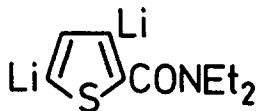


DIMETALLATIONS OF 2-SUBSTITUTED FURANS AND THIOPHENES :
APPROACHES TO THE 2,3,5-TRISUBSTITUTED HETEROCYCLES

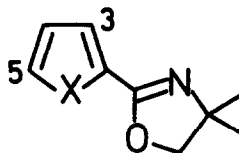
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Abstract: The preparation and reactions of 3,5-dilithiated furan and thiophene derivatives bearing the 4,4-dimethyloxazolin-2-yl 2-substituent are reported. The 2-*tert*-butoxycarbonyl analogues cannot be prepared by direct dimetallation of the corresponding esters but sequential monometallation with *in situ* trapping by Me₂SiCl ultimately affords the 3,5-disilylated products : the 3-metallation of the 5-silylated intermediate is accelerated by LiCl.

In a recent paper in this journal,¹ Doadt and Snieckus have reported the preparation of a 3,5-dilithiated thiophene-2-carboxamide (1) and its reactions with a variety of electrophiles. Their work prompts us to present our own results on the dimetallation of



(1)

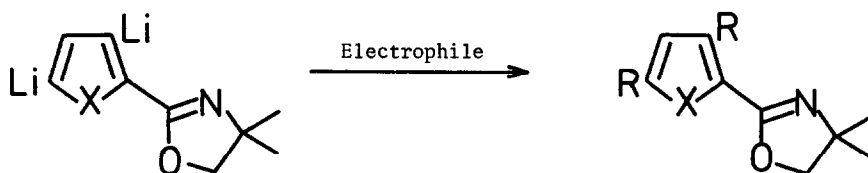


(2) X = S; (3) X = O

2-(2-thienyl)- and 2-(2-furyl)-oxazolines, (2) and (3), which show that the technique is of more general applicability. Furthermore, our observations on the difficulties attendant on amide hydrolysis (the forcing conditions for which can cause substrate destruction and/or expulsion of substituents)² and on the ease of transformation of oxazolino into other functionality³ suggest that the dimetallated oxazoline derivatives will prove to be of more general synthetical appeal.

A thorough review of metallation conditions with monitoring of the extent of lithiation

via MeOD work-up and ^1H n.m.r. analysis as in our previous work^{2,3} indicates that the greatest levels of dilithiation in the thienyl-oxazoline (2) case are achieved when the compound is treated with 3.3 equivalents of *sec*-butyl-lithium in tetrahydrofuran (THF) at -20°C for 0.5h. Under these conditions, lithiation at the 3-position is essentially total and 93% at the 5-position. Best dilithiation levels in the analogous furan (3) require the same base and solvent (at -78°C for 2h) but also admixture of 3.3 equivalents of tetramethylethylenediamine (TMEDA) : lithiation levels are 96 and 98% at the 3- and 5-positions respectively. Treatment of the dilithio-intermediates with a range of electrophiles (Table) affords the 2,3,5-trisubstituted compounds in excellent yields.

TABLE^a

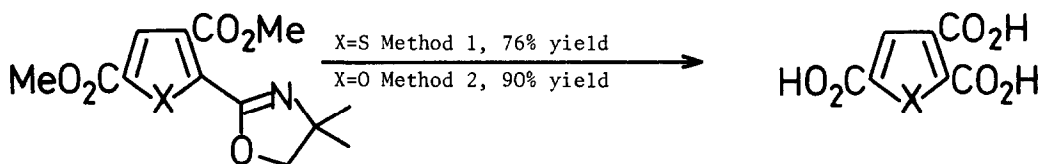
X	Electrophile	R	Yield (%)	Compound
S	CO_2 then HCl aq.	CO_2H	97 ^b	(4)
S	Me_2S_2	SMe	89	(5)
S	Me_3SiCl	SiMe_3	93	(6)
O	CO_2 then HCl aq.	CO_2H	88 ^b	(7)
O	I_2	I	94	(8)

^a Satisfactory analytical data were obtained on all compounds.

^b Characterised as the dimethyl esters.

We have previously demonstrated that the oxazoline moiety can be transformed into carboxy functionality whilst retaining the integrity of the heteroaromatic rings and their

substituents.³ For the present purposes, this is illustrated by the conversion of the dimethyl esters derived from compounds (4) and (7) into the triacids in excellent yields (Scheme).

Scheme ^a

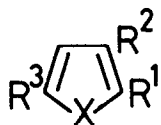
^a Products were characterised as the trimethyl esters.

Method 1 : NaOCl, H₂O, EtOAc, Bu₄^tN⁺HSO₄⁻, 12h, 20°C; then KOH aq., 5h, 20°C.

Method 2 : MeI, 36h, 20°C then KOH aq., 12h, reflux.

Although the dilithiation methodology is unsuccessful when applied to *t*-butyl furan-2-carboxylate (9) due to corruption of the substrate during reaction, it is possible to prepare 3,5-disubstituted derivatives of *t*-butyl furan- and thiophene-2-carboxylates *via* sequential monolithiation and *in situ* trapping with an electrophile compatible with the metallation environment. Thus, treatment of esters (9) and (10) with a THF solution containing an excess of lithium di-isopropylamide (LDA) and Me₃SiCl at -78°C for 0.5 - 1h

X	R ¹	R ²	R ³	Compound
O	CO ₂ Bu ^t	H	H	(9)
S	CO ₂ Bu ^t	H	H	(10)
O	CO ₂ Bu ^t	SiMe ₃	SiMe ₃	(11)
S	CO ₂ Bu ^t	SiMe ₃	SiMe ₃	(12)
O	CO ₂ Bu ^t	H	SiMe ₃	(13)
S	Oxazoline	H	SiMe ₃	(14)



gives the 3,5-disilylated esters (11) and (12) in *ca.* 95% yields. Oxazolines (2) and (3) may similarly be disilylated, again in yields approaching quantitative. If these metallations are carried out in the absence of Me₃SiCl and MeOD is then added

subsequently, only 5-deuteriated material is observed showing that only *monolithiation* occurs and that the sequence of events in the presence of an *in situ* trap is : 5-lithiation, trapping, 3-lithiation, trapping. In support of this, the 5-mono-silylated intermediates (13) and (14) have been prepared independently and subjected to metallation in the presence of Me_3SiCl : in both cases, the 3,5-disilylated products are obtained in >90% yield. Interestingly, admixture of LiCl equimolar with the metallating agent seems essential for achievement of a high yield (in the sequential metallation experiments, LiCl is generated during the reaction of the 5-lithio-intermediates with Me_3SiCl). Since *ipso*-⁴ or fluoride-induced-⁵ desilylation in the presence of a variety of electrophiles is feasible in these systems, the disilyl compounds are potential precursors of a range of 2,3,5-trisubstituted derivatives.

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