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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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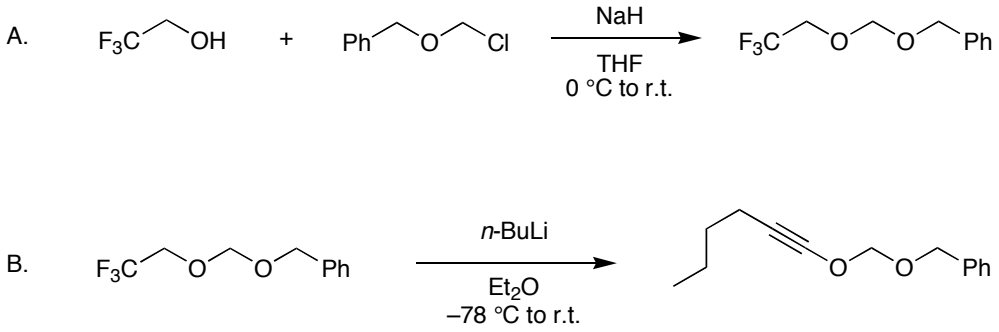
PREPARATION OF A 1-ALKOXY-1-ALKYNE FROM REACTION OF A 2,2,2-TRIFLUOROETHYL ETHER WITH AN ALKYLLITHIUM REAGENT: 1-BENZYLOXYMETHOXY-1-HEXYNE



Submitted by P. J. Kocienski and T. N. Snaddon.[1]
Checked by K. M. Brummond and T. O. Painter.

1. Procedure

Caution! Benzyl chloromethyl ether is a powerful alkylating agent and a potential carcinogen. Furthermore, it is a mild lachrymator and reacts with water and alcohols, forming hydrogen chloride. The procedure should be conducted in a well-ventilated fume hood, and inhalation and skin contact should be avoided.

A. *Benzyloxymethoxy 2,2,2-trifluoroethyl ether*. An oven-dried 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, a thermometer (–100 °C to 30 °C range), a rubber septum (containing nitrogen inlet and outlet needles) and a glass stopper is charged with sodium hydride (3.8 g, 95 mmol, 1.2 equiv) (Note 1) by temporary removal of the septum and 10 mL of pentane (Note 2) is added by syringe through the septum. The resulting gray suspension is stirred for 1 min and is allowed to settle. The pentane is slowly removed by syringe and the process is repeated (Note 2). Tetrahydrofuran (300 mL) (Note 3) is added and the resulting gray suspension cooled to 0 °C (internal temperature) using an ice–water–sodium chloride bath whereupon 2,2,2-trifluoroethanol (6.4 mL, 87 mmol, 1.1

equiv) (Note 4) is added drop wise *via* syringe at a rate sufficient to maintain the reaction temperature at 0 °C (approximately 10 min) [*caution:* gas evolution!]. When effervescence ceases the cooling bath is removed and the reaction is allowed to warm to 22 °C (*approximately* 15 min) giving a slightly turbid, light gray mixture. The mixture is cooled to 0 °C with an ice–water–sodium chloride bath and benzyl chloromethyl ether (11.0 mL, 79 mmol, 1.0 equiv) (Note 5) is added dropwise over 5 min by syringe. The reaction mixture is stirred at 0 °C for 30 min to produce a fine white suspension. The cooling bath is removed and the suspension is allowed to warm to 22 °C and is stirred for 1.75 h. The septum is removed and water (70 mL) is added. The mixture is transferred to a 1-L separatory funnel and the aqueous layer is separated and then extracted with dichloromethane (3 × 70 mL). The combined organic layers are dried over magnesium sulfate for 15 min, filtered and the filter cake is washed with dichloromethane (3 × 50 mL). The combined filtrates are concentrated on a rotary evaporator (Note 6) and the residual colorless oil (19.3 g) is purified by short path distillation (Note 7). The fraction boiling at 79–80 °C/15 mmHg is collected to afford 15.8 g (72 mmol, 91%) (Note 8) of pure benzyloxymethoxy 2,2,2-trifluoroethyl ether (Note 9).

B. *1-Benzyloxymethoxy-1-hexyne*. An oven-dried 500-mL, three-necked round-bottomed flask equipped with a magnetic stir bar, a thermometer (–100 °C to 50 °C range), a 125-mL pressure equalizing dropping funnel (with rubber septum) and a rubber septum (containing nitrogen inlet and outlet needles) is charged with benzyloxymethoxy 2,2,2-trifluoroethyl ether (11 g, 50 mmol, 1.0 equiv) and 150 mL of diethyl ether (Note 10) by temporarily removing the septum. The pressure-equalizing dropping funnel is charged with 98 mL of *n*-butyllithium (1.53 M in hexanes, 150 mmol, 3.0 equiv) (Note 11). The reaction flask is cooled to –75 °C (internal temperature) with a dry ice-acetone bath and the *n*-butyllithium added dropwise over 40 min at a rate sufficient to maintain the reaction temperature below –70 °C. The resulting yellow solution is allowed to warm to 0 °C slowly with stirring over 3.5 h while still in the cooling bath. Thereafter the dry ice-acetone bath is removed and the mixture is allowed to warm to 20 °C over 30 min (Note 12), and maintained at this temperature for an additional 30 min. The turbid, yellow–orange reaction mixture is transferred by cannula to a vigorously-stirred slurry of 50 g of ice and 100 mL of brine, which is cooled with an ice-water bath. After complete

transfer, 50 mL of diethyl ether is added and the layers are separated. The aqueous layer is extracted with 150 mL of diethyl ether–hexanes, 1:1) (Note 13). The combined organic layers are dried over magnesium sulfate for 15 min, filtered and the filter cake is washed with diethyl ether/hexanes, 1:1 (3 × 100 mL) (Note 14). The combined filtrates are concentrated on a rotary evaporator (Note 6) to afford 11.2 g of a pungent, yellow–orange oil. The crude product is purified by short path distillation (Note 15, bp 114–115 °C/0.3 mmHg) to afford 5.4 g (25 mmol, 50%) of 1-benzyloxymethoxy-1-hexyne (Note 16) as a pale-yellow oil (Note 17).

2. Notes

1. Sodium hydride (60% dispersion in mineral oil) was purchased from Alfa Aesar and used without further purification.

2. Reagent grade pentane was distilled prior to use from powdered calcium hydride under an atmosphere of dry nitrogen. The supernatant washes are carefully quenched by the slow addition of water.

3. Anhydrous 99.9%, inhibitor free tetrahydrofuran was purchased from Aldrich and purified with alumina using the Sol-Tek ST-002 solvent purification system directly before use. The submitters used reagent grade tetrahydrofuran that was freshly distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen.

4. 2,2,2-Trifluoroethanol (99%) was purchased from Alfa Aesar and distilled prior to use from anhydrous calcium sulfate and sodium hydrogen carbonate (5:1) under an atmosphere of dry nitrogen.

5. Benzyl chloromethyl ether was prepared (0.19 mol scale) according to the procedure of Boeckman *et al.*[2] and was distilled (bp 70–71 °C/3.0 mmHg) from anhydrous calcium chloride. The pure benzyl chloromethyl ether can be stored over calcium chloride at –20 ºC for up to two weeks prior to use. The pure material was taken directly from storage and added to the reaction mixture via a syringe equipped with a PALL Life Sciences Acrodisc CR 13 mm syringe filter (0.2 μm PTFE membrane). The submitters prepared it similarly (0.4 mol scale) according to the procedure of Boeckman *et al.* and freshly distilled it (bp 47–48 °C/0.05 mmHg) from anhydrous calcium chloride directly before use. Calcium chloride (fused granular, general purpose grade) was dried in an oven at 140 °C for 24 h prior to use.

6. Bath: 20–23 °C; vacuum: approximately 12 mmHg.

7. Short path distillation was performed with a non-jacketed, non Vigreaux still head.

8. Yields of 88–91% were obtained on full scale and a yield of 85-88% was obtained on half scale.

9. IR (neat): 3035, 2954, 2897, 1498, 1455, 1428, 1384, 1281, 1159, 1060, 970, 742 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.97 (q, 2 H, J_{H-F} = 8.5 Hz), 4.66 (s, 2 H), 4.85 (s, 2 H), 7.33-7.41 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.7 (q, J_{C-F} = 34.5 Hz), 70.1, 94.8, 124.2 (q, J_{C-F} = 276.8 Hz), 128.2, 128.7, 137.3 Anal. Calcd. for $C_{10}H_{11}F_3O_2$: C, 54.55; H, 5.04. Found: C, 54.65; H, 5.06.

10. Anhydrous diethyl ether was purchased from Fisher Chemical and purified with alumina using the Sol-Tek ST-002 solvent purification system directly before use. The submitters used diethyl ether that was freshly distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen.

11. *n*-Butyllithium (1.6 M in hexanes) was purchased from Sigma–Aldrich. Its molarity was determined by titration[3] with 0.2 g of 1,3-diphenylacetone *p*-tosylhydrazone (Aldrich) in 5 mL of tetrahydrofuran immediately prior to use.

12. Upon reaching 5 °C a slightly turbid yellow mixture was obtained, which became more viscous as the temperature increased.

13. The use of diethyl ether–hexanes (1:1) aided phase separation; however, the extraction mixture should be drained of water up to the bottom of the emulsion and this separation process repeated 5 times before combining the remaining emulsion with the organic layers.

14. Care should be exercised during the addition of magnesium sulfate to the mixture due to its high water content. The drying agent was added in 3 portions with ice-water bath cooling of the flask to avoid an exotherm. Once addition was complete and bubbling had ceased, the mixture was allowed to stand at room temperature.

15. The acid-sensitivity of the product required some precautions. The vessels used to store the crude product and all components of the distillation apparatus were soaked in isopropanolic potassium hydroxide for 4–24 h, before being washed with deionized water, isopropanol, then acetone, and finally oven dried at 140 °C overnight, prior to use. The submitters report that this glassware was soaked in methanolic potassium hydroxide for 4 h, before being washed with methanol, then acetone, and finally oven-dried before use.

16. Yields of 46–50% were obtained on full scale and a yield of 51% was obtained on half scale. A by-product fraction that appeared to contain some unreacted starting material, as determined by proton NMR, was collected at 68–72 °C as a colorless oil (approximately 2.9 g on full scale). The submitters reported a 60% yield on full scale and that the desired product was collected by distillation at 92–95 °C/0.05 mmHg as a colorless oil.

17. IR (neat): 2957, 2931, 2872, 2270, 1497, 1456, 1382, 1216, 1159, 1119, 902, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, 3 H, J = 7.0 Hz), 1.39–1.49 (m, 4 H), 2.16 (t, 2 H, J = 7.0 Hz), 4.78 (s, 2 H), 5.03 (s, 2 H), 7.32–7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 17.1, 22.0, 31.8, 39.6, 71.5, 87.6, 99.6, 128.3, 128.6, 136.6. The checkers were unable to obtain acceptable CHN analytical data. The submitters reported that CHN analysis was obtained immediately after the final distillation using an in-house service due to the sensitivity of the 1-alkoxy-1-alkyne. This afforded the following data: C, 76.95; H, 8.55. Analysis of the proton NMR indicated the presence of minor impurities, the most prevalent at 4.8–4.9 ppm, 4.6–4.7 ppm, and 3.9–4.0 ppm. These impurity peaks accounted for less than 5% of the total proton integration value.

Safety and Waste Disposal Information

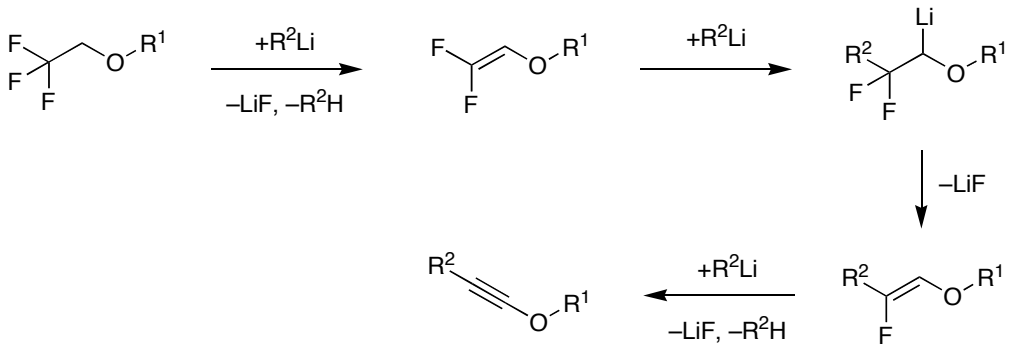
All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The synthesis of 1-benzyloxymethoxy-1-hexyne[4] exemplifies a general method for the synthesis of 1-alkoxy-1-alkynes and 1-aryloxy-1-alkynes reported by Nakai and co-workers.[5] A 2,2,2-trifluoroethyl ether, prepared by the nucleophilic substitution of an alkyl halide by sodium 2,2,2-trifluoroethoxide, reacts with 3 equiv of an alkyllithium reagent to give the 1-alkoxy-1-alkyne in 35–80% yield (see Table). 1°-, 2°- and 3°-alkyllithiums participate equally well in the reaction according to the mechanism shown in Scheme 1. In the cases where R^1 is phenyl, the requisite 2,2,2-trifluoroethyl ether is prepared by the reaction of sodium

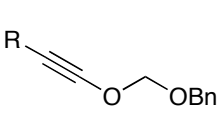
phenolate with 2,2,2-trifluoroethyl tosylate. The sequence can also be used for the synthesis of 1-alkyl thio-and 1-arylthio-1-alkynes.[5]

Scheme 1

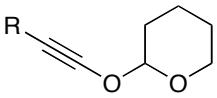


TABLE

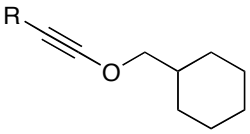
1-ALKOXY-1-ALKYNES DERIVED FROM 2,2,2-TRIFLUOROETHYL ETHERS[4]



R	%
s-Bu	49
t-Bu	50



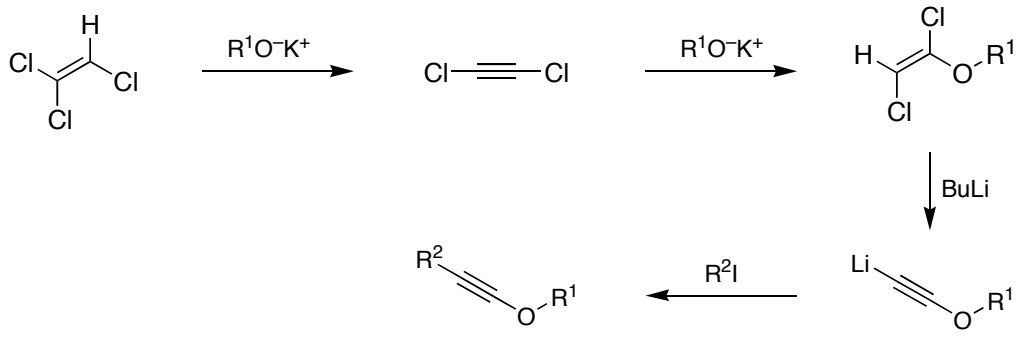
R	%
n-Bu	35
s-Bu	53
t-Bu	44



R	%
n-Bu	73
s-Bu	73
t-Bu	80

Greene and co-workers[6] developed an alternative one-pot procedure that is especially useful in the cases where the alkyllithium reagent R^2Li is inaccessible. Their procedure, depicted in Scheme 2, entails the reaction of an alcohol successively with potassium hydride (2 equivalents), trichloroethylene (1 equivalent), *n*-butyllithium (2.2 equivalents), and a primary iodoalkane (large excess). In this case the potassium alkoxide first generates dichloroacetylene by β-elimination of trichloroethylene and then adds to it. The resulting adduct, on treatment with *n*-butyllithium, undergoes elimination to the lithium acetylide whose alkylation affords the final product. Witulski and Alayric[7] have reviewed the syntheses and reactions of 1-heteroalkyl-1-alkynes.

Scheme 2



1. School of Chemistry, Leeds University, Leeds, LS2 9JT, UK

2. Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K.; Medwid, J. B. *Org. Synth. Coll. Vol. VI* **1988**, 101-103.

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5. Tanaka, T.; Shiraishi, S.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, *19*, 3103-3106.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Sodium hydride; (7647-69-7)

2,2,2-Trifluoroethanol (75-89-8)

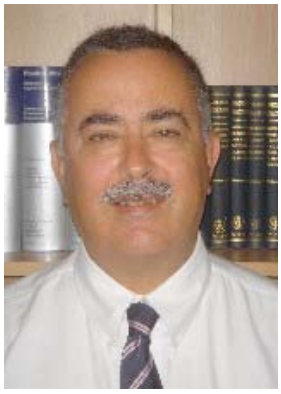
Benzyl chloromethyl ether: Benzene, [(chloromethoxy)methyl]-; (3587-60-8)

Benzyloxymethoxy-2,2,2-trifluoromethyl ether: Benzene, [[(2,2,2-trifluoroethoxy)methoxy]methyl]-: (153959-88-7)

n-Butyllithium (109-72-8)

1-Benzyloxymethoxy-1-hexyne: Benzene, [[(1-hexyn-1-yloxy)methoxy]methyl]-; (162552-11-6)

1,3-Diphenylacetone *p*-tosylhydrazone: Benzenesulfonic acid, 4-methyl-, [2-phenyl-1-(phenylmethyl)ethylidene]hydrazide; (19816-88-7)



Philip Kocienski was born in Troy, New York, in 1946. His research career began under Alfred Viola while an undergraduate at Northeastern University and was further developed at Brown University, where he obtained his PhD under Joseph Ciabattoni. Postdoctoral study under George Büchi at MIT and later with Basil Lythgoe at Leeds University confirmed his interest in natural product synthesis. He has held academic appointments at Leeds University (1979-1985), Southampton University (1987-1997), and Glasgow University (1997-2000). In 2000 he returned to Leeds where his research has focussed on the applications of organometallic chemistry to natural product synthesis.

Thomas N. Snaddon was born in Stirling, Scotland in 1981. He received a B.Sc. (Hons.) in Biomolecular and Medicinal Chemistry (2003) and M.Phil. in synthetic organic chemistry (2004) from the University of Strathclyde in Glasgow. In October 2004 he moved to the University of Leeds as a Society of Chemical Industry (SCI) John Gray Scholar to pursue doctoral studies with Professor Philip J. Kocienski in the arena of natural product synthesis. In early 2008 he will move to a post-doctoral position with Professor Alois Fürstner at the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany.

Thomas Painter was born in 1980 in Pittsburgh, Pennsylvania. During his undergraduate studies he interned at Valspar Corporation in 2002 and obtained his B.S. degree in chemistry from the University of Pittsburgh in 2003. He is currently pursuing graduate studies as a Bayer Fellow in the laboratory of Professor Kay Brummond at the University of Pittsburgh. His graduate research has included work on the synthesis of electron- deficient trienones and ε-lactams, and progress toward bicyclic analogs of irofulven using rhodium(I)-catalyzed cycloisomerization reactions.

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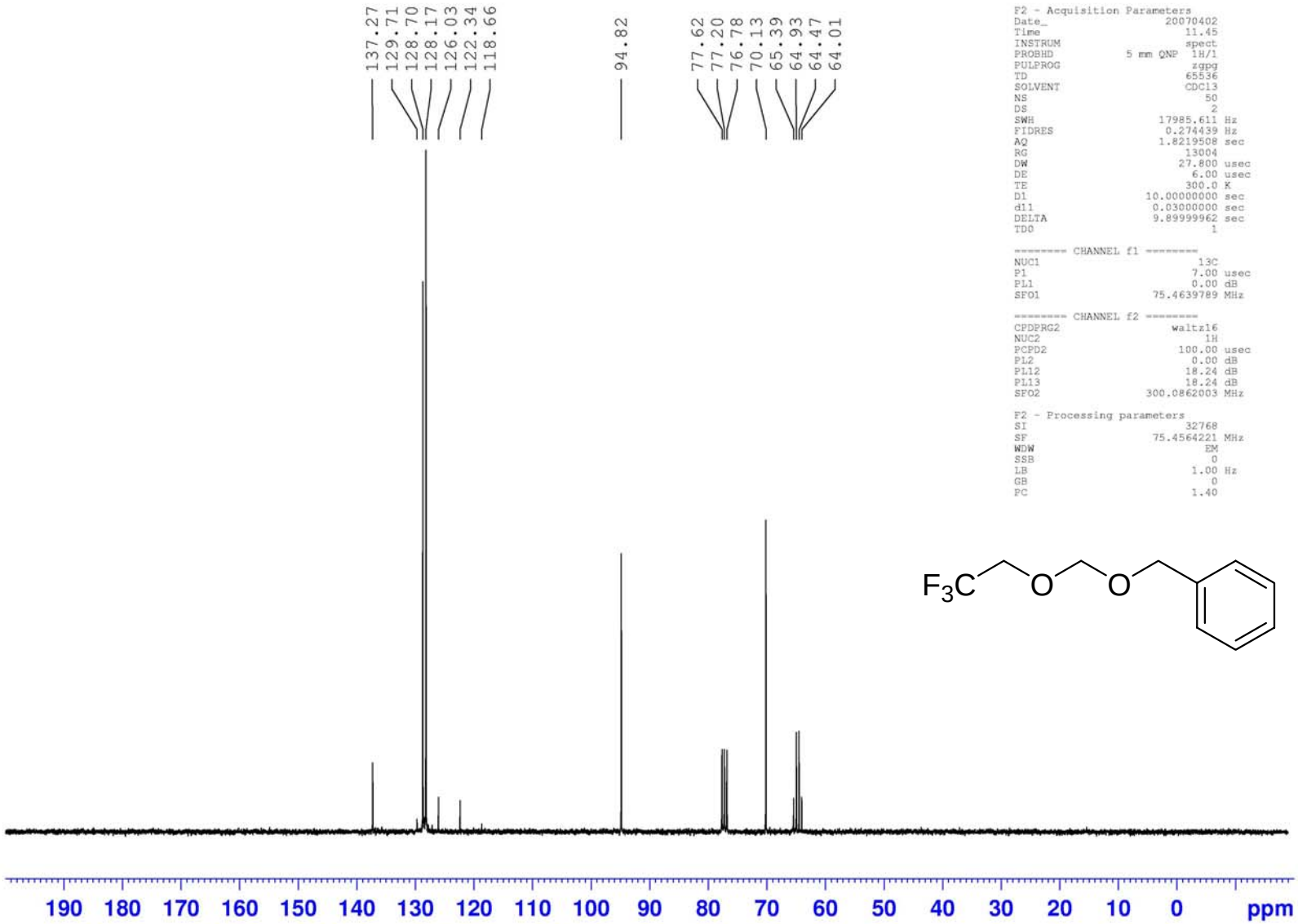


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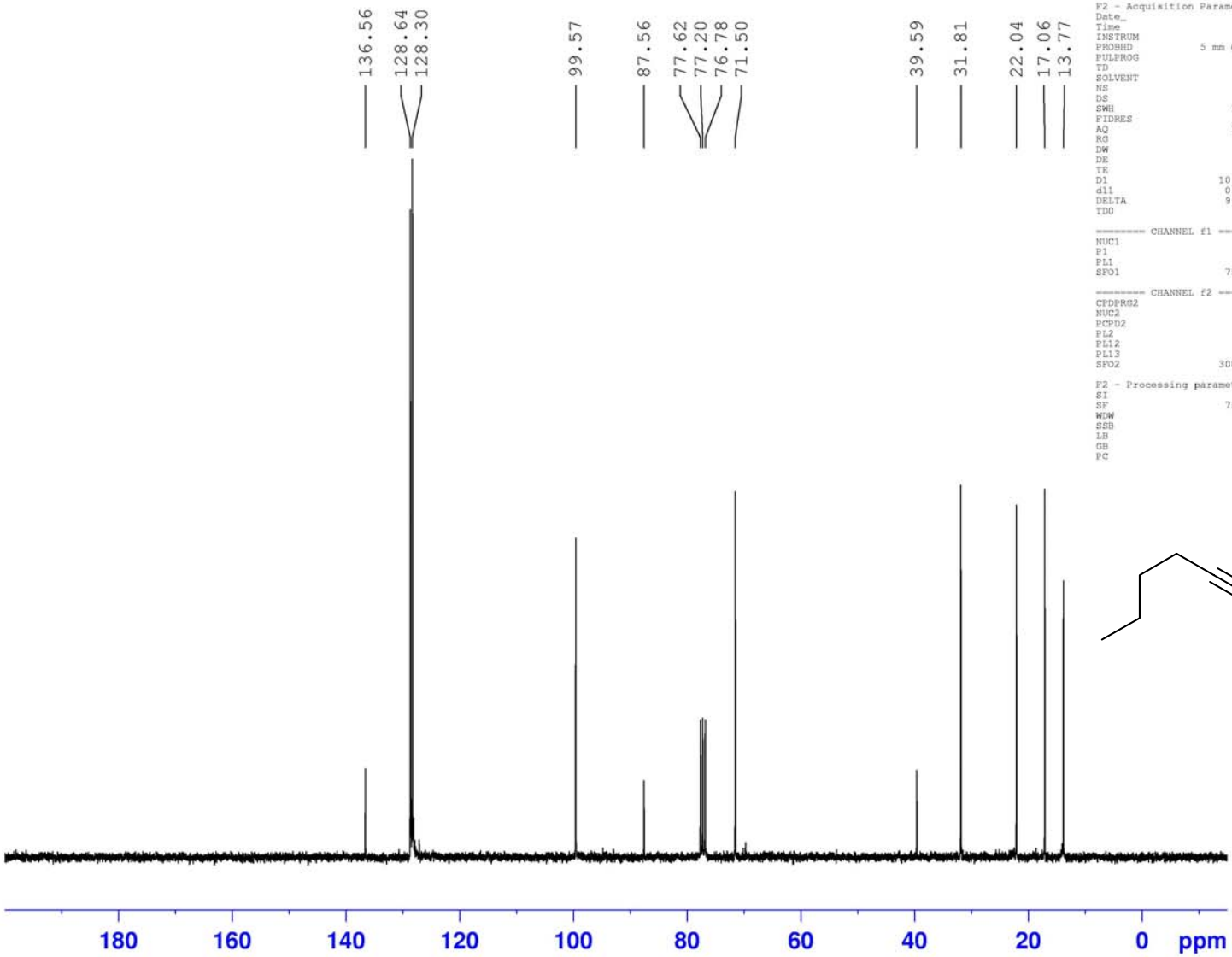


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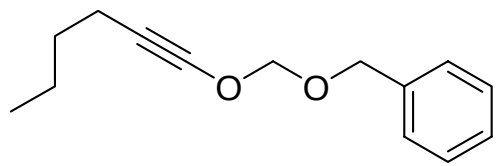

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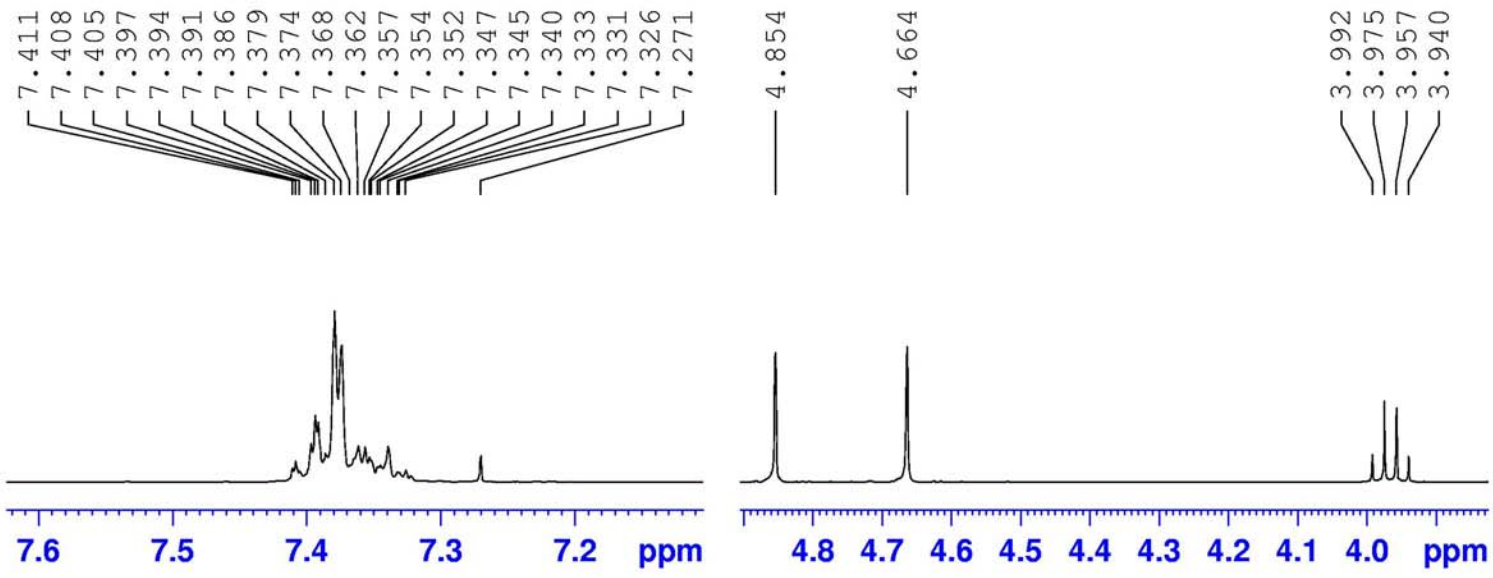


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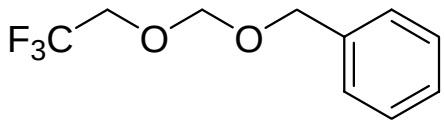

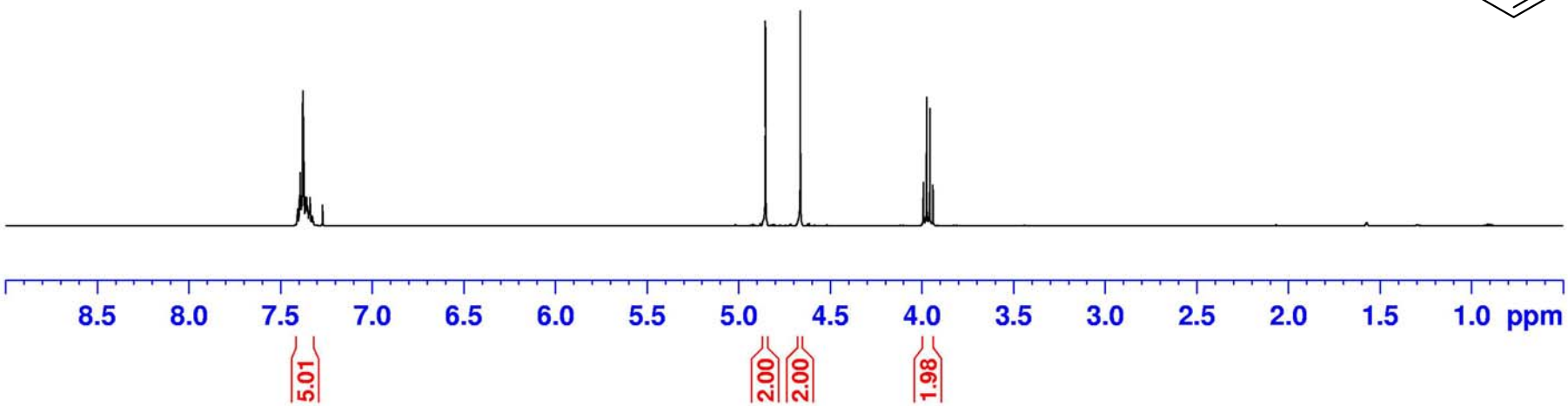

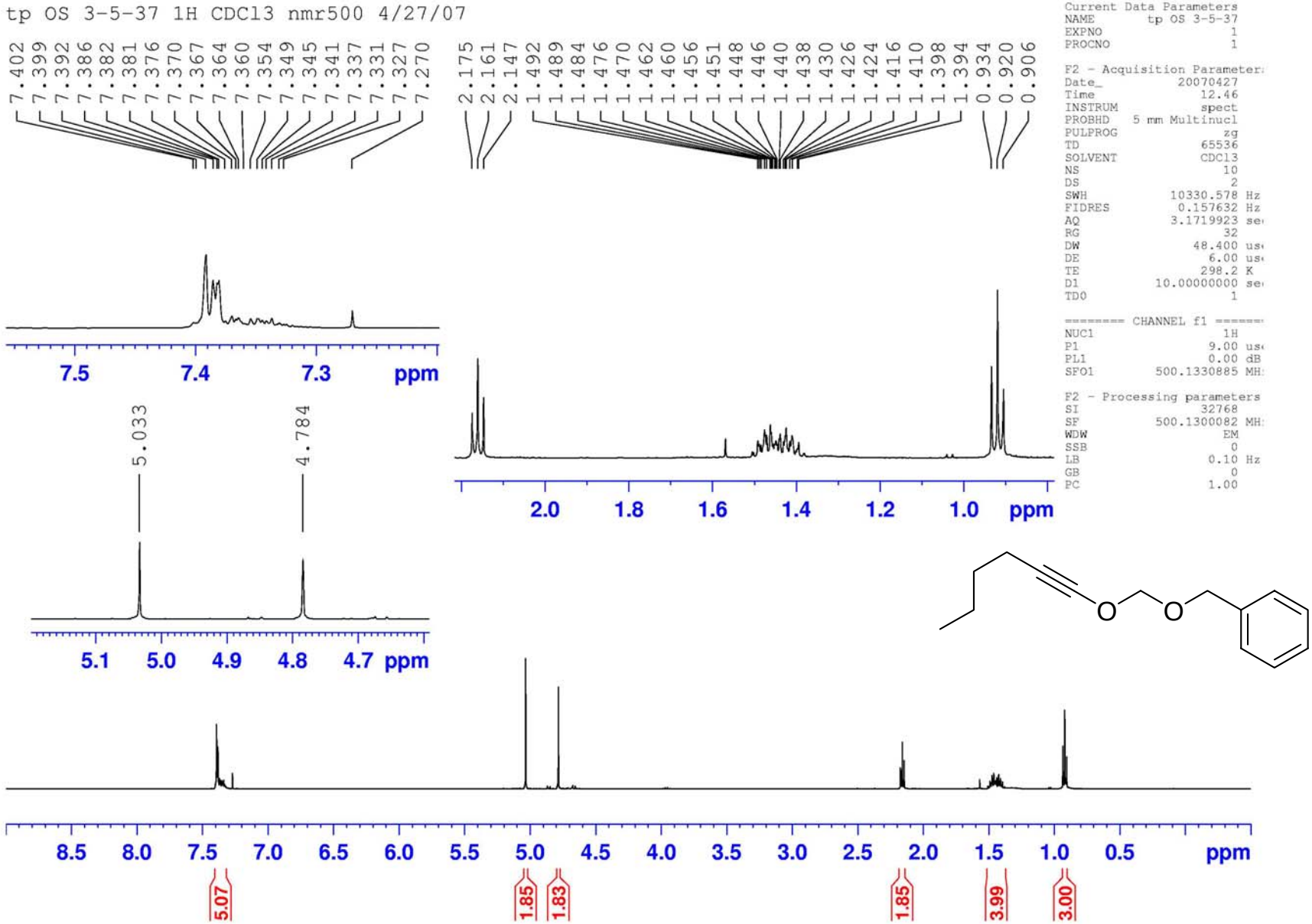
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P1 9.00 us
PL1 0.00 dB
SFO1 500.1330885 MH
F2 - Processing parameters
SI 32768
SF 500.1300082 MH
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
7.5 7.4 7.3 ppm
5.033
4.784
5.1 5.0 4.9 4.8 4.7 ppm
2.0 1.8 1.6 1.4 1.2 1.0 ppm
O
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.07
1.85
1.83
1.85
3.99
3.00