h at 80°C) in a solid-state Wagner-Meerwein rearrangement ([1,2/2,1]-rearrangement) [76] without melting to give pure **133** [11]. A quantitative uncatalyzed [1,5]-shift reaction has been realized in the solid state with the symmetric bis-spiro compound **416** to yield the unsymmetric isomer **417** [132]. The acyloin compound **418** with a 16β -methyl substituent undergoes a substitutive rearrangement with HCl gas to give stereospecifically product **419** with 100% yield [133]. The most probable

mechanism starts with acid catalyzed migration of the 13,17-bond, enolization, vinylogous substitution of OH by Cl and 1,3-H-shift. This unprecedented reaction did not occur in CH_2Cl_2 . Several further solid-state acyloin-type substitutive rearrangements are known in the steroid field; however, these do not provide one single product with quantitative yield [133].



Scheme 73

A thermal solid-state N-N double inversion between kinetically stable invertomers (*exo/endo*-isomerism) was studied by high temperature X-ray diffraction. The conversion of the less stable isomer of the Diels-Alder product **420** into the more stable isomer **421** occurred at 175°C from single crystal to polycrystalline material [134]. The rearrangement of the 1,2-disiladioxetane **422** into the 1,3-disiladioxetane **423** occurs in the crystal (also in solution) at r.t. and below. It is stereospecific with retention of the configuration at silicon [135]. The crystalline vinyl(vinylidene)rhodium complexes **424** rearrange on standing at r.t. and form the alkynyl(ethene) complexes **425**. Conversely, the corresponding η^3 -2,3,4-*trans*-butadienyl complexes are obtained in benzene solution at 50°C [136]. Furthermore, the quantitative rearrangement of the rhodium complex **426** to give **427** is stereoselective [137]. Further reactions of that type are reported [137].

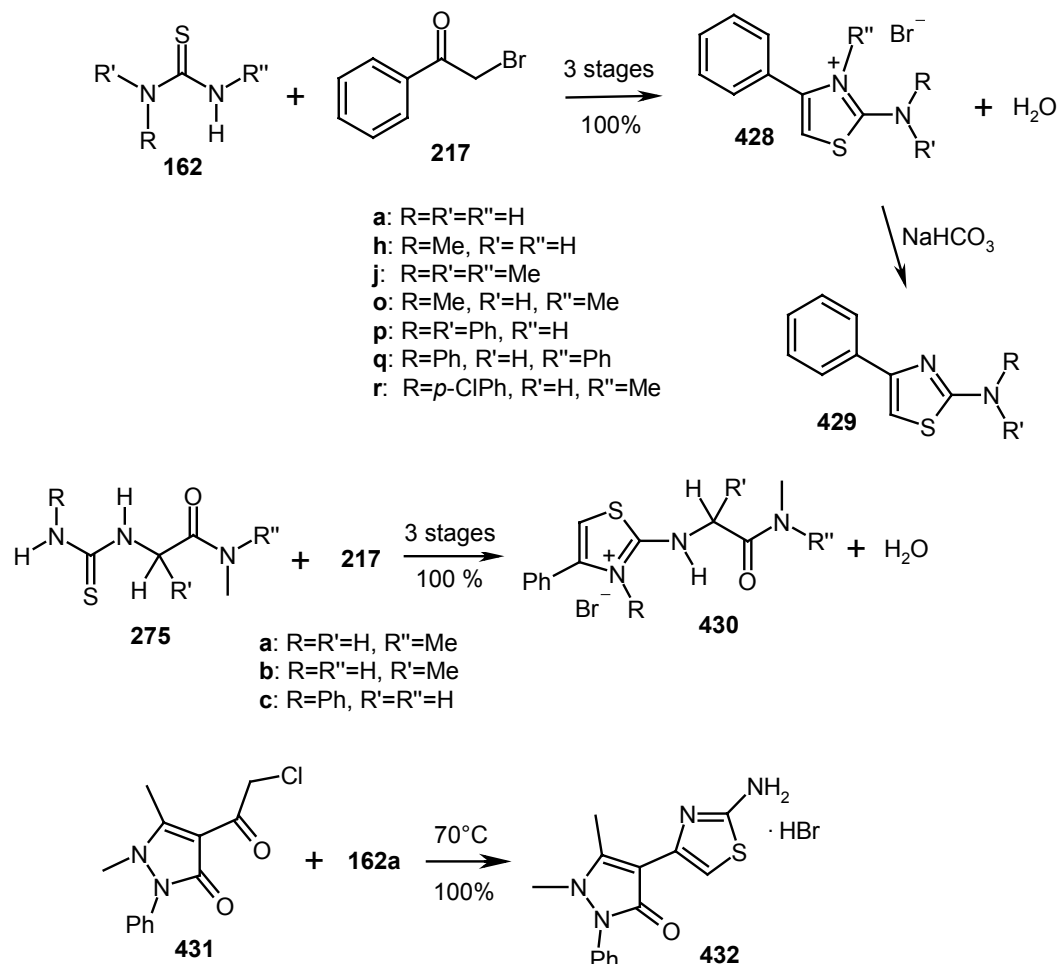


Scheme 74

25 CASCADE REACTIONS

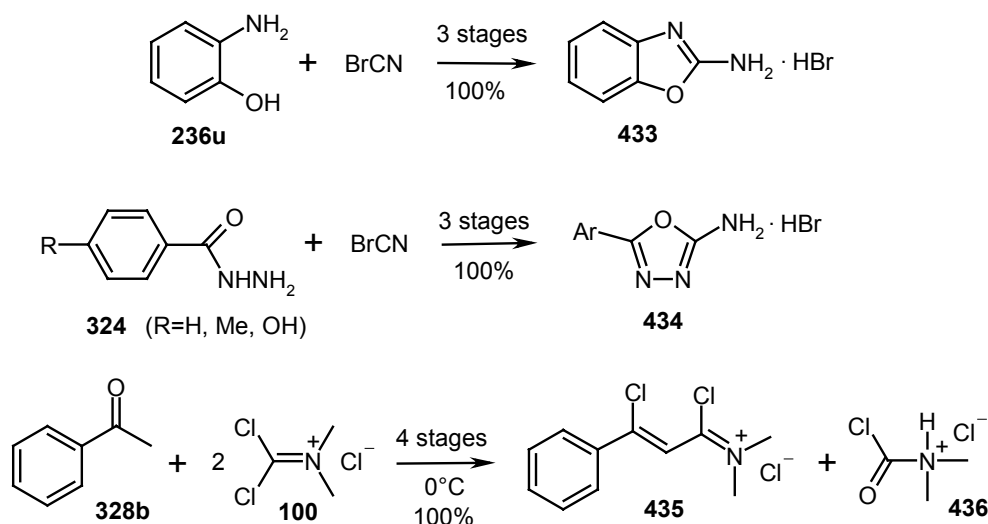
It is highly rewarding that solid-state reactions with 100% yield of one product are not restricted to single reaction steps. Several multi-step reactions have already been described in the preceding sections (for example diazotizations, etc.). Reaction cascades imply a sequence of separate reaction steps preferably of different type. For example, in the reaction of 2-chloromethylbenzimidazol with hexamethylenetetramine to give *7H,16H-8,17-methano-9H,18H-dibenzimidazo[1,2-*c*:1',2'-*h*][1,3,6,8]tetrazecine* (an isomer of compound **417**) eight new bonds must be formed in a solvent-free melt reaction at $120\text{--}160^{\circ}\text{C}$ [132]. While such extreme reaction cascades were not yet observed in the solid state it is nevertheless surprising that numerous cascade reactions occur in the solid state and give 100% yield. This fact stresses convincingly the occurrence and necessity of molecular migrations upon chemical reaction within the crystal. An already great number of 2- to 5-cascades proceed with quantitative yield without melting in the solid state and the phase rebuilding mechanism as detected by AFM is the same as for one-step reactions except that it becomes multi-step in the phase rebuilding stage. These unusual reactions are of unmatched atom economy. Most of the now synthetically used quantitative cascade reactions involve an initial substitution step. That is quite clear at the reactions of acylhalides with thioureas to give 2-aminothiazolium salts. The 3-cascade consists of substitution to form the thiuronium salt, specific cyclization with the more nucleophilic of the amino groups and elimination of water. In all reported cases, the product crystal takes up the water of reaction and it can be removed by heating to about 80°C in a vacuum. For example, if the thioureas **162** and phenacylbromide **217** are stoichiometrically ball-milled at r.t. for 30 min, quantitative yields of the pure products **428** are obtained in all cases after drying at 0.01 bar at 80°C [10]. The free bases **429** can be obtained by trituration of **428** with NaHCO_3 solution. Furthermore, the

thioureido-acetamides **275** react correspondingly with **217** to give quantitative yields of the salts **430** from which the free bases can be obtained by NaHCO₃-trituration [96]. An extension of the technique is the milling of the heterocyclic chloroacetyl derivative **431** with thiourea (**162a**) at 70°C, which gives a quantitative yield of the salt **432** [138].



Scheme 75

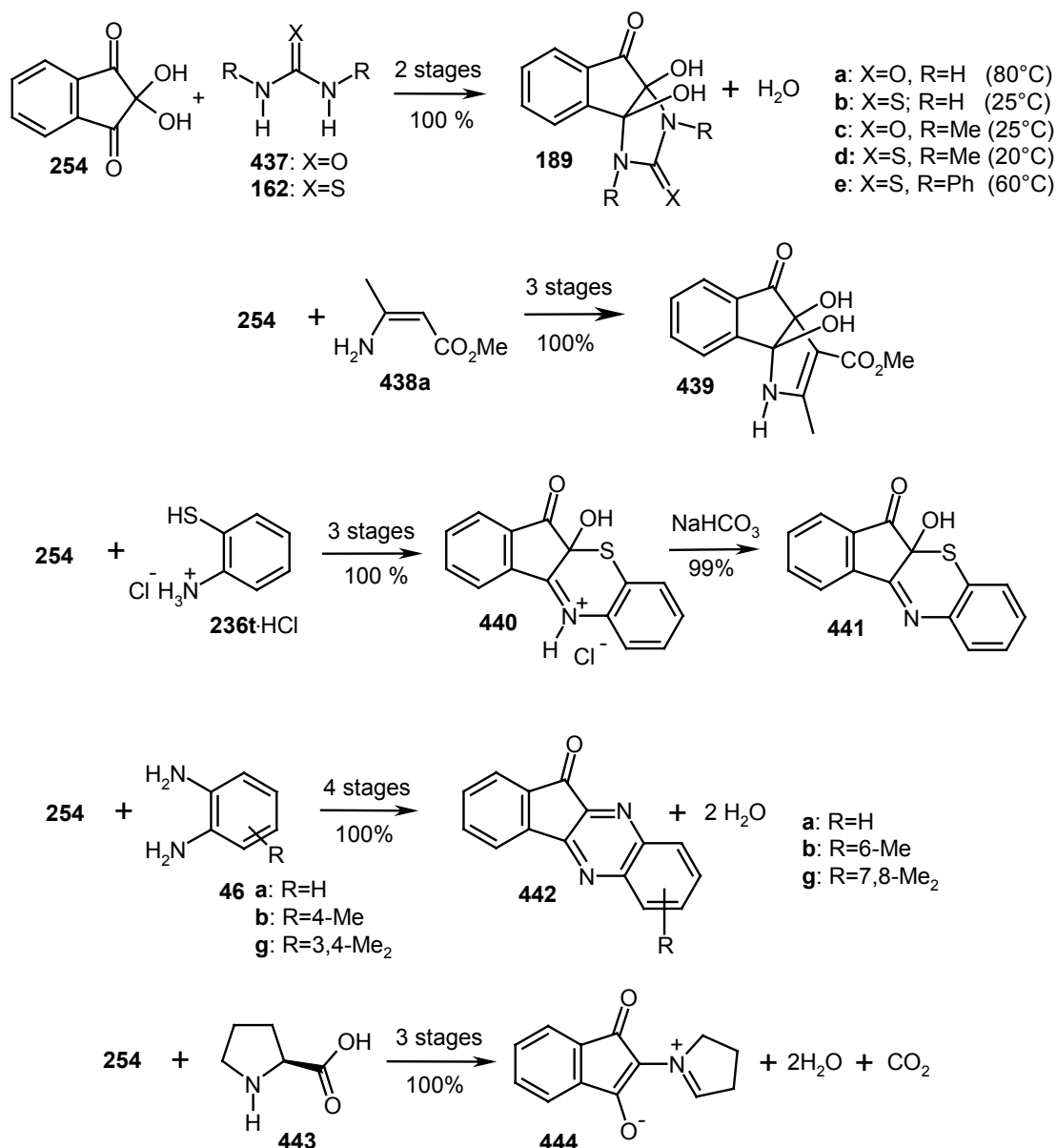
The interaction of cyanogen bromide vapors with solid *o*-hydroxyaniline (**236u**) or the solid benzhydrazides **324** at r.t. provides the 2-aminobenzoxazole (**433**) or the 2-amino-5-aryl-aminooxadiazole salts **434** [92]. These 3-cascades imply formation of the cyanamide, its cyclization and tautomerization.



Scheme 76

The quantitative solid-state reaction of Viehe salt (**100**) with acetophenone (**328b**) by stoichiometric comilling at 0°C leads to the highly labile iminium salt **435** and the couple product **436** [9]. A 4-cascade is assumed consisting of substitution (Cl by enol-C of **328b**), reaction of the oxygen with a second molecule of **100**, chlorine migration, and elimination of **436**.

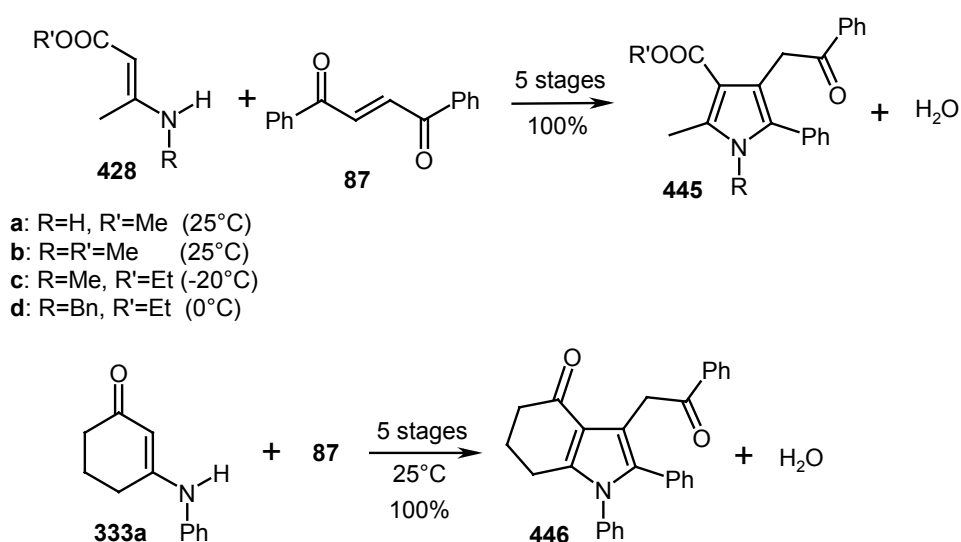
The easy access of a hydroxy group of ninhydrin (**254**) to its substitution and the presence of the carbonyl groups makes this highly reactive compound an interesting starting point for cascade reactions with amino compounds. These have been mechanistically investigated with AFM on six different faces of **254** and strictly relate to the crystal packing [94]. The reactions of (thio)ureas with ninhydrin (**254**) are 2-cascades (substitution and addition) to give stable N/O-semiacetals (**189**) with 100% yield by stoichiometric milling at the temperatures given in Scheme 77 and drying at 140°C in a vacuum. The 3-cascades of **254** with **438a** or the hydrochloride of **236t** provide the products **439** and **440** with 100% yield. In both cases the amino group adds to a carbonyl group of **254**, there is a substitution step (enamine or SH replacing OH) and tautomerisation or elimination of water, respectively. The 4-cascades of **254** with the *o*-phenylenediamines **46a, b, g** are fully regiospecific and also quantitative upon milling at -5°C and drying at 80°C in a vacuum. This is an easy access to **442** with well-defined substitution. A reasonable sequence of events is addition to C=O, substitution of OH and two eliminations of water [94]. It is remarkable that the *semi*-N/O-acetals **189 a, b** and **439** do not eliminate water under ordinary and rather sharp conditions. On the other hand, the six-membered rings in **440** and **442** exhibit the double bonds as a consequence of elimination of water already during the solid-state reactions. The reaction of ninhydrin with the secondary amino acid (*L*)-proline (**443**) is of particular interest as the 3-cascade (substitution, elimination, decarboxylation) provides the versatile azomethine ylide **444** with 100% yield both in small and in large runs [8], whereas tedious solution syntheses gave yields of 82% at best in small runs with difficult purification procedures required [139].



Scheme 77

The large scale procedure demonstrates the breakthrough in sustainable chemistry by profiting from the bargain of the crystal packing: A stoichiometric mixture of ninhydrin (**254**) and (*L*)-proline (**443**) (200 g) was milled in a 2 L horizontal ball-mill (Simoloyer^R) with steel balls (100Cr6, 2 kg, diameter 5 mm) at 1100 rpm for 40 min until the liberation of CO₂ was complete. The temperature varied from 15°C at the water-cooled walls to 21°C in the center. The power was 800 W. Quantitative reaction to give **444** was secured by weight (146 g, 100%) and by spectroscopic techniques. The product was not separated in a cyclone but the milling-out towards the end was completed with 4 times 250 mL of water, each. This part of the highly disperse (<1 μm) pure azomethine ylide **444** was obtained after centrifugation and drying in a vacuum. The combined water phase contained 0.2 g of **444** [8].

The solid-state interaction of enamines (**428**, **333a**) with *trans*-1,2-dibenzoyl ethene (**87**) provides quantitative yields of the pyrrole derivatives **445** or **446** [140]. These remarkable 5-cascades consist of initial vinylogous Michael addition, enol/keto tautomerism, imine/enamine tautomerism, cyclization, elimination, all within the crystal without melting. A waste-free extraordinary atom economy is achieved that cannot be nearly obtained in solution. The milling times are unusually long here (3 h) but it's certainly worth the effort as no purifying workup is required. The milling temperatures are listed in Scheme 78. Only in the reaction of **428c** was the elimination of water not complete upon milling and had to be finalized by short heating to 150°C. Drying of the products **445** and **446** was performed 80°C in a vacuum.



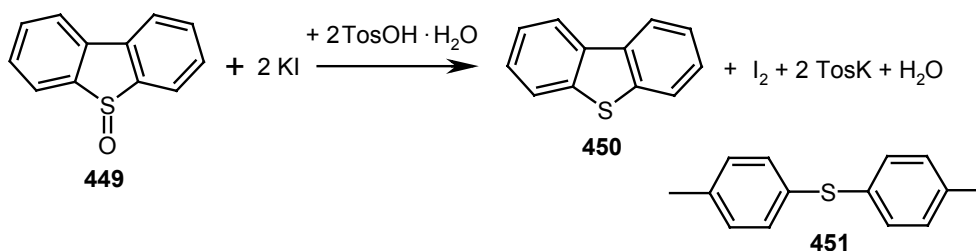
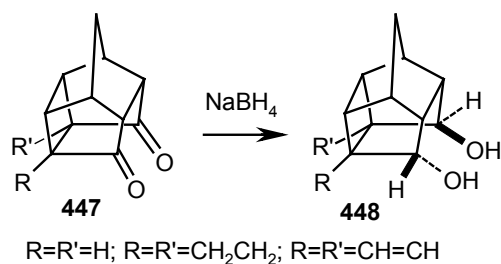
Scheme 78

An interesting double rearrangement is quantitatively observed in the solid state if *O,O'*-diacetyldihydroindigo is ball-milled with the stoichiometric amount of DDQ to give *N,N'*-diacetylingo and DDQH [22]. Apparently, the first acetyl group migrates from O to N while both hydrogen atoms are abstracted from the nitrogen atoms by DDQ and the second acetyl group undergoes a 1,5-shift from O to N. The corresponding reaction with solid KMnO_4 as the oxidizing agent is less clean [22].

There are a number of further solid-state cascade reactions or solvent-free cascade reactions that cannot be treated here in detail because their yield is not quantitative or because they proceed as melt reactions. But some useful examples may be mentioned here: The gas-solid hydrolysis of *N*-arylmethylenimines (**175**) yields Troeger's base derivatives [10]. The isothiocyanate function can be transferred to aromatic aniline derivatives from 1,2-diisothiocyanatobenzene with the concomitant formation of 2-mercaptobenzimidazole (first milling at r.t. then sublimation at 100-120°C in a vacuum) [22]. 2-Aminophenylthiol (**236t**) or thioureido-acetamides (**275**) were reacted with dimethyl-acetylenedicarboxylate to form benzothiazepinone derivatives [84] or iminomethylenethiazolidinones [96]. Unsubstituted five- to seven-membered lactames yield spiroaminals/aminoalkylimines at 270°C in the presence of LiOH in preparatively useful reaction cascades [141].

26 REDUCTION

There are numerous preparatively useful solid-state reductions with potential for quantitative conversion and yield [142]. It appears, however, that these have not been tried under more favorable conditions in ball-mills. The stereospecific reductions of **447** to give **448** used enormous excessive amounts of reducing agent (NaBH_4 , 21-fold) in order to achieve 100% yield upon grinding and agitating (7 days) [143]. It is to be expected that proper solid-state techniques may avoid such waste of time and reagent.



Scheme 79

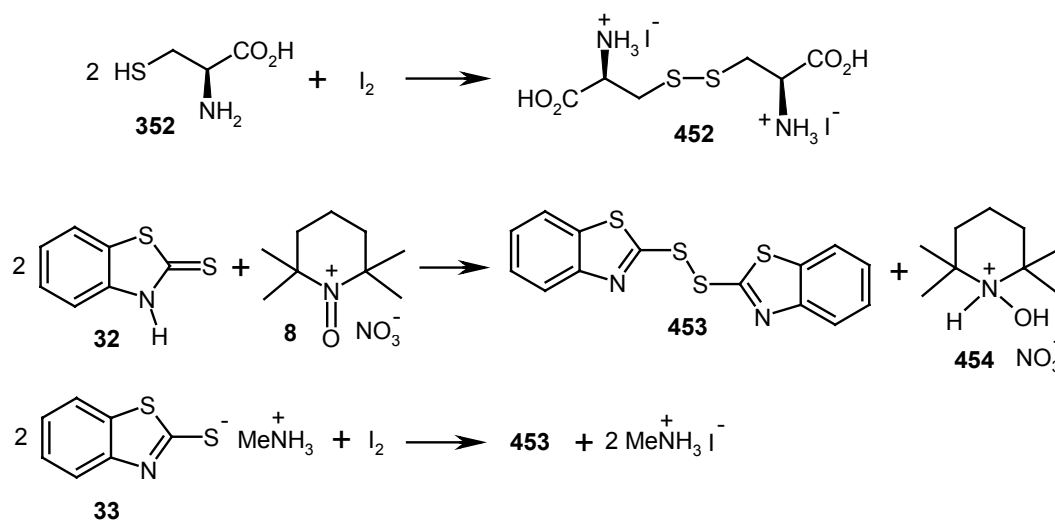
Solid-state reductions of sulfoxides such as **449** have been performed with potassium iodide and *p*-toluenesulfonic acid monohydrate [144]. Dibenzothiophene (**450**) or similarly bis-4-tolylsulfid (**451**) are obtained with 100% yield.

The interaction of hydrogen with organometallic complexes is reviewed in [68].

27 OXIDATION

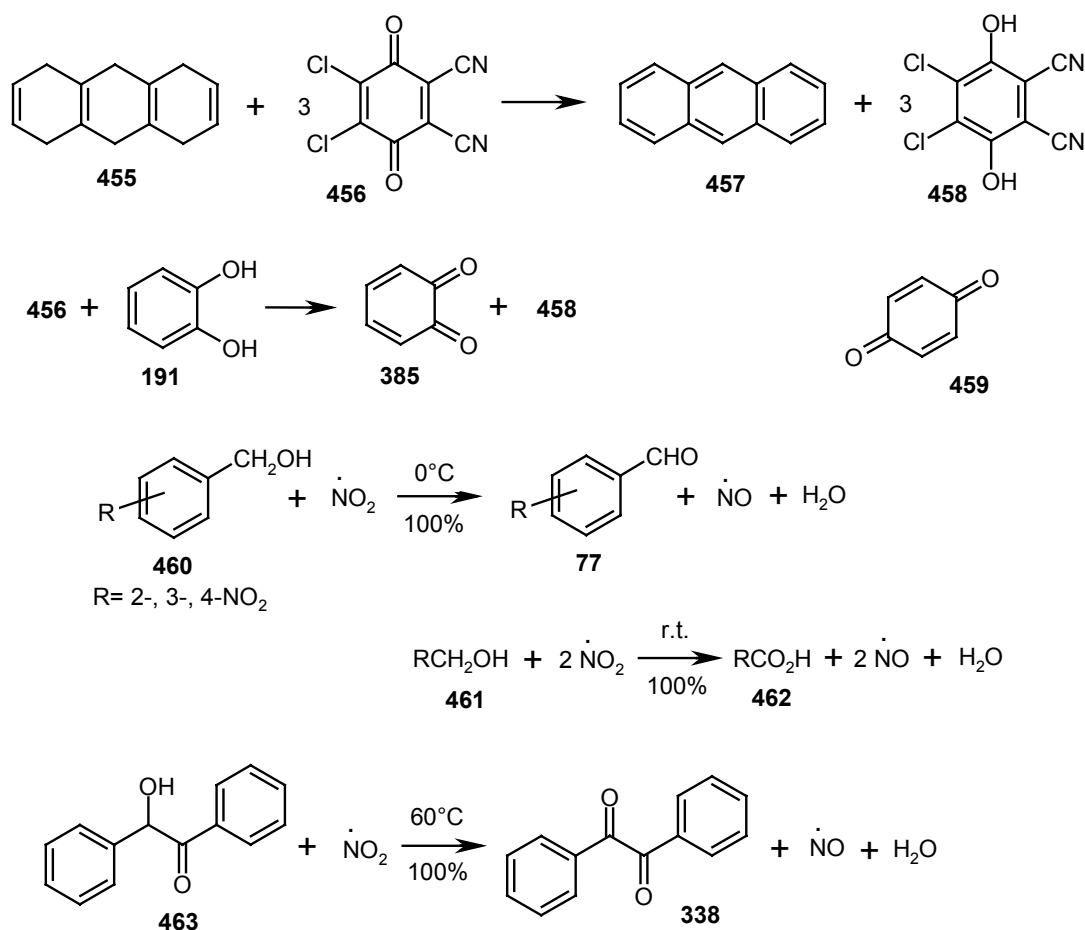
A review on solvent-free oxidation procedures with numerous oxidizing agents is given in [142]. However, the solid-state reactions did not find much preparative interest or were not conducted to completion (see, however, the one-electron transfer reactions of stable radicals in Section 3) or the removal of the stoichiometrically reduced coproduct caused losses in the yield. The quantitative solid-solid oxidation of (*L*)-cysteine (**352**) by iodine to give (*L,L*)-cystine dihydroiodide (**452**) (in moist air deliquescence occurs) can serve as precedence for countless useful and benign solid-state oxidations [22]. Nitrosonium nitrates such as **8** oxidized 2-mercaptobenzothiazole (**32**) to give **453** and **454** upon milling. This reaction has also been mechanistically studied by AFM [1] and SNOM [15]. While solid 2-mercaptobenzothiazole (**32**) is not efficiently oxidized by solid iodine, its methylamine salt **33**

is quantitatively oxidized by milling with iodine and gives **453** with 100% yield after washings with water and drying [22].



Scheme 80

Hexahydroanthracene (**455**) is quantitatively converted to anthracene (**457**) by milling with three equivalents of dichloro-dicyano-parabenzquinone (DDQ, **456**). The intermediate products cannot be quantitatively obtained at 1:1 or 1:2 ratios of the reagents, as product mixtures occur [22]. Importantly, pyrocatechol (**191**) is quantitatively oxidized by milling with **456**. The highly reactive *o*-benzoquinone (**385**) is most easily reacted with solid addition



Scheme 81

partners directly in the mill. For example, diphenylfulvene **383a** was comilled to form the addition product **386** that could be extracted from DDQH (**458**) in quantitative yield [22]. Hydroquinone is oxidized by **456** and parabenzoquinone (**459**) easily sublimed off for isolation. A 100% yield of *p*-hydroxybenzaldehyde was obtained by stoichiometric milling (1 h) of *p*-hydroxybenzyl alcohol and DDQ. The aldehyde could be easily extracted from the DDQH [103].

Nitroarylbenzhydrols (**460**) can be quantitatively oxidized by gaseous nitrogen dioxide to quantitatively give the aldehydes **77**, whereas long-chain solid primary aliphatic alcohols (**461**) provide the carboxylic acids **462** under these conditions and secondary alcohols with sufficiently high melting point give ketones. For example, benzoin (**463**) gives benzil (**338**) with 100% yield [91].

Numerous oxidative additions to organometallic complexes occur with 100% yield in the solid state. A review is given in [68]. Well-guided combustion reactions of solids proceed almost quantitatively and may be relevant despite the gaseous products.

28 CONCLUSION

Quantitative waste-free solid-state reactions are far from being fully appreciated. The numerous known and new examples for almost all important reaction types that are collected in this review clearly demonstrate the environmental and preparative use as well as the mechanistic background that is so important for the further exploration. Clearly, there are

some crystallographic conditions and the melting points of reactants and products must not be too low. But it can be confidently assessed, that the solids described here will be also amenable to further solid-state reaction types. If the solid-state equipment (vacuum facilities, mortar, mill, ultra sound cleaning bath) is not available it can always be tried to perform the solid-solid reactions as melt reactions at much higher temperatures and a quantitative yield might be obtained in some exceptional cases, but unfortunately not in most cases. That is to say the profit of having quantitative yield with 100% of pure product in a short time at low temperatures without workup requirement by using the benefits of the crystal packing is lost in melt reactions. There may, however, still be advantages of stoichiometric melt reactions over solution reactions. But milling may also be suitable and possible if very insoluble and low viscosity liquid partners are stoichiometrically reacted. Such reactions are, however, omitted in this review. Fortunately, the solid-state techniques supercede all other techniques in terms of sustainability, avoiding wastes, energy savings, time savings, work savings, easiness of conduction, safety, and unmatched performance in the synthesis of highly sensitive products. Furthermore, numerous products that cannot be obtained by any other technique become available now. If solid-state reactions don't work for reasons that are discussed in this review it should be tried to engineer them for work by using the developed principles. Further exploration is worth the effort and unavoidable if people get acquainted with the new principles of solid-state reactivity [1, 3] and start to appreciate the avoidance of solvents and other auxiliaries including purifying workup just by profiting from the bargain benefits of the crystal structure packing and if they trust that scale-up is possible such as has been demonstrated in various instances.

There is still much to explore. For example quantitative solid-state Wittig and Grignard reactions await exploration (see less than quantitative examples in [67]). First experiments are promising, but the authors did not yet care for running the reactions to completion or they did not assess the solid state even though interesting stereoselectivities emerged (Review in [67]). Materials for a complete students course have been widely spread by the OECD. This can also be downloaded from the author's homepage for use in students' education for really sustainable syntheses in the future [145].

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