Use of Dimethylformamide as a Solvent for the Knoevenagel Reaction

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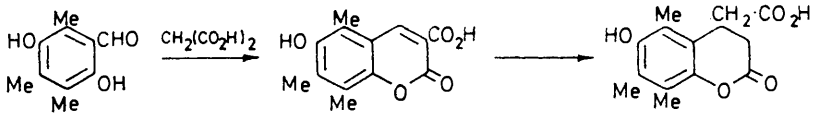
Dimethylformamide is shown to be a useful solvent in a variety of Knoevenagel-type condensations.

A WIDE variety of reactants and conditions has been used for the Knoevenagel reaction.[1] Where the condensation is between an aromatic aldehyde and a malonic acid derivative with piperidine as a catalyst and pyridine or benzene as solvent, a cinnamic acid derivative (I) is the

$$ArCHO + XH_2C{\cdot}CO_2H \longrightarrow ArCH{=}CHX \text{ (I)} \quad \text{or} \quad ArCH{=}CX{\cdot}CO_2H \text{ (II)}$$

$$X = CO_2H,\ CO_2R,\ \text{or CN}$$

usual product, whereas arylmethylenemalonic acid derivatives (II) are commonly the major products when formed in Knoevenagel condensations, although this has potential synthetic utility as well as mechanistic significance. When anthraldehyde is condensed with cyanoacetic acid in DMF, the anion of the hydroxy-acid (VIII) can be isolated in high yield as the potassium salt. The corresponding acid readily loses water to give the cyano-acid (IX). However, if the original basic reaction mixture is refluxed, *decarboxylative* dehydration takes place to give the nitrile (X). The isolation of the hydroxy-acid salt strongly supports the Hann and Lapworth mechanism [8] where the anion of the active-methylene component attacks the carbonyl compound. An alternative mechanism originally proposed by Knoevenagel,[9] involving initial addition of the amine to the carbonyl component, is clearly excluded in this example.



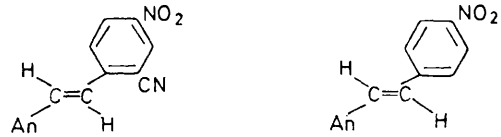
(IV) (III) (V)

Reactants [a]	Base [b]	Solvent [c]	Temp. (°C)	Time (h)	Product (%)
(IV) + $CH_2(CO_2H)_2$	$PhNH_2$	Py	20	100	(III), 50 [d]
	$PhNH_2$	Py	80; 100	3·5; 1·5	(III), 30; (V), 16
	Pip	Py	20	30	(III), 1 [e]
	Pip	DMF	20	30	(III), 20
	$PhNH_2$	DMF	20	30	0 [e]
	Pyd	DMF	40	1	(III), 60
AnCHO + ArMe	Pip	C_6H_6	80	24	0 [e,f]
	Pip	DMF	100	10	(VI), 73
AnCHO + $ArCO_2H$	Pip	DMF	20; 100	1; 5	(VII), 38 [g]
AnCHO + $NC{\cdot}CH_2{\cdot}CO_2H$	Mor	DMF	90; 150	1; 5	(X), 90 [h]

[a] AnCHO = 9-anthraldehyde, ArMe = 2-methyl-5-nitrobenzonitrile, $ArCO_2H$ = 4-nitrophenylacetic acid. [b] Pip = piperidine, Pyd = pyrrolidine, Mor = morpholine. [c] Py = pyridine. [d] See ref. 4. [e] Starting material recovered in high yield. [f] See ref. 5. [g] See refs. 6 and 7. [h] See text for further discussion.

ethanol is used as solvent and ammonium salts as catalysts. However, it is frequently impossible to ensure the formation of a single desired product by adjustment of the conditions in this way. In the course of some studies in photoconductivity [2] and chemiluminescence [3] the preparations of the coumarin (III) from the aldehyde (IV) and of the stilbenes (VI) and (VII) from 9-anthraldehyde were investigated. The Table illustrates the effectiveness of dimethylformamide (DMF) as a solvent for these reactions.

It is not often possible to isolate the intermediates



(VI) (VII)

An = 9-anthryl

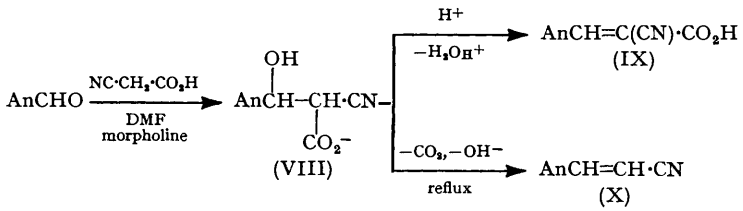
These findings suggest that DMF is a useful solvent for a wide variety of Knoevenagel-type condensations.

[1] G. Jones, *Org. Reactions*, 1967, **15**, 204.
[2] R. A. Hann, R. Marshall, and G. Read, in preparation.
[3] R. A. Hann, D.Phil. Thesis, University of Sussex.
[4] R. Adams and T. E. Bockstahler, *J. Amer. Chem. Soc.*, 1952, **74**, 5346.
[5] S. Gabriel and A. Thieme, *Ber.*, 1919, **52**, 1079.
[6] V. Baliah and K. Ganapathy, *J. Indian Chem. Soc.*, 1955, **32**, 336.
[7] P. Pfeiffer, *Ber.*, 1915, **48**, 1777.
[8] A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 46.
[9] E. Knoevenagel, *Ber.*, 1898, **31**, 738.

It is particularly useful in facilitating difficult reactions and may considerably extend the scope of this class of reaction.

EXPERIMENTAL

N.m.r. spectra (100 MHz) were obtained on a JEOL JMN-MH-100, i.r. spectra (for KBr pellets and Nujol mulls) on a Perkin-Elmer 237, u.v. spectra on a Unicam SP 800, and mass spectra on an A.E.I. MS9 instrument. Analyses were performed by the microanalytical serivces of the Universities of Exeter and Sussex.



Condensations with 2,5-Dihydroxy-3,4,6-trimethylbenzaldehyde (IV).—(*a*) The aldehyde (IV) (0·17 g), malonic acid (0·11 g), and pyrrolidine (0·2 cm³) were dissolved in DMF (1 cm³). The solution was kept at 40 °C for 1 h, then acidified with 2M-hydrochloric acid (10 cm³), and set aside for 1 h at room temperature. The 3-carboxy-6-hydroxy-5,7,8-trimethylcoumarin (III) which crystallised from the solution was filtered off, washed with water, and recrystallised from ethanol to give yellow needles (0·125 g, 62%), m.p. 266—267° (lit.,[10] 260°) $\bar{\nu}_{max.}$ 3460, 1740, 1678, and 1597 cm⁻¹; τ [$(CD_3)_2SO$] 1·51 (1H, s) and 7·74, 7·84, and 7·96 (9H total) (Found: C, 63·0; H, 4·9. Calc. for $C_{13}H_{12}O_5$: C, 62·9; H, 4·9%).

(*b*) The aldehyde (3 g), malonic acid (7 g), and aniline (0·15 g) were heated in pyridine (5 cm³) at 80 °C for 3·5 h, and then at 100 °C for 1·5 h. Work-up as before gave coumarin (III) (1·1 g, 30%). The mother liquors were evaporated to dryness, and the residual solid was extracted (Soxhlet) with chloroform to give *3,4-dihydro-6-hydroxy-5,7,8-trimethyl-2-oxo-2H-benzo*[b]*pyran-4-ylacetic acid* (V) (0·7 g, 16%), m.p. 229—230° (from ethanol–toluene) (Found: C, 63·5; H, 6·3. $C_{14}H_{16}O_5$ requires C, 63·6; H, H, 6·1%); $\bar{\nu}_{max.}$ 3440, 3000br (acid OH str), 1745, and 1710 cm⁻¹; τ [$(CD_3)_2SO$] 1·97br (1H, s, D_2O-exchangeable, phenol OH), 6·5 (1H, m), 7·18—7·32 (2H, m), 7·64—7·84 (2H, m), 7·88 (3H, s), and 7·92 (6H, s); *m/e* 264 (M^+).

Condensations with 9-Anthraldehyde.—(*a*) Piperidine (0·5 cm³) was added to a solution of anthraldehyde (2 g) and 2-methyl-5-nitrobenzonitrile (1·6) g in DMF (5 cm³). The mixture was heated for 10 h at 100 °C, then left overnight at 0 °C. Bright orange prisms of *2-[β-(9-anthryl)vinyl]-5-nitrobenzonitrile* (VI), m.p. 243—248° (2·5 g, 73%), were deposited. Recrystallisation from chloroform–benzene gave material of m.p. 247—249° (Found: C, 78·8; H, 4·15; N, 8·0. $C_{23}H_{14}N_2O_2$ requires C, 78·8; H, 4·0; N, 8·0%); $\lambda_{max.}$ (EtOH) 253 (log ε 5·07), 282 (4·14), 366 (3·66), 384 (3·80), and 488 (3·84) nm; $\bar{\nu}_{CN}$ 2160 cm⁻¹; *m/e* 350 (M^+).

(*b*) Piperidine (2 cm³) was added to a solution of anthraldehyde (3 g) and 4-nitrophenylacetic acid (2·7 g, 1·6 mol. equiv.) in DMF (11 cm³). The mixture was stirred at room temperature until crystallisation occurred (5 min), and set aside for 1 h. It was then heated for 5 h at 100 °C and left overnight at 0 °C to deposit crystals of *9-(4-nitro-β-styryl)anthracene* (VII) (1·8 g, 38%), m.p. 224—227°. Recrystallisation from chloroform gave material of m.p. 226·5—227° (Found: C, 81·0; H, 4·8; N, 4·4. $C_{22}H_{15}NO_2$ requires C, 81·2; H, 4·65; N, 4·3%).

(*c*) Morpholine (0·7 cm³) was added to a solution of anthraldehyde (1·03 g) and cyanoacetic acid (0·52 g, 1·2 mol. equiv.) in DMF (6 cm³) and the mixture was heated at 90 °C for 1 h to give a solution (A). A solution of potassium hydroxide (1·0 g) in water–methanol (1 : 2) (1·5 cm³) was added, followed by ether (5 cm³), to precipitate *potassium 3-(9-anthryl)-2-cyano-3-hydroxypropanoate* (1·55 g, 94%). Recrystallisation from methanol gave fine yellow needles, m.p. 260° (decomp.) (Found: C, 65·55; H, 3·7; N, 4·1. $C_{18}H_{12}KNO_3$ requires C, 65·8; H, 3·4; N, 4·3%); $\nu_{max.}$ 3500, 2220, and 1633 cm⁻¹; τ [$(CD_3)_2SO$] 1·1—2·5 (9H, m), and 6·42 (1H, s). Addition of mineral acid to an aqueous solution of the potassium salt precipitated a yellow solid, presumed to be the acid, which rapidly decomposed to give an orange powder. Recrystallisation of this material from 1,2-dichlorobenzene gave orange needles of *3-(9-anthryl)-2-cyanoacrylic acid* (IX), m.p. 270° (decomp.) (Found: C, 79·35; H, 4·0; N, 5·3. $C_{18}H_{11}NO_2$ requires C, 79·1; H, 4·1; N, 5·1%); $\bar{\nu}_{max.}$ 2220 (CN) and 1658 (CO) cm⁻¹; τ [$(CD_3)_2SO$] 0·79 (1H, s, vinyl CH, shifts to 0·95 on addition of aqueous NaOH) and 1·2—2·9 (9H, m).

Alternatively, solution (A) was refluxed for 5 h and then left overnight at −10 °C to give yellow needles (0·49 g, 43%), m.p. 204—207°; a second crop (0·55 g, 47%), m.p. 195—206°, was obtained by dilution of the mother liquors with water. Recrystallisation from benzene–light petroleum (1 : 1) gave pure *3-(9-anthryl)acrylonitrile* (X), m.p. 209·5—210·5° (Found: C, 89·3; H, 4·8; N, 6·0. $C_{17}H_{11}N$ requires C, 89·05; H, 4·8; N, 6·1%); *m/e* 229 (M^+), $\bar{\nu}_{max.}$ 2200 cm⁻¹; τ ($CDCl_3$) 1·4—2·7 (9H, m), 1·84 (1H, d, *J* 17 Hz), and 4·24 (1H, d, *J* 17 Hz).

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