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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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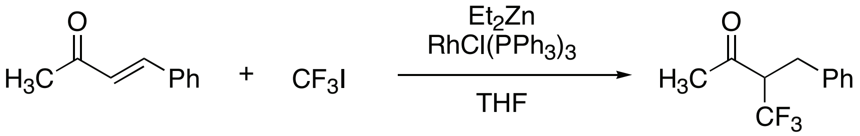
TRIFLUOROMETHYLATION AT THE α-POSITION OF α,β-UNSATURATED KETONES: 4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE



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Discussion Addendum *Org. Synth.* **2012**, *89*, 374

1. Procedure

4-Phenyl-3-trifluoromethyl-2-butanone. A flame-dried, 500-mL, four-necked, round-bottomed flask is equipped with a rubber septum, a dry ice/isopropyl alcohol cooled cold-finger condenser topped with a nitrogen stopcock inlet, a pressure-equalizing dropping funnel topped with a rubber septum, a Teflon-coated thermocouple (Note 1), and a Teflon-coated magnetic stirring bar. The reaction vessel is charged with 4-phenylbut-3-en-2-one (7.310 g, 50 mmol), $RhCl(PPh_3)_3$ (925 mg, 1.0 mmol) (Note 2), and 190 mL of tetrahydrofuran (THF) is added under nitrogen (Note 2). The brown solution is cooled in an isopropyl alcohol bath to –30 °C (Note 3). In a graduated tube equipped with a three-way stopcock attached to a nitrogen inlet from a Schlenk line, 7 mL (ca. 86 mmol) of trifluoroiodomethane (CF_3I) (Note 4) is condensed at –78 °C by using a dry ice/isopropyl alcohol bath. After the CF_3I condenses, the three-way stopcock is closed and the top of the stopcock is fitted with a rubber septum. The condensed CF_3I is added to the reaction mixture quickly through a cannula by warming the graduated tube with a water bath. After almost all of CF_3I is transferred to the reaction vessel, 10 mL of THF is added to the graduated test-tube through the septum, and the THF is transferred to the reaction vessel through the cannula by briefly evacuating the reaction vessel through a hose to the Schlenk line. The reaction mixture is immersed in an ice-bath, and then diethylzinc in hexane solution (75 mL 1.0 M) (Note 5) is gradually added to the solution through the presser-equalizing dropping funnel over 2 h. During the addition, the temperature of the solution is kept below 5 °C by cooling with an ice bath. The reaction mixture is allowed to warm to room temperature over 30 min after removing the ice-bath, whereupon it is stirred at room temperature for 1 h (Note 6). The progress of the reaction is followed by thin layer chromatographic (TLC) analysis (Note 7), which confirms that the reaction is complete (Note 8). The resulting mixture is carefully poured into a mixture of 10% HCl (150 mL) and ice (about 50 g) in a 1-L Erlenmeyer flask equipped with a Teflon-coated magnetic stirring bar (Note 9). The ice melts in a few minutes, then the mixture is extracted with Et_2O (4 x 150 mL). The combined organic layers are washed with brine (100 mL) and then are dried over $MgSO_4$ (about 20 g). The $MgSO_4$ is removed by filtration through a sintered glass-filter, and the solvent is removed under reduced pressure on a rotary evaporator (23 °C, 30 mm Hg). The residue is purified by silica gel (Note 10) column chromatography (190 g, diameter = 50 mm, eluted with hexane/ethyl acetate, 30/1; 1.2 L) to remove small amounts of impurities and most of the black color. The product-containing portions are concentrated under reduced pressure, and are purified by reduced-pressure distillation using short path distillation apparatus (66–68 °C / 3 mmHg) to afford 7.610 g (72 %) of 4-phenyl-3-(trifluoromethyl)butan-2-one as a clear, colorless oil (Notes 10 and 11).

2. Notes

1. A PFA coated thermocouple probe, Type K (Omega Engineering, Inc.) was inserted through the septum.

2. 4-Phenylbut-3-en-2-one (>99%) and $RhCl(PPh_3)_3$ (>99.99%) were purchased from Aldrich Chemical Co. and were used without further purification. The reaction apparatus is shown in Figure 1. The submitters used argon.

3. Anhydrous THF was obtained by filtration through an alumina drying column on a GlassContour system (Irvine, CA).

4. CF_3I was purchased from Aldrich Chemical Co. (99%). Its boiling point is –22.1 °C, and density is about 2.4 g/mL. CF_3I was transferred from the container to the graduated test-tube by using the apparatus shown in Figure 2. The tube was evacuated and cooled below –78 °C in a dry ice/isopropyl alcohol bath. Then the vacuum line was closed, stopcock **A** was opened and the correct amount of CF_3I was collected in the graduated test-tube.

5. Diethylzinc (1.0 M in hexane solution) was purchased from Aldrich Chemical Co. It was transferred to the pressure-equalizing

addition funnel via cannula by briefly evacuating the reaction flask through the Schlenk line.

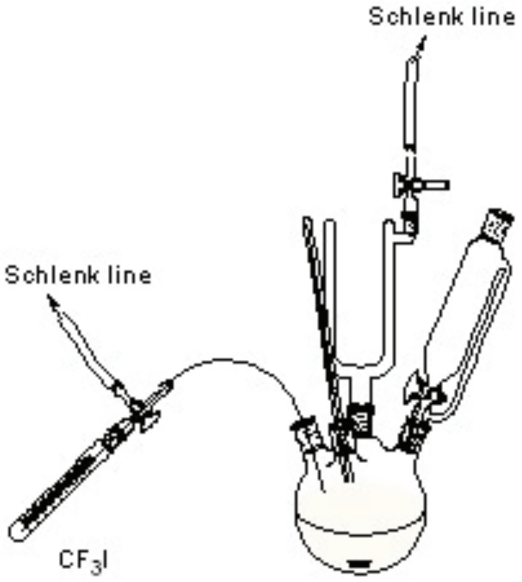


Figure 1. Reaction Apparatus for the Synthesis of α-CF_3 Ketones

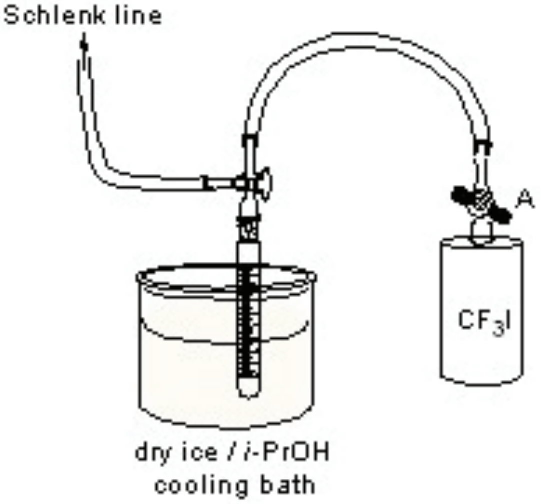


Figure 2. Apparatus for Collecting CF_3I

6. A mild evolution of gas was observed upon addition of diethylzinc. The composition of the gas was not determined, but it is most likely

trifluoromethyl iodide and/or ethylene. As the reaction mixture was warmed to room temperature, slight gas evolution was observed, and the color of the solution changed to dark brown.

7. TLC analysis was performed on Merck silica gel plates with QF-254 indicator and hexane/ethyl acetate, 9/1 as eluent. Visualization was accomplished with UV light and $KMnO_4$ staining solution.

8. An aliquot of the reaction mixture was removed and quenched with 10% aq. HCl, then Et_2O was added. The organic phase was analyzed by TLC (see Note 7). 4-Phenylbut-3-en-2-one (R_f = 0.23) almost disappeared after 0.5 h, but 4-phenylbutan-2-one, (R_f = 0.29) which can be generated by quenching the corresponding rhodium enolate was still present. After 1.0 h, 4-phenylbutan-2-one disappeared and only 4-phenyl-3-(trifluoromethyl) butan-2-one (R_f = 0.50) was detected. The submitters used gas chromatography to monitor the reaction progress.

9. Vigorous evolution of gas was observed upon quenching.

10. The submitters found that 4-phenyl-3-(trifluoromethyl)butan-2-one is stable at room temperature under an argon atmosphere over three months.

11. The final product had the following characteristics; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.08 (s, 3 H), 3.06 (dd, 1 H, J = 13.8, 4.3 Hz), 3.18 (dd, 1 H, J = 13.8, 10.8 Hz), 3.56 (dqd, 1 H, J = 10.8, 8.6, 4.1 Hz), 7.15–7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 31.6 (q, $J_{C\text{-}F}$ = 1.8 Hz), 31.8 (q, $J_{C\text{-}F}$ = 2.8 Hz), 57.4 (q, $J_{C\text{-}F}$ = 24.9 Hz), 124.4 (q, $J_{C\text{-}F}$ = 279.5 Hz), 127.0, 128.7, 128.8, 136.4, 201.3 (q, $J_{C\text{-}F}$ = 1.5 Hz); ^{19}F NMR ($CDCl_3$, 396 MHz) δ: –67.72 (d, 3 F, J = 7.5 Hz); IR (KBr) cm^{-1}: 3033, 2942, 1731, 1606, 1499, 1457, 1422, 1362, 1301, 1263, 1161, 1115, 1081, 1505, 874, 747, 704; MS *m*/*z*: 216 (M^+); HRMS Calc. $C_{11}H_{11}OF_3$: 216.0762 (M^+), Found: 216.0763; Elemental Analysis Calc. for $C_{11}H_{11}OF_3$: C, 61.11; H, 5.13; F, 26.36. Found: C, 60.87; H, 5.04; F, 26.68.

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

Trifluoromethylated (CF_3) compounds constitute one of the most important classes of fluorine-containing compounds, and there are many reports on trifluoromethylation reactions. However, the reactions for introducing a CF_3 group at the α-position of ketones are limited to trifluoromethylation of metal enolates of carbonyl compounds or imides,[2] electrophilic trifluoromethylation with calcogenium reagents,[3] and photochemical[4a] and ultrasonic[4b] reactions of enamines with CF_3I.

Recently, our group reported that α,β-unsaturated ketones react with ethyl bromodifluoroacetate and Et_2Zn in the presence of a rhodium catalyst to give unexpected products, in which either the CF_2COOEt group was introduced on the α-carbon of α,β-unsaturated ketones or the expected 1,2-addition product proceeded in good yields depending on the solvent.[5] On the basis of this result, we treated α,β-unsaturated ketones with CF_3I in the presence of Et_2Zn and $RhCl(PPh_3)_3$ to prepare α-CF_3 ketones.[6] This method was found to be superior to previous routes for synthesis of α-CF_3 ketones because it did not need special reagents, could be carried out under mild conditions, and provided the product in good yield. Moreover, trifluoromethylation at the α-position of α,β-unsaturated ketones had not been reported.

A mechanistic proposal is shown below (Figure 3).[6] A β-hydrogen atom in Et_2Zn appears to play an important role in this reaction because dimethylzinc does not work at all.

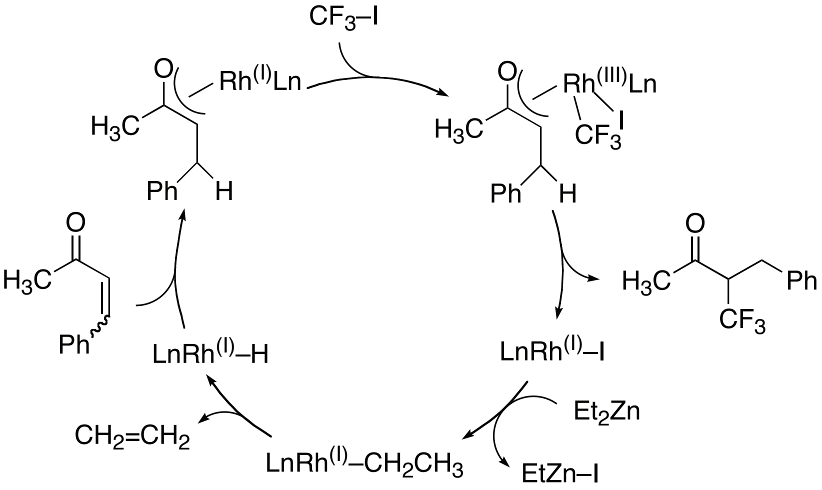
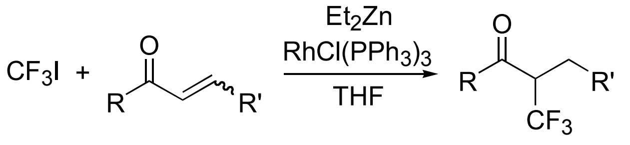


Figure 3. Proposed Mechanism

Following the procedure described above, various α-CF_3 ketones were obtained in good yields as shown in Table 1. The yields reported in the Table are based on reactions performed on a 2-mmol scale.

Table 1. Synthesis of Various α-CF_3 Ketones



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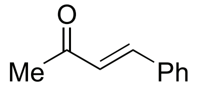
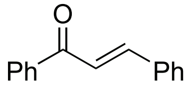
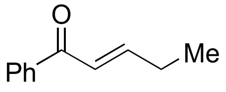
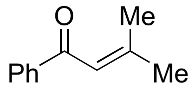
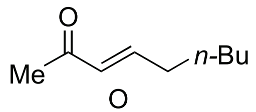
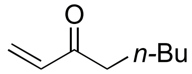
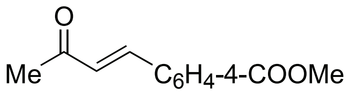
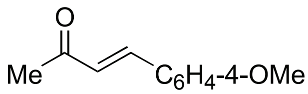
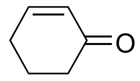
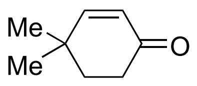
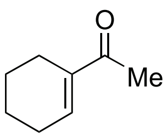
1		0.5	77
2		1	31
3		1	35
4		3	0
5		1	67
6		1	59
7		1	65
8		1	65
9		0.5	55
10		1	53
11		0.5	0[b]

(a) Isolated yield. (b) 1,4-adduct was obtained in 54%.

1. Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan
2. (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649-651. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961-974.
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4. (a) Crusiani, G.; Margaretha, P. *J. Fluorine Chem.* **1987**, *37*, 95-101. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191.
5. Sato, K.; Tarui, A; Kita, T.; Ishida, Y.; Tamura, H.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2004**, *45*, 5735-5737.
6. Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Lett.* **2004**, *6*, 4359-4361.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-Phenyl-3-buten-2-one; (122-57-6)
$RhCl(PPh_3)_3$: Rhodium, chlorotris(triphenylphosphine)-, (SP-4-2)-; (14694-95-2)
Trifluoroiodomethane; (2314-97-8)
Diethylzinc; (557-20-0)
4-Phenyl-3-(trifluoromethyl)butan-2-one: 2-Butanone, 4,4,4-trifluoro-3-(phenylmethyl)-; (808105-43-3)

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 distillation

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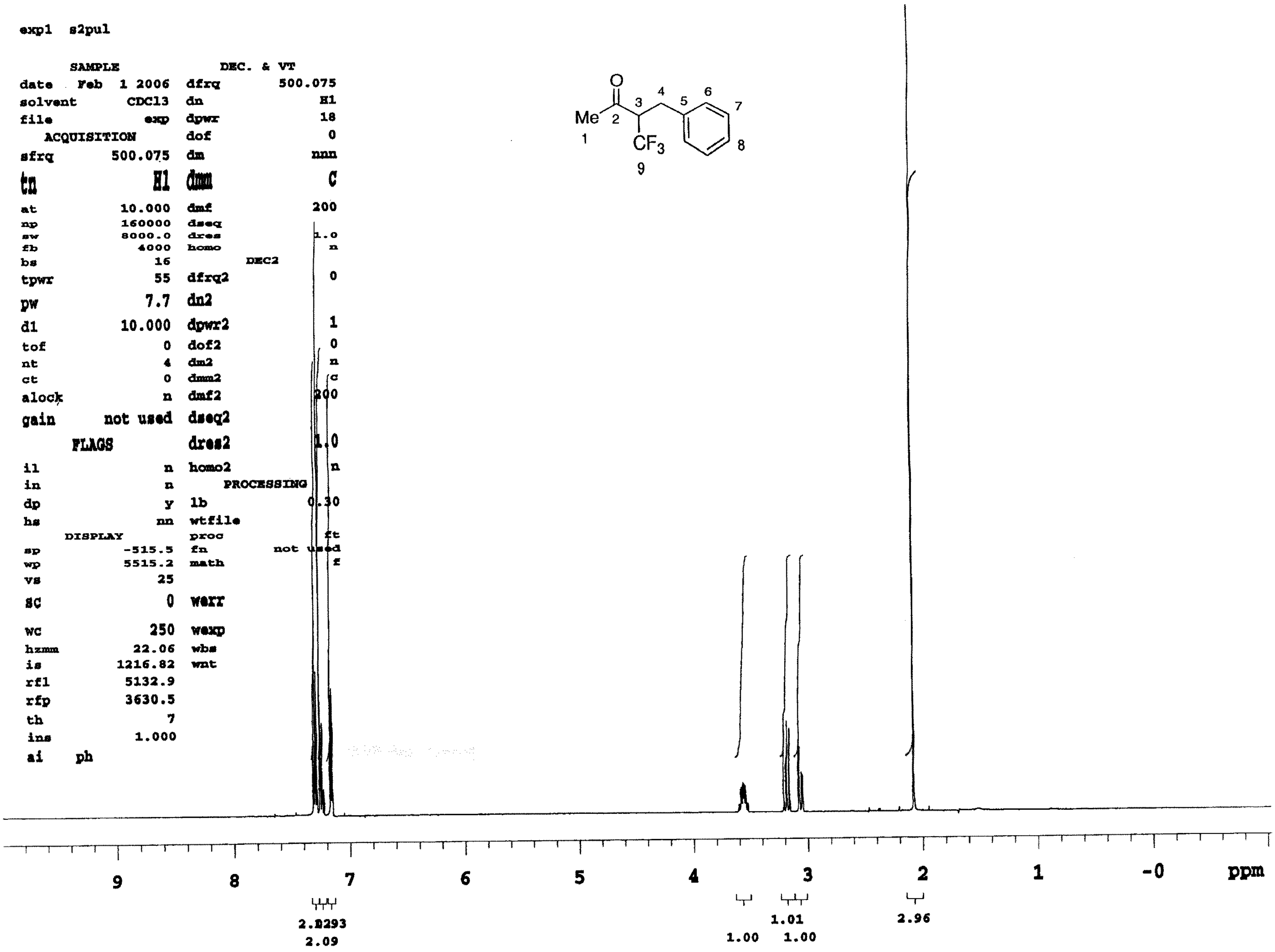

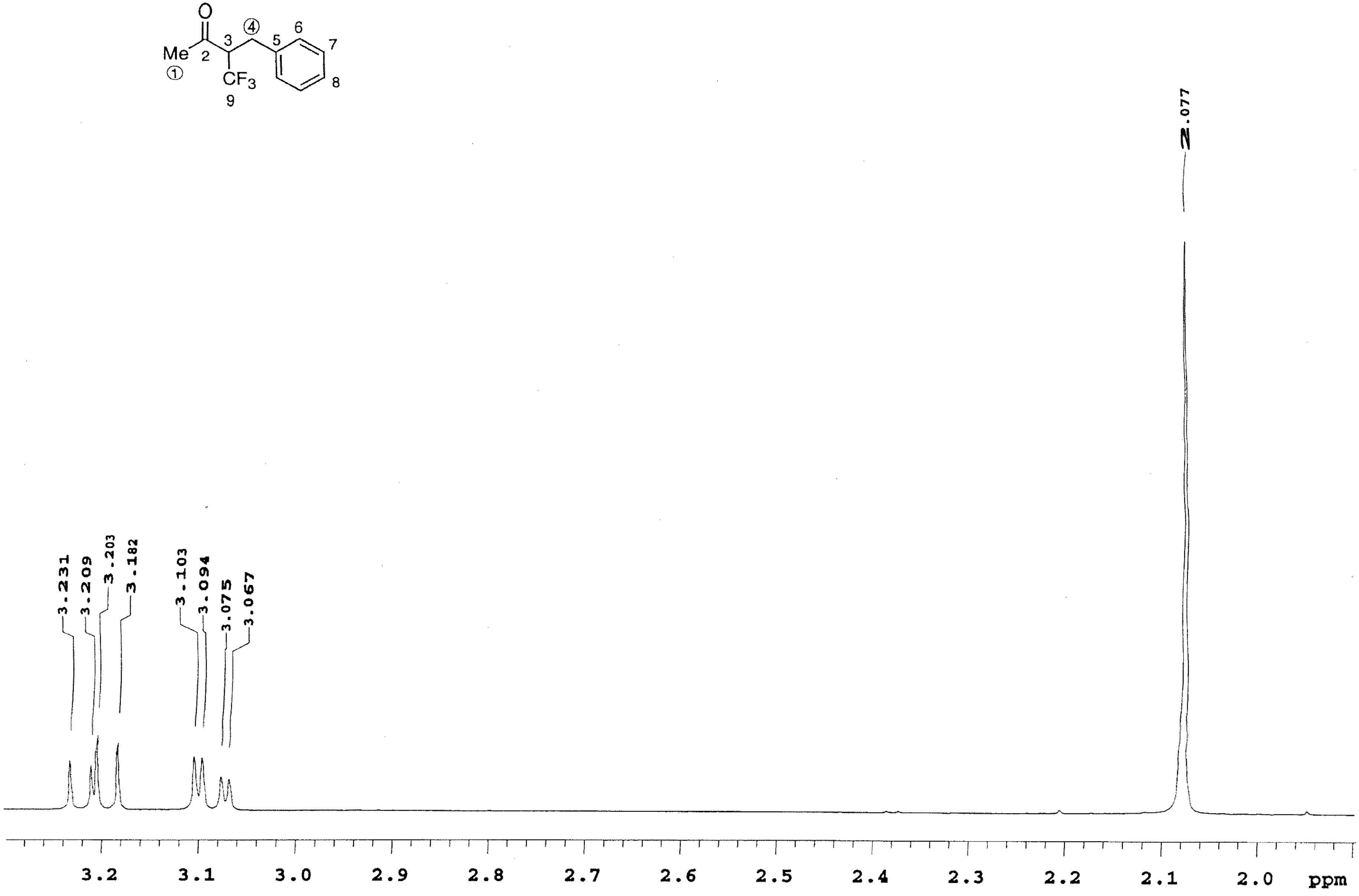
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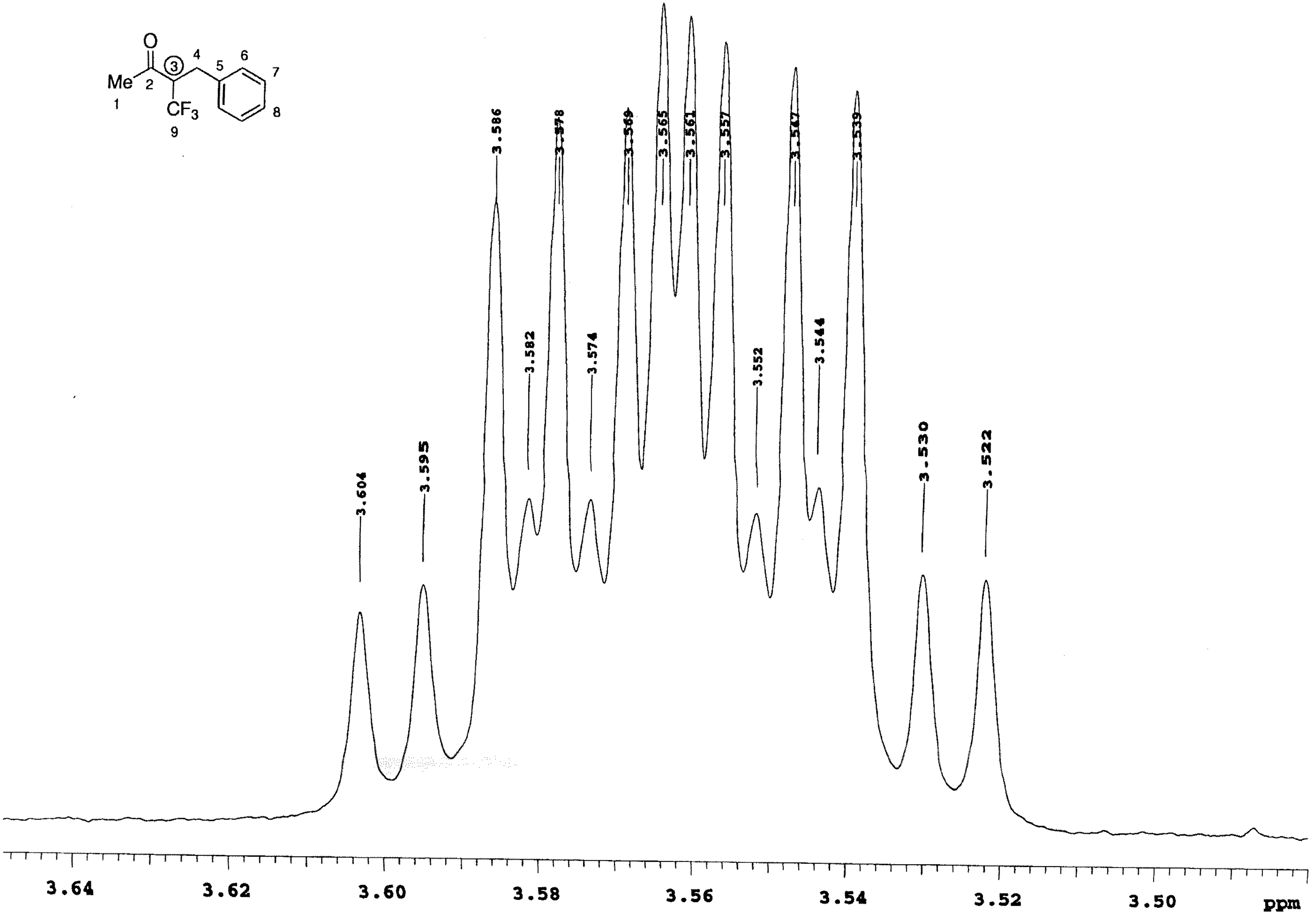
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