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ONE-POT FORMATION OF FUNCTIONALISED 2-PIPERIDINONES FROM ARYLIDENECYANOACETATES AND METHANOLIC AMMONIA *VIA* TANDEM REACTIONS

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Abstract – Aryl aldehydes react with ethyl cyanoacetate in methanolic ammonium acetate to expeditiously furnish, besides high yields of arylidenecyanoacetates, 4,6-diaryl-3,5-dicyano-5-ethoxycarbonyl-2-piperidinones in low yields. But preformed arylidenecyanoacetates react with methanolic ammonia to furnish the same functionalised 2-piperidinones in much better yields. The actual stereostructure of one of the products was determined by single crystal X-ray diffraction analysis, and novel tandem reactions occurring in one pot are proposed for the formation of the products.

INTRODUCTION

The importance of heterocyclic compounds as drugs is well documented.[1] Our ongoing interest in the development of newer synthetic routes to heterocyclic molecules having proven and/or potential bioactivity[2] drew our attention to substituted 3-cyanopyridin-2(1*H*)-ones since they exhibit plant growth inhibitory, cardiotonic, hypoglycemic and antiviral properties.[3] In fact, three such compounds are available commercially.[4] This class of compounds are mainly prepared by the reaction of β-diketones, β-ketoesters, conjugated enones or enals with cyanoacetamide using a variety of bases, phase transfer catalysts, resins or enzymes as the catalysts.[5] But most of these methods have their own disadvantages, for which newer synthetic routes to this class of compounds continue to be developed.[6]

In response to this continuing need, we planned to develop a new synthetic route to functionalised 3-cyano-

2-pyridones by the reaction of aryl aldehydes, ethyl cyanoacetate, a methyl ketone and ammonium acetate in methanol – a modification of a recent report.[7] Accordingly, benzaldehyde and isobutyl methyl ketone were used in the above mentioned reaction. It furnished, apart from the corresponding Knoevenagel condensate as the major product, a minor product which was not the target molecule, which did not involve the ketone at all and whose formation could not be explained by any straightforward mechanism. The product was identified as 3,5-dicyano-4,6-dipheyl-5-ethoxycarbonyl-2-piperidinone. A rational follow-up of this observation led to development of a better, general route to the formation of similarly substituted 2-piperidinones from arylidenecyanoacetates. We propose a sequence of tandem reactions occurring in one pot for their formation. Our findings, since mechanistically significant, are presented briefly in this paper.

RESULTS AND DISCUSSION

As stated above, initially benzaldehyde (**1a**) was treated with equimolar amounts of ethyl cyanoacetate (**2**), isobutyl methyl ketone and ammonium acetate in methanol at room temperature. The reaction, complete in five minutes, resulted in the formation of two products (TLC). The major (42%), less polar product was identified spectroscopically as the Knoevenagel condensate, *E*-ethyl 2-cyanocinnamate (**3a**). The minor (14%), more polar product, $C_{22}H_{19}N_3O_3$ (HR EI-MS), was unambiguously identified as 3,5-dicyano-4,6-diphenyl-5-ethoxycarbonyl-2-piperidinone (**4a**) by combined spectroscopic analysis. The depicted stereostructure of **4a** was ascertained from its single crystal X-ray diffraction analysis,[8] and the ORTEP diagram of **4a** is shown in Figure 1. The reactions along with the expected and isolated products are shown in Scheme 1.

This unexpected observation prompted us to check the generality of the reaction before looking into its mode of formation. Accordingly, the reaction was repeated with each of eight benzaldehydes (**1a**-**f**, **h**, **i**)

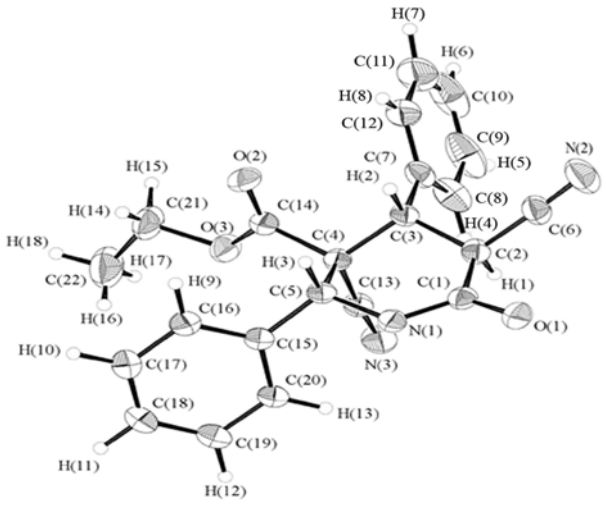
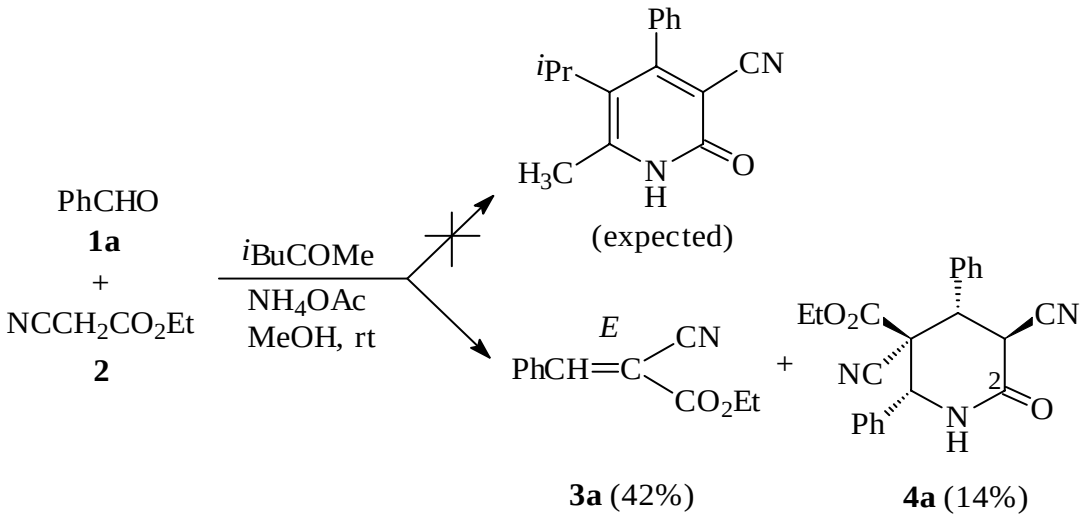


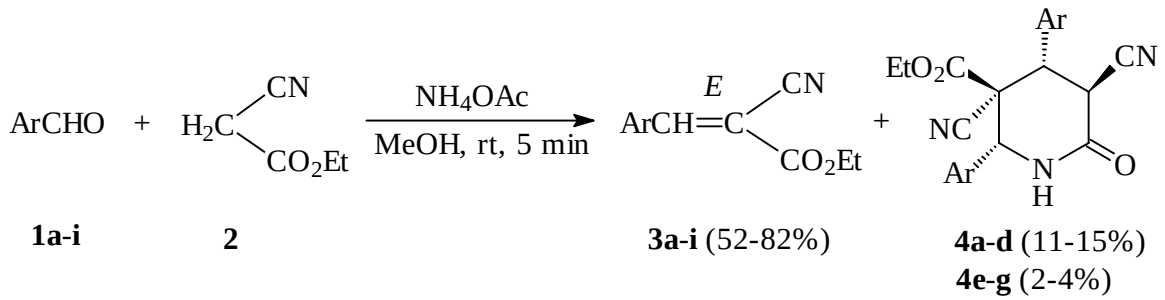
Figure 1: The ORTEP diagram of compound **4a**



Scheme 1

and 2-naphthaldehyde (**1g**), but without using the ketone. All the reactions were complete within five minutes, furnishing single product from each of **1h** and **1i** and two products - one major and one minor - from each of the rest of the substrates. The major products (52-81%) from **1a-g** and the only products from **1h** (82%) and **1i** (79%) were identified as the corresponding Knoevenagel condensates, i.e. the corresponding *E*-arylidenecyanoacetates (**3a-i**) from their ^{1}H NMR spectra and by comparing their melting points with those reported in the literature (*vide* Experimental). The minor products (2-15%) from **1a-g** were identified spectroscopically as the respective 4,6-diaryl-3,5-dicyano-5-ethoxycarbonyl-2-piperidinones (**4a-g**). The depicted stereostructures of **4b-g** were assumed from the similarity of their mainly NMR spectroscopic data to those of **4a**. Noticeably, 4-nitrobenzaldehyde (**1h**) and veratraldehyde (**1i**) did not furnish the respective 2-piperidinones. The reactions are presented in Scheme 2 and the results in Table 1.

A survey of the literature at this stage revealed that Nagai *et al.* had previously prepared the 2-piperidinones **4a** (38.4%) and **4f** (15.5%) from the same substrates (viz. **1a** and **1f**) as ours but by using ethanolic ammonia (instead of methanolic ammonium acetate, used by us) and by keeping these solutions in fridge for ten days.[9] They also subjected **1b** and **1h** separately to similar reaction conditions, but none of them furnished either the Knoevenagel condensates (**3b**/**3h**) or the corresponding 2-piperidinones (**4b**/**4h**). Since Nagai's work lacked generality (involved only two 2-piperidinones) and the reactions required ten days, we



Scheme 2

Table 1. Reactions of ArCHO with $NCCH_2CO_2Et$ and NH_4OAc-MeOH

Entry	(**1**) Ar = 4-R-C_6H_4 (for **a**-**f**, **h**)	Yield (%) of (**3**)[a]	Yield (%) of (**4**)[b]	Overall Yield (%)
1	**a**: R = H	58	15	73
2	**b**: R = Cl	52	13	65
3	**c**: R = Br	69	11	80
4	**d**: R = CN	62	14	76
5	**e**: R = Me	73	4	77
6	**f**: R = OMe	81	2	83
7	**g**: 2-naphthyl	69	4	73
8	**h**: R = NO_2	82	—	82
9	**i**: veratryl	79	—	79

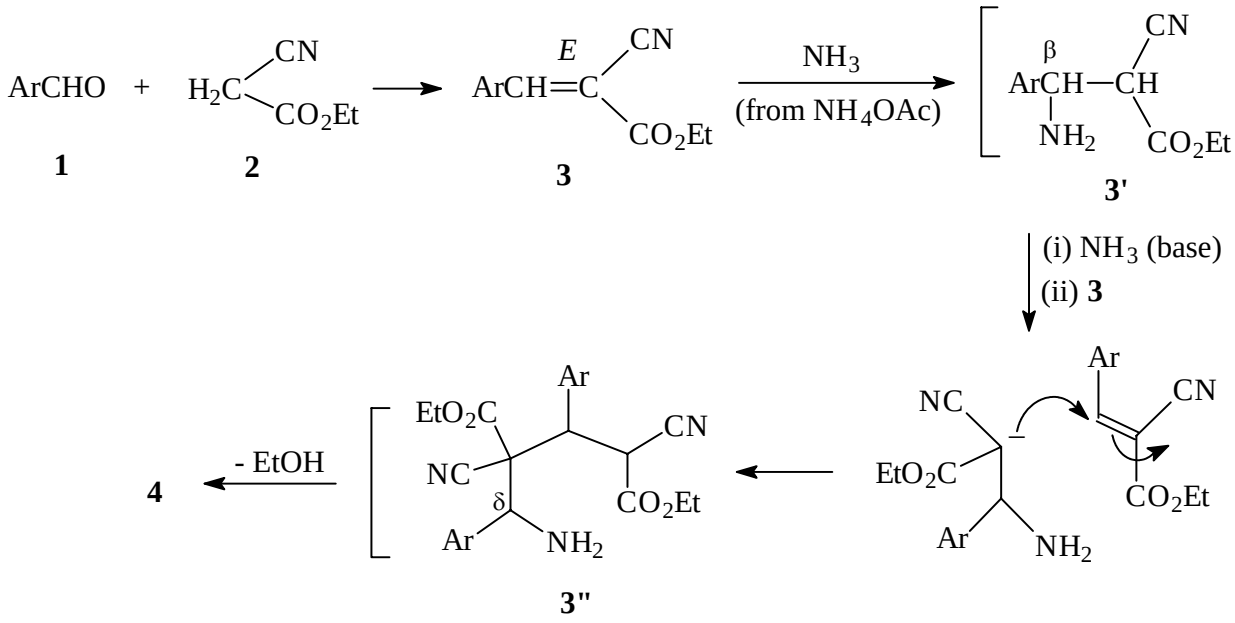
[a]Identified by ^{1}H NMR and mps; [b]Identified by spectroscopic (IR, ^{1}H and ^{13}C NMR, DEPT 135, LR/HR EI/FAB/ESI-MS) and elemental analysis.

went ahead with our study.

We envisaged the following sequence of tandem reactions to explain the formation of **4**. We believed, the initially formed Knoevenagel condensates (**3**) are the actual substrates. They then undergo Michael attack by one molecule of ammonia, formed in situ from ammonium acetate, to result in the formation of the unisolated β-aminoesters (**3′**). The derived anion, formed by ammonia as the base, triggers a second Michael addition at the β-position of another molecule of **3** to form the δ-aminoester (with respect to the terminal ethoxycarbonyl group) (**3″**). Finally, cyclocondensation with the loss of one molecule of ethanol furnishes the substituted 2-piperidinones (**4**) (Scheme 3).

Since the Knoevenagel condensates (**3**) were considered by us to be the initial products, each of **3a** and **3b**, as representative molecules, was separately treated with ammonium acetate in methanol at room temperature. In each case, the starting **3** remained partly unconsumed even after a prolonged reaction period (5 h), leading, however, to the isolation of **4a** and **4b** in better yields, viz. 24% and 35%, respectively. This observation thus lent support to the proposed mechanism.

Since the yields of the isolated 2-piperidinones **4a** and **4b** obtained from the respective Knoevenagel condensates **3a** and **3b** and methanolic ammonium acetate were still not satisfactory, a number of preformed arylidenecyanoacetates (**3a**-**i**) were treated separately with methanolic ammonia, instead of methanolic ammonium acetate, at room temperature, in order to obtain better yields of the 2-piperidinones. The reaction with the anisylidene derivative (**3f**) was inordinately sluggish (18 h) and furnished **4f** in only



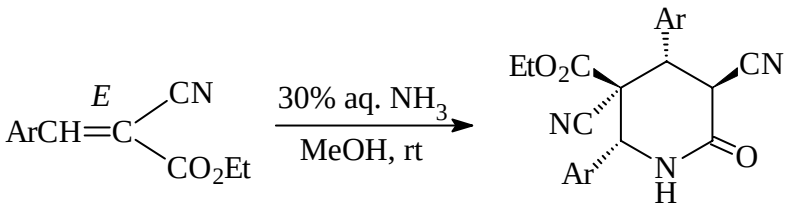
Scheme 3

5% yield, whereas **3h** and **3i** did not react at all. For the rest of the substrates, the reactions were complete within 20-60 minutes, furnishing the respective 2-piperidinones (**4a**-**e**, **g**) in even better (than for the reactions of aryl aldehydes or arylidenecyanoacetates with methanolic ammonium acetate) yields, viz. 30-69% (except for **4f**, 5%). These reactions are presented in Scheme 4 and the results in Table 2.

That the reactions with **3h** and **3i** did not produce any 2-piperidinone and that **3f** furnished **4f** in extremely low yield, constitutes an evidence in support of the proposed mechanism, since the presence of either a strong electron-withdrawing group (as in **3h**) or strong electron-donating groups (as in **3f** and **3i**) render these molecules weaker Michael acceptors.

Pertinently, some of these functionalised 2-piperidinones, viz. **4a**, **b**, **f** have been recently reported to be formed by the reaction of the preformed arylimines and ethyl cyanoacetate using sodium ethoxide in ethanol[10] and have been shown to display antibacterial property.[11]

In conclusion, while trying to develop a new route to substituted 3-cyano-2-pyridones, we have found out that (i) the arylidenecyanoacetates (**3**), i.e. the Knoevenagel condensates are better substrates (than the aryl aldehydes themselves) for the preparation of the functionalised 2-piperidinones (**4**), specially if the aryl aldehydes do not bear a strong electron-donating group (e.g. **1f**, **i**) or electron-withdrawing group (e.g. **1h**),



3a-i **4a-e**, **g** (30-69%)
4f (5%)

Scheme 4

Table 2. Reactions of arylidenecyanoacetates (**3**) with NH_3-MeOH

Entry	(**3**): Ar = 4-R-C_6H_4 (for **a**-**f**, **h**)	Time	Yield (%)[a] of (**4**)[b]
1	**a**: R = H	20 min	30
2	**b**: R = Cl	20 min	48
3	**c**: R = Br	20 min	60
4	**d**: R = CN	60 min	50
5	**e**: R = Me	35 min	69
6	**f**: R = MeO	18 h	5
7	**g**: 2-naphthyl	30 min	35
8	**h**: R = NO_2	—	—
9	**i**: veratryl	—	—

[a]Refer to isolated, pure products; [b]Identified by spectroscopic (IR, ^{1}H and ^{13}C NMR, DEPT 135, LR/HR EI/FAB/ESI-MS) and elemental analysis.

and (ii) methanolic ammonia at room temperature brings about the reactions (of **3**) much faster (20-60 min) than does ethanolic ammonia (10 days in fridge) for the aryl aldehydes (**1**). We have also established for the first time the actual stereostructure of **4** by single crystal X-ray diffraction analysis (of **4a**), which renders the stereostructures suggested for **4** by Nagai (based on Dreiding model) and by Rai (based on assumption) invalid.

In view of the fact that the last decade witnessed a large number of functionalised piperidines entering preclinical and clinical trials,[12] our present work assumes importance since these δ-lactams can be reduced chemoselectively to the corresponding piperidines in the presence of other reducible groups.[13] Moreover, these δ-lactams contain cyanide and ethoxycarbonyl groups and a carbanion-generating centre (CH-3), all of which can be used as handles for various chemical transformations.[14] The δ-lactams as well as their transformation products are likely to have bioactive potential, which, though not yet explored, adds to the importance of the present work.

EXPERIMENTAL

Mps were determined on a Toshniwal apparatus and are uncorrected. IR spectra (nujol) were recorded in a Nicolet Impact 410 FT-IR spectrophotometer, and ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, both 1D and 2D, including DEPT 135, in a Bruker DRX 500 NMR spectrometer. The LR EI/FAB-MS, HR EI/FAB-MS (using *m*-nitrobenzyl alcohol as the liquid matrix) and HR ESI-MS were recorded in JEOL JMS-AX505HA, JEOL JMS-700 MStation and Qtof Micro YA263 mass spectrometers,

respectively. Column Chromatography (CC) was carried out over silica gel (60-120 mesh, Qualigens, India). PE refers to petroleum ether, bp 60-80 °C.

General experimental procedure. Reactions of aryl aldehydes (1) with NH_4OAc/MeOH. To a solution of NH_4OAc (3 mmol) in MeOH (8-10 mL) were added successively **1** (2 mmol) and **2** (2 mmol), and the resulting solution was stirred at rt until the reaction was complete (TLC). Water (5 mL) was then added to the reaction mixture and the solution extracted with EtOAc (3×15 mL). The combined solvent extracts were washed with water, dried (Na_2SO_4) and the solvent removed. The resulting residue was purified by CC to furnish **3** and **4** in 3-5% and 15-25% EtOAc/PE eluates, respectively.

Reactions of 3 with 30% aq. NH_3/MeOH. To a solution of **3** (1 mmol) in MeOH (10 mL) was added 30% aq. NH_3 (2 mL), and the resulting solution was stirred at rt. After the reaction was complete (TLC), the reaction mixture was heated on steam-bath to remove both NH_3 and MeOH. The resulting residue was purified by CC, as before, to furnish **4a**-**g**.

Mps of compounds **3**: **3a**: oil (lit.,[15] 49-50 °C); **3b**: 90-91 °C (PE-EtOAC) (lit.,[16] 91-92 °C); **3c**: 95-96 °C (PE-EtOAc) (lit.,[17] 96 °C); **3d**: 170-171 °C (PE-CH_2Cl_2) (lit.,[18] 168.5-168.9 °C); **3e**: 90-91 °C (PE-EtOAc) (lit.,[19] 90 °C); **3f**: 88-89 °C (PE-EtOAc) (lit.,[20] 89-90 °C); **3g**: 124-125 °C (PE-EtOAc) (lit.,[21] 125-126 °C); **3h**: 168-169 °C (EtOAc) (lit.,[20] 169-170 °C); **3i**: 155-157 °C (EtOAc) (lit.,[20] 157 °C).

Spectroscopic data of the known piperidinones (**4a**, **b**, **f**) are not furnished here. Their mps: **4a**: 180-181 °C (PE-EtOAc) (lit.,[10] 171-173 °C); **4b**: 188-190 °C (PE-CH_2Cl_2) (lit.,[10] 192-194 °C); **4f**: 207-210 °C (decomp) (PE-EtOAc) (lit.,[9] 211-214 °C).

4,6-Bis(4-bromophenyl)-3,5-dicyano-5-ethoxycarbonyl-2-piperidinone (**4c**): mp 244-246 °C (PE-EtOAc); IR: 3354, 2249, 1744, 1681, 1490, 1249, 1075, 1010, 844, 824, 764 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.83 (3H, t, J=7 Hz), 3.85 (1H, dq, J_1=11 Hz, J_2=7 Hz), 3.89 (1H, dq, J_1=11 Hz, J_2=7 Hz), 4.59 (1H, d, J=13 Hz), 5.06 (1H, d, J=13 Hz), 5.34 (1H, s), 7.23 (2H, d, J=8.5 Hz), 7.41 (2H, d, J=8.5 Hz), 7.62 (2H, d, J=8 Hz), 7.63 (2H, d, J=8 Hz), 8.97 (1H, s); ^{13}C NMR : δ 14.1 (CH_3), 64.2 (CH_2), 39.1, 47.0, 60.7, 130.5, 131.5, 132.5, 132.8 (all CH), 58.9, 114.6, 117.1, 123.6, 123.7, 134.1, 134.7, 163.7, 164.7 (all C); EI-MS: *m/z* (%) 533 (M^++4, <5), 531 (M^++2, <5), 529 (M^+, <5), 281 (71), 279 (62), 252 (83), 251 (100), 250 (81), 249 (59), 236 (39), 234 (54), 209 (15), 208 (21), 207 (28), 206 (23), 200 (19), 182 (19), 180 (21), 171 (33), 155 (38), 127 (67), 100 (16), 44 (26); HRMS (FAB+): calcd for $C_{22}H_{18}N_3O_3{}^{79}Br^{81}Br$, 531.9694 ($M^+$+H); found 531.9682; Anal. Calcd for $C_{22}H_{17}N_3O_3{}^{79+81}Br_2$: C, 49.71; H, 3.20; N, 7.91. Found: C, 49.75; H, 3.21; N, 7.93.

4,6-Bis(4-cyanophenyl)-3,5-dicyano-5-ethoxycarbonyl-2-piperidinone (**4d**): mp 188-190 °C (PE-EtOAc); IR: 3257, 2223, 1738, 1686, 1609, 1276, 1083, 1001, 844, 724 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.80 (3H, t, *J*=7 Hz), 3.84 (1H, dq, J_1=11 Hz, J_2=7 Hz), 3.87 (1H, dq, J_1=11 Hz, J_2 = 7 Hz), 4.76 (1H, d, *J*=13 Hz), 5.22 (1H, d, *J*=13 Hz), 5.46 (1H, s), 7.47 (2H, d, *J*=8.5 Hz), 7.67 (2H, d, *J*=8.5 Hz), 7.91 (2H, d, *J*=8.5 Hz), 7.94 (2H, d, *J*=8.5 Hz), 9.09 (1H, br s); ^{13}C NMR: δ 14.1 (CH_3), 64.5 (CH_2), 38.8, 47.4, 60.9, 129.6, 130.5, 133.5, 133.8 (all CH), 58.4, 113.2, 113.3, 114.3, 116.9, 119.02, 119.04, 139.8, 140.3, 163.6, 164.4 (all C); LR FAB-MS (+): *m*/*z* 424 (M^++H), 447 (M^++Na); HRMS (FAB+): calcd for $C_{24}H_{18}N_5O_3$, 424.1409 (M^++H); found 424.1418; Anal. Calcd for $C_{24}H_{17}N_5O_3$: C, 68.08; H, 4.02; N, 16.55. Found: C, 68.13; H, 4.01; N, 16.58.

4,6-Bis(4-tolyl)-3,5-dicyano-5-ethoxycarbonyl-2-piperidinone (**4e**): mp 184-186 °C (PE-EtOAc); IR: 3200, 2249, 1735, 1676, 1513, 1252, 1096, 1063, 1019, 813, 718 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.83 (3H, t, *J*=7 Hz), 2.29 (3H, s), *ca.* 2.3 (3H, s), 3.83 (1H, dq, J_1=14 Hz, J_2=7 Hz), 3.84 (1H, dq, J_1=14 Hz, J_2=7 Hz), 4.49 (1H, d, *J*=13 Hz), 4.93 (1H, d, *J*=13 Hz), 5.31 (1H, s), 7.19 (2H, d, *J*=8 Hz), 7.20 (2H, d, *J*=9.5 Hz), 7.21 (2H, d, *J*=9.5 Hz), 7.33 (2H, d, *J*=8 Hz), 8.87 (1H, br s); ^{13}C NMR: δ 14.2, 21.54, 21.57 (all CH_3), 63.8 (CH_2), 39.3, 47.3, 61.0, 128.2, 129.1, 129.9, 130.2 (all CH), 59.6, 115.1, 117.4, 131.9, 132.5, 139.4, 139.8, 163.9, 164.9 (all C); FAB-MS (+): *m*/*z* 402 (M^++H); HRMS (FAB+): calcd for $C_{24}H_{24}N_3O_3$, 402.1818 (M^++H); found 402.1812; Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.82; H, 5.73; N, 10.47. Found: C, 71.86; H, 5.72; N, 10.49.

4,6-Bis(2-naphthyl)-3,5-dicyano-5-ethoxycarbonyl-2-piperidinone (**4g**): mp 199-200 °C (PE-EtOAc); IR: 3184, 2256, 2223, 1759, 1686, 1600, 1255, 1222, 1089, 1009, 870, 817, 758 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.67 (3H, t, *J*=7 Hz), 3.79 (1H, dq, J_1=14 Hz, J_2=7 Hz), 3.81 (1H, dq, J_1=14 Hz, J_2=7 Hz), 4.83 (1H, d, *J*=13 Hz), 5.22 (1H, d, *J*=13 Hz), 5.61 (1H, s), 7.46 (1H, d, *J*=8 Hz), 7.53-7.58 (4H, m), 7.63 (1H, d, *J*=8 Hz), 7.87 (1H, s), 7.93 (2H, d, *J*=8 Hz), 7.97 (4H, dd, J_1=8 Hz, J_2=2.5 Hz), 8.04 (1H, s), 9.12 (1H, s); ^{13}C NMR: δ 14.1 (CH_3), 63.9 (CH_2), 39.4, 47.8, 61.5, 125.54, 125.55, 127.5, 127.6, 127.81, 127.84, 128.2, 128.4, 128.6, 129.0, 129.1, 129.7, 129.8, 130.0 (all CH), 59.6, 115.1, 117.4, 133.0, 133.25, 133.28, 133.5, 134.1, 135.4, 163.9, 165.0 (all C); FAB-MS (+): *m*/*z* 474 (M^++H); HRMS (FAB+): calcd for $C_{30}H_{24}N_3O_3$, 474.1818 (M^++H); found 474.1815; Anal. Calcd for $C_{30}H_{23}N_3O_3$: C, 76.11; H, 4.86; N, 8.88. Found: C, 76.18; H, 4.85; N, 8.89.

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8. Crystal data for **4a**: $C_{22}H_{19}N_3O_3$, *FW* = 373.41, colourless, crystal dimension 0.25 × 0.25 × 0.30 mm, monoclinic, space group *P2₁/n (#14)*, *a* = 6.132(2) Å, *b* = 20.905(4) Å, *c* = 16.083(2) Å, α = β = γ =

90.0000°, V = 2061.8(8) Å^3, Z = 4, d_c = 1.203 g/cm^3, λ = 1.54178 Å, μ(Mo K_α) = 0.665 mm^{-1}, F(000) = 784.00, $2\theta_{max}$ = 145.3°, R = 0.102, wR_2 = 0.153. Crystallographic data (excluding structure factors) for **4a**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-639606. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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