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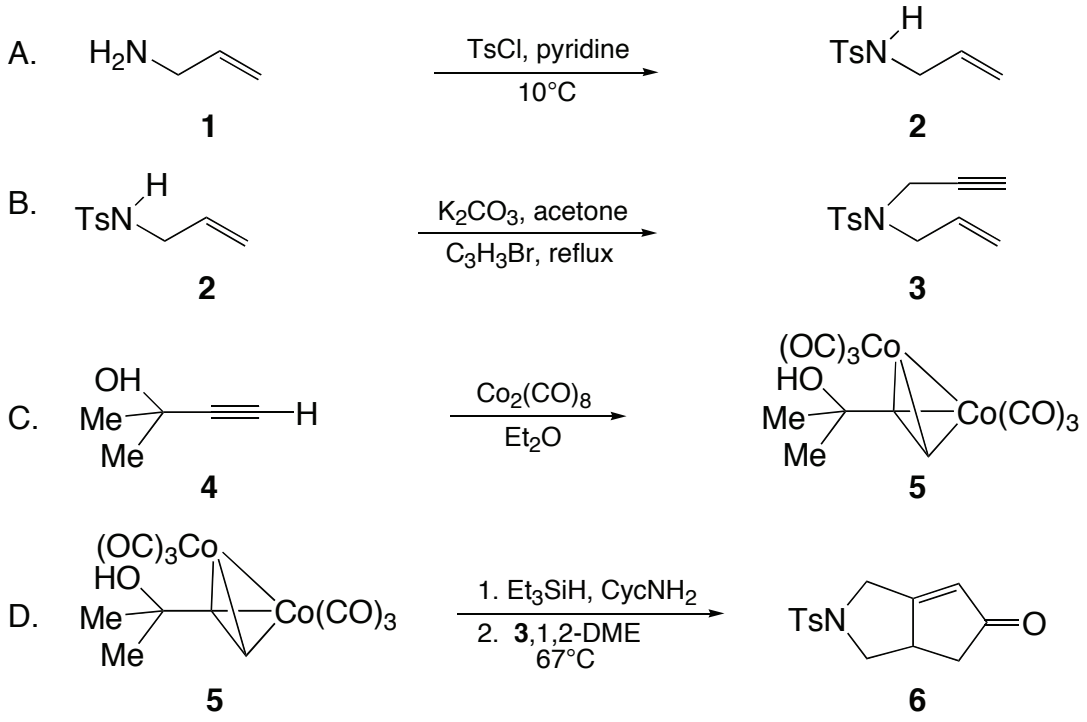
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.080.0093
Organic Syntheses, Vol. 80, p. 93-103 (2003); Coll. Vol. 11, p. 442-449 (2009).

THE CATALYTIC INTRAMOLECULAR PAUSON-KHAND REACTION: 2,3,3α,4-TETRAHYDRO-2-[(4-METHYLBENZENE) SULFONYL]CYCLOPENTA[C]PYRROL-5(1*H*)-ONE [(Cyclopenta[b]pyrrol-5(1*H*)-one, 2,3,3a,4-tetrahydro-1-[(4-methylphenyl)sulfonyl]-)]



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Checked by Kyung-Hee Kim and Marvin J. Miller.

1. Procedure

A. N-(2-Propenyl)-4-methylbenzenesulfonamide (**2**). A 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, internal thermometer and powder funnel is charged with *p*-toluenesulfonyl chloride (97.2 g, 0.51 mol) (Note 1). The powder funnel is replaced with a rubber septum connected to a positive pressure of argon and an oil bubbler. The apparatus is flushed with argon and charged with tetrahydrofuran (THF) (400 mL, (Note 2)) and pyridine (42.9 mL, 0.53 mol). The flask is placed in an ice bath and, after the reaction mixture has cooled to ca. 10 °C,

allylamine (37.5 mL, 0.50 mol) (Note 3) is added portion-wise by syringe over ca. 40 min (exothermic) maintaining the internal temperature below 15 °C. The ice bath is removed and the resulting solution is allowed to warm to room temperature. After 4 h the rubber septum is removed and the mixture is treated with 75 mL of a 2M aqueous solution of sodium hydroxide. After another 4 h, the reaction mixture is transferred to a separatory funnel, the organic phase is separated, and the aqueous phase is extracted with two 100-mL portions of ethyl acetate (EtOAc). The combined organic phases are washed with brine (50 mL) and dried with magnesium sulfate ($MgSO_4$) in the presence of activated carbon (4 g). The solution is filtered through a plug of silica gel (diameter: 5 cm; height: 3 cm) and the cake is washed with EtOAc (300 mL). The combined filtrate and washes are concentrated under reduced pressure. The crude product is recrystallized from 275 mL of 30% EtOAc/hexanes to afford 65 g (62%) of allyl tosylamide as a first crop. A second crop of 27 g (26%, 88% in total) is obtained from the mother liquor (Note 4).

B. N-(2-Propenyl)-N-(2-propynyl)-4-methylbenzenesulfonamide (**3**). A 500-mL, single-necked, round-bottomed flask equipped with a Teflon-coated stirring bar (Note 1) is charged with allyl tosylamide (31.7 g, 150 mmol), anhydrous potassium carbonate (K_2CO_3) (24.8 g, 1.2 equiv, 180 mmol) (Note 5), 1-bromo-2-propyne (20.0 mL, 1.2 equiv, 180 mmol), and acetone (300 mL). The flask is equipped with a water-cooled condenser fitted with a rubber septum. The apparatus is flushed with argon introduced through the septum and a positive pressure of argon is maintained with an argon-filled balloon (Note 6). The reaction mixture is heated to reflux with stirring for 24 h. After complete consumption of starting material, monitored by thin layer chromatography (TLC, (Note 7)), the reaction mixture is allowed to cool and is concentrated under reduced pressure on a rotary evaporator. The residue is diluted with EtOAc (250 mL) and water (125 mL) and the organic phase is separated. The aqueous phase is extracted with 200 mL of EtOAc and the combined organic phases are washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure with a rotary evaporator. The residue is recrystallized from 2.5 mL of ether and 250 mL of 20% EtOAc/hexanes to afford ca. 30 g (80%) of **3** as nearly colorless crystals. A second crop totaling 5.9 g (16%, 96% in total) is also obtained (Note 8).

*C. Hexacarbonyl[μ-[(3,4-η:3,4-η)-2-methyl-3-butyn-2-ol]]dicobalt (**5**).* A single-necked, 50-mL, round-bottomed flask (Note 9), equipped with a Teflon-coated stirring bar, is charged with dicobalt octacarbonyl ($Co_2(CO)_8$) (1.7 g, 5.0 mmol, 1.0 equiv) (Note 10). After attaching a rubber septum, the flask is flushed with carbon monoxide (CO), then charged with 25 mL of degassed diethyl ether (Note 11). The flask is placed in an ice bath and, after 10 min, a bubbler is connected through the septum, followed immediately by the addition of 2-methyl-3-butyn-2-ol (0.51 mL, 5.3 mmol, 1.05 eq). After removing the ice bath and stirring for 3 h at ambient temperature, the resultant solution is filtered through a pad of Celite (diameter: 3 cm; height: 1 cm) (Note 12), which is washed with ether until the washes are clear (ca. 75 mL).

The alkyne cobalt complex is purified by silica gel chromatography. To the red solution is added 2 g of silica gel and the mixture is concentrated on a rotary evaporator (Note 13). The silica gel is then placed under vacuum (1 mm) until effervescence ceases (about 10 min). The dried silica gel is placed at the top of a column of silica gel (diameter: 3 cm; height: 9 cm), eluting first with hexane to remove non-polar by-products and subsequently with 15% ether/hexane. The desired product elutes as a red band. Concentration of the appropriate fractions on a rotary evaporator (Note 13) and under high vacuum (0.7 mm for 10 min) affords 1.4 g (79%) of 5 as a fine red powder (Note 14).

D. 2,3,3α,4-Tetrahydro-2-[(4-methylbenzene)sulfonyl]cyclopenta[c] pyrrol-5(1H)-one (**6**). A 250-mL, two-necked, round-bottomed Schlenk flask, equipped with a thermometer and Teflon-coated stirring bar, is charged with 6.0 g (24.1 mmol) of enyne 3 prepared in Step B (Note 1). A 12-cm, air-cooled condenser is attached to the flask. The top of the condenser is fitted with a rubber septum, which is connected to a CO supply and the apparatus is flushed with CO through the Schlenk valve (Note 15) for several min. After the CO purge is completed, the flask is charged with 120 mL of 1,2-dimethoxyethane (1,2-DME) (Note 16). Meanwhile, another 50-mL, round-bottomed Schlenk flask is charged with the $Co_2(CO)_6$-alkyne complex **5** (445 mg, 1.20 mmol, 5 mol%) (Note 9) and flushed with CO with a CO-filled balloon as described above. To the flask containing the $Co_2(CO)_6$-alkyne complex **5** are added sequentially 22.5 mL of 1,2-DME, cyclohexylamine (0.413 mL, 3.61 mmol, 15 mol%), 3 eq of amine/cobalt

dimer) and triethylsilane (Et_3SiH) (2.40 mL of a 0.5M solution in xylenes, 1.20 mmol, 5 mol%). The assembly is heated in an oil bath at 67 °C for 15 min (Note 17), then transferred via cannula under an atmosphere of CO to the Schlenk flask containing enyne **3** (Note 18). The resulting mixture is heated at 67 °C for 24 h, when the reaction is usually complete as determined by TLC analysis (Note 19). After complete carbocyclization, the reaction mixture is transferred (in air) to a single-necked flask and concentrated on a rotary evaporator. The dark residue is dissolved in 150 mL of dichloromethane (CH_2Cl_2), washed with 10% aqueous sulfuric acid (2 × 15 mL), water (15 mL), and brine (45 mL) and treated with ca. 4 g of activated carbon and anhydrous sodium sulfate (Na_2SO_4). After 4 h the solution is filtered through a pad of Celite (diameter: 5 cm; height: 2 cm) (Note 12) and concentrated on a rotary evaporator to afford a brown solid. Purification by flash chromatography with silica gel (Note 20) affords 5.8-6.2 g (86-93% yield) of **6** as a slightly yellow solid. Colorless microcrystalline material may be obtained by recrystallization from a cold (−20 °C) solution of 1:1 2-propanol:CH_2Cl_2 (4.6-5.1 g, 69-77%) (Notes 21, 22).

2. Notes

1. All glassware is dried in a 200 °C oven overnight prior to use, assembled while hot, and allowed to cool to room temperature under dry argon.

2. Mallinckrodt ChromAR® HLPC grade THF was used as received.

3. Allylamine was purchased from Acros Organics and distilled from calcium sulfate before use.

4. The checkers obtained 80 g (76%). Properties of **2:**[10] mp 58.0-59.0 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.49 (app t, J = 5.95, 2H), 4.96-5.12 (m, 2H), 5.23 (s, 1H), 5.57-5.68 (m, 1H), 7.21 (d, J = 8.2, 2H), 7.69 (d, J = 8.2, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.2, 45.5, 117.2, 126.9, 129.5, 132.9, 136.9, 143.2.

5. Unless otherwise noted, all solvents and reagents were purchased from VWR Scientific or Aldrich Chemical Co., Inc. and used as received. $CDCl_3$ was filtered through basic alumina (Aldrich Chemical Co., Inc.) prior to use.

6. The checkers used a double needle in the septum, one for argon supply and the other attached to an argon-filled balloon.

7. The R_f of the starting material and product is 0.30 and 0.52, respectively (1:1 EtOAc:hexanes).

8. The checkers obtained 33.2 g (89%). Properties of **3**: mp 60.8-61.5 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ: 1.96 (t, *J* = 2.4, 1 H), 2.35 (s, 3H), 3.76 (d, *J* = 6.5, 2H), 4.02 (d, *J* = 2.4, 2H), 5.25-5.14 (m, 2H), 5.72-5.59 (m, 1 H), 7.23 (d, *J* = 8.1, 2H), 7.66 (dd, *J* = 8.3, 1.5, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.3 (CH_3), 35.7 (CH_2), 48.9 (CH_2), 73.6 (CH_2), 119.7 (CH_2), 127.6 (CH), 129.3 (CH), 131.8 (CH), 136.0 (C), 143.4 (C); IR (thin film) cm^{-1}: 3257, 3049, 2987, 2885, 2117, 1646, 1601, 1425, 1330, 1165.

9. The glassware must be cooled to room temperature before use.

10. *Caution. Dry $Co_2(CO)_8$ can be pyrophoric*. $Co_2(CO)_8$ is toxic and should be handled in a glove box or well-ventilated hood. $Co_2(CO)_8$ was purchased from Strem Chemical Co., Inc. High purity $Co_2(CO)_8$ is critical for successful catalytic reactions. A freshly opened sample of $Co_2(CO)_8$ stored in a dry box is often sufficiently pure to be used directly in this reaction provided three eq of cyclohexylamine per $Co_2(CO)_8$ are added to the reaction mixture. However, a more reliable approach is to generate the active cobalt catalyst in situ as described herein.

11. Ether was distilled from a purple solution of sodium/ benzophenone ketyl and degassed by bubbling with argon.

12. Celite 545 was purchased from Fluka.

13. The bath temperature of the rotary evaporator must be kept below 35 °C.

14. The checkers obtained 1.35 g (75%) Properties of **5:**[10] ^{1}H NMR ($CDCl_3$) δ: 1.55 (s, 6H), 1.70 (s, 1 H), 6.01 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ: 33.4, 71.7, 72.9, 76.8, 107.3, 200.0 (m).

15. Carbon monoxide is highly toxic and should be handled in a well-ventilated hood.

16. All solvents must be rigorously degassed for the Pauson-Khand step. 1,2-DME obtained from VWR Scientific was freshly distilled from a deep blue solution of sodium/benzophenone ketyl and degassed with argon prior to use.

17. The internal temperature of the mixture is 64 °C. Temperatures above 70 °C lead to catalyst decomposition.

18. To facilitate transfer of the catalyst, the CO source connected to the large reaction vessel is removed and replaced with a line leading to a mineral oil bubbler. When the transfer is complete, the bubbler is disconnected and a CO-filled double-walled balloon is connected to the top of the condenser and used to maintain a CO atmosphere throughout the reaction. Strict exclusion of air during these transfers is critical.

19. The course of the reaction may be monitored by TLC: R_f of **3** and **6** is 0.82 and 0.36, respectively (1:1 EtOAc:hexanes). The color of the reaction mixture typically turns from burgundy to dark brown at the end of the reaction.

20. The solid residue is dissolved in a minimum of dichloromethane and purified by flash chromatography on silica gel (8 cm diameter by 15 cm long column), eluting with 1.5 % EtOH in CH_2Cl_2.

21. The crystals are collected by filtration on a fritted glass filter funnel, rinsed with ether and dried under reduced pressure.

22. The checkers obtained 4.3 g (65%). Properties of **6**: mp 147.0-148.0 °C (2-PrOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 1.96-2.03 (dd, J = 17.9, 3.7, 1H), 2.37 (s, 3H), 2.48-2.60 (m, 2H), 3.04-3.10 (m, 1H), 3.93-4.00 (dd, J = 14.3, 5.1, 2H), 4.27 (d, J = 16.5, 1H), 5.92 (s, 1H), 7.29 (d, J = 8.1, 2H), 7.66 (d, J = 8.2, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.0 (CH_3), 39.3 (CH_2), 43.4 (CH), 47.1 (CH_2), 51.9 (CH_2), 125.6 (CH), 126.9(CH), 129.5 (CH), 133.0 (C), 143.6 (C), 178.2 (C), 206.8 (C); IR (KBr) cm^{-1}: 3067, 1711, 1648, 1343, 1162, 1090.

Waste Disposal Information

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

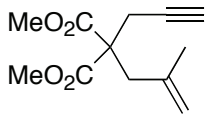
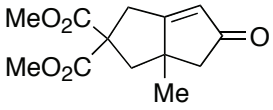
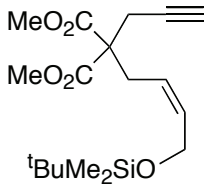
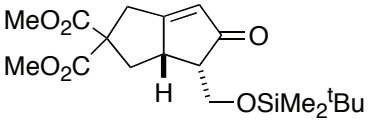
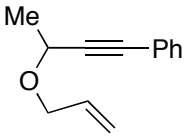
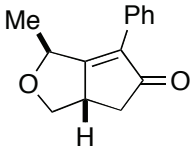
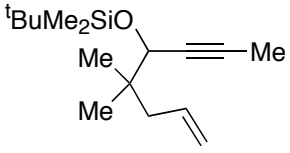
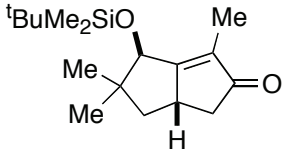
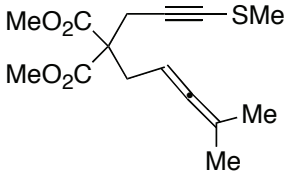
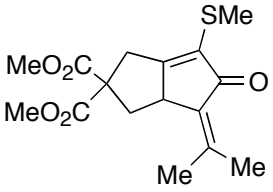
3. Discussion

The Pauson-Khand reaction is one of the most convenient methods for the synthesis of cyclopentenones, and both inter- and intramolecular

variations exist.[3,4] In the classical procedure, the enyne is mixed with one equivalent of $Co_2(CO)_8$ and the mixture is heated (either at reflux or in a sealed tube) for several hours to days. The synthetic ease of the Pauson-Khand reaction was enhanced when it was discovered that silica gel, tertiary amine *N*-oxides and DMSO all markedly accelerated the reaction.[4] The Pauson-Khand reaction is compatible with enynes containing esters, ethers, amines, sulfides, 1,2-disubstituted olefins and substituted or terminal alkynes. A major drawback to large scale, classical Pauson-Khand reactions is the requirement for stoichiometric quantities of $Co_2(CO)_8$. We recently reported the first catalytic Pauson-Khand reaction conveniently operative at 1 atmosphere of CO.[5,6] The key factors of successful catalytic cyclizations are the use of highly purified $Co_2(CO)_8$, strictly anaerobic conditions, and temperature control. To circumvent the requirement for very pure $Co_2(CO)_8$ we developed a chemically robust, air-stable $Co_2(CO)_6$-alkyne complex as a source of pure $Co_2(CO)_8$ when released by silylative decomplexation.[7] This procedure employs cyclohexylamine, which has been shown to accelerate stoichiometric Pauson-Khand reactions[8] and minimizes the sensitivity of the catalyst to oxygen. The scope of the catalytic Pauson-Khand has been further enhanced by the discovery that 2,2,2-trifluoroethanol as a co-solvent minimizes some non-carbonylative isomerization processes.[9] The utility of the method is demonstrated by the diverse range of substrates shown in the Table.

TABLE

THERMALLY PROMOTED CATALYTIC PAUSON-KHAND CYCLIZATIONS

Entry	Enyne	Product	Yield (diastereomer ratio)
1			95[a]
2			90[b] (>30:1)
3			96[a,c] (30:1)
4			74[a,d] (2.5:1)
5			84[b]

[a]5 mol% $Co_2(CO)_8$. [b]10 mol% $Co_2(CO)_8$. [c]Reaction solvent was 2,2,2-trifluoroethanol; see ref.9. [d]Reaction solvent was 2,2,2-trifluoroethanol:1,2-DME (2:1); see ref.9.

1. The University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N-(2-Propenyl)-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl- (9); (50487-71-3)

p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

Allylamine: 2-Propen-1-amine (9); (107-11-9)

Pyridine (8, 9); (110-86-1)

N-(2-Propenyl)-*N*-(2-propynyl)-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl-*N*-2-propynyl-(9); (133886-40-5)

1-Bromo-2-propyne: 1-Propyne, 3-bromo- (9); (106-96-7)

Hexacarbonyl[μ[(3,4-η:3,4-η)-2-methyl-3-butyn-2-ol]]dicobalt: Cobalt, hexacarbonyl [μ-[(3,4-η:3,4-η)-2-methyl-3-butyn-2-ol]]di-, (Co-Co) (9); (40754-33-4)

Dicobalt octacarbonyl: Cobalt, di-(-carbonylhexacarbonyl di-, (Co-Co) (8, 9); (10210-68-1)

2-Methyl-3-butyn-2-ol: 3-Butyn-2-ol, 2-methyl- (8, 9); (115-19-5)

2,3,3α,4-Tetrahydro-2-[(4-methylbenzene)sulfonyl]cyclopenta[c]pyrrol-5(1*H*)-one: Cyclopenta[b]pyrrol-5(1*H*)-one, 2,3,3a,4-tetrahydro-1-[(4-methylphenyl)sulfonyl]- (9); (205885-50-3)

Carbon monoxide (8, 9); (630-08-0)
1,2-Dimethoxyethane: Ethane, 1,2-dimethoxy- (8, 9); (110-71-4)
Cyclohexylamine: Cyclohexanamine (9); (108-91-8)
Triethylsilane: Silane, triethyl- (8, 9); (617-86-7)