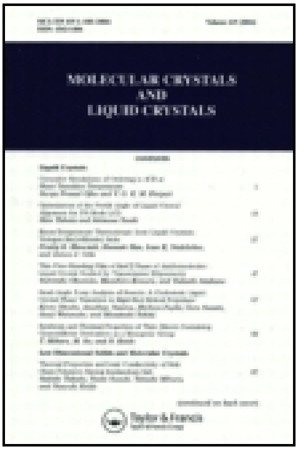

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Gas-Solid Reactions in Organic Synthesis

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GAS-SOLID REACTIONS IN ORGANIC SYNTHESIS

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Abstract Various new branches in the field of preparative scale organic gas-solid reactions (additions, substitutions, eliminations, condensations) are elaborated following a historical review. Polar gases (HBr, HCl, HI, $HSCH_3$) react at 1 bar and temperatures from 40 to -80°C with gram quantities of crystalline N-vinylimides, -amides, -amines, and S-vinylthioethers usually in the Markovnikov orientation, but there is also an exception. The polar gases H_2O and NH_3 transform some of the crystalline addition products and H_2O may be added catalytically to N-vinylphthalimide. All reactions run to high conversion rapidly and several of the highly sensitive products cannot be synthesized in solution. Liquid compounds like N-vinylpyrrolidinone which polymerize in solution crystallize and add polar gases smoothly upon freezing. Polar gases are applied to crystalline chalcone, cinnamic acid, and stilbenes with variable success. Pd-doped crystals are hydrogenated. Contrary to literature reports chlorine and bromine add to crystalline stilbene non-stereospecifically and without significant substitution. The results are discussed with respect to X-ray structures and powder diffraction patterns. Educt and product crystals are not isotypical. Various solid state decompositions are uncovered and the synthetic value is stressed.

HISTORICAL INTRODUCTION

Organic gas-solid reactions have a long history, but they did not become very popular and this is strikingly shown by two citations from review articles[1-2] which cover solid state reactivity:

Progress in studying these reactions is greatly hampered by the lack of interest, on the part of organic chemists, in solid state phenomena

Morawetz (1966)

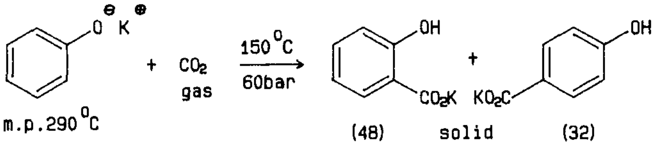
Beaucoup de chimistes organiciens semblent considérer que l'état solide organique est inerte vis-à-vis des gaz

Lamartine (1976)

It is unusual, that organic gas-solid reactions are still not covered by textbooks or laboratory manuals. Therefore it is useful to outline the historical background of reactions which occur when crystals are exposed to gases and thereby give crystalline products without passing through a liquid phase.

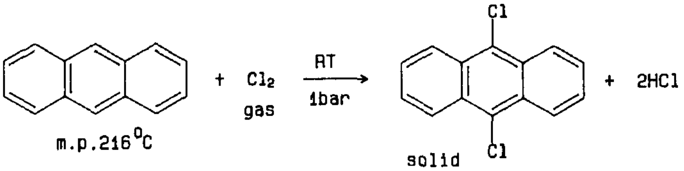
Aromatic substitutions according to Kolbe/Schmitt[3] or Liebermann[4] are known since 1860/1885 or 1870. They have been studied in more detail recently[5].

Additions of Br_2 to crystalline compounds are known since 1863.[6] Enantiomeric crystals of chalcones may react enantioselectively[7] and Br_2 or Cl_2 have been added to stilbenes[8]. A gas-solid ozonolysis was reported in 1976[9] and finally numerous catalytic hydrogenations which use spillover effects[10] should be mentioned here.

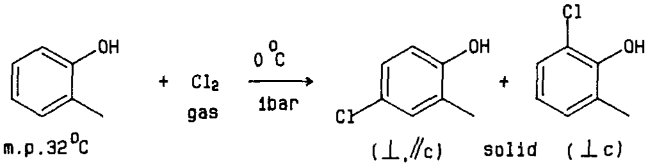


Kolbe/Schmitt (1860/1885)

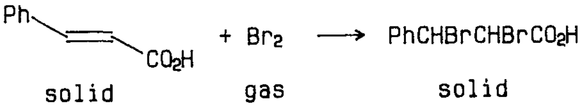
Lamartine (1974)



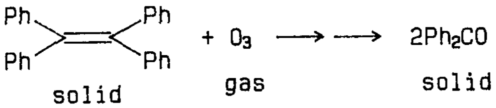
Liebermann (1870)



Lamartine since 1973



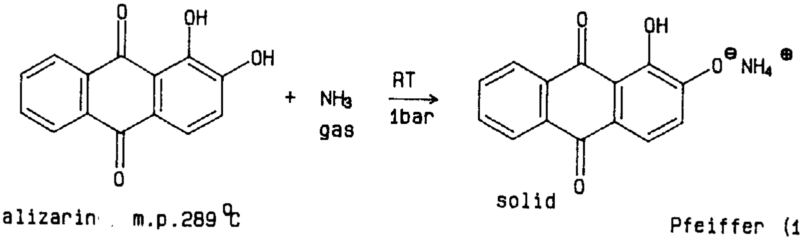
Schmitt (1863)



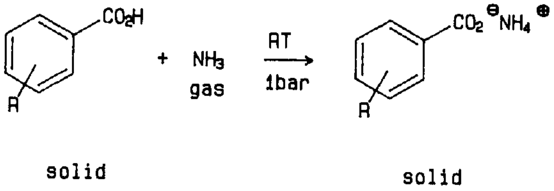
Desvergne, Bouas-Laurant
(1976)

Gas-solid acid/base reactions appear obvious. They work with phenols[11] and with acids[12].

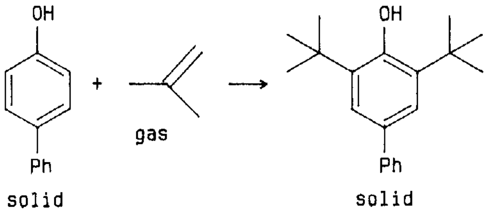
More recent are alkylations of phenols (catalytic)[13] and phenolates[14].



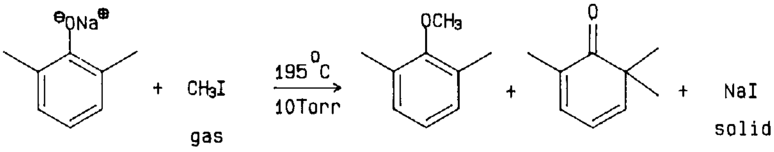
Pfeiffer (1930)



Curtin (1971)



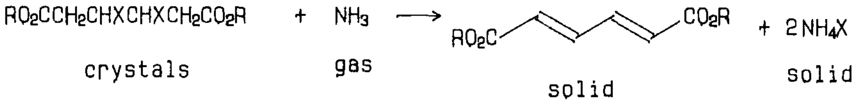
Lamartine (1972)



Curtin (1969)

Also gas-solid eliminations were studied and their stereochemical outcome compared to solution chemistry[15].

$$\underset{\text{crystals}}{NCCH_2CHBrCHBrCH_2CN} + \underset{\text{gas}}{NH_3} \longrightarrow \underset{\text{3 solid stereomers}}{NCCH{=}CH{-}CH{=}CHCN} + \underset{\text{solid}}{NH_4Br}$$



R = CH_3; $PhCH_2$

X = Cl; Br

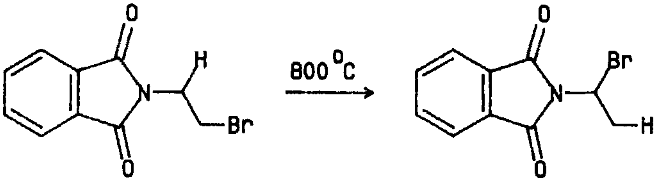
Lahav, Schmidt (1972)

Despite these beneficial facts and even though these gas-solid reactions are run particularly easily and favorably in terms of ecological aspects, it is still difficult to find sponsors for a broader synthetic development of these rather potent reactions. This might be the major reason for the general delay in the synthetic use of their capabilities.

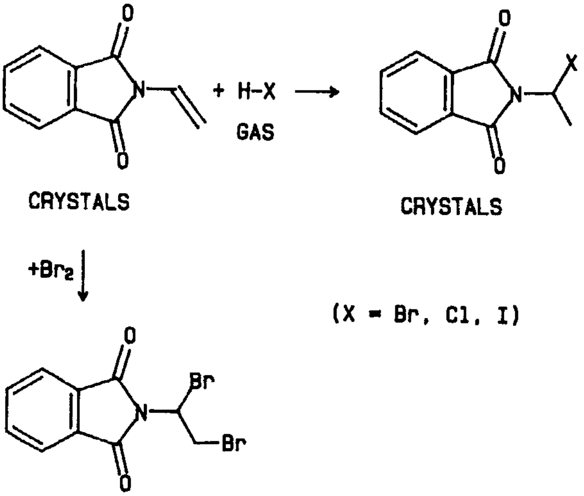
N-VINYLIMIDES, -AMIDES, -AMINES, AND S-VINYLTHIOETHERS

Unpolar gases (Br_2, Cl_2, O_3, H_2/catalyst) have been used previously in organic gas-solid additions. It appeared necessary to find reactive crystals in new compound classes for polar gases and for further reaction types.

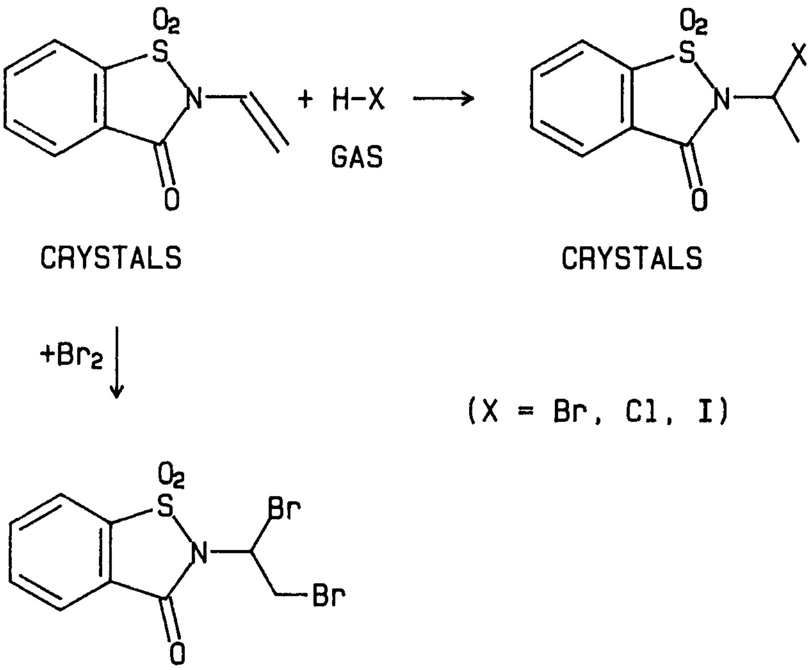
When N-(2-bromoethyl)-phthalimide is heated to 800°C over carbon, the pyrolysate then condensed into a cold trap, and finally warmed-up to room temperature without evaporation of the HBr, N-(1-bromoethyl)-phthalimide is formed (84%) in a [1,2/2,1]-rearrangement reaction[16]. Here gaseous HBr is added very fast and efficiently to crystalline N-vinylphthalimide. On the other hand, N-vinyl-



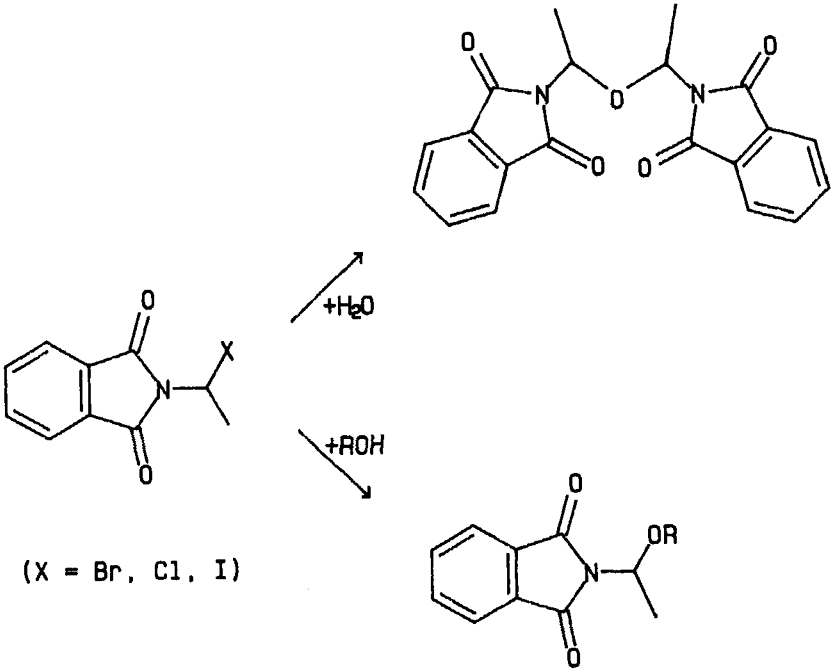
phthalimide is the product (86%), if the HBr is evaporated under vacuum during the warming-up period. These observations can be used for the synthesis of the crystalline 1-bromo-, 1-chloro-, 1-iodo-, and also 1,2-dibromoethylphthalimides as powdered N-vinylphthalimide reacts almost quantitatively on a gram scale with the corresponding gases at 1 bar for half an hour at room temperature (16 h for Br_2). The products are very sensitive to hydrolysis. Solid state polymerisation is suppressed. Similarly, crystalline N-vinylsaccharin reacts with the same gases on



a gram scale, to give the corresponding products very efficiently. Highly reactive and highly sensitive products are formed very easily on a preparative scale. They may

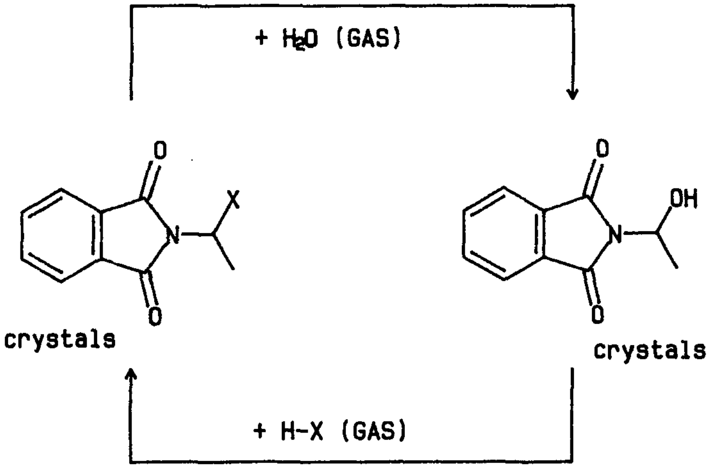


be used for substitution reactions as shown here for alcohols and limited quantities of water in solutions[16]. The alcohols studied are methanol, isopropanol, 2,2,2-trifluoroethanol, (S)-ß-citronellol, and ergosterol. Phenols (e.g. eugenol, thymol, carvacrol) yield the corresponding N/O-acetals. Also various aminals with corresponding structures have been prepared by reacting amides (e.g. caprolactam) or heterocyclic amines (e.g. 2-,4-aminopyridine, cytosine, adenine) with the bromides. The saccharine derivatives are more sensitive to acid hydrolysis than the phthalimide ones.

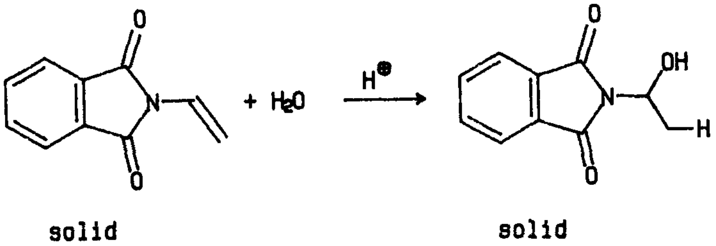


(X = Br, Cl, I)

Our system is even more profitable. It reveals the first aliphatic gas-solid substitutions. If gaseous water is applied to the bromide, chloride, or iodide in a flow reactor, stable crystals of the hemiacetal are obtained quantitatively. This hemiacetal has been previously postulated as to be an extremely labile, presumably undetectable intermediate[17]. However, it turns out to be stable enough for recording spectra in solutions. Interestingly its crystals react with HCl, HBr, and HI by expelling water and reforming the initial halides. Similarly, an acid catalyzed addition of gaseous water to N-vinylphthalimide works equally well. On a gram scale N-vinylphthalimide



crystals form quantitatively the hemiacetal within 3 hours, if some per cent of its HBr-adduct had been added to it[16].



This, of course, constitutes a new solid state catalytic technique.

Prior to proceeding with further synthetic applications, the X-ray structure of N-vinylphthalimide[18] was determined. All angles and distances were found to be quite normal.

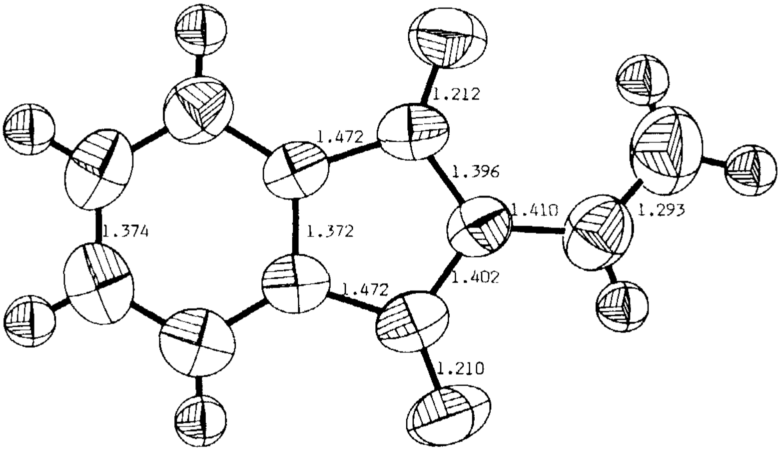


FIGURE 1. ORTEP drawing of N-vinylphthalimide with bond lengths (Å) and 50% probability plots for thermal ellipsoids.

The molecular packing is indicated in the stereoscopic drawing. It shows interlocked parallel layers and some compression of the side chain, but no holes and no sufficiently large channels for accomodation of the gases at regular sites of the lattice. Thus, the X-ray structure does not give a hint to gas-solid reactivity of this compound. This lack of correlation is substantiated even better by X-ray powder diffraction diagrams[18] of N-vinylphthalimide and N-(1-bromoethyl)-phthalimide. They lack any similarity and thus show, that the educt and product crystals are <u>not isotypical</u>. Furthermore, there is additivity of the patterns at incomplete conversions. Undoubted-

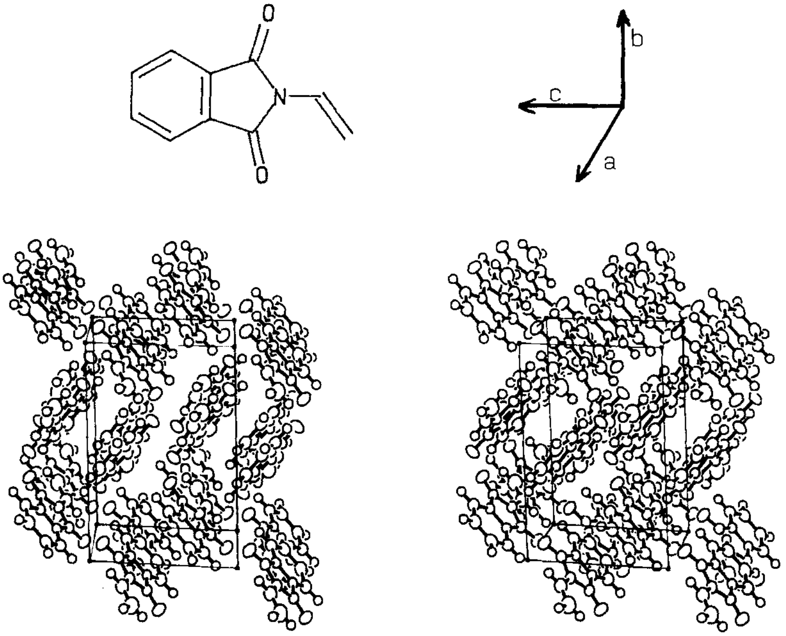
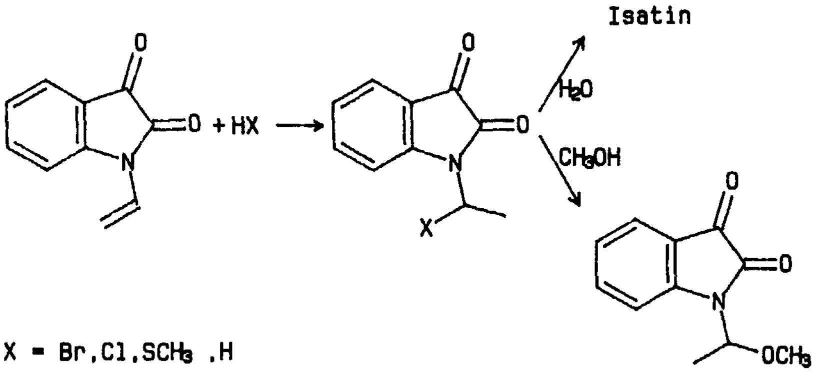
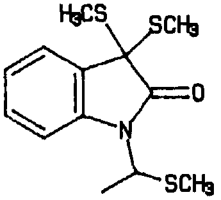


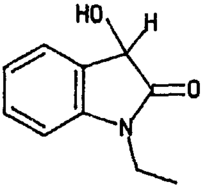
FIGURE 2. Stereoscopic view of the molecular packing for N-vinylphthalimide.

ly, the crystal structure remains the salient feature for the gas-solid reactivity, but we cannot easily derive it from the idealizing X-ray results and thus must proceed empirically.

N-vinylisatin crystals add the gases HBr, HCl, $HSCH_3$ in the usual way[19] to give the N-(1-X-ethyl) -isatins at -60(2h), -80(2h), and 20°C(21h). Remarkably even $HSCH_3$ adds in the Markovnikov orientation, as do the much stronger acids (in solution thiols tend to add anti-Markovnikov via radical chain mechanisms).[20] A second product (ratio 3:2) arises via condensation of $HSCH_3$ with the carbonyl group next to the benzene ring. This appears to be the







first organic gas-solid condensation. Again, the reactions run to completion without intermediate melting. Highly interesting is the gas-solid hydrogenation of N-vinylisatin to give both N-ethylisatin and N-ethyldioxindol (45°C, 2 d, 1 bar, 74% and 16%, resp.). Doping of the crystals with traces of Pd is necessary for the reaction to occur, which remains present in the preparation[21] even after two crystallizations, but is absent after sublimation. The Pd is uniformely distributed within the crystals, as far as a microscopic inspection can tell. This catalysis technique is totally different from the spillover-effect of Lamartine[10].

The X-ray structure of N-vinylisatin[18] again shows no striking peculiarities in terms of bond lengths and bond angles. Both crystallographic different species give the same parameters within two standard deviations.

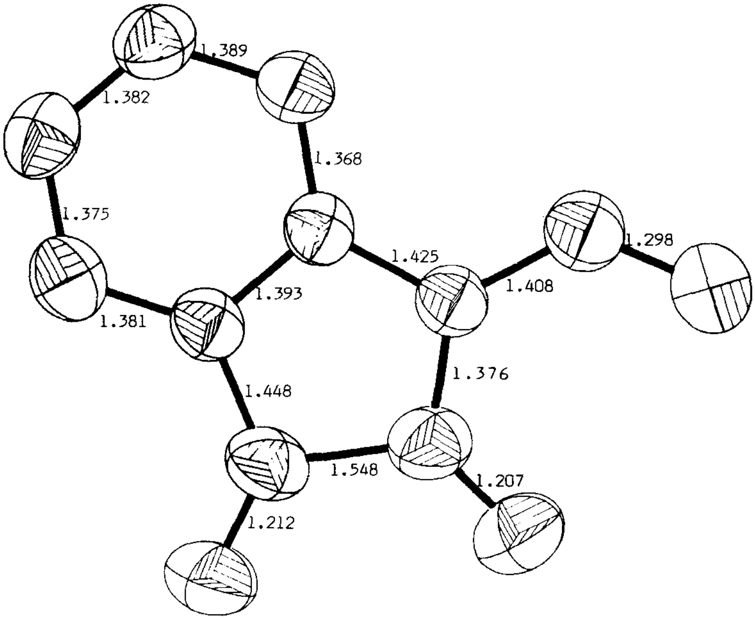


FIGURE 3. ORTEP drawing of N-vinylisatin with bond lengths (Å) and 50% probability plots for thermal ellipsoids.

Again, the packing pattern does not show holes or sufficiently large channels for the accommodation of the reactive gases. The smallest diameter found from nitrogen center to nitrogen center being 3.2 Å. Thus, again there is no X-ray structure/reactivity correlation and this is again fully substantiated by X-ray powder diagrams which show that the crystals of N-vinylisatin are <u>not isotypical</u> with those of N-ethyl- or N-(1-bromoethyl)-isatin at various amounts of transformation. The new crystals assume immediately the same crystal modification as is found after purification and recrystallization.

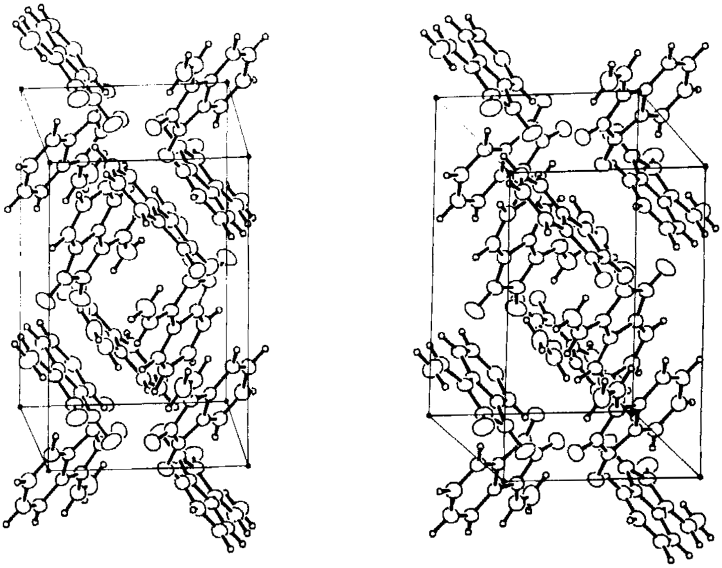
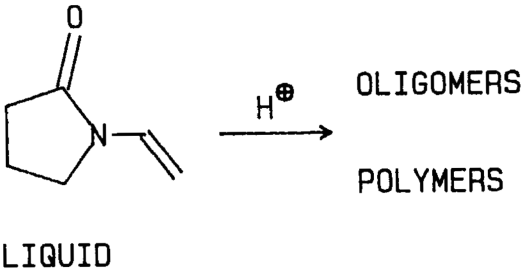
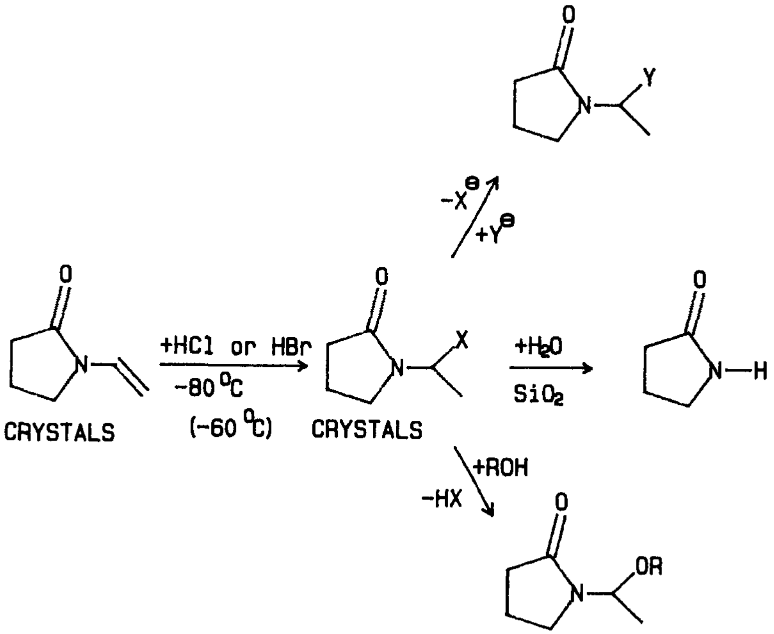


FIGURE 4. Stereoscopic view of the molecular packing for N-vinylisatin.

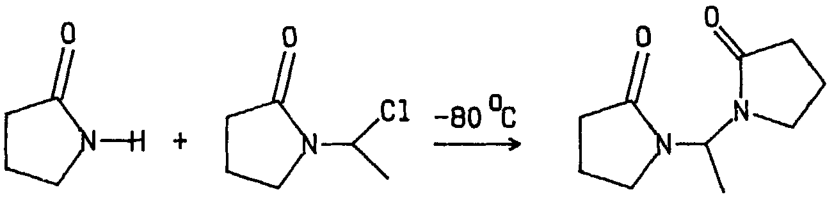
A major benefit of organic gas-solid reactions is shown by transformations of N-vinylpyrrolidinone.[19] This compound polymerizes very rapidly as a liquid or in solution



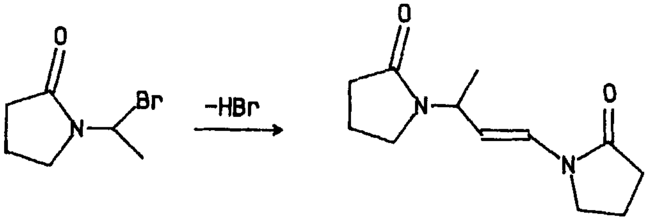
with traces of acids present, so the use of gas-solid techniques is unavoidable, if its monomeric adduct with HCl or HBr are to be synthesized. Upon freezing below -20°C liquid N-vinylpyrrolidinone crystallizes. Several grams of these crystals react rapidly with HCl or HBr (1 bar, 2 h) at rather low temperatures and thereby quantitatively give the crystalline N-(1-halogenoethyl)-pyrrolidinones.



These adducts are by far too reactive to be handled at room temperature. Therefore, stable derivatives have to be prepared at low temperatures. The high versatility of their substitutions is shown by the reaction with pyrrolidinone, which reacts at -80 or -50°C in CH_2Cl_2 to



give 68% of the symmetric product. Upon warming the bromide to room temperature, it does not melt but expels HBr and forms the substituted enamide in a complicated solid state reaction.



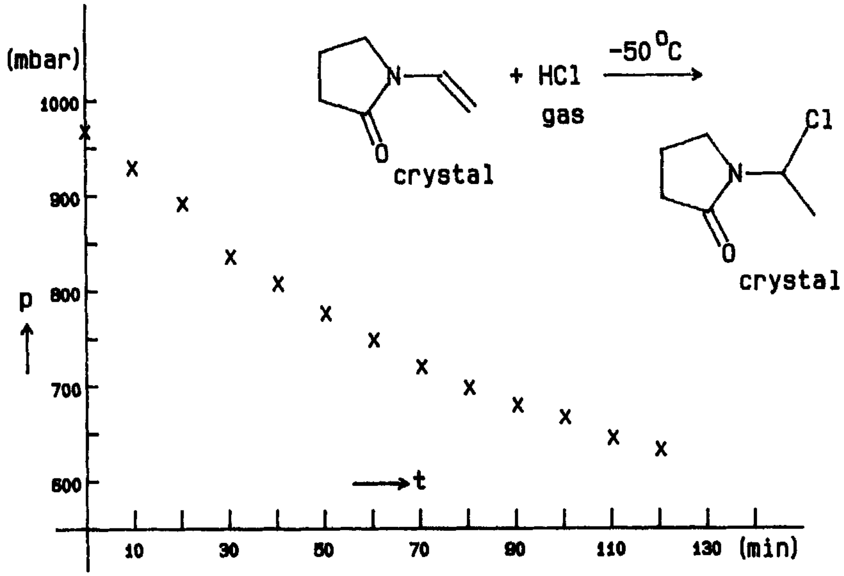
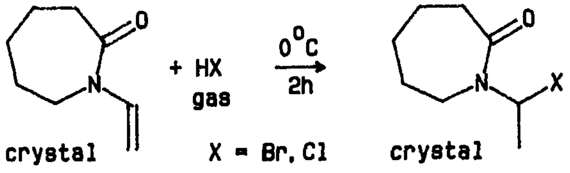
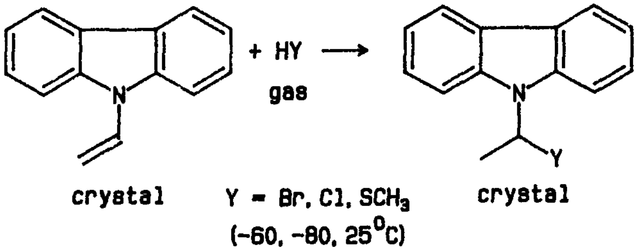


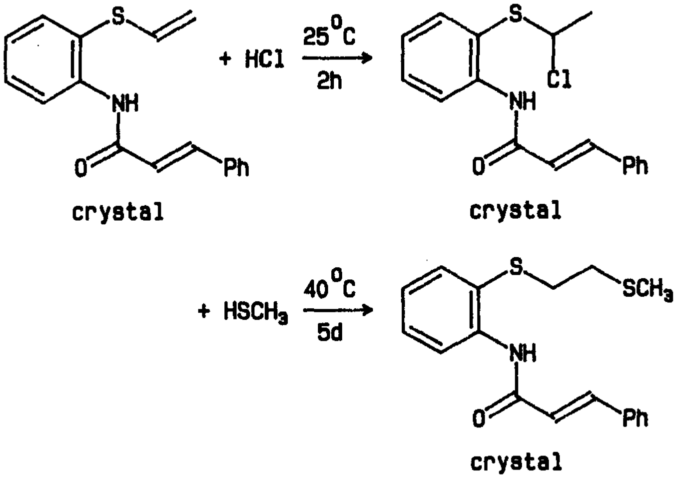
FIGURE 5. Gas uptake for HCl and N-vinylpyrrolidinone at -50°C as shown by decrease in pressure.

In the solid-gas reactions of N-vinylpyrrolidinone the crystals are very compact (not powdered as usual). It is interesting to note that the gas uptake is rather smooth and does not show any induction period (Figure 5).

Further crystalline enamides, enamines and also S-vinylthioethers react with HCl and $HSCH_3$ gas. Some of them are shown here in order to demonstrate the high syn-







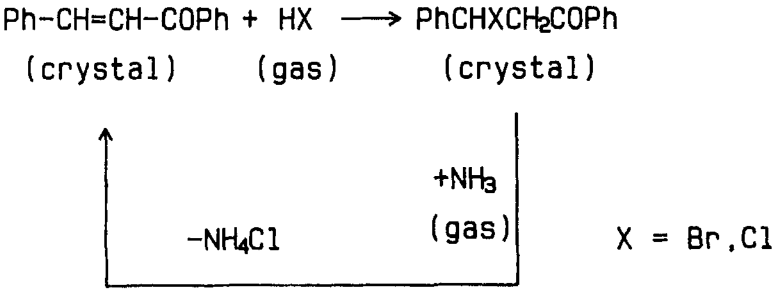
thetic potential. Again all reactions are run at 1 bar initial pressure. As usual Markovnikov orientation is observed exclusively. However, the S-vinylthioether to $HSCH_3$ addition constitutes the first example of a gas-solid addition with anti-Markovnikov orientation. None of the isomeric product is observed.

It is obvious that crystalline vinylic ethers and sulfones should be included in further studies and that diastereomeric selectivities with chiral substrates should be investigated as well.

CHALCONE AND CINNAMIC ACID

As the additions of polar gases to crystals of vinylic compounds worked so successfully, and in order to substantiate early reports,[22] the studies were extended to chalcone and cinnamic acid (α-modification).

Both, HCl and HBr are added by crystalline chalcone[19] at room temperature (1 bar) within one week to an extent of 72 and 88%, resp. The crystalline products are higher melting than the starting material. The regioselectivity of the addition does not differ from that in solution (CH_2Cl_2). In this system the addition of Br_2 by the crystals

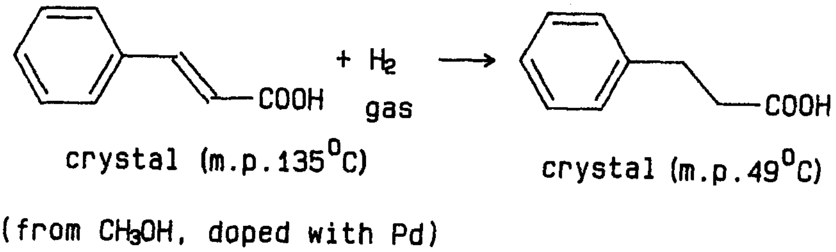


(cf. Ref.[7]) is considerably faster than that of the polar gases. X-ray powder diagrams again show that the educt and product crystals are not isotypical.

Interestingly, the application of ammonia gas to these crystalline HX-adducts does not yield any substitution products but gives exclusively gas-solid elimination to form the starting chalcone.

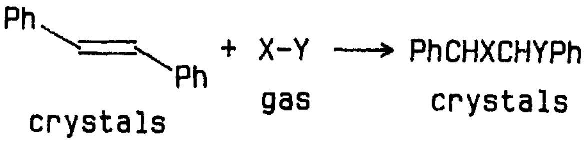
Cinnamic acid (α-modification) does not add HCl or HBr under our conditions (1 bar, 25°C, 5 d), whereas its addition of Br_2 is one of the oldest organic gas-solid reactions.[6]

Cinnamic acid includes some Pd when crystallized from methanol which is 10^{-4} molar in $Na_2[PdCl_4]$. The doped crystals again can be hydrogenated (30°C, 1 bar, 6 d, 48%). This once more differs from the spillover effect hydrogenations,[10] because the traces of Pd are uniformely distributed in the crystals. The overall solubility of H_2 in undoped cinnamic acid (air-dry) is determined at 25°C to be 0.3 - 0.45 mol%.



STILBENES

The crystals of trans-stilbene are highly disordered.[23] They add gaseous Cl_2 and Br_2[8], but we were not able to add HCl, HBr, or HI to them (-60 to 20°C, 1 bar, 1 d). Highly interesting are the literature reports of exclusive



X-Y = HCl; HBr; HI: no reaction

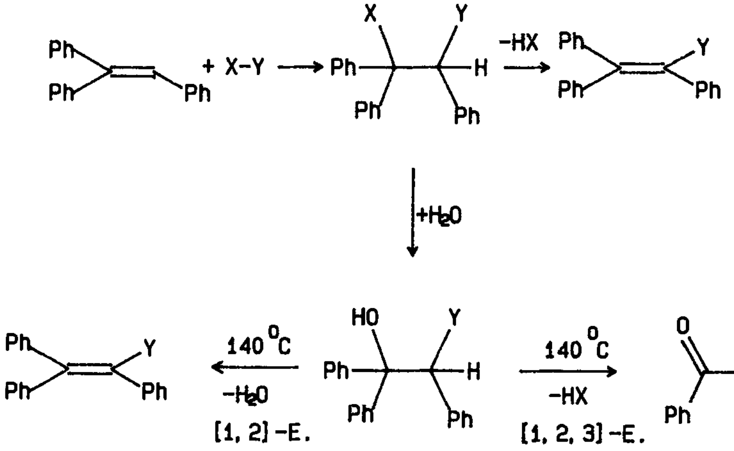
X-Y = Br_2 : meso/dl = 62: 38 (in CS_2 84: 16)

X-Y = Cl_2 : meso/dl = 39: 61 (in CH_2Cl_2 40: 60)

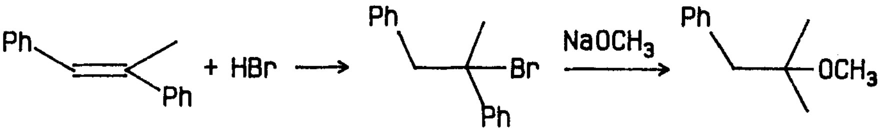
HCl + Cl_2 : meso/dl = 15: 85

cis-addition of Cl_2 (single crystals, all faces, 30% conversion)[24] and of complete and specific substitution of all *p*-positions in solid-gas brominations of various stilbenes.[8] Our results differ completely (1 g, 6 h, 1 bar, 25°C, 40%): There are only traces of products with more than two halogen atoms; the *meso*- and *dl*-adducts are formed in the ratios given.[19] These do not differ considerably from the solution results. Thus, Br_2 favours the *trans*- and Cl_2 favours the *cis*-addition to *trans*-stilbene. A multigas effect is observed when a 1:1-mixture of Cl_2 and HCl acts on *trans*-stilbene: The *cis*-selectivity increases to 85% even though HCl alone is not reactive. The reasons for this still have to be elucidated.

Also in the case of crystalline triphenylethylene there is no addition of HCl, HBr, or HI.[19] However, Br_2 and Cl_2 are efficiently added. Even here there are only traces of products which contain more than two chlorine or bromine atoms, and this contrasts with previous literature reports.[8] The initial products are solid. They eliminate HBr or (less completely) HCl in solid state decompositions at room temperature. Upon prompt hydrolysis the chloro(bromo)hydrine is obtained which decomposes at higher temperatures, as indicated, in terms of competing [1,2]- and [1,2,3]-eliminations[25].



It must be the crystal structure of α-methylstilbene that permits its regiospecific gas-solid addition of HBr (0.3 g, 1 bar, 0°C, 21 h, 94%). Also trans-4-methoxystilbene



adds gaseous HBr at 0°C (orientation not known yet). Both of these reactions do not occur at -50°C. These results show that it is not the thermodynamics which prevents the gas-solid additions of HX to stilbene and triphenylethylene to occur. Unfortunately the temperatures cannot be increased here, because the product melting points are low. The underlying effects deserve more detailed studies.

CONCLUSION

Organic gas-solid reactions are easily performed. These versatile tools for preparative chemistry owe enhanced consideration because of their particular advantages (new, labile or hydrolysing products, suppression of polymerization, no solvents, very simple experimental techniques, regioselectivities). New systems and further reactive gases will have to be applied and further reaction types added to the increasing field.

Somehow the crystal structure determines which crystalline materials will be reactive and which gases will react (thermodynamics permitting). However, as there is no obvious way to correlate X-ray structures with gas-solid reactivity, empirical work, to collect data on a preparative scale still has to be done with different modifications of reactive compounds and, perhaps, with the inclusion of expitaxial effects.[26]

There are still many mechanistic questions open for investigation. How are the new phases formed? Are there microscopic liquid phases during the reaction which allow crystal transformations or do enantioselective reactions with enantiomeric crystals[7] or upon single face exposure[27] prove just the opposite? The search for enantio- or diastereospecific gas-solid reactions on a preparative scale certainly remains one of the major goals in this field which appears to be a highly promising one.

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