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of Reliable Methods
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.

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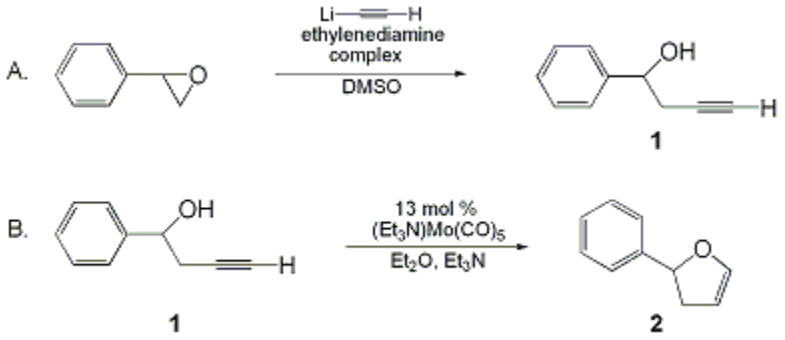
MOLYBDENUM CARBONYL-CATALYZED ALKYNOL CYCLOISOMERIZATION: PREPARATION OF 2-PHENYL-2,3-DIHYDROFURAN

[Furan, 2,3-dihydro-2-phenyl-]



Submitted by Frank E. McDonald and Brian H. White[1] .
Checked by Peter B. Ranslow and Louis S. Hegedus.

1. Procedure

Caution: All manipulations should be conducted in a well-ventilated fume hood.

A. 1-Phenyl-3-butyn-1-ol (**1**) (Note 1). A 1000-mL, oven-dried, three-necked, round-bottomed flask is equipped with a magnetic stir bar and pressure-equalizing addition funnel, fitted with a rubber septum, and placed under an argon atmosphere. The flask is charged with lithium acetylide-ethylenediamine complex (50 g, 543 mmol) (Note 2), which is dissolved in anhydrous dimethyl sulfoxide (360 mL) (Note 3) with stirring. The flask is placed in a room temperature water bath (Note 4), the addition funnel is charged with styrene oxide (42.0 mL, 368 mmol) (Note 5), and styrene oxide is added dropwise over a period of approximately 5 min. The reaction mixture is stirred for 2 hr and quenched by pouring slowly into 600 mL of ice water in a 4-L beaker (Note 6). The contents are transferred to a 2-L separatory funnel, and the mixture is extracted with diethyl ether (6 × 350 mL). The combined organic extracts are washed once with water and decanted with evaporation of solvents by rotary evaporation. The crude product is purified by vacuum distillation. Any remaining traces of solvent and water distill over first, followed by the product (88-89°C, 1.0 mm) to provide 1-phenyl-3-butyn-1-ol (**1**, 43.98 g, 82% yield) as a colorless oil.

B. 2-Phenyl-2,3-dihydrofuran (**2**). A 500-mL, oven-dried Airfree® reaction flask (Note 7) containing a magnetic stir bar is charged with molybdenum hexacarbonyl ($Mo(CO)_6$, 3.21 g, 12.2 mmol) (Note 8) and fitted with a rubber septum, with an argon atmosphere introduced via the side-arm. Triethylamine (Et_3N, 220 mL, 1.58 mol) (Note 9) is added, followed by diethyl ether (Et_2O, 180 mL) (Note 10), and the mixture is stirred for 10-15 min, until the molybdenum hexacarbonyl has dissolved. The solution is placed in a Rayonet Photochemical Reactor Chamber (Notes 11, 12, 13) equipped with 350-nm ultraviolet lamps. The septum is removed under positive argon pressure, and a reflux condenser bearing a rubber septum that has been previously flushed with argon is quickly fitted onto the Schlenk tube. The solution is irradiated for 1 hr under argon while the photochemical reactor interior is cooled with the built-in cooling fan. The light is turned off and the reaction mixture is allowed to cool to room temperature while maintaining an inert atmosphere to afford a yellow solution of triethylamine-molybdenum pentacarbonyl . The condenser is removed and a septum is quickly refitted while under a positive flow of argon. A solution of 1-phenyl-3-butyn-1-ol (**1**, 13.50 g, 92.3 mmol) in diethyl ether (40 mL) is injected into the solution, and the mixture is stirred at room temperature under a slow argon

stream for 72 hr; the solution slowly turns dark red over this period. The solvent is then removed by rotary evaporation, leaving a dark red liquid and a precipitate of molybdenum-containing by-products, which are removed by sublimation by heating under vacuum (35°C, 0.5 mm) The remaining liquid is vacuum distilled through a short-path distillation column (45-47°C, 0.5 mm) to give 2-phenyl-2,3-dihydrofuran (**2**, 10.3 g, 76% yield) as a clear liquid (Notes 14, 15).

2. Notes

1. This preparation was previously described by Brandsma.[2] Substrate **1** can be prepared in enantiomerically pure form beginning with chiral, non-racemic styrene oxide, available as either antipode from Aldrich Chemical Company, Inc. , or by kinetic resolution of racemic styrene oxide .[3]
2. Lithium acetylide-ethylenediamine complex was purchased from the Aldrich Chemical Company, Inc. , and used as received.
3. Anhydrous dimethyl sulfoxide was purchased from the Aldrich Chemical Company, Inc. , and used as received in a Sure/Seal bottle.
4. This reaction is somewhat exothermic, and the water bath serves as a heat sink to maintain the reaction temperature under 25°C.
5. Styrene oxide was purchased from the Aldrich Chemical Company, Inc. , and used without purification. *Caution! Styrene oxide is listed as a cancer suspect agent.*
6. The quench should be done by pouring the reaction mixture *very slowly* into ice water, as the quench is rather violent on occasions when unreacted lithium acetylide is present.
7. This glass flask is Kjeldahl-shaped, with a ground glass 24/40 top joint and side-arm fitted with a 2-mm ground glass stopcock, and was purchased from Chemglass (part number AF-0520-08), 3861 North Mill Road, Vineland, NJ 08360, phone 1-800-843-1794.
8. Molybdenum hexacarbonyl was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
9. Triethylamine was purchased from Fisher Scientific Company , and purified immediately before use by distillation from calcium hydride under an inert atmosphere.
10. Diethyl ether was purchased from Mallinckrodt Baker, Inc. , and purified immediately before use by distillation from sodium / benzophenone under inert atmosphere.
11. The model used was a RPR-100 reactor purchased from the Southern New England Ultraviolet Company, Branford, CT.
12. The photochemical step could also be accomplished by adding $Mo(CO)_6$, Et_3N and Et_2O to a photochemical immersion well, and irradiating under an inert atmosphere with a Hanovia medium pressure 450W mercury vapor lamp for 20-30 min. Commercially available immersion wells generally require > 800 mL of solvent in order to work effectively (so that the solvent is level with the lamp), and the submitters have found that the more concentrated solution reported here (ca. 450 mL) is more effective.
13. If photochemical apparatus is not available, the cycloisomerization reaction can be conducted using trimethylamine N-oxide to promote oxidative decarbonylation of molybdenum hexacarbonyl in a mixture of Et_3N and Et_2O, followed by addition of 1-phenyl-3-butyn-1-ol (**1**).[4a] In the submitters' hands, this procedure required somewhat higher loading of molybdenum hexacarbonyl , and purification of the 2-phenyl-2,3-dihydrofuran (**2**) product required silica gel chromatography.
14. 2-Phenyl-2,3-dihydrofuran (**2**) tends to turn pale yellow after cooling and exposure to air, but no significant decomposition is revealed by NMR.
15. Characterization data for compound **2**: IR (neat) cm^{-1}: 3053, 2923, 2858, 1620, 1493, 1451, 1136, 1051, 930, 782, 697 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.59-2.66 (m, 1 H), 3.06-3.13 (m, 1 H), 4.97 (q, 1 H, J = 2.8), 5.53 (dd, 1 H, J = 2, 8.4), 6.47 (q, 1 H, J = 2), 7.28-7.38 (m, 5 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.1, 82.5, 99.3, 125.8, 127.8, 128.7, 143.2, 145.5 ; MS (70 eV, EI) 146, 117, 105, 91, 77, 57, 43 ; HRMS (EI) calcd for $C_{10}H_{10}O$ 146.0732; found 146.0742 . Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.07; H, 6.88.

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

The single-step transformation of alkynyl alcohols to endocyclic enol ethers was unknown until the submitters' discovery that trialkylamine-molybdenum pentacarbonyl reagents catalyzed the cycloisomerization of 1-phenyl-3-butyn-1-ol (**1**) into 2-phenyl-2,3-dihydrofuran (**2**).[4] Cycloisomerization of alkynol **1** to dihydrofuran **2** was previously accomplished by multistep synthesis, including hydroboration/oxidation of the alkyne of **1** followed by hemiacetal acylation and thermal elimination.[5] A two-step preparation of **2** involving the stoichiometric reaction of **1** with chromium pentacarbonyl-diethyl ether complex and subsequent thermal reaction with dimethylaminopyridine was reported after their initial communications.[6] The title compound **2** has also been prepared by pyrolysis of 1-phenyl-2-vinyloxirane at 450°C and 15 mm.[7] Palladium -catalyzed Heck reactions of 2,3-dihydrofuran with iodobenzene or phenyl triflate provide compound **2** along with the 2,5-dihydro regioisomer, although regioselectivity can be enhanced for either isomer depending on the choice of ligands and additives.[8] An enantioselective Heck synthesis of title compound **2** has also been reported.[9]

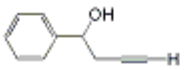
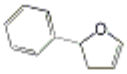
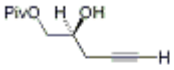
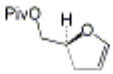
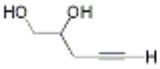
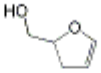
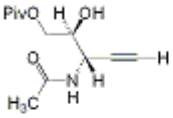
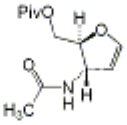
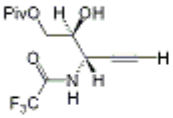
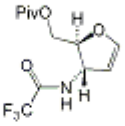
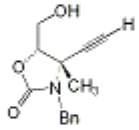
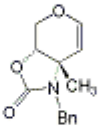
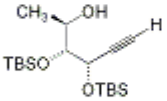
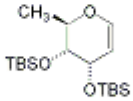
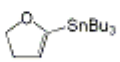
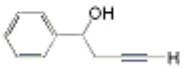
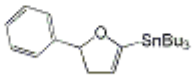
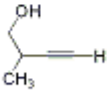
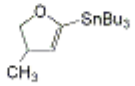
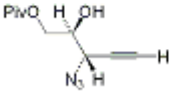
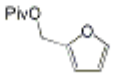
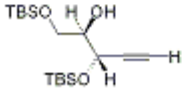
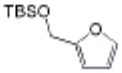
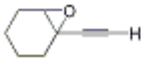
The molybdenum -catalyzed cyclization procedure works well for a variety of homoprogargylic alcohols to afford the cycloisomeric 2,3-dihydrofuran compounds, as shown in Table I. The transformation was originally discovered with the reagent arising from reaction of molydbenum hexacarbonyl and trimethylamine oxide ,[4a] but catalyst turnover and product isolation yields are significantly improved with the current procedure, which involves photolysis of molybdenum hexacarbonyl in the presence of excess triethylamine prior to addition of the alkynyl alcohol substrate.[4b] Chiral non-racemic alkynyl alcohol substrates undergo cycloisomerization without racemization at stereogenic centers (entries 2, 4-7).[10,11] The method is compatible with ester, amide, and silyl ether functional groups, and five-membered ring products are generally produced in good yields. The submitters have observed that good leaving groups at the propargylic position tend to provide furan products by a cyclization/elimination process (entries 11-13).[4,11]

The molybdenum -catalyzed alkynol cycloisomerization is the key transformation in short, stereoselective syntheses of the anti-AIDS drug d4T,[10] the antibiotic cordycepin,[10] and puromycin aminonucleoside.[11] Reaction in the presence of tributyltin triflate affords the corresponding 5-tributylstannyl-2,3-dihydrofuran products (entries 8-10).[12] Tungsten carbonyl-catalysis has recently been demonstrated for the efficient cycloisomerization of bishomopropargylic alcohols to the corresponding six-membered ring dihydropyran products (entry 7).[13] Analogous cycloisomerization reactions of terminal alkynes tethered to nitrogen,[14] carbon,[15] and sulfur[16 17] nucleophiles have also been developed.

Table I

TABLE I

PREPARATION OF ENDOCYCLIC ENOL ETHERS VIA ALKYNOL CYCLOISOMERIZATION

Entry	Alkynyl alcohol	Endocyclic enol ether	Isolated yield	Reference
1			89%[a] (4.6 mmol) 80%[a] (75 mmol) 71%[b]	4b (this work) 4a
2			80%[b]	10, 11
3			53%[b]	4a
4			89%[a]	11
5			92%[a]	11
6			35%[a] (+49% recovered alkynol)	17
7			98%[c]	13
8			64%[d]	12
9			65%[d]	12
10			45%[d]	12
11			60%[a]	11
12			76%[a]	11
13			85%[a]	4b

[a] cat. $(Et_3N)Mo(CO)_5$, Et_3N, Et_2O. [b] cat. $Mo(CO)_6$, Me_3NO, Et_3N, Et_2O.
[c] cat. $W(CO)_6$, Et_3N, Et_2O, hv (350 nm), [d] cat. $(Et_3N)Mo(CO)_5$, Bu_3SnOTf, Et_3N, Et_2O

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

2-Phenyl-2,3-dihydrofuran:
Furan, 2,3-dihydro-2-phenyl- (8,9); (33732-62-6)

1-Phenyl-3-butyn-1-ol:
Benzenemethanol, α-2-propynyl- (9); (1743-36-8)

Lithium acetylide-ethylenediamine complex:
Ethylenediamine, compd. with
lithium acetylide ($Li(HC_2)$) (1:1) (8); 1,2-Ethanediamine, compd. with
lithium acetylide ($Li(HC_2)$) (1:1) (9); (6867-30-7)

Dimethyl sulfoxide:
Methyl sulfoxide (8);
Methane, sulfinylbis- (9); (67-68-5)

Styrene oxide:
Benzene, (epoxyethyl)- (8);
Oxirane, phenyl- (9); (96-09-3)

Molybdenum hexacarbonyl:
Molybdenum carbonyl (8);
Molybdenum carbonyl,(OC-6-11) (9); (13939-06-5)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)