Studies with Polyfunctionally Substituted Heteroaromatics: A Novel Synthesis of Substituted 4,8-Diaminoisoquinolines as Potential Antiparasitic Agents†

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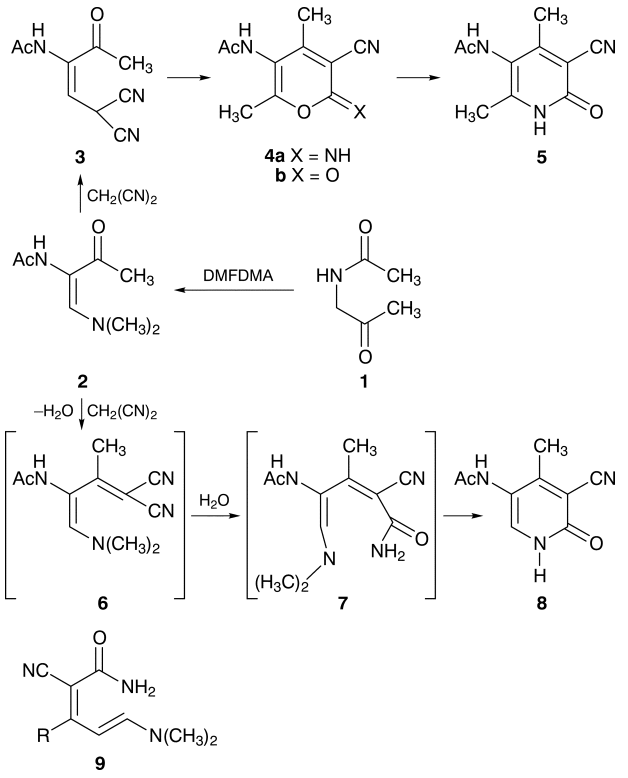
Fatima Al-Omran,* Adel Abou El-Khair and Mohammed Hilmy Elnagdi

Department of Chemistry, Faculty of Science, University of Kuwait, P.O. Box 5969, Safat, 13060-Kuwait

New routes for the synthesis of 4,8-diaminoisoquinolines and pyridine utilizing a 3,4-diaminobut-3-en-2-one (**2**) as starting material are reported.

Aminobenzoazines are interesting as potential drugs for the treatment of parasitic infections[1–3] and as potential male fertility regulators.[4,5] In conjunction with biological programmes directed to developing new antiparasitic drugs and male fertility regulators, samples of several substituted diaminoquinolines and diaminoisoquinolines were required. We noted that existing synthetic approaches to these diamino derivatives are generally multistage, tedious and require several not readily available starting materials.[6–8] To remedy this we decided to develop efficient synthetic routes to these compounds that utilize inexpensive available starting materials. In this article we report a novel simple efficient route to the synthesis of 4,8-diaminoisoquinoline. Acetylaminoacetone **1** reacts with dimethylformamide dimethyl acetal (DMFDMA) in refluxing xylene to yield the 3-acetylamino-4-dimethylaminobut-3-en-2-one **2** in good yield (Scheme 1). This was treated with malononitrile to yield a condensation product *via* dimethylamine elimination. Several structures were considered for this product. We first assumed that the reaction product is formed *via* initial addition of active methylene nitrile to the α,β-unsaturated linkage and subsequent dimethylamine elimination. This is similar to the well accepted mechanism of reaction of enaminones with carbon nucleophiles.[9–12] This can lead to compound **3** or ring tautomers **4a**. However, spectral and chemical evidence did not fit with either structures. For example, ^{13}C NMR indicated the presence of only one CN signal. The reaction product proved stable on refluxing in ethanolic hydrochloric acid, a condition expected to affect either rearrangement of **4a** into **5** or its conversion into the corresponding pyranone (**4b**). The structure **5** was readily ruled out based on ^{13}C NMR which revealed the carbon linked to the methyl function to be connected to two other carbon atoms. We thus considered that the initial step in the reaction involved condensation of the carbonyl function in **2** with malononitrile yielding the diene **6** which is hydrolysed to an intermediate amide **7** and then cyclizes to **8**. In support of the proposed structure, compound **8** was also formed on treating **2** with cyanoacetamide in refluxing pyridine.

The reaction sequence finds a parallel to the recently observed formation of compound **9** in reaction of dimethylaminobuten-2-one with malononitrile.[10] Structure **8** could be readily established for the reaction product as it behaved like 4,5-methylpyridine carbonitriles. Thus, reaction of **8** with ylidenemalononitriles **10a–d** afforded the expected diaminoisoquinolines **13a–d** (Scheme 2). These are formed, most likely, *via* an established reaction sequence of **10** with an alkylazinylcarbonitrile,[12] which in this case would first afford **11** then cyclize into **12**, which loses HCN to yield aromatic **13**. The spectral data for compounds **13a–d** were in complete agreement with the proposed structure.



Scheme 1

Condensation of cyanothioacetamide with compound **2** in pyridine yields a 2-thioxopyridine-3-carbonitrile **14**. Structure **14** is considered most likely for the product based on its similarity to the well established behavior of enaminones towards cyanothioacetamide. The product is thus assumed to be formed by the addition of the active methylene of the cyanothioacetamide to the activated double bond in **2** followed by cyclization and dimethylamine elimination to yield **14**.

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-470 Spectrometer, ^{1}H and ^{13}C NMR on a Bruker 80 MHz spectrometer with $(CD_3)_2SO$ as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a GS/MS INCOS XL Finnigan MAT. Microanalyses were performed on a LECO CHNS-932 instrument. Compound **1** was prepared by the published procedure.[13]

*To receive any correspondence.

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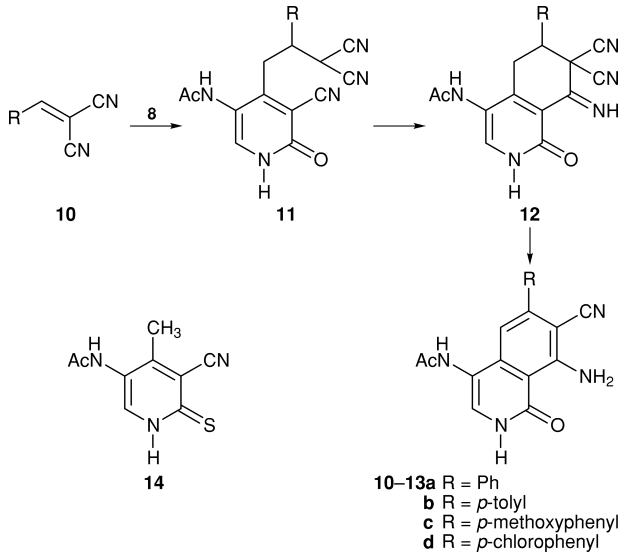

Scheme 2

3-*Acetylamino*-4-*dimethylaminobut*-3-*en*-2-*one* **2**.—A mixture of compound **1** (1.15 g, 0.01 mol) and dimethylformamide dimethyl acetal (2.13 g, 0.01 mol) in 30 ml xylene was heated at reflux for 5–6 h. The solvent was evaporated under reduced pressure and the residue crystallized from ethanol to give brown crystals. Yield 82%, mp 121–122 °C (Found: C, 56.54; H, 8.36; N, 16.76. Calc. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46%. $\tilde{\nu}_{max}$: 3437 (NH) and 1643 cm^{-1} (CO). δ_H (DMSO): 1.89 (s, 3 H, CH_3); 1.94 (s, 3 H, CH_3); 2.96 [s, 6 H, $N(CH_3)_2$]; 7.27 (s, 1 H, H-4); 8.40 (bs, 1 H, NH). δ_C (DMSO): 192.60 (C-2); 170.36 (CO); 147.01(C-4); 106.82 (C-3); 42.01 [$N(CH_3)_2$]; 25.24 (CH_3) and 22.84 (CH_3).

5-*Acetylamino*-1,2-*dihydro*-4-*methyl*-2-*oxopyridine*-3-*carbonitrile* **8**.—*Method a*. A mixture of compound **2** (1.71 g, 0.01 mol) and malononitrile (0.01 mol, 0.60 g) in ethanol (30 ml) was treated with a few drops of piperidine. The reaction mixture was refluxed for 6 h, then poured into water. The solid product was filtered off and crystallized from EtOH–DMF (3:1) as brown crystals. Yield 72%, mp 200–220 °C (Found: C, 56.39; H, 5.01; N, 21.57. Calc. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98%). $\tilde{\nu}_{max}$: 3341, 3216 (NH), 2194 (CN) and 1639 cm^{-1} (CO). δ_H (DMSO): 1.99 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 7.95 (s, 1 H, H-6), 9.31 (bs, 1 H, NH) and 12.2 (bs, 1 H, NH) δ_c (DMSO): 169.5 (CO); 159.96 (C-2); 149.74 and 148.54 (C-5 and C-6); 116.64 (C-4); 116.05 (CN); 99.55 (C-3); 23.05 (CH_3) and 16.42 (CH_3).

Method b.—A mixture of compound **2** (1.71 g, 0.02 mol) and cyanoacetamide (0.01 mol) in pyridine (20 ml) was refluxed for 3 h. The solvent was then removed *in vacuo* and the remaining product triturated with water, acidified with dilute hydrochloric acid and the solid filtered off and identified as **8**, yield 68%.

4-*Acetylamino*-8-*amino*-6-*aryl*-1,2-*dihydro*-1-*oxoisoquinoline*-7-*carbonitrile* **13a**–**d**.—In a 100 ml flask, a suspension of compound **8** (1.91 g, 0.01 mol) in pyridine (30 ml) was treated with an arylylidenemalononitrile (0.01 mol). The reaction mixture was refluxed for 4–6 h, left to cool to room temperature, poured into ice-cold water, and neutralized with HCl (10%). The solid product was filtered off and crystallized from DMF–ethanol (1:1).

4-*Acetylamino*-8-*amino*-1,2-*dihydro*-1-*oxo*-6-*phenylisoquinoline*-7-*carbonitrile* **13a**.—Orange crystals, 73%, mp 190–192 °C (Found: C, 67.91; H, 4.70; N, 17.62. Calc. for $C_{18}H_{11}N_4O_2$: C, 67.91; H, 4.43; N, 17.60%). $\tilde{\nu}_{max}$: 3448, 3290 (NH_2 and NH); 2221 (CN) and 1660 cm^{-1} (CO). δ_H (DMSO): 2.06 (s, 3 H, CH_3); 6.80–7.64 (m, 8 H, aromatic H and NH_2); 8.02 (s, 1 H, H-3); 9.40 (bs, 1 H, NH) and 12.21 (bs, 1 H, NH). δ_C 169.70 (CO); 159.48 (C-1); 155.32 (C-8); 147.72 (C-3); 146.53 (C-4); 137.55, 135.72, 129.78, 129.08, 127.73, 125.80, 120.32, 116.97 (aromatic carbons); 116.05 (CN); 108.39 (C-7) and 22.87 (CH_3).

4-*Acetylamino*-8-*amino*-1,2-*dihydro*-1-*oxo*-6-(p-*tolyl*)*isoquinoline*-7-*carbonitrile* **13b**.—Orange crystals, 72%, mp 355–357 °C (Found: C, 69.01; H, 5.15; N, 16.63. Calc. for $C_{19}H_{16}N_4O_2$; C, 68.66; H, 4.85; N, 16.85%). $\tilde{\nu}_{max}$: 3288 (NH_2 and NH), 2218 (CN) and 1662 cm^{-1} (CO). δ_H (DMSO): 2.08 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 6.89–7.92 (m, 7 H, aromatic H and NH_2), 8.01 (s, 1 H, H-3), 9.38 (bs, 1 H, NH), 12.11 (bs, 1 H, NH) δ_C (DMSO): 169.67 (CO); 159.48 (C-1); 156.00 (C-8); 146.69 (C-3); 146.52 (C-4); 139.78, 137.59, 132.98, 130.12, 129.69, 127.72, 124.99 and 118.18 (aromatic carbons); 15.82 (CN); 99.69 (C-7); 22.82 (CH_3) and 21.02 (CH_3).

4-*Acetylamino*-8-*amino*-1,2-*dihydro*-6-(p-*methoxyphenyl*)-1-*oxoisoquinoline*-7-*carbonitrile* **13c**.—This was obtained as dark orange crystals, 73%, mp 345–347 °C (Found: C, 65.87; H, 5.03; N, 16.07. Calc. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08%). $\tilde{\nu}_{max}$: 3282 (NH_2 and NH), 2223 (CN) and 1660 cm^{-1} (CO). δ_H (DMSO): 1.99 (s, 3 H, CH_3); 3.81 (s, 3 H, OCH_3); 6.80–7.95 (m, 7 H, aromatic H and NH_2), 8.05 (s 1 H, H-3); 9.57 (bs, 1 H, NH); 12.27 (bs, 1 H, NH).

4-*Acetylamino*-8-*amino*-6-(p-*chlorophenyl*)-1,2-*dihydro*-1-*oxoisoquinoline*-7-*carbonitrile* **13d**.—Crystallized from DMF as red solid crystals, 96%, mp > 300 °C (Found: C, 61.05; H, 4.07; N, 15.99. Calc. for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88%). $\tilde{\nu}_{max}$: 3446, 3276 (NH_2 and NH), 2218 (CN) and 1661 cm^{-1} (CO). δ_H (DMSO): 2.49 (s, 3 H, CH_3), 6.88–8.04 (m, 8 H, aromatic H and NH_2); 8.15 (bs, 1 H, NH); 12.25 (bm, 1 H, NH) δ_C (DMSO): 169.92 (CO); 159.37 (C-1); 155.84 (C-8); 147.44 (C-3); 146.02 (C-4); 138.93, 138.67, 135.92, 134.69, 134.30, 129.26, 129.08, 125.99 (aromatic carbons); 117.85 (CN); 104.23 (C-7); 22.80 (CH_3).

5-*Acetylamino*-1,2-*dihydro*-4-*methyl*-2-*thioxopyridine*-3-*carbonitrile* **14**.—A mixture of compound **2** (1.71 g, 0.01 mol) and cyanothioacetamide (0.01 mol) was refluxed in 30 ml pyridine for 3–4 h, then poured into ice-cold water and neutralized with 10% HCl. The resulting product was filtered off and crystallized from dimethylformamide–ethanol (2:1) as yellow crystals, 72%, mp 260–262 °C (Found: C, 52.31; H, 4.38; N, 20.37; S, 15.53. Calc. for $C_9H_9N_3OS$: C, 52.15; H, 4.37; N, 20.27, S, 15.47%. $\tilde{\nu}_{max}$: 3485–3286 (NH), 2229 (CN) and 1651 cm^{-1} (CO). δ_H (DMF): 2.11 (s, 3 H, CH_3); 2.48 (s, 3 H, CH_3); 8.09 (s, 1 H, H-6); 9.67 (bs, 1 H, NH); 14.0 (bs, 1 H, NH).

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