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HIGH-YIELD SYNTHESES OF 2,3-DISUBSTITUTED FURANS AND THIOPHENES

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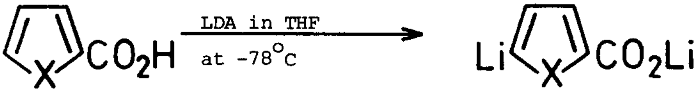
Summary: The course of lithiation of furan- and thiophene-2-carboxylic acids is critically dependent on the identity of the lithium base allowing high-yielding syntheses of 2,3- and 2,5-disubstituted thiophenes: the proposed use of a trimethylsilyl blocking group to control metallation in the furan acid provides a useful route to 2,3-disubstituted furans.

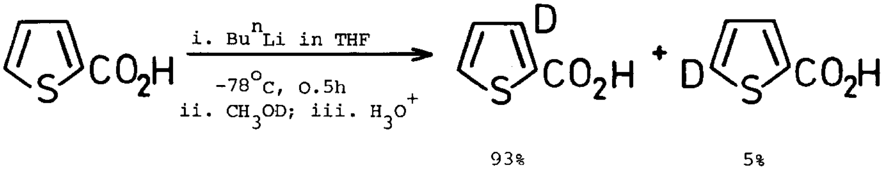
In recent papers,[1,2] Knight and Nott have demonstrated that furan- and thiophene-2-carboxylic acids may be metallated regioselectively by lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at -78°C to yield the 5-lithio-furan- and -thiophene-2-carboxylates [(1), X = O,S], thus furnishing a useful route to a range of 2,5-disubstituted derivatives. We have recently become interested in the more taxing problem of preparing the corresponding 2,3-disubstituted systems which are not readily available by conventional methodology, and have established[3,4,5] the utility of oxazolino- and amido-directed metallation in this connection. During the course of this work, it occurred to us that the carboxylate anion might itself function in directing metallation



(1)

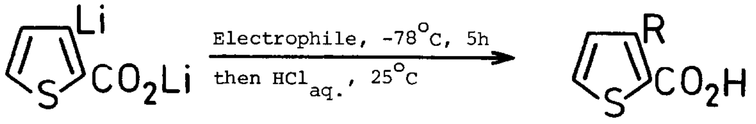
to an adjacent ring position if conditions could be found which avoided significant competition from nucleophilic attack on the carboxylate carbonyl group by an organolithium reagent, and if the latter were chosen to be less 'co-ordinatively saturated'[6] than LDA. The results that we have now obtained demonstrate the feasibility of this idea in thiophene and furan chemistry, show that Knight and Nott's observations are but special cases of more complex metallation patterns, and lend the lie (at least for these systems) to the widely-held view that 'direct <u>ortho</u> lithiation of arylcarboxylic acids is generally not feasible because of the increased electrophilicity of the carboxylate group'.[6]

Treatment of thiophene-2-carboxylic acid with 2.2 equivalents of n-butyl-lithium in THF at -78°C for 0.5h and subsequent addition of CH_3OD gave deuteriated material ^1H n.m.r. of which showed the presence of 93% 3-deuteriothiophene-2-carboxylic acid, only 5% of the 5-deuterio-isomer, and no product derived from nucleophilic addition to the carbonyl group. This result, which is in marked contrast to that of Knight and Nott[2]



who found no trace of β-(3- or 4-) metallo intermediates, shows importantly that the pattern of regioselectivity of metallation of thiophene-2-carboxylic acid can be almost totally transformed by the simple expedient of change of metallating agent. The technique can be used to provide easy access to a wide variety of 2,3-disubstituted thiophene derivatives through reaction of the dilithio-intermediate with a range of electrophiles: the yields shown in the Table of isomerically pure products obtained

Table [a]



Electrophile:	$(CH_3)_3SiCl$	$(CH_3)_2S_2$	CH_3I	I_2	$C_6H_5CH_2Br$
R :	$(CH_3)_3Si$	CH_3S	CH_3	I	$C_6H_5CH_2$
Yield (%):	85	94	83	94	70

[a] Satisfactory analytical data were obtained on all compounds.

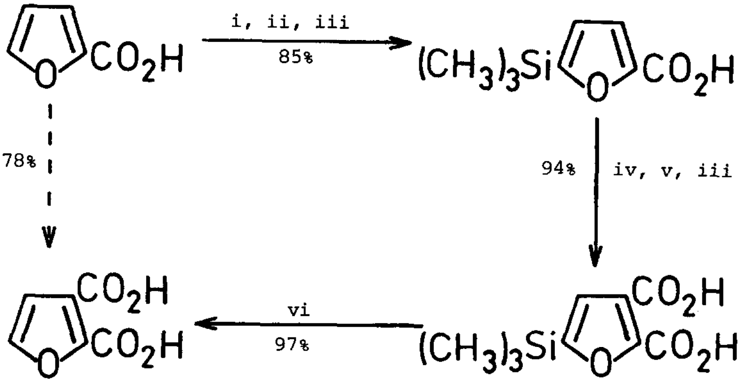
after a single recrystallisation are typical.

It is important that the temperature of the dilithio-intermediate is not allowed to rise too quickly after addition of the electrophile. Work-up with chlorotrimethylsilane (TMSCl) and removal of the cooling bath after 5m gave (after 3h at 25°C) a *ca.* 1:1 mixture of 2,3- and 2,5-disubstituted thiophenes, probably *via* transmetallation processes.

Application of this methodology to the corresponding furan carboxylic acid gave high metallation levels but with low regioselectivity (typically 5:3 3- to 5-deuteriated material). This again contrasts with earlier work[1] with LDA as the base, in which only 5-deuteriation could be detected and further serves to emphasise the importance of the correct choice of metallating agent.

As alternative routes to 2,3-disubstituted furans, we recommend either conversion of carboxy into oxazolino or amido functionality[4,5] and subsequent directed metallation, or preliminary blocking of the 5-position of furan-2-carboxylic acid with the trimethylsilyl group, metallation as above, and fluoride ion-induced desilylation: a representative

Scheme



Reagents: i, LDA, THF, -78°C, 0.5h; ii, TMSCl, -78 - 25°C, 2h; iii, $HCl_{aq.}$, 25°C; iv, Bu^nLi, THF, -78°C, 0.5h; v, CO_2, ether, -78 - 25°C, 2h; vi, $Bu^n_4N^+F^-$, THF, 67°C, 12h.

example of this latter procedure, given in the Scheme, has an overall yield of 78%.

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