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for the Preparation
of Organic Compounds

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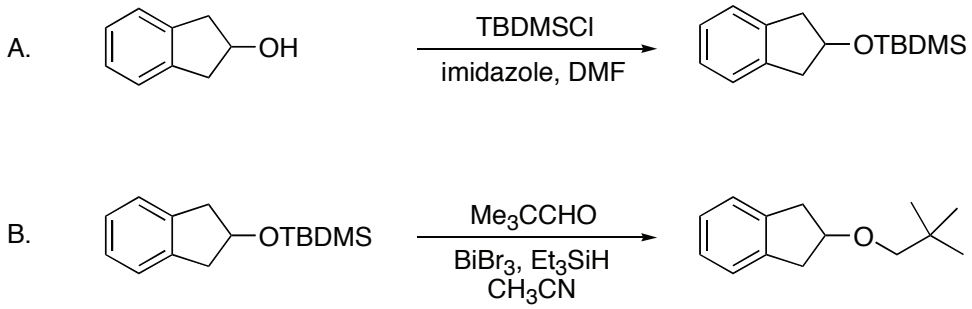
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.083.0155
Organic Syntheses, Vol. 83, p. 155-161 (2006); Coll. Vol. 11, p. 46-51 (2009).

2-(2′,2′-DIMETHYLPROPOXY)-2,3-DIHYDRO-1*H*-INDENE



Submitted by Joginder S. Bajwa,[1] Kapa Prasad and Oljan Repič.
Checked by Sigrid Holle and Alois Fürstner.

1. Procedure

A. *2,3-Dihydro-2-tert-butyldimethysiloxy-1H-indene.* A flame-dried 500-mL, four-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a pressure-equalizing dropping funnel, a nitrogen inlet, an internal thermometer and a glass stopper is charged successively under nitrogen atmosphere with 2-indanol (13.42 g, 100 mmol), imidazole (8.17 g, 120 mmol) and 60 mL of dry *N,N*-dimethylformamide (DMF) (Note 1). The mixture is stirred until a clear solution has formed (Note 2). The flask is immersed in an ice bath and a solution of *tert*-butyldimethylsilyl chloride (16.32 g, 108 mmol) in 40 mL of dry DMF (Note 3) is added over a period of 10 min at such a rate that the reaction temperature remains below 10 °C. The ice-water bath is removed, the mixture is allowed to warm to ambient temperature and stirring is continued for 45 min (Note 4). Deionized water (150 mL) is added slowly via the dropping funnel, causing a slight exotherm (Note 5), followed by the addition of 100 mL of *n*-heptane. The resulting mixture is filtered through a pad of Celite (Note 6), the organic layer is separated, and the aqueous phase is extracted with 100 mL of *n*-heptane. The combined organic phases are washed with 100 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation (40 °C/10 mmHg). The crude product is purified by flash chromatography on 100 g of silica gel (Note 1) packed in a 4.5 x 38 cm column. Elution with *n*-heptane (650 mL) followed by 2% ethyl acetate in *n*-

heptane (about 1 L) provides 22.5 g (91 %) of 2,3-dihydro-2-*tert*-butyldimethysiloxy-1*H*-indene as a colorless oil (Notes 7, 8).

B. *2-(2,2-Dimethylpropoxy)-2,3-dihydro-1H-indene.* A 250-mL, flame-dried three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a distillation head attached to a Liebig condenser, a nitrogen inlet and an internal thermometer is charged under nitrogen with 2,3-dihydro-2-*tert*-butyldimethysiloxy-1*H*-indene (10.6 g, 42.66 mmol) and 75 mL of dry acetonitrile (Note 1). The flask is immersed in a preheated oil bath and the resulting solution is refluxed such that approximately 25 mL of the solvent is distilled off at atmospheric pressure (Note 9). The solution is allowed to reach ambient temperature and the distillation head is replaced by a glass stopper. Bismuth tribromide (1.32 g, 2.94 mmol) (Notes 1, 10) is added in one portion and stirring is continued for 10 min. The glass stopper is then replaced by a rubber septum. Triethylsilane (8.2 mL, 51.34 mmol) (Note 1) is added via syringe over 5 min causing the immediate formation of a black suspension. The mixture is cooled in an ice-water bath to 0–5 °C before trimethylacetaldehyde (5.1 mL, 46.96 mmol) (Note 1) is added via syringe at such a rate (Note 11) as to maintain the internal temperature below 15 °C. The ice-water bath is removed, the mixture is allowed to warm to ambient temperature over 30 min and stirring is continued for an additional 30 min. (Note 12). The mixture is filtered through a pad of Celite (Note 13) to remove the black precipitate. The filtrate is concentrated by rotary evaporation (40 °C/10 mmHg) to give a mixture of clear and orange oils. To this residue are added 100 mL of *n*-heptane and 40 g of silica gel (Notes 1, 14). The mixture is concentrated by rotary evaporation (40 °C/10 mmHg) to afford a free-flowing powder that is placed at the top of a column (4.5 x 38 cm) of 100 g of silica gel. The column is eluted with *n*-heptane (1 L) followed by 2% ethyl acetate in *n*-heptane (about 1.2 L) to give 7.51 g (86 %) of 2,3-dihydro-2-(2′,2′-dimethylethoxy)-1*H*-indene as a colorless oil (Notes 15, 16).

2. Notes

1. Triethylsilane, 2-indanol and trimethylacetaldehyde were purchased from Acros Organics and used as received. Imidazole, *tert*-butyldimethylsilyl chloride and bismuth tribromide were purchased from Aldrich Chemical Company, Inc. and used as received. Dimethylformamide (water content < 0.02%), acetonitrile (water content, 0.003%), ethyl acetate,

n-heptane and silica gel (200-425 mesh) were purchased from Fisher Scientific and were used as such. The checkers used DMF dried by distillation over CaH_2.

2. The dissolution of 2-indanol and imidazole in dimethylformamide is endothermic. The temperature of the solution changes from 22 °C to 12 °C over 5 min.

3. *tert*-Butyldimethylsilyl chloride was dissolved in DMF by heating the mixture in warm water bath (40 °C).

4. The progress of the reaction is monitored by TLC on silica gel (elution with 10% ethyl acetate in *n*-heptane; visualized with 254-nm UV lamp and phosphomolybdic acid). The product TBS ether has an $R_f = 0.81$ and the alcohol starting material an $R_f = 0.19$. TLC analysis indicates that the reaction is complete after stirring for 45 min at room temperature.

5. The temperature rises from 21 °C to 35 °C upon addition of water.

6. An orange-brown rag layer is formed at the interface of the phases and is removed by filtration through a pad of Celite (3.0 g in 4.5 cm diameter Büchner funnel) to facilitate separation of the layers.

7. The submitters reported a yield of 23.7 g (95%). The spectral data for 2,3-dihydro-2-*tert*-butyldimethylsiloxy-1*H*-indene are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 6 H), 0.89 (s, 9 H), 2.87 (dd, $J = 5.9$, 15.6 Hz, 2 H), 3.11 (dd, $J = 6.8$, 15.6 Hz, 2 H), 4.63–4.69 (m, 1 H), 7.11–7.18 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.7, 18.2, 25.9, 42.6, 73.9, 124.5, 126.4, 141.2. IR (neat): 2952, 2929, 2856, 1471, 1461, 1252, 1101, 1064, 987 cm^{-1}.

8. The product is > 96% pure as determined by GC analysis on a 0.53 mm i.d. x 30 m capillary column (DB-1) at 50-260 °C, heating increment 25 °C/min. Retention time is 7.4 min.

9. Partial distillation azeotropically removes traces of water.

10. Bismuth tribromide is hygroscopic and should be handled in a glove box. Use of wet $BiBr_3$ in this reaction significantly lowers the yield of the product.

11. The reaction is highly exothermic. However, the exotherm is easily controlled by external cooling and slow (10 min) addition of trimethylacetaldehyde.

12. The reaction is monitored by TLC on silica gel (2% ethyl acetate in *n*-heptane; product $R_f = 0.56$, TBS ether $R_f = 0.39$) and is complete after 30 min at room temperature.

13. Celite (3.0 g) is used on top of a filter paper in a 4.5 cm diameter Büchner funnel.

14. The evaporation of *n*-heptane removes any residual acetonitrile that causes poor separation of the product from the silicon by-products.

15. The spectral data for 2,3-dihydro-2-(2′,2′-dimethylethoxy)-1*H*-indene are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (s, 9 H), 2.95 (dd, J = 5.2, 16.0 Hz, 2 H), 3.13 (s, 2 H), 3.16 (dd, J = 6.8, 16.0 Hz, 2 H), 4.26–4.33 (m, 1 H), 7.13–7.16 (m, 2 H), 7.17-7.21 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.8, 32.0, 39.4, 79.6, 80.7, 124.6, 126.3, 141.2; IR (neat): 2952, 2866, 1480, 1362, 1110, 1091 cm^{-1}; Calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1516 ([M^+]).

16. The product is >99% pure as determined by GC analysis performed under the same conditions as described in Note 8. The retention time of the product is 6.7 min.

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

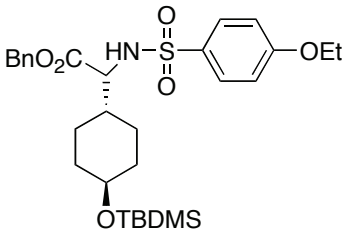
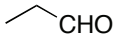
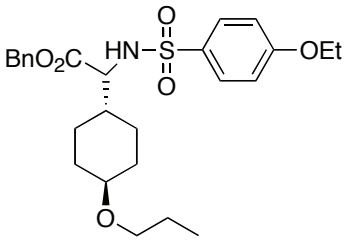
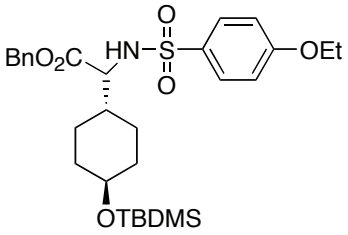
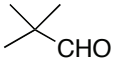
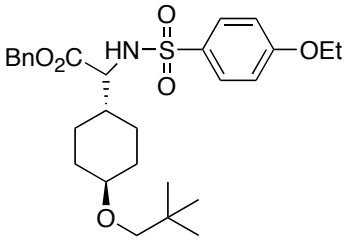
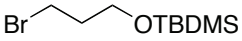
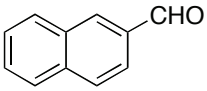
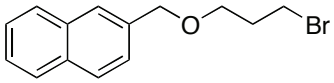
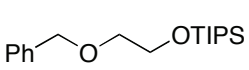
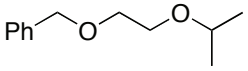
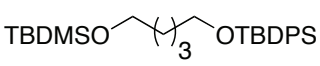
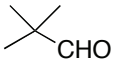
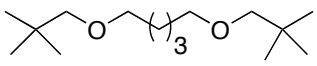
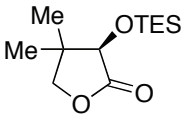
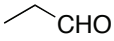
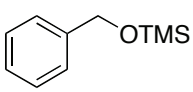
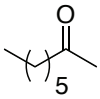
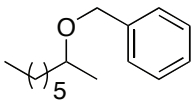
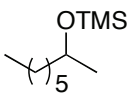
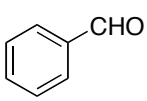
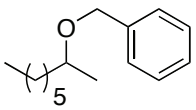
Ethers are usually prepared by the Williamson method whereby an alkoxy anion is reacted with an alkyl halide or sulfonate.[2] The presence of base-labile functionalities in the reactants and competing eliminations with the use of secondary and tertiary halides can limit the use of this method. Alternatively, ethers can be synthesized by triethylsilane-mediated reductive alkylation of carbonyl compounds catalyzed by various Lewis acids such as $TrClO_4$,[3] BF_3OEt,[4] TMSOTf,[5] and metal triflates.[6] As compared to these catalysts, bismuth tribromide was found to work more efficiently.[7]

The present method for the preparation of ethers is a variation of the procedure originally described by Komatsu,[7] who used only TMS ethers as the substrates. Since TMS ethers are hydrolytically rather labile, the reaction was successfully extended[8] to more stable silyl ethers such as triethylsilyl (TES), triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBDMS) ethers (Table 1). The reaction is very sensitive to moisture. Even a trace amount of water in the reaction mixture leads to a substantial amount of desilylated by-

product alcohol.[9] Therefore, it is necessary that the solvent and the reagents are rigorously anhydrous. The reaction is highly exothermic, however, the exotherm is easily controlled by slow addition of aldehyde and by external cooling. We believe that $BiBr_3$ by itself does not act as a Lewis acid. Instead, it reacts with Et_3SiH to generate elemental bismuth, hydrogen bromide and triethylsilylbromide.[8]

Overall, the procedure described above constitutes a general and effective method for the synthesis of dialkyl ethers. Its utility and scope are evident from the examples compiled in Table 1, some of which are not easily accessible by the classical Williamson's method.

Table 1. Transformation of Silyl Ethers into Dialkyl Ethers with $BiBr_3$ and Et_3SiH

Silyl Ether	Aldehyde or Ketone	Product	Yield (%)
			88[a]
			92[a]
			81[a]
			85[a]
			45[a]
		No Reaction	0[a]
			96[b]
			88[b]

[a] Reference 8; [b] Reference 7.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

1*H*-indene, 2-(2,2-dimethylpropoxy)-2,3-dihydro-2-Indanol: 1*H*-Inden-2-ol, 2,3-dihydro-; (4254-29-9)

Silane, [(2,3-dihydro-1*H*-inden-2-yl)oxy](1,1-dimethylethyl)dimethyl-; (216884-03-6)

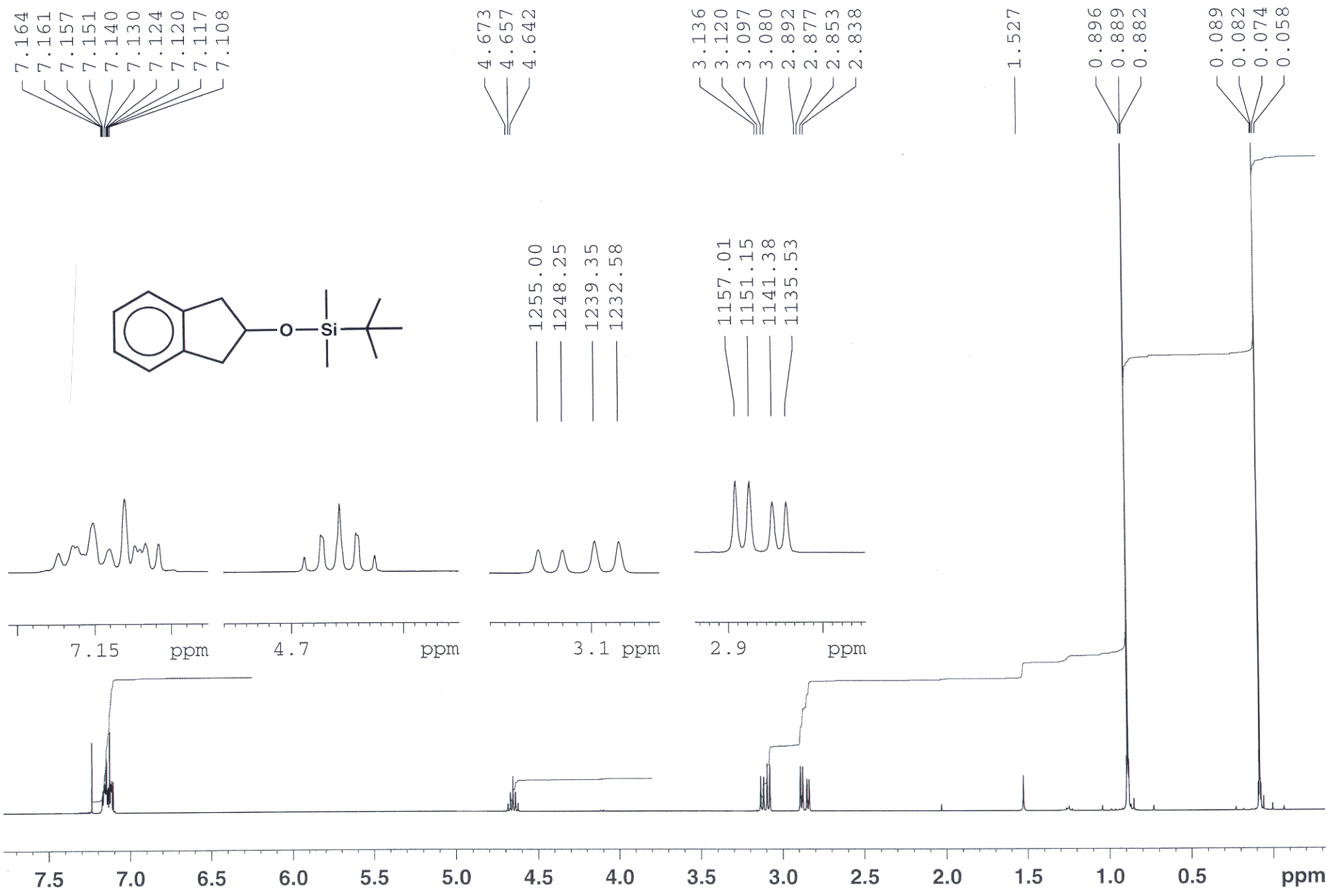
Imidazole: 4*H*-Imidazole; (288-32-4)

tert-Butyldimethylsilyl chloride: Silane, chloro(1,1-dimethylethyl)-dimethyl-; (18162-48-6)

Bismuth bromide: Bismuthine, tribromo-; (7787-58-8)

Triethylsilane: (617-86-7)

Trimethylacetaldehyde: Propanal, 2,2-dimethyl-; (630-19-3)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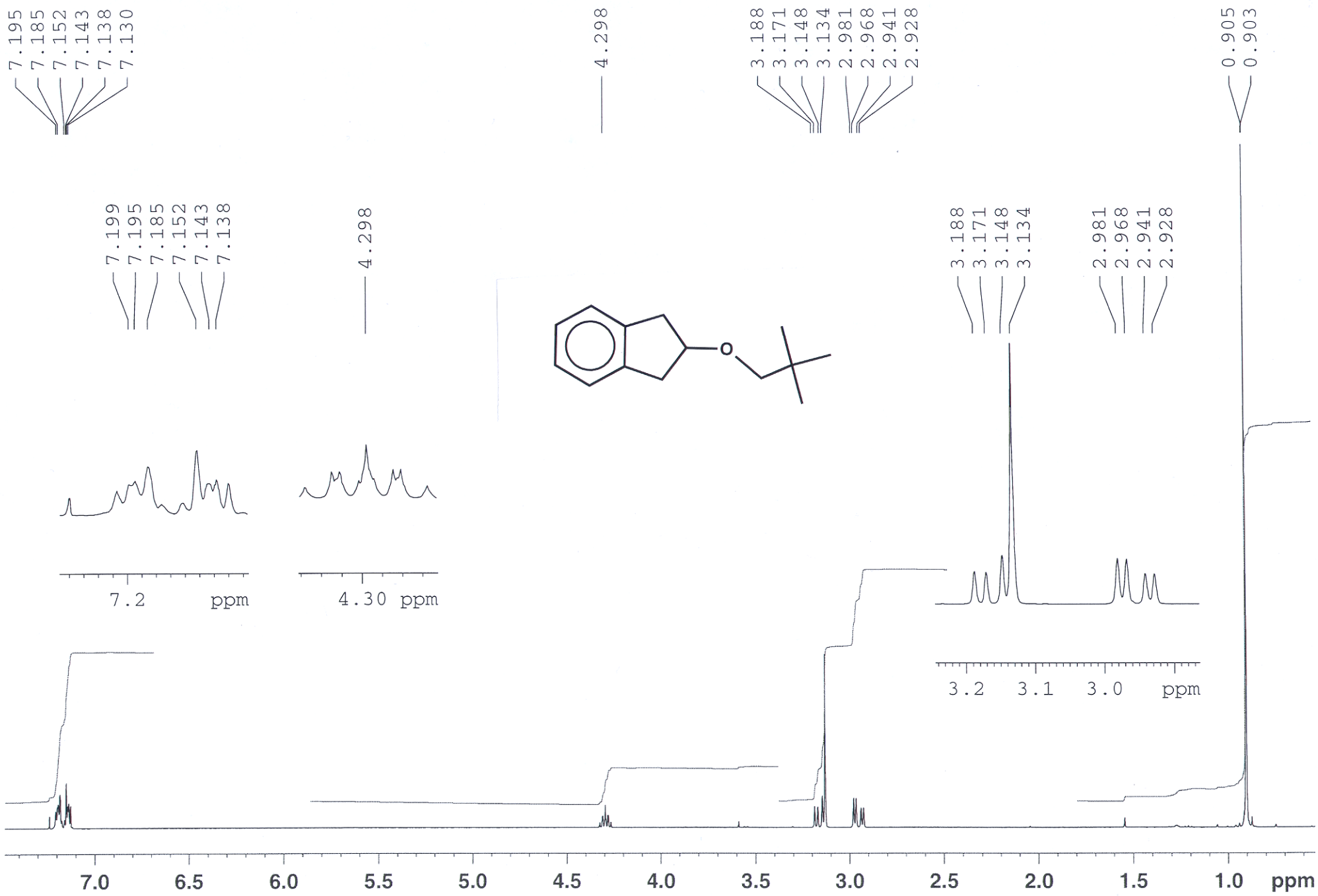
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