Wasteless stoichiometric organic syntheses with 100% yield and their scaling up to industrial range are certainly a worthwhile goal

More than 1000 of them have been developed since 1985 in the solid state, without any auxiliary whatsoever. But they are still not fully acknowledged, even though pure product is obtained without workup

These are SS-reactions without intermediate melt that perform excellent but against textbooks claiming Schmidt‘s topochemistry, and most people refuse to read and avoid the liquid phase.

Adding “a little solvent“ (as in Friscics LAG) is a detrimental way back!

So I am glad and thankful to report on solid-state reactions here

I cannot also deal here with mechanochemistry, the mechanical breaking of chemical bonds

Sorry, there are problems with misconceptions:

„Topochemistry“ of 1964 (minimal atomic und molecular movements in crystals; d < 4.2 Å; but exceptions from the beginning) and no molecular migrations “allowing“ within crystals **seriously hampered molecular solid-state chemistry** by denial of basic physics in textbooks also by referees!

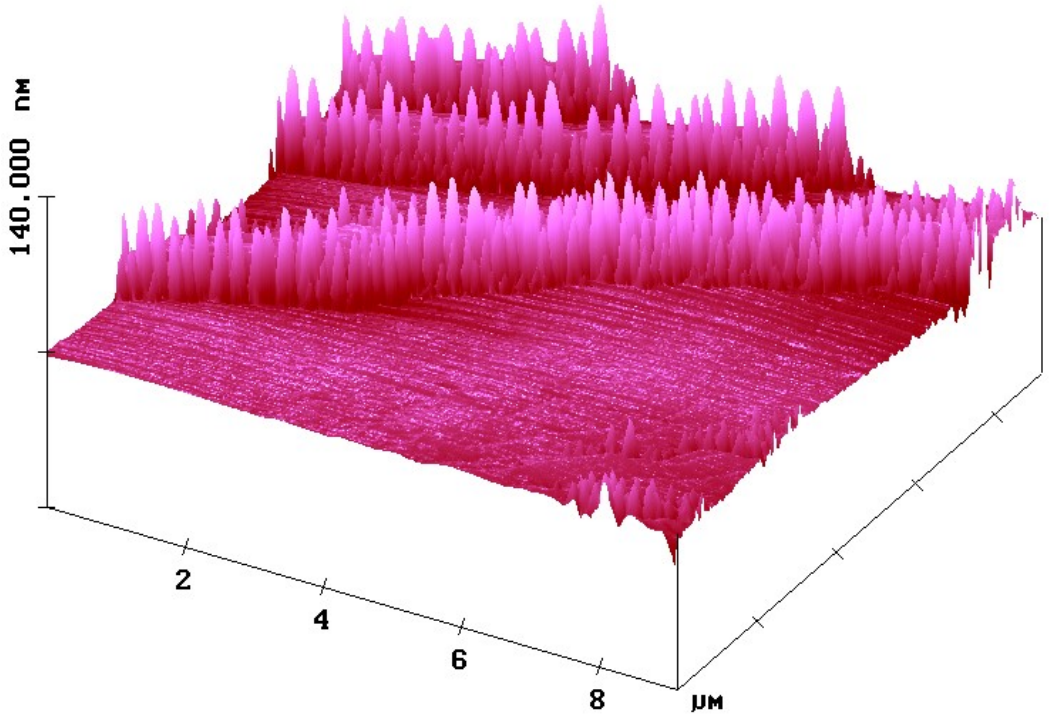
The error of topochemistry: local pressure formation is disregarded (still unusual hype prevailing)

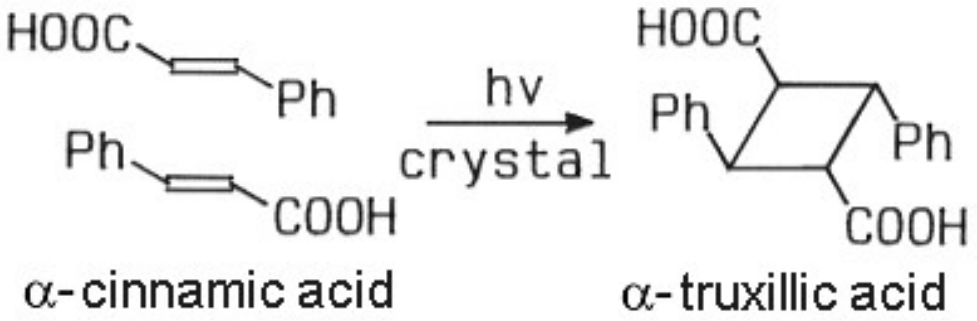
Remedy: experimental results since 1985 with AFM:

Syntheses: **Gas-solid and solid-solid reactions go to completion!**

AFM and SNOM and GID: **Molecules migrate anisotropically long distances up to the µm-range and beyond the surface** (that is release of local stress)

AFM: Anisotropic molecular migrations also with the crown witness of „topochemistry“, so what?





Answer: Topochemistry is a misconception without any predictive power!

G. Kaupp, Angew. Chem. Int.Ed. Engl. **1992**, *31*, 592; Mol. Cryst. Liq. Cryst. **1998**, *313*, 193

Prediction of solid-state chemistry: G. Kaupp in Making Crystals by Design, Wiley-VCH, **2006**, 87-148

If you have crystals don‘t dissolve, or melt, or wet them for reactions.

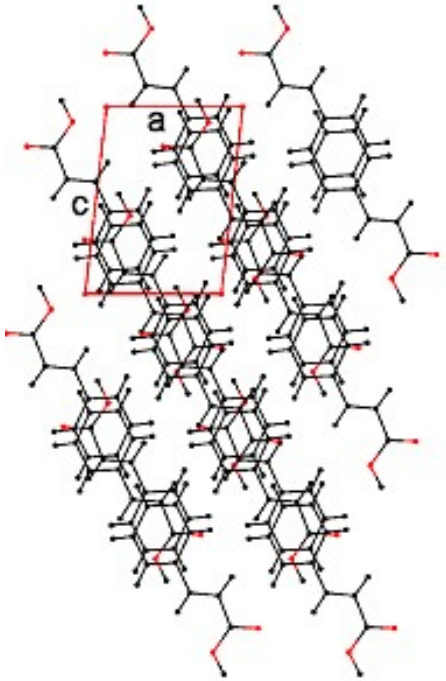
You would waste the bargain of favorable self-assembled alignment and deactivate the molecules by solvation, which is not sustainable.

Once more, do not follow Braga and Fricics with „a little solvent“
(low yield, long kneading times, catalysts, choromatograhy instead of 100% rapid SS-milling)

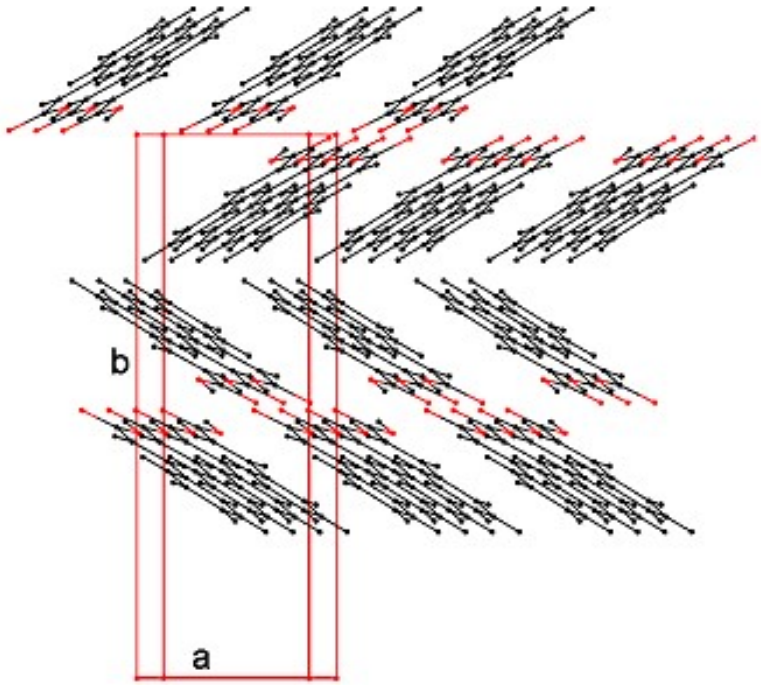
Only properly executed gas-solid and stoichiometric solid-solid reactions proceed with sudden end (zero-order) and decreased activation energy (thus mostly avoiding catalysts), despite molecular migrations within crystals along slip-planes or crystallographic channels

http://kaupp.chemie.uni–oldenburg.de

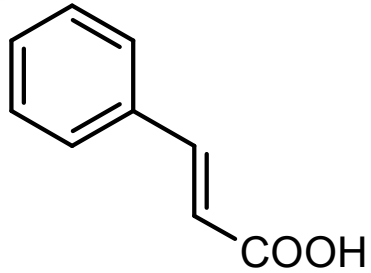
Cleavage planes of α-cinnamic acid predict solid-state reactivity



(010)/(10-1)



(001)/(010)

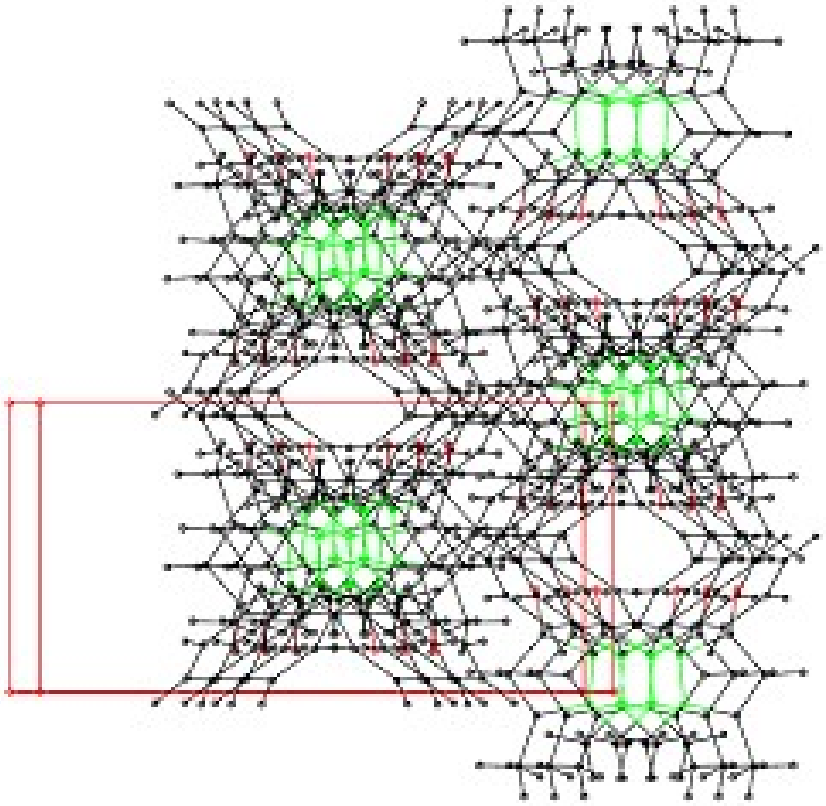


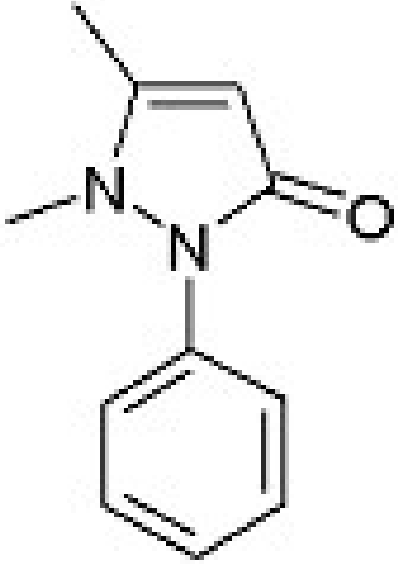
Prediction: photoreactive solids are also reactive in gas-solid and intercrystalline solid-solid reactions (here solid-state bromine addition with face specifity and stereospecific *trans*-addition to *erythro*-adducts).

Anisotropic molecular migrations along the cleavage planes for pressure release!

G. Kaupp, Prediction of reactivity in solid-state chemistry, in Making Crystals by Design, (Eds.: D. Braga, F. Grepioni), Wiley-VCH, **2007,** pp. 87-148

Antipyrine along [001] (slightly rotated) with elliptical channel





Solid-state reactivity towards HCl, HBr, Br_2; complexations

G. Kaupp in Making Crystals by Design, Wiley-VCH, **2006**, 87-148

Systematics of anisotropic migrations within reacting crystals (the molecular packing is crucial)

negative pressure	no pressure	positive pressure
shrinkage	no geometric change	expansion
migration	no migration	migration
depressions	no surface features	surface features
frequent	extremely few approved cases	very frequent

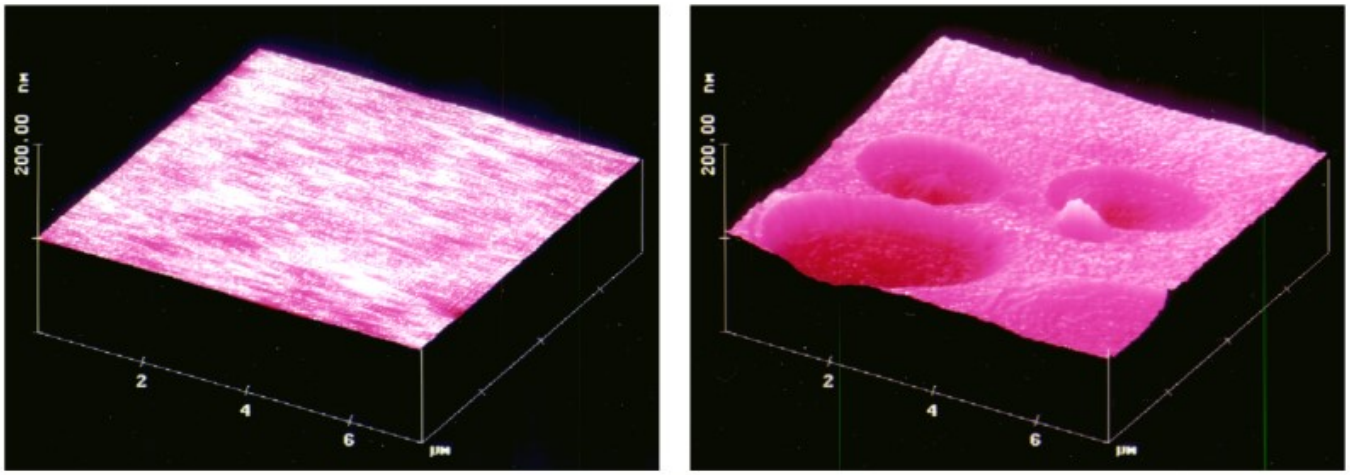
The 4.2 Å distance and minimal movements claim of topochemists is not predictive but unreasonable; close distance may help or impede; only crystal packing is crucial and its analysis is not at all difficult (use databases)

Neglecting pressure and its relief is a severe and basic error, textbooks must be rewritten !

G. Kaupp, J. Phys. Org. Chem. **2008**, 21, 630-643; DOI 10.1002/poc.1340

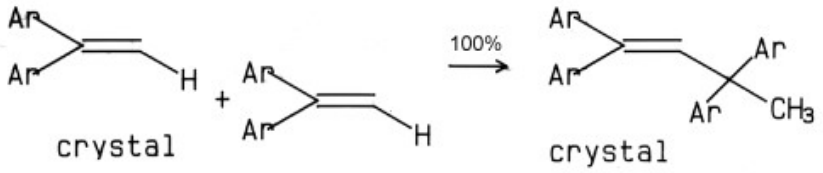
Molecular migrations within crystals not imposed by positive pressure but due to shrinking with accommodation to the original lattice

Catalytic solid-state dimerization of 1,1-bis(4-tolyl)ethene; AFM analysis



(100)-face after treatment with gaseous HCl

Reason: molecules are 3D-interlocked, cannot add HCl (requires migrations)
but molecules can dimerize and shrink, thus craters form



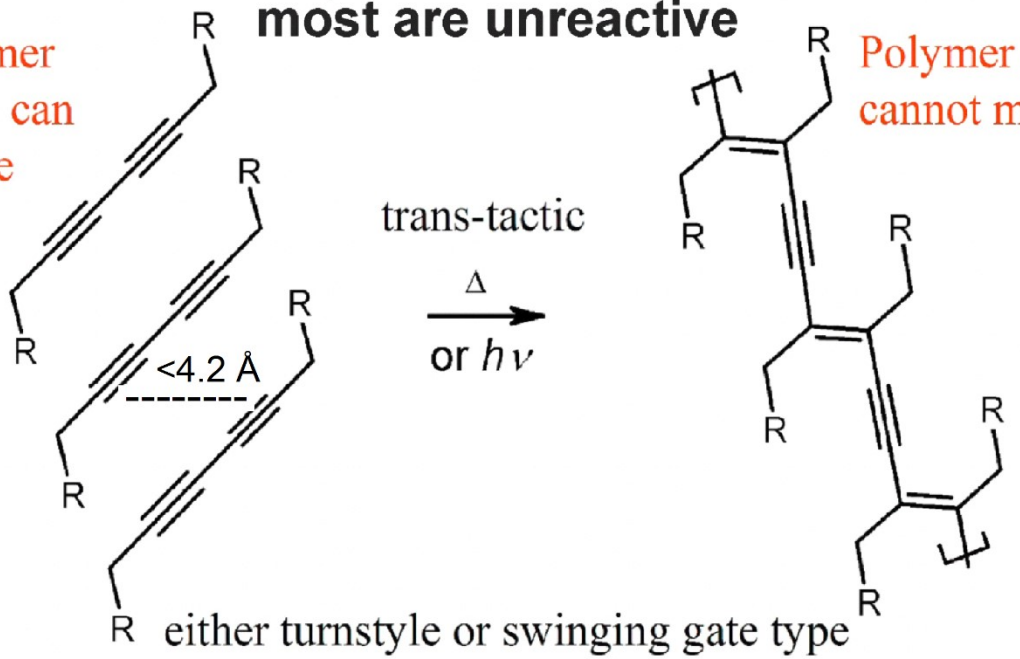
Ar = 4-H; $-CH_3$; $-OCH_3$
gaseous catalysts: HCl; HBr; BF_3; XeF_2

G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

A special case for (almost)"no pressure"polymerization, but topochemistry-hype wasted millions of research $ for decades: the distances are <4.2 Å

(more than 90%)
most are unreactive

Monomer (stack) can migrate



Polymer (period) cannot migrate

It is so simple!

Periods are 4.90 to 4.91 Å

Stacks 4.90 to 4.97: polymer

Stacks >4.98: no polymer

Stacks <4.9: no polymer

Examples:

R = 4-Pyr ··· $(HOOCCH_2NHCOC)_2$: stack 4.93 Å; period 4.9 Å, coincidence, polymerization

R = OSO_2-4-fluorophenyl: long stack 5.80 Å, period 4.9 Å, too far migration, at best oligomer

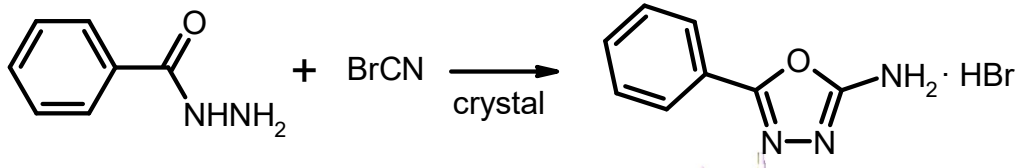
R = CH_3: short stack 3.8 Å, period 4.9 Å, polymer would be longer, no polymerization

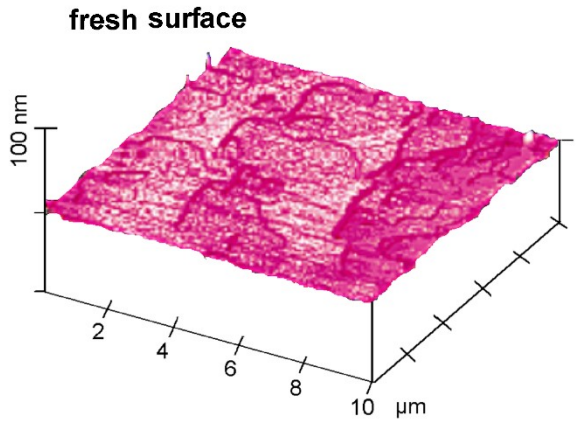
Shorter is here detrimental! Only the migrational issue provides the correct answers

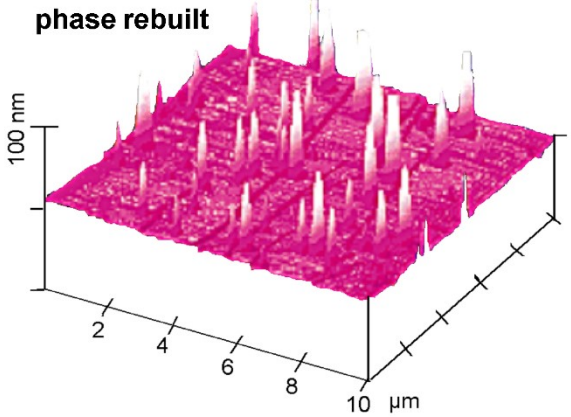
G. Kaupp, J. Phys. Org. Chem. 2008, **21**, 630 - 643

The ingenuous three-step mechanismus of all solid-state reactions

double layer (100)
cleavage plane (010)



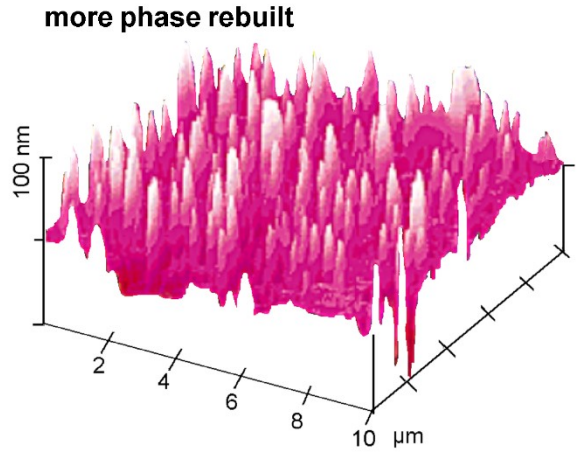


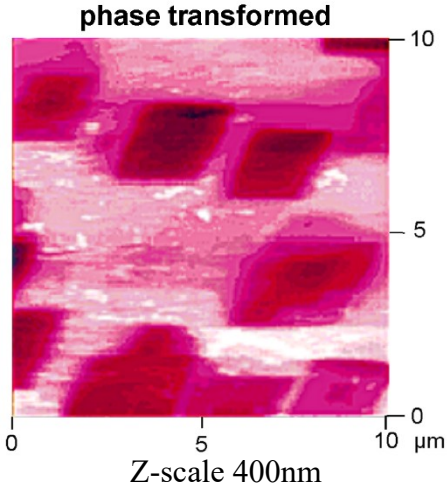


solid-solid AFM



no mechanical
impact is necessary!





Z-scale 400nm

Shortly thereafter
disintegration

Chemically driven; everything works without mechanical impact

Ingenuous three-step solid-state mechanism giving 100% yield under preparative conditions

G. Kaupp, Atomic Force Microscopy, Scanning Nearfield Optical Microscopy and Nanoscratching - Application to Rough and Natural Surfaces, Springer Series NanoScience and Technology, 2006

BENEFIT: organic gas-solid and solid-solid reactions

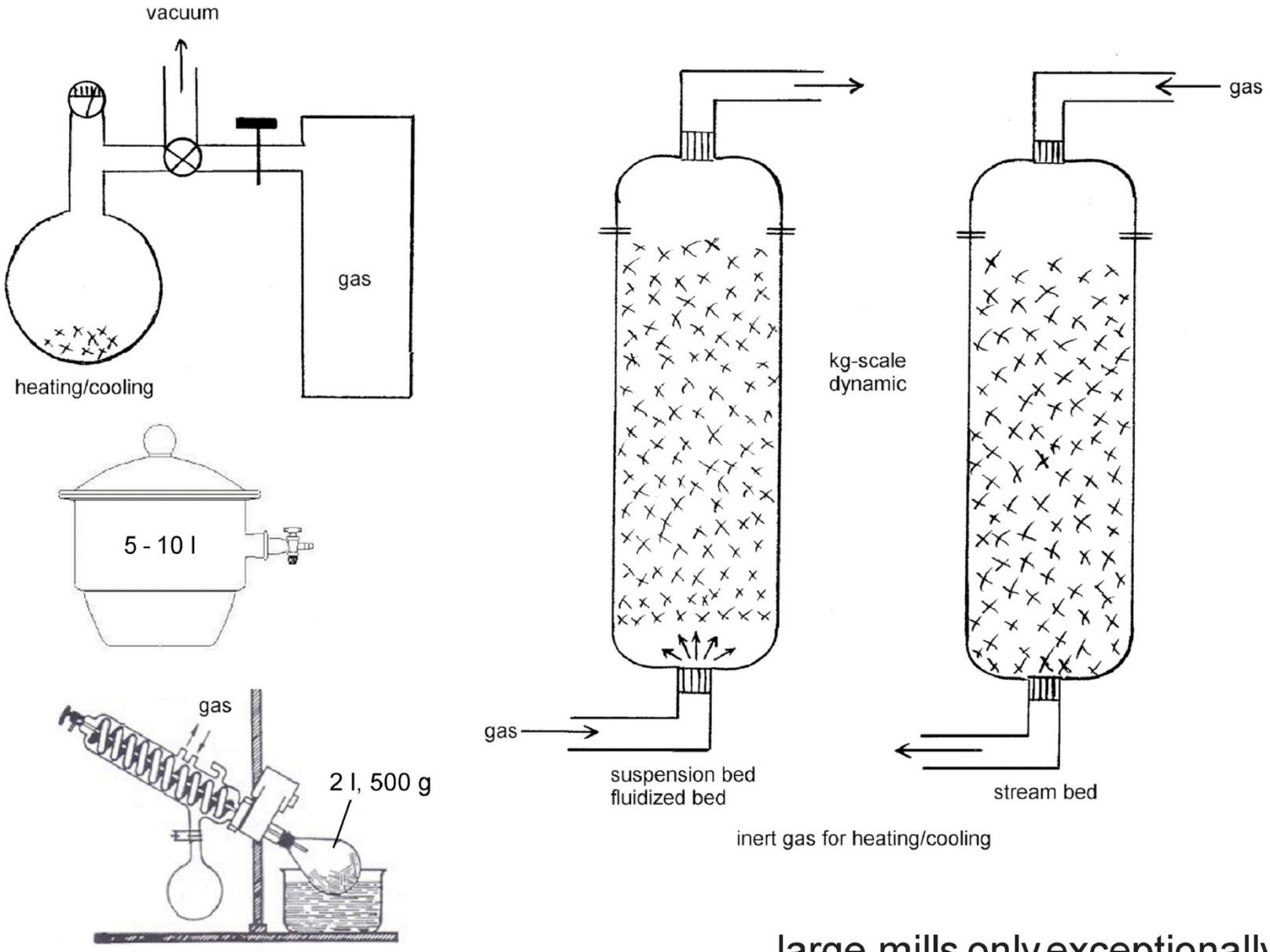
ORGANIC SOLID-STATE REACTION TYPES	
inclusion reactions	condensation of carbonyls
electron transfers	cycloadditions
proton transfers	cycloreversions
oxygen transfers	substitutions with RX
oxygenations	aromatic substitutions
hydrogenations	cyclizations
additions of RR'NH, H_2O, ROH	methylations
additions of halogens and HX	nitrations at N and C
eliminations	diazotations
rearrangements	azocouplings
C-C bond formations	Sandmeyer reactions
carboxylations with CO_2	cascade reactions
catalyzed reactions	

More than 1000 100% yield reactions within these types

All what they need is slip planes or channels and multiple contacts; minutes to <1h

Top. Curr. Chem. 254, 95 – 183 (2005); Springer, ISSN 0340-1022; additions in further reviews

Gas-Solid Equipment



large mills only exceptionally

G. Kaupp, Waste-free large-scale syntheses without auxiliaries, CrystEngComm 2006, 8, 794-804

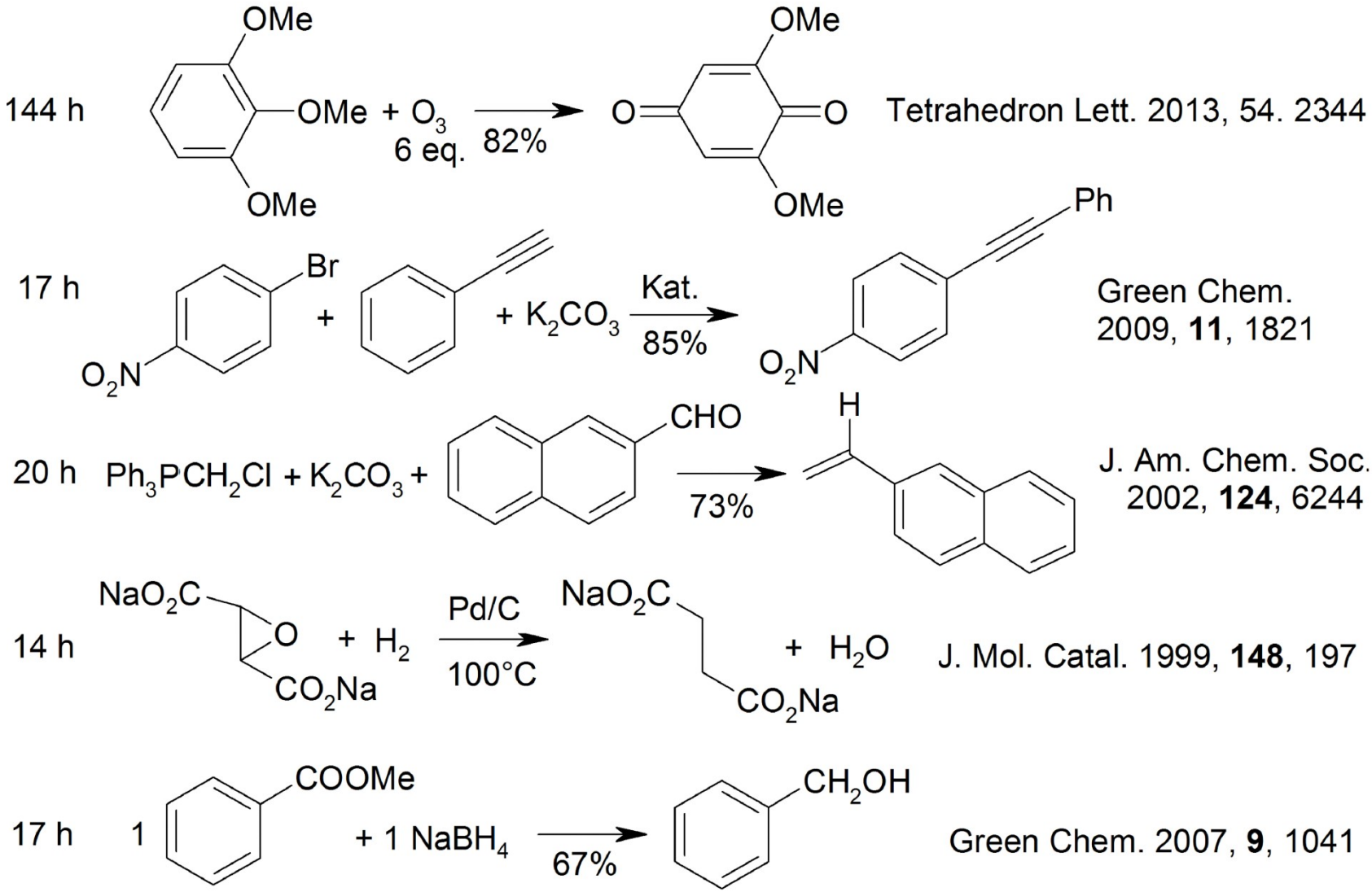
Lab-size ball mill with 20 ml beakers, one of them with temperature control since 1985



Temperature control is state of the art since 1985 (–78 to >100°C); not taking care of temperature is a severe error!

http://kaupp.chemie.uni–oldenburg.de

Undue Milling Times in Shaker/Tumbler Mills without Temperature Control



Avoid liquefaction or clogging by temperature and impact control!

Do not add “a little solvent“. It does not „assist“ but it impedes!

Planetary mill



F

Don‘t use! Poor results!

No temperature control!

Cannot stop a self-sustained process (risk of explosion)

Very long milling times for solid-state reactions due to too-high impact, producing clogging.

This is more of a kneading than milling.

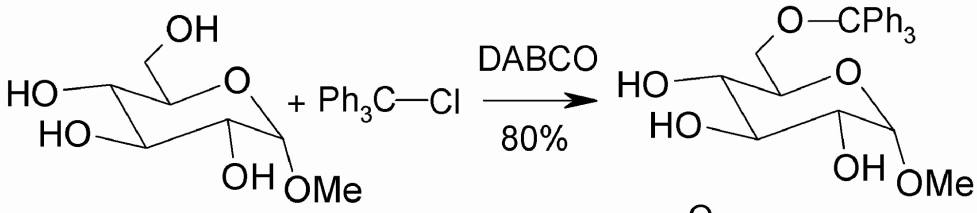
Numerous small balls would require collection of the materials with solvents

No scale-up possibility

Herewith most reported reactions involve melts above eutectics and should be better performed in heated flasks.

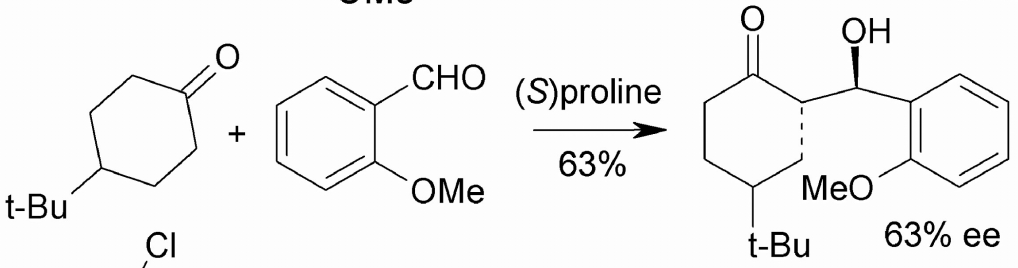
Some Solid-State Milling Times in Planetary Mills

15 h



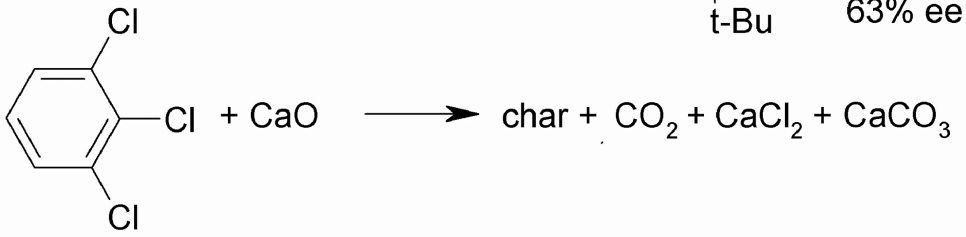
J. Carbohydr. Chem. 2008, **27**, 279

36 h



Chem. a Eur. J. 2007, **13**, 4710

6 h



J. Mater. Sci. 2004, **39**, 5497

40 h C + Si → SiC Appl. Phys. Lett. 1995, **66**, 1903

120 h C + α-Fe_2O_3 → Fe_3O_4 + FeO + CO_2 Mater. Sci. Forum 2004, **449-452**, 257

18 h SiO_2 + La_2O_3 → $SiLa_2O_5$ J. Solid. State Chem. 2006, 179, 522

Try temp. controlled shaker/rotor ball mills without clogging at appropriate impact!

Reason: not solid-state but obviously melts (inorganics with clogging to the wall)

100 L production unit horizontal ball mill, set for inert gas operation



(up to 900 L temperature controlled rotation ball mills are available)

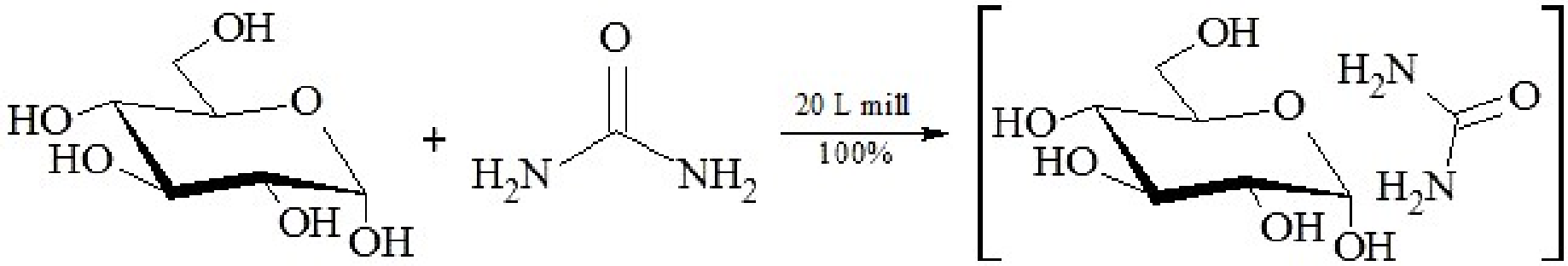
Image of Simoloyer® 100L, courtesy of Zoz Ltd, Wenden, Maltoz Street, Germany.





Images courtesy of Zoz Ltd, Wenden, Maltoz Street, Germany

Large-scale synthesis (2 kg) of a glucose-urea complex (in solution it took half a year until crystals for seeding were obtained)



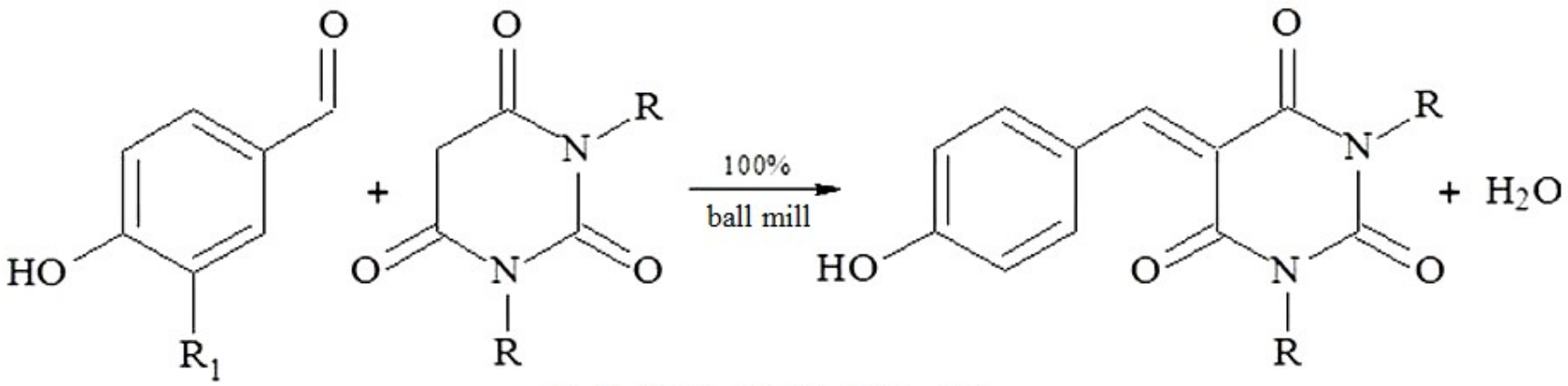
α-D-glucose

urea glucosyl complex

25°C, 2 kg, 100% in 5 min

G. Kaupp, Waste-free large-scale syntheses without auxiliaries, CrystEngComm 2006, 8, 794-804

Knoevenagel condensations at strict temperature control at 2 or 8 liter horizontal rotating ball mills in short times without intermediate melts

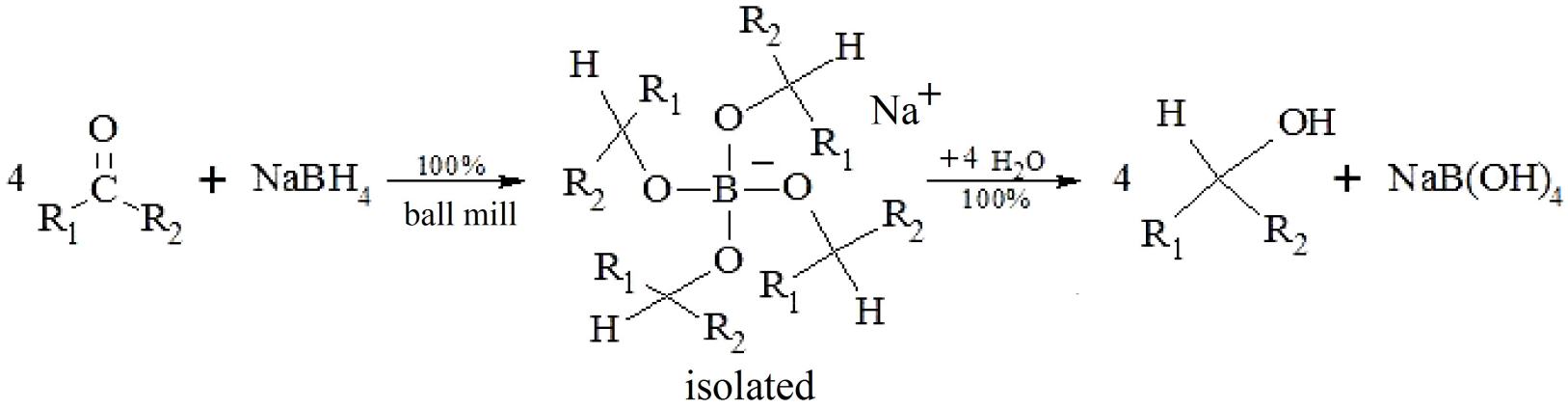


a: R=H (50°C, 30min) (200g, 2L)
b: R=Me (25°C, 5min) (200g, 2L)
c: R=H, R_1=OMe (10°C, 5min) (500g, 8L)

The water of reaction is taken up by the crystals. It can be removed in a vacuum at 80°C

G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

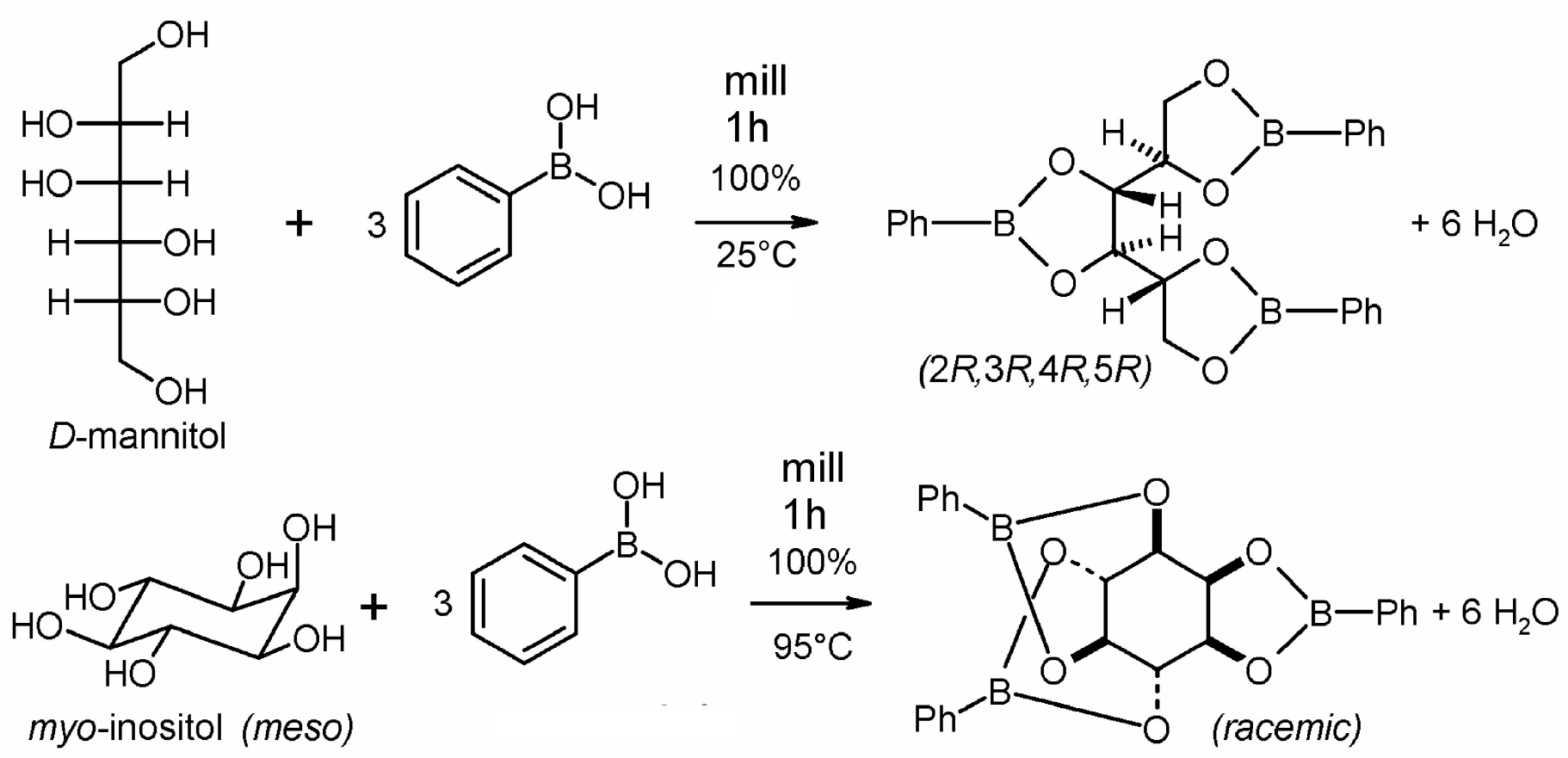
Highly sensitive products toward hydrolysis within 30 min that cannot be obtained differently (34 cases)



All four hydrogens of $NaBH_4$ are used for the reduction; the reactive isolated salt can be reacted with nucleophiles; the hydrolysis with water vapor is an example

Eur. J. Org. Chem., **2009**, 3567-3572

Complete Protection of natural polyols

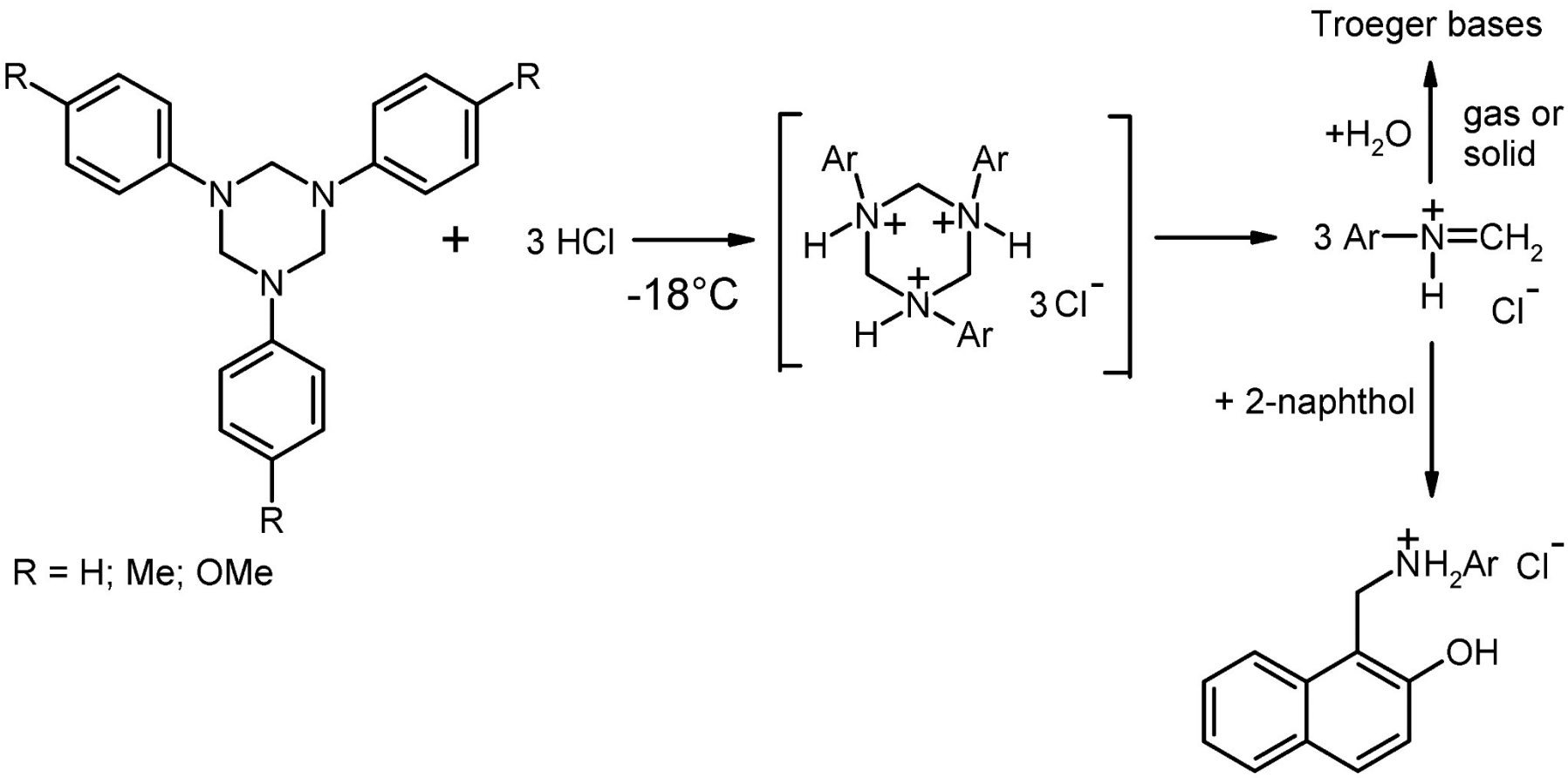


(the crystals of the reactants exhibit proper channels)

We published numerous furthercomplicated cascade reactions in crystals

G. Kaupp, M.R. Naimi-Jamal, V.A. Stepanenko, Chem. Eur. J. **2003**, *9*, 4156-4161

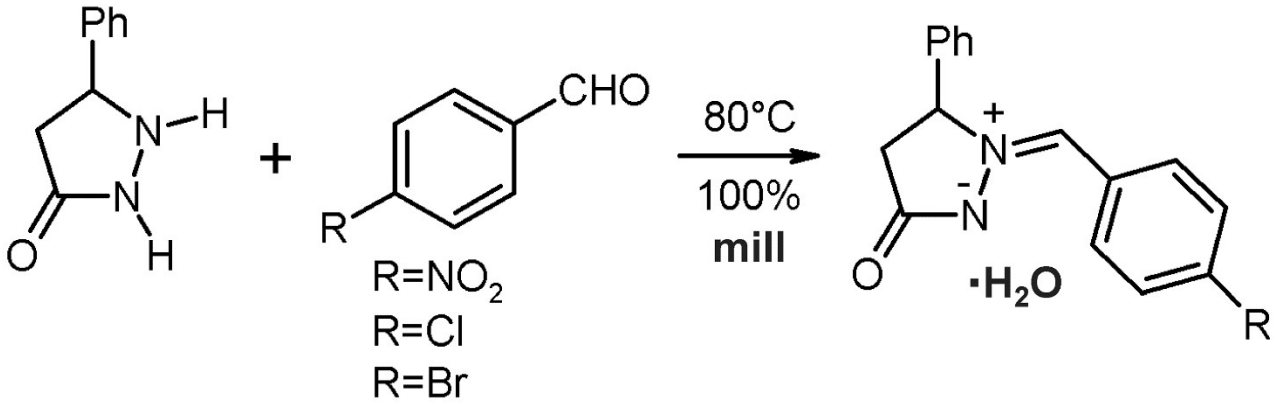
Elusive aminomethylene hydrochlorides are only stable in the solid state (IR: 1733 and 1714 cm^{-1})



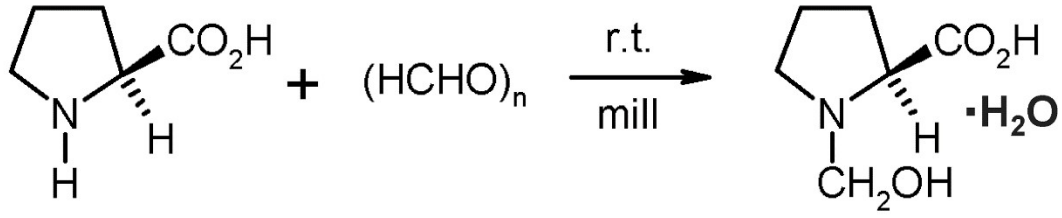
Aminomethylations only in the solid state

J. Prakt. Chem. **2000**, *342*, 269-280

Azomethinimines



N/O-hemiacetals (200g batches)



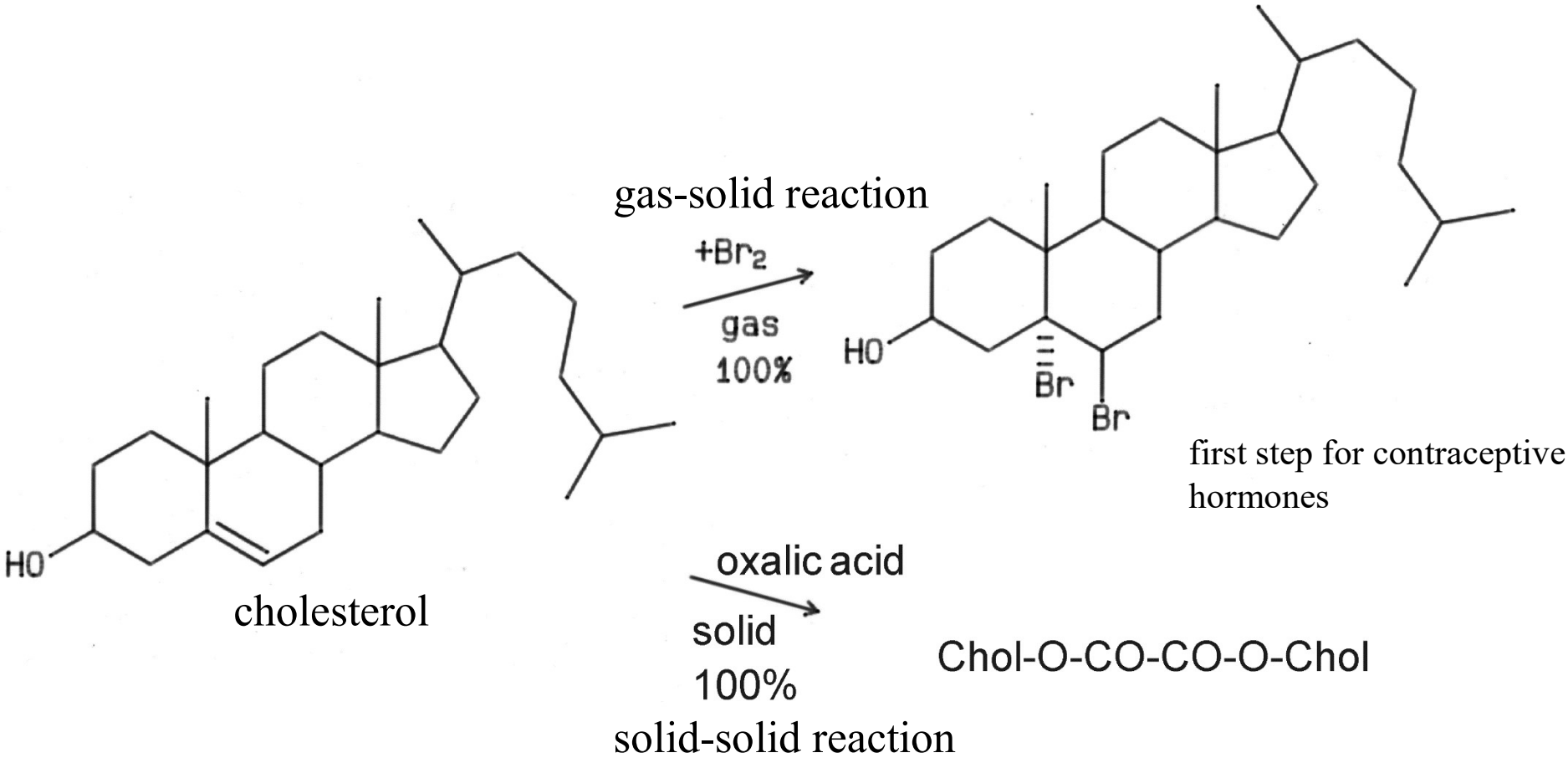
L-proline **(channels)**

similarly imidazole at 0°C **(cleavage plane)**
similarly benzimidazole at room temperature **(channels)**

In the absence of catalysts the crystal water can be evaporated at 80°C without decomposition.

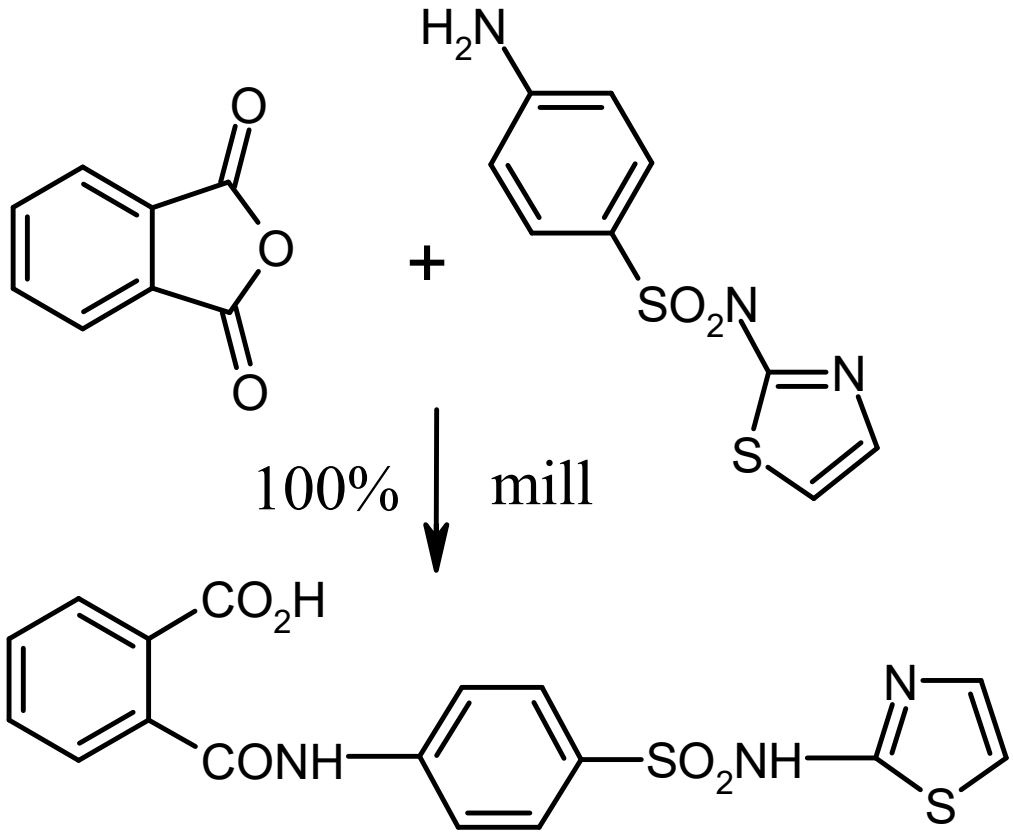
G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

Steroid Reactions



G. Kaupp et al. Angew. Chem. Int. Ed. Engl. 27 (1988) 1511

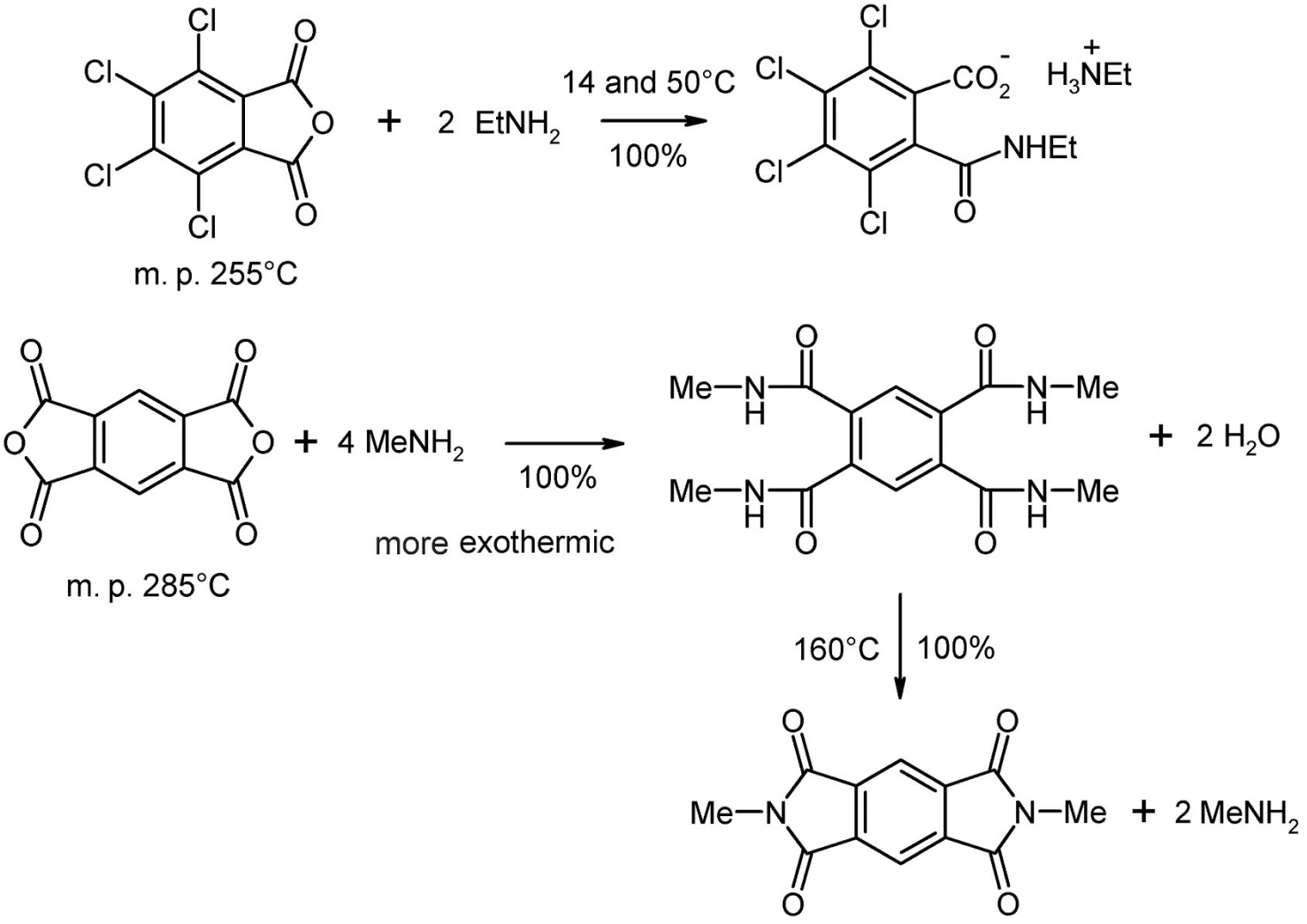
Pharmaceuticals (wasteless 200g autobatches)



The antibacterial sulfonamide Phthalazole (20 min) is obtained free of imide and bisamide byproducts upon stoichiometric milling of the crystalline reactants for the acylation (these byproducts occur upon reaction in melts or solution)

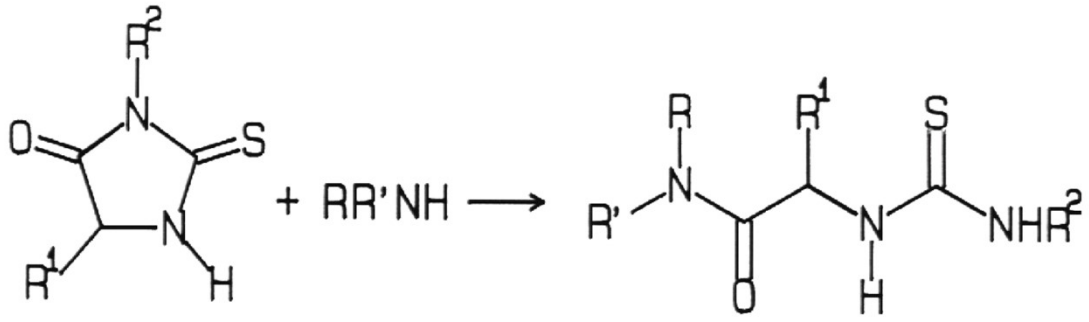
G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

500 g in 2 l flask at a rotovapor with 0.6-0.8 bar amine gas under initial cooling



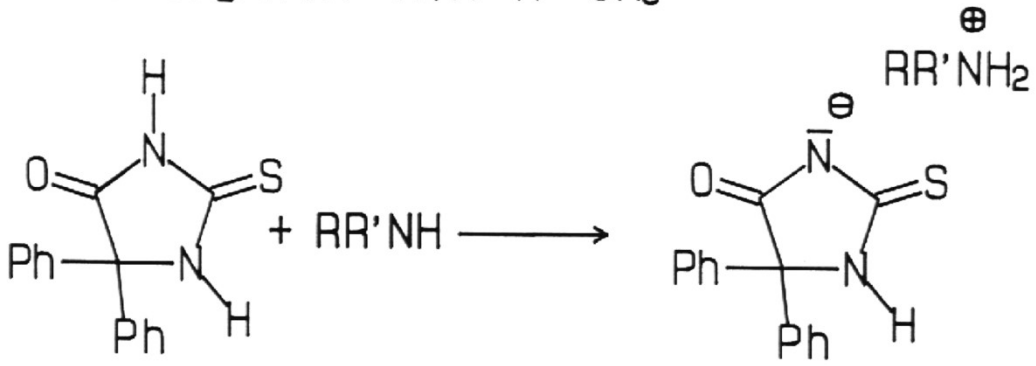
G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

Gas-solid ring opening of thiohydantoins in desiccator runs



a: $R^1=R^2=R=H, R'=CH_3$
b: $R^1=R^2=H, R=R'=CH_3$
c: $R^1=R=H, R^2=Ph, R'=CH_3$
d: $R^1=H, R^2=Ph, R=R'=CH_3$
e: $R^1=CH_2Ph, R^2=R=H, R'=CH_3$
f: $R^1=CH_2Ph, R^2=H, R=R'=CH_3$

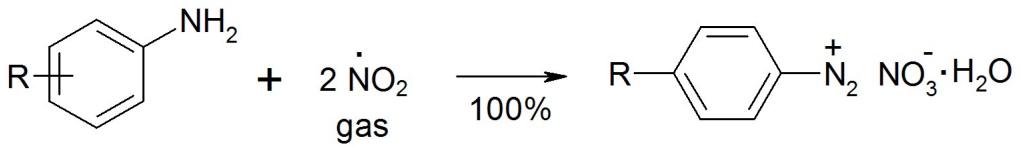
yields: 100%



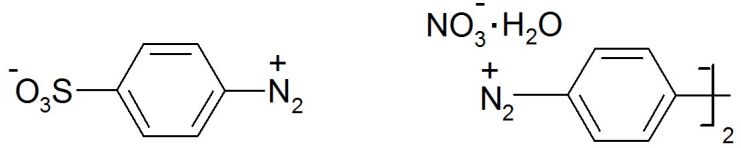
yields: 100%

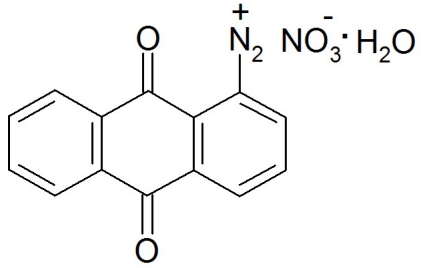
G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

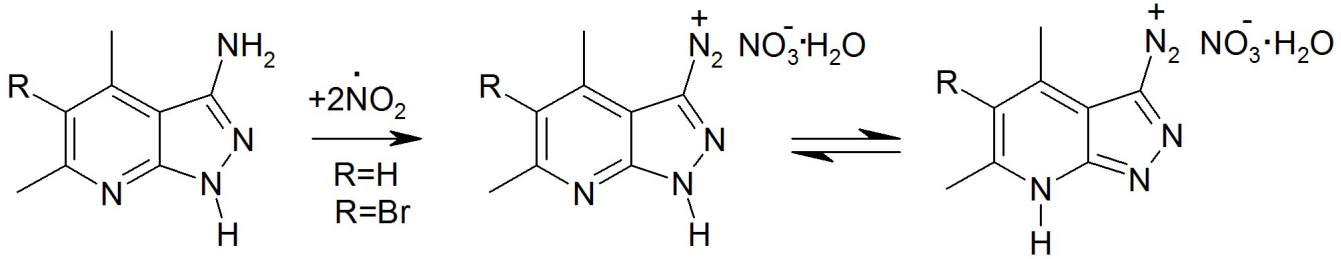
Gas-solid diazotization: 100% yield of solid diazonium nitrates (various reactions with gases; when using for solid-solid syntheses grind cautiously (do not mill, shock sensitive)



R=4-Cl
R=4-Br
R=2-CO_2H
R=4-CO_2H
R=2-SO_3H
R=4-SO_3H
R=4-CN
R=3-NO_2
R=4-NO_2
R=4-OCH_3
R=4-(4-$C_6H_4NH_2$)
R=2,3-(C=OC_6H_4C=O)







G. Kaupp, Organic solid-state reactions with 100% yield, Top. Curr. Chem. **2005**, *254*, 95-183

Conclusions

Molecular solid-state reactions: simple, fast, sustainable; 100% yield without workup all across chemistry (beware of „topochemistry“ or „a little solvent“!) The waste-free reactions would not exist. **Temperature control is indispensable.**

Misleading concepts (topochemistry,“a little solvent“) are hopefully replaced by reading our experimental evidence for a more sustainable future.

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