1-Bromo-3,5-bis(trifluoromethyl)benzene: A Versatile Starting Material for Organometallic Synthesis

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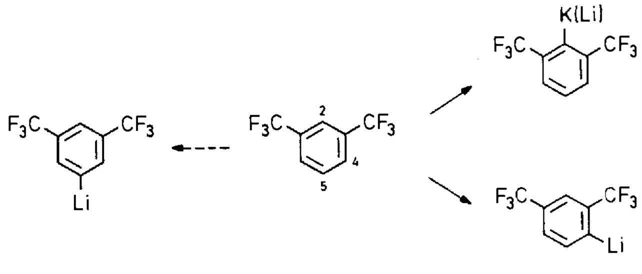
1-Bromo-3,5-bis(trifluoromethyl)benzene (**1**) can be selectively prepared by treatment of 1,3-bis(fluoromethyl)benzene with *N,N'*-dibromo-5,5-dimethylhydantoin in strongly acidic media. A number of synthetically useful reactions via 3,5-bis(trifluoromethyl)phenylmagnesium, -lithium, and -copper intermediates were accomplished.

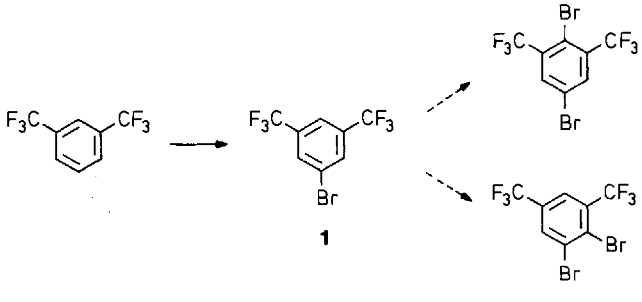
Optional site selectivity can be established in numerous neighboring group-assisted metalation reactions of arenes by mechanism-based substrate/reagent matching[1–3]. A striking application of this principle has been reported for 1,3-bis(trifluoromethyl)benzene[4]. When treated with the superbasic mixture of butyllithium and potassium *tert*-butoxide, it selectively undergoes a hydrogen/metal exchange at the 2-position, the most acidic site since it is flanked by both electron-withdrawing substituents. After carboxylation, 78% of the corresponding acid could be isolated. In contrast, *N,N,N',N'',N''*-pentamethyldiethylenetriamine-(PMDTA-)complexed *sec*-butyllithium, apparently a bulkier reagent, deprotonates preferentially the more readily accessible 4-position. The regioisomeric acid is obtained in 56% yield after carboxylation.



Unfortunately, the third isomer carrying the metal at the 5-position cannot be obtained by direct metalation. The best result, accomplished with *tert*-butyllithium in tetrahydropyran, was a concomitant attack at the 4- and the 5-position, affording after carboxylation the corresponding acids in about a 1:1 ratio. Therefore, the only convenient way to generate isomerically uncontaminated 5-metalated 1,3-bis(trifluoromethyl)benzenes is to submit 1-iodo- or 1-bromo-3,5-bis(trifluoromethyl)benzene to a reductive treatment with magnesium or to a halogen/lithium interconversion.

Both halogenated compounds are commercially available but are, because of laborious preparation[5,6], prohibitively expensive. As little as 10 mmol of the bromide and the iodide cost 15 and 50 SFr, respectively. These prices have to be compared with 1 SFr for the same molar quantity of 1,3-bis(trifluoromethyl)benzene.

We have now been able to elaborate an improved access to 1-bromo-3,5-bis(trifluoromethyl)benzene (**1**). *N,N'*-Dibromo-5,5-dimethylhydantoin has recently been identified as a particularly selective bromination reagent[7]. This compound, in the presence of trifluoromethanesulfonic (120 h at 25 °C) or concentrated sulfuric acid (24 h at 0 °C), was indeed found to transform 1,3-bis(trifluoromethyl)benzene into its bromo derivative **1** with roughly 90% yield and without forming more than trace amounts of by-products such as 2,5-dibromo-1,3-bis(trifluoromethyl)benzene and 1,2-dibromo-3,5-bis(trifluoromethyl)benzene.



Various organometallic intermediates can be prepared from bromide **1**. When its ethereal solution was stirred with magnesium, a Grignard reagent resulted[8] which was condensed with allyl bromide to give 3-[3,5-bis(trifluoromethyl)phenyl]prop-1-ene (66%). After consecutive treatment with butyllithium and cuprous iodide a heterocuprate was obtained that underwent nucleophilic 1,4-addition onto methyl acrylate affording methyl 3-[3,5-bis(trifluoromethyl)-phenyl]propanoate (**3**; 41%). Another organocopper species was produced by insertion of in situ generated trifluoromethylcopper(I)[9] into the carbon-halogen bond of bromide **1**, but instantaneously decomposed by reductive elimination of cuprous bromide to give 1,3,5-tris(trifluoromethyl)benzene (**4**; 72%).

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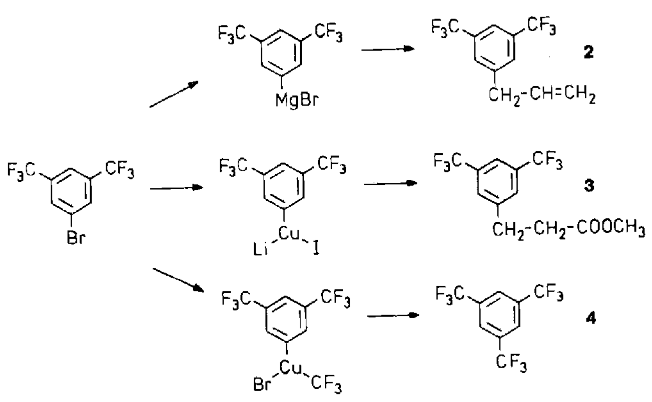
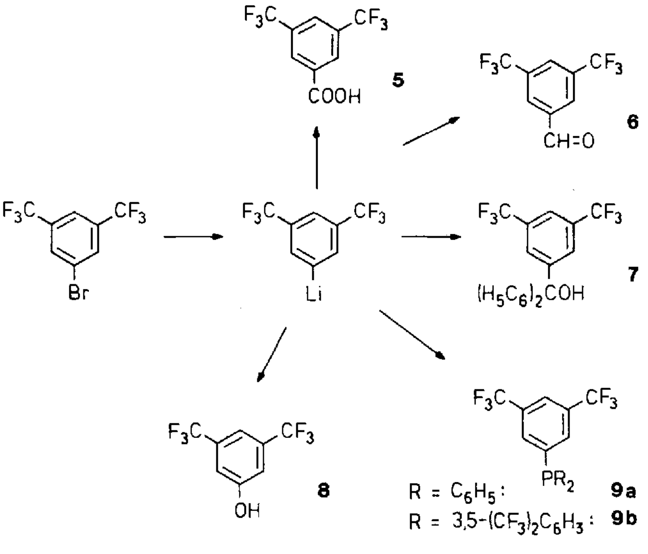


The most convenient way to activate bromide **1** is by halogen/metal interconversion using butyllithium (1 equiv.) or *tert*-butyllithium (2 equiv.). The organolithium intermediate thus formed was found to react with a variety of electrophiles such as carbon dioxide, *N,N*-dimethylformamide, dioxygen, benzophenone, and phosphorus trichloride. The products 3,5-bis(trifluoromethyl)benzoic acid (**5**; 94%), 3,5-bis(trifluoromethyl)benzaldehyde (**6**; 82%), [3,5-bis(trifluoromethyl)phenyl]diphenylmethanol (**7**; 76%), 3,5-bis(trifluoromethyl)phenol (**8**; 52%), [3,5-bis(trifluoromethyl)-phenyl]diphenylphosphane (**9a**; 76%), and tris[3,5-bis(trifluoromethyl)phenyl]phosphane (**9b**; 36%) were isolated in excellent to fair yields.



As far as one can judge from the few specimens described in the literature, 1,3-bis(trifluoromethyl)phenyl derivatives are fairly resistant to acids, bases, thermal stress, oxidants, and metabolic degration. The chemical stability in combination with specific steric and electronic properties makes this class of compounds attractive materials. For example, [1,3-bis(trifluoromethyl)phenyl]diphenylphosphane and tris[1,3-bis(trifluoromethyl)phenyl]phosphane might be used as ligands of catalytically active transition elements. Up till now, however, suitable precursors were too expensive to encourage large-scale applications. The simple access to 1-bromo-3,5-bis(trifluoromethyl)benzene (**1**) disclosed above and its smooth conversion into a variety of reactive organometallic intermediates will hopefully contribute to remove such limitations.

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Experimental

For laboratory routine and technical details, see related articles, e.g. ref.[10]. In contrast to habits adopted in previous publications, the ^{19}F-NMR chemical shifts are reported relative to trichlorofluoromethane as the reference.

1-Bromo-3,5-bis(trifluoromethyl)benzene (**1**): Ice-cooled concentrated (96%) sulfuric acid (6.7 ml, 12.3 g, 0.12 mol) was added to 1,3-bis(trifluoromethyl)benzene (16 ml, 21 g, 0.10 mol) and *N,N'*-dibromo-5,5-dimethylhydantoin (17 g, 60 mmol). The mixture was stirred for 24 h at 0°C before being extracted with hexane (5 × 25 ml). The combined organic layers were washed with a 2% aqueous solution of sodium thiosulfate (50 ml), water (25 ml), and brine (25 ml). Upon distillation a colorless liquid was collected that, according to gas chromatography (2 m, 10% SE-30, 100 → 200°C) contained only trace amounts of 1,2-dibromo-3,5-bis(trifluoromethyl)-benzene and 2,5-dibromo-1,3-bis(trifluoromethyl)benzene ($\leq$1 and $\leq$0.5%, respectively; 3 and 1% prior to distillation); m.p. -17 to -16°C; b.p. 153–154°C; n_D^{20} = 1.4368; yield 87%. – ^{1}H NMR: δ = 7.79 (2H, q, J = 0.6 Hz), 7.83 (1H, sept, J = 0.8 Hz). – ^{19}F NMR: δ = -63.6.

When the concentrated sulfuric acid was replaced by trifluoromethanesulfonic acid (11 ml, 18 g, 0.12 mol), it took 120 h at 25°C to obtain yields in the order of 90%. Under these conditions, no dibromination occurred at all.

3-[3,5-Bis(trifluoromethyl)phenyl]prop-1-ene (**2**): Allyl bromide (2.2 ml, 3.0 g, 25 mmol) was added to an ethereal solution of [3,5-bis(trifluoromethyl)phenyl]magnesium bromide [prepared from bromide **1** (25 mmol) and magnesium turnings (1.0 g, 41 mmol) in diethyl ether (50 ml)]. After 2 h of heating at reflux, the solvent was evaporated and the product isolated by distillation; b.p. 126–128°C/100 Torr; n_D^{20} = 1.4118; d_4^{20} = 1.2639; yield 66%. – ^{1}H NMR: δ = 7.73 (1H, s), 7.64 (2H, s); 5.96 (1H, ddt, J = 17.0, 10.0, 6.8 Hz), 5.20 (1H, dq, J = 10.0, 1.3 Hz), 5.16 (1H, dq, J = 17.0, 1.5 Hz), 3.52 (2H, d, J = 6.8 Hz). – ^{19}F NMR: δ = -63.4. – $C_{11}H_8F_6$ (254.2): calcd. C 51.98, H 3.17; found C 51.99, H 3.19.

Methyl 3-[3,5-Bis(trifluoromethyl)phenyl]propionate (**3**): At -75°C and with vigorous stirring, precooled solutions of **1** (4.3 ml, 7.3 g, 25 mmol) in diethyl ether (15 ml) and, 15 min later, purified[11] copper(I) iodide (4.8 g, 25 mmol) in diethyl ether (35 ml) were added to butyllithium (25 mmol) or *tert*-butyllithium (50 mmol) from which the commercial solvent (hexane) had been evaporated. After another 15 min of stirring at -25°C, the mixture was cooled again to -75°C. Boron trifluoride–diethyl ether[12] (2.3 ml, 1.1 g, 25 mmol) and methyl acrylate (2.3 ml, 2.2 g, 25 mmol) were consecutively added. After 15 min at -75°C, the mixture was allowed to reach 25°C in the course of 30 min. Concentration and distillation gave the oily product; b.p. 148–150°C/10 Torr; n_D^{20} = 1.4243; yield 41%. – ^{1}H NMR: δ = 7.74 (1H, s), 7.67 (2H, s), 3.69 (3H, s), 3.09 (2H, t, J = 7.6 Hz), 2.70 (2H, t, J = 7.6 Hz). – ^{19}F NMR: δ = -63.4. – $C_{12}H_{10}F_6O_2$ (300.2): calcd. C 47.99, H 3.11; found C 48.18, H 3.11.

1,3,5-Tris(trifluoromethyl)benzene (**4**): With vigorous stirring, a mixture of **1** (4.3 ml, 7.3 g, 25 mmol), dry sodium trifluoroacetate (14 g, 0.10 mol), and copper iodide (9.5 g, 50 mmol) in *N,N*-dimethylformamide (100 ml) was heated 6 h to 150 °C. Then it was acidified with 2 M HCl to pH 1. The product was isolated by steam distillation, followed by extraction of the aqueous condensate (200 ml) with diethyl ether (3 × 50 ml) and identified by gas chromatography (2 m, 10% SE-30, 50 → 150 °C); m.p. 8–9 °C; b.p. 128–130 °C (ref.[13] m.p. 9 °C; b.p. 119.6 °C/750 Torr); yield 72%.

3,5-Bis(trifluoromethyl)benzoic Acid (**5**): At −75 °C, precooled diethyl ether (50 ml) and **1** (4.3 ml, 7.3 g, 25 mmol) were consecutively added to butyllithium (25 mmol) from which the commercial solvent (hexane) had been evaporated. A white precipitate formed instantaneously. After 15 min at −75 °C, the mixture was poured on freshly crushed dry ice. The acid was collected as a white powder after acidification with 2 M HCl of the aqueous phase obtained upon extraction with 2 M NaOH (3 × 25 ml) and was recrystallized from hexane; m.p. 141–142 °C (ref.[4] 137–138 °C); yield 94%. – ^{1}H NMR: δ = 8.54 (2 H, s), 8.07 (1 H, s). – ^{19}F NMR: δ = −63.5.

3,5-Bis(trifluoromethyl)benzaldehyde (**6**): With *N,N*-dimethylformaldehyde (1.9 ml, 1.8 g, 25 mmol) rather than carbon dioxide; isolated after neutralization with 2 M HCl, ethereal extraction, and distillation; m.p. −11 to −9 °C; b.p. 95–98 °C/12 Torr (ref.[14] 50 °C/3 Torr); yield 82%. – ^{1}H NMR: δ = 10.14 (1 H, s), 8.35 (2 H, s), 8.13 (1 H, s). – ^{19}F-NMR: δ = −63.6.

[3,5-Bis(trifluoromethyl)phenyl]diphenylmethanol (**7**): Using benzophenone (4.6 g, 25 mmol) rather than dry ice; isolated by distillation after washing and concentrating the ethereal extract; m.p. 0–3 °C; b.p. 140–142 °C/0.5 Torr; n_D^{20} = 1.5314; d_4^{20} = 1.3270; yield 76%. – ^{1}H NMR: δ = 7.85 (2 H, s), 7.80 (1 H, s), 7.3 (6 H, m), 7.2 (4 H, m), 2.92 (1 H, s, broad). – ^{19}F NMR: δ = −63.2. – $C_{21}H_{14}F_6O$ (396.3): calcd. C 63.64, H 3.56; found C 64.06, H 3.67.

3,5-Bis(trifluoromethyl)phenol (**8**): Rather than to pour the reaction mixture onto dry ice, air was bubbled into it for 45 min at −75 °C. After extraction with a saturated aqueous solution of sodium hydrogen sulfite (25 ml) and a 10% aqueous solution of sodium carbonate (2 × 25 ml), the combined aqueous layers were neutralized with concentrated hydrochloric acid and extracted with diethyl ether (3 × 25 ml). Distillation afforded the pure product; m.p. 19–20 °C (ref.[15] 20–21 °C); b.p. 85–88 °C/42 Torr (ref.[15] 97 °C/50 Torr); yield 52%. – ^{1}H NMR: δ = 7.46 (1 H, s), 7.27 (2 H, s), 5.68 (1 H, s, broad). – ^{19}F NMR: δ = −63.6.

[3,5-Bis(trifluoromethyl)phenyl]diphenylphosphane (**9a**): Using chlorodiphenylphosphane (4.5 ml, 5.5 g, 25 mmol) as the electrophile, absorbing the reaction mixture on silica gel (10 g) and eluting it with ethyl acetate from a column filled with more silica (40 g); m.p. 120–122 °C; b.p. 138–141 °C/0.5 Torr; n_D^{20} = 1.5580; yield 76%. – ^{1}H NMR: δ = 7.82 (1 H, s, broad), 7.70 (2 H, d, J = 6.2 Hz), 7.4 (6 H, m), 7.3 (4 H, m). – $C_{20}H_{13}F_6P$ (398.3): calcd. C 60.13, H 3.29; found C 59.98, H 3.01.

Tris[3,5-bis(trifluoromethyl)phenyl]phosphane (**9b**): Generating the organolithium intermediate with *tert*-butyllithium (2.0 equiv.) rather than with butyllithium and using phosphorus trichloride (0.70 ml, 1.10 g, 8.0 mmol) instead of chlorodiphenylphosphane; m.p. 120–122 °C; b.p. 128–130 °C/0.5 Torr; yield 32%. – ^{1}H NMR: δ = 7.99 (3 H, s, broad), 7.74 (6 H, d, J = 7.0 Hz). – ^{19}F NMR: δ = −63.6. – $C_{24}H_9F_{18}P$ (670.3): calcd. C 43.01, H 1.35; found C 43.50, H 1.00.

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