Studies on Polyfunctionalised Heteroaromatics: a Novel Synthesis of Polyfunctionalised Pyridine, Pyridazine and Pyrido[2,3-*c*]pyridazine Derivatives

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Mohamed Hilmy Elnagdi,*[a] Magda Abdel-aziz Barsy,[b] Fawi Mohamed Abdel-Latif[b] and Kamal Usef Sadek*[c]

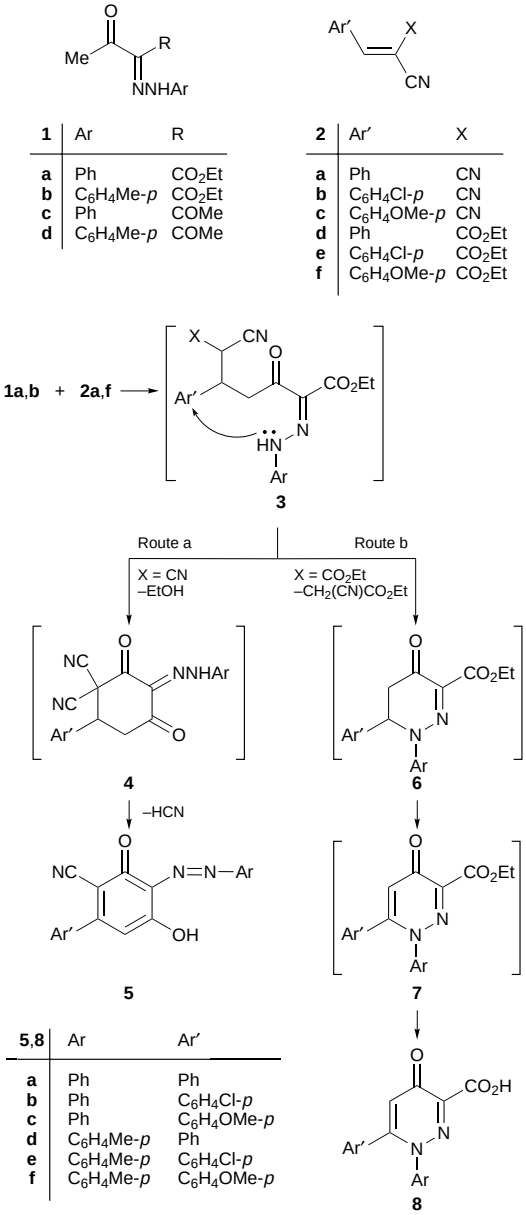
[a]*Department of Chemistry, Faculty of Science, University of Kuwait, P.O. Box 5969, Safat 13060, Kuwait*
[b]*Department of Chemistry, Faculty of Science, South Valley University, Aswan, Egypt*
[c]*Department of Chemistry, Faculty of Science, Minia University, 61519, Minia, Egypt*

Ethyl 2-arylhydrazono-3-oxobutyrates react with α,β-unsaturated nitriles to afford either pyridopyridazine or pyridine derivatives depending on the structure of the unsaturated nitrile.

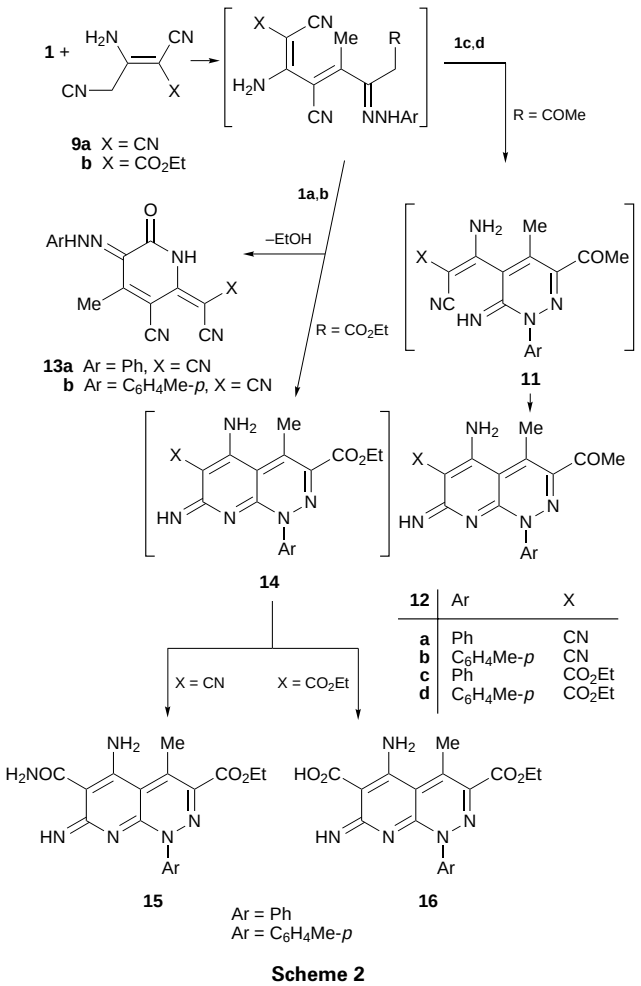
As a part of our programme aimed at synthesising pyridazinones with substitution patterns required for a biological chemistry programme, we report here a novel synthesis of several pyridazines and condensed pyridazines which are difficult to obtain through established synthetic routes.[11–13]

Ethyl 3-oxo-2-phenylhydrazonobutyrate (**1a**) (Ar = Ph, R = CO_2Et) reacted with **2a** in the presence of ammonium acetate to yield 3,5-dihydroxy-4-phenylazobiphenyl-2-carbonitrile (**5a**). The formation of **5a** is assumed to proceed through a Michael-type addition of the methyl function in **1a** to the activated double bond in **2a**, affording the acyclic adducts **3** which then cyclises *via* loss of ethanol and then aromatise *via* elimination of HCN to yield **5** (Scheme 1, route a).

Similarly **1a** reacted with **2b**,**c** and **1b** reacted with **2a–c** to afford **5b–f**, the ^{1}H NMR spectrum for the reaction products revealed in each case a multiplet for aromatic and penta-substituted benzene protons and two one-proton signals for OH groups. In contrast, the reaction of **1a** with **2d** afforded a compound of molecular formula $C_{17}H_{12}N_2O_3$ [*m*/*z* 293 [M^+)]. The ^{1}H NMR spectrum of the reaction product revealed only a multiplet at δ 7.12–7.77 integrating for aromatic protons. Moreover, we could detect by TLC the presence of ethyl cyanoacetate in the reaction mixture. Structure **8a** was suggested for the reaction product. The formation of **8a** is assumed to proceed through the intermediacy of the Michael



Scheme 1



Scheme 2

*To receive any correspondence.

adduct **3** which loses ethyl cyanoacetate *via* an S_N2 displacement into dihydropyridazinone (**6**) which undergoes hydrolysis and autooxidation under the reaction conditions affording the acid **8a**. Similarly, the reaction of **1a** with **2e**,**f** and of **1b** with **2d–f** afforded **8b–f**.

Compounds **1c**,**d** reacted with 2-amino-1,1,3-tricyanopropene (**9a**) *via* a Knoevenagel condensation to yield the intermediate **11**, which then cyclised into pyridopyridazines **12a**,**b**.

In the reaction of **1c**,**d** with **9b** the formed esters were hydrolysed to give the corresponding acids **12c**,**d** by the water eliminated during the condensation step (see Scheme 2).

The reaction of **9a** with the ethyl arylhydrazonoacetoacetate **1a** afforded a mixture (1.2:1) of two products of molecular formulae $C_{16}H_{10}N_6O$ ($M^+ = 302$) and $C_{18}H_{18}N_6O_3$ ($M^+ = 365$), respectively. The former was identified as the pyridine derivative **13a** and the latter as the pyridazinecarboxamide **15a**. Structural assignments were based on analytical and spectral data. Thus, compound **13a** is coloured due to the presence of the hydrazone chromophore which is indicated by a strong UV band at 380 nm. The IR spectrum revealed the presence of a ring CO band at 1680 cm^{-1}, as well as two cyano bands at 2225 cm^{-1}. The ^1H NMR spectrum of **13a** indicated the expected aromatic multiplets, as well as signals at δ 8.22 for an NH proton and δ 2.35 for a methyl group. The IR spectrum of **15a** indicated the presence of bands for amide CO and NH_2 groups. The ^1H NMR spectrum was also in accordance with the proposed structure. A possible mechanism for the formation of both **13** and **15** is depicted in Scheme 2: in each case a Knoevenagel condensation would yield an intermediate **10**, cyclisation of which *via* the elimination of an ethanol molecule would afford **13**, while intramolecular cyclisation and hydrolysis would give **15**.

Similarly, **13b** and **15b** were formed from the reaction of **1b** with **9a**. The reaction of **1a**,**b** with ethyl 3-amino-2,4-dicyanoprop-2-enoate (**9b**) afforded only the carboxylic acids **16a**,**b** which are believed to be formed *via* hydrolysis of the esters **14c**,**d**.

Techniques used: ^1H NMR, MS

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