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SHORT COMMUNICATION

NMR Study of the Solid-State Rearrangement of 3-Amino-1- and -2-(chloroacetyl)pyrazole to 3-(Chloroacetamido)pyrazole

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Reaction of 3-aminopyrazole (1) with chloroacetyl chloride gives a mixture of 3-amino-1- and -2-(chloroacetyl)pyrazole (2 and 3), both of which rearrange in the solid-state to 3-(chloroacetamido)pyrazole (4) over a period of a few days. The course of the rearrangements was monitored directly by CP/MAS NMR and indirectly by ^{1}H NMR spectroscopy; the results suggest that the mechanism involves 3 → 2 → 4.

KEY WORDS NMR ^{13}C CP/MAS ^{1}H Solid-state rearrangement 3-Amino-1- and -2-(chloroacetyl)pyrazole

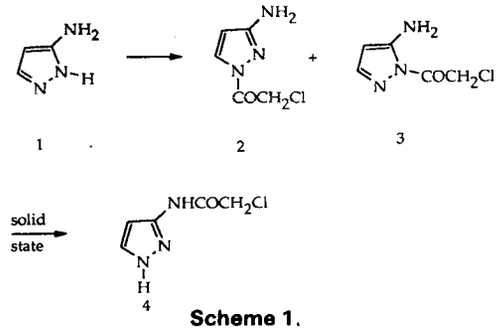
INTRODUCTION

Transformations which occur spontaneously in the solid state are well known, but remain an unusual aspect of the reactivity of organic molecules.[1,2] Many of these processes involve isomerization or rearrangement, and typical examples include ring–chain tautomerism of 1,3-oxazolidine ring systems[3] or the rearrangement of a dimethylaminobenzenesulphonic acid ester to its corresponding zwitterionic form.[4] Acyl group migrations have also been reported, although only at elevated temperatures close to the melting point of the substrate.[5,6] During an investigation of the monoacylation reactions of 3-aminopyrazole (**1**), we have discovered an intriguing system in which at least two solid-state rearrangement processes take place simultaneously under exceedingly mild conditions *ca.* 100 K below the melting point. We report here a study of these processes using a combination of cross-polarization magic angle spinning (CP/MAS) and conventional NMR techniques, which we believe will be generally applicable to the investigation of solid-state reactions.

RESULTS AND DISCUSSION

Treatment of 3-aminopyrazole (**1**) with one equivalent of chloroacetyl chloride and of triethylamine in dichloromethane gives a mixture of the 1- and 2-(chloroacetyl) compounds **2** and **3** in 79% overall yield as a colourless solid (Scheme 1). These products were characterized by their ^{1}H NMR spectra: the 1-isomer shows $^3J(4,5) = 3.0$ Hz and the 2-isomer has $^3J(4,5) = 1.7$ Hz, in agreement with previous observations on similar compounds.[7,8] The two isomers were formed in various proportions in separate runs, but the 1-isomer **2** was generally in excess. To our surprise, this solid mixture was found to rearrange cleanly at room temperature over a period of a few days to give 3-(chloroacetamido)-pyrazole (**4**). None of this compound was formed from a solution of the mixture in acetone, under conditions which caused complete rearrangement of the solid; longer reaction times caused decomposition.

Two NMR methods were used to follow the progress of the solid-state reaction. First, it was monitored directly in the solid-state at 306 and 310 K in the probe of a Bruker MSL500 spectrometer operating in the CP/MAS mode. Samples were contained in 4 mm ZrO_2 rotors, which were spun at 5–8 kHz. A standard CP sequence incorporating a 1 ms contact time was employed. The temperature controller and probe were



Scheme 1.

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calibrated by the phase changes of standard samples.[9] Spectroscopic assignments were made on the basis of the solution ^{13}C NMR shifts, and were assisted by running non-quaternary suppressed spectra to identify quaternary carbon atom signals; typical spectra are shown in Fig. 1. The $t = 0$ spectrum is dominated by the signals of **2**, which shows carbonyl and C-3 quaternary peaks at δ_C 163.5 and 161.2 (which could not be unambiguously distinguished) and methine peaks at δ_C 105.2 and 131.6 due to the 4- and 5-positions, respectively. The peak at δ_C 89.4 in this spectrum is characteristic of the 4-position of the minor isomer **3**, but the other signals of this compound were not assigned further. The spectra recorded at $t = 96$ and 128 min show the presence of essentially pure acetamido compound **4**, (signals at δ_C 165.7, 148.0, 130.2 and 96.0 due to the carbonyl and the 3-, 5- and 4-positions, respectively). The methylene signals of all three compounds **2**–**4** occur as a broad peak in the range 40–50 ppm.

The reaction rate could be estimated by the disappearance of peaks at δ_C 163.5, 161.2 and 105.2 and the appearance of the peaks at δ_C 165.7, 148.0 and 96.0. Both processes followed apparent first-order kinetics, and the average rate constant (at 306 K) was $3.6 \pm 0.4 \times 10^{-5}$ s^{-1}. The possibility of *in situ* detection of reaction intermediates is an important feature of the CP/MAS NMR experiment for monitoring such reactions but, as can be seen from Fig. 1, no substantial levels were found in this case.

Second, a solid sample of the mixture of **2** and **3** was kept at 299 K and aliquots were examined in acetone solution by conventional ^1H NMR spectroscopy. Remarkably, the decay of the minor 2-isomer **3** followed reasonable first-order kinetics ($k = 1.1 \pm 0.1 \times 10^{-5}$ s^{-1}), whereas the concentration of the 1-isomer **2** remained almost constant for a number of days before decaying, again by an apparent first-order process ($k = 5.4 \pm 0.8 \times 10^{-6}$ s^{-1}). This behaviour could be explained qualitatively by a sequential process in which the minor isomer **3** was first transformed to the major isomer **2** prior to the final rearrangement to the acylamido compound **4**. As predicted on the basis of this mechanism, when a pure sample of the 1-isomer **2** was allowed to rearrange in the absence of **3**, the reaction took place without a significant induction period and at

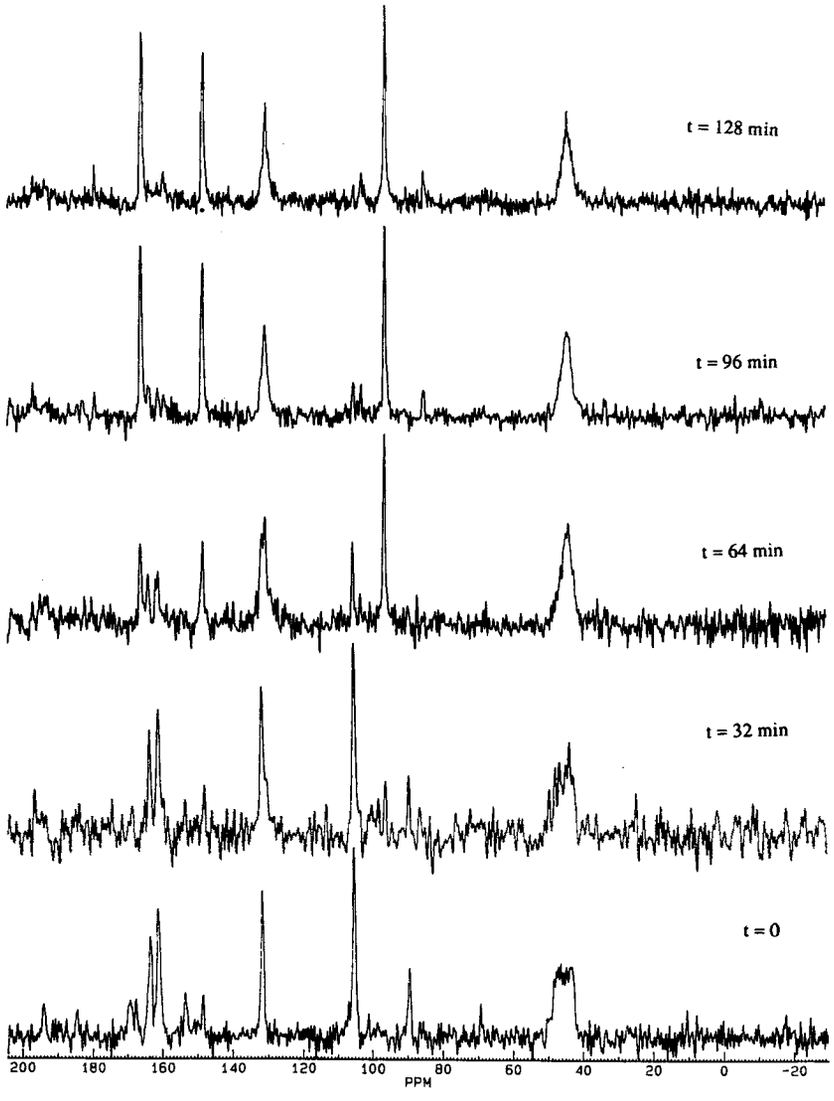

Figure 1. CP/MAS ^{13}C NMR spectra of a reacting mixture of **2** and **3** at 306 K showing formation of **4**.

the same rate as found above ($k = 6.1 \pm 0.5 \times 10^{-6}$ s^{-1}). In addition, none of the 2-isomer **3** was observed during the course of this reaction, and so **2** and **3** are not in equilibrium under these conditions.

We have therefore demonstrated by solid-state and solution-phase NMR methods that at least two separate processes with similar rate constants take place simultaneously at room temperature in the solid samples of these chloroacetyl compounds. The 2-isomer **3** is transformed into the 1-isomer **2**, and meanwhile the 1-isomer is itself decomposing to the thermodynamically stable acylamido compound **4**. We believe that the direction of this sequence rules out the possibility of the final rearrangement to **4** being intramolecular, and that the most likely mechanism involves intermolecular cascades, possibly initiated at crystal defects.[1,4] Work is in progress to define better the scope and mechanism of these remarkable transformations.

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