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PRELIMINARY NOTE

New Aspects of the Chemistry of 2,4,6-Tris(trifluoromethyl) Benzoic Acid and Related Compounds

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SUMMARY

1,3,5-Tris(trifluoromethyl)benzene reacts with n-butyllithium and carbon dioxide to give a high yield of 2,4,6-tris(trifluoromethyl)benzoic acid. The acid has been well characterized by spectral and pK_a data. The acid chloride is formed only slowly under stringent conditions. The acid fails to undergo normal esterification with ethanol because of steric hindrance to the required tetrahedral intermediate. The ester does form via the linear acylium ion. A highly substituted phenolic ester of the acid has been obtained via a mixed anhydride. Attempts to prepare the corresponding acetophenone and a related vinyl ketone are described.

Chambers and coworkers [1] have shown that 2,4,6-tris(trifluoromethyl)phenyllithium (1), a sterically crowded, thermally stable molecule, undergoes a variety of

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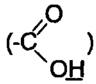
transformations, including the formation of mercury, tin and copper derivatives. Edelmann [2] and Schmutzler [3] recently reported detailed studies on a range of phosphorus and arsenic derivatives of this system.

In this preliminary report, we present new chemistry of 2,4,6-tris(trifluoromethyl) benzoic acid (2) and related carbonyl compounds. Although (2) was described previously [1], we have more fully characterized this acid and have examined its reactivity in greater detail.

2,4,6-Tris(trifluoromethyl) benzoic acid (2)

The acid was readily prepared in about 80% yield by lithiation (n-BuLi) of 1,3,5-tris(trifluoromethyl)benzene, followed by reaction with dry ice and hydrochloric acid. The pure crystalline acid, m.p. 190-191° (185-186° [1]) is hygroscopic and exhibits some solubility in water. Its structure has been confirmed by elemental analysis, pK_a determination, and infrared and proton magnetic resonance spectroscopy. The ^1H nmr exhibits resonance at δ 8.07 (aromatic H) and δ 8.58 ( $-C(=O)O\underline{H}$) in a ratio of 2:1. The infrared spectrum (KBr) reveals broad absorption in the 3300-2800 cm^{-1} region (H-bonded dimer) with strong >C=O absorption at 1718 cm^{-1}. The dimer does not exist in chloroform solution, however, with only weak absorption near 3480 cm^{-1}, and a carbonyl band at 1738 cm^{-1}. The anticipated shift of $\nu_{C=O}$ to higher frequency, owing to the 2,6-CF_3 groups, is substantiated by comparison with mesitoic acid, 2,4,6-$C_6H_2(CH_3)_3CO_2H$ (3), $\nu_{C=O}$ 1685 cm^{-1}.

The pK_as of (2) and (3) were determined by potentiometric titration. As expected, (2), pK_a 3.0, is more acidic than (3), pK_a 3.8 (3.43[4], 3.44 [5]).

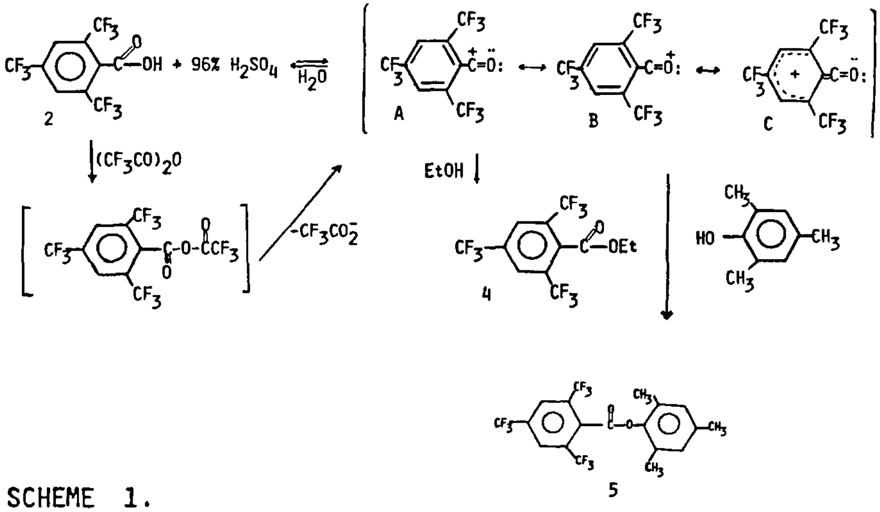
Chemical Reactivity

1. Reaction with $SOCl_2$: The acid (2) is very resistant to attack by thionyl chloride. After heating the mixture at 70° for 48 hours, only a small yield (ca. 10-15%) of acid chloride ($\upsilon_{C=O}$, 1810, 1783 cm^{-1}) was obtained.

2. Hydrolytic stability of CF_3 groups:
    a. Heating of (2) with concentrated NaOH solution at reflux for 24 hours led to near quantitative recovery of (2) after acidification.
    b. Heating of (2) with 96% H_2SO_4 at reflux for 24 hours gave a brown solution which, after addition of water, provided a near quantitative recovery of (2).

Esters of (2)

A low yield of the methyl ester of (2) was obtained on reaction of (1) with dimethyl carbonate. Steric effects hindered the formation of diaryl ketone [1]. We observed that normal acid-catalyzed esterification of (2) with ethanol was unsuccessful. Mesitoic acid behaves similarly because steric crowding by the ortho substituents precludes formation of tetrahedral intermediates essential for the generation of ester. The steric problem may be obviated, however, by formation of a linear acylium ion intermediate which reacts with a nucleophile (ROH or H_2O) to give the desired product. Thus, hydrolysis of methyl mesitoate or esterification of mesitoic acid in 96-100% H_2SO_4 are successful due to "steric acceleration" [6,7]. The acylium ion derived from (2) is strongly destabilized by structure C of the resonance hybrid (Scheme 1). Nevertheless, we have achieved a low conversion of (2) to its ethyl ester (4), identified by its infrared and proton magnetic resonance spectra.

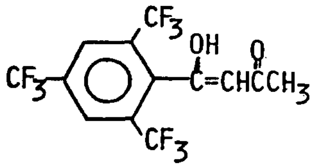


SCHEME 1.

Alternatively, an acylium ion can be generated via a mixed anhydride [8]. Thus, heating a mixture of acid (2), 2,4,6-trimethylphenol and trifluoroacetic anhydride afforded a 44% yield of the very highly substituted phenolic ester (5), (Scheme 1), whose carbonyl frequency is shifted markedly to 1795 cm^{-1} from the 1738 cm^{-1} observed for the non-fluorinated analog, which we prepared from mesitoic acid.

Ketones derived from (2)

2,4,6-Tris(trifluoromethyl)acetophenone (6) is apparently formed on reaction of (1) with acetyl chloride, but (6) rapidly undergoes hydrogen-metal exchange with (1). An aldol-type reaction between the resulting enolate of (6) and acetyl chloride gives the 1,3-diketone (7) as the nearly exclusive product [1].

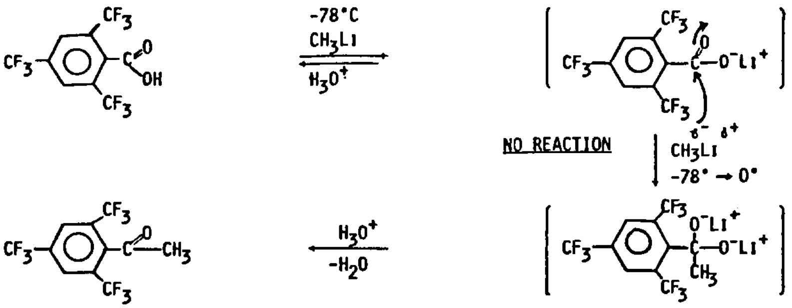


(7)

We have confirmed these observations and have sought other approaches to this elusive ketone (6), with very limited success.

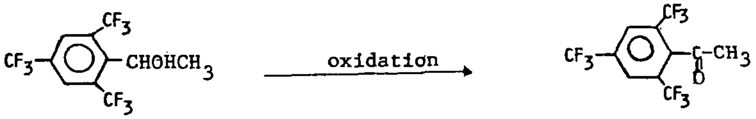
a. We anticipated that 1,3,5-tris(trifluoromethyl)benzene would fail to undergo Friedel-Crafts acylation because the CF_3 groups strongly deactivate the aryl ring toward electrophilic substitution. Indeed, there was no reaction with acetyl chloride and anhydrous $AlCl_3$.

b. Reaction of lithium carboxylates with alkyl or aryl lithiums is a useful method for preparing ketones [9]. Acid (2) and methyl lithium gave the lithium salt, but the subsequent reaction with excess CH_3Li to yield the methyl ketone (6) did not occur. Starting acid was recovered on acidification. We attribute this lack of reactivity to steric inhibition to formation of the requisite tetrahedral intermediate (Scheme 2).



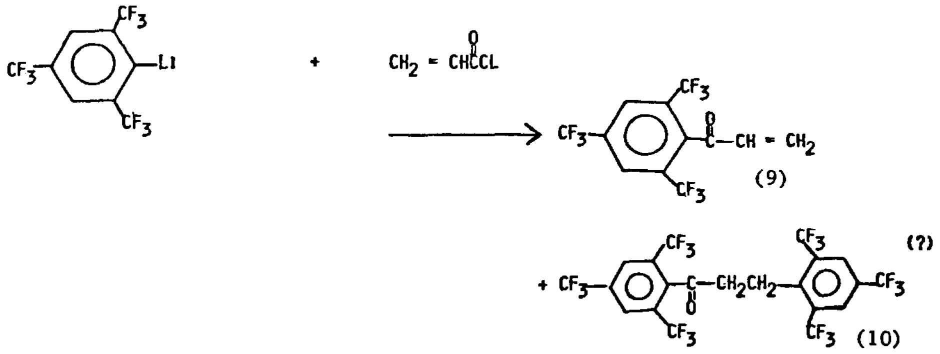
SCHEME 2.

c. We have confirmed the preparation of the secondary alcohol (8) from (1) and acetaldehyde[10]. Oxidation of (8) with Jones reagent was observed by the change in color (orange, Cr^{VI} to green, Cr^{III}). Although the infrared spectrum of crude material shows distinct carbonyl absorption, we have, thus far, been unable to isolate the ketone.



(8) (6)

An important objective of this research was the preparation of the aryl vinyl ketone (9), which cannot undergo the exchange and aldol reactions observed with (6). Reaction of (1) with acryloyl chloride gave a mixture of two products, which, as yet, have not been separated. However, the infrared and ^{1}H NMR spectra strongly indicate two ketones, one of which seems to be (9), and the other, the Michael addition product (10), derived from (9) and the strong nucleophile (1) (Scheme 3).



SCHEME 3.

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1 G.E. Carr, R.D. Chambers, T.F. Holmes and D.G. Parker, J. Organometall. Chem., 325 (1987) 13.

2 M. Scholz, H.W. Roesky, D. Stalke, K. Keller and F.T. Edelmann, J. Organometall. Chem., 366 (1989) 73.

3 L. Heuer, P.G. Jones and R. Schmutzler, J. Fluorine Chem., 46 (1990) 243.

4 J.F.J. Dippy, S.R.C. Hughes and J.W. Laxton, J. Chem. Soc., (1954) 1470.

5 J.M. Wilson, N.E. Gore, J.E. Sawbridge and F. Cardenas-Cruz, J. Chem. Soc. B, (1967) 852.

6 M.S. Newman, J. Am. Chem. Soc., 63 (1941) 2431.

7 M.S. Newman and N.C. Deno, J. Am. Chem. Soc., 73 (1951) 3651.

8 R.C. Parish and L.M. Stock, J. Org. Chem., 30 (1965) 927.

9 R. Filler, A.E. Fiebig and M.Y. Pelister, J. Org. Chem., 45 (1980) 1290 and references therein.

10 E.T. McBee and R.A. Sanford, J. Am. Chem. Soc., 72 (1950) 5574.