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> METHODS FOR THE HOMOLOGATION OF BENZOFURANCARBOXYLIC ACIDS USING DIANIONIC INTERMEDIATES

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<u>Summary</u>: Dianions (2), (5), and (10), can be derived from the corresponding benzofurancarboxylic acids using lithium diisopropylamide, and are useful intermediates for the homologation of the parent acids.

The benzofuran nucleus occurs in a diverse range of natural products. Some of these compounds together with many synthetic benzofurans have significant pharmocological activities.¹ We report herein new methods for the homologation of various benzofurancarboxylic acids based on the intermediacy of dianionic species, derived from the parent acids by metallation using lithium diisopropylamide (LDA).

In common with many heterocycles,² benzofuran itself undergoes direct metallation at the carbon α to the heteroatom, when treated with <u>n</u>-butyllithium² or LDA³, to give 2-lithiobenzofuran. This useful intermediate can also be obtained from 2-bromobenzofuran by halogen-lithium exchange with n-BuLi.^{4,5} It was therefore anticipated⁶ that 3-benzofurancarboxylic acid $(1)^7$ could give rise to dianion (2) on treatment with two equivalents of a strong base. In the event, reaction between (1) and 2.1 equivalents of LDA in tetrahydrofuran (THF) at -78° for 0.5 h., gave an orange solution which was instantly decolourised on addition of chlorotrimethylsilane. Acidic work-up then gave the 2-trimethylsilyl derivative (3a) in virtually quantitative yield. The material was pure according to its ¹H n.m.r. spectrum; subsequent crystallisation gave analytically pure (3a) in ca. 80% yield.⁸ Similar reactions with benzaldehyde and heptanal were slower, but after allowing the reaction mixture to warm to room temperature, (3b) and (3c) respectively were obtained in ca. 75% isolated yield. Unfortunately, attempted alkylations of (2) with ethyl iodide failed to give more than traces of (3d) under a variety of conditions. Alkylations of dianions related to (2) have also been found to be unsatisfactory.⁶ On warming, the dianion (2) was slowly protonated (THF as proton source?); for example, when a solution of (2) was allowed to reach 0°C during 0.5 h., then quenched with Me₃SiCl, only a 35% conversion to (3a) occurred, the remainder of the product being starting

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material (1).

We have also investigated the possibility of utilising this method for the homologation of benzofuran-2-carboxylic acid (4a).⁹ Dean <u>et.al</u>.³ have reported that (4a), on treatment with 2 equivalents of LDA followed by CO₂, gave a good yield of benzofuran-2,3-dicarboxylic acid together with some of the acetylenic acid (6a), arising from ring opening of the intermediate dianion (5a). We have been unable to extend the utility of this reaction; attempts to trap dianion (5a) with a variety of electrophiles (Me₃SiCl, MeI, RCHO) all failed to give more than traces of the desired products, even when the reactions were carried out at low temperatures (< -90°C). In all cases, the major or exclusive product was the acetylenic acid (6a).^{4,5} Indeed, treatment of a benzofuran-2-carboxylic acid with 2.1 equivalents of LDA at -78°C, followed by warming to room temperature is, in our opinion, an effective method for the preparation of (2-hydroxyphenyl)propynoic acids (6)!

By contrast, metallation of 5-methoxybenzofuran-2-carboxylic acid $(4b)^9$ using LDA at -90°C followed by the addition of methyl iodide, benzaldehyde, or <u>n</u>-heptanal gave the desired products, (7a), (7b), and (7c) respectively, in <u>ca</u>. 90% yield accompanied by, at most, only traces of the ring opened product (6b). Presumably, the "<u>para</u>" methoxy group stabilises the intermediate dianion (5b), with respect to ring opening, by causing the furan oxygen to be a poorer leaving group than in the unsubstituted dianion (5a). Similarly, dianion (5d), in which the methoxy substituent is <u>ortho</u> to the furan oxygen, could also be trapped by the same electrophiles at -90°C to give (8a), (8b), and (8c). In these cases, the stabilising effect was not so great and the ring-opened product (6d) was present to an extent of <u>ca</u>. 20% in the isolated products. Nevertheless, the desired products (8a-c) could be obtained in 50-60% yield after chromatography. In line with these observations, the 6-methoxy acid (4c),⁹ in which the methoxy group is <u>meta</u> to the furan oxygen, underwent rapid ring opening at -90°C to give only the acetylenic acid (6c).

In an attempt to circumvent the problem of ring opening in benzofuran-2carboxylic acid (4a), we investigated the possibility of forming a dianionic species $(10)^{10}$, from 3-methylbenzofuran-2-carboxylic acid $(9)^{11}$. We were pleased to find that the bright-red dianion (10) could indeed be obtained and that it coupled with a range of electrophiles to give the desired products (11a-e) in <u>ca</u>. 90% isolated yields. We have found that these reactions are best carried out using 2.1 equivalents of LDA in THF at -10° C. In contrast to the vinyl carbanions (<u>vide supra</u>), dianion (10) also reacted very efficiently with ethyl iodide, to give (11g) in 80% yield, and with 1,2-epoxybutane to give (11f) in 93% yield. Thus, this method appears to have considerable potential for the efficient synthesis of many 3-substituted benzofuran-2carboxylic acids.







(đ) R=Et



(a)

 $R^{1}=R^{2}=R^{3}=H;$

(b)





(c)
$$R^1 = R^3 = H; R^2 = OMe;$$

 $R^{1}=OMe; R^{2}=R^{3}=H;$ (d) $R^1 = R^2 = H$; $R^3 = OMe$.



- (a) R=Me
- (b) R=CH (OH) Ph
- (c) R=CH(OH)<u>n</u>-hex



CH₃ CO2H (9)



CH₂R CO₂H (11)

- (a) R=Me
- (b) R=SiMe₃
- R=CH (OH) Ph (c)
- (d) R=C Me.(OH)Ph
- R=CH(OH)<u>n</u>-hex (e)
- R=CH2CH(OH)Et (f)
- R=Et (g)

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