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Working with Hazardous Chemicals

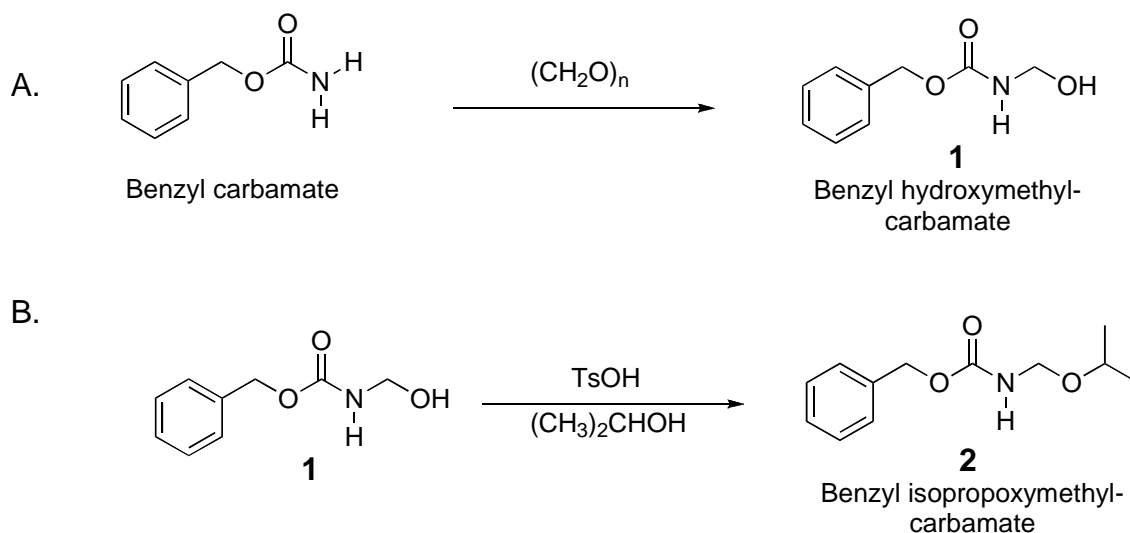
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

**BENZYL ISOPROPOXYMETHYL CARBAMATE – AN
AMINOMETHYLATING REAGENT FOR MANNICH REACTIONS
OF TITANIUM ENOLATES**



Submitted by Hartmut Meyer,¹ Albert K. Beck,² Radovan Sebesta,² and Dieter Seebach.²

Checked by Scott E. Denmark and Tyler W. Wilson.

1. Procedure

A. *Benzyl hydroxymethyl carbamate (1)*. A 500-mL, four-necked, round-bottomed flask, fitted with a thermocouple, a reflux condenser, an adapter with a nitrogen inlet and an overhead mechanical stirrer (Note 1) is charged with benzyl carbamate (24.2 g, 0.16 mol) (Note 2) and dist. water (120 mL). Aqueous formaldehyde solution (37% in water, 30 mL, *ca.* 0.4 mol) (Note 3) and anhydrous potassium carbonate (0.44 g, 3.2 mmol) are added with stirring (400 rpm) at room temperature. The flask is then immersed into an oil bath, preheated to 65 °C, and the mixture is vigorously stirred until complete reaction has taken place (Note 4). The reaction flask is then transferred into an ice-water bath and vigorous stirring is continued until the product precipitates. After 2 h, water (120 mL) and anhydrous potassium carbonate (0.44 g, 3.2 mmol) are added, and the resulting mixture

is stirred (600 rpm) at room temperature for 24 h until all of the product precipitates (Note 5). The solids are collected by suction filtration through a porcelain Büchner funnel (100 mm, Whatman #1, 90 mm), then are washed carefully with water (120 mL) and dried, first over night in air, then under vacuum (100 mmHg) at room temperature, to afford 20.1 g (69%) of **1**. This product is used without further purification (Note 6) in the next step.

B. Benzyl isopropoxymethyl carbamate (2). A 1-L, single-necked, round-bottomed flask fitted with a stir bar and nitrogen inlet is charged with benzyl hydroxymethyl carbamate (**1**) (19.6 g, 108 mmol), *tert*-butyl methyl ether (TBME, 200 mL) and isopropyl alcohol (50 mL). Next, *p*-toluenesulfonic acid hydrate (200 mg) (Note 7) is added to the solution and stirring is continued at room temperature for 24 h (Notes 8 and 9). Sodium hydrogen carbonate (2.0 g) and anhydrous magnesium sulfate (12 g) are added, and stirring is continued for another 2 h to remove the acid and the water formed. After removal of the solids by filtration through a glass-sintered Büchner funnel (45 mm, coarse) and washing the residue with TBME (50 mL), most of the solvent is removed from the filtrate under reduced pressure (Note 10). The crude product is purified by chromatographic filtration (Note 11) to give 23.5 g (97%) of **2** as a colorless solid (Notes 12 and 13).

2. Notes

1. The submitters reported using a 45 g rugby-ball-shaped stir bar. However, more reproducible results were found by employing a mechanical stirrer (7.6 cm Teflon paddle).

2. Benzyl carbamate is commercially available (Fluka Chemie AG) or can be easily prepared by modification of a literature procedure:³ A 2-L, three-necked round-bottomed flask fitted with an overhead stirrer, dropping funnel and a reflux condenser with a gas adapter is charged with *conc.* aqueous ammonium hydroxide solution (1 L). Under ice-bath cooling benzyl chlorocarbonate (200 mL, 1.42 mol) is added over a period of 30 min. Stirring is continued for 2 h, after which the precipitated product is filtered off, then is washed carefully with water (2 L) and dried in air for two days. The crude product thus obtained is dissolved, under slight warming, in ethyl acetate (600 mL). Anhydrous magnesium sulfate is added for drying, then is filtered off and part of the solvent (*ca.* 400 mL) is evaporated until

precipitation ensues. Hexane (600 mL) is added to complete the precipitation, the solids are isolated to give 180.5 g (84%) benzyl carbamate. Checkers obtained benzyl carbamate from Sigma-Aldrich (99%) and it was used as received.

3. Aqueous formaldehyde solution (37 wt. % solution in water, ACS-grade) was obtained from Sigma-Aldrich and was used as received. The submitters used aqueous formaldehyde solution (36.5% stabilized with 10% methanol) obtained from Fluka Chemie AG.

4. At the beginning of the reaction the solid ester floats on the surface. After ca. 10 min, the mixture reaches a temperature of 45 °C, whereupon the solid material melts and the reaction begins. After 20 min, the internal temperature is 58 °C, and almost complete conversion occurs, as indicated by TLC. Benzyl carbamate $R_f = 0.28$, **1**, $R_f = 0.1$ (silica gel, hexane/ethyl acetate, 3:2).

5. This protracted stirring is needed to cleave water soluble multi-addition products of formaldehyde. The yield of **1** increases from 45% (without this step) up to about 65%. The checkers noted that without mechanical stirring during this step a yield of 55% was typically obtained.

6. Higher purity product can be obtained by recrystallization: 56.0 g of compound **1** are dissolved, with warming, in 60 mL of ethyl acetate; 220 mL of hexane are added in portions. After being cooled to 5 °C (refrigerator), the product **1** is collected and washed with an ice-cold solution of hexane/ethyl acetate, 2:1 to give 50.2 g (90%) of **1**. (Products containing up to 15% starting material from incomplete reaction may be effectively purified by adding only half the volume of hexane relative to the used ethyl acetate.) The checkers obtained an analytically pure sample by recrystallizing 1.0 g of **1** from 15 mL of hot *tert*-butyl methyl ether (TBME). Filtration and washing with cold TBME afforded 0.56 g of **1** as white needles (56% recovery). mp 87.5-88.5 °C; ^1H NMR (500 MHz, CDCl_3 , 70 mM) δ : 7.38-7.31 (m, 5 H), 5.9 (br s, 0.1 H) and 5.75 (br s, 0.8 H), 5.13 (s, 2H), 4.72 (br d, $J = 6.6$ Hz), 3.16 (br s, 0.7 H) and 2.63 (br d, 0.05 H) equilibrium mixture of rotamers. ^{13}C NMR (125 MHz, CDCl_3 , 470 mM) rotamers observed, δ for major rotamer: 156.8, 135.9, 128.5, 128.2, 128.0, 68.8, 67.0; minor signals observed δ : 66.9 and 65.9. IR (KBr) cm^{-1} : 3350, 3033, 2956, 2899, 1698, 1524, 1458, 1294, 1230, 1138, 1082, 1041, 973, 906, 747, 697; HRMS (ESI) m/z : calcd. for $\text{C}_9\text{H}_{11}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, 204.0637; found $[\text{M}+\text{Na}]^+$, 204.0636. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.91; H, 6.32; N, 7.81.

7. Isopropyl alcohol (99.5%, ACS reagent), *tert*-butyl methyl ether (99%, ACS reagent), *p*-Toluenesulfonic acid monohydrate (98.5%, Reagent plus[®]) and sodium bicarbonate (99.7%, ACS reagent) were obtained from Sigma-Aldrich. Magnesium sulfate (certified anhydrous) was obtained from Fisher.

8. The reaction progress was monitored by TLC: **2**, $R_f = 0.40$ (silica gel, hexane/ethyl acetate, 3:2)

9. If the reaction is not complete at this point, more *p*-toluenesulfonic acid hydrate (100 mg) is added and stirring at room temperature is continued for 24 h.

10. Rotary evaporation at 45 °C and 20 mmHg. The checkers noted that after removing ca. 85% of the solvent the product would precipitate. Redissolution prior to chromatography was then achieved by adding 10 mL of dichloromethane and heating the mixture to 40 °C.

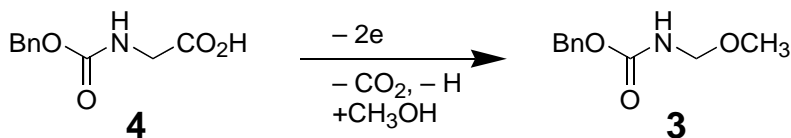
11. A chromatography column (6 cm diameter) is prepared with a 6 cm high bed of silica gel (ca. 100 g) packed with TBME. The crude product is placed on the column as a concentrated solution in TBME (ca. 25 mL) and is eluted with the same solvent (1000 mL in 25-mL fractions). The product-containing fractions are combined, evaporated and dried under vacuum (100 mm Hg) at room temperature. An analytical sample was obtained after drying 0.5 g the product in an Abderhalden at 55 °C at 100 mmHg for 12 h.

12. The product has the following physicochemical properties: mp 71.5-72.0 °C; ¹H NMR (500 MHz, CDCl₃) δ: 7.36-7.32 (m, 5 H), 5.51 (br s, 0.9 H) and 5.35 (br s, 0.1 H), 5.18 (br s, 0.2 H) and 5.13 (s, 1.8 H), 4.70 (d, $J = 7$ Hz, 1.8 H) and 4.63 (br s, 0.2 H), 3.8 (sept, $J = 6.1$ Hz, 0.9 Hz) and 3.7 (br s, 0.2 H), 1.17 (d, $J = 6.1$ Hz, 5.6 H) and 1.12 (br s, 0.8 H) equilibrium mixture of rotamers; ¹³C NMR (125 MHz, CDCl₃) δ: 156.3, 136.2, 128.5, 128.2, 128.1, 70.1, 69.0, 66.9 22.3; IR (KBr) cm⁻¹: 3331 (br), 3066, 3028, 2967, 2926, 1718, 1522, 1458, 1374, 1312, 1240, 1176, 1126, 1096, 1042, 993 958, 754, 696; HRMS (ESI) m/z : calcd. for C₁₂H₁₇NO₃Na [M+Na]⁺, 246.1106; found {M+Na}⁺, 246.1100. Anal. Calcd. for C₁₂H₁₇NO₃: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.56; H, 7.86; N, 6.37.

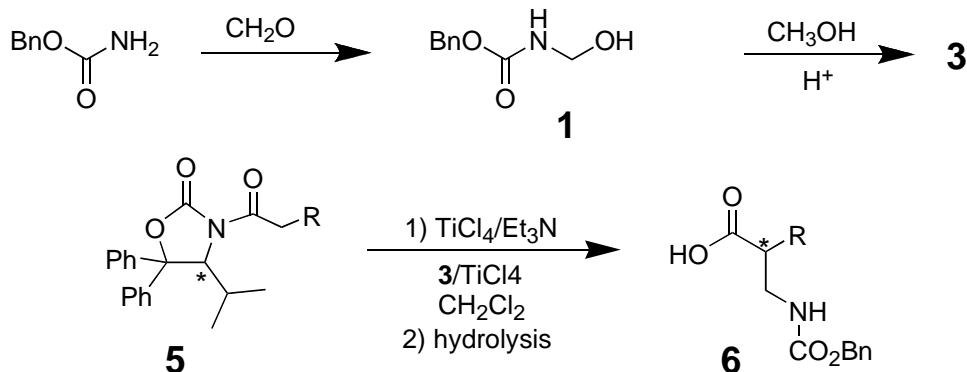
13. In contrast to the analogous, oily, methoxy-derivative **3** (see Discussion),⁴ the product **2** can be stored at room temperature for months without decomposition.

3. Discussion

Benzyl methoxy-carbamate (**3**) was first prepared in 1951 by oxidative electrochemical decarboxylation (Hofer-Moest-electrolysis) of *N*-benzyloxycarbonyl-glycine (**4**) in methanol,^{5,6} a method which is also applicable to other amino acid derivatives⁷⁻¹¹ and to peptides.^{8,11-13}



The use of carbamate **3** as a carbamidomethylating reagent for titanium enolates (Mannich reaction) was reported 46 years later.⁴ The authors of this report have prepared compound **3** by an alternative method, similar to that described herein: reaction of benzyl carbamate with formaldehyde to give the *N*-hydroxymethyl derivative **1** and acid-catalyzed methanolysis. Reagent **3** was employed extensively for the enantioselective preparation of β^2 -amino-acids¹⁴ of type **6**, using the titanium enolates of *N*-acyl-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one (**5**, DIOZ derivatives)¹⁵ as nucleophiles¹⁶⁻¹⁹ (*cf.* accompanying procedure).



The isopropoxy derivative **2** had not been reported before. This derivative has the practical advantage of being solid and stable on storage under exclusion of moisture at room temperature, whereas the methoxy derivative **3** is an oil and has to be stored in a deep freezer (-15 °C). Other preparative advantages of **2** over **3** are described in the accompanying procedure employing the benzyl isopropoxymethyl carbamate.

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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Benzyl hydroxymethyl carbamate: Carbamic acid, (hydroxymethyl)-, phenylmethyl ester; (31037-42-0)

Benzyl carbamate: Carbamic acid, phenylmethyl ester; (621-84-1)

Aqueous formaldehyde solution; (50-00-0)

Potassium carbonate; (584-08-7)

p-Toluenesulfonic acid: Benzenesulfonic acid, 4-methyl-; (104-15-4)



Dieter Seebach received his Ph.D. from the Technische Hochschule Karlsruhe, Germany, with Rudolf Criegee. After a postdoctoral stay in Elias J. Corey's group and a lectureship at Harvard University, he returned to the University of Karlsruhe and became a full Professor of Organic Chemistry at the Justus-Liebig-Universität in Giessen, Germany, in 1971. From 1977-2003 he was Professor of Chemistry at the Eidgenössische Technische Hochschule (ETH) in Zürich. Since 2003 he is officially retired; as Professor Emeritus he continues doing research with postdoctoral coworkers. His research activities include: development of new synthetic methods, natural-product synthesis, structure determination, chiral dendrimers, the biopolymer PHB, β -peptides. The results have been described in over 800 research papers.



Hartmut H. Meyer graduated in 1970 from the Technische Hochschule Hannover (Germany) under the supervision of W. Theilacker and F. Klages. After postdoctoral work with Professor D. Seebach at the University of Giessen in 1972, he returned to the University of Hannover and started work on syntheses of enantiopure natural products. In 1987 he became Privatdozent with a Habilitation on studies of the benzidine rearrangement. Since 1996 he has been a Professor at the Leibniz Universität Hannover. His current research interests are synthetic methodology, chemo-enzymatic syntheses and biochemical studies, in cooperation with other research groups.



Albert Karl Beck was born in 1947 in Karlsruhe (Germany), completing a chemistry technician's apprenticeship at the University of Karlsruhe in 1966, and joined the Seebach research group in 1968. Between 1969 and 1972 he continued his education, obtaining official certification as a chemical technician at the Fachschule für Chemotechnik in Karlsruhe. In 1971 he joined the Institute for Organic Chemistry at the University of Giessen, and in 1974 he engaged in a six-month research visit to the California Institute of Technology in Pasadena (USA). He has been an active part of the Laboratory for Organic Chemistry at the ETH in Zürich since 1977. During his association with the Seebach research group he has participated in essentially all of the group's research themes, as evidenced by his coauthorship of more than 80 publications.



Radovan Šebesta was born in 1975 in Myjava, Slovakia. He completed his undergraduate studies at the Comenius University in Bratislava where he also obtained Ph.D. with Prof. Sališová in 2002. Then he worked with Prof. Seebach at the ETH Zürich as a postdoctoral coworker (synthesis of β -aminoacids and peptides) and with Prof. Feringa in Groningen (asymmetric catalysis using phosphoramidites). In 2005 he moved back to Comenius University in Bratislava where he is currently Associate Professor at the Department of Organic Chemistry, working on asymmetric catalysis using ferrocene ligands.



Tyler W. Wilson was born in 1976 in Sacramento, California. After graduating high school, he headed to Portland, Oregon where he worked in carpentry and studied soft-glass blowing at the Pacific Northwest College of Arts. In 1999, he began undergraduate studies at Boise State University in chemistry where he studied the synthesis of conducting polymers. After obtaining a B.S. in chemistry in 2004 he moved to the University of Illinois at Urbana-Champaign and started his graduate education in the laboratories of Scott E. Denmark. His current research is focused on the asymmetric construction of quarternary carbons through the Lewis base catalyzed addition reactions of silyl ketene imines.

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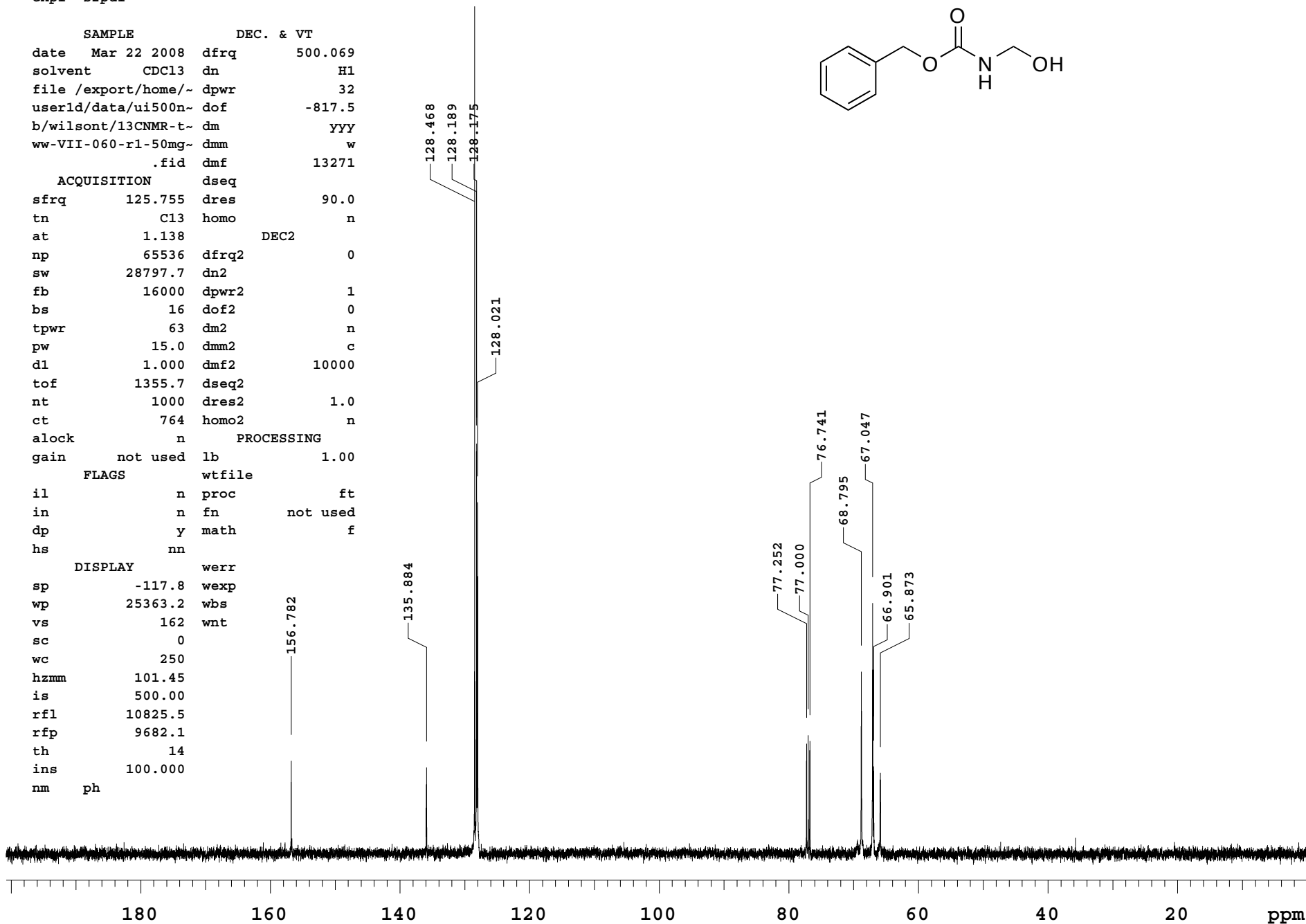
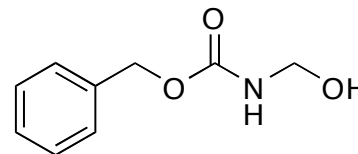
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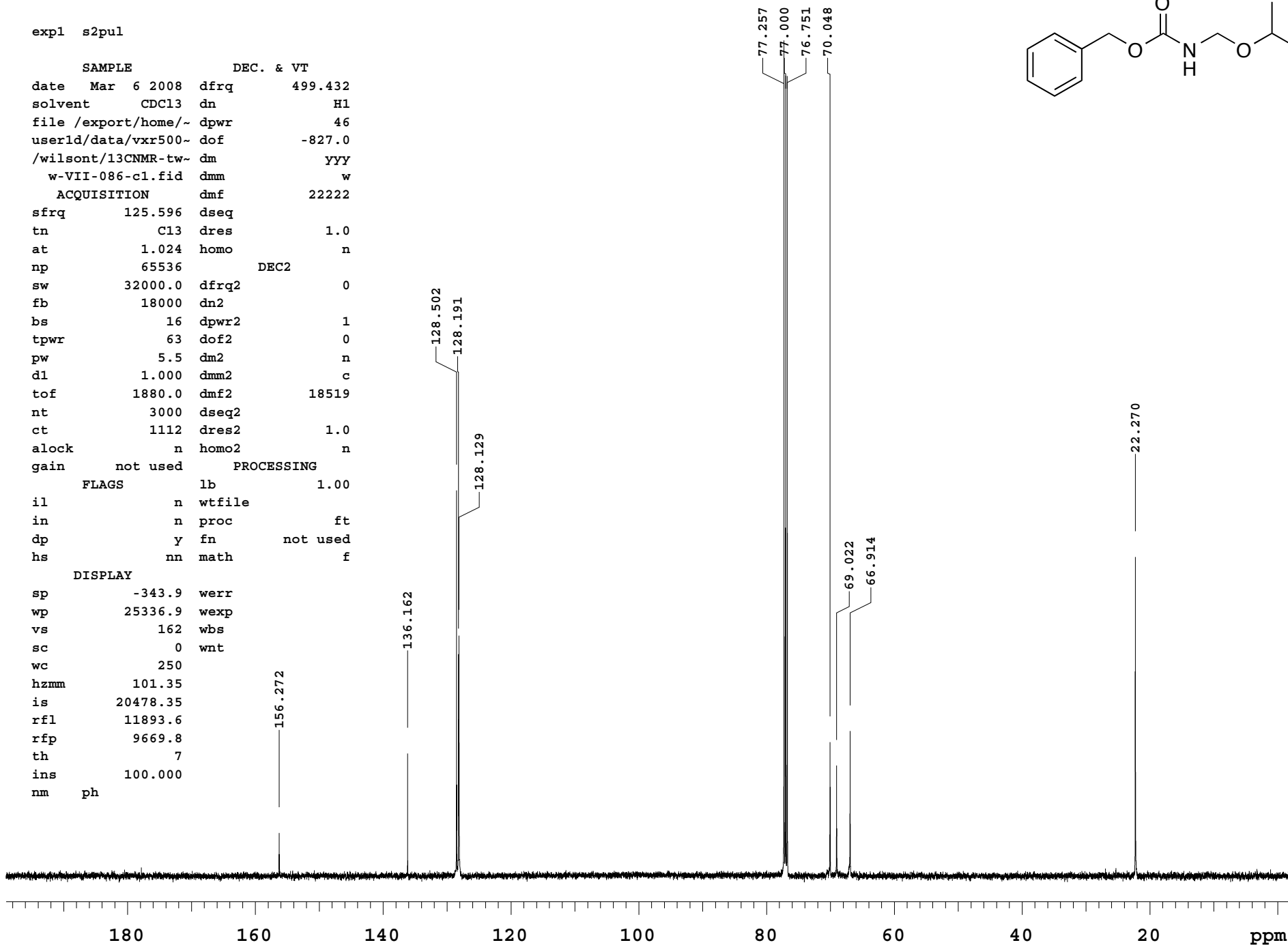
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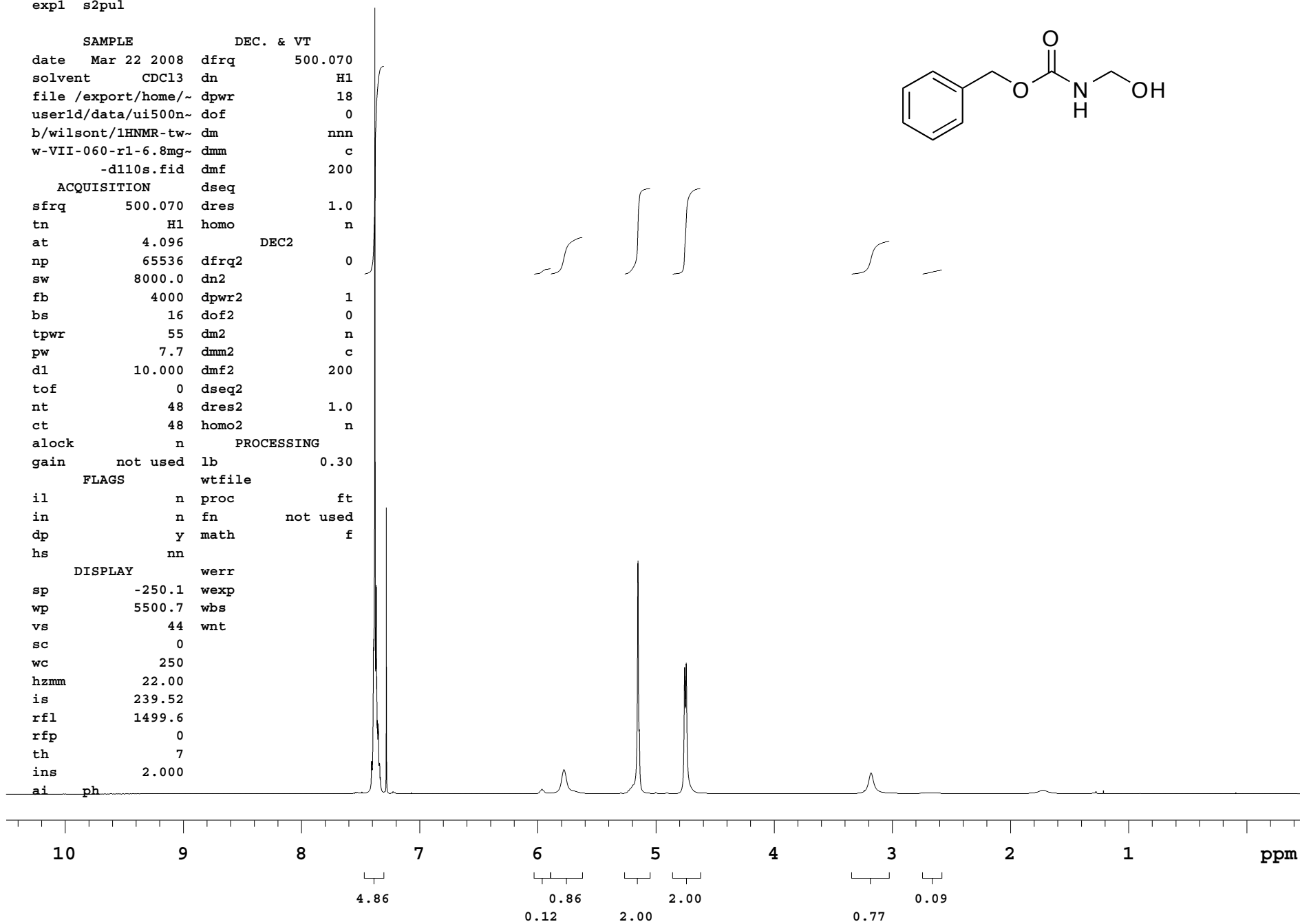
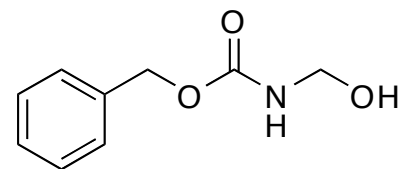
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