A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

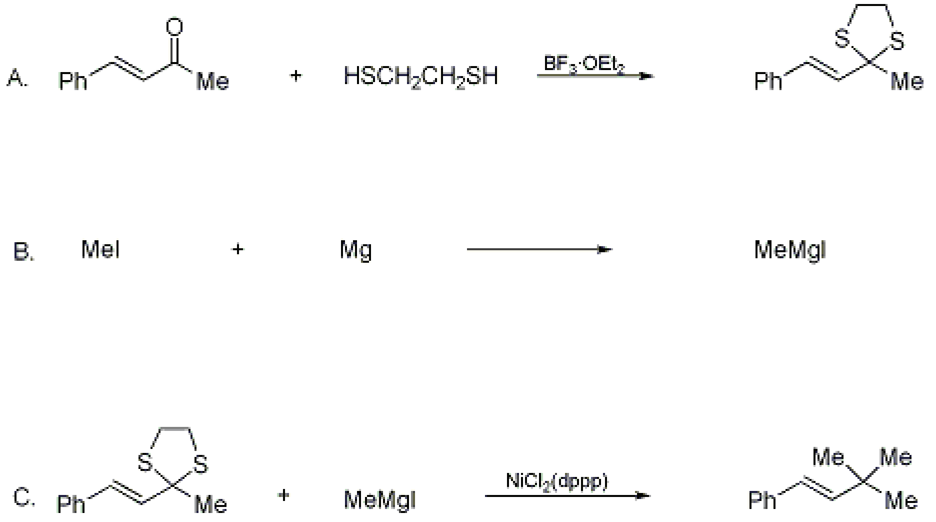
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.074.0187

Organic Syntheses, Coll. Vol. 9, p.649 (1998); Vol. 74, p.187 (1997).

NICKEL-CATALYZED, GEMINAL DIMETHYLATION OF ALLYLIC DITHIOACETALS: (E)-1-PHENYL-3,3-DIMETHYL-1-BUTENE

[Benzene, (3,3-dimethyl-1-butenyl)- (E)-]



Submitted by Tien-Min Yuan and Tien-Yau Luh[1].
Checked by Yugang Liu and Robert K. Boeckman, Jr..

1. Procedure

CAUTION! 1,2-Ethanedithiol has a powerful stench. Steps A and C should be performed in a well-ventilated hood.

A. *(E)-2-Methyl-2-(2-phenylethenyl)-1,3-dithiolane*. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 29.2 g (0.2 mol) of (E)-4-phenyl-3-buten-2-one (Note 1) and 20.7 g (0.22 mol) of 1,2-ethanedithiol in 200 mL of methanol. To the stirred solution is added 11 mL (12.4 g, 0.087 mol) of boron trifluoride etherate. The mixture is stirred at room temperature for 45 min. To the mixture is added 50 mL of aqueous 10% sodium hydroxide, and the methanol is removed under reduced pressure. Dichloromethane (300 mL) is introduced and the solution is washed with aqueous 10% sodium hydroxide solution (2 × 100 mL). The aqueous layer is extracted with dichloromethane (3 × 200 mL). The combined organic layers are washed with 200 mL of water, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed under reduced pressure and the residue is fractionally distilled to give 24.9–27.1 g (56–61%) of (E)-2-methyl-2-(2-phenylethenyl)-1,3-dithiolane (Note 2) and (Note 3) as a yellowish liquid, bp 109–112°C (0.16 mm), that solidifies on standing, mp 52–53°C.

B. *Methylmagnesium iodide*. A 500-mL, three-necked, round-bottomed flask containing 9.7 g (0.4 g-atom) of magnesium turnings is equipped with a rubber septum, reflux condenser, an addition funnel, and a magnetic stirring bar. The system is flame-dried and flushed with nitrogen. Anhydrous ether (20 mL, (Note 4)) is introduced to cover the magnesium. As the contents of the flask are stirred, iodomethane (56.7 g, 0.4 mol) in 180 mL of anhydrous ether is added dropwise through the addition funnel. The addition requires about 2 hr; the mixture is then stirred for an additional 30 min.

C. *(E)-1-Phenyl-3,3-dimethyl-1-butene*. In a 1-L, two-necked, round-bottomed flask fitted with a reflux condenser, rubber septum, and a magnetic stirring bar are placed 17.8 g (0.08 mol) of 2-methyl-2-

(2-phenylethenyl)-1,3-dithiolane and 2.17 g (0.004 mol) of [1,3-bis(diphenylphosphino)propane] nickel(II) chloride [$NiCl_2$(dppp)] (Note 5). The flask is evacuated and flushed with nitrogen three times. To the above mixture is added 300 mL of anhydrous tetrahydrofuran (Note 6). The ether solution of methylmagnesium iodide prepared in Step B is introduced with a double-ended needle in one portion (Note 7). The mixture is heated under reflux for 24 hr, cooled to room temperature, and treated with 200 mL of saturated ammonium chloride solution. The organic layer is separated and the aqueous layer is extracted with ether (3 × 200-mL). The combined organic layers are washed twice with aqueous 10% sodium hydroxide solution (100 mL) and with brine (100 mL). The organic solution is dried over anhydrous magnesium sulfate. The solvent is removed under reduced pressure and the residue is filtered through a short column packed with 30 g of silica gel (Note 8) and flushed under a positive nitrogen pressure with 350 mL of hexane. After the solvent is evaporated under reduced pressure, the yellowish residue is distilled through a spinning band (Note 9) to give 10.4 g (81%) of (E)-1-phenyl-3,3-dimethyl-1-butene (Note 10) as a colorless liquid, bp 91–93°C/30 mm.

2. Notes

1. (E)-4-Phenyl-3-buten-2-one was purchased from Division of Janssen Pharmaceutica and used directly.
2. A 6-cm Vigreux column was employed for fractional distillation.
3. The spectral properties of the (E)-2-methyl-2-(2-phenylethenyl)-1,3-dithiolane are as follows: IR (neat) cm^{-1}: 3025, 2922, 1637, 1600, 1494, 1446, 1275, 1065, 964, 754, 692; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.01 (s, 3 H), 3.33–3.46 (m, 4 H), 6.47 (d, 1 H, J = 15.5), 6.63 (d, 1 H, J = 15.5), 7.21–7.43 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 40.1, 65.4, 126.6, 127.0, 127.5, 128.4, 135.0, 136.4; MS m/e (rel) 222 (M^+, 100), 207 (17), 194 (59), 161 (44), 129 (45), 117 (39); HRMS calcd for $C_{12}H_{14}S_2$: 222.0537. Found 222.0546.
4. Ethyl ether is distilled from sodium-benzophenone ketyl before use.
5. [1,3-Bis(diphenylphosphino)propane]nickel(II) chloride was purchased from Aldrich Chemical Company, Inc., and used without further purification. The catalyst can also be prepared according to literature procedures.[2]
6. Tetrahydrofuran is distilled from sodium-benzophenone ketyl before use.
7. An excess of the Grignard reagent is required to maximize the yield; otherwise the reaction is incomplete.
8. Silica gel (230–400 mesh) was purchased from E. Merck Co.
9. A spinning band distillation setup is employed (800 Mirco Still, B/R Instrument Corporation, 3000 rpm, theoretical plates 23–26). The mixture was heated under reflux for 3 hr to reach equilibrium before distillation (reflux/distillation ratio = 5–10/1).
10. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3027, 2960, 1648, 1598, 1493, 1362, 1266, 968, 746, 693; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.16 (s, 9 H), 6.30 (d, 1 H, J = 16.2), 6.34 (d, 1 H, J = 16.2), 7.18–7.41 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 33.3, 124.6, 126.0, 126.7, 128.4, 138.1, 141.8; MS m/e (rel) 160 (M^+, 35), 145 (100), 117 (21), 105 (11), 103 (11), 91 (25), 77 (12); HRMS calcd for $C_{12}H_{16}$: 160.1252, Found 160.1250.

Waste Disposal Information

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

3. Discussion

Geminal dimethylation at a carbon center is useful in organic synthesis. Much effort has been devoted to the attachment of a tert-butyl group or a quaternary carbon center to olefinic carbon atom(s) in order to synthesize crowded olefins.[3] [4] [5] [6] [7] Although Tebbe-like reagents are effective for converting a carbonyl group into a gem-dimethyl substituent, their application to an allylic carbonyl substrate is limited by poor regioselectivity.[8,9,10,11,12,13] The present procedure is based on a series of reports on the nickel-catalyzed cross coupling reactions of dithioacetals with Grignard reagents.[14,15,16,17,18,19,20] α,β-Unsaturated aldehydes or ketones react as the dithioacetal in a polar solvent (such as tetrahydrofuran) or non-polar aromatic solvent (such as benzene or toluene) with methylmagnesium iodide in the presence of a catalytic amount $NiCl_2$ (dppp) or [1,2-bis(diphenylphosphino)ethane]nickel(II) chloride [$NiCl_2$ (dppe)], under a nitrogen atmosphere to give the corresponding geminal dimethylation products.[15,16,17] Substrates with structural variety react smoothly.[15,16,17] Allylic orthothioesters, on the other hand, give the corresponding trimethylation products with different regioselectivity.[16]

References and Notes

1. Department of Chemistry, National Taiwan University, Taipei, Taiwan 106, Republic of China.
2. Van Hecke, G. R.; Horrocks, W. DeW., Jr. *Inorg. Chem.* **1966**, *5*, 1960.
3. For examples: (a) Mulzer, J.; Lammer, O. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 628;
4. Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622;
5. Ager, D. J. *J. Chem. Soc., Perkin Trans. I* **1986**, 183;
6. Smegal, J. A.; Meier, I. K.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 1322;
7. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Ganboa, I.; Cossio, F. P.; Lecea, B.; López, C. *J. Org. Chem.* **1990**, *55*, 2498.
8. Posner, G. H.; Brunelle, D. J. *Tetrahedron Lett.* **1972**, 293.
9. Meisters, A.; Mole, T. *J. Chem. Soc., Chem. Commun.* **1972**, 595.
10. Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 900.
11. Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, C. S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733.
12. Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.
13. Reetz, M. T.; Westermann, J.; Kyung, S.-H. *Chem. Ber.* **1985**, *118*, 1150.
14. Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257.
15. Yang, P.-F.; Ni, Z.-J.; Luh, T.-Y. *J. Org. Chem.* **1989**, *54*, 2261.
16. Tzeng, Y.-L.; Yang, P.-F.; Mei, N.-W.; Yuan, T.-M.; Yu, C.-C.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 5289.
17. Yuan, T.-M.; Luh, T.-Y. *J. Org. Chem.* **1992**, *57*, 4550.
18. Ni, Z.-J.; Mei, N.-W.; Shi, X.; Tzeng, Y.-L.; Wang, M. C.; Luh, T.-Y. *J. Org. Chem.* **1991**, *56*, 4035 and references therein.
19. Ni, Z.-J.; Yang, P.-F.; Ng, D. K. P.; Tzeng, Y.-L.; Luh, T.-Y. *J. Am. Chem. Soc.* **1990**, *112*, 9356.
20. Yu, C.-C.; Ng, D. K. P.; Chen, B.-L.; Luh, T.-Y. *Organometallics* **1994**, 1487 and references therein.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

sodium-benzophenone ketyl

$NiCl_2$ (dppp)

Benzene (71-43-2)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

magnesium,
magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

toluene (108-88-3)

iodomethane (74-88-4)

methylmagnesium iodide (917-64-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

1,2-ethanedithiol (540-63-6)

(E)-4-phenyl-3-buten-2-one

(E)-1-Phenyl-3,3-dimethyl-1-butene,
Benzene, (3,3-dimethyl-1-butenyl)- (E)- (3846-66-0)

(E)-2-Methyl-2-(2-phenylethenyl)-1,3-dithiolane (107389-59-3)

2-methyl-2-(2-phenylethenyl)-1,3-dithiolane

[1,3-Bis(diphenylphosphino)propane]nickel(II) chloride (15629-92-2)

[1,2-bis(diphenylphosphino)ethane]nickel(II) chloride (15793-01-8)