Nitriles in heterocyclic synthesis: the preparation of novel indeno[1,2-*d*]pyridazines, fused pyrazolo [5,1-*c*][1,2,4]triazines, and fluorenones†

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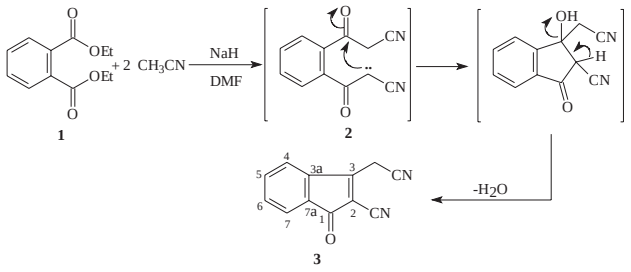
Treatment of the novel compound (2-cyano-1-oxo-1*H*-indene-3-yl) acetonitrile (**3**) with various reagents affords a variety of heterocyclic compounds in which the indenone system is incorporated into polycyclic compounds of potential pharmacological interest.

Keywords: nitriles, heterocyclic synthesis

Aroyl acetonitriles (ω-cyanoacetophenone and its derivatives) are versatile reagents and find many applications in heterocyclic synthesis. Many problems are encountered with the synthesis of such compounds. We report here a novel synthesis of new intermediate for the synthesis of heterocycles.

We have carried out intensive studies with activated nitriles as potential intermediates for the preparation of variety of heterocyclic systems for biological screening programs in our laboratory,[1-4] and as an extension of our recently reported procedures for the preparation of active cyanomethylene groups we tried to use diethyl phthalate as starting material to prepare the di(cyanomethyl) diketone **2** by the method of Hackler *et al*.[10] However, the reaction unexpectedly afforded a yellowish product with molecular ion peak at *m/z* 194 (100%) which corresponded to the structure (2-cyano-1-oxo-1*H*-indene-3-yl) acetonitrile (**3**), formed via the non-isolable intermediate **2** by loss of one molecule of water under the reaction conditions (Scheme 1).

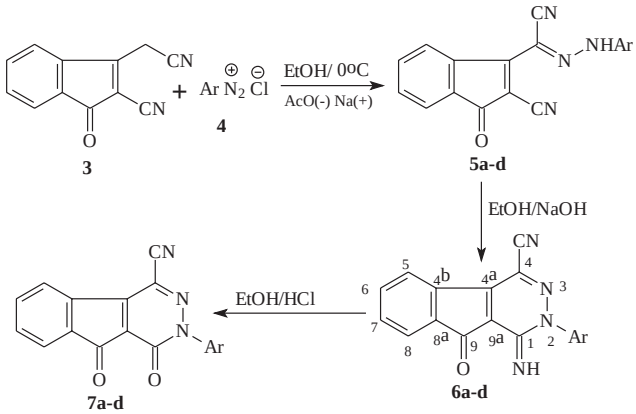


1 **2** **3**

Scheme 1 Formation of the indenone **3**.

Compound **3** proved to be a versatile starting material for the synthesis of a variety of fused heterocyclic compounds. Thus, when **3** was coupled with diazotised aromatic amines (**4a–d**) in ethanol in presence of sodium acetate[11] quantitative yields of highly violet coloured products in each case which were assigned as hydrazones **5** (Scheme 2). The IR spectrum (KBr) of **5a** revealed the presence of NH group at 3301, two (CN) functions at 2195 and 2185, and carbonyl group at 1658 cm^{-1}, the ^1H NMR spectrum (DMSO-d_6) revealed, in addition to the expected signals, a D_2O exchangeable singlet signal attributed to the NH function at 6.45 ppm. Also its mass spectrum revealed (M^+) at *m/z* = 298 (100%) corresponding to the molecular formula $C_{18}H_{10}N_4O$.

The derivatives **5a–d** underwent cyclisation on reflux in ethanolic sodium hydroxide[14] to afford the 2-aryl-1-imino-9-oxo-9*H*-indeno[1,2-*d*]pyridazine-4-carbonitriles (**6a–d**). Compounds **6a–d** could be converted into the corresponding 1,9-dioxo compounds **7a–d** by boiling in ethanolic HCl[14] (Scheme 2).



3 **4** **5a-d** **6a-d** **7a-d**

4-7a, Ar = C_6H_5
b, Ar = C_6H_4-CH_3(p)
c, Ar = C_6H_4-OCH_3(p)
d, Ar = C_6H_4-Cl(p)

Scheme 2 Synthesis of indeno[1,2-*d*]pyridazine derivatives **6**.

Structures **6** and **7** were consistent with their analytical and spectral data.

We next tried coupling of compound **3** with some diazotised heterocyclic amines[1] under the same experimental conditions. When compound **3** was treated with substituted pyrazole-5-diazonium chlorides **8a–d** violet coloured products were isolated which were formulated as 5-amino-6 (2-cyano-1-oxo-1*H*-inden-3-yl)-pyrazolo[5,1-*c*][1,2,4]triazine derivatives **10a–d**, formed via the intermediates **9** (Scheme 3). Both elemental and spectral data of **10a–d** are consistent with the assigned structures. Thus, their IR spectra showed absorptions at 3425–3340 cm^{-1} due to stretching vibrations of the NH_2 function, as well as CN stretching absorption peaks at 2190–2198 cm^{-1}. Formation of **10a–d** was assumed to proceed via electrophilic substitution in **3** followed by intramolecular cyclisation.

The pyrolysis[12] of **10a–d** at 300–320 ºC gave moderate yields (55–60%) of pentacycles formulated as 6-amino-7*H*-indeno[1',2':4,5]pyrido[2,3-*e*][pyrazolo[5,1-*c*][1,2,4]triazin-7-one derivatives **11a–d**. Their IR showed the presence of NH_2, and the absence of CN, stretching bands in **11a–c**.

Analogously, the coupling of compound **3** with 1,2, 4-triazole-3-diazonium nitrate (**12**) afforded compound **13**. The pyrolysis of compound **13** under the same experimental conditions as those applied to **10** gave the pentacyclic compound **14**. Its structure was established on the basis of the correct values in elemental analyses and compatible spectral data. Thus, there was IR and ^1H NMR spectral evidence for the presence of an NH_2 group, but no IR evidence for a CN group.

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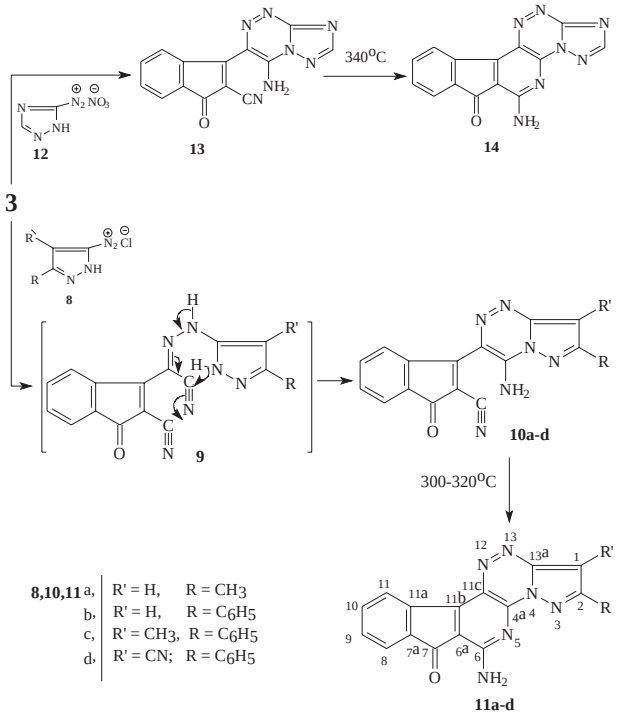
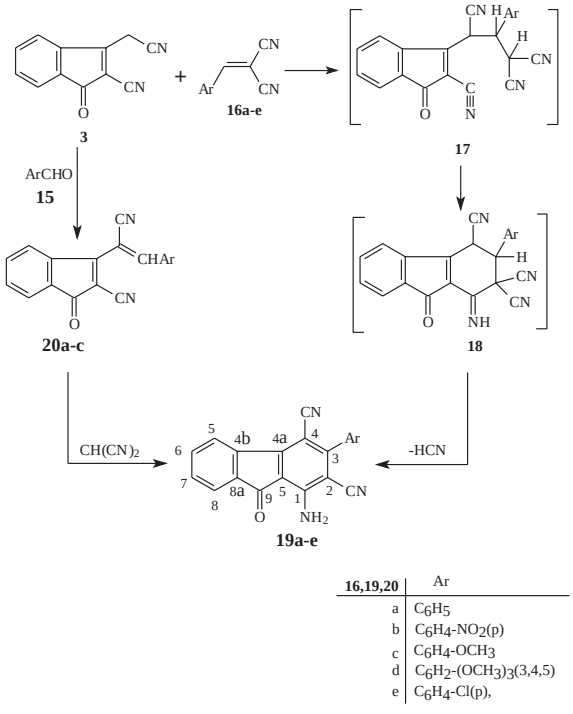
† Dedicated to the memory of the late Professor Zaghloul E. Kandeel



Scheme 3 Formation of polycyclic fused triazines **10–14**.



Scheme 4 Routes to the fluorenones **19a–e**.

Finally, our study was extended to investigate the behaviour of **3** towards some benzylidenemalononitriles. The work gave rise to the development of convenient approaches to the synthesis of a variety of polyfunctionally substituted fluoren-9-one derivatives in reasonable yield. Thus, compound **3** reacted with equimolar amounts of **16a–e** in absolute ethanol containing a catalytic amount of piperidine under reflux to yield the corresponding 1 : 1 adducts **19a-e**, in acceptable yields (Scheme 4). Compounds **19a–e** are believed to be formed via Michael type addition of active methylene in **3** to the double bond in **16** to yield a Michael adduct **17** which cyclises yielding **18** which in turn aromatises by loss of hydrogen cyanide to give the final isolated fluorenone derivatives **19a–e** under the reaction conditions.[4] Support for structure **19** for the reaction products was obtained from their alternative synthesis via condensation of **3** with the appropriate aryl aldehydes **15a–c** to yield the indenone derivatives **20a–c**, which in turn reacted with malononitrile to afford products that were identified as **19a–c**.

Techniques used: IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry

References: 16

Schemes: 4

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