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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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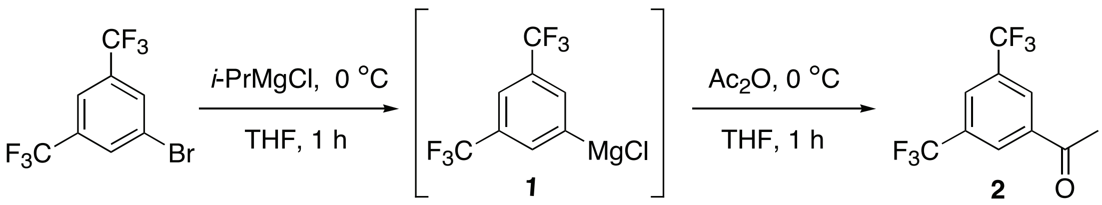
A PRACTICAL AND SAFE PREPARATION OF 3,5-BIS(TRIFLUOROMETHYL)ACETOPHENONE

(1-[3,5-Bis(trifluoromethyl)phenyl]-ethanone)



Submitted by Johnnie L. Leazer Jr. and Raymond Cvetovich.[1]
Checked by Kevin M. Maloney and Rick L. Danheiser.

1. Procedure[2]

A 100-mL, three-necked, round-bottom flask equipped with a teflon-coated thermocouple probe, inert gas inlet, a 100-mL pressure-equalizing addition funnel fitted with a rubber septum, and a magnetic stirbar is charged with 3,5-bis(trifluoromethyl)bromobenzene (20.0 g, 11.8 mL, 68.3 mmol) and 35 mL of anhydrous THF (Notes 1, 2, 3). The solution is cooled to -5 °C in a ice-salt water bath and a solution of *i*-PrMgCl in THF (37.6 mL, 2M, 75.2 mmol) is added dropwise over 1 hr at a rate such that the internal reaction temperature does not exceed 0 °C (Notes 4, 5). Upon completion of the addition, the reaction mixture is stirred for 1 hr at 0 to -10 °C.

A 250-mL, three-necked, round-bottomed flask equipped with a teflon-coated magnetic stir bar, a reflux condenser fitted with an inert gas inlet, a glass stopper, and a septum pierced by a teflon-coated thermocouple probe (Note 1) is charged with acetic anhydride (24.4 mL, 258 mmol) (Note 6) and then cooled to -5 °C in a ice-salt water bath. The solution of 3,5-bis(trifluoromethyl)phenylmagnesium chloride (at -5 °C, prepared as described above) is transferred into the flask containing acetic anhydride via an 18-gauge, 2-ft, double-ended needle at a rate such that the internal reaction temperature does not exceed 0 °C (ca. 2 hr) (Note 7). The resulting pale yellow solution is stirred for 30 min at 0 °C. The flask is removed from the ice-water bath and 35 mL of deionized water is added dropwise over 1 hr

(Note 8). The resulting biphasic mixture is heated at 60 °C in an oil bath for 15 min (Note 9). The reaction mixture is then allowed to cool to room temperature. The organic layer is separated (Note 10) and diluted with 35 mL of MTBE (Note 11). The resulting solution is transferred to a 250-mL Erlenmeyer flask and vigorously stirred at 15 °C while 2 mL of aqueous 2.5N NaOH is added dropwise so that the pH of the aqueous phase reaches 7.1. The organic phase is separated and washed with two 20-mL portions of saturated aqueous $NaHCO_3$ solution and 20 mL of brine, dried over Na_2SO_4, and concentrated by rotary evaporation (20 mmHg) at room temperature. The residue is transferred to a 50-mL, one-necked, pear-shaped flask. Purification by bulb-to-bulb distillation at 25 mmHg (distillate collected at 122-132 °C) affords 15.1-15.2 g (86-87%) of 3,5-bis(trifluoromethyl)-acetophenone as a clear, colorless oil (Note 12).

2. Notes

1. The apparatus was flame-dried and maintained under an atmosphere of argon (checkers) or nitrogen (submitters) throughout the course of the reaction.

2. 3,5-Bis(trifluoromethyl)bromobenzene was purchased from Aldrich Chemical Company, Inc., and used without further purification. Use of 3,5-bis(trifluoromethyl)bromobenzene prepared as described by Leazer et al.[2] gave identical results.

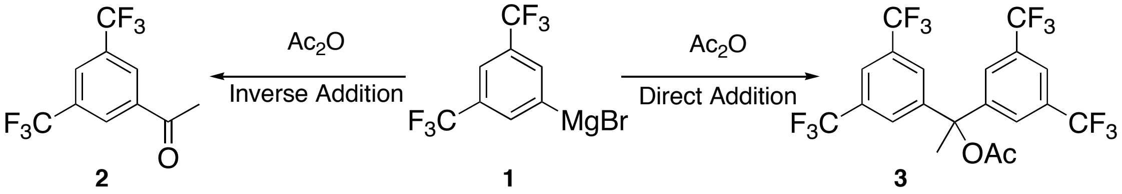
3. The submitters purchased anhydrous THF (HPLC grade) from EM Scientific and used it without further purification. Karl Fischer titration indicated there was 34 μg of water per mL of solvent. The checkers dried THF by pressure filtration under argon through activated alumina.

4. All temperatures refer to internal reaction temperatures.

5. A solution of *i*-PrMgCl (2M in THF) was purchased from Aldrich Chemical Company, Inc., and used as received.

6. Acetic anhydride (certified) was purchased from Fisher Scientific and used without further purification.

7. Addition of acetic anhydride to a freshly prepared solution of **1** gave bis-adduct **3** as the exclusive product. On the other hand, addition of Grignard reagent **1** to an excess of acetic anhydride gave acetophenone **2** in 90% isolated yield. Thus, excess acetic anhydride is required to obtain desired acetophenone.



8. The reaction mixture warms to room temperature during the addition of water.

9. The 60 °C age is necessary in order to destroy residual Ac_2O.

10. The separation of layers is facile. No emulsion problems are encountered. The organic layer is clear and yellow. The aqueous layer is clear and colorless. The reaction mixture turns bright cloudy yellow after addition of 5 mL of water. A gummy residue is observed coating the flask wall after addition of 15 mL of water; however, this residue completely dissolves upon addition of 25 mL of water. Vigorous stirring is used during the addition of water.

11. HPLC grade methyl *tert*-butyl ether (MTBE) was purchased from Fisher Scientific Co. and used without further purification.

12. Product **2** has the following physical properties: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72 (s, 3H), 8.09 (s, 1H), 8.40 (s, 2H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 26.7 (s), 123.2 (q, J = 272.9 Hz), 126.3 (sept, J = 3.6 Hz), 128.3, (q, J = 3.4 Hz), 132.5 (q, J = 34.0 Hz), 138.6 (s), 195.1 (s); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -63.67; IR (neat) 1705, 1610, 1005, 720 cm^{-1}; Anal. Calcd for $C_{10}H_6F_6O$: C, 46.89; H, 2.36. Found: C, 46.49; H, 2.37.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The trifluoromethylphenyl moiety is a functionality frequently encountered in pharmaceutical drugs,[3] catalysts,[4] and synthetic intermediates.[5] Trifluoromethylphenyl ketones can be classically prepared *via* addition of dimethyl copper lithium to an acid chloride in ethereal solvent;[6] however, the cryogenics make this method unsuitable for large scale synthesis. A more convenient method involves direct acetylation of Grignard reagent **1**. Preparation of the requisite 3,5-bis(trifluoromethyl)-phenyl Grignard reagent is not straightforward, as there are references to detonations of trifluoromethylphenyl Grignard reagents.[7] One such detonation resulted in loss of life.[8] The chemical community is thus in need of a safe and reliable preparation of these valuable reagents.

Our data indicates that detonations associated with formation of trifluoromethylphenyl Grignards using Mg^0 may be attributed to loss of contact with solvent, runaway exothermic side reactions, and potentially, the presence of a highly activated form of Mg. Use of Mg to generate trifluoromethylphenyl Grignard reagents should be avoided if possible. If these reagents are to be generated from Mg, the reaction should be done in THF, and well below reflux, since loss of solvent contact can cause a runaway exothermic reaction.[2] The Knochel procedure should be used whenever possible as it bypasses the factors leading to runaway reactions.[2,9] Knochel's procedure for the low- temperature halogen-magnesium exchange has exhibited no propensity toward runaway reaction. The exchange is rapid (<1h) at cold temperatures (0 °C) and suitable for multi-kilogram scale-up.

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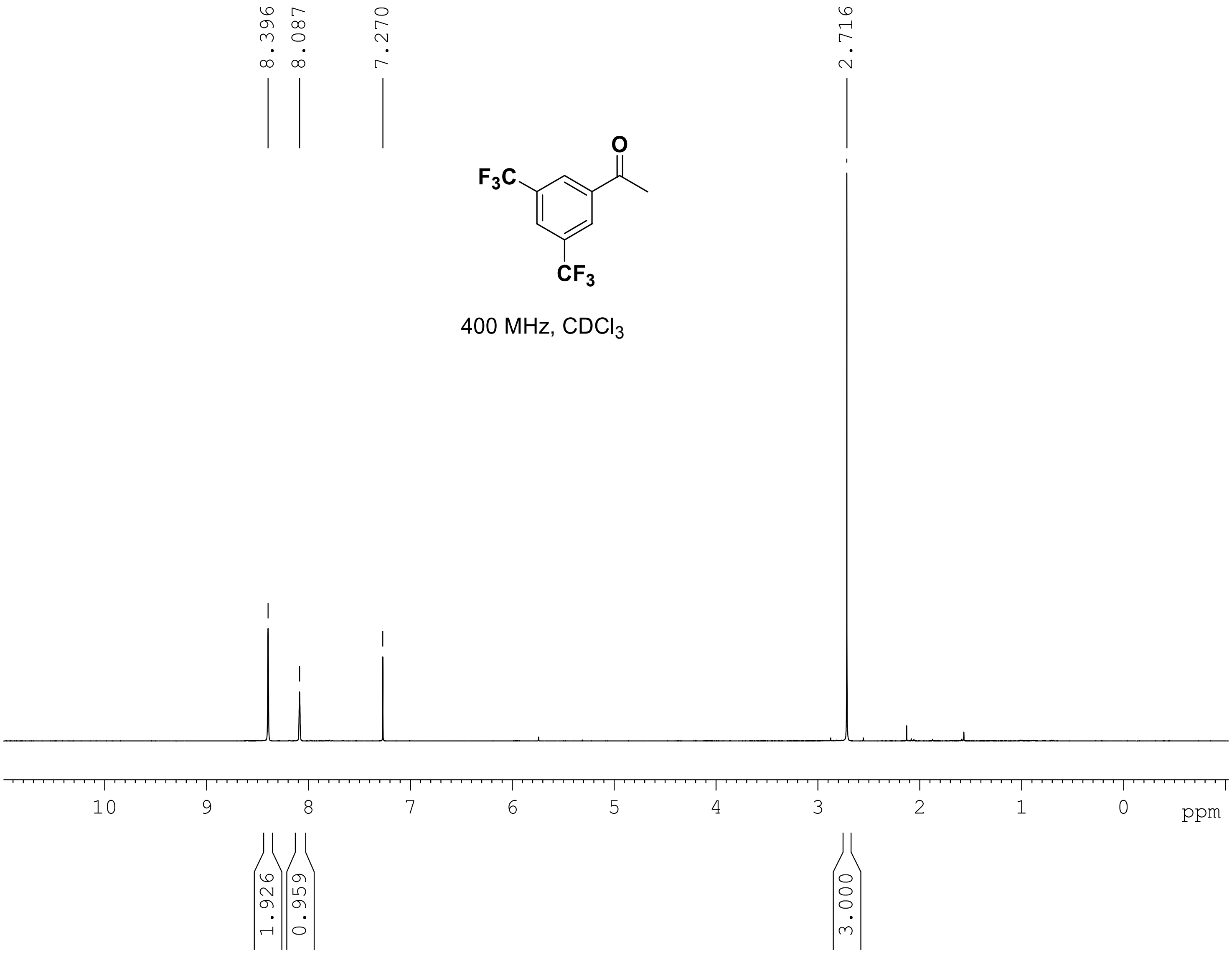
Appendix
Chemical Abstracts Nomenclature (Registry Number)

3,5-Bis(trifluoromethyl)bromobenzene: 1-Bromo-3,5-bis(trifluoromethyl) benzene; (328-70-1)

3,5-Bis(trifluoromethyl)-acetophenone: 1-[3,5-Bis(trifluoromethyl)phenyl] ethanone; (30071-93-3)

Isopropylmagnesium chloride: Magnesium, chloro(1-methylethyl)-; (1068 55-9)

Acetic anhydride: Acetic acid, anhydride; (108-24-7)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8.087
7.270
2.716
F3C
O
CF3
400 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.926
0.959
3.000