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REACTIONS OF β-KETO ESTERS WITH 2-CYANO-1,2,5,6-TETRAHYDROPYRIDINES

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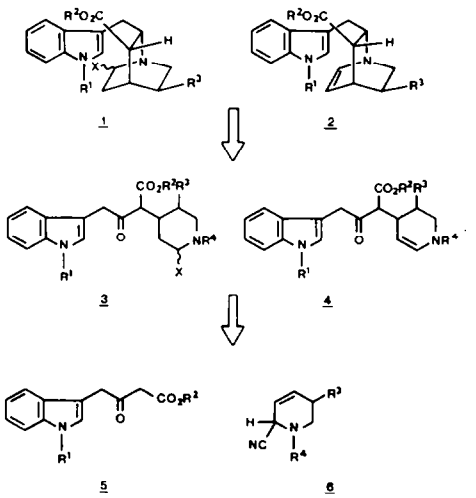
Abstract—Reaction of the sodium salts of β-keto esters **13a** and **13b** with the 2-cyano-tetrahydropyridines **11** and **12** afforded the 4-substituted piperidine derivatives **21–23**. The structures were assigned on the basis of their ^{1}H- and ^{13}C-NMR spectra and by comparison with the model compounds **24–26**. The stereochemistry and mechanism of the reactions are discussed.

In view of the intense current interest in the chemistry of 2-cyano-1,2,5,6-tetrahydropyridines[1–18] and particularly their use in alkaloid synthesis we are prompted to report our own preliminary findings in this area. Our attention was originally drawn to these compounds as a means of generating the 4-substituted piperidine derivatives **3** and **4** required for the synthesis of indole linked quinuclidines of type **1** and **2** (Scheme 1).

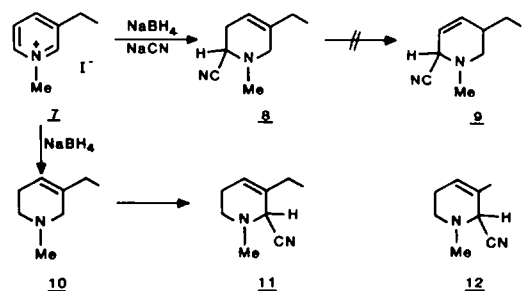
For this purpose we ideally required the 5-substituted 2-cyano-1,2,5,6-tetrahydropyridine **6** which it was envisaged would react with the β-keto ester **5** to give the required adducts **3** and **4**. However, in common with other groups,[5] we were frustrated in achieving this goal by the lack of availability of the 5-substituted tetrahydropyridine **6**. Thus, reductive cyanation[19] of N-methyl-3-ethylpyridinium iodide **7** afforded only the 2-cyano-1,2,3,6-tetrahydropyridine **8** and all attempts to isomerise this to the required 2-cyano-1,2,5,6-tetrahydro isomer **9** were unsuccessful. Furthermore, application of the modified Polonovski reaction to N-methyl-3-ethyl-1,2,5,6-tetrahydropyridine **10** gave only the known 3-substituted 2-cyano-1,2,5,6-tetrahydropyridine **11**. We therefore chose to examine in the first instance the reactions of the more readily available 2-cyano-1,2,5,6-tetrahydropyridines **11** and **12** with appropriate β-keto esters and it is the results of this study which are reported herein.

A variety of methods leading to the required β-keto esters **13a** and **13b** were investigated (Scheme 3). The best method for the preparation of these compounds was found to involve reaction of the corresponding acyl imidazole derivatives **14a** and **14b** with the magnesium enolate of monoethyl or monomethyl malonate which gave the required β-keto esters in overall yields of 75 and 50% respectively from indole acetic acid.

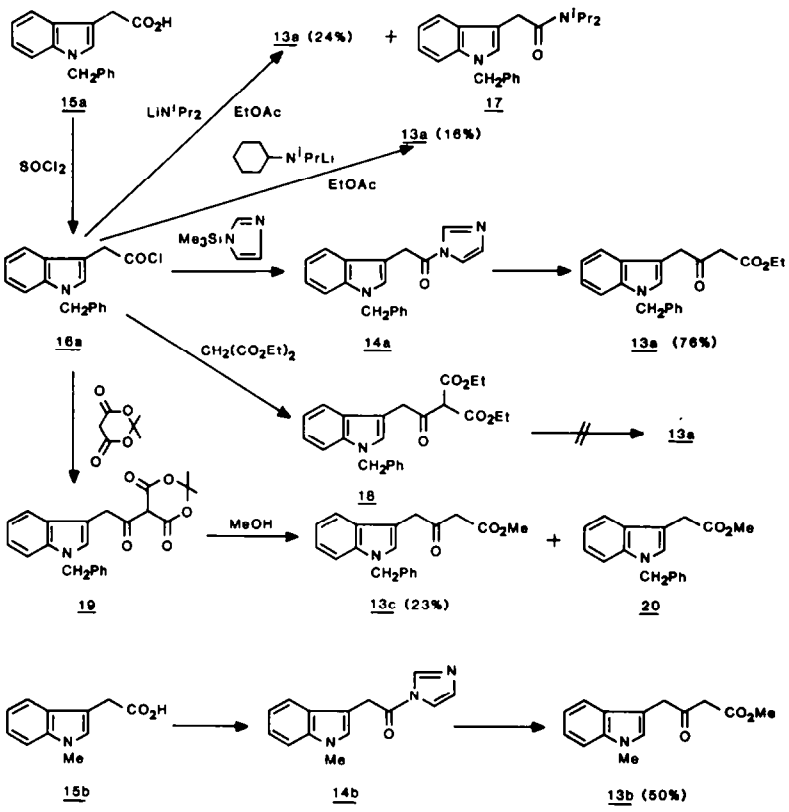
Treatment of the sodium enolate of **13a** with the amino-nitrile **11** in the presence of silver tetrafluoroborate afforded a mixture of the nitrile adduct **21** and the enol ether **22** whose relative proportions could be estimated by reverse phase HPLC. A longer reaction time gave the nitrile **21** and the presence of the enol ether **22** was not detected. The use of zinc chloride[7] in place of silver tetrafluoroborate gave the nitrile as the major product and lead to only minor amounts of the oxygen heterocyclic product. The use of the silyl enol ether[14,15] in place of the sodium enolate of **13** was precluded by the difficulty of purifying and characterising the required silyl enol ether. In an effort to optimise the yield of the nitrile adduct the reaction of the sodium enolate of **13b** with amino-nitrile **12** was immediately followed by treatment of the crude product with excess



Scheme 1.



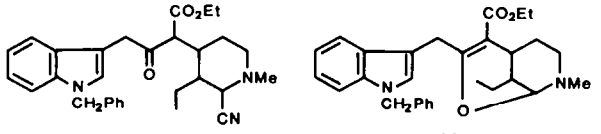
Scheme 2.



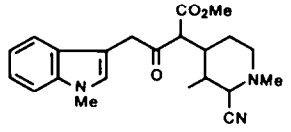
Scheme 3.

potassium cyanide which indeed led to the isolation of **23** as the sole product from this reaction.

structural assignments for these compounds and exclude the alternative enamine structure (e.g. **27**) (cf.



$AgBF_4$	2–3 hr. r.t.	43%	32%
$AgBF_4$	13 hr. r.t.	43%	0%
$ZnCl_2$	22 hr. 60°	major	minor



The structures assigned to compounds **21** and **23** were based primarily on the analysis of their ^{1}H- and ^{13}C-NMR spectra (Tables 1 and 2) and in particular upon their comparison with model compounds **13, 15** and **24–26**. In the case of **21** and **23** the ^{13}C-spectra in particular indicated that more than one diastereoisomer was present, although in each case one major component could be identified and could be further purified by preparative HPLC. Comparison of the ^{13}C-NMR spectra of **23** and **24**[1] on the one hand, and **22** and **26**[1] on the other prove beyond doubt the **25**)[14] from further consideration. Thus, for example, the presence of signals at 114.7(s), 62.4(d) and 37.7(d) are seen to be characteristic of the CN, C-2′ and C-3′ carbon atoms in **23** and **24**,[1] and the absence of signals at 132.2(d) and 108.3(s) which are observed for **25**[14] exclude the enamine formulation **27**. Furthermore, the signals at 202.8(s), 56.4(d) and 168.9(s) are seen to be typical of the intact β-keto ester grouping. In the case of the cyclic enol ether **22** the absence of the peaks at 202.8 and 56.4 and their replacement by peaks at 167.9(s) and 100.5(s) is seen to be characteristic of the replacement of

Table 1. ^{1}H-NMR spectral data†

	15a	15b	13a	13b	24a[1]	25[14]	26[1]	21	22	23
NCH$_2$Ph	5.27 s	—	5.20 s	—	—	—	—	5.24 d(16) 5.33 d(16)	5.30 s	—
NCH$_3$	—	3.60 s	—	3.62 s	—	—	—	—	—	3.61 s
CH$_3$CO	—	—	—	—	2.23 s	2.27 s	2.31 s	—	—	—
CH$_2$CO	3.67 s	3.60 s	3.40 s	3.40 s	—	—	—	4.2 m	4.03 d(14) 4.48 d(14)	3.8 m
COCH$_2$CO	—	—	3.87 s	3.82 s	—	—	—	—	—	—
COCHO	—	—	—	—	3.63 d 3.71 d	3.50 br	—	4.3 m	—	3.9 m
OCH$_2$CH$_3$	—	—	4.06 q(6)	—	—	—	—	4.24 q(7)	4.20 m	—
OCH$_2$CH$_3$	—	—	1.16 t(6)	—	—	—	—	1.33 t(7)	1.28 t(7)	—
OCH$_3$	—	—	—	3.57 s	3.76 s	3.74 s	3.68 s	—	—	3.77 s
N^{1}CH$_3$	—	—	—	—	2.41 s	2.40 s	2.42 s	2.61 s	2.17 s	2.32 s
H-2′	—	—	—	—	3.93 m	5.41 br s	4.69 s	4.28 br s	4.57 s	3.8 m
H-3′	—	—	—	—	—	—	1.96 m	1.8 m	1.68 m	1.9 m
H-4′	—	—	—	—	1.5–2.1 m 1.5–2.0 m		2.79 br s	2.0 m	2.91 br s 2.4 m	
H-5′	—	—	—	—			1.65 m	2.5 m	1.80 m	
H-6′	—	—	—	—	2.74 m	2.58 m	2.55 m	2.78 m	2.40 m	2.7 m
CCH$_2$CH$_3$	—	—	—	—	1.32 m	2.17 q(7)	1.40 m	1.57 m	1.11 m	—
CCH$_2$CH$_3$	—	—	—	—	0.97 t(6)	0.92 t(7)	0.95 t (7)	0.92 t(7)	0.83 t(7)	—
CCH$_3$	—	—	—	—	—	—	—	—	—	0.83 d(6)

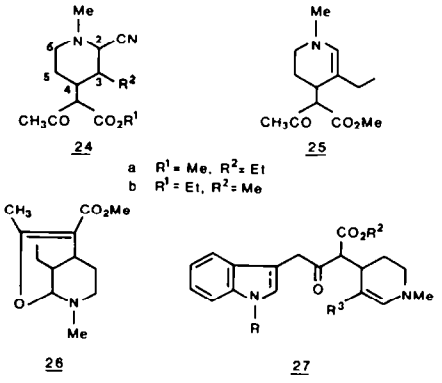
† Spectra recorded in $CDCl_3$ solution, except for **15a** and **15b** which were recorded in d_6-DMSO.

Table 2. ^{13}C-NMR spectral data†

	15a	15b	13a	13b	24b	25[14]	26	21	22	23
C-2	127.23	128.14	127.59	128.22	—	—	—	127.41	126.88	128.40
C-3	107.07	106.98	106.88	105.91	—	—	—	103.11	112.33	105.84
C-4	127.83	127.56	127.96	127.62	—	—	—	127.33	127.58	127.67
C-5	121.29	121.11	122.27	121.92	—	—	—	121.90	121.40	121.89
C-6	118.94	118.51	119.79	119.41	—	—	—	119.30	119.85	119.41
C-7	118.74	118.76	118.89	118.65	—	—	—	118.45	118.86	118.59
C-8	109.92	109.43	109.92	109.40	—	—	—	109.90	109.31	109.49
C-9	138.13	136.52	137.28	136.98	—	—	—	137.72	137.85	137.01
NCH$_2$Ph	48.93	—	50.08	—	—	—	—	49.77	49.80	—
NCH$_3$	—	32.07	—	32.60	—	—	—	—	—	32.57
Ph	135.96	—	136.71	—	—	—	—	136.46	136.28	—
	126.97	—	126.88	—	—	—	—	126.39	126.67	—
	128.41	—	128.63	—	—	—	—	128.64	128.52	—
	127.53	—	127.73	—	—	—	—	126.54	127.35	—
C-10	30.85	30.79	40.08	39.91	29.42	29.9	19.48	—	30.80	39.46
C-11	172.95	173.06	201.10	201.14	201.99	200.3	168.47	—	167.92	202.85
C-12	—	—	47.75	47.35	59.16	58.8	104.48	—	100.55	56.36
C-13	—	—	167.35	167.75	168.62	167.4	168.23	171.67	169.38	168.97
OCH$_2$CH$_3$	—	—	61.27	—	67.86	—	—	60.34	59.54	—
OCH$_2$CH$_3$	—	—	14.07	—	16.05	—	—	14.19	14.42	—
OCH$_3$	—	—	—	52.10	—	50.5	50.88	—	—	51.87
C-2					62.43	132.2	92.22	63.26	91.24	62.40
C-3′					37.65	108.3	27.80	37.25	29.20	37.75
C-4′					35.58	37.3	39.04	33.93	39.78	35.38
C-5′					29.63	26.9	21.92	24.90	22.74	26.97
C-6′					50.53	49.7	45.35	45.78	45.30	50.47
C—CH$_2$CH$_3$					—	22.1	23.74	22.95	27.93	—
C—CH$_2$CH$_3$					—	11.0	11.78	12.03	11.27	—
C—CH$_3$					14.07	—	—	—	—	15.77
N′—CH$_3$					43.70	43.9	42.74	43.55	42.00	43.55
CN					114.74	—	—	115.62	—	114.71

† Spectra recorded in $CDCl_3$ solution, except for **15a** and **15b** which were recorded in d_6-DMSO.

the ketone group by an enol ether moiety. Finally, the attachment of an O atom at C-2′ is characterised by the appearance of this carbon at 91.2 ppm in line with the model compound **26**.[1]

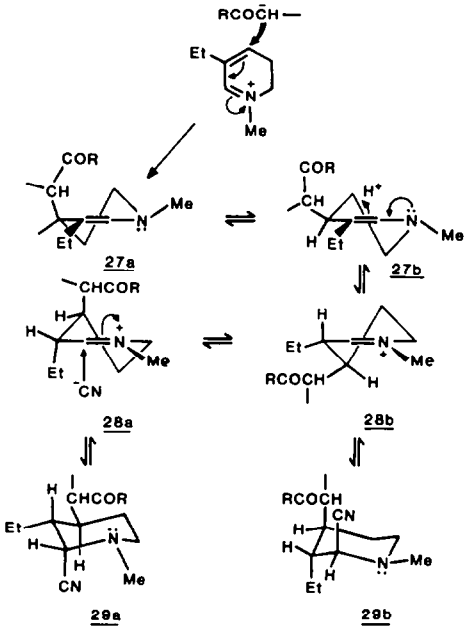


24 25

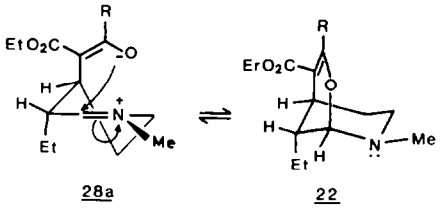
a R^1 = Me, R^2 = Et
b R^1 = Et, R^2 = Me

26 27

In considering the mechanisms of the various reactions taking place it is assumed that the first step involves loss of cyanide from the 2-cyano-1,2,5,6-tetrahydropyridine (e.g. **11**) to generate a 5,6-dihydropyridinium salt which undergoes addition by the β-keto ester enolate to give the enamine (**27**); under the reaction conditions employed the subsequent steps outlined in Scheme 4 can then occur. A more detailed understanding of the stereochemical consequences of the process can be obtained by considering a number of fundamental principles which are known to apply to enamine reactions. Thus it has been deduced[20] that electrophilic addition to 1,2,3,4-tetrahydropyridines occurs in an axial fashion on the same face of the molecule as the N lone pair. This implies that starting from the preferred conformation of the enamine **27b** the minimum ion **28a/b** would be generated. Attack by CN^- from the face opposite to protonation[2] could in



Scheme 4.



28a 22

Scheme 5.

principle generate either **29a** or **29b**. The currently available evidence would suggest that the former is preferred and this can be rationalized on the assumption that attack from the underface of **28b** is precluded by steric factors.

The formation of the cyclic ether **22** also involves the iminium ion **28a** which this time undergoes internal attack from the top face by the oxyanion. This allows maximum overlap in the transition state between the incoming nucleophile and the developing lone pair on nitrogen,[20,21] while retaining the chair conformation of the 6-membered ring. This would clearly be preferable to the alternative cyclisation of **28b** which could only be achieved at the expense of adopting a boat conformation.

EXPERIMENTAL

IR spectra were recorded on a Pye Unicam SP150 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian HA 100 and XL 100 instruments using TMS as internal standard. 360 MHz spectra were provided by the Edinburgh University WH-360 NMR Service. Mass spectra were recorded on an A.E.I. MS9 double focusing instrument at 250° and 70 V.

THF was distilled over calcium hydride and stored under N_2. CH_2Cl_2 was passed down an alumina column and distilled.

Column chromatography was carried out with Merck 7734 silica and flash chromatography with Merck 9385 using CH_2Cl_2/EtOAc (19/1) as eluent.

1-Methyl-2-cyano-5-ethyl-1,2,3,6-tetrahydropyridine **8**

To a stirred soln of KCN (5.0 g, 77 mmol) in water (10 ml) layered with ether (15 ml) was added a soln of 5 N HCl (6 ml, 30 mmol), keeping the temp below 15°. 1-Methyl-3-ethyl-pyridinium iodide (2.62 g, 21 mmol) was added portionwise followed by $NaBH_4$ (1.00 g, 26 mmol), and the stirring continued for 5 hr at room temp. The ether layer was separated, cooled and treated with MeI (0.2 ml) at 5° for 30 min to react with any other reduced material. No ppt was observed. The soln was concentrated to an orange oil (1.53 g) which was purified by column chromatography an alumina (CH_2Cl_2/hexane 10%) to give **8** (0.91 g, 58% yield) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.05 (t, 3H, CH_3), 1.85 (m, 2H, CH_2), 2.00–3.5 (m, H-3 and H-6), 2.40 (s, N—CH_3), 3.80 (dd, 1H, H-2), 5.65 (m, 1H, H-4). MS *m/e* (rel. int.) 150 (M^+, 13.8%), 135 (20.8%), 123 (38.4%), 122 (100%), 121 (49.8%).

Attempted isomerization of amino nitrile **8**

The nitrile **8** (0.40 g, 2.7 mmol) in 2.2 N HCl was stirred at 80° for 30 min, cooled, and then treated with KCN until the soln was basic. Extraction with ether yielded only starting material.

1-Benzylindole 3-acetic acid **15a**

To a stirred soln of 75% NaH (7.36 g, 230 mmol) in HMPA (40 ml) and THF (250 ml) at 0° was added a soln of indole-3-acetic acid (20.0 g, 115 mmol) in THF (50 ml), followed after 10

min by benzyl chloride (26.5 ml, 230 mmol). The mixture was stirred at room temp overnight under N_2. Excess hydride was destroyed by addition of MeOH and water, and the soln extracted with ether. The aqueous layer was acidified with 6 N HCl and the organic layer separated, washed several times with water and the resulting cream coloured ppt filtered off and dried over P_2O_5 under vacuum at 35° to give the **15a** (29.07 g, 96% yield). IR 1710, 2500–3300 cm^{-1}. M.p. 154–156° (lit. 148°,[24] 150°[25]).

1-*Benzylindole* 3-*acetyl chloride* **16a**

To a stirred suspension of **15a** (10 g, 37.8 mmol) in dry ether (175 ml) at −10° was added $SOCl_2$ (30 ml) and the mixture refluxed for 10 min. The soln was evaporated to give **16a** (10.5 g), a brown oil, which was used without further purification. ^{1}H-NMR ($CDCl_3$) as δ 4.15 (s, 2H, CH_2), 5.10 (s, 2H, N—CH_2), 6.85–7.85 (m, 10H, arom.).

Ethyl 4-(1-*benzylindol*-3-*yl*)-3-*oxobutanoate* **13a**

(i) *Using lithium diisopropylamine*/EtOAc. n-BuLi (8.76 ml, 13.4 mmol) was added over 15 min to diisopropylamine (1.39 g, 13.7 mmol) while stirring at −10°. After a further 15 min at the temp THF (25 ml) was added and the mixture cooled to −70°. A soln of EtOAc (0.59 g, 6.7 mmol) in THF (10 ml) was added dropwise over 5 min followed after 10 min by a soln of **16a** (1.90 g, 6.7 mmol) in THF (25 ml). The temp was maintained at −70° for a further 10 min and then allowed to reach −25° over 20 min. The soln was then quenched with 20% HCl (10 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with sat Na_2CO_3 aq (50 ml), water (50 ml) dried over $MgSO_4$ and evaporated to give a brown oil (2.46 g) which was purified by flash chromatography. Pure **13a** (10.56 g, 24% yield) m.p. 67° was obtained after recrystallization from benzene/pet. ether, IR 1720, 1740 cm^{-1}. (Found: C, 75.3; H, 6.21; N, 4.18%. Calc for $C_{21}H_{21}NO_3$: C, 75.3; H, 6.31; N, 4.18%.)

Diisopropylamide **17** (0.39 g, 16.9% yield) was also obtained. ^{1}H-NMR ($CDCl_3$) δ 1.0 (d, 6H, 2 × CH_3), 1.4 (d, 6H, 2 × CH_3), 3.4 (q, 1H, CH), 4.0 (q, 1H, CH), 3.75 (s, 2H, CH_2), 5.2 (s, 2H, N—CH_2), 6.9–7.7 (m, 10H, arom.). MS *m/e* (rel. int.) 348 (M^+, 9.0%), 220 (81.9%).

(ii) *Using lithium* N-*isopropylcyclohexylamine*/EtOAc. To N-isopropylcyclohexylamine (2.32 g, 23 mmol) under N_2 at −10° was added 1.33 M n-BuLi (15.03 ml, 23 mmol) over 15 min and the mixture left stirring a further 15 min. THF (20 ml) was added followed, at −73°, by EtOAc (1.013 g, 11.5 mmol). After 5 min, a soln of **16a** (3.24 g, 11.5 mmol) in THF (10 ml) was added and stirred for a further 10 min at this temp. The mixture was quenched with 20% HCl (10 ml), allowed to reach room temp; and then extracted with ether (3 × 20 ml). The combined ether extracts were washed with sat Na_2CO_3 aq (2 × 20 ml), water (2 × 20 ml), dried over Na_2SO_4 and concentrated to a brown oil (3.24 g). This was purified by flash chromatography to give **13a** (0.60 g, 16% yield).

(iii) *Attempted preparation via malonate* **18**. To 60% NaH (0.564 g, 14.1 mmol) in THF (40 ml) at 0° under N_2 was added with stirring a soln of diethyl malonate (2.26 g, 14.1 mmol) in THF (10 ml). Stirring was continued for 2 hr and **16a** (4 g, 14.1 mmol) dissolved in THF (20 ml) was added. The mixture was stirred at room temp for a further 2 hr before being quenched with 20% HCl (10 ml) and extracted with ether (3 × 20 ml). The combined ether extracts were washed with water (3 × 20 ml), dried over Na_2SO_4 and evaporated to give a brown oil (3.68 g). The crude material was refluxed for 4 hr in THF/5% water and Al_2O_3 (10 g), the alumina was removed by filtration and the filtrate extracted with ether (3 × 20 ml). The combined ether extracts were dried over Na_2SO_4 and concentrated to a brown oil. This was purified by column chromatography on silica to give only **18** (1.87 g). ^{1}H-NMR ($CDCl_3$) δ 1.2 (dt, 6H, 2 × CH_3), 3.3 (s, < 1 H, D_2O exchanged, OH), 3.4(s), 3.5(s), 3.7(s), 4.1 (dq, 4H, 2 × CH_2), 5.0 (d, 2H, N—CH_2), 6.72(s), 6.8(s), 6.8–7.6 (m, 10H, arom.).

A soln of KOH (0.224 g, 4 mmol) in dioxan (20 ml) and EtOH (4 ml) was added dropwise over 15 min to a stirred soln of **18** (1.55 g, 3.8 mmol) and 18-crown-6 in dioxan (30 ml) kept below 15°. The mixture was stirred at room temp overnight and then refluxed for 7 hr. The soln was cooled, pentane (50 ml) added, followed by 3 N HCl (1.5 ml). The organic layer was removed, washed with sat KCl aq (30 ml), dried over $MgSO_4$ and evaporated to give a brown oil. This was purified by filtration through alumina (pentane eluent). Flash chromatography led to the recovery of **18** (1.1 g).

(iv) *Via acyl imidazole* **14a**. A soln of **16a** (9.5 g, 33.5 mmol) in dry benzene (20 ml) was added to a stirred soln of N-trimethylsilylimidazole[22] (4.7 g, 33.5 mmol) in dry benzene (20 ml) at 0°. This was stirred for 45 min at room temp and then concentrated to give the derivative **14a** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ 4.0 (s, 2H, CH_2), 5.0 (s, 2H, NCH_2), 6.8–7.5 (m, 12H, arom.), 8.2 (s, 1H).

A stirred soln of $Mg(OEt)_2$ (3.65 g, 32 mmol) and hydrogen ethyl malonate[23] (4.22 g, 32 mmol) in THF (60 ml) was heated at 70–73° for 1 hr. The solvent was evaporated off, dry benzene added and this similarly removed. This was repeated four times to leave a white powder. To the powder stirred in THF (50 ml) was added a soln of **14a** (11 g, 32 mmol) in THF (50 ml) and left stirring under N_2 at 75° for 2.5 hr. The solvent was removed at < 40° and the residue treated with conc HCl (6.0 ml), water (1.0 ml) and, after 10 min agitation, sat NaCl aq (30 ml). This mixture was extracted with CH_2Cl_2 (4 × 30 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a brown fibrous solid (11.12 g). Purification by flash chromatography gave **13a** (8.56 g, 76% yield).

Methyl 4-(1-*benzylindol*-3-*yl*)-3-*oxobutanoate* **13c**

A soln of **16a** (2.92 g, 12 mmol) in THF (20 ml) was added dropwise to a stirred soln of Meldrum's acid (2.3 g, 16 mmol) and dry pyridine (1.8 ml, 22 mmol) in THF (20 ml) under N_2 at 0°. The mixture was stirred for 1 hr at this temp and a further 1 hr at 25°. A small amount of red solid was filtered off, the filtrate concentrated to about half volume and MeOH (30 ml) added. The soln was refluxed for 2 hr and then concentrated to a brown oil which was dissolved in CH_2Cl_2 (30 ml). The organic soln was washed with 1 N HCl (2 × 20 ml), 0.5 M $NaHCO_3$ (2 × 20 ml), water (2 × 20 ml), dried over $MgSO_4$ and evaporated to give a brown oil. This was purified by flash chromatography to give, as oils, **13c** (0.88 g, 23% yield). ^{1}H-NMR ($CDCl_3$) δ 3.40 (s, 2H, $COCH_2CO$), 3.55 (s, 3H, OCH_3), 3.85 (s, 2H, CH_2CO), 5.15 (s, 2H, NCH_2), 6.9–7.6 (m, 10H, arom.). MS *m/e* (rel. int.) 321 (M^+, 7.8%), 290 (3.0%), 289 (8.2%), 220 (40.9%), 91 (100%) and **20** (0.3 g, 9% yield). ^{1}H-NMR ($CDCl_3$) δ 3.65 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2CO), 5.20 (s, 2H, NCH_2), 6.9–7.7 (m, 10H, arom.). MS *m/e* (rel. int.) 279 (M^+, 20.1%), 220 (36.2%), 91 (100%).

1-*Methylindole* 3-*acetic acid* **15b**

To 75% NaH (4.76 g, 150 mmol) stirred in THF (220 ml) at 0° under N_2 was added a soln of indole 3-acetic acid (10.5 g, 60 mmol) in THF (100 ml). After 15 min a soln of MeI (28.4 g, 200 mmol) in THF (100 ml) was added at 0° and stirred at room temp overnight. Excess hydride was destroyed by addition of MeOH and water. Ether was added, the aqueous layer removed and acidified with 6 N HCl. This was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated to about 75 ml. Pet. ether (40–60°) was added slowly until a cream coloured solid precipitated out. This was dried over P_2O_5 under vacuum to give **15b** (10.8 g, 95% yield) m.p. 127° (lit. 127°). IR 1720, 2600–3200 cm^{-1}. MS *m/e* (rel. int.) 189 (M^+, 34.2%), 145 (10.7%), 144 (100%). (Found: C, 70; H, 5.85; N, 7.30%. Calc for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%.)

Methyl 4-(1-*methylindol*-3-*yl*)-3-*oxobutanoate* **13b**

To a stirred suspension of **15b** (3.78 g, 20 ml) in dry ether (50 ml) at −10° was added $SOCl_2$ (17 ml) and the mixture refluxed for 15 min. The solvent and excess $SOCl_2$ were removed to leave a brown oil (4.13 g) identified as the acid chloride. IR 1800 cm^{-1}.

A soln of the acid chloride (4.13 g, 20 mmol) in dry benzene (20 ml) was added dropwise to a stirred soln of N-trimethylsilylimidazole[22] (2.80 g, 20 mmol) in dry benzene (20 ml) at 0°. The mixture was stirred for a further 45 min at room temp and then concentrated to a brown fibrous tar (**14b**) which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ 3.60 (s, 3H, NCH_3), 4.15 (s, 2H, IND—CH_2—), 6.9–7.3 (m, 5H, arom.), 7.4 (6s, 2H, imidazole), 8.15 (bs, 1H, imidazole).

A mixture of $Mg(OMe)_2$ (2.15 g, 19 mmol) and hydrogen ethyl malonate[23] (2.3 g, 19.4 mmol) in THF (30 ml) was stirred while heating at 70–73° for 1 hr under N_2. The solvent was evaporated off, dry benzene added (20 ml) and this similarly removed. This was repeated four times to leave a white powder. To the powder in THF (30 ml) was added the soln of **14b** in THF (30 ml) and stirred for 2.5 hr at room temp. The soln was concentrated to a brown tar which was treated with conc HCl (5 ml) and water (1 ml), shaken for 10 min and then sat NaCl aq (30 ml) added. This mixture was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated to give a brown oil (4.75 g). Flash chromatography gave **13b** (2.45 g, 50% yield) as a brown oil. IR 1720, 1740 cm^{-1}.

Amino nitrile **21** *and enol ether* **22**

(i) $AgBF_4$ *catalyst.* To 75% NaH (0.095 g, 3 mmol) in THF (10 ml) at 0° under N_2 was added a soln of **13a** (1.005 g, 3 mmol) in THF (20 ml) and stirred for 1 hr at room temp. To a stirred soln of $AgBF_4$ (0.584 g, 3 mmol) in THF (10 ml) under N_2 was added a soln of **11** (0.42 g, 2.8 mmol) in THF (10 ml). The mixture was cooled to 0° over 5 min and the soln of the β-keto ester sodium salt was introduced. This mixture was stirred at room temp for 3 hr then treated with 10% NH_4OH (75 ml) and extracted with CH_2Cl_2 (4 × 30 ml). The combined organic extracts were washed with 10% NH_4OH (3 × 30 ml), water (3 × 30 ml), filtered through celite, dried over Na_2SO_4 and evaporated to give a brown oil (1.33 g). Flash chromatography led to recovery of **13a** (0.31 g, 31%) but gave poor separation of other components so that only small amounts of products as oils sufficiently pure for identification were isolated. However, reverse phase HPLC analysis (spherisorb ODS. MeOH/20% water) enabled an estimate of the yields to be made. Amino nitrile **21** (43%) IR 1720, 1740, 2220 cm^{-1}. MS *m/e* (rel. int.) 485 (M^+, 0.8%), 484 (2.1%), 458 (2.6%). Enol ether **22** (32%) IR 1610, 1700. MS *m/e* (rel. int.) 458 (M^+, 3.6%), 335 (11.3%), 290 (3.4%), 289 (4.9%), 238 (17.2%), 220 (72.8%), 91 (100%).

Extending the reaction time to 13 hr gave crude material which by reverse phase HPLC was shown to contain **13a** and **21** but no **22**. Purification by flash chromatography led to the recovery of **13a** (23%) and isolation of **21** (43%).

(ii) $ZnCl_2$ *catalyst.* To $ZnCl_2$ (0.041 g, 0.3 mmol) in THF (5 ml) under N_2 was added with stirring a soln of **11** (0.45 g, 3 mmol) in THF (5 ml). After 10 min a soln of the Na salt of **13a** (3 mmol), prepared as described above, was added. The stirring was continued for 24 hr at 60°, 10% NH_4OH (75 ml) was added and the mixture extracted with CH_2Cl_2 (4 × 30 ml). The combined organic extracts were washed with 10% NH_4OH (3 × 30 ml), water (2 × 30 ml), dried over Na_2SO_4 and evaporated to give a brown oil (1.39 g). Flash chromatography produced unreacted **13a** (0.41 g, 40%) and a mixture (0.43 g), the major component of which was shown by reverse phase HPLC to be **21** with **22** present as a minor component.

Amino nitrile **23**

To 75% NaH (0.25 g, 7.75 mmol) in THF (10 ml) at 0° under N_2 was added, with stirring, a soln of **13b** (1.9 g, 7.75 mmol) in THF (20 ml). The stirring was continued for 1 hr at room temp. To a stirred soln of $AgBF_4$ (1.51 g, 7.75 mmol) in THF (20 ml) under N_2 was added a soln of **12** (1.05 g, 7.75 mmol) in THF (10 ml). The mixture was cooled to 0° over 5 min and the soln of the Na salt of **13b** was added. The soln was stirred for 3 hr at room temp then 10% NH_4OH (100 ml) was added and the soln extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were washed with 10% NH_4OH (3 × 50 ml), water (3 × 50 ml), dried over $MgSO_4$ and evaporated to give a brown oil. This was immediately dissolved in CH_2Cl_2 (200 ml) and a soln of KCN (1.63 g, 25 mmol) in water (20 ml) was added with stirring. The pH was adjusted to 2.5 by addition of citric acid. The mixture was stirred for 1 hr diluted with water (50 ml) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated to give a brown oil (2.12 g) which was purified by flash chromatography. Unreacted **13b** (0.45 g) was recovered and **23** (1.10 g, 37%). IR 1720, 1740, 2220 cm^{-1}.

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