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THE METALATION OF 1,3-BIS(TRIFLUOROMETHYL)BENZENE BY n-BUTYLLITHIUM

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Summary

Treatment of the lithium reagent from 1,3-bis(trifluoromethyl)benzene (I) with carbon dioxide gave a 60/40 mixture of 2,4- and 2,6-bis(trifluoromethyl)-benzoic acids (IV) and (II). The lithiation/carbonation of 1,3-bis(trifluoromethyl)benzene-5-*d* (VIII) gave (II) and (IV) without loss of deuterium. This result indicates that (I), unlike trifluoromethylbenzene, does not lithiate *meta* to a CF_3 group.

Introduction

Grocock et al. [1] have recently reported on the products obtained when the lithium reagent formed from 1,3-bis(trifluoromethyl)benzene (I) was treated with solid carbon dioxide. A 40/60 mixture of 2,6- and 3,5-bis(trifluoromethyl)-benzoic acids (II) and (III) was isolated when the reagent was prepared from n-butyllithium and only the 2,6-isomer (II) was formed with n-butyllithium/*N*,*N*,*N*,*N*-tetramethylethylenediamine (eqn. 1). The structure of the 2,6-acid (II) was established from the ^1H NMR spectrum and the difficulty in esterification. The 3,5-isomer (III) was isolated as the methyl ester and the structure assigned based on the similarity of the ^1H NMR spectrum with *N*,*N*-dimethyl-3,5-bis-trifluoromethylaniline [1].

We have also carried out the lithiation/carbonation of (I) and found that a mixture of 2,4- and 2,6-(IV) and (II) rather than 2,6- and 3,5-bis(trifluoromethyl)benzoic acids (II) and (III) are formed. In this report we put forth data to establish the structures of (II) and (IV) and also some work comparing the lithiation of (I) with trifluoromethylbenzene (V).

Results and discussion

The lithiation of a diethyl ether solution of 1,3-bis(trifluoromethyl)benzene (I) by commercial n-butyllithium in hexane followed by treatment with solid

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carbon dioxide gave an acid fraction in 85% yield. Reaction of this product with diazomethane afforded a liquid ester that gave two components in a 60/40 ratio when analyzed by vapor phase chromatography (VPC). The two esters were readily separated by preparative VPC into fractions A and B. The major fraction (A) was easily hydrolyzed by 2*N* sodium hydroxide into a crystalline acid while the minor fraction (B) resisted hydrolysis in refluxing 2*N* sodium hydroxide, 2*N* hydrochloric acid or cold concentrated sulfuric acid.

Because of the resistance to hydrolysis and the AB_2 ^1H NMR system centered at δ 7.8 ppm the minor component (B) has been assigned as methyl 2,6-bis(trifluoromethyl)benzoate.

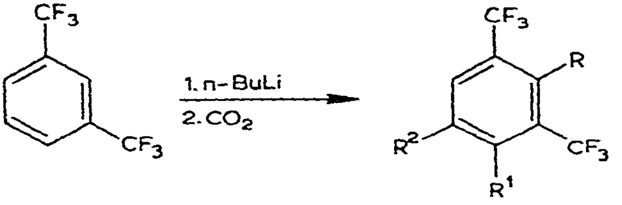
Comparison of the ^1H NMR spectrum of the crystalline acid (m.p. 110°; 3H singlet at δ 7.93 ppm) with authentic 3,5-bis(trifluoromethyl)benzoic acid [2] (m.p. 142°; AB_2 system at δ 8.00 and 8.45 ppm) revealed they were not identical. The major isomer must therefore be 2,4-bis(trifluoromethyl)benzoic acid (IV) and not the 3,5-acid as previously reported [1].

When the lithiation/carbonation of (I) was carried out in tetrahydrofuran at 25° and —5° the ratio of (II)/(IV) was approximately the same as in diethyl ether although the total yield of acids were 85% at 25° and 45% at —5°. At —50° only recovered (I) was obtained indicating that lithiation failed to occur.

The isomers obtained in the lithiation/carbonation of (I) are interesting when compared to those reported with trifluoromethylbenzene (V). Treatment of the lithiated product obtained from (V) and n-butyllithium with solid carbon dioxide was reported to give a mixture of *o*- and *m*-trifluoromethylbenzoic acids (VI) and (VII) in a ratio of 5/1 with ether [3] and 3/1 with an ether/hexane [4] solvent (eqn. 2). By analogy with these results it is surprising that (I) did not give any lithiation *meta* to a CF_3 group and form the 3,5-isomer (III) after carbonation.

The lack of formation of (III) can be explained by assuming that (I) does not lithiate *meta* to a CF_3 group or that lithiation did occur in the *meta* position (IX) and then isomerization to the *ortho* isomers (X) or (XI) occurred (eqn. 3). Steric grounds for the failure of *meta*-lithiation may be discounted.

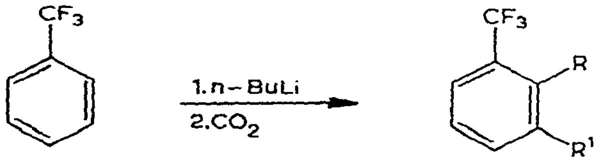
To distinguish between these possibilities 1,3-trifluoromethylbenzene-5-*d* (VIII) was treated with n-butyllithium, carbonated and the resultant methyl esters separated by preparative VPC. Comparison of the NMR spectrum of these esters with those obtained from (I) confirmed that no measureable amount of deuterium had been lost. The lithiation of (I), unlike that of (V) did not give rise to any metalation *meta* to a CF_3 group.



(1)

(I)

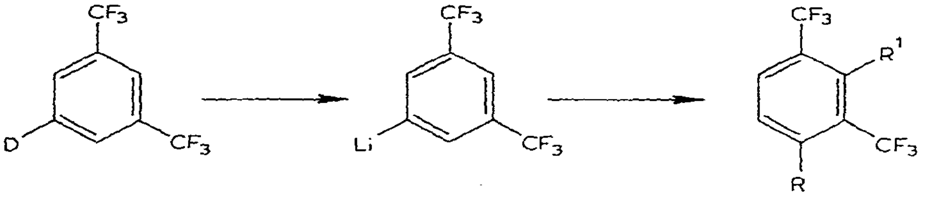
(II), R = COOH, R^1 = H, R^2 = H
(III), R = H, R^1 = H, R^2 = COOH
(IV), R = H, R^1 = COOH, R^2 = H



(V)

(VI) $R = COOH, R^1 = H$
(VII) $R = H, R^1 = COOH$

(2)



(VIII) (IX)

(X), $R = Li, R^1 = H$
(XI), $R = H, R^1 = Li$

(3)

Experimental

General

Melting points were determined on a Thomas—Hoover capillary melting point apparatus and have not been corrected. Infrared spectra were taken on a Perkin—Elmer "Infracord" Spectrophotometer. Proton NMR were measured on a Varian Associates A-60 spectrometer using $SiMe_4$ as an internal reference.

The vapor phase chromatography (VPC) analysis were carried out on a F and M Model 720 Vapor Fractometer equipped with a thermal conductivity detector and a 12′ 0.25 in. O.D. copper tube packed with 10% Hyprose SP-80 deposited on 60/80 mesh silicone treated Chromosorb W. The determinations were carried out at a column temperature of 150° and a helium flow rate of 50 ml/min.

Lithiation/carbonation of 1,3-bis(trifluoromethyl)benzene (I) in diethyl ether

A stirred solution of 5.0 g (0.023 mol) of (I) in 25 ml of anhydrous diethyl ether was blanketed with nitrogen and then treated dropwise with 17.5 ml (0.028 mol) of 1.6 *M* n-butyllithium in hexane (Foote Chemical Co.) at such a rate that the internal temperature did not exceed 20°. After an additional 1 h stirring at room temperature the solution was poured onto ca. 100 g of crushed solid carbon dioxide and allowed to stand for ca. 20 h. The resultant residue was treated successively with 75 ml of 2*N* NaOH and 75 ml of diethyl ether. The caustic layer was separated, washed with 50 ml of diethyl ether and then acidified with cold conc. hydrochloric acid. The acidified layer was saturated with NaCl and then extracted four times with 50 ml of $CHCl_3$. The combined $CHCl_3$ extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to give 5.1 g (85%) of (II) and (IV), m.p. 78—107°; neutralization equivalent for $C_9H_4F_6O_2$: calcd. 258; found 258. (Found: C, 41.7; H, 1.4. $C_9H_4F_6O_2$ calcd.: C, 41.9; H, 1.6%.)

A solution containing 10 g of the acid mixture (II) and (IV) in 100 ml of diethyl ether was treated at room temperature with a three-fold molar excess of diazomethane in diethyl ether. After ca. 0.5 h the solution was concentrated in vacuo and the resultant distilled to give 10.0 g (95%) of the methyl esters of (II) and (IV), b.p. 95—98°/15 mm. A VPC analysis gave two components A (60%) and B (40%) in order of elution. (Found: C, 44.3; H, 2.2. $C_{10}H_6F_6O_2$ calcd.: C, 44.1; H, 2.2%.)

A 500 mg sample of the above mixed esters were separated by preparative VPC. The first component [A: (IV) methyl ester] was isolated as an oil: NMR ($CDCl_3$) δ 3.95 (3H,s,CH_3), 7.87 (2H, broadened s, H-5 and H-6) and 8.02 ppm (1H,s,H-3); IR (neat) 5.75 μ (C=O). The second component [B: (II) methyl ester] was isolated as an oil that solidified on standing, m.p. 33—34°; NMR ($CDCl_3$) δ 3.93 (3H,s,CH_3), 7.65 (1H,m,H-4) and 7.88 ppm (2H,m,H-3 and H-5); IR (CH_2Cl_2) 5.72 μ (C=O).

Hydrolysis of the methyl esters of (II) and (IV)

Ten g of the methyl esters of (II) and (IV) was dissolved in a solution of 250 ml of 2*N* NaOH and stirred at room temperature for ca. 20 h. The solution was evaporated in vacuo and the resultant pasty residue was treated with 50 ml of water and 100 ml of diethyl ether and then stirred for about 2 h. The ether layer was separated and washed with 25 ml of water and the combined water fractions were acidified with cold concd. HCl and then extracted with three 50 ml portions of $CHCl_3$. The combined $CHCl_3$ fractions were dried (Na_2SO_4), filtered and evaporated in vacuo. The residue (6.2 g) was crystallized (diethyl ether/pentane) to give 5.7 g of 2,4-bis(trifluoromethyl)benzoic acid (IV), m.p. 110—111°; NMR ($CDCl_3$/DMSO-d_6) δ 7.93 (3H,s,H-3,H-5 and H-6) and 11.10 ppm (1H, broad s, COOH).

The NMR ($CDCl_3$/DMSO-d_6) of 3,5-bis(trifluoromethyl)benzoic acid [(III) Pierce Chemical Co.] gave δ 8.00 (1H,s,H-4), 8.45 (2H,s,H-2 and H-6) and 12.00 ppm (1H,s, COOH).

A sample of (IV) was treated with diazomethane in diethyl ether and the resultant methyl ester analyzed by VPC. The single component had the same retention time as the methyl ester of Component A isolated from the lithiation/carbonation of (I). (Found: C, 41.8; H, 1.4. $C_9H_4F_6O_2$ calcd.: C, 41.9; H, 1.6%.)

Lithiation/carbonation of 1,3-bis(trifluoromethyl)benzene (I) in tetrahydrofuran

In three separate experiments 5.0 g (0.023 mol) of (I) in 25 ml of anhydrous THF was blanketed with nitrogen and then treated dropwise with 17.5 ml (0.028 mol) of 1.6 *M* n-butyllithium in hexane at such a rate that the internal temperature was controlled at 25° (Exp. 1), —5° (Exp. 2) and —50° (Exp. 3). After an additional 1 h stirring at the above temperatures the solution was poured into ca. 100 g of crushed solid carbon dioxide and allowed to stand for ca. 20 h. Each experiment was processed in the same manner as the diethyl ether lithiation/carbonation of (I).

From Exp. 1 (25°) there was obtained 5.1 g (85%) of mixed acids (II) and (IV). The VPC analysis of the mixed methyl esters gave a 62/38 ratio of acid (IV) and (II) respectively.

From Exp. 2 (−5°) there was obtained 2.7 g (45%) of mixed acids (II) and (IV). The VPC analysis of the mixed methyl esters gave a 59/41 ratio of acid (IV) and (II) respectively.

From Exp. 3 (−50°) no acid fraction was isolated.

Preparation of 1,3-bis(trifluoromethyl)benzene-5-d (VIII)

A stirred mixture of 2.50 g (0.105) of magnesium shavings and 25 ml anhydrous diethyl ether maintained under a dry nitrogen atmosphere was treated dropwise (1.5 h) with a solution of 29.3 g (0.10 mol) of 5-bromo-1,3-bis(trifluoromethyl)benzene in 75 ml of diethyl ether. The mixture was then refluxed for 1.0 h, cooled in an icebath and treated dropwise (0.75 h) with a solution containing 5.0 ml of deuterium oxide (99.8% deuterium), 100 ml of diethyl ether and 50 ml of absolute tetrahydrofuran. After standing overnight at room temperature the reaction mixture was treated with 25 g of anhydrous sodium sulfate, filtered and distilled at atmospheric pressure through a Nester and Faust 36 in. spinning band column to give 12.2 g (57%) of (VIII), b.p. 110—112°/15 mm, n_D^{20} 1.3801 [(I), n_D^{20} 1.3800] : NMR ($CDCl_3$) δ 7.82 ppm (broadened singlet). The NMR of (I) in $CDCl_3$ gave multiple peaks between δ 7.45—7.97 ppm.

Lithiation/carbonation of 1,3-bis(trifluoromethyl)benzene-5-d (VIII)

A 5.0 g sample of (VIII) was lithiated and treated with solid carbon dioxide as described for (I) to give 5.1 g (84%) of mixed acids.

A 410 mg sample was dissolved in 10 ml of diethyl ether and treated with excess diazomethane in diethyl ether. After ca. 1.5 h the solvent was removed in vacuo and the residue [420 mg: analytical VPC; 61% (IV)-5-*d* and 39% (I)-5-*d*] separated by preparative VPC. The first component, methyl 2,4-bis(trifluoromethyl)benzoate-2-*d* was an oil: NMR ($CDCl_3$) δ 3.92 (3H,s,CH_3), 7.82 (1H, broad singlet) and 7.94 ppm (1H, broad singlet); IR (neat) 5.73 μ (C=O).

The second component, methyl 2,6-bis(trifluoromethyl)benzoate-4-*d* was an oil: NMR ($CDCl_3$) δ 3.92 (3H,s,CH_3), 7.88 ppm (2H,s,C_6H-3 and C_6H-5); IR (neat) 5.70 μ (C=O).

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