A Novel Thermal Rearrangement in the Pyrido[1,2-*a*]pyrimidine Series: Transformation of 3-Acetyl-4-phenylaminopyrido[1,2-*a*]pyrimidin-2-one into 3-Acetyl-2-phenylaminopyrido[1,2-*a*]pyrimidin-4-one

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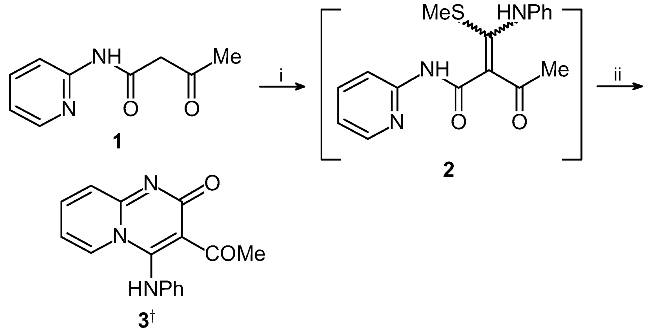
3-Acetyl-4-phenylaminopyrido[1,2-*a*]pyrimidin-2-one has been synthesized from acetoacetic acid *N*-(pyrid-2-yl)amide and phenylisocyanate and converted on heating into 3-acetyl-2-phenylaminopyrido[1,2-*a*]pyrimidin-4-one.

Pyrido[1,2-*a*]pyrimidines (PP) have been studied extensively due to their range of biological activity (see, *e.g.*, review[1]). However, little is known about their amino derivatives, especially the 4-aminopyrido[1,2-*a*]pyrimidines (APP). Recently APP were reported to be readily obtained by the cyclization of cyanoacetic acid *N*-(pyrid-2-yl)amide on treatment with HCl/EtOH or by the high pressure interaction of 2-aminopyridine with ethylcyanoacetate.[2]

Some *N*,*N*-disubstituted APP were synthesized in poor yields from 2-aminopyridines and reagents prepared by mixing *N*,*N*-dialkylcarbonylacetamides with $POCl_3$.[3] The reaction products also contained the isomeric 2-amino-[1,2-*a*]pyrimidines.

We now wish to report a novel synthetic approach to the APP derivatives. Ketene-acetal **2**, readily obtained from acetoacetic acid *N*-(pyrid-2-yl)amide **1**, was found to undergo cyclization into 3-acetyl-4-phenylaminopyrido[1,2-*a*]pyrimidin-2-one at ambient temperature in THF/H_2O (Scheme 1).



Scheme 1 *Reagents and conditions*: i, PhNCS, BTEA-Cl, K_2CO_3, DMF, Et_3N, MeI (20–80 °C); ii, THF/H_2O, ~ 20 °C, 20 days.[1]

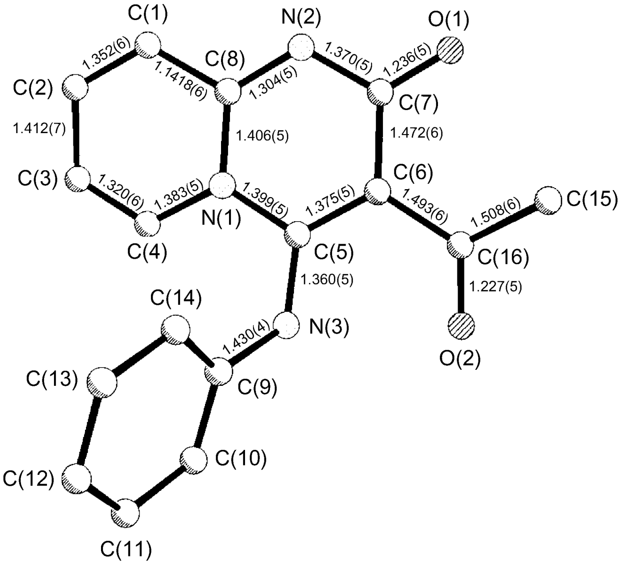


Fig. 1

The structure of **3** was unambiguously established by a single crystal X-ray diffraction study (Fig. 1).‡

The conformation of the pyrimidine ring in compound **3** is a slightly distorted, essentially flattened boat. The displacements of N(1) and C(7) from the C(5), C(6), C(8), N(2) least-squares plane are 0.10(1) and 0.08(1) Å, respectively.

The bonds in the pyridine ring are delocalized to a considerable extent. The delocalization in the aminopyrimidine part of the molecule takes place in the N(1)–C(5)–C(6) fragment. On the contrary, the bond length C(8)–N(2) of 1.304(5) Å is close to the C=N value of aliphatic imines (1.28 Å[5]). The bond length N(3)–C(9) of 1.430 Å reveals the considerable distortion of conjugation between the π-systems of the phenyl group and the aminoheterocycle owing to rotation of the Ph fragment around N(3)–C(9) [torsion angle C(5)–N(3)–C(9)–C(14) −21.9(6)°]. The exocyclic NH group takes part in intramolecular hydrogen bond formation with the acetyl group O [distance H...O is 2.02(1) Å, angle N(3)–H(3N)...O(2) is 135.6(8)°].

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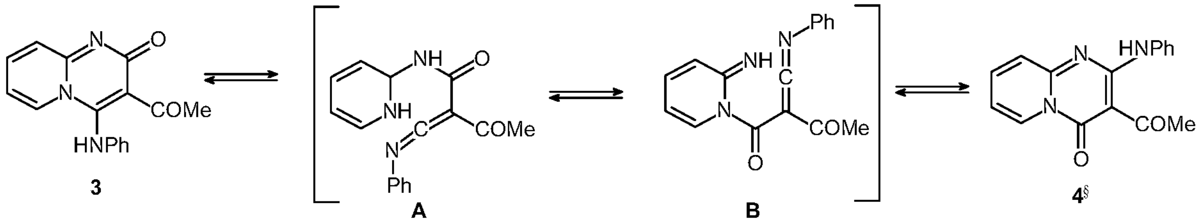
† *Reaction procedure*: A solution of PhNCS (3.49 g, 25.8 mmol) in DMF (5 ml) was added at room temperature to a stirred suspension of **1**[4] (4.39 g, 24.6 mmol), K_2CO_3 (7.05 g, 51.1 mmol) and benzyltriethylammonium chloride (BTEA-Cl) (5 mol%) in DMF (7 ml). After 1 h Et_3N (0.15 ml) and MeI (3.53 g, 24.9 mmol) in DMF (5 ml) were added dropwise. The reaction mixture was stirred at room temperature for an additional 4 h, then heated rapidly to 80 °C, cooled and evaporated under reduced pressure. THF (10 ml), H_2O (10 ml) and NaCl (~ 2 g) were added to the dark residue and the resulting orange precipitate was filtered off. The THF layer in the filtrate was separated, THF (30 ml) was added and the solution was allowed to stay at ambient temperature for 20 days. All the resulting orange solids were combined, washed with THF and ether, dried in vacuum and treated with 0.1 M AcOH (30 ml). The yellow powder formed was filtered off, washed with water and dried under reduced pressure over P_2O_5 at room temperature to give **3**, 4.45 g (65%). Yellow prisms (DMSO, acetonitrile); m.p. 177.5–179 °C (decomp.). UV-VIS (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 340 (5700), 270 (22000), 230 (24500), 207 (28000); IR (KBr) ν_{max}/cm^{-1} 3400 (br), 3200 (br) (NH), 1660, 1636, 1626 (C=O, C=N).
^{1}H NMR ($CDCl_3$) δ 2.80 s (3H, Me), 6.44 dd (1H, H-7), 7.59 d (1H, H-6), 6.7–7.5 (7H, Ph, H-8, H-9), 11.32 s (1H, NH). ^{13}C NMR ($CDCl_3$) 32.1 (Me), 166.9 (C-2), 108.1 (C-3), 150.1 (C-4), 129.6 (C-6), 112.0 (C-7), 136.2 (C-8), 124.8 (C-9), 150.5 (C-10), 120.6, 125.1, 129.9, 138.6 (Ph), 203.2 (CO).

‡ The crystal of **3** is monoclinic. At 20 °C a = 11.880(5), b = 9.260(2), c = 13.074(4) Å, β = 110.79(2)°, V = 1344(1) Å^3, d_{calc} = 1.09 g cm^{-3}, Z = 4, space group $P2_1/n$. Cell parameters and intensities of 1258 unique reflections with $F > 60\sigma(F)$ were measured on an automatic four-cycle diffractometer Syntex $P2_1$ (λ MoK, graphite monochromator, $\theta/2\theta$-scan, $2\theta_{max}$ = 60°).
The structure was solved by direct methods using the SHELXTL PLUS program package. The hydrogen atom positions were determined from difference maps of electronic density. Refinement on F by a full-matrix least-squares method in an anisotropic approach (isotropic for hydrogen atoms) was carried out to R = 0.054 (R_w = 0.054, S = 0.85).



Scheme 2

Compound **3** has been found to rearrange into isomeric 3-acetyl-2-phenylaminopyrido[1,2-*a*]pyrimidin-4-one **4** on heating. This transformation (which was accompanied by partial tar-formation) gave **4** in 40% yield (under optimal conditions: ~ 100 °C, DMF, 4 h).

The isomerisation process (see Scheme 2) is likely to involve: pyrimidine ring-opening¶ and formation of ketene-imine intermediate **A**, followed by (1,3 N→N) acyl migration and cyclization of pyridoneimine **B** into thermodynamically stable **4**.

The structure of **4** has been confirmed by ^{1}H and ^{13}C NMR high resolution spectra and by a comparison with those of APP previously described.[2] UV, IR and mass-spectra were also studied.*

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§ *Reaction procedure*: A solution of **3** (522 mg, 1.87 mmol) in absolute DMF (12 ml) was heated at ~ 100 °C (water-bath) for 4 h. The reaction mixture was evaporated in vacuum, washed with methanol and ether and dried under reduced pressure to give **4**, 210 mg (40%), m.p. 145–146.5 °C [subl., light yellow needles (MeOH)]. UV-VIS (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 357 (12600), 286 (28600), 242 (16700), 205 (29000); IR (KBr) ν_{max}/cm^{-1} 3400 br (NH), 1686 (C=O), 1656, 1626 (C=O, C=N). ^{1}H NMR (CDCl$_3$) δ: 2.81 s (3H, Me), 6.97 dd (1H, H-7), 8.96 d (1H, H-6), 7.1–7.8 (7H, Ph, H-8, H-9), 12.65 s (1H, NH). ^{13}C NMR (CDCl$_3$) δ: 33.4 (Me), 159.0 (C-2), 94.7 (C-3), 158.5 ($^3J_{C,H\text{-}6}$ 2, C-4), 128.3 ($^1J_{C,H}$ 189, C-6), 113.6 ($^1J_{C,H}$ 171, C-7), 139.4 ($^1J_{C,H}$ 165, C-8), 124.6 ($^1J_{C,H}$ 172, C-9), 151.8 (C-10), 122.9, 124.4, 128.7, 138.4 (Ph), 200.7 (CO). MS, *m/z* 279 (M$^+$).

Compounds **3** and **4** had satisfactory elemental analyses.

¶ The unsubstituted 4-aminopyrido[1,2-*a*]pyrimidin-2-one has been found to open the pyrimidine ring upon heating and to transform into *N*-pyridyl-2-cyanoacetamide.[2] The ring-chain isomerization of 3-cyano-4-iminomethylenemalononitrile has also been described.[6]

* The anisotropic effect of the C=O group in **4** causes a downfield shift of the H-6 signal (*e.g.*, *cf.* **3**).[1]