A Convenient Synthesis of 3-Furoic Acid and 3-Acetylfuran

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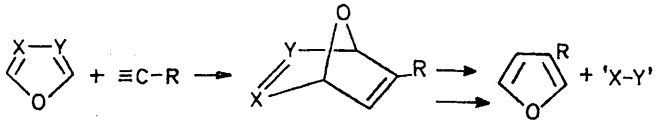
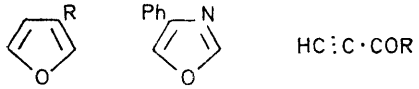
Reaction of 4-phenyloxazole with propiolic acid gave 3-furoic acid (37%); reaction of 4-phenyloxazole with ethynyl methyl ketone gave 3-acetylfuran (41%). No Diels–Alder reaction was detected between the acetylenes and 1,3,4-oxadiazole.

Among the simplest structures possible for a heterocyclic molecule is that of the mono 3-substituted furan (I). Despite apparent simplicity, this structural type is surprisingly difficult to prepare in the laboratory, and routes to these compounds are long, with low overall yields.[1] On the other hand, there are very many natural products which contain this moiety;[2] a few molecules of this type show biological properties.[3]



Scheme



(I) (II) (III)

Of the many ways which might, in principle, be used for constructing a furan ring bearing only a 3-substituent, there is particular attraction to the route shown in the Scheme.

'X–Y' may be considered a template, or bridging element[4] enabling the C–O–C fragment to be presented to the C–C portion during the Diels–Alder reaction with the acetylene. Subsequently 'X–Y' is to be lost in a reverse Diels–Alder process; it remains to make a suitable choice of X and Y.

If X = Y = C, then the starting material is furan. In this case the intermediate bicyclic compound has to be hydrogenated[5] in an extra step. Final thermolysis eliminates 'X–Y' as ethylene.

Recently, Grigg and his co-workers have provided[6] neater examples of the process. With X = C, Y = N, the starting material is an oxazole and in this instance it is possible to go through to the furan without isolation of the intermediate bicyclic compound. The Diels–Alder addition and the reverse reaction can take place in one stage by heating together suitable oxazoles and acetylenes, and 'X–Y' is eliminated in the form of a nitrile. In the researches of Grigg and his co-workers, multiple substituted oxazoles and acetylenes were used so that the resulting furans carried several substituents. It is the purpose of the present work to show that this reaction may be extended to give a short synthesis of mono 3-substituted furans.

Initially the reaction type where X = Y = N was investigated, using the readily available[7] 1,3,4-oxadiazole as starting material. 'X–Y' Would be lost as

[1] See for example P. Bosshard and C. H. Eugster, *Adv. Heterocyclic Chem.*, 1966, **7**, 378; M. A. Gianturco and P. Friedel, *Canad. J. Chem.*, 1964, **44**, 1083; D. Miller, *J. Chem. Soc.* (*C*), 1969, 12.

[2] *E.g.*, T. R. Govindachari, *J. Indian Chem. Soc.*, 1968, **45**, 1063; C. F. Wong, E. Auer, and R. T. LaLonde, *J. Org. Chem.*, 1970, **35**, 517.

[3] *E.g.*, B. G. Hegarty, J. R. Kelly, R. J. Park, and M. D. Sutherland, *Austral. J. Chem.*, 1970, **23**, 107; H. Minato, G.P., 1,930,712 (*Chem. Abs.*, 1970, **72**, 133,150g); W. J. Fanshawe *et al.*, G. P. 1,933,853 (*Chem. Abs.*, 1970, **73**, 3807m).

[4] S. Turner, *Chem. in Britain*, in the press.

[5] L. Mavoungou-Gomes, *Bull. Soc. chim. France*, 1967, 1764.

[6] R. Grigg and J. L. Jackson, *J. Chem. Soc.* (*C*), 1970, 552.

[7] C. Ainsworth and R. E. Hackler, *J. Org. Chem.*, 1966, **31**, 3442.

nitrogen providing a driving force for the second step; furthermore, the loss of nitrogen as gas would give an indication of the progress of the reaction and ease separation of the products. But it was not possible to realise this approach in practice. Apparently 1,3,4-oxadiazole is too 'stable' to undergo ready Diels–Alder addition. Furthermore, its relatively strong basicity brought about decomposition of the activated acetylenes (III) with which it was to react.

Hence it was necessary to return to the case where X = C, Y = N. 4-Phenyloxazole (II) was chosen as starting material since it is readily available [8] in one step from phenacyl bromide; 'X–Y' is to be eliminated as the stable molecule, benzonitrile. The acetylenes used were commercially available propiolic acid (III; R = OH) and ethynyl methyl ketone (III; R = Me),* the reactions were followed by i.r. spectroscopy (disappearance of the acetylenic band at 2120 cm^{-1} with appearance of the nitrile band at 2240 cm^{-1} and a sharp furan band at 870—880 cm^{-1}). After reaction with the oxazole (II), the resulting furans, 3-furoic acid (I; R = CO_2H), and 3-acetylfuran (I; R = Ac) were isolated in reasonable yields under the best conditions (see Table). This method therefore provides a most convenient two-step preparation of these simple substances.

TABLE

Mol of 4-phenyloxazole (II) at 115°	1½	5
Yield of recryst. 3-furoic acid	3%	24%
Yield of recryst. 3-acetylfuran	13%	31·5%

The reactions between the oxazole (II) and the activated acetylenes (III) were investigated under a variety of conditions. The reaction temperature chosen was 115° since reactions were slow at 100°; the use of five equivalents of oxazole (II) gave much superior yields to the use of 1½ equivalents (see Table), the excess of oxazole cutting down unwanted Diels-Alder addition between product furan and unchanged acetylene. The excess of oxazole was easily recovered for recycling. Reactions involving propiolic acid (III; R = OH) were carried out under nitrogen, but those with ethynyl methyl ketone (III; R = Me) were carried out in air in order not to carry away the acetylenic ketone (b.p. 85°) in the effluent gases. The product furans were identified by analytical data and it is worth noting that 3-acetylfuran (I; R = Ac) is a volatile solid which could not be subjected to pressures of about 20 mmHg at 20° for long without appreciable loss.

EXPERIMENTAL

N.m.r. spectra were obtained on a JEOL Co. 100 MHz spectrometer. Mass spectra were determined in an AEI MS9 spectrometer.

3-Furoic acid (I; R = CO_2H).—4-Phenyloxazole (14·9 g) [8] and propiolic acid (1·5 g) were heated under nitrogen for 16·5 h on an oil-bath maintained at 115°. The reaction was cooled, poured into 10% aqueous sodium hydroxide (28 ml), and extracted thrice with ether. The combined ether extracts were washed once with water, dried (Na_2SO_4), and evaporated *in vacuo* to yield a brown liquid (13·6 g) (see below).

The combined aqueous layers were acidified with 10% sulphuric acid (45 ml) and extracted with ether (×5). The combined ether layers were dried (Na_2SO_4) and evaporated *in vacuo* to yield a brown solid (1·27 g), which was chromatographed on silica (65 g); the following fractions were eluted: benzene (18 × 15 ml), 10% ether–benzene (7 × 15 ml), 40% ether–benzene (20 × 15 ml). Combination of fractions 26—32 yielded 3-furoic acid (0·89 g, 37%), m.p. 106—112°, identified and shown to be substantially pure by i.r. spectrum. Crystallisation from water gave 3-furoic acid (0·584 g, 24%), m.p. 118—118·5° (lit.,[10] m.p. 122—123°), τ −1·60br (1H, COO*H*), 1·88 (1H, d, $J \leqslant 1{\cdot}5$ Hz, 2-H), 2·55 (1H, t, $J \leqslant 1{\cdot}5$ Hz, 5-H), 3·22 (1H, d, $J \leqslant 1{\cdot}5$ Hz 4-H) [$C_5H_4O_3$ requires *M*, 112. Found *M*, 112 (mass spectrum)].

The brown liquid (13·6 g) obtained above was distilled at 24 mmHg to give a fore fraction (1·37 g), b.p. 94—104°, largely benzonitrile, and a main fraction of 4-phenyloxazole (10·64 g), b.p. 104—114°.

3-Acetylfuran (I; R = Ac).—4-Phenyloxazole (12·0 g) [8] and ethynyl methyl ketone (1·03 g) were heated on an oil-bath at 115° for 18 hr. The cold reaction mixture was chromatographed on silica (60 g), the following fractions being eluted: 2% ether–pentane (13 × 15 ml), 4% ether–pentane (7 × 15 ml), 5% ether–pentane (7 × 15 ml), 10% ether–pentane (13 × 15 ml), 40% ether–pentane (8 × 15 ml), 40% ether–pentane (1 × 50 ml), and ether (1 × 50 ml). Fractions 6—17 were retained as recovered 4-phenyloxazole; fractions 18—50 (7·2 g) contained the furan ($\nu_{max.}$ 870 cm^{-1}) and were chromatographed a second time. In this instance fractions 11—20 were recovered 4-phenyloxazole; fractions 41—48 yielded pure crystalline 3-acetylfuran (0·503 g); fractions 21—40 (3·98 g) were unseparated and were resolved by a final, third chromatography.

Thus was obtained 3-acetylfuran (0·689 g, 41%), m.p. 43—45°, identified and shown to be substantially pure by i.r. spectrum. Crystallisation from pentane gave 3-acetylfuran (0·525 g, 31·5%), m.p. 48—49°, mixed m.p. with a sample (m.p. 50—50·5°) prepared [11] by the action of MeLi on 3-furoic acid 48·5—49·5° (lit.,[10] m.p. 51—52°), τ 1·98 (1H, s, 2-H), 2·57 (1H, t, $J \leqslant 1{\cdot}5$ Hz, 5-H), 3·22 (1H, d, $J \leqslant 1{\cdot}5$ Hz, 4-H), and 7·54 (3H, s, Ac) [$C_6H_6O_2$ requires *M*, 110. Found *M*, 110 (mass spectrum)].

Combined fractions containing recovered oxazole (10·7 g) were distilled at 32 mmHg yielding a fore fraction (1·67 g), b.p. 94—104°, largely benzonitrile, and a main fraction of 4-phenyloxazole (7·69 g), b.p. 104—114°.

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* Prepared by oxidation [9] of an aqueous solution of but-3-yn-2-ol (Koch–Light).

[8] A modification of the method of H. Bredereck and R. Gompper, *Chem. Ber.*, 1954, **87**, 700, omitting basification before extraction of the product with ether.

[9] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

[10] S. Gronowitz and G. Sorlin, *Arkiv Kemi*, 1962, **19**, 515; *Acta Chem. Scand.*, 1961, **15**, 1419.

[11] R. Massy-Westropp, *Austral. J. Chem.*, 1966, **19**, 891.