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A simple one-pot, multi-component synthesis of cyano-functionalized bis-β-diketones

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ABSTRACT

Mild, multi-component Knoevenagel condensation/Michael addition reactions of dibenzoylmethane (Hdbm) and methylene-active cyano molecules with formalin in ethanol gave cyano methylene-bridged bis-diketones. The syntheses of 1,1,5,5-tetrabenzoyl-3,3-dicyanopentane (1) and 1,1,7,7-tetrabenzoyl-3,5-dicyano-3,5-dimethoxycarbonyl-heptane (4) are reported. Increasing the reaction time with the reagents for 1 led to the formation of the ester (2,2-dicyano-4-benzoylbutyl) benzoate (2). The isolation of 2,2-dicyano-4,4-dipivaloyl-1-butanol (3a), the *tert*-butyl analogue of a proposed intermediate in the formation of 2, provides evidence for a possible reaction pathway. Methylene-bis(dibenzoylmethane) (mdbm) was obtained in good yield from the reaction between Hdbm and formalin, by the addition of the base triethylamine. The X-ray crystal structures of 1–4 and mdbm were determined using synchrotron radiation.

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The installation of dicyano groups onto organic scaffolds remains an interesting topic as a result of the varied avenues of further modification such groups allow.¹ Of further interest are a number of biologically relevant molecules that contain polycyano functionalities, which have been shown to possess either fungicidal,² arthropodicidal,³ antimicrobial⁴ or insecticidal⁵ properties. The evaluation of antiviral⁶ and antimitotic⁷ properties of some species is a parallel focus.

Malononitrile and related species are a convenient source of dicyano groups and exhibit reactivity towards a range of substrates, including alkyl halides and aldehydes, as well as self-reactivity by di- and tri-merization.⁸ The reactivity of malononitrile with β -diketones in the presence of formaldehyde has been largely used to impart aromatic functionalities⁹ and for cycloaddition.¹⁰ Retention of dicyano functionality is unusual for such reactions, which usually replace the methylene hydrogen atoms by a double bond.¹¹ This probably results from the reactivity of dinitrile moieties towards ketone-containing species.¹²

Our interest in cyano-functionalized β -diketones is derived from our recent studies with small cyano anions¹³ and on lanthanoid dibenzoylmethanide cluster chemistry.¹⁴ The ability to synthesize ligands that contain bidentate metal binding groups (e.g., β -diketones), yet retain a reactive cyano-functionality may allow the synthesis of porous coordination polymers (CPs) possessing the ability to impart selective cyanation of substrates. Here we report our progress in synthesizing such ligands with the facile one-pot synthesis and characterization of three quaternary dicyano moieties, including a bis- β -diketone species bearing cyano functionalities. In a simple one-pot reaction, dibenzoylmethane [Hdbm or dipivaloylmethane (Hdpm)] and a CH₂-acidic cyano compound such as malononitrile [CH₂(CN)₂, mn] or methyl cyanoacetate [CH₂(CN)(CO₂Me), mca] were reacted with formalin in boiling ethanol. In the absence of the cyano compound, we obtained the well-known methylenebis(dibenzoylmethane) (**mdbm**), for which we have determined the crystal structure for the first time. Catalyst-free domino reactions involving formaldehyde and 1,3-dicarbonyl compounds are well established in the synthesis of organic compounds.¹⁵

Dibenzoylmethane (Hdbm), formalin and malononitrile $[CH_2(CN)_2]$, in a 2:2:1 stoichiometric ratio, yielded 1,1,5,5-tetrabenzoyl-3,3-dicyanopentane (1) within 2 h of heating. It was found to crystallize from the reaction solution upon cooling in a yield of 37%. A longer reaction time, independent of an excess of Hdbm and formalin, resulted in colourless (2,2-dicyano-4-benzoylbutyl) benzoate (2) being precipitated from the boiling solution, its insolubility in ethanol preventing further reaction (Schemes 1 and 2).

To prepare **1**, two formaldehyde molecules were condensed to form two methylene bridges, which link the central dicyano methane moiety to the two outer dibenzoylmethane groups. Product **2** is formally composed of one equivalent of Hdbm and malononitrile, and 2 equiv of formaldehyde. This reaction was repeated and monitored by ¹H NMR spectroscopy at 30 min intervals (performed on the crystallized products obtained upon cooling). The spectra revealed that the majority of **1** was formed within 1.5 h. Its





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Scheme 1. Condensation products.



Scheme 2. Proposed reaction path for the formation of compounds 1 and 2.

concentration in the crystallized samples was then found to decrease and that of **2** increase, until, after 4 h, **2** was the main product, **1** and **mdbm** also being detectable. After 15 h, **2** was found to precipitate exclusively (66% yield) and with high purity. Each of the isolated crystalline products **1–4** and **mdbm** is shown in Figure 1. A crystallographic summary is given in Table 1.

The addition of triethylamine to a hot solution of Hdbm and formalin in ethanol led to the exclusive precipitation of methylenebis(dibenzoylmethane) (**mdbm**) within minutes, which could be collected by filtration in high purity and yield. The triethylamine prevents the formation of the mixed products described above and greatly accelerates the formation of **mdbm**. It and other bisdiketones have also been synthesized by Claisen-condensations, the reaction between bis(acyl chlorides) and diketo alkali salts,¹⁶ and the iron-catalysed oxidative reactions of 1,3-dicarbonyl compounds and *N*,*N*-dimethylaniline.¹⁷ It has also been found that the formation of bis- β -diketones occurs at room temperature with the addition of a different base (e.g., piperidine).^{16b} The acetylacetone (Hacac) analogue of **mdbm**, 3,5-diacetylheptane-2,6-dione,



Figure 1. X-ray crystal structures of compounds **1–4** and **mdbm**; carbon, oxygen and nitrogen atoms are depicted in grey, red and blue, respectively. All hydrogen atoms and lattice solvent molecules were omitted for clarity. Thermal ellipsoids are shown at 50% probability.

was reported earlier and its synthesis is similar, and proceeds without the addition of base.¹⁸ A 1:1 reaction of Hacac/CH₂O in ethylene glycol at 60 °C for 5.5 hours afforded a 2:2 Hacac/formal-dehyde pyran heterocycle in 42% yield.¹⁹ This heterocycle is the product of the initially formed 3,5-diacetylheptane-2,6-dione, analogous to **mdbm**. Its subsequent reaction with a further formaldehyde molecule followed by intramolecular cyclization gives 1,1',1''-[(5*R*S,6*R*S)-6-hydroxy-6-methyl-3,4,5,6-tetrahydro-2*H*-pyr-an-3,3,5-triyl]-triethanone.¹⁹ The linear 3:2 Hacac/formaldehyde 3,5,5,7-tetraacetylnonane-2,8-dione has also been isolated.²⁰ It was obtained after three days of stirring of the reactants (in a 3:2 molar ratio) in ethanol at room temperature.

Formation of **1** occurs by the condensation reaction of 2 equiv of Hdbm and formaldehyde with one equivalent of malononitrile (Scheme 2). Continued heating of **1** in the presence of water probably instigates fragmentation of **1** into product **3** (**3a** being the isolated *tert*-butyl analogue, see below) and Hdbm.

The intramolecular cyclization in which the hydroxyl arm of the intermediate species **3** attacks the carbonyl group, affords a cyclic six-membered pyran intermediate (Scheme 2) (see above for the analogous acacH/CH₂O species¹⁹). This is followed by a rearrangement with concomitant decyclization, affording the thermody-namically favoured benzoate ester **2** (Scheme 2). The related 4,4-diacetylheptanedinitrile was obtained previously from a reaction of acrylonitrile, a Michael-acceptor, with acacH, in a 2:1 mole ratio, under basic conditions.²¹ In this case, both protons of the diketo-backbone carbon atom were replaced by the Michael-acceptor, acrylonitrile.

¹H and ¹³C NMR spectroscopy, microanalyses and mass spectrometry measurements confirmed the composition of products **1** and **2**. The characteristic methylene and backbone proton

Table 1
Crystallographic data for compounds 1–4 and mdbm

	1	2	3a	4	mdbm
Chemical formula	$C_{38}H_{32}N_2O_5$	$C_{20}H_{16}N_2O_3$	$C_{16}H_{24}N_2O_3$	$C_{41}H_{34}N_2O_8$	$C_{31}H_{24}O_4$
Formula mass	596.66	332.35	292.37	682.70	460.50
Crystal system	Triclinic	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	$P\overline{1}$	$P\overline{1}$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a (Å)	10.4150(5)	7.3407(4)	15.149(3)	5.7910(12)	11.253(2)
b (Å)	10.6451(4)	10.9839(7)	6.2870(13)	11.958(2)	12.634(3)
<i>c</i> (Å)	14.6761(6)	11.2795(6)	17.798(4)	26.661(5)	17.590(4)
α (°)	82.271(2)	73.916(2)	90	78.34(3)	95.01(3)
β (°)	81.506(2)	82.005(2)	105.70(3)	86.70(3)	98.49(3)
γ (°)	80.132(2)	72.542(2)	90	78.11(3)	104.45(3)
Unit cell volume (Å ³)	1575.48(12)	832.05(8)	1631.8(6)	1769.1(6)	2375.0(8)
Temperature (K)	123(1)	123(1)	100(2)	100(2)	100(2)
Ζ	2	2	4	2	4
Reflections observed	19789	11250	25244	28000	39605
Unique reflections	7096	3726	3739	7401	10095
R _{int}	0.0352	0.0180	0.0787	0.0354	0.0280
Final R_1 values $(I > 2\sigma(I))$	0.0478	0.0472	0.0517	0.0694	0.0459
Final $wR(F^2)$ values $(I > 2\sigma(I))$	0.1159	0.1342	0.1306	0.1872	0.1204
Final R_1 values (all data)	0.0774	0.0611	0.0647	0.0787	0.0521
Final <i>wR</i> (<i>F</i> ²) values (all data)	0.1301	0.1690	0.1400	0.1958	0.1261
Goodness of fit on F ²	1.053	0.602	1.064	1.084	0.980

resonances, and their different shifts and splitting patterns allow easy distinction between the compounds. Compound **2** has a unique $-COO-CH_2-C(CN)_2$ - singlet resonance at 5.00 ppm, and the diketo-backbone $-(CO)_2-CH-CH_2$ - triplet protons of **1** and **mdbm** are at 6.04 ppm and 5.74 ppm, respectively. The striking absence of a vibrational nitrile stretching band (usually around 2250 cm⁻¹) in the infrared spectra of both **1** and **2** is likely due to the electronwithdrawing groups attached to the carbon atom binding both nitriles, which is known to result in very weak or absent bands.²² However, this characteristic nitrile stretching feature was detected by Raman spectroscopy at 2250 cm⁻¹.

We reasoned that increasing the steric bulk of the diketone would inhibit the intramolecular cyclization/ring-opening pathway (Scheme 2), hence 2,2,6,6-tetramethyl-heptane-3,5-dione (dipivaloylmethane, Hdpm) was substituted for Hdbm. This resulted in the formation of 2,2-dicyano-4,4-dipivaloyl-1-butanol (**3a**), the *tert*-butyl analogue of the intermediate **3** shown in the rectangle in Scheme 2. This demonstrated that the inclusion of a bulky *tert*-butyl group does prevent the attack on the nearest carbonyl group by the intermediate alcohol (Scheme 2). This result is important, as it highlights a means of controlling the location of the labile ester in a product derived from the use of unsymmetrical diketone starting materials. Ester **2** can thus be regarded as a protected alcohol. Its deprotection offers a handle for further modification that may be used in the synthesis of complex dicyano-containing species such as fused 6,7,5-tricarbocyclic systems.²³

A reaction involving methyl cyanoacetate (mca), another active methylene compound, in an excess relative to Hdbm, promotes the formation of 1,1,7,7-tetrabenzoyl-3,5-dicyano-3,5-dimethoxycarbonylheptane (**4**) when reacted with formalin. Two equiv of Hdbm and mca reacted with three equivalents of formaldehyde. This demonstrates that exchanging the electron-withdrawing group positioned adjacent to the cyano group does not inhibit the overall reactivity. An excess of mca and formalin was required, as reactions performed analogously to those that led to the isolation of compounds **1** and **2** yielded only Hdbm after refluxing for 15 h in ethanol.

The insolubility of the synthesized compounds involving Hdbm in ethanol is highly advantageous for the separation of the products from the reaction solutions. All the compounds precipitated either upon cooling (**1**, **4** and **mdbm**) or directly from the boiling solution (**2**). The formation of the 2:3:2 product **4** instead of the 2:2:1 products (**1** and **3a**) is a result of the slightly changed acidity of the methylene protons in mca compared with malononitrile. Thus, an excess of mca compared with Hdbm is required for the reaction to proceed. The crystal structures of all the compounds reveal that they exist exclusively as the keto form in the solid state, and that the diketo carbon backbone has a tetrahedral stereochemistry in all cases (Fig. 1).

In conclusion, the fast and simple one-pot reaction of a diketone, formalin and methylene-active compounds such as malononitrile or methyl cyanoacetate leads to the formation of cyanofunctionalized methylene-bridged bis-diketones **1** and **4**. The outcome of the reaction is highly dependent on the stoichiometry and reaction times. The precipitation of an insoluble ester **2** from the boiling reaction solution was observed. Product **2** is considered to result from an intramolecular cyclization/ring-opening process. Evidence for the intermediate species is provided by the isolation of a trapped *tert*-butyl-analogue **3a**. These species offer great promise as ligands in porous coordination polymers which may show cyanation activity, as well as a novel means of grafting cyano groups onto organic scaffolds.

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Supplementary data

CCDC 916898 (1), 916899 (2), 916900 (3), 916901 (4) and 916902 (**mdbm**) contain the supplementary crystallographic data. These data can be obtained free of charge via http://www.ccdc.ca-m.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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