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THE SYNTHESIS OF 2,5-DISUBSTITUTED FURANS

David J. Ager

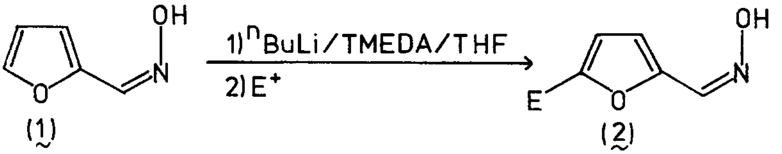
Department of Chemistry, University of Toledo, 2801 W. Bancroft St., Toledo, Ohio 43606, U.S.A.

Summary: The dianion derived from the oxime of furfuraldehyde (1) reacts with electrophiles at the 5-position of the furan ring; subsequent hydrolysis of the oxime provides a useful method for the synthesis of 2,5-disubstituted furans.

As part of our studies towards the synthesis of macrolide and ionophoric antibiotics[1], we have been investigating various aspects of the use of substituted furans as a means of introducing a tetrahydrofuran ring[2]. One of the most versatile methods for the preparation of furans is the coupling of a metallated furan with an electrophile[3]. It has been shown, in this context, that the dianions derived from furan carboxylic acids may be used to synthesize substituted furans[4,5]. This prompted us to investigate the use of a masked carbonyl group[6].

It has been shown that the anion derived from 2-(2-furyl)-1,3-dithiane undergoes a furan-ring opening reaction and condensations occurred in only moderate yield[7] and, as a consequence, a non-sulphur masking group was sort. Other studies[6] led to the use of the oxime(1).

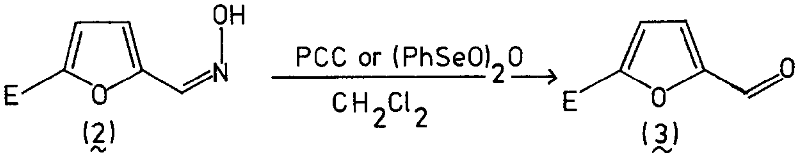
The oxime(1) was prepared by a standard method[8,9] and only one isomer was obtained[10] which has been shown to be *anti*[11]. The dianion was formed by the addition of two equivalents of n-butyllithium to the oxime in THF at -78°C in the presence of *N*,*N*,*N*^{1},*N*^{1}-tetramethylethylenediamine[12,13]. Reactions of the dianion with various electrophiles are summarized in the table and scheme:

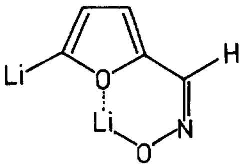


where E⁺=an electrophile

The table shows that the dianion of (1) may be alkylated in good yield with primary alkyl halides. The dianion also reacted with carbonyl compounds in good to high yield except when enolizable ketones, such as cyclohexanone, were employed. The yields in these cases were much lower, a marked contrast to the furan carboxylic acids[5]. In all cases the 2,5-disubstituted furan was formed, no metallation at the 3-position of the furan ring was detected. The anti-isomer of the oxime was used in these investigations[10] which exists in the s-cis form[11]. The conformation of the dianion, therefore, may not be related to the oxime(1) but may be as shown in (4)[15]. 2,5-Substituted furans were still formed exclusively when the TMEDA was omitted[13].

The oxime group was converted to the aldehyde group by reaction with pyridinium chlorochromate[16] or phenylselenic anhydride[17]; both reagents have been used before for this transformation and gave high yields (see table) of the appropriate aldehyde.





(4)

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Table

Alkylation of the dianion formed from furfuraldehyde oxime(**1**) (see schemes)

Electrophile (E^+)	Yield (%) (**2**)[a]	Yield (%) (**3**)[3]
D_2O	99	89[b] 87[c]
MeI	95	80[b] 83[c]
EtI	82	75[b] 78[c]
^{n}PrI	79	71[b] 75[c]
^{s}PrI	20[e]	-[d]
^{n}BuI	80	73[b] 78[c]
Me_3SiCl	90	-
$^{n}Bu_3SnCl$	77	-
EtCHO	79	69[b,f]
$^{n}C_5H_{11}CHO$	78	-
PhCHO	92	84[b,f] 80[c,f]
Me_2CO	20[e]	-
$^{c}C_6H_{10}O$	10[e]	-
Ph_2CO	79	61[b,f]

[a] All new compounds have been characterized. All yields are isolated unless stated otherwise.

[b] The oxidation was carried out with PCC.

[c] The oxidation was carried out with $(PhSeO)_2O$.

[d] Denotes that this transformation was not carried out.

[e] Approximate yield (by n.m.r.)

[f] The alcohol was protected as the t-butyldimethylsilyl ether which involved protection/ deprotection steps and the yield quoted refers to just the oxidation step.

References and Notes

1) D. J. Ager and R. C. Cookson, Tetrahedron Lett., 1982, **23**, 3419.

2) This type of strategy has, for example, been sued in the synthesis of nonactic acid. See W. Wierenga in "The Total Synthesis of Natural Products", vol. 4, Ed. J. ApSimon, Wiley, New York, 1981, p 263ff and references therein.

3) For examples see V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1216; G. Büchi and H. Wüest, *J. Org. Chem.*, 1966, **31**, 977; T. Masamune, M. Ono and H. Matuse, *Bull. Chem. Soc., Japan*, 1975, **48**, 491; G. M. Davies and P. S. Davies, *Tetrahedron Lett.*, 1972, 3507; D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans. I*, 1975, 641 and D. J. Chadwick, J. Chambers, P. K. G. Hodgson, G. D. Meakins and R. L. Snowden, *J. Chem. Soc., Perkin Trans. I*, 1974, 1141. See also reference 5 and papers cited therein.

4) D. W. Knight, *Tetrahedron Lett.*, 1979, 469.

5) D. W. Knight and A. P. Knott, *J. Chem. Soc., Perkin Trans. I*, 1981, 1125.

6) The use of oximes as acyl anion equivalents will be published shortly.

7) M. J. Taschner and G. A. Kraus, *J. Org. Chem.*, 1978, **43**, 4235.

8) W. J. Criddle and G. P. Ellis "Qualitative Organic Chemical Analysis", Butterworths, London, 1967.

9) O. L. Brady and R. F. Goldstein, *J. Chem. Soc.*, 1927, 1959.

10) The oxime(**1**) was produced almost quantitatively and had m.p. 91-92°C.

11) R. Wasylishen and T. Schaefer, *Canad. J. Chem.*, 1972, **50**, 274.

12) A typical procedure is as follows: n-butyllithium (20mmol of a solution in hexane) was added to the oxime(**1**)(1.12g, 10mmol) and TMEDA (4ml, 26mmol) in THF(35ml) at -78°C. After 1h, the electrophile 9neat or in THF solution) was added, the reaction allowed to warm to room temperature and the product isolated by crystallization or chromatography after extractive work-up.

13) The use of TMEDA aids the formation of the dianion; reaction of the oxime with n-butyllithium in the absence of TMEDA still gave the dianion but the yield was decreased because of the addition of the alkyllithium to the C-N double bond.

14) c.f. D. J. Chadwick and C. Willbe, *J. Chem. Soc., Perkin Trans. I*, 1977, 887.

15) The *S-cis* geometry (ref. 11.) means that the oxime's nitrogen lone pair is not available for complex formation with a lithium at the 3-position.

16) J. R. Maloney and R. E. Lyle, *Synthesis*, 1978, 212.

17) D. H. R. Barton, D. J. Lester and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 1977, 445.

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