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# 1,2,4-Tris(trifluoromethyl)benzene : Selective Lithiation and Subsequent Electrophilic Substitution

**Manfred Schlosser *, Jacek Porwisiak and Florence Mongin**

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland

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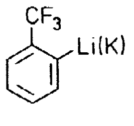
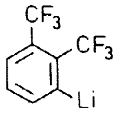
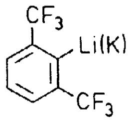
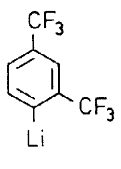
*Abstract* : 1,2,4-Tris(trifluoromethyl)benzene quantitatively undergoes a hydrogen/metal exchange when treated with an ethereal solution of lithium 2,2,6,6-tetramethylpiperidide. Proton abstraction occurs concomitantly from positions 5 and 6, the ratios varying from 80 : 20 to 90 : 10, depending on the reaction conditions. Pure 5-iodo-1,2,4-tris(trifluoromethyl)benzene can be readily obtained by fractional crystallization of the regioisomeric mixture and allows one to prepare 5-substituted derivatives of 1,2,4-tris(trifluoromethyl)benzene by consecutive reaction with *tert*-butyllithium and an electrophile.

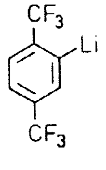
The trifluoromethyl moiety exerts only a moderate acidifying effect in its immediate vicinity. For example, the *ortho*-metalation of trifluoromethylbenzene requires a superbasis reagent to proceed satisfactorily [1] while poor yields and imperfect regioselectivities are found when butyllithium in refluxing diethyl ether is used to accomplish the metalation [2, 3]. The situation improves when two trifluoromethyl groups operate conjointly. Thus, the *ortho* [4], *meta* [5] and *para* [6] isomers of bis(trifluoromethyl)benzene afford the corresponding acids with acceptable yields when consecutively treated with butyllithium alone or with *N,N,N',N'*-tetramethylethylenediamine activated butyllithium and carbon dioxide.

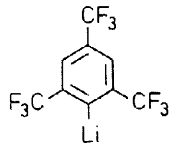












Naively one might assume that the introduction of additional trifluoromethyl groups into the same aromatic nucleus should further increase the lithiation rates. This would, however, mean to neglect two adverse factors.

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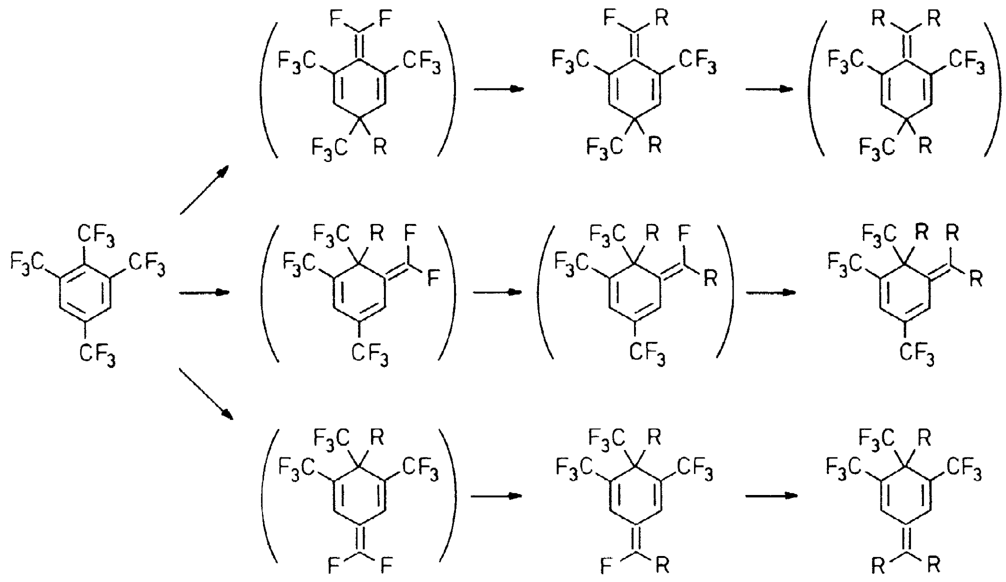
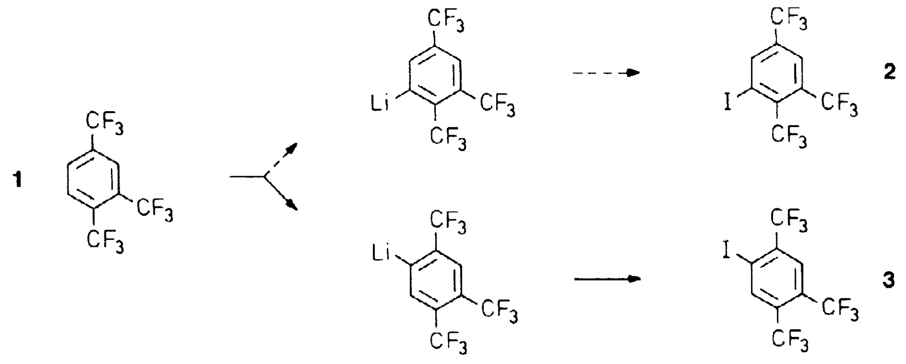
The accumulation of trifluoromethyl groups causes considerable steric crowding. As a consequence, proton abstraction from the angular 2-position of 1,3-bis(trifluoromethyl)benzene can only be accomplished with relatively small bases whereas bulky ones attack preferentially or exclusively the 4-position [1, 5 - 8]. Even more importantly, the multiplication of electronegative substituents inevitably amplifies the acceptor properties of the substrate. Under these circumstances, the organometallic reagent will tend to combine with the oligo(trifluoro methyl)arene in an addition reaction rather than to abstract a proton from it. While 1,3,5-tris(trifluoromethyl)-benzene [9] can still be submitted to metalation, this is no longer the case with 1,2,3,5- and 1,2,4,5-tetrakis-(trifluoromethyl)benzene. Actually, after treatment of 1,2,3,5-tetrakis(trifluoromethyl)benzene with phenyllithium or *tert*-butyllithium [R = $C_6H_5$ or $C(CH_3)_3$; see scheme below], Dmowski *et al.* [10] have isolated and characterized a variety of methylenecyclohexadienes which have incorporated two or three hydrocarbon moieties delivered by the organometallic reagent and, at the same time, lost two and, respectively, three of the fluorine atoms originally present in the starting material. In analogy to the formation of a Meisenheimer complex from 1,2,4,5-tetrakis(trifluoromethyl)benzene [11], a nucleophilic addition/elimination sequence was suggested. However, in view of the regioselectivity observed and the formation of a reduction product (H instead of R), a radical-chain process involving single-electron transfer from the organolithium reagent to the electron-poor substrate might also have occurred [12].

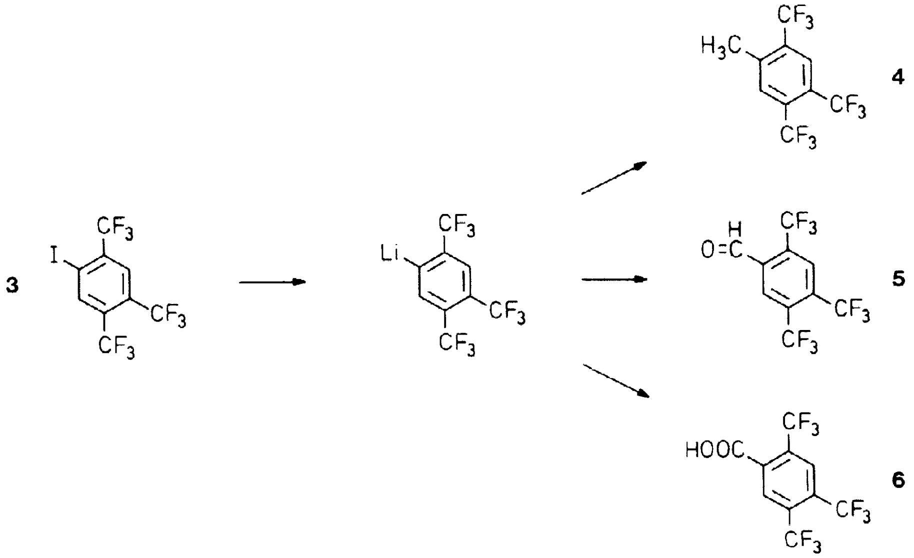


As we have recognized now, 1,2,4-tris(trifluoromethyl)benzene (**1**) [13] represents a borderline case. The substance decomposes rapidly to form tars when treated with organometallic reagents in any solvent. In contrast, with lithium 2,2,6,6-tetramethylpiperidide in diethyl ether at temperatures in the range of -25 to -100 °C, smooth and virtually quantitative deprotonation occurs. After trapping with a suitable electrophile such as chlorotrimethylsilane or iodine a 4 : 1 to 9 : 1 mixture of 5- and 6-substituted regioisomers (**3** and **2**,

**respectively) is obtained while no attack at the 3-position is detected. Obviously, the observed site selectivities are mainly dictated by varying degrees of steric congestion** [14, 15].



Fortunately, a simple crystallization suffices to remove the regioisomeric contamination from the main product 5-iodo-1,2,4-tris(trifluoromethyl)benzene (**3**). This compound can now be submitted to a halogen/metal exchange reaction, for example, by employing two equivalents of *tert*-butyllithium. Being isomerically pure, the resulting organolithium intermediate can be cleanly converted into derivatives, in particular into 2,4,5-tris-(trifluoromethyl)toluene (**4**; 63% with dimethyl sulfate), 2,4,5-tris(trifluoromethyl)benzaldehyde (**5**; 76% with *N*,*N*-dimethylformamide) and 2,4,5-tris(trifluoromethyl)benzoic acid (**6**; 88% with dry ice).



Lithium 2,2,6,6-tetramethylpiperidide in diethyl ether (or potassium *tert*-butoxide activated lithium diisopropylamide in tetrahydrofuran [16] at -25 °C is powerful enough to bring about also the lithiation of 1,3-bis-(trifluoromethyl)benzene and 1,3,5-tris(trifluoromethyl)benzene (82 - 99% of trapping products). With lithium 2,2,6,6-tetramethylpiperidide, even the *ortho*-lithiation and subsequent carboxylation of 1,4-bis(trifluoromethyl)benzene (87% yield of acid), 1,2-bis(trifluoromethyl)-benzene (50% yield) and (trifluoromethyl)benzene (39% yield) can be accomplished [17]. By the way, 2,2,6,6-tetramethylpiperidine, the precursor to the lithium amide used, may be advantageously replaced by 4-methoxy- or 4-ethoxy-2,2,6,6-tetramethylpiperidine, readily accessible by alkylation of the relatively inexpensive 4-hydroxy-2,2,6,6-tetramethylpiperidine [18].

## EXPERIMENTAL

### 1. Generalities

*Starting materials* have been purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Hohenbrunn), unless literature sources or details of the preparation are given. *Butyllithium* was supplied by CheMetall, Frankfurt. All commercial reagents were used without further purification.

*Air and moisture sensitive compounds* were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen.

*Diethyl ether* and *tetrahydrofuran* were obtained anhydrous by careful azeotropic distillation, by distillation from sodium wire after the characteristic blue color of *in situ* generated sodium diphenyl ketyl was found to persist [19, 20]. *Ethereal extracts were dried* with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice methanol baths is consistently indicated as -75 °C and "room temperature" (22 - 26 °C) as 25 °C. *Melting ranges* (mp) are reproducible after resolidification, unless otherwise stated ("dec."), and are corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75°C. If reduced pressure is not specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

Silica gel (Merck Kieselgel 60) of 70 - 230 mesh (0.06 - 0.20 mm) particle size was used for *column chromato-graphy*. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder obtained by absorption of the crude product mixture on 15 - 20 g silica gel and subsequent evaporation of the solvent was poured on top of the column.

*Nuclear magnetic resonance spectra* of hydrogen-1 nuclei were recorded of deuterochloroform solutions at 400 MHz and of fluorine-19 nuclei at 376 MHz. Chemical shifts δ refer to the signal of tetramethylsilane in the case of $^1$H spectra and to trichlorofluoromethane in the case of $^{19}$F spectra. Coupling constants (*J*) are measured in Hz. Abbreviations of coupling patterns : s (singlet) and q (quadruplet).

*Elementary analyses* were executed by the laboratory of I. Beetz, D-96301 Kronach. The expected numbers are calculated on the basis of atomic weights according to the 1986 IUPAC recommendations.

### 2. Lithiation of 1,2,4-Tris(trifluoromethyl)benzene With Lithium 2,2,6,6-Tetramethylpiperidide

a) Precooled (-75 °C) diethyl ether (70 mL) and 2,2,6,6-tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol) were consecutively added to butyllithium (50 mmol) from which the commercial solvent (hexane) had been stripped off. 1,2,4-Tris(trifluoromethyl)benzene (**1**) [13] (4.6 mL, 7.1 g, 25 mmol) was added at -75 °C. After 1 h at -25 °C, the resulting brown solution was cooled to -75 °C and treated with chlorotrimethylsilane (7.0 mL, 6.0 g, 55 mmol). When the mixture had reached 25 °C, the solvent was evaporated and the residue distilled to afford a 1 : 4 mixture of **trimethyl[2,3,5-tris(trifluoromethyl)phenyl]silane** and **trimethyl[2,4,5-tris**

**(trifluoromethyl)phenyl]silane**; bp 100 - 104 °C /12 mmHg; 84%. - $^1$H-NMR : δ 8.15 (1 H, s), 8.09 (0.2 H, s), 8.06 (0.8 H, s), 0.39 (0.8 × 9 H, q, *J* 1.1), 0.04 (0.2 × 9 H, q, *J* 3.2). - $^{19}$F-NMR : δ -55.3 (0.2 × 3 F, q, *J* 15.0), -59.5 (0.2 × 3 F, q, *J* 15.0), -60.1 (0.8 × 3 F, s), -60.8 (0.8 × 3 F, q, *J* 12.2), -61.0 (0.8 × 3 F, q, *J* 12.2), -64.7 (0.2 × 3 F, s).

b) In a second reaction, carried out analogously, though on a 10-fold scale (0.25 mol), the lithiated intermediate was intercepted with iodine (63 g, 0.25 mol). When the reaction mixture had reached 25 °C, it was washed with a 2 M aqueous solution of sodium thiosulfate (2 × 100 mL) and brine (2 × 100 mL). After evaporation of the solvent, a sample was purified by sublimation (50 °C /1 mmHg) to give a 1 : 4 mixture of **1-iodo-2,3,5-tris(trifluoromethyl)benzene (2)** and **1-iodo-2,4,5-tris(trifluoromethyl)benzene (3)**; 95%. - $^1$H-NMR : δ 8.54 (0.2 H, s), 8.48 (0.8 H, s), 8.09 (0.2 H, s), 8.04 (0.8 H, s). - $^{19}$F-NMR : δ -58.9 (0.2 × 3 F, q, *J* 16.5), -59.4 (0.2 × 3 F, q, *J* 16.9), -61.0 (0.8 × 6 F, s), -64.7 (0.2 × 3 F, s), -65.2 (0.8 × 3 F, s).

The bulk of the material was purified by filtration of its solution in hexane over basic alumina and was crystallized three times from acetone at -75 °C. In this way, the pure isomer **3** was obtained; mp 62 - 64 °C; 48%. - $^1$H-NMR : δ 8.49 (1 H, s), 8.05 (1 H, s). - Analysis : calc. for $C_9H_2F_9I$ (408.01) C 26.49, H 0.49; found C 26.49, H 0.51%.

## 3. Generation of Pure 2,4,5-Tris(trifluoromethyl)phenyllithium by Halogen/Metal Exchange

a) Precooled (-75 °C) diethyl ether (50 mL) and 1-iodo-2,4,5-tris(trifluoromethyl)benzene (10 g, 25 mmol) were consecutively added to *tert*-butyllithium (50 mmol) from which the commercial solvent (pentane) had beforehand been stripped off. After 30 min at -75 °C, dimethyl sulfate (2.4 mL, 3.3 g, 25 mmol) were added. **2,4,5-Tris(trifluoromethyl)toluene (4)** was isolated by distillation; bp 146 - 149 °C; $n_D^{20}$ 1.3852; 63%. - $^1$H-NMR : δ 8.07 (1 H, s), 7.80 (1 H, s), 2.64 (3 H, s). - Analysis : calc. for $C_{10}H_5F_9$ (296.14) C 40.56, H 1.70; found C 40.88, H 2.01%.

b) In an analogous reaction, dimethyl sulfate was replaced by *N*,*N*-dimethylformamide (2.0 mL, 1.9 g, 26 mmol). The reaction mixture was washed with 1 M hydrochloric acid (2 × 15 mL) and brine (2 × 25 mL). Distillation afforded **2,4,5-tris(trifluoromethyl)benzaldehyde (5)**; mp -13 to -15 °C; bp 94 - 97 °C /12 mmHg; $n_D^{20}$ 1.4346; 76%. - $^1$H-NMR : δ 10.46 (1 H, q, *J* 2.0), 8.60 (1 H, s), 8.28 (1 H, s). - Analysis : calc. for $C_{10}H_3F_9$ (310.11) C 38.73, H 0.98; found C 39.07, H 1.00%.

c) In an analogous reaction, the mixture was poured on freshly crushed dry ice. The product was taken up in 5% aqueous sodium hydroxide (2 × 25 mL). Acidification to pH 1, extraction with diethyl ether (3 × 20 mL) and evaporation of the solvent gave a residue which was dried on fireclay and crystallized from toluene to afford colorless **2,4,5-tris(trifluoromethyl)benzoic acid (6)**; mp 132 - 133 °C; 61%. - $^1$H-NMR : δ 10.12 (s, broad), 8.36 (1 H, s), 8.23 (1 H, s). - Analysis : calc. for $C_{10}H_3F_9O_2$ (326.11) C 36.83, H 0.93; found C 37.11, H 1.11%.

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