



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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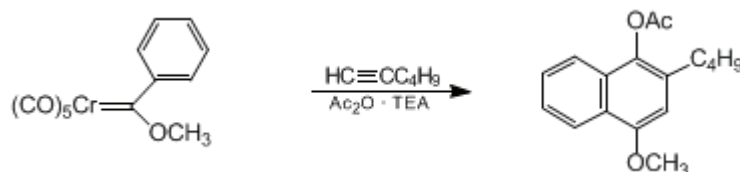
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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SYNTHESIS OF 2-SUBSTITUTED NAPHTHALENEDIOL DERIVATIVES USING CHROMIUM CARBENE COMPLEXES: 1- ACETOXY-2-BUTYL-4-METHOXYNAPHTHALENE

[1-Naphthalenol, 2-butyl-4-methoxy-, acetate]



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1. Procedure

Caution! All operations should be conducted in a well-ventilated hood with breathing protection. The chromium carbene complex generally is contaminated with the very volatile and toxic chromium hexacarbonyl, which is also generated as a by-product of the reaction.

An oven-dried, 2-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet, magnetic stirring bar, thermometer, and reflux condenser, under an inert nitrogen atmosphere (Note 1), is charged with 1.22 g (10 mmol) of 4-dimethylaminopyridine (Note 2), 500 mL of tetrahydrofuran (Note 3), 11.0 mL (95.7 mmol) of 1-hexyne (Note 4), 13.2 mL (140 mmol) of acetic anhydride (Note 5), 9.8 mL (70 mmol) of triethylamine (Note 2), 20.0 g (64.0 mmol) of pentacarbonyl[phenyl(methoxy)chromium] carbene (Note 1) and (Note 6), and a final 100-mL rinse of tetrahydrofuran. The solution is heated to reflux with an oil bath and heating is maintained until TLC indicates that the chromium complex is totally consumed (about 45–60 min, (Note 7)). The solution is then cooled to ambient temperature, 30 g of silica gel is added (Note 8), and volatile organic material is removed under reduced pressure (rotary evaporator). The green solids are transferred to a filter funnel and washed with hexane until TLC indicates that all products have been removed (5×100 mL) (Note 9). The hexane filtrate is then concentrated under reduced pressure to give crude product contaminated with chromium hexacarbonyl. To the mixture is added 20 mL of isopropyl alcohol and the insoluble chromium hexacarbonyl is removed by filtration (Note 9). The filtrate is concentrated under reduced pressure to give 14.0 g of crude product which is purified by silica gel chromatography (Note 10). Appropriate fractions are combined and the solvent is removed under reduced pressure to give 1-acetoxy-2-butyl-4-methoxynaphthalene (11.8 g, >95% pure based on HPLC, 68% yield based on the carbene complex, (Note 6) and (Note 11)) as a light yellow oil which crystallizes on standing (Note 12). If desired, the product can be crystallized from isopropyl alcohol (2.5 mL/g) to give white crystals, mp 49–50°C (>99% pure based on HPLC).

2. Notes

1. Although slowly decomposed by exposure to air (oxygen), the chromium carbene complex is sufficiently stable to handle using ordinary nitrogen drybox techniques. The complex should be stored at refrigerator temperature. All solvents and liquid reagents were routinely deoxygenated prior to use with a slow stream of nitrogen.
2. 4-Dimethylaminopyridine and triethylamine were obtained from the Aldrich Chemical Company, Inc., and used without further purification. If 4-dimethylaminopyridine is omitted, the level of impurities rises.²
3. Tetrahydrofuran, UV grade, was obtained from Burdick and Jackson or Mallinkrodt Inc. and used

after distillation from calcium hydride.

4. 1-Hexyne was obtained from Farchan Chemical Company or Aldrich Chemical Company, Inc., and used without further purification.

5. Acetic anhydride was obtained from Mallinckrodt Inc. or Aldrich Chemical Company, Inc., and used without further purification.

6. Pentacarbonyl[phenyl(methoxy)carbene]chromium was prepared by the checkers in 75% yield according to the literature: Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth., Coll. Vol. VIII* **1993**, 216. This material was stored under nitrogen at -30°C and purified immediately prior to use by filtration through a plug of Celite (hexane solvent). If the chromium carbene is purchased from Aldrich Chemical Company, Inc., the submitters found it was only 65% pure based on capillary GLC analysis.

7. Analytical thin layer chromatography (TLC) was conducted on 10×2.5 -cm precoated glass plates (silica gel GF, 0.25-mm thickness, Analtech), eluted with 10% ethyl acetate in hexane, and visualized with both UV (254 nm) and aqueous 50% sulfuric acid spray/heating. The carbene complex moves as an orange spot on TLC; the reaction is complete when this spot is no longer visible.

8. The chromium complex degrades into chromium hexacarbonyl and an intractable green chromium tar. The addition of silica gel prior to solvent removal adsorbs this material before it can form a tar.

9. The solid material containing chromium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to approved procedures

10. Silica gel (obtained from E. Merck or Alfa Products, Morton/Thiokol Inc.) was used (420 g, 70–230 mesh) in a 5.5×60 -cm column eluted with 10% ethyl acetate in hexane.

11. This reaction has been performed on a scale up to 20 times larger by the submitters (400 g of chromium carbene complex) with identical results.

12. The NMR spectrum was as follows: ^{13}C NMR (75 MHz, CDCl_3) δ : 17.3, 20.2, 23.1, 31.4, 67.4, 127.1, 127.2, 127.9, 128.2, 128.3, 128.6, 128.7, 130.1, 130.3, 141.2, 172.0, 216.1.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. (See (Note 9)).

3. Discussion

The regioselective preparation of 2-substituted naphthalenediol derivatives having the diols differentially protected in a predictable and straightforward manner, previously not directly attainable, is readily accomplished using chromium carbene complexes. First prepared by E. O. Fischer, chromium carbene complexes react readily with alkynes (extensively investigated by K. H. Dötz, and others).³ Steric effects dictate the substitution pattern observed^{2,4} and the reaction mechanism has been widely studied.²

The title compound (U-66,858) and analogues are of interest as lipoxygenase inhibitors with potential application to the treatment of asthma and related disorders.

References and Notes

1. The Upjohn Company, Kalamazoo, MI 49001.
 2. Yamashita, A.; Timko, J. M.; Watt, W. *Tetrahedron Lett.* **1988**, 29, 2513, and references therein.
 3. For a recent review, see Dötz, K. H. *Pure Appl. Chem.* **1983**, 55, 1689.
 4. Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, 103, 7677; Wulff, W. D.; Chan, K.-S.; Tang, P.-C.; *J. Org. Chem.* **1984**, 49, 2293; Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, 27, 3471; and references therein.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

30 g of silica gel

Pentacarbonyl[phenyl(methoxy)carbene]chromium

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

acetic anhydride (108-24-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

isopropyl alcohol (67-63-0)

carbene (2465-56-7)

chromium (7440-47-3)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-Hexyne (693-02-7)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

4-dimethylaminopyridine (1122-58-3)

chromium hexacarbonyl (13007-92-6)

chromium carbene

1-Acetoxy-2-butyl-4-methoxynaphthalene,
1-Naphthalenol, 2-butyl-4-methoxy-, acetate (99107-52-5)

pentacarbonyl[phenyl(methoxy)chromium]carbene