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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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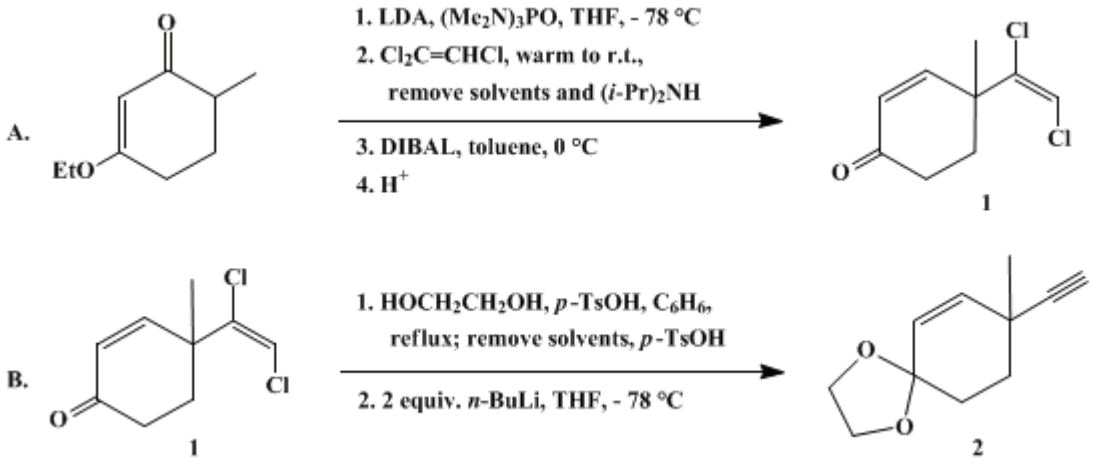
DICHLOROVINYLATION OF AN ENOLATE: 8-ETHYNYL-8-METHYL-1,4-DIOXASPIRO[4.5]DEC-6-ENE

[1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl-]



Submitted by Andrew S. Kende and Pawel Fludzinski[1].
Checked by P. Wovkulich, F. Barcelos, and Gabriel Saucy.

1. Procedure

Caution! Hexamethylphosphoric triamide and trichloroethylene are suspected carcinogens. All operations with either one should be performed in an efficient hood. The use of disposable gloves is highly recommended. Glassware should be rinsed with copious amounts of water into separate waste containers before removal from the hood.

A. *4-[(E)-1,2-Dichlorovinyl]-4-methyl-2-cyclohexen-1-one* **(1)**. A dry, 3-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The flask is charged with 1500 mL of anhydrous tetrahydrofuran (Note 2) and 38.9 g (54 mL, 0.38 mol) of diisopropylamine (Note 3). The flask is cooled to 0°C with an ice bath. A 1.51 *M* hexane solution of butyllithium (255 mL, 0.38 mol) is added dropwise with stirring over a 30-min period. The resulting lithium diisopropylamide is cooled to −78°C with a dry ice-acetone bath (Note 4). A solution of 57.8 g (0.38 mol) of 3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 5) in 400 mL of anhydrous tetrahydrofuran is added dropwise with stirring at −78°C over a 90-min period, followed immediately by the addition of 68 g (66 mL, 0.38 mol) of neat hexamethylphosphoric triamide (Note 6) over a 5-min period. The solution is stirred at −78°C for 45 min, followed by the dropwise addition of 52.6 g (36 mL, 0.40 mol) of neat trichloroethylene (Note 7). The solution is allowed to warm to room temperature slowly over a 6-hr period. As the solution warms, the color changes from pale yellow to olive green, to pale red, and finally to black. After 6 hr (Note 8) the solution is quenched with 1000 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 250 mL of diethyl ether. The organic phases are combined and washed four times with 750 mL of water and twice with 750 mL of brine and dried over magnesium sulfate. The solvent is removed on a rotary evaporator and recovered starting material is removed by fractional distillation at 91–93°C (1 mm) through a 15-cm Vigreux column. The residual crude 6-[(*E*)-1,2-dichlorovinyl]-3-ethoxy-6-methyl-2-cyclohexen-1-one (Note 9) is dissolved in 400 mL of toluene and placed in a dry, 2-L, one-necked, round-bottomed flask, equipped with a mechanical stirrer; a 500-mL pressure-equalizing dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to 0°C with an ice bath. A 1 *M* hexane solution of diisobutylaluminum hydride (400 mL, 0.40 mol) (Note 10) is added dropwise with stirring at 0°C over a 1-hr period. The solution is stirred for 2 additional hr

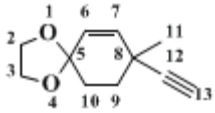
at 0°C. To quench the reaction 200 mL of methanol is carefully added to the stirred reaction mixture, followed slowly at first then more rapidly with 400 mL of water and then 300 mL of 10% sulfuric acid solution. After the mixture is stirred for 10 min, it is transferred to a separatory funnel and 500 mL of 10% sulfuric acid solution is added. The separatory funnel is shaken vigorously for 5 min and the organic phase is separated. The aqueous phase is extracted four times with 300 mL of diethyl ether. The organic phases are combined and washed twice with 300 mL of saturated sodium bicarbonate solution, twice with 300 mL of water, twice with 300 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short-path distillation at reduced pressure affords 31–34 g (40–44%, based on 3-ethoxy-6-methyl-2-cyclohexen-1-one) of 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one (1) as a colorless oil, bp 75–78°C (0.1 mm) (Note 11).

B. *8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene* **(2)**. A dry, 1-L, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and reflux condenser. The flask is charged with 500 mL of benzene, 12.0 g (0.059 mol) of 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one, 12.2 g (11 mL, 0.20 mol) of ethylene glycol and 40 mg (a catalytic amount) of *p*-toluenesulfonic acid. After the solution is refluxed for 24 hr, it is poured into 200 mL of saturated sodium bicarbonate solution. The organic phase is separated and the aqueous phase is extracted four times with 50 mL of diethyl ether. The organic phases are combined and washed twice with 100 mL of water and once with 100 mL of brine and are dried over magnesium sulfate. The solvent is removed on a rotary evaporator, and the resulting crude 8-[(*E*)-1,2-dichlorovinyl]-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene (Note 12) is dissolved in 200 mL of anhydrous tetrahydrofuran and placed in a dry, 1-L, one-necked, round-bottomed flask equipped with a magnetic stirrer and a 500-mL pressure-equalizing dropping funnel. The dropping funnel is fitted with a rubber septum and the air in the system is replaced with dry nitrogen (Note 1). The solution is cooled to −78°C with a dry ice-acetone bath (Note 4). A 1.51 *M* hexane solution of butyllithium (76 mL, 0.12 mol) is added dropwise with stirring at −78°C over a 30-min period. The solution is stirred at −78°C for 2 hr, the cold bath is removed, and stirring is continued for 90 min. The solution is poured into 100 mL of water and the organic phase is separated. The aqueous phase is extracted four times with 25 mL of diethyl ether. The organic phases are combined and washed twice with 75 mL of water, twice with 75 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator followed by short-path distillation at reduced pressure yields 5.5-6.3 g (52–60%) of 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene as a colorless oil, bp 88–90°C (1 mm) (Note 13).

2. Notes

1. This procedure is accomplished by alternatively evacuating and filling the funnel with dry nitrogen two times; an oil bubbler is used to maintain a slight positive pressure throughout the reaction.
2. Tetrahydrofuran is freshly distilled from sodium and benzophenone, as is all tetrahydrofuran used in this procedure.
3. Diisopropylamine is distilled from calcium hydride.
4. The flask is cooled with the dry-ice–acetone bath for 1 hr before the next addition to insure complete cooling of the solution.
5. See *Org. Synth. Coll. Vol. VII* **1990**, 208.
6. Hexamethylphosphoric triamide (HMPA) is freshly distilled from calcium hydride. Because of the suspected carcinogenicity of HMPA, the editors of *Organic Synthesis* rechecked all procedures in which it has been used. In the case of the present procedure, it was found that the decrease in yield in Step A was very large (55% ρ 16%) and that the product was a mixture of **1** and the corresponding chloroalkyne. Thus DMPU, the suggested substitute solvent,[2] is unsatisfactory in the present case.
7. Trichloroethylene is freshly distilled from phosphorus pentoxide.
8. On a smaller scale, the reaction warms to room temperature more quickly and can be worked up after 4 hr. Extended reaction times (e.g., overnight) lead to the formation of by-products.
9. Distillation is not necessary at this point. Spectroscopic data for 6-[(*E*)-1,2-dichlorovinyl]-3-ethoxy-6-methyl-2-cyclohexen-1-one is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, 3 H, J = 6), 1.48 (s, 3 H), 1.8–2.7 (m, 4 H), 3.96 (q, 2 H, J = 6), 5.44 (s, 1 H), 6.36 (s, 1 H). A purified sample (bp 140–142°C, 1 mm) gave satisfactory analyses. Anal. calcd. for $C_{11}H_{14}Cl_2O_2$: C, 53.02; H, 5.68. Found: C, 53.20; H, 5.43.
10. Diisobutylaluminum hydride was purchased from Aldrich Chemical Company, Inc. Since the reagent is not titrated, excess is used to ensure complete reduction.

11. Spectroscopic data for 4-[(*E*)-1,2-dichlorovinyl]-4-methyl-2-cyclohexen-1-one are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 3 H), 1.8-2.8 (m, 4 H), 5.92 (d, 1 H, *J* = 10), 6.34 (s, 1 H), 7.04 (d, 1 H, *J* = 10); ms (mass spectrum) (75 eV) *m/e* 204; IR ($CHCl_3$) cm^{-1}: 1680. Anal. calcd. $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 53.08, H, 5.03.
12. Spectroscopic data for 8-(*E*-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene is as follows: ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 3 H), 1.6–2.6 (m, 4 H), 3.88–4.08 (m, 4 H), 5.56 (d, 1 H, *J* = 10), 6.08 (d, 1 H, *J* = 10), 6.28 (s, 1 H).
13. Spectroscopic data for 8-ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 3 H), 1.6–2.2 (m, 4 H), 2.12 (s, 1 H), 3.88–4.04 (m, 4 H), 5.64 (AB q, 2 H, *J* = 10); ms (75 eV) *m/e* 178; IR (neat) cm^{-1}: 3290, 2100. Anal. calcd. for $C_{11}H_{14}O_2$: (at C-11) C, 74.13; H, 7.92. Found: C, 73.96; H, 7.78. ^{13}C NMR ($CDCl_3$) δ: 28.1 (at C-11), 30.5 (at C-9 or C-10), 31.4 (at C-8), 34.6 (at C-9 or C-10), 64.0 (at C-2 or C-3), 64.3 (at C-2 or C-3), 68.4 (at C-13), 88.3 (at C-12), 104.5 (at C-5), 126.3 (at C-6), 137.0 (at C-7).



3. Dissusion

3. Discussion

Trichloroethylene serves as an effective reagent for the dichlorovinylation of lithium enolates of several conjugated ketones. Under similar reaction conditions, 2,6-dimethyl-cyclo-2-hexen-1-one and 2-ethyl-5-methoxy-1-tetralone give the analogous dichlorovinyl adduct in comparable yield.[3] This procedure represents an heretofore unknown, uncatalyzed[4] carbon–carbon bond forming reaction between enolates and a polychloroolefin that can subsequently provide access to α- and γ-acetylenic ketones.[5]

References and Notes

1. Department of Chemistry, University of Rochester, Rochester, NY 14627.
2. Seebach, D. *Chimia* **1985**, *39*, 147.
3. Kende, A. S.; Benechie, M.; Curran, D. P.; Fludzinski, P.; Swenson, W.; Clardy, J. *Tetrahedron Lett*. **1978**, 4513.
4. For examples of Ni-catalyzed vinylation and arylation of enolates by bromides and iodides, see Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc*. **1977**, *99*, 4833.
5. The trichloroethylene condensation has been shown to proceed by way of dichloroacetylene as an obligatory intermediate in a carbanion chain mechanism. See Kende, A. S.; Fludzinski, P. *Tetrahedron Lett*. **1982**, *23*, 2369, 2373; Kende, A. S.; Fludzinski, P.; Hill, J. M.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc*. **1984**, *106*, 3551.

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

brine

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

trichloroethylene (79-01-6)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

hexamethylphosphoric triamide (680-31-9)

p-toluenesulfonic acid (104-15-4)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

3-Ethoxy-6-methyl-2-cyclohexen-1-one (62952-33-4)

8-Ethynyl-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene,
1,4-Dioxaspiro[4.5]dec-6-ene, 8-ethynyl-8-methyl- (73843-26-2)

2,6-dimethyl-cyclo-2-hexen-1-one

2-ethyl-5-methoxy-1-tetralone

phosphorus pentoxide (1314-56-3)

4-[(E)-1,2-Dichlorovinyl]-4-methyl-2-cyclohexen-1-one (73843-27-3)

6-[(E)-1,2-dichlorovinyl]-3-ethoxy-6-methyl-2-cyclohexen-1-one (73843-25-1)

8-[(E)-1,2-dichlorovinyl]-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene,
8-(E-1,2-dichlorovinyl)-8-methyl-1,4-dioxaspiro[4.5]dec-6-ene

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