

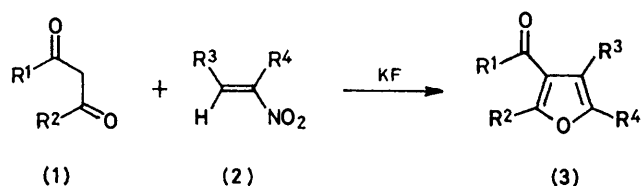
Synthesis of 3-Acylfurans from 1,3-Dicarbonyl Compounds and Aliphatic Nitro-olefins

By Tetsuji Yanami, Annie Ballatore, Masaaki Miyashita, Michiharu Kato, and Akira Yoshikoshi,*
Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Sendai 980, Japan

Some 1,3-dicarbonyl compounds (acetylacetone, cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, and ethyl acetoacetate) and aliphatic nitro-olefins (2-nitropropene, 2-nitrobut-1-ene, and 2-nitrobut-2-ene) directly gave 3-acylfurans (8)—(15) in a KF-catalysed reaction.

BOBERG *et al.* reported a two-step synthesis of 3-furoates (3; R¹ = EtO) from β-keto-esters and nitro-olefins.¹ They obtained, in moderate to high yields, the products by heating the initial Michael adducts from β-keto-esters and nitro-olefins in methanol containing urea. On the other hand, Nielsen and Archibald also described that, as an exceptional result, the reaction of dimedone (1; R¹, R² = CH₂CM₂CH₂) and 2-nitro-1-phenylpropene (2; R³ = Ph, R⁴ = Me) was catalysed with sodium methoxide to yield a 3-acylfuran derivative (3; R¹, R² = CH₂CM₂CH₂, R³ = Ph, R⁴ = Me) in low yield.² The above authors have chiefly used, as the Michael acceptors, aryl-conjugated nitro-olefins which are comparatively stable under strong alkaline conditions. In a preliminary communication we showed that, as an example of the reaction of 2-unsubstituted 1,3-dicarbonyl compounds with alkali-sensitive aliphatic nitro-olefins, the reaction of dimedone (5,5-dimethylcyclohexane-1,3-dione) and 2-nitropropene (2; R³ = H, R⁴ = Me) was catalysed by KF in hot xylene to give 2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one (10) in moderate yield.³

Here, we describe both an extension of this one-step synthesis of 3-acylfurans to other substrates and the experimental detail. The reaction is shown by the following equation.



Acetylacetone, cyclohexane-1,3-dione, dimedone, and ethyl acetoacetate were used as the dicarbonyl compo-

¹ F. Boberg and G. R. Schultze, *Chem. Ber.*, 1957, **90**, 1215; F. Boberg and A. Kieso, *Annalen*, 1959, **626**, 71.

² A. T. Nielsen and T. G. Archibald, *Tetrahedron*, 1969, **25**, 2393.

nents, and 2-nitropropene,⁴ 2-nitrobut-1-ene,⁴ and 2-nitrobut-2-ene⁴ were selected as the nitro-olefin components. The procedure is simple and the product could be obtained in moderate to high yield merely by heating a mixture of the reactants and KF in organic solvent. The results are summarized in the Table.

The dimedone reaction was examined in some detail in order to find the optimum conditions (see entries 3—5). Although the reaction seemed faster in 1,2-dimethoxyethane than in xylene, both solvents, in general, gave acceptable yields. Aprotic polar solvents such as dimethyl sulphoxide, however, resulted in poor yields in addition to problems of emulsion formation during work-up (entry 3c). Benzene was also employed in place of xylene but required longer reaction times to give comparable yields. Without the catalyst, the reaction proceeded slowly to give low yields even after prolonged reaction time (entry 5a).

Recently Belsky obtained high yields of addition products in the KF-catalysed Michael reaction using a crown ether.⁵ 18-Crown-6⁶ was added to the reaction of dimedone and 2-nitrobut-1-ene in xylene affording somewhat improved results (entry 4a).

Ethyl acetoacetate gave the corresponding furoates on reaction with nitro-olefins bearing no β-alkyl substituent (*e.g.* 2-nitropropene and 2-nitrobut-1-ene; entries 6 and 7). Surprisingly, in xylene the acetoacetate failed to react with 2-nitrobut-2-ene which has a β-alkyl substituent although it reacted normally in 1,2-dimethoxyethane (entry 8). We believe that this difference arises from the presence of the cisoid enolate of the acetoacetate, in nonpolar solvents such as xylene. Thus in (4a), a repulsive interaction between the ethoxy (or

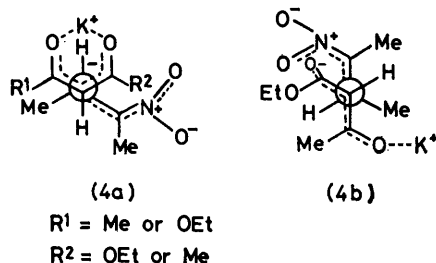
³ T. Yanami, M. Kato, and A. Yoshikoshi, *J.C.S. Chem. Comm.*, 1975, 726.

⁴ M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Amer. Chem. Soc.*, 1976, **98**, 4679 and references cited.

⁵ I. Belsky, *J.C.S. Chem. Comm.*, 1977, 237.

⁶ C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017.

methyl) group of the acetoacetate and the nitro-group of 2-nitrobut-2-ene would prevent the approach of the



reactants. In contrast in 1,2-dimethoxyethane, the transoid enolate allows interaction between the posi-

With primary nitro-olefins such as nitroethylene, we obtained only intractable tarry products under the above reaction conditions. This is probably a result of the equilibrium between the nitro (5) and *aci* (6) forms of the Michael adduct, the α -alkyl substituent (R) assisting in a preponderance of the latter form, from which the furan (7) is derived (Scheme); we could not, however, prove the formation of a 1 : 1 Michael adduct from nitroethylene and dimedone.

EXPERIMENTAL

I.r. spectra (liquid film) were taken on a Hitachi EPI-S2 spectrophotometer. N.m.r. spectra were recorded on a JEOL-60HL spectrometer (60 MHz) using SiMe_4 (δ 0) as

Synthesis of 3-acylfurans from 1,3-dicarbonyl compounds and nitro-olefins

Entry	Dicarbonyl compound	Nitro-olefin (mol. equiv.)	Mol. equiv. of KF	Solvent ^a	Reaction conditions		Product	Isolated yield (%) ^b
					Temp. (°C)	Time (h)		
1	Acetylacetone	2-Nitropropene (2)	1.3	A	120	48	(8)	81 ^c
2a	Cyclohexane-1,3-dione	2-Nitropropene (2)	1.3	A	115	21	(9)	34
2b		(1.5)	1.0	B	90	7		42
3a	Dimedone	2-Nitropropene (2)	1.3	A	120	9.5	(10)	52
3b		(1.5)	1.0	B	90—100	7		51
3c		(1.5)	1.0	C	75—80	23		15
4a	Dimedone	2-Nitrobut-1-ene (1.5)	1.0	A	100—110	8	(11)	39 (48) ^d
4b		(1.5)	1.0	B	100	6		43
5a	Dimedone	2-Nitrobut-2-ene (1.5)	1.0	A	100—110	6	(12)	57 (9) ^e
5b		(1.5)	1.0	B	90—100	6		58
6a	Ethyl acetoacetate	2-Nitropropene (1.5)	1.3	A	110	30	(13)	64
6b		(1.5)	1.0	B	90—100	30		41
7a	Ethyl acetoacetate	2-Nitrobut-1-ene (1.5)	1.0	A	100—110	75	(14)	52
7b		(1.5)	1.0	B	90—100	30		58
8a	Ethyl acetoacetate	2-Nitrobut-2-ene (1.5)	1.0	A	100—110	75	(15)	0
8b		(1.5)	1.0	B	100	24		65

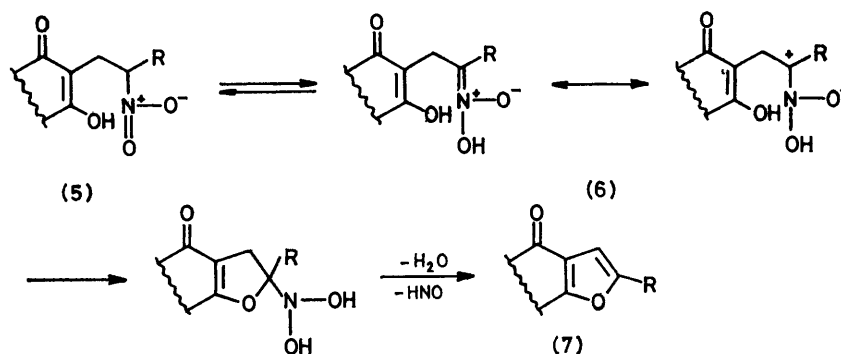
^a A = xylene, B = 1,2-dimethoxyethane, C = dimethyl sulphoxide. ^b Based on dicarbonyl compound used. ^c The yield is based on 2,4-dinitrophenylhydrazone obtained from the crude product. ^d About 0.1 mole equivalent of 18-crown-6 was added. ^e This yield was obtained without the catalyst after 22 h.

tively charged nitrogen and the ester carbonyl [see (4b)] this leading to the necessary transition state.

Long reaction times were necessary for acetylacetone (entry 1) and ethyl acetoacetate (entries 6—8) in order to

an internal standard. Coupling constants (J) are given in Hz.

General Procedure for the Preparation of 3-Acylfurans.—A suspension of the 1,3-dicarbonyl compound (1) (1 mmol)

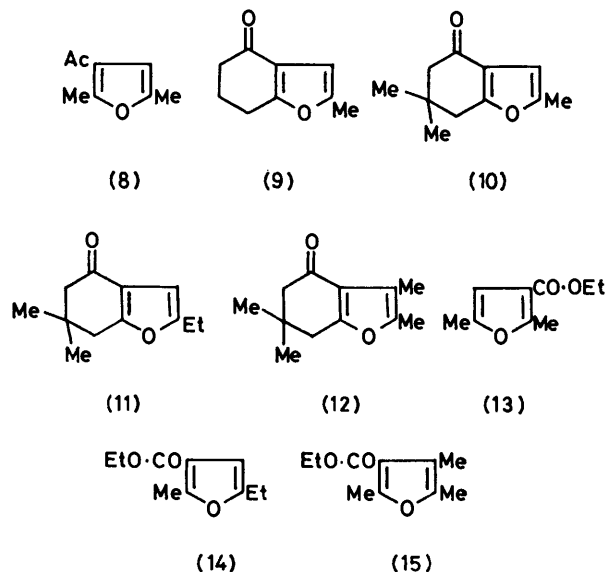


SCHEME

obtain acceptable yields; this is probably a result of their low acidities compared with those of the cyclic analogues.

and KF (1—1.3 mmol) in the solvent (*ca.* 2.5 ml) was stirred for 30 min at room temperature, and the nitro-olefin (1.5—2.0 mmol) was added to the mixture; the mixture was then

heated and stirred. It was then filtered through a short silica-gel column with ether as eluant. The filtrate was



evaporated, and the residue was purified by single distillation or thick layer chromatography using light petroleum-ether (or light petroleum-methylene chloride) mixture as solvent.

3-Acetyl-2,5-dimethylfuran⁷ (8).—A volatile oil, ν_{\max} 3 120w, 1 676, 1 614, 1 570, 1 400, 1 060, 1 008, 946, and 800 cm^{-1} ; $\delta(\text{CDCl}_3)$ 2.26 (3 H, s), 2.36 (3 H, s), 2.55 (3 H, s), and 6.25br (1 H, s) (Found: C, 69.5; H, 7.2. Calc. for $\text{C}_8\text{H}_{10}\text{O}_2$: C, 69.5; H, 7.3%). 2,4-Dinitrophenylhydrazone, m.p. 194–195 °C (recrystallised from ethanol) (Found: C, 52.55; H, 4.4; N, 17.7. $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_5$ requires C, 52.8; H, 4.4; N, 17.6%).

2-Methyl-6,7-dihydrobenzofuran-4(5H)-one⁸ (9).—B.p. 80–85 °C (bath temp.)/5 mmHg, ν_{\max} 3 120w, 1 674, 1 582, 1 432, 1 122, 1 010, 892, and 810 cm^{-1} ; $\delta(\text{CDCl}_3)$ 2.0–3.0 (6 H, m), 2.30br (3 H, s), and 6.30 (1 H, q, *J* 1)

⁷ H. Gilman and N. O. Calloway, *J. Amer. Chem. Soc.*, 1933, **55**, 4197; H. Gilman and R. R. Burtner, *ibid.*, 1935, **57**, 909; C. D. Hurd and K. Wilkinson, *ibid.*, 1948, **70**, 739; R. Levine, J. V. Heid, and M. W. Farrar, *ibid.*, 1949, **71**, 1207; J. A. Blanchette and E. V. Brown, *ibid.*, 1952, **74**, 2098.

⁸ D. A. H. Taylor, *J. Chem. Soc.*, 1959, 2767; H. Stetter and R. Lauterbach, *Annalen*, 1962, **652**, 40; K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, 1962, **295**, 645.

⁹ H. J. Schaeffer and R. Vince, *J. Org. Chem.*, 1962, **27**, 4502; R. Verhe, N. Schamp, L. De Buyck, N. De Kimpe, and M. Sadones, *Bull. Soc. chim. belges.*, 1975, **84**, 747.

(Found: C, 72.4; H, 6.5. Calc. for $\text{C}_9\text{H}_{10}\text{O}_2$: C, 72.0; H, 6.7%).

2,6,6-Trimethyl-6,7-dihydrobenzofuran-4(5H)-one⁹ (10).—B.p. 85–90 °C (bath temp.)/4 mmHg, ν_{\max} 3 120w, 1 675, 1 586, 1 432, 1 034, 900, 812, and 798 cm^{-1} ; $\delta(\text{CDCl}_3)$ 1.12 (6 H, s), 2.32 (2 H, s), 2.36 (3 H, s), 2.72 (2 H, s), and 6.28br (1 H, s) (Found: C, 74.0; H, 7.8. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 74.1; H, 7.9%).

2-Ethyl-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (11).—B.p. 115 °C (bath temp.)/4 mmHg, ν_{\max} 3 100w, 1 675, 1 610, 1 585, 1 445, 1 030, 928, and 810 cm^{-1} ; $\delta(\text{CCl}_4)$ 1.14 (6 H, s), 1.25 (3 H, t, *J* 7.6), 2.23 (2 H, s), 2.63 (2 H, q, *J* 7.6), 2.66 (2 H, s), and 6.17br (1 H, s) (Found: C, 74.85; H, 8.8. $\text{C}_{12}\text{H}_{16}\text{O}_2$ requires C, 75.0; H, 8.4%).

2,3,6,6-Tetramethyl-6,7-dihydrobenzofuran-4(5H)-one (12).—B.p. 110–115 °C (bath temp.)/3 mmHg, ν_{\max} 1 670, 1 590, 1 444, 1 052, and 1 030 cm^{-1} ; $\delta(\text{CCl}_4)$ 1.12 (6 H, s), 2.05 (3 H, s), 2.16 (2 H, s), 2.20 (3 H, s), and 2.60 (2 H, s) (Found: C, 74.7; H, 8.5. $\text{C}_{12}\text{H}_{16}\text{O}_2$ requires C, 75.0; H, 8.4%).

2,5-Dimethyl-3-ethoxycarbonylfuran^{10,11} (13).—B.p. 85 °C (bath temp.)/10 mmHg, ν_{\max} 3 130w, 1 710, 1 626, 1 590, 1 408, 1 200, 1 006, 925, 840, 815, and 776 cm^{-1} ; $\delta(\text{CDCl}_3)$ 1.33 (3 H, t, *J* 6.8), 2.26 (3 H, s), 2.54 (3 H, s), 4.32 (2 H, q, *J* 6.8), and 6.28 (1 H, s) (Found: C, 64.7; H, 7.4. Calc. for $\text{C}_9\text{H}_{12}\text{O}_3$: C, 64.3; H, 7.2%).

3-Ethoxycarbonyl-5-ethyl-2-methylfuran¹² (14).—B.p. 110 °C (bath temp.)/10 mmHg, ν_{\max} 3 120w, 1 710, 1 620, 1 585, 1 410, 1 226, 936, 817, and 776 cm^{-1} ; $\delta(\text{CCl}_4)$ 1.24 (3 H, t, *J* 7.5), 1.33 (3 H, t, *J* 6.8), 2.52 (3 H, s), 2.57 (2 H, q, *J* 6.8), 4.20 (2 H, q, *J* 7.5), and 6.12br (1 H, s) (Found: C, 66.0; H, 7.9. Calc. for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 65.9; H, 7.7%).

2,4,5-Trimethyl-3-ethoxycarbonylfuran^{11,13} (15).—B.p. 115 °C (bath temp.)/16 mmHg, ν_{\max} 1 708, 1 644, 1 585, 1 208, and 1 053 cm^{-1} , $\delta(\text{CCl}_4)$ 1.33 (3 H, t, *J* 7.2), 2.02 (3 H, s), 2.13 (3 H, s), 2.44 (3 H, s), and 4.22 (2 H, q, *J* 7.2) (Found: C, 66.1; H, 7.55. Calc. for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 66.0; H, 7.7%).

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¹⁰ E. W. Scott and J. R. Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 2549; A. P. Dunlop and C. D. Hurd, *J. Org. Chem.*, 1950, **15**, 1160; R. M. Acheson and R. Robinson, *J. Chem. Soc.*, 1952, 1127; O. Dann, H. Distler, and H. Merkel, *Chem. Ber.*, 1952, **85**, 457; K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, 1962, **295**, 627; P. Dominique and G. Rene, *Compt. rend.*, 1972, **C274**, 2084; A. W. McCulloch and A. G. McInnes, *Canad. J. Chem.*, 1975, **53**, 1496.

¹¹ L. Cromble and K. Mackenzie, *J. Chem. Soc.*, 1958, 4417.

¹² T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, 1933, **16**, 6.

¹³ T. Reichstein, H. Zschokke, and W. Syz, *Helv. Chim. Acta*, 1932, **15**, 1112; F. G. González, F. J. L. Aparicio, and F. S. Lulhe, *Anales real Soc. españ. Fis. Quim.*, 1954, **50B**, 407 (*Chem. Abs.*, 1955, **49**, 13206g).