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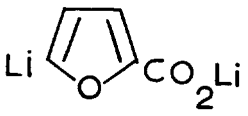
FORMATION AND REACTIVITY OF DIANIONS DERIVED FROM 2- and 3-THIOPHENCARBOXYLIC ACIDS

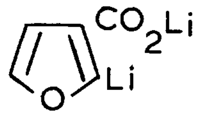
David W. Knight* and Andrew P. Nott
Department of Chemistry, University Park
Nottingham, NG7 2RD, U.K.

Dianions (3) and (6) can be generated in high yield from the corresponding thiophencarboxylic acids with lithium diisopropylamide and react with a number of representative electrophiles to give fair to good yields of 5-substituted-thiophen-2-carboxylic acids and 2-substituted thiophen-3-carboxylic acids respectively.

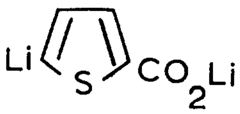
We have recently reported that the dianionic species (1) and (2) can be readily prepared from the corresponding furancarboxylic acids upon treatment of the latter with lithium diisopropylamide (LDA) at low temperatures, and that such intermediates can be used to prepare a range of substituted furancarboxylic acids.[1] In view of the broadly similar chemistry of furyl-lithium and thienyl-lithium species, we reasoned that it was possible that dianionic intermediates analogous to (1) and (2) could be obtained from thiophencarboxylic acids. Herein, we report our preliminary results aimed at testing this supposition.



(1)



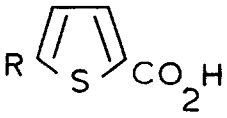
(2)



(3)

Treatment of a solution of thiophen-2-carboxylic acid in tetrahydrofuran at -78° with two equivalents of LDA gave a white suspension, samples of which were withdrawn and immediately quenched with D_2O. Analysis of the products by ^{1}H n.m.r. showed ca. 80% deuterium incorporation exclusively at the 5-position[2], after 10 minutes; no further incorporation was observed after this period. We therefore concluded that dianion (3) had been formed, a reasonable result in view of the formation of (1) from the corresponding furancarboxylic acid and the usual preference for metallation at an α-position in both furans and thiophens.

The reactivity of (3) turned out to be somewhat different to that of (1)[1]. Reaction of (3) with methyl iodide and ethyl iodide was rapid and led to the isolation of 5-methyl-(4a) and 5-ethylthiophen-2-carboxylic acid (4b), respectively in <80% yield[3].



(4)

a; $R=CH_3$.

b; $R=C_2H_5$.

c; $R=(CH_3)_3Si$.

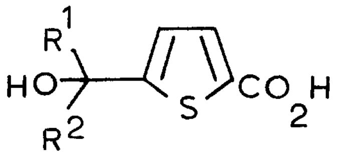
d; $R=CH_2{=}CH.CH_2$.

e; $R=PhCH_2$.

Coupling of (3) with chlorotrimethylsilane was also very rapid at -78° leading to (4c) in 85% yield.

In contrast to the chemistry of (1) was the formation of (4d), the adduct of (3) and allyl bromide, albeit in only ca. 30% yield[4,5]. ((1) failed to couple with allylic or benzylic halides). The yield of (4d) was improved to ca. 50% by the addition of two equivalents of TMEDA while the addition of HMPA did not improve the yield and a change of solvent to either ether, toluene or dimethoxyethane or the addition of Cu(I)I resulted in complete failure. The use of n-BuLi/TMEDA as base, in tetrahydrofuran gave similar yields of (4d) to those obtained using LDA alone. Dianion (3) also reacted with benzyl bromide to give 5-benzylthiophencarboxylic acid (4e) in 57% yield[5]; a slight improvement in yield was noted when TMEDA (2 eq.) was added

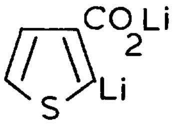
The reactions of (3) aldehydes and ketones were rather sluggish, and with heptanal, benzaldehyde and acetone, the adducts (5a-c) were obtained in ca. 50% yield along with ca. 50% unreacted starting thiophen-2-carboxylic acid[4,5]. Dianion (3) did not couple with triethyl orthoformate or diphenyl disulphide.


(5)

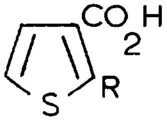
a; R^1=$CH_3(CH_2)_5$; R^2=H.

b; R^1=Ph; R^2=H.

c; R^1=R^2=CH_3.


(6)

We then turned to an examination of the behaviour of thiophen-3-carboxylic acid with LDA and found that only the dianion (6) was formed, not unexpectedly in view of the formation of (2) from furan-3-carboxylic acid[1]. The dianion (6) reacted with methyl iodide to give 2-methylthiophen-3-carboxylic acid (7a) in 87% yield; however reactions between (6) and both

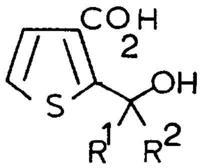

(7)

a; R=CH_3.

b; R=C_2H_5.

c; R=$(CH_3)_3Si$.

d; R=CH_2=CH.CH_2.


(8)

a; R^1=n-Hexyl; R^2=H.

b; R^1=Ph; R^2=H.

c; R^1=R^2=CH_3.

ethyl iodide and chlorotrimethylsilane were less efficient and necessitated leaving the reaction mixture at ambient temperature for a number of hours to obtain (7b) and (7c) in 31% and 55% yields respectively[5]. Dianion (6) also reacted slowly with allyl bromide to give (7d) in 22% yield[5], but no adduct was formed with benzyl bromide. Similarly (6) condensed with aldehydes and ketones slowly at room temperature leading to (8a-c) in yields[5] of 55%, 43%, and 65% from heptanal, benzaldehyde, and acetone, respectively.

In general terms, the dianions (3) and (6) are more stable and less reactive than the corresponding dianions (1) and (2) derived from furancarboxylic acids[1]. Whereas the latter are protonated quite rapidly above -30° (presumably the solvent tetrahydrofuran acts as the proton source), the thiophen derivatives (3) and (6) seem to be stable at this temperature but are slowly protonated above 0°. Also notable is the marked difference in the reactions with aldehydes and ketones which are very rapid at -78° in the cases of (1) and (2), but very much slower with (3) and (6). The success of the coupling reactions between (3) and (6) and allyl bromide (similar reactions fail completely with (1) and (2)) also attests to the softer nature of (3) and (6).

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1. D.W. Knight, Tetrahedron Letters, 1979, 46.
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2. Inferred from the disappearance of the resonance at τ 2.4 - see M.L. Martin, C. Andrieu, and G.J. Martin, Bull.Soc.chim.France, 1968, 698.
3. Yields quoted are for pure, isolated compounds having satisfactory analytical and spectral data, unless otherwise stated.
4. In cases where conversion was incomplete, the products were purified by silica-gel chromatography using mixtures of chloroform and methanol as eluants.
5. In all cases where conversion was incomplete, the remainder of the material balance was pure starting acid.

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