

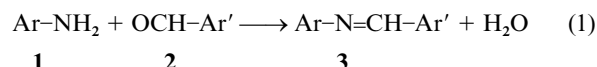
Jens Schmeyers,^a Fumio Toda,^{*a} Juergen Boy^b and Gerd Kaupp^{*b}

^a Department of Chemistry, Ehime University Matsuyama, Japan

^b Fachbereich 9 – Org. Chem. I – University of Oldenburg, Germany

Twenty preparatively useful azomethines have been quantitatively (100% yield at 100% conversion) obtained as hydrates by grinding together solid anilines with solid benzaldehydes without passing through liquid phases. Unlike (acid catalyzed) azomethine syntheses in solution, the solid–solid condensations proceed ‘waste-free’. The solid-state mechanisms have been elucidated by atomic force microscopy (AFM) and in part by scanning near-field optical microscopy (SNOM) in three cases. The results indicate long distance migration of the aldehydes into the lattice of the aniline derivatives. Stumpy protrusions are formed at the direct points of contact but also close distance sublimation (100 nm range) is successful in the case of *p*-chlorobenzaldehyde and *p*-nitroaniline. Long-range flow of 4-hydroxybenzaldehyde molecules on its (010)-face into contacting crystals of *p*-toluidine or *p*-anisidine occurs along two different cleavage planes. Steep hills and valleys are left behind. The molecular migrations through the sites of contact are interpreted in terms of crystal packing. The ease of these solid–solid condensation reactions relies on the crystal packing.

Azomethines are important building blocks in enantioselective oxidations (chiral oxaziridines),¹ cycloadditions² and cyclizations.³ The synthesis of azomethines **3** from anilines **1** and aromatic aldehydes **2** [reaction (1)] is usually carried out in solution by acid catalysis and removal of the water formed in the reaction. Yields are rarely reported but may reach 80–95% after work-up including neutralization and crystallization. The recent observation that gaseous carbonyl compounds condense quantitatively with carbonyl reagents, such as 2,4-dinitrophenylhydrazine, without acid catalysts, if liquid phases are avoided,⁴ suggests improvements in azomethine syntheses using solid-to-solid reactions⁵ of **2** and **3**. We report on the quantitative preparation of 20 compounds of type **3** by grinding together stoichiometric amounts of **1** and **2** in the 10 mmol range. The solid-state mechanism was investigated by AFM in three selected systems because little was known about the reasons for the success of solid–solid chemical reactions, while submicroscopic investigations of reacting crystal surfaces had been successful in the elucidation of gas–solid reactions.⁴



When **1** and **2** are ground together at room temperature, the reaction starts immediately usually with gentle heat production but without melting because azomethines have high melting points (Table 1). Indications of softening for some seconds followed by immediate hardening were visually observed only in syntheses with vanillin (systems **e**, **j**, **t** in Table 1).

Initial phase diagrams with four components are rather complicated and cannot be studied in great detail because of rapid chemical reaction. However, DSC measurements of *p*-toluidine + *p*-hydroxybenzaldehyde (system **d**, no grinding, 20 °C min⁻¹) showed melting peaks at 48.6, 117 and 216 °C in addition to some minor peaks (60, 140, 185 °C) and even in the unfavourable 9:1 ratio of **1** and **2**, the mixture does not start to melt below 37 °C. The water produced in the reaction is fully absorbed by the crystals of **3**, but it may be removed in a vacuum at 80 °C. However, the reactions are not disturbed by

Table 1 Melting points of quantitatively formed azomethines **3** by solid–solid reaction of **1** and **2** at room temperature

	1 : Ar (Mp/°C)	2 : Ar' (Mp/°C)	Mp of 3 /°C (Lit. mp/°C)	Ref.
a	4-MeC ₆ H ₄ (44–46)	4-ClC ₆ H ₄ (47–50)	125 (126)	6
b		4-BrC ₆ H ₄ (55–58)	136	
c		4-NO ₂ C ₆ H ₄ (105–108)	125 (124.5)	7
d		4-HOC ₆ H ₄ (117–119)	221 (215)	8
e		4-HO, 3-MeOC ₆ H ₃ (81–83)	116 (117)	9
f	4-MeOC ₆ H ₄ (57–60)	4-ClC ₆ H ₄ (47–50)	124–125 (123)	10
g		4-BrC ₆ H ₄ (55–58)	148	10
h		4-NO ₂ C ₆ H ₄ (105–108) ^a	134 (134–136)	11
i		4-HOC ₆ H ₄ (117–119)	210 (210–211)	12
j		4-HO, 3-MeOC ₆ H ₃ (81–83)	132 (133.5)	13
k	4-NO ₂ C ₆ H ₄ (148–151)	4-ClC ₆ H ₄ (47–50)	168 (170)	14
l	4-ClC ₆ H ₄ (68–71)	4-HOC ₆ H ₄ (117–119)	187 (184–185)	15
m	4-BrC ₆ H ₄ (62–64)	4-HOC ₆ H ₄ (117–119)	192 (193–194)	15
n	4-HOC ₆ H ₄ (188–190)	4-ClC ₆ H ₄ (47–50)	181 (179)	14,16
o	4-(4-H ₂ NC ₆ H ₄)C ₆ H ₄ (125–128)	4-ClC ₆ H ₄ (47–50)	262–263 (264)	17
p	1-Naphthyl (48–50)	4-ClC ₆ H ₄ (47–50)	103–104 (102.5)	18
q		4-BrC ₆ H ₄ (55–58)	92	
r		4-NO ₂ C ₆ H ₄ (105–108)	165 (161–162)	19
s		4-HOC ₆ H ₄ (117–119)	190 (191–191.5)	15
t		4-HO, 3-MeOC ₆ H ₃ (81–83)	110 (107–108)	20

^a Reaction at 50 °C for 24 h or 30 min at room temperature in a ball mill (see Note in Experimental).

this water even in the three cases of intermediate wetting. Thermal gravimetric analysis (TGA) measurements of the unvacuated products **3d,j,l-n,t** showed losses of 1 mol water between 80 and 90 °C. The melting points of the products (without work-up) correspond to the known literature values (Table 1). The solid hydrates of the products **3** have now acquired increased synthetic value, due to the fact that their solid–solid synthesis avoids waste by not requiring any work-up procedures if pure **1** and **2** are used as the starting materials.

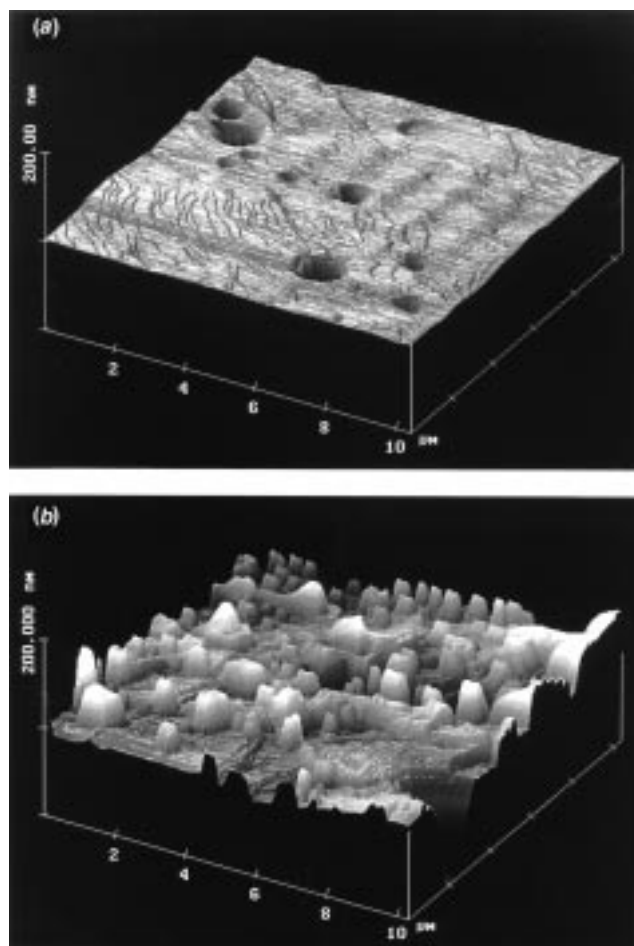


Fig. 1 AFM topographies of *p*-nitroaniline on (100); (a) pure and (b) after reaction with a tiny crystal (*ca.* 0.3 mg) of *p*-chlorobenzaldehyde, which had completely disappeared after 4 h, in the previously covered area. The sites of the same crystal species before and after reaction are not identical, but it has a fairly uniform appearance throughout.

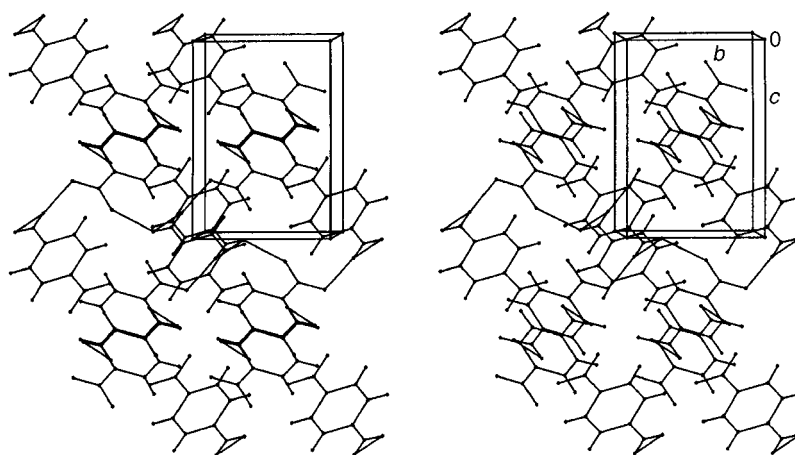


Fig. 2 Stereoscopic view of the molecular packing of *p*-nitroaniline ($P2_1/n$) on (100); the amino groups are traced as triangles to distinguish them from the nitro groups; all short (N)H–O(N) contacts (2.226 and 2.447 Å) are drawn in order to indicate the two three-dimensional strings of H-bonding within the chosen segment of the crystal model (of course, all molecules are involved in two strings at either side)

Larger runs could be performed in ball mills under heat control.

Little is known about the mechanisms of these solid–solid reactions.^{21,22} In the reactions of **1** and **2** it turns out that only the aldehydes **2** move into the lattice of the amines **1** in all the cases studied. Thus, if a small crystal of *p*-chlorobenzaldehyde is placed on a larger crystal of *p*-toluidine (system **a**) or *p*-anisidine (system **f**) the latter turns yellow but only in the covered area.

In this case both of the reacting molecules are of a similar size and the aldehyde component **2** has to move into the crystal lattice of the aniline derivative **1**. This feature resembles the solid-state formation of charge-transfer complexes²³ and the solid–solid formation of cocrystals,²⁴ processes that could not previously be theoretically interpreted.²⁴ However, the success of supermicroscopic techniques which have indicated long-range molecular migrations rather than minimal movements in gas–solid and various solid–solid reactions,^{4,21,22} suggests a detailed AFM study of the systems **d,i**, and **k**. These systems were chosen with the aim of detecting molecular movements both on an aniline derivative (which accepts migrating molecules) and on a benzaldehyde derivative (which loses migrating molecules) in relation to known crystal packings. A small crystal of *p*-chlorobenzaldehyde [$P2_1/a$,²⁵ lath-shaped crystals with rough (001) face] was laid down on the (100) surface of a single crystal of *p*-nitroaniline (system **k**; the initial roughness was $R_{ms} = 11.1$ nm). After several hours the aldehyde crystal disappeared completely both by reaction and by sublimation (control experiments showed that 0.3–0.4 mg of *p*-chlorobenzaldehyde volatilized within 3–4 h in air at 22 °C). This behaviour allowed AFM measurements to be made in the region that was initially covered by **2**. Fig. 1 shows the typical initial surface (exhibiting some craters with 100–240 nm depth) and the topography after consumption of the *p*-chlorobenzaldehyde. It is seen in Fig. 1(b) that a flat overall surface prevails with craters remaining and with numerous stumpy protrusions of 10–40 nm height and 10–20° steepness. It must be concluded that no uniform close contact is achieved between the two surfaces and this fact is further confirmed by AFM measurements on the (001) face of *p*-chlorobenzaldehyde. These reveal the occurrence of edged protrusions that are typically 1 μm wide and 100–300 nm high. Of course, such features keep on changing in shape due to the rather rapid sublimation. Clearly, the ‘stumps’ occur at the points of direct solid–solid contacts where the migrating molecules can pass through the phase boundary. Undoubtedly, the volume must expand at the sites of reaction as the product molecules **3** are larger. It follows that the stumpy protrusions above the basic surface in Fig. 1(b) consist of the product. However, AFM

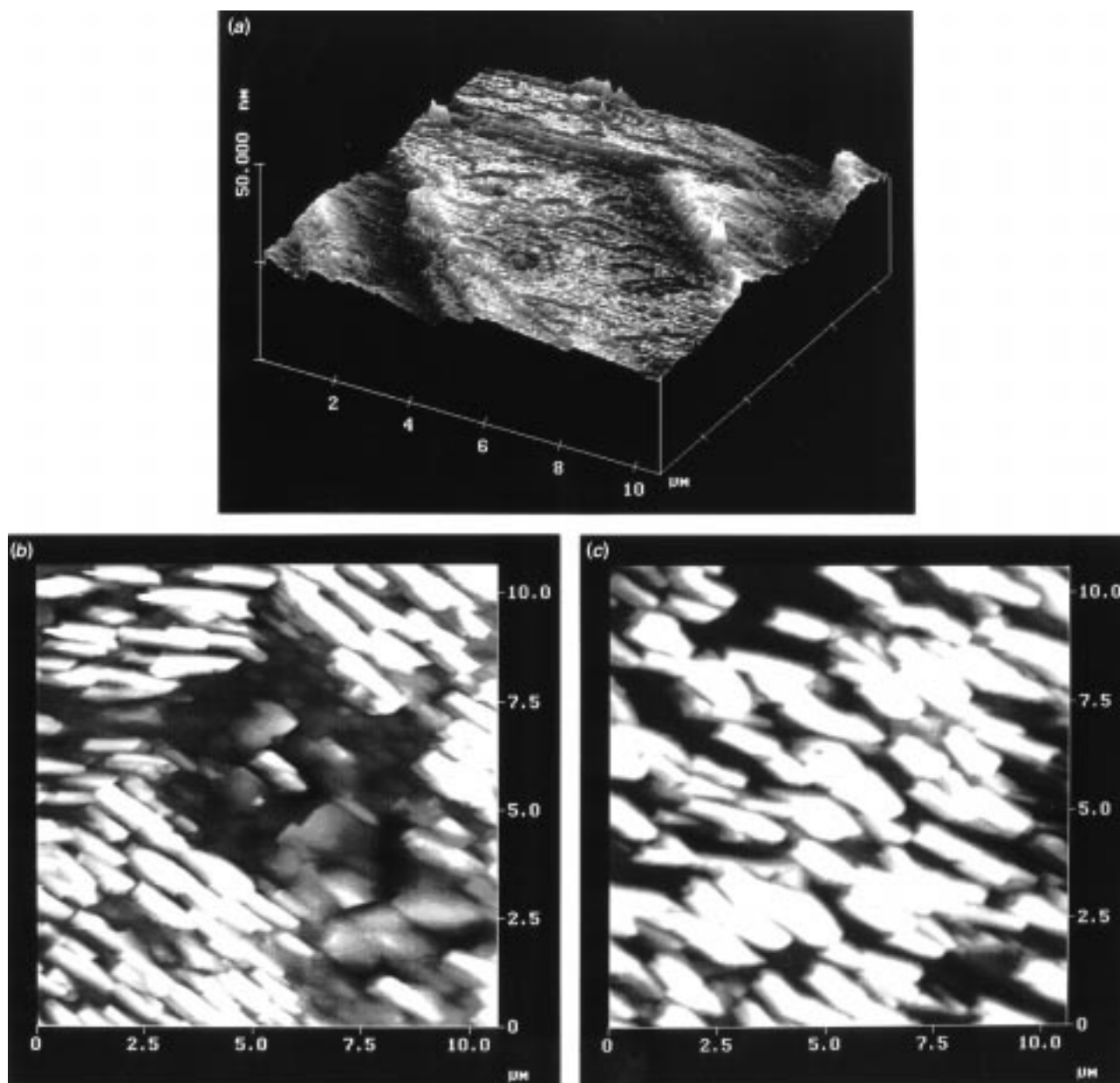


Fig. 3 AFM topography of 4-hydroxybenzaldehyde ($P2_1/c$) on (010); (a) pure, (b) 10 min after placing a crystal of *p*-toluidine on it with the crystal edge at 0.2 mm from the left side of the image and (c) 90 min after putting a crystal of *p*-anisidine on another fresh crystal at 0.2 mm distance from the edge. The direction of measurement (left to right in the images) was inclined by 35° with respect to the [100] direction in the crystal; the edges of the small crystals are roughly parallel to the left edge of the 2D images; the contrast in (b) and (c) covers 1.0 μm height.

cannot give information as to whether the basic surface region is also chemically transformed or not. Such distinctions are only possible with SNOM measurements.²² Highly sensitive internal reflection SNOM^{22,26} gave no optical contrast that distinguished the material at the stumps from the one at the basic plane surface. This observation indicates that product formation had also occurred between the stumps in Fig. 1(b). The polarities of *p*-nitroaniline **1** and the hydrate of its *p*-chlorophenylazomethine **3** are certainly sufficiently different to expect a chemical contrast with SNOM^{22,26} if both were present at different sites in Fig. 1(b). Apparently, 'short distance sublimation' of volatile *p*-chlorobenzaldehyde bridged the gap of roughly 100 nm between non-contacting surface areas. This mechanism is similar to the one known for solid–solid imbibitions of pantolactone.^{21b} A more detailed understanding is obtained by correlation of AFM data to crystal structure data. According to the crystal packing of *p*-nitroaniline²⁷ (Fig. 2) a phase rebuilding mechanism^{4,22,26} is discernible: the *p*-nitroaniline molecules are inclined at $\pm 49^\circ$ to the (100) face in four different orientations (Fig. 2) and it is seen that the molecules are interlocked and form infinite H–N–H–O–N–O– hydrogen-

bond networks, the N(H₂)–O(NO) distances being 3.066 and 3.122 Å.²⁷ Thus, the only chance for molecular movements is above the surface. Only half of the molecules at the (100) surface have their amino group directed out from the surface (*i.e.* are accessible for reaction). After reaction the water produced enters into the crystal and can break the hydrogen bonds between amino and nitro groups and the lattice will become distorted. Furthermore, the azomethine molecules **3** are longer and cannot fit into the interlocked H-bridged lattice of *p*-nitroaniline. The product molecules **3** must therefore try to relieve stress by moving above the crystal surface. Due to this movement the *p*-nitroaniline molecules that had their amino groups initially directed inwards become accessible and have a chance to react. For the same reasons the deeper layers are reached. Due to the interlocking (no cleavage planes) and uniform steepness of all the differently oriented *p*-nitroaniline molecules in the crystal, no characteristically shaped features^{4,22} are to be expected. Their anisotropy in the *z*-direction ([100]) is a mere consequence of the contact sites.

The migration of the aldehyde component into the amine crystals is even more easily demonstrated when a small crystal

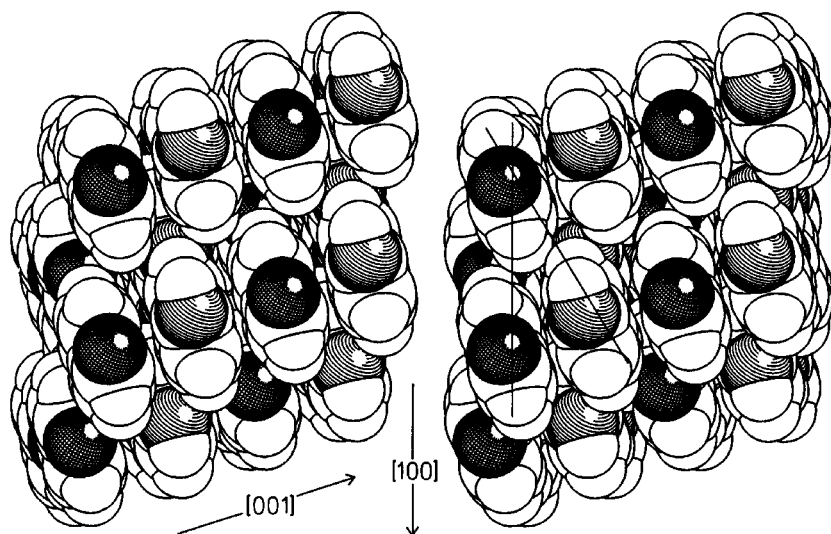


Fig. 4 Stereoscopic space filling view of the molecular packing of *p*-hydroxybenzaldehyde on (010); hydroxy O is indicated with circles, aldehyde O is indicated with latitudes and meridians; the origin is at the upper left corner of the model; the two directions of preference are at an angle of 32° and follow the directions of the cleavage planes that are perpendicular to (010)

of *p*-toluidine or of *p*-anisidine is laid down on the (010) face of a single crystal of *p*-hydroxybenzaldehyde (systems **d** and **i**; Fig. 3). Only the *p*-toluidine or the *p*-anisidine crystal turn yellow and start to disintegrate at their edges after 10 min.

AFM investigation shows that the initially moderately corrugated surface of *p*-hydroxybenzaldehyde [Fig. 3(a), $R_{ms} = 1.32$, $R_{max} = 14.1$ nm] adopts parallel hills that reach heights of more than 1 μm and that are divided by deep valleys and interrupted by side-valleys at right angles. The slopes of the hills are steeper than the angles of the pyramidal tip ($>55^\circ$). These features assume two directions that are at an angle of ca. 30°, as is illustrated with Fig. 3(b). In most images, e.g. Fig. 3(c), only one of these directions (usually [100]) is seen. The directions chosen seem to depend on the contact of molecules with respect to the edges of the accepting crystal.

It is easily comprehended that the same features and the same directions occur in both cases **d** and **i**, as we only see erosion by removal of material: the *p*-hydroxybenzaldehyde molecules move along cleavage planes that are evident from the crystal packing²⁸ in Fig. 4. One of the planes is the (001) face, the other is at an angle of 32°. It is also perpendicular to the (010) face. The angle of 32° is in excellent agreement with these observations [Fig. 3(b)]. Clearly, the features seen are not the result of a chemical reaction in the scanned area (the reaction happens only in the remote crystal that turns yellow), but of molecular flow along either one or both of the cleavage planes. As the molecules are removed by reaction with the remote aniline derivative, erosion of the aldehyde crystal occurs that is reminiscent of the erosive formation of valleys and side-valleys by flowing water in geology.

Our experimental investigation has revealed that the reasons for the particular ease of the environmentally benign solid-state synthesis of azomethine hydrates are again nicely elucidated by AFM and SNOM on the basis of crystal packing and feature-forming molecular migrations.²² Further applications will be numerous.

Experimental

Preparation of aromatic imines

All solid–solid reactions were performed by grinding together 10 mmol of the pure aniline **1** with 10 mmol of the pure aldehyde **2** in a mortar and keeping the mixture at room temperature for 2 h (**3b**, **e**, **j**, **p**, **q**, **s**), 6 h (**3a**, **d**, **f**, **g**, **i**, **l**), 24 h (**3c**, **m**, **n**, **r**, **t**), 36 h (**3k**) or 120 h (**3o**). Only **3h** needed 24 h at 50 °C in order to be

formed quantitatively.† The completion of the reaction was checked by IR spectroscopy in KBr. The water produced in the reaction was removed at 80 °C under vacuum. 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 (Table 1) confirmed the purity of the products **3**. The AFM and SNOM techniques and our DSC/TGA equipment have been described in detail elsewhere.^{4,21,22,26}

Acknowledgements

F. T. is grateful for a Grant-in-Aid for Scientific Research on Priority Areas, No. 06242105 from the Ministry of Education, Science, Sports and Culture. G. K. thanks the Deutsche Forschungsgemeinschaft for support in running the AFM and SNOM.

† *Note added in proof.* The rate of reaction may be considerably increased if these reactions are performed in ball mills (G. Kaupp, J. Boy and J. Schmeyers, *J. Prakt. Chem./Chem.-Ztg.*, in the press). Thus, **3h** and **3o** can be qualitatively obtained in less than 30 min at room temperature when stoichiometric mixtures of the starting materials (Table 1) are ball-milled.

References

- 1 F. Toda and M. Ochi, *Enantiomer*, 1996, **1**, 85.
- 2 F. Toda and M. Imai, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2673; M. J. Brown, *Heterocycles*, 1989, **29**, 2225; T. Wagner-Jauregg, *Synthesis*, 1976, 349; A. Robert, *Tetrahedron*, 1973, **29**, 463.
- 3 L. Strekowski, M. I. Cegla, D. B. Harden, S. L. Mokroc and M. S. Mokroc, *Tetrahedron Lett.*, 1988, **29**, 4265; N. S. Isaacs, *Chem. Soc. Rev.*, 1976, **5**, 181; A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, 1975, **97**, 2345; E. Ziegler and H. D. Hanus, *Monatsh. Chem.*, 1968, **99**, 2024.
- 4 G. Kaupp, U. Pogodda and J. Schmeyers, *Chem. Ber.*, 1994, **127**, 2249.
- 5 Recent reviews: K. Tanaka, F. Toda, *Chem. Rev.*, in the press; F. Toda, in *Comprehensive Supramolecular Chemistry*, ed. D. D. MacNicol, F. Toda and R. Bishop, Elsevier, Oxford, 1996, vol. 6, p. 465–516.
- 6 J. M. Lohar and D. S. Shah, *Mol. Cryst. Liq. Cryst.*, 1974, **28**, 293; I. Bar and J. Bernstein, *Acta Crystallogr., Sect. B*, 1983, **39**, 266.
- 7 P. Frocyen, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 1993, **81**, 1; 37.
- 8 J. R. Merchant, R. J. Shah and R. M. Bhandakar, *Recl. Trav. Chim. Pays-Bas*, 1962, **81**, 131.

- 9 M. Rai, S. Kumar, B. Singh, K. Krishnan and A. Singh, *J. Indian Chem. Soc.*, 1982, **59**, 80.
- 10 D. W. Allen, P. E. Cropper, P. G. Smithurst, P. R. Ashton and B. F. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1989.
- 11 J. P. Schroeder and D. C. Schroeder, *J. Org. Chem.*, 1968, **33**, 591; S. J. Smith, H. Zimmer, E. Fluck and P. Fischer, *Phosphorus Sulfur*, 1988, **35**, 105.
- 12 P. Grammaticakis and H. Texier, *Bull. Soc. Chim. Fr.*, 1971, 1323.
- 13 A. S. Wheeler, *J. Am. Chem. Soc.*, 1913, **35**, 977.
- 14 M. Nakamura, K. Komatsu, Y. Gondo, K. Ohta and Y. Ueda, *Chem. Pharm. Bull.*, 1967, **15**, 585.
- 15 A. Senier and R. B. Forster, *J. Chem. Soc.*, 1914, **105**, 2470.
- 16 G. M. Janini, A. M. Ai-Ghoul and G. H. Hovakeemian, *Mol. Cryst. Liq. Cryst.*, 1989, **172**, 69.
- 17 R. v. Walther and W. Raetze, *J. Pr. Chem. 2*, 1902, **65**, 265.
- 18 M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, *J. Am. Chem. Soc.*, 1952, **74**, 573.
- 19 G. Guastalla, *Atti R. Accad. Sci. Torino*, 1928, **63**, 128; *Chem. Zentralbl.*, 1928, **II**, 984.
- 20 D. M. Ritter, *J. Am. Chem. Soc.*, 1947, **69**, 46.
- 21 (a) G. Kaupp, M. Haak and F. Toda, *J. Phys. Org. Chem.*, 1995, **8**, 545; (b) G. Kaupp, J. Schmeyers, F. Toda, H. Takumi and H. Koshima, *ibid.*, 1996, **9**, 795.
- 22 G. Kaupp, in *Comprehensive Supramolecular Chemistry.*, ed. J. E. D. Davies and J. A. Ripmeester, Elsevier, Oxford, 1996, vol. 8, p. 381–423; *Chemie unserer Zeit*, 1997, **31**, 129, English translation available at <http://kaupp.chemie.uni-oldenburg.de>.
- 23 N. B. Singh, R. J. Singh and N. P. Singh, *Tetrahedron*, 1994, **50**, 6441–6493; the term 'surface migration' remained largely unspecified.
- 24 M. C. Etter and D. A. Adsmond, *J. Chem. Soc., Chem. Commun.*, 1990; 589; M. C. Etter, G. M. Frankenbach and J. Bernstein, *Tetrahedron Lett.*, 1989, **30**, 3617.
- 25 D. Britton, *J. Chem. Crystallogr.*, 1994, **24**, 553.
- 26 G. Kaupp and A. Herrmann, *J. Phys. Org. Chem.*, 1997, **10**, 675; G. Kaupp, A. Herrmann and M. Haak, *J. Vac. Sci. Technol. B*, 1997, **15**, 1521; G. Kaupp, A. Herrmann, *Ultramicroscopy*, 1998, in the press.
- 27 M. Colapietro, A. Domenicano, C. Marcianti and G. Portalone, *Z. Naturforsch., Teil B*, 1982, **37**, 1309, data in Cambridge Database; the 120K structure (M. Tonogaki, T. Kawata, S. Ohba, Y. Iwata and I. Shibuya, *Acta Crystallogr., Sect. B*, 1993, **49**, 1031) has shorter N(H₂)–O(NO) distances, 3.034 and 3.087 Å.
- 28 F. Iwasaki, *Acta Crystallogr., Sect. B*, 1977, **33**, 1646.

Paper 7/04633B

Received 1st July 1997

Accepted 14th January 1998