Dimerisation of Knoevenagel Condensation Products obtained from Simple Unconjugated and α,β-Unsaturated Ketones

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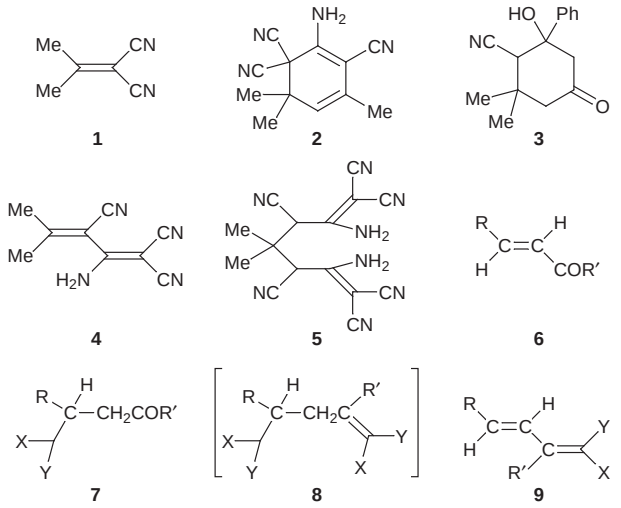
The reaction of 3-acetyl-2*H*-1-benzopyran-2-ones with malononitrile affords dicyanomethylene derivatives which dimerise to 1-amino-3,5,5-bis(2-oxo-2*H*-1-benzopyran-3-yl)-5-methyl-1,3-cyclohexadiene-2,6,6-tricarbonitrile derivatives and related dimeric intermediate products.

As part of a programme aimed at synthesising dicyanomethylene derivatives for screening as potential tyrosine kinase inhibitors,[1] we have examined the reactions of some β-enones (α,β-unsaturated ketones), as well as unconjugated ketones, with malononitrile. In recent years, it has been shown that the initial products of such reactions undergo considerable subsequent change, affording a wide variety of end products, some of them quite complex.[2]

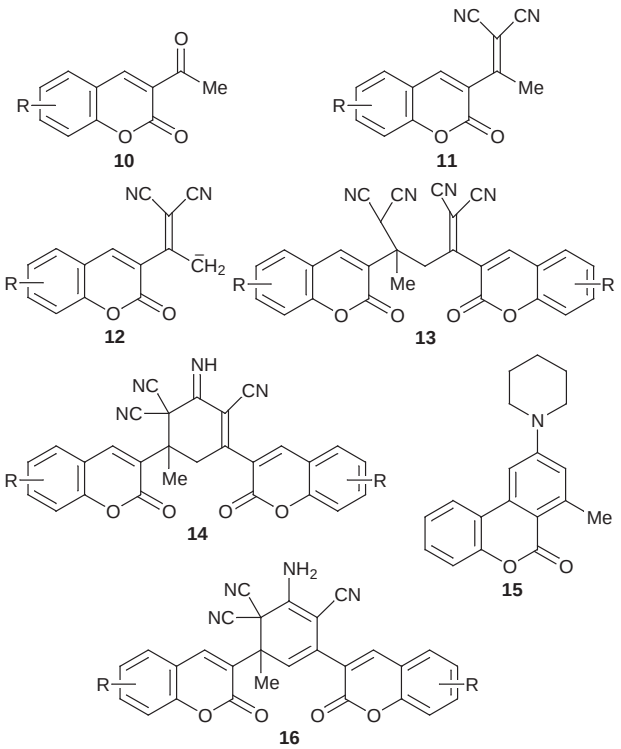
The condensation of simple unconjugated ketones such as acetone with compounds containing an active methylene group (such as malononitrile) has been the subject of considerable attention. The product formed by the base-catalysed reaction of acetone with malononitrile (and also by the piperidine-catalysed dimerisation of isopropylidenemalonitrile **1**) is the cyclohexadiene derivative **2**.[2,3]



When the methylene component of the Knoevenagel condensation is less reactive than malononitrile, facile dimerisation does not occur in the same way. Thus, the piperidine-catalysed reaction of acetone with benzoylacetonitrile affords the cyclohexane product **3**, by a reaction involving acetone and the nitrile component in a 2 : 1 ratio. (Earlier workers found that in the presence of ammonium acetate, this reaction afforded a Hantzsch-type 1,4-dihydropyridine derivative,[6,7] while in polyphosphoric acid it afforded a 1,(2)-dihydropyridin-2-one.[8] The reaction of acetone with 'malononitrile dimer', however, affords the simple 1 : 1 product **4**, together with traces of the 1 : 2 product **5**.

When β-enone derivatives are used in the reaction instead of unconjugated ketones, further variation is possible in the products.

The initial reaction of a compound containing a reactive methylene group with a β-enone derivative such as **6** may in theory occur at either of two possible sites—at the vinylene double bond with formation of **7** by Michael addition, or at the carbonyl group with formation of **9** by Knoevenagel condensation. A survey of recent β-enone literature indicates that under mild experimental conditions the Michael addition is favoured, to the virtual exclusion of the Knoevenagel condensation. Despite these findings, however, it now seems that the Knoevenagel condensation may also take place. The formation of the product **9** (R = Ph, R^1 = Me, X = Y = CN) from the reaction of 4-phenylbut-3-en-2-one **6** (R = Ph, R^1 = Me) with malononitrile under very vigorous conditions (catalytic ammonium acetate/acetic acid, with prolonged heating in a Dean-Stark apparatus) has been reported in the earlier literature,[12] and we now find that it is also formed under quite mild conditions (in ethanolic solution with catalytic piperidine). While there is an apparent contradiction between these results, it is possible to explain it by envisaging a mechanism such as **6** → **7** → **8** → **9**, where the initial Michael addition **6** → **7** is subsequently reversed in a retro-Michael reaction **8** → **9**.



a R = H; **b** R = 6-OMe; **c** R = 5-Br

* To receive any correspondence.

The bicyclic 3-acetyl-2*H*-1-benzopyran-2-one compounds **10** display some of the structural features of *β*-enones, and may be regarded as special instances of the latter. The reaction of **10a** with malononitrile, in ethanol containing piperidine, affords (by Knoevenagel condensation) the dicyanomethylene compound **11a** as the main product. Similarly, the 6-methoxy derivative **10b** affords **11b**. However, the product obtained from the reaction of the 5-bromo derivative **10c** is the dimer **16c**. This is structurally analogous to the cyclohexadiene product **2** which has been obtained from the reaction of malononitrile with acetone.[2]

A suggested mechanism for the formation of **2** in the presence of the base involves Michael addition followed by Thorpe cyclisation.[3] The corresponding mechanism for benzopyran derivatives would involve the sequence **11** + **12** → **13** → **14** → **15**.

In the course of the synthesis of the monomer **11a**, supporting evidence for this mechanism is obtained when small amounts of the dimeric product **13a** are formed. This dimer is not stable in solution; when it is heated under reflux in dimethylformamide, it is converted into the monomer **11a**, presumably by a retro-Michael reaction. In solution in [$^2H_6$]DMSO, the NMR spectra show that both monomerisation (to **11a**) and cyclisation (to **14a**) take place to a limited extent, the signals for both products appearing together with the parent **13a**.

The cyclised dimer **14a** is the sole product isolated from attempts to dimerise the preformed monomer **11a** at room temperature. At higher temperatures, decomposition occurs, the only isolable material being the byproduct **15**, which is obviously formed from **11a** in a reaction involving both solvent (acetone) and catalyst (piperidine).

Some corrections to the relevant literature are necessary. A claim[15] to have synthesised the monomeric product **11a** cannot be accepted, as the details supplied are not compatible with the structure **11a** or with the results obtained by us. The structure **11a** has also been ascribed to a compound obtained by heating the *β*-enone **10a** with malononitrile in dimethylformamide under reflux;[16] the details supplied in this case suggest that this product may actually have been the dimer **13a** (which of course has the same empirical formula as **11a**). A recent report[17] that the condensation of **10a** with malononitrile in benzene in the presence of ammonium acetate and acetic acid affords **11a** is correct.

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

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