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N-(6-Methyl-2-pyridyl)acrylamide: a case of amide hydrolysis without the assistance of acid or base in the synthesis of water-driven H-bonded polymeric chains

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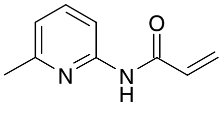
Abstract—Amide hydrolysis of *N*-(6-methyl-2-pyridyl)acrylamide without the assistance of either acid or base produces the aminopyridinium carboxylate salt at low or room temperature. The carboxylate ion and the free amine functionalities are cooperatively involved in hydrogen bonding with lattice water to form a new hydrogen-bonded polymeric chain.

Substituted pyridine is a versatile motif in the context of the synthesis of various fused heterocycles[1] and also in the preparation of heteroatom-based supramolecular hosts[2] for various biologically important guests. In the majority of cases, the pyridine nitrogen was found to react with an ester carbonyl pendant at the 2-position to afford substituted 4*H*-quinolizin-4-ones.[3] Chandler et al. devised an alternative route for the Skraup reaction for the synthesis of naphthyridine using the same protocol.[4] In their approach, condensation between 2-amino-6-methylpyridine and ethyl acetoacetate with phosphoric acid, initiates kinetically favored ring formation onto the ring nitrogen of the pyridine, which on thermal isomerization at 350 °C leads to the 1,8-naphthyridine ring system in moderate yield. This ring switching strategy has become increasingly important in the cleavage of lactone or lactam rings situated at position 2 of the pyridine ring with simultaneous formation of other heterocyclic systems. Based on the above and our research on the synthesis of supramolecular hosts[5] as well as the identification and characterization of important hydrogen bonding synthons, we report here cleavage of the amide bond of 2-acryloylamino-6-methylpyridine **1** with simultaneous regeneration of hydrogen bonding motifs in the construction of a new water-driven hydrogen-bonded polymer.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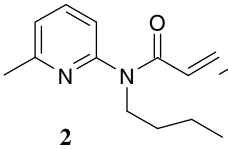
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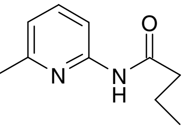
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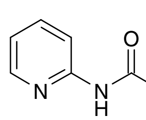
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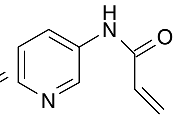
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Compound **1**[6] was obtained by reacting 2-amino-6-methylpyridine with 2-propenoyl chloride in the presence of Et_3N in dry CH_2Cl_2. Amide **2** was prepared in two steps as outlined in Scheme 1. Alkylation of 2-amino-6-methylpyridine at the amino group was performed according to the reported procedure.[7]

Compound **3** was obtained from 2-amino-6-methylpyridine via reaction with butyryl chloride in the presence of Et_3N in dry CH_2Cl_2. Under similar conditions, compounds **4** and **5** were obtained by reacting 2-propenoyl chloride with 2- and 3-aminopyridine, respectively. All the compounds were characterized by conventional methods. Interestingly, the characterization of **1** by ^1H NMR (in $CDCl_3$) adequately supported its structural

Keywords: Hydrogen bonding synthon; Amide cleavage; Hydrogen-bonded polymeric chain; Lattice water; 2-Amino-6-methylpyridine.

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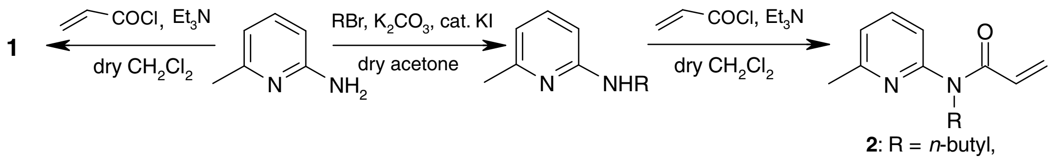
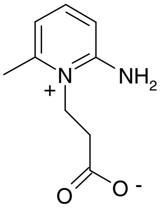


Scheme 1. Syntheses of compounds **1** and **2**.

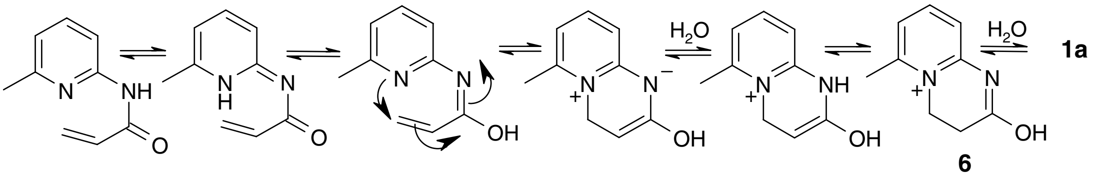
features. However, on storing in the absence of solvent in a freezer for a couple of days, compound **1** produced a white, chloroform insoluble solid **1a**,[6] which exhibited a different ^{1}H NMR spectrum (in DMSO-d_6). Careful analysis of the ^{1}H NMR spectrum of the newly formed solid revealed the disappearance of the vinylic protons (δ 6.45, 6.25, and 5.77 ppm) with the appearance of new signals centered at δ 4.26 and 2.33 ppm. Also, FTIR analysis showed significant changes in the carbonyl stretching frequencies (1676 cm^{-1} in **1** changed to 1668 cm^{-1} in **1a**). The amide NH stretch at 3270 cm^{-1} in **1**, appeared as two peaks (3408 and 3290 cm^{-1}) in the chloroform insoluble solid. This indicated the presence of a free amine functionality in the newly formed solid. Mass analysis showed a peak at m/z 181.2 (M+H) instead of m/z 162 for **1**. A single crystal of this solid was prepared from chloroform/methanol and analysis confirmed structure **1a**.[8]



1a

This finding is interesting and to the best of our knowledge, is unknown in the literature. The generation of **1a** can be explained by invoking the following suggested mechanism where the pyridine amide proton on tautomeric shift[8] presumably initiates the reaction. Michael type addition of the pyridine nitrogen to the pendant group at C-2 of pyridine gives the cyclic imine **6**, which on hydrolysis in the presence of atmospheric water, produces **1a**. In this regard, cleavage of amide linkage followed by intermolecular alkylation on the pyridyl ring nitrogen to afford **1a** cannot be excluded. Compound **1**, in absence of solvent, was found to undergo complete conversion to **1a** after 35 days in a freezer at 5 °C. The same conversion was 10% complete on keeping for 35 days in the open atmosphere at room temperature (26 °C). The low temperature favors the conversion possibly due to the insoluble nature of **1a** that separates as a solid from the starting material, which is gummy in nature. The reaction is reversible and the kinetically favored product **1a** is fully converted to the thermodynamically stable amide **1** on heating in boiling xylene for 1–2 h. Reformation of amide **1** in boiling xylene is presumably ascribed to the azeotropic loss of water. The conversion of **1a** into **1** is also feasible in solution phase. In dry ethyl acetate, **1a** was completely converted to **1** at room temperature after 2 h. In dry $CHCl_3$, CH_3OH, and THF the same conversion was only 20%, 10%, and 50% complete, respectively, after one day. Methanol, a polar H-bond donor solvent, stabilizes **1a** by solvating the carboxylate ion as well as the amine group through H-bonding and makes the conversion of **1** to **1a** less facile. The free amine salt **1a** was very labile such that we could not form an amide with butyryl chloride; instead we isolated **1** as the sole product. The presence of an electron-donating methyl group in **1** promotes the amide cleavage possibly by increasing the donor capacity of the pyridine ring nitrogen in the Michael type addition reaction in Scheme 2. This was established by reacting compound **4**, which under similar conditions was stable, although Szafran et al.[9b] had reported the nucleophilic reaction of 2-aminopyridine itself with 3-bromopropionic acid to afford 3-(2-aminopyridinium)propionate. Compound **5** was also stable under similar conditions. In addition, this conversion was not observed with derivatives **2** and **3** suggesting the kinetic inertness of the 3° and saturated 2° amides, respectively. Compound **1a** crystallized in the triclinic system with one water molecule in the asymmetric unit and is interesting in the context of the synthesis of new hydrogen bonding synthons in supramolecular chemistry. During the rearrangement of **1** as shown in Scheme 2, the hydrogen-bonding pattern (AD; A = H-bond acceptor; D = H-bond donor) was altered to an AADD pattern in **1a** (Fig. 1).

This hydrogen bond alteration particularly, has a profound role in the synthesis of supramolecules of great interest. Figure 2 shows the ORTEP plot of **1a**·H_2O with atom numbering scheme. In the unit cell, two charged pyridyl rings with carboxylate ions are aligned



Scheme 2. Probable mechanism of the rearrangement.

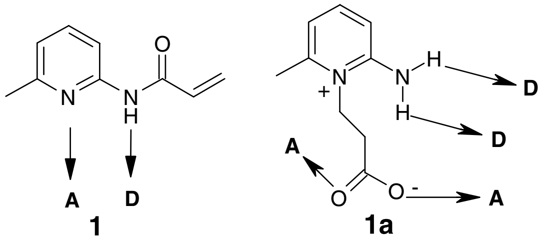


Figure 1. Hydrogen bonding groups in **1** and **1a** (A = hydrogen bond acceptor, D = hydrogen bond donor).

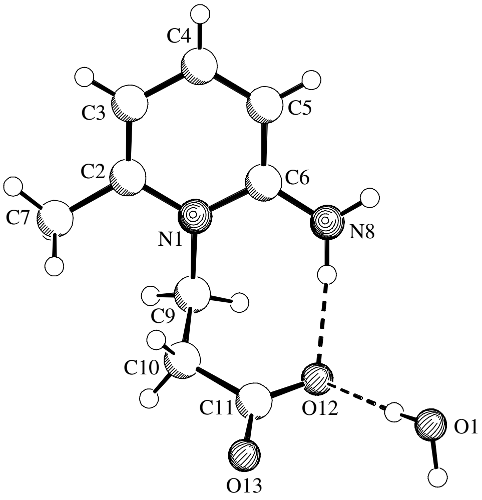


Figure 2. SCHAKAL plot of **1a**·H_2O.

in opposite directions with a distance of separation of 3.860 Å to avoid electrostatic repulsion.

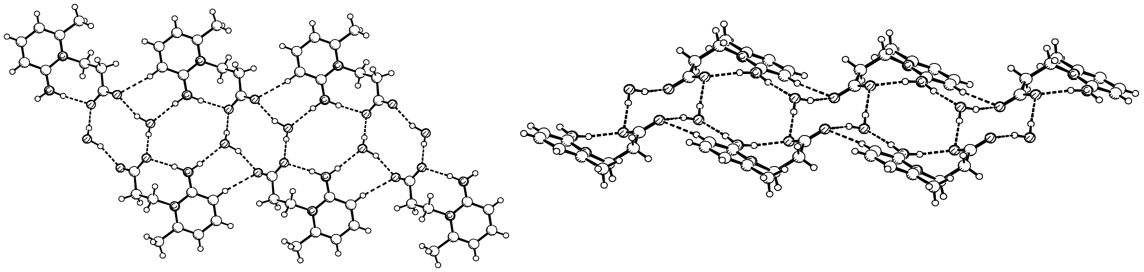


Figure 3. Two different views of the ladder-like chains through hydrogen bonding in **1a**.

In the present case, the free amine and the carboxylate ion are intramolecularly hydrogen bonded forming an 8-membered ring being suggested as optimal for hydrogen bonding in a cyclic array. The heavy atom separation is consistent with a strong bond, and the N–H···O angle is not far off linear (N8–H8B···O12: 0.91 Å, 1.85 Å, 168°). The AADD hydrogen bonding groups have converged into bifunctional AD groups, which on H-bond linking with lattice water gives a water-driven H-bonded polymer. In a layer, each single chain, which arises due to C5–H···O13 hydrogen bonds, is further connected to the adjacent chain through water. Close examination of the molecular packing (Fig. 3) indicates that the water molecules are associated by O–H···O (O1–H1A···O12: 0.89 Å, 1.94 Å, 177° and O1–H1B···O13#: 0.94 Å, 1.85 Å, 160°) and N–H···O (H8–H8A···O1#: 0.91 Å, 1.98 Å, 171°) hydrogen bonds and adopts a trigonal planar arrangement. These two different types of hydrogen bonds (O–H···O and N–H···O) result in self-assemblies into ladder-like chains that consist of two different alternate 12-membered rings. Both rings adopt a favorable chair-like arrangement with two water molecules at opposite ends of the chair. These cooperative interactions help not only to form a hydrogen-bonded polymer but also to stabilize the whole structure.

In summary, we have identified the lability of the amide linkage of *N*-(6-methyl-2-pyridyl)acrylamide, which undergoes clean hydrolysis without the assistance of acid or base to produce 3-(2-amino-6-methylpyridinium)propionate monohydrate **1a**, which forms hydrogen-bonded polymeric chains. This observation forms the basis of the synthesis of new hydrogen-bonding synthons in supramolecular chemistry. Further work is in progress in our laboratory.

Acknowledgments

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References and notes

1. (a) Ma, Y.; Kolotuchin, S. V.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2002**, *124*, 13757–13769; (b) Bernstein, J.; Stearns, B.; Shaw, E.; Lott, W. A. *J. Am. Chem. Soc.* **1947**, *69*, 1151–1158; (c) Fenlon, E. E.; Murray, T. Z.; Baloga, M. H.; Zimmerman, S. C. *J. Org. Chem.* **1993**, *58*, 6625–6628, and references cited therein.
2. (a) Bielawski, C.; Chen, Y.-S.; Zhang, P. *Chem. Commun.* **1998**, 1313–1314; (b) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139–1159.
3. (a) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433–2480; (b) Kolar, P.; Petrie, A.; Tisler, M. *J. Heterocycl. Chem.* **1997**, *34*, 1067–1098.
4. Chandler, C. J.; Deady, L. W.; Reiss, J. A.; Tzimos, V. *J. Heterocycl. Chem* **1982**, *19*, 1017–1019.
5. (a) Ghosh, K.; Masanta, G. *Chem. Lett.* **2006**, *35*, 414–415; (b) Ghosh, K.; Masanta, G. *Tetrahedron Lett.* **2006**, *47*, 2365–2369.

6. Compound **1** was purified by column chromatography using 20% EtOAc in pet ether. Compound **1**, gummy in nature, ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) 8.46 (1H, s), 8.10 (1H, d, $J = 8$ Hz), 7.61 (1H, t, $J = 8$ Hz), 6.90 (1H, d, $J = 8$ Hz), 6.45 (1H, d, $J = 16.8$ Hz), 6.25 (1H, m), 5.77 (1H, d, $J = 10.4$ Hz), 2.44 (3H, s), FTIR (ν cm^{-1}, KBr) 3270, 1676, 1602, 1577, 1455. Mass (ESI) 185.0 (M+Na$^+$), 163.3 (M+H)$^+$, 145.1, 109.2. Compound **1a**, mp = 126 °C, ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm) 7.63 (1H, t, $J = 8$ Hz), 6.87 (1H, d, $J = 8$ Hz), 6.71 (1H, d, $J = 8$ Hz), 4.26 (2H, t, $J = 4.8$ Hz), 2.49 (3H, s), 2.33 (2H, m), free –NH_2– was not found, FTIR (ν cm^{-1}, KBr) 3408, 3290, 1668, 1602, 1537, 1455. Mass (ESI) 181.2 (M+H)$^+$, 163.2, 109.3.
7. Mazik, M.; Radunz, W.; Sicking, W. *Org. Lett.* **2002**, *4*, 4579–4582.
8. Crystal data of **1a**·H_2O: $C_9H_{14}N_2O_3$, triclinic, space group $P-1$ (No. 2), $a = 7.377(1)$, $b = 8.423(1)$, $c = 8.498(1)$ Å, $\alpha = 97.81(1)$, $\beta = 93.24(1)$, $\gamma = 113.22(1)°$, $V = 477.2(1)$ Å^3, $T = 223(2)$ K, $Z = 2$, $\rho_{\mathrm{calcd}} = 1.379$ mg m^{-3}, λ (Cu-Kα) = 1.54178 Å, 3901 total reflections of which 1582 were independent, 1541 observed [$I > 2\sigma(I)$]. Structure solution and refinement with SHELXS-97 and SHELXL-97, final refinement against F^2 with 144 parameters, hydrogen atoms at N8 and O1 from difference Fourier map and refined free with isotropic thermal parameters, other calculated and refined riding, R_1 [$I > 2\sigma(I)$] = 0.037, $wR_2 = 0.099$. CCDC 611076.
9. (a) Katritzky, A. R.; Ghiviriga, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1651–1653; (b) Szafran, M.; Kowalczyk, I.; Katrusiak, A. *J. Mol. Struct.* **2006**, *786*, 25–32.