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Formation and Reactivity of Bis-Anions derived from Furoic Acids

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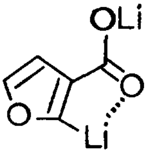
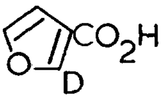
One of the most versatile methods for the homologation of furans is the coupling of simple metallated furans with electrophiles. The metallated species can be formed either by metal-halogen exchange[1,2] (e.g. 3-furyllithium from a 3-halofuran and n-butyl lithium) or by the direct metallation of the furan nucleus, normally with n-butyl lithium.[3,4] In this note, we wish to report that furoic acids undergo efficient and regioselective ring metallation on reaction with lithium diisopropylamide (LDA) to give bis-anionic species which react well with a number of electrophiles.

Initial studies were performed using 3-furoic acid. Addition of a solution of the acid in tetrahydrofuran (THF) to two equivalents of LDA in THF at -78° resulted in the formation of a white precipitate (presumably the lithium salt of the acid) which slowly dissolved during 0.5h. to give a clear, yellow solution. A sample was removed and treated immediately with an excess of deuterium oxide. A ^{1}H n.m.r. spectrum of the product from this reaction revealed a complete absence of resonances at 1.91 τ (furyl 2-H); in addition the two remaining furyl protons appeared as simple doublets. Thus, it was concluded that the product was 2-D-3-furoic acid (2), arising via the intermediacy of bis-anion (1). The authenticity of (2) was confirmed by i.r.,



(1)

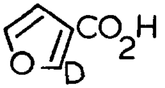
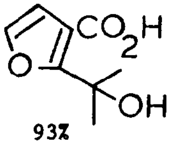
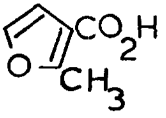
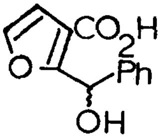
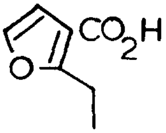
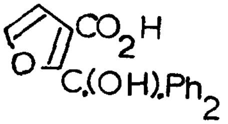
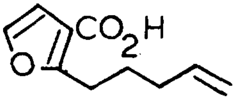
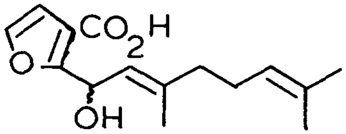


(2)

u.v. and mass spectra and subsequent work showed that it could routinely be prepared in ca. 95% yield with >98% deuteration at the 2-position. No trace of any other deuterated products was detected. The reactions of bis-anion (1) with various electrophiles were then examined; the results are presented in Table 1. The reactions with carbonyl compounds all gave very high

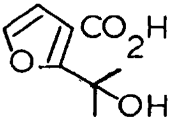
TABLE 1

Reactions of Lithium 2-Lithio-3-furoate (1) with Electrophiles

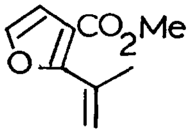
Electrophile	Product	Electrophile	Product
D_2O	 95%	Acetone	 93%
CH_3I	 90%	PhCHO	 96%
EtI	 42% (89%)	Ph_2CO	 93%
5-Iodo-1-pentene	 25% (88%)	Citral	 91%

Yields in parenthesis are based on recovered 3-Furoic acid.

yields and were complete within 5 minutes at -78°. However, with the exception of methyl iodide, which also reacted rapidly at -78°, alkylating agents did not react with (1) at -78° but required temperatures of -20° to -10°. (T.l.c. and ^1H n.m.r. monitoring). Although the conversions to the 2-alkylated products were not high, the reactions were clean and high overall yields were obtained by chromatographic recovery[5] of unreacted 3-furoic acid. Unfortunately allylic and benzylic halides (geranyl bromide, benzyl bromide) gave only traces of alkylated products under a variety of conditions and 3-furoic acid was recovered in high yield.



(3)



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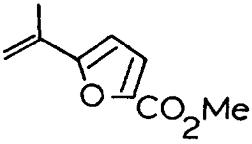
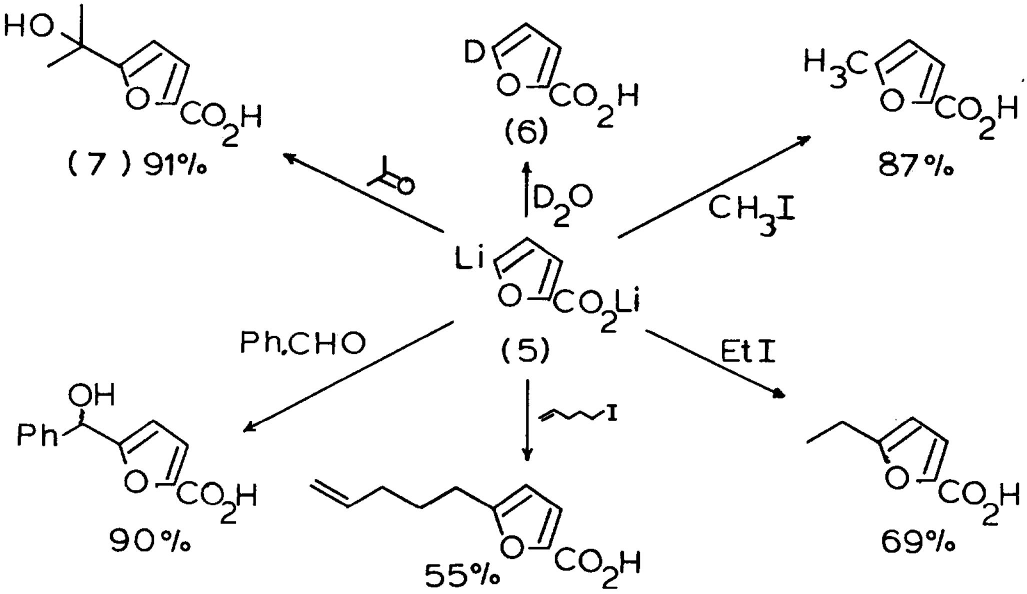


(8)

The condensation product from acetone (3) could be converted into furan (4) by sequential esterification (CH_2N_2) and dehydration (*p*-toluenesulphonic acid in hot benzene) in 79% yield; this is thus a viable method for the introduction of an α-isopropylidene group into furoic acids.

TABLE 2

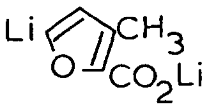


The possibility of generating *bis*-anions from 2-furoic acid was next examined. Treatment of a solution of the acid in THF with two equivalents of LDA at -78° for 0.5h. resulted in the formation of a cloudy, orange solution. A sample was withdrawn and treated with excess deuterium oxide; a ^{1}H n.m.r. of the product revealed a complete absence of resonances at 2.31 τ. All other spectral data was consistent with it being 5-D-2-furoic acid (6)[2], indicating the intermediacy of *bis*-anion (5). The behaviour of (5) with electrophiles was found to be similar to that of the *bis*-anion (1) from 3-furoic acid. (Table 2). Reactions with carbonyls were again very rapid and clean at -78° while coupling with alkylating reagents only occurred at temperatures $>-30^{\circ}$ but yields were significantly higher than with 3-furoic acid. However, as with 3-furoic acid, only traces of alkylated products could be isolated when the *bis*-anion was treated with allylic or benzylic halides. The tertiary alcohol (7), derived from acetone, could be converted into furan ester (8) in high yield, in an identical manner to that used for the obtention of ester (4).

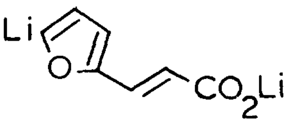
3-Methyl-2-furoic acid on treatment with lithium diisopropylamide was converted into *bis*-anion (9); here formation of (9) was complete in *ca.* 3 minutes at -78° (n.m.r. sampling) and the metallated species was completely soluble in THF (3ml/mM). The reactions of (9) were closely similar to those of 2-furoic acid, and no evidence of reaction at the 3-methyl group was found.

Finally, the behaviour of 2-furylacrylic acid with LDA was examined. In contrast to the foregoing series, a *bis*-anion could only be formed to an extent of *ca.* 50% under a variety of conditions. That metallation had occurred at the 5-furyl position, implying the intermediacy of (10), was proven by examination of the ^1H n.m.r. spectrum of a deuterated sample. There was no evidence of deuteration at any other position in the molecule. Treatment of the partially formed *bis*-anion with excess methyl iodide followed by esterification (CH_2N_2) resulted in the isolation, by preparative gas chromatography,[5] of the 5-methyl derivative (11) in 45% yield together with 46% of methyl 2-furylacrylate.[6]

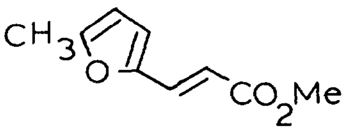
We are, at present, investigating the potential of these reactions for the synthesis of natural furans and other furanoid derivatives.



(9)



(10)



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References

1. S. Gronowitz and G. Sörlin, *Acta. Chem. Scand.*, 1961, **15**, 1419 and *Arkiv för Kimi*, 1962, **19**, 515; Y. Fukuyama, T. Tokoroyama and T. Kubota, *Tetrahedron Letters*, 1972, 3401; L. Mangoni, M. Adinolfi, G. Laonigro and R. Caputo, *Tetrahedron*, 1972, **28**, 611; D.W. Knight and G. Pattenden, *J.C.S. Perkin I*, 1975, 635, 641.

2. D.J. Chadwick, J. Chambers, P.K.G. Hodgson, G.D. Meakins and R.L. Snowden, *J.C.S. Perkin I*, 1974, 1141.

3. V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1216; G. Büchi and H. Wüest, *J. Org. Chem.*, 1966, **31**, 977.

4. N.D. Ly and M. Schlösser, *Helv. Chim. Acta.*, 1977, **60**, 2085.

5. Acidic products were recovered using silica gel chromatography with chloroform-methanol mixtures as elutants. Alternatively, the acidic products were esterified with diazomethane and subjected to preparative gas chromatography using a Pye 105 chromatograph and a 15' x ⅜" 3% OV225 on Gas Chrom Q column at temperatures between 180° and 200°.

6. ^1H n.m.r. of 5-methyl derivative (**11**):- τ($CDCl_3$) 2.61 (d, 16,.CH:CH.CO_2Me), 3.49 (d, 3, Furyl-3-H), 3.77 (d, 16, .CH:CH.CO_2Me), 3.92 (d, 3, Furyl-4-H), 6.23 (CO_2Me) and 7.68 (Furyl-5-CH_3); *cf* ^1H n.m.r. of methyl 2-furylacrylate:- τ($CDCl_3$) 2.49 (d, 1.5, Furyl-5-H), 2.52 (d, 16, .CH:CH.CO_2Me), 3.37 (d, 3, Furyl-3-H), 3.53 (dd, 3 and 1.5, Furyl-4-H), 3.68 (d, 16, .CH:CH.CO_2Me) and 6.23 (CO_2Me).

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