

How are Waste Entirely Avoided in Solid-State Productions?

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Abstract

The mechanism, synthetic application, scaling, and industrial production with gas-solid and solid-solid reactions without producing wastes is outlined. These reactions profit from lowered activation energy (with respect to melt reactions), favorable kinetics with definite end of reaction, and mostly reaction specificity giving only one product in pure form without workup necessity. They proceed thus solventless (not only "solvent free") and wasteless. The bargain of the solid-state should not be given up by heating to melt (e.g., milling without temperature control) or by "adding a little solvent". Molecular (or ionic) solid-state reactions, be they gas-solid or solid-solid, profit from the presence of cleavage-planes, channels or voids for intracrystalline long-range anisotropic molecular migrations. Such release of internal local pressure upon chemical change is essential. This is experimentally verified. In the solid-solid case mixing and contacting leads to the thermodynamically more stable product, but this does not exclude kinetic control. It is of utmost importance to control the temperature so that eutectic temperatures (melts) are not reached during all reaction stages. Typical examples out of more than already thousand 100% yield reactions from 26 reaction types for particularly delicate (not otherwise available) or otherwise interesting products are presented, and the scaling up to continuous industrial production is exemplified. Also, mechanochemical reactions (for example counter-thermodynamic mechanical bond breaking of infinite covalent materials) can be waste-free, ending with the most stable possibility when the bond-breaking ceases at the nanoscale. The proper experimentation (most important is strict temperature control) is outlined and easily and safely achieved.

Keywords: Activation energy decrease; Gas-solid production; Scaling up to industrial; Solid-solid production; Wasteless

Introduction

Since as early as 1985 it is known that molecular solid-state reactions (gas-solid and stoichiometric solid-solid reactions proceed to completion. Pure solid products are obtained without waste forming solvent use for purification from side products, starting materials, catalysts and other auxiliaries. AFM-measurements proved with molecular precision that no melts are involved and that surface-specific anisotropic molecular migrations occur beyond these surfaces. Clearly, avoiding (intermediate) melts is the requirement for making profit from the solid-state, be it crystalline or amorphous. Thus, temperature control is essential.

Roughly, these solid-state reactions proceed rapidly at about 100 K lower temperatures than melt reactions, and they stop when eutectic temperatures are reached, if that is not avoided by proper cooling. Nevertheless, these very profitable bargains of the solid-state (more than 1000 quantitative wasteless syntheses due to favorable kinetics and decrease of activation energy) have not widely been appreciated, because it is at variance with a hypothesis of Schmidt, Tel-Aviv, Israel, of 1964 (called "Schmidt's topochemistry"), "forbidding" long-range molecular migrations within crystals. Since such disproved thinking is still widely in use, people tried with molecular milling without temperature control via melts, or even with adding "a little solvent" [1] later called LAG (liquid assisted grinding) and claimed this to be an advancement [2]. However, this is at best applicable to recrystallizations with formation of cocrystals and supramolecular objects by kneading (not grinding), and the here mechanistically incorrect term "mechanochemistry" should not be applied. When LAG is applied to molecular reactions involving covalent bond formation (rather than mechanical bond breaking, cf. the Review [3]) it is a severe retrogression by losing the bargain of the solid state. Typically, such procedures, are incomplete (e.g., 59% yield, not citing the review with more than 1000 waste-free solid-state reactions in at least 26 different reaction types all with 100% yield [4], and wasteful with producing side products requiring chromatography. These could

be wastefree syntheses when liquid phases are avoided. A typical example (34 cases) for the latter is the authors' temperature controlled solventless milling of aldehydes/ketones with NaBH_4 (4:1 ratio) to obtain quantitatively the elusive high melting sodium-tetraalkoxyborates in pure form even with liquid carbonyls, from where the free alcohols can be quantitatively obtained with water vapor, leaving pure sodium borate for reuse [5]. Nevertheless, the journal "Green Chemistry" had published the wasteful reduction by "high speed ball milling" of four arylaldehydes and four acetylbenzenes with NaBH_4 (all 1:1) but without temperature control at 95% conversion and yields from 65-70% [6]. It followed a paper of the carbonyl reductions with $\text{NH}_3\text{-BH}_3$ (explosive borazane from $\text{NaBH}_4 + (\text{NH}_4)_2\text{SO}_4$ in THF+gaseous H_2), using only one of the three B-H bonds in water, giving poor yields (85%) after chromatographic workup and production of huge amounts of waste. Remarkably, this paper [7] claims to be "environmentally benign" and does not even cite the unbeatably sustainable paper [5]. Or Fiscic's group, mills carbodiimides, isocyanates, and isothiocyanates as long as 2 h to add amine derivatives according to the "LAG technique" requiring copperchloride-catalysis with poor yield (e.g., claimed 59% or 74%) and chromatographic workup [8], but not citing [4,9], where more than 18 (hetero)cumulenes, provide waste free solid-state syntheses without added solvent and thus without catalyst giving 100% yield without producing wastes. Milling of melts without temperature control in planetary mills with too much impact (clogging) require exceedingly long reaction times. For example, 2,2 4-phenyl-cyclohexanone + 2.0

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4-nitro-benzaldehyde+0.2 (S)proline give 42% aldol condensate and 29% recovered aldehyde after 48 h planetary milling at 250-400 rpm [10].

Using mills as heating source for milling melts, or LAG for bond-forming reactions (not only recrystallization) are severe retrogressions. They do not consider proper experimentation, but are apparently appreciated in "green chemistry", despite their vast inferiority in terms of cost and sustainability. It appears therefore timely to point out the much superior solid-state techniques in both the mechanistic and scale-up sense as a viable supplement to the review in [4].

Mechanism of solid-state molecular and salt reactions

Solid-state reactions are kinetically favorable and experience lowered activation energy when compared to melt or solution reactions. The benefits are shown in Figure 1. These do not cover mechanochemical reactions that require mechanical breakage of covalent bonds.

The solid-state mechanism was exhaustively studied with atomic force microscopy since the 1980s. Figure 2 shows that unlike the hypothesis of "Schmidt's topochemistry" of 1964 molecules migrate upon chemical reaction anisotropically within crystals along channels or cleavage planes in the phase-rebuilding stage and at a certain conversion sudden transformation occurs into the product phase in the reaction zone, followed by disintegration, creating fresh surface for further reaction. This has been called the "phase-rebuilding mechanism". The formed surface features are face-selective depending on the orientation of channels and/or cleavage-planes. An exhaustive review of submicroscopic features classifies about 8 basic types with various characteristic appearances [11]. These provide also proof at the molecular scale that liquid phases are excluded. If these occur the scanning contact-AFM tip would plough and smear materials along its path [11]. The reason for the molecular migrations is the local internal pressure by the geometrical change upon the chemical reaction that must be immediately released. The phase transformation occurs when the product lattice becomes energetically more favorable. Such features occur equally in solid-state photoreactions, thermal reactions, gas-solid and solid-solid reactions.

When the mechanistic requirements are obeyed in the experimentation, complete reactions (close to zero order reactions) with 100% yield are obtained at decreased activation energy (roughly 100 K temperature decrease with respect to melt reactions is possible [12]). This has been verified with more than 1000 reactions all across molecular chemistry in 26 reaction types (Table 1) [4], mostly with highest specificity (one product), and that represents unbeatable "atom economy". The importance of the results as listed in Table 1 appears

to urgently list the major requirements for proper application of the mechanistic requirements in Table 2.

Gas-solid reactions

Figure 3 shows the easy lab-scale equipment for gas-solid reactions. Temperature control is primarily obtained by slow addition of the reactive gas to the evacuated vessels that may be cooled or heated when required [13]. Vacuum tightness is essential. The flow-systems must use inert gas mixtures to calm down the reaction, because cooling from outside may not be sufficient. Care has to be taken for extra free volume if the powder volume increases.

Some examples for the particular wealth of gas-solid reactions, for example completely anhydrous conditions allowing for the synthesis of otherwise inaccessible new products, shall be exemplified [14]. For example, elusive aminomethylene hydrochlorides are only stable as solids at low temperatures (here -18°C) (Figure 4). The now available aminomethylene-hydrochlorides are important highly reactive building blocks.

A long-standing problem has been solved by gas-solid addition of HCl gas to obtain the crystalline unrearranged camphene hydrochloride in pure form. There are not the moisture problems with that technique [15]. In solution, this addition product undergoes Wagner-Meerwein rearrangement and no pure product could ever be obtained. Now the solid-state thermal rearrangement of camphene hydrochloride to isobornylchloride can be studied kinetically and with synchrotron X-ray (the within-crystal transformation is complete after 3 years at room temperature and 6 h at 80°C without melting), which might give a clue for a revival of the non-classical carbocation question (Figure 5).

The quantitative diazepine syntheses in Figure 6 proceed only with gaseous acetone [16]. If liquid phase acetone is used one needs expensive catalysts, supports and microwave in 80 times smaller runs with far from quantitative yield and chromatographic purification in six following papers of others. These are, of course, neither green nor sustainable as claimed, and surprisingly, they do not cite our early work. Nobody should create enormous amounts of dangerous wastes for these reactions any more [17].

Large scale gas-solid exhaust-gas purification of acetone vapor from exhaust gas atmospheres has been achieved in a two-column system below detection limit in a fluidized bed. At well-adjusted acidity, the volatile products are expelled at 80°C according to $(\text{H}_2\text{NOH})_3 \cdot \text{H}_3\text{PO}_4 + \text{K}_2\text{HPO}_4 \cdot x\text{H}_2\text{O} + 3\text{Me}_2\text{C}=\text{O} \rightarrow 3\text{Me}_2\text{C}=\text{NOH} + 2\text{KH}_2\text{PO}_4 + (x+3)\text{H}_2\text{O}$. The acetone-oxime is condensed and separated from the water of reaction, KH_2PO_4 is a value added couple product.

The gas-solid addition of bromine gas to cholesterol [18] (Figure 7) provides directly a better quality intermediate dibromide for hormone production of technical interest. If necessary, the hydroxyl group of cholesterol can be protected by solid-solid esterification with oxalic acid.

Gas-solid additions of HCl to oxiranes a low temperatures (where these are solidified) occur stereoselectively (Figure 8). Others occur stereospecifically in the synthesis of contraceptive steroid hormones [4,19]. More complicated gas-solid reactions with elimination of water and rearrangements (not available in solution) in steroid-hormone syntheses are found in [20].

Carbonic acid halfester salts are highly versatile merchandisable reagents. They are synthesized in suspension bed columns from commercial alcoholates with carbon dioxide that is initially strongly diluted with nitrogen, to remove the enormous heat that is produced

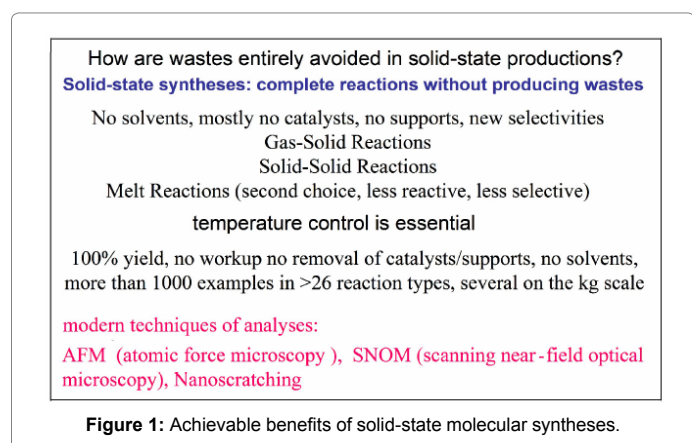


Figure 1: Achievable benefits of solid-state molecular syntheses.

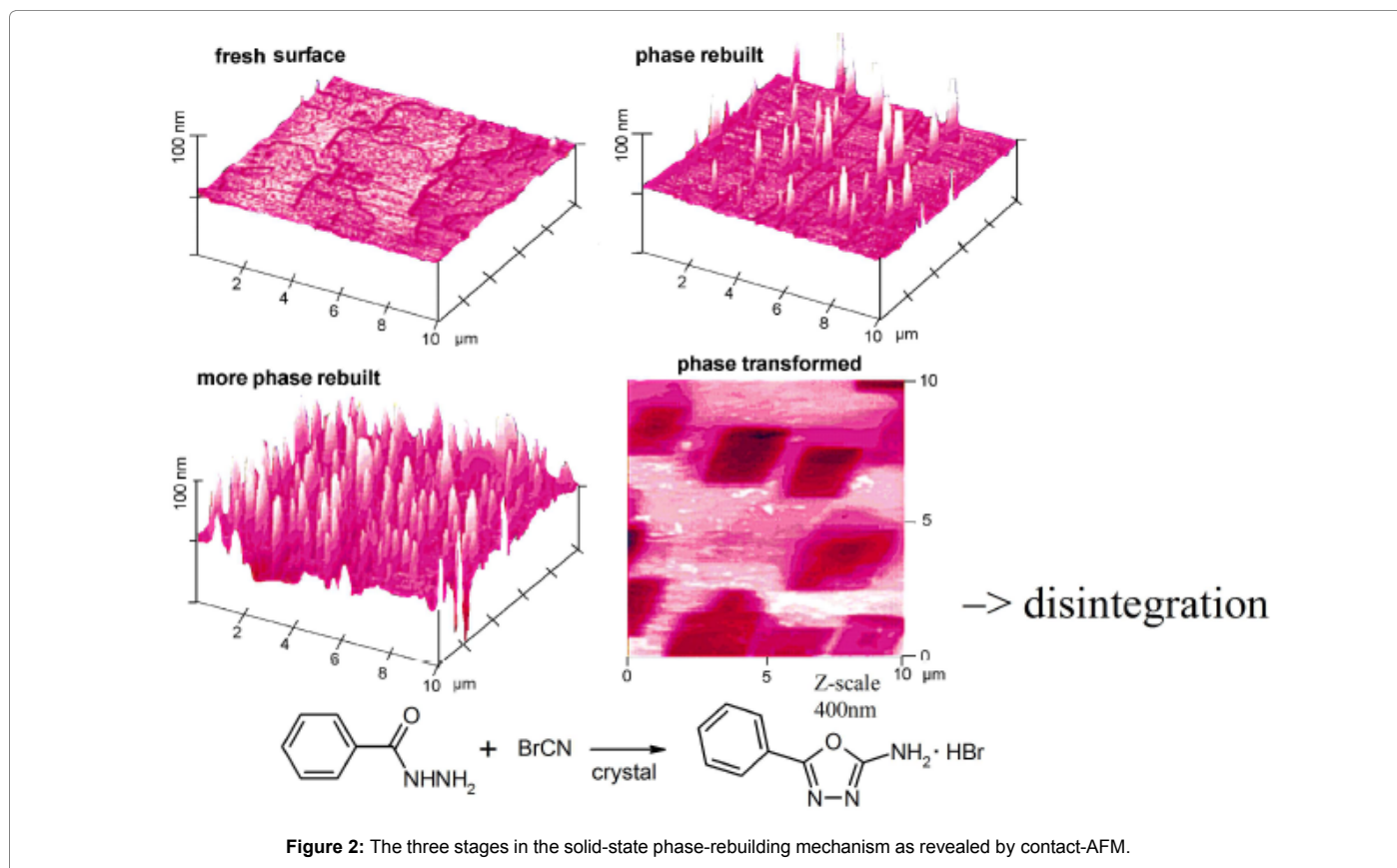


Figure 2: The three stages in the solid-state phase-rebuilding mechanism as revealed by contact-AFM.

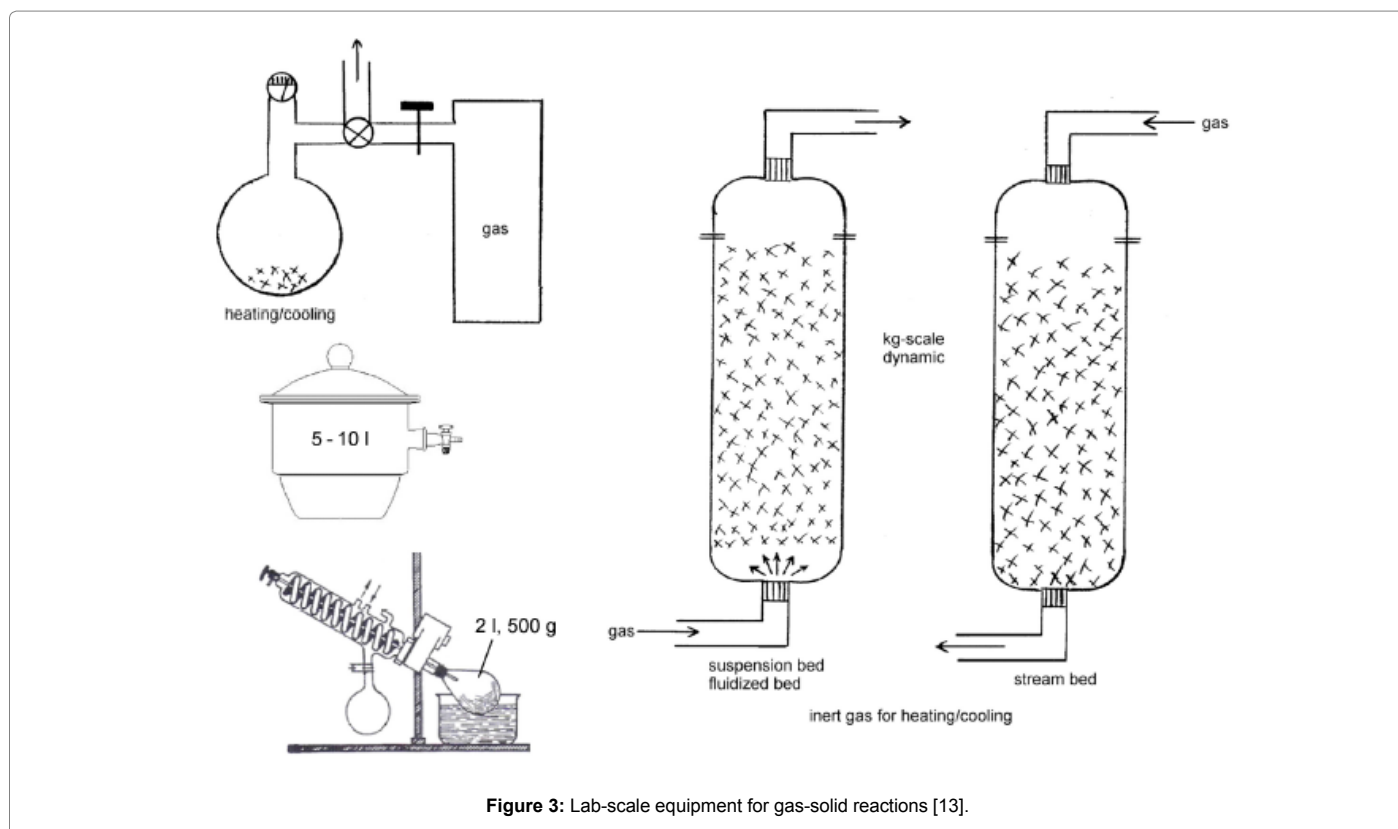


Figure 3: Lab-scale equipment for gas-solid reactions [13].

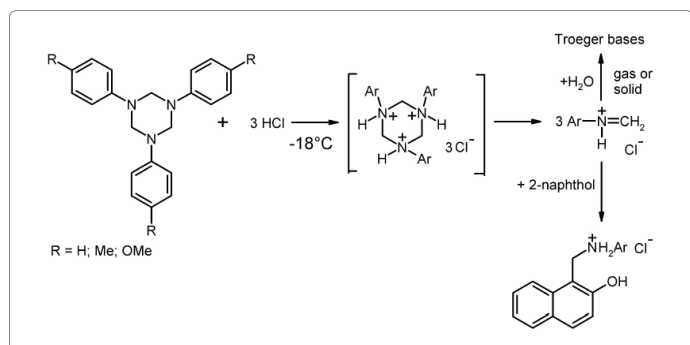


Figure 4: Synthesis of aminomethylene hydrochlorides by quantitative gas-solid reaction at $-18^{\circ}C$ [14].

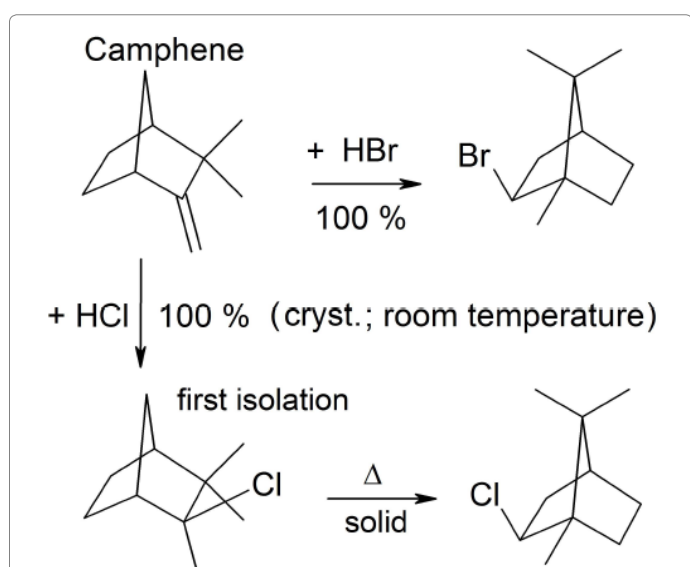


Figure 5: Gas synthesis of unrearranged camphene hydrochloride and its thermal rearrangement to isobornylchloride, similar to the directly obtained isobornylbromide.

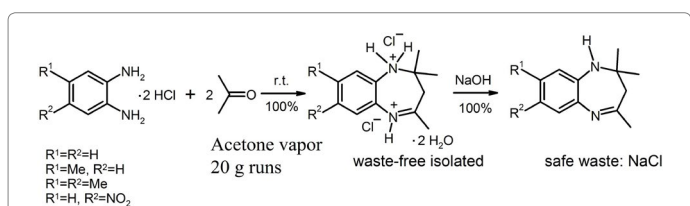


Figure 6: Gas-solid syntheses of 1,4-diazepines from o-phenylenediamine dihydrochlorides with acetone vapor [16,17].

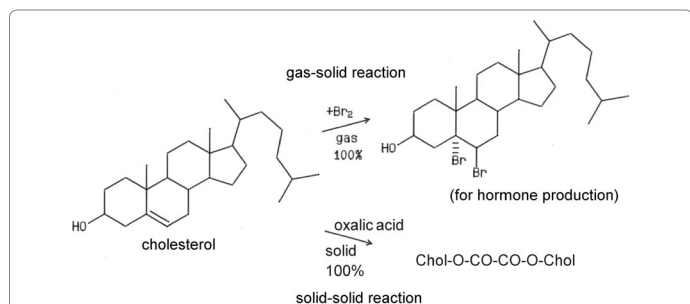


Figure 7: Quantitative gas-solid addition of bromine to cholesterol and the solid-solid esterification of cholesterol with oxalic acid.

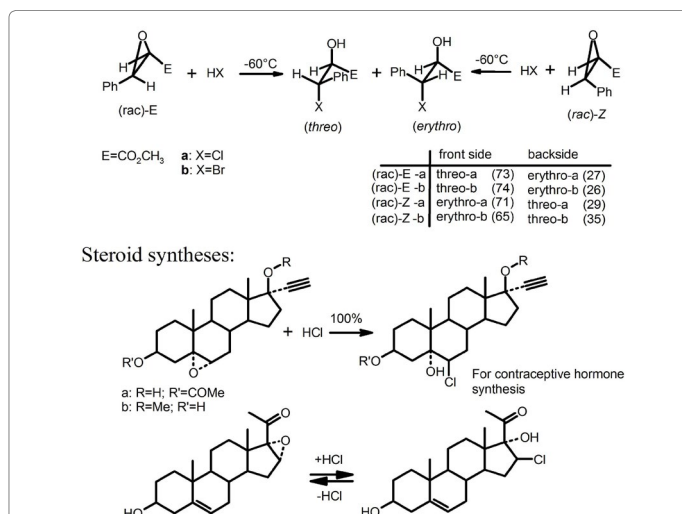


Figure 8: Stereoselective and stereospecific gas-solid additions of HCl to oxiranes.

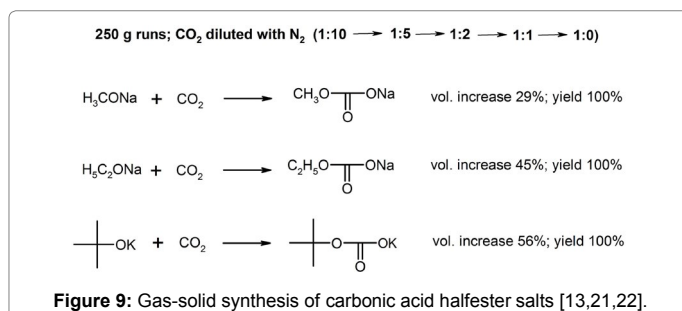


Figure 9: Gas-solid synthesis of carbonic acid halfester salts [13,21,22].

Inclusion reaction	Condensation of carbonyls
Electron transfers	Cycloadditions
Proton transfers	Cycloreversions
Oxygen transfers	Substitutions with RX
Oxygenations	Aromatic substations
Hydrogenations	Cyclization's
Additions of AR'NH ₂ .H ₂ O.ROH	Methylations
Additions of halogens and HX	Nitration's at N and C
Eliminations	Diazotations
Rearrangements	Azocouplings
C-C bond formations	Sandmeyer reactions
Carboxylation's with CO ₂	Diazo transfer
Catalysed reactions	Cascade reactions

More than 1000 rapid 100% yield one-product reactions in these types

Table 1: Optimized organic gas-solid and solid-solid reactions.

(Figure 9). At the end, pure CO₂ completes the reaction [21]. Free space has to be provided due to strong volume increases. Numerous further gas-solid syntheses including large and technical ones [13] are to be found in [4].

Solid-solid reactions

Quantitative wasteless solid-solid reactions require mills. Grinding in mortar are for initial tests, and with shock-sensitive materials like solid diazonium salts that must not be milled. Figure 10 depicts a temperature controlled vibration ball-mill MM₂ (Retsch Ltd, Germany) with double-walled beaker for milling up to about 200 mg organic stoichiometric mixtures, and for finding the temperatures that are below any eutectics for large-scale milling [22].

A larger scale 2 L horizontal rotor ball-mill and semibatch powder feeding and powder collection equipment is shown in Figure 11. In the absence of continuous production one does not need the feeding/collection equipment but leaves about 10% of the material in the mill during milling-out through a cyclone and bypass for protection of the balls. Furthermore, one determines the yield with the following batches. Such mills can be obtained up to 900 L size with fully continuous operation in industry. The 2 L version can be run in academic labs due to low trembling of the balls-driving rotor and moderate noise [23].

Figure 12 depicts a 400 L Simoloyer® mill, Figure 13 illustrates the blueprint of the feeding/collection device and Figure 14 shows it at work. Temperature control of the larger mills (≥ 2 L) is by cooling with cooling mantels and automatic alternating milling with cooling cycles using the different processing state. Since several hundreds of waste-free solid-solid syntheses have been reported in the exhaustive review [4] we select here the already realized large-scale examples of solid-solid molecular reactions [24].

Figure 15 contains two examples of unbeatable stereo specificity. The six OH-groups of D-mannitol (r.t.) or meso-inositol (95°C) are completely regio- and stereo-specifically condensed with stoichiometric phenylboronic acid upon milling in the temperature controlled MM₂ vibration mill [25] and in the 2 L Simoloyer [13]. The water of reaction is taken up by the product crystals and can be removed by evaporation in a vacuum. This more than underlines the profit of solid-solid reactions, all starting materials exhibiting proper channels for the necessary molecular migrations. As expected, the corresponding solution reactions lead to intractable mixtures of stereoisomers.

Less spectacular are formations of molecular complexes by stoichiometric milling of the components, which is also possible at different molecular ratios. Figure 16 gives typical examples with caffeine. This is certainly an interesting and easy processing for drug formulations and many others expected; also different ratios.

It is also possible to achieve the synthesis of pharmaceuticals. For example, the antibacterial sulfonamide phthalazole 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 is performed for the acylation reaction as in Figure 17 [13].

Two of the early quantitative 2 mmol Knoevenagel solid-solid



Figure 10: Lab-size vibration ball-mill: 20 ml beakers with temperature control (-78 to 100°C) for initial tests (do not use planetary mills) [23].



2 L horizontal rotor ball-mill



Powder charging and collection

Figure 11: Technical double-walled ball mill Simoloyer® C01, 2 L of Zoz Group Ltd, Wenden, Germany with temperature control and feeding/collecting equipment for semibatch operation [23,24].

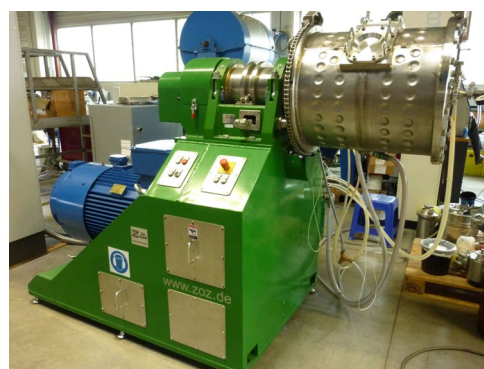
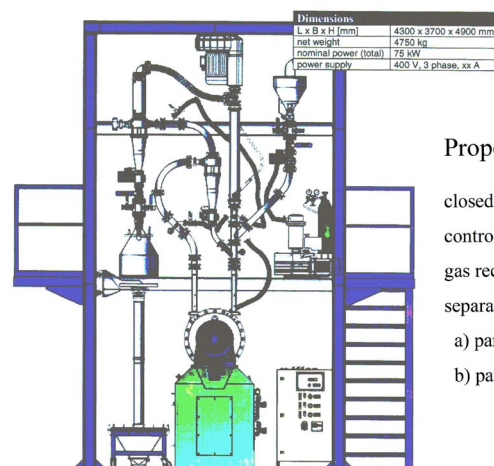


Figure 12: 400 L Simoloyer® ball-mill (extensions up to 900 L); with kind permission of the Zoz-group Ltd, Wenden, Germany.



Properties:

- closed system
- controlled atmosphere
- gas recycling
- separation/classification for
 - a) particle size
 - b) particle mass

Figure 13: Scheme of the large scale semicontinuous feeding/collecting equipment. With kind permission of Zoz-Group Ltd, Wenden, Germany.

syntheses (in Figure 18a and 18b) between the aldehyde and barbituric acid [9,12] were waste-free scaled to 200 g in the 2 L Simoloyer [13] at typical out-milling times of 10 min. The reaction with vanillin (in Figure 18c) occurs already as melt reaction at 50°C. It was directly scaled 2500-fold from 200 mg at 0°C in the cooled MM₂ vibration mill to 500 g in the 8 L Simoloyer at $\leq 10^\circ\text{C}$ without any problems [26]. The water of reaction was taken up by the product crystals and did thus not impede, and the reaction time is very short.



Figure 14: Different 100 L Simoloyer® ball-mills and Auto-batch-operation (continuous production). We thank the Zoz-Group Ltd. Wenden, Germany for permission to present these images.

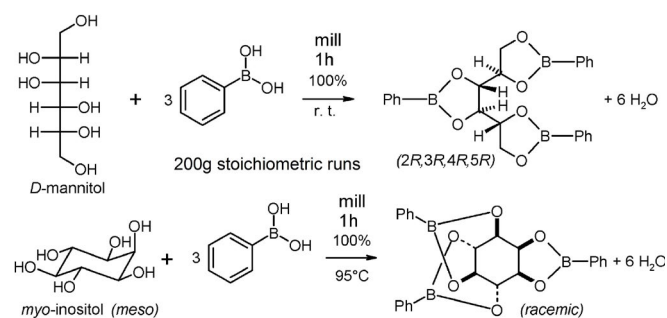


Figure 15: Waste-free multi cascades of sugar alcohols upon stoichiometric molecular milling [13,25].

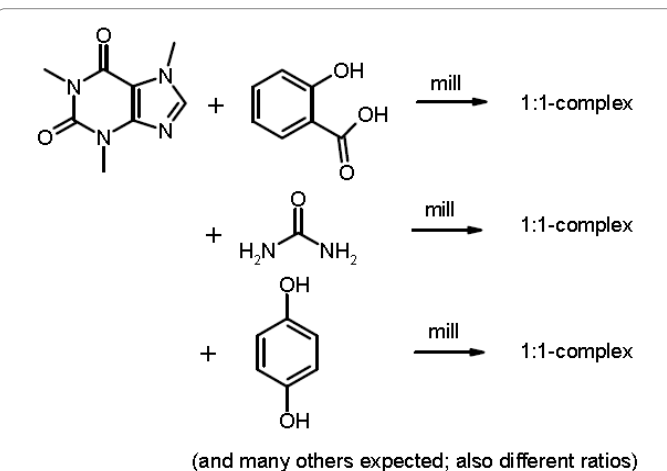


Figure 16: Waste-free 200 g batches at 25-30°C in the 2 L Simoloyer; milling time 20 min at 1000 rpm with 100% yield.

Scaling in the ≥ 2 kg ranges requires the 20 L Simoloyer. The 1:1-milling of glucose with urea for 5 min gave the glucose-urea complex, providing new reactivity to the glucose [23]. This complex cannot be obtained from solution. This technique shall also enable formulation of urea complexes in cosmetics and to synthesize ureidoglucoses. 2 kg of a stoichiometric mixture were milled and out-milled at a maximum

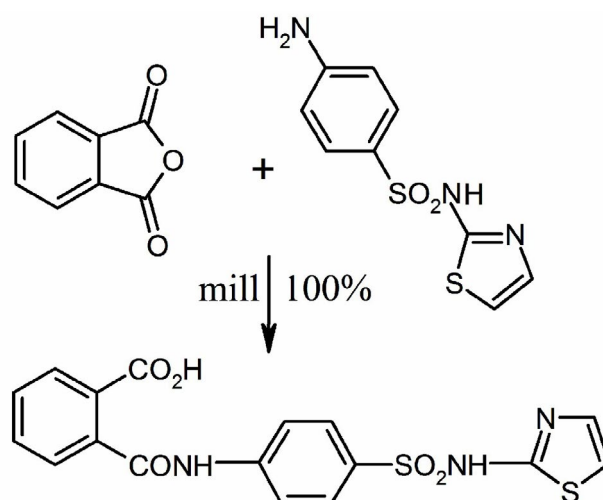


Figure 17: Solid-solid synthesis of the directly pure pharmaceutical sulfonamide by milling of 200 g stoichiometric batches in the 2 L Simoloyer ball-mill at 25-30°C.

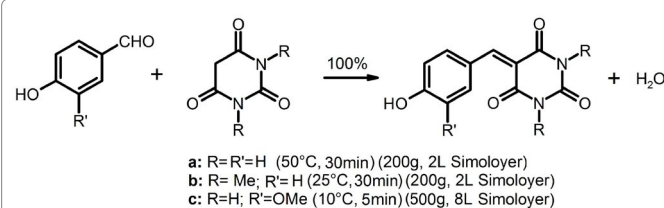


Figure 18: Quantitative large-scale solid-solid Knoevenagel condensations.

of 25°C using the automatically intermitting cooling times at lower rotation speed. The complexation (Figure 19) that had previously succeeded at the 200 g scale (2 L mill [13]) is complete within 5 min, so this process could easily be continuously performed.

Also salt formations with CO₂ release succeeded at the 2 kg scale in the 20 L Simoloyer at 25-30°C. 185 L of CO₂ had been manually released [26]. The quantitative reactions in Figure 20 that had previously succeeded at the 200 g scale proceeded fully selectively, depending on the stoichiometric sodium carbonate or sodium hydrogen carbonate [13]. The tartaric salts are widely used food additives. No detour via sodium hydroxide is required and costly evaporation of water is avoided.

Mechanochemical reactions

Also, genuine mechanochemical (with covalent bond-breaking at 3D-covalent networks) syntheses (Review [3]) are waste-free by proper milling at stoichiometric ratios of the components. Figure 21 contains four 200 g batches in the 2 L Simoloyer [13] and various general reaction types. A particular characteristic is the exclusive formation of the most stable product that survives despite further bond breaking and recombination until no further breakage can occur at the nanoscale.

It is seen in Figure 2 that a wide variation of successful oxide combinations reacts quantitatively. In the literature, most of these have only been performed small-scale in planetary mills. But our 200 g batches in the C01Simoloyer indicate, that much shorter milling times (30-60 min) would be possible in temperature controlled small vibrating or large rotor ball-mills. Of industrial interest is the continuous milling of aluminum with multi-walled technical carbon nanotubes (Baytubes®),

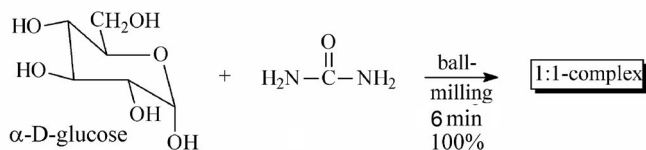


Figure 19: Rapid solid-solid synthesis of an otherwise not available glucose-urea complex at the 2 kg scale in the 20 L Simoloyer at 25-30°C [26].

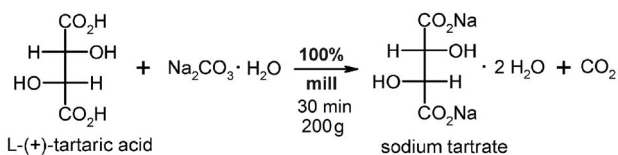


Figure 20: Quantitative stoichiometric solid-solid syntheses of sodium tartrates at the 200 g and 2 kg scale in the 20 L Simoloyer ball-mill with CO₂ release.

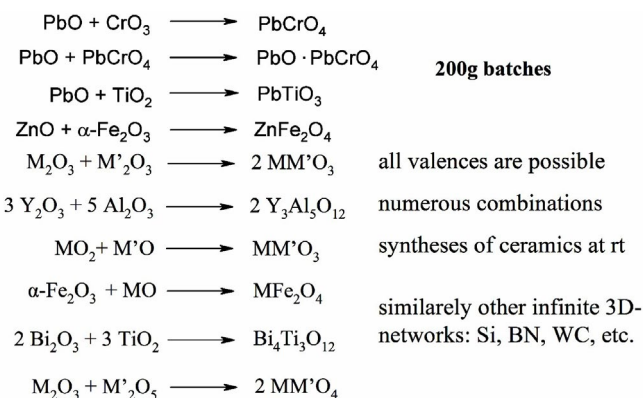


Figure 21: Mechanochemical cold syntheses of ceramics by reactive milling of oxides (always 3D-covalent networks).

giving Zentallium® (grain-size controlled aluminum by milling at 700 MPa) [27]. This material after passivation and hot extrusion is lighter than aluminum and as strong as steel. It can be used for helicopter shafts, threads, rod/billet, fasteners, etc. Its density is 2.63 g/cm³, specific strength 270 MPa/g/cm³. The C20 Simoloyer ball mill at autobatch processing provides 120 kg/d. The safety of the process has been officially checked by BGIA, Germany, excluding aerosol emission of the industrial process (Figure 22).

Still another waste-free industrial process is the production of nanocement, simply by continuous milling of dried blast slag, a genuine mechanochemical processing. The obtained high performance cement is called "Futurcement". It provides futurconcrete at high strength and super durability by the sub-micronizing of the blast furnace slag. It is 3 times stronger (140 MPa) and of superior durability (95% GP) than Portland cement concrete. Its production saves 20% of the latter's CO₂-emission. The milling consumes 347 kWh/ton of futurcement. At a production of 43.000 tons p.a. the remarkable advantages are obtained for 7,00 €/ton extra costs. But that is superceded by the saved CO₂-emission costs. Figure 23 shows the construction of a public traffic bridge in Germany out of futurconcrete.

No spoiling with dusts!

Safety in Nanotechnology at the example of Carbon-Nanotubes (Baytubes®) and Zentallium®



Determination of the Nano-Particle Emission (Nano-Aerosol-Concentration) during Zentallium®-manufacturing
 BGIA and Bayer AG at Zoz GmbH, Wenden, 09./10.06.2009

The concluding remark of the final examination report from January 2010:

"No interrelation between the application of Baytubes® (Bayer Carbon-Nanotubes) and the nano-aerosol concentration could have been detected" It means that the process does not emit any detectable nano-particles and insofar does not generate any danger for human and environment.

- The entire processing is under inert gas or vacuum in closed circuits
- These explorations are appreciated at the highest importance:
 - one of the first public examinations with respect to nano-particles and occupational safety in general
 - it helps to set-up the standards for generating best information and ability

Figure 22: Exclusion of spoiling by aerosols from the industrial Zentallium® production.



Figure 23: A public bridge built out of futurcement/futurconcrete.

1	Obey the consequences of the experiences of the experimental three-stage solid state mechanism (avoid thinking in terms of misleading Schmidt's topochemistry hypothesis)
2	Avoid solvents after reaction for collection of directly pure product
3	Do not add "a little solvent" (a misleading concept, relic "topochemistry")
4	Use the favourable bargain of the solid state that decreases the activation energy and serves with kinetics close to zero order, which provides complete conversion
5	Care for temperature control from about -78 to +12°C (also frozen liquids work)
6	Catalysis should be avoided, due to reaction at much lower temperature than in liquid
7	If rarely necessary use only gaseous catalysts that can be waste less recovered
8	Use precise stoichiometric ratio of pure starting materials to avoid workup
9	When producing gaseous couple products collect them for further use.
10	Adjust milling impact, do not exaggerate (e.g., in planetary mills)
All of that is straight forward and published since the 1980s	

Table 2: Easy essentials for reaching waste-free productions.

Conclusions

Wasteless syntheses and productions requires gas-solid stoichiometric solid-solid processing without (intermediate) liquid phases. Thus, temperature control and cooling below eutectic temperatures is

essential. This is not possible in planetary mills, but no problem with small vibration and large rotor ball-mills. Clearly, ball-mills should never be used as heating devices for generating melt reactions. Only the bargain of the solid-state leads to decrease of activation energy, to mostly complete specificity when also further paths would appear feasible, and to favorable kinetics with definite completion of the reaction (close to zero order). It is thus counterproductive to add "a little solvent", and the so-called liquid assisted grinding (LAG) loses all benefits of the solid-state, being a severe retrogression. Even when recrystallization of cocrystals might occur with formation of supramolecular objects by kneading (not grinding) it is not profiting from the solid-state and thus no advancement.

Solid-state syntheses make available otherwise not accessible delicate products at proper experimentation with respect to the long-known "phase-rebuilding mechanism", involving pressure relieving far-reaching anisotropic molecular migrations. Molecular (also ionic) solid-state reactions require mixing/contacting and lead to more stable product. They are thermodynamically governed. Mechanochemical reactions (mechanical bond breaking) start counter-thermodynamically. Proper experimentation is easy, and the scaling up to industrial production has been pointed out with striking examples from more than 1000 waste less ones not requiring workup with solvents. Numerous further applications are envisioned and should be used for a cleaner environment.

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