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for the Preparation
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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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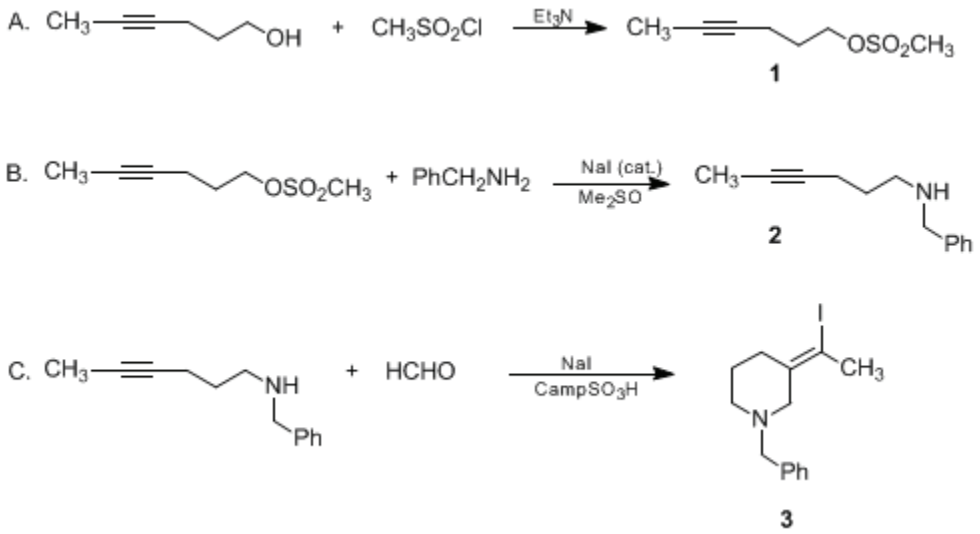
Organic Syntheses, Coll. Vol. 9, p.46 (1998); Vol. 70, p.111 (1992).

(E)-1-BENZYL-3-(1-IODOETHYLIDENE)PIPERIDINE: NUCLEOPHILE-PROMOTED ALKYNE-IMINIUM ION CYCLIZATIONS

[Piperidine, 3-(iodoethylidene)-1-(phenylmethyl)-(E)-]



Submitted by H. Arnold, L. E. Overman, M. J. Sharp, and M. C. Witschel[1].
Checked by Antje Grützmann, Thomas Hache, and Ekkehard Winterfeldt.

1. Procedure

A. *4-Hexyn-1-yl methanesulfonate* (**1**). An oven-dried, 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is flushed with argon and 260 mL of dichloromethane is added (Note 1). The flask is sealed with a rubber septum inlet and cooled to ca. −10°C in an ice-salt bath. To this flask are added via syringe 11 mL (80 mmol) of triethylamine, 5.0 g (51 mmol) of 4-hexyn-1-ol (Note 2), and 4.3 mL (56 mmol) of methanesulfonyl chloride (Note 3). The resulting solution is stirred for an additional 30 min and then quenched by adding 30 mL of ice-water. The organic layer is separated and washed successively with 1 M hydrochloric acid solution (30 mL), saturated aqueous sodium bicarbonate solution (30 mL), and brine (30 mL). The organic layer is dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give 8.3–9.0 g (93–100%) of crude 4-hexyn-1-yl methanesulfonate (**1**) which was used directly in the next step (Note 4).

B. *N-Benzyl-4-hexyn-1-amine* (**2**). An oven-dried, 100-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a rubber septum inlet is flushed with argon and charged with 200 mg of sodium iodide. The crude mesylate **1**, 40 mL of dimethyl sulfoxide (Note 5) and 10.9 g (102 mmol) of benzylamine are added via syringe. The resulting solution is heated in an oil bath at 47–53°C for 5 hr (Note 6) and then allowed to cool to room temperature. The reaction solution is poured into a separatory funnel containing 200 mL of aqueous 1% sodium hydroxide solution and the resulting mixture is extracted with ether (3 × 100 mL). The combined ether extracts are washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator. The residue (ca. 9 g) is purified by flash chromatography (ca. 300 g of silica gel using 1:1 hexane-ether containing 5% triethylamine as the eluent) (Note 7) to give 7.2–7.5 g (75–79% overall) of **2** as a colorless liquid (Note 8).

C. *(E)-1-Benzyl-3-(1-iodoethylidene)piperidine* (**3**). A 250-mL, one-necked, round-bottomed flask containing a magnetic stirring bar and a reflux condenser topped with a rubber septum inlet is flushed with argon and charged with 4.0 g (21 mmol) of alkynylamine **2**, 11 g (73 mmol) of sodium iodide

(Note 9), 35 mL of 37% w/w formaldehyde solution, 5.4 g (22 mmol) of camphorsulfonic acid monohydrate (Note 10) and 80 mL of water. The resulting mixture is heated at reflux under an argon atmosphere for 15 min (Note 11) and then allowed to cool to room temperature. This solution is made basic by adding 5 M aqueous potassium hydroxide solution and then poured into a separatory funnel where it is extracted with dichloromethane (3 × 50 mL) (Note 12). The combined organic layers are dried over sodium sulfate, filtered, and concentrated with a rotary evaporator. The resulting residue is purified by flash chromatography (ca. 150 g of silica gel, 1:1 hexane-ethyl ether containing 5% triethylamine as eluent) to give 5.4–6.2 g (79–90%) of **3** as a colorless oil (Note 13) and (Note 14).

2. Notes

1. Dichloromethane is distilled from calcium hydride (CaH_2) and added directly from the still to the reaction flask.
2. This alcohol is readily prepared in standard fashion from the tetrahydropyranyl ether of 4-pentyn-1-ol and iodomethane: A hexane solution of butyllithium (46 mL of a 2.2 M solution, 100 mmol) is added dropwise under an argon atmosphere to a dry ice-cooled solution of tetrahydro-2-(4-pentynyloxy)-2H-pyran (14.4 g, 84 mmol, prepared from commercially available 4-pentyn-1-ol[2]) in 100 mL of dry tetrahydrofuran. After 10 min, 7.0 mL (110 mmol) of iodomethane is added dropwise to the dry ice-cooled, stirring solution of the alkynyllithium intermediate. The reaction mixture is maintained at dry ice temperature for 1 hr, and, after warming to room temperature, the tetrahydrofuran is removed by mild rotary evaporation (or distillation at atmospheric pressure). The crude product is dissolved in 100 mL of ether and washed with brine (50 mL), and the aqueous phase is back-extracted with ether (25 mL). The combined organic phases are concentrated and the residue is dissolved in 200 mL of methanol. p-Toluenesulfonic acid (4 g) is added and the resulting solution is heated at reflux for 3 hr. The solvent is removed by distillation through an 8–10 cm Vigreux column, the residue is dissolved in 100 mL of ether and this solution is extracted with 25 mL of aqueous 10% sodium carbonate solution. After the solution is dried over $MgSO_4$, the solvent is removed by distillation and the residue is distilled through a 50-cm concentric tube column. The fraction boiling at 92–93°C (10 mm Hg) is collected to give 7.8 g (94%) of 4-hexyn-1-ol, which is >95% pure by GC analysis (30 m, Supelco SPB-5 capillary column).
3. Triethylamine, distilled from CaH_2, and methanesulfonyl chloride, vacuum distilled at ca. 60°C (20 mm), are employed.
4. The spectrum is as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78 (t, 3 H, J = 2.5), 1.91 (apparent pentaplet, 2 H, J = 6.5), 2.25–2.35 (m, 2 H), 3.03 (s, 3 H), 4.35 (t, 2 H, J = 6.1).
5. Dimethyl sulfoxide, distilled at 20 mm from CaH_2, and benzylamine, freshly distilled at 20 mm, are employed.
6. The reaction is easily monitored by TLC (silica gel, 1:1 ether-ethyl acetate): mesylate R_f = 0.9, amine R_f = 0.4.
7. This material can also be purified by vacuum distillation; however, some decomposition results.
8. This material is 97% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column). Spectral data are as follows: IR (film) cm^{-1}: 3330, 1453, 1120, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69 (apparent pentaplet, 2 H, J = 7), 1.77 (t, 3 H, J = 2.5), 2.15–2.25 (m, 2 H), 2.73 (t, 2 H, J = 7.0), 3.80 (s, 2 H), 7.2–7.4 (m, 5 H); MS (isobutane CI): 188 (MH), 172, 120, 91; high resolution MS (70 eV, EI) 187.1331 (187.1261 Calcd for $C_{13}H_{17}N$).
9. Fisher *Certified* sodium iodide is used as received.
10. Fisher *Certified* A.C.S. formaldehyde solution is used as received. Aldrich Chemical Company, Inc., camphorsulfonic acid monohydrate is recrystallized from ethyl acetate prior to use.
11. This conversion is easily monitored by TLC (silica gel, 1:1 hexane-ethyl acetate containing 5% triethylamine): **2**, R_f = 0.4, **3**, R_f = 0.7.
12. The free base of this iodoamine darkens slowly when exposed to room light. The isolation procedure should be conducted rapidly or the separatory funnel and rotary evaporator bulb should be wrapped in aluminum foil to exclude room light.
13. This material is at least 95% pure by capillary GC analysis (30 m, J & W DB-5 fused silica column); a small unknown impurity (ca. 2%) with characteristic ^{1}H NMR signals at δ 3.41, 4.77 and 4.92 is apparent in some chromatography fractions. Spectral data for **3** are as follows: IR (film) cm^{-1}: 1646, 1228, 1138, 1119, 1061, 739; ^{1}H NMR δ: 1.55–1.8 (m, 2 H), 2.40 (t, 2 H, J = 6.3), 2.45 (s, 3 H), 2.56 (t, 2 H, J = 5.5), 3.10 (s, 2 H), 3.57 (s, 2 H), 7.2–7.4 (m, 5 H); MS (isobutane CI): 328 (MH), 202, 200,

112, 110, 92. High resolution MS (70 eV, EI): 327.0465 (327.0484 calcd for $C_{14}H_{18}NI$).
14. The maleate salt is prepared in good yield and crystallizes as fine needles (ca. 1 g of salt/10 mL) from absolute ethanol: mp 143–144°C. This salt can be stored at room temperature in room light with no noticeable decomposition. Anal. Calcd. for $C_{18}H_{22}INO_4$: C, 48.77; H, 5.00; N, 3.16. Found: C, 48.70; H, 5.00; N, 3.09.

Waste Disposal Information

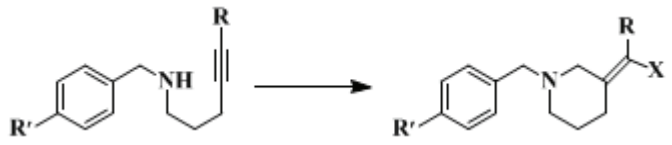
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

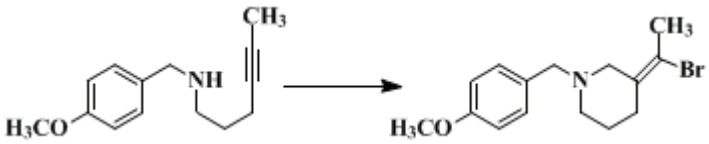
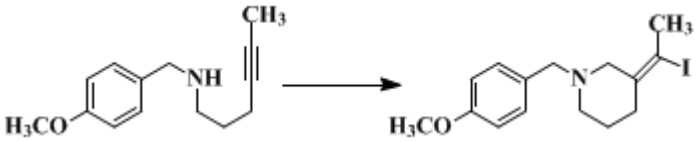
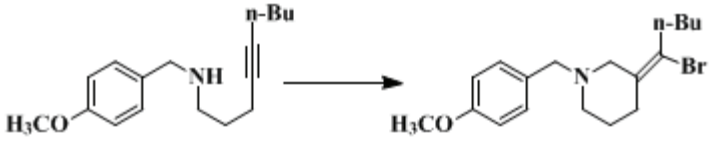
3. Discussion

Simple alkynes do not undergo intramolecular reactions with weakly electrophilic iminium ions in the absence of strong external nucleophiles.[3] For example, the formaldiminium ion derived from 4-hexynylamine, formaldehyde, and camphorsulfonic acid does not cyclize when maintained in acetonitrile at 100°C for 1 hr.[3] Iminium ion-alkyne cyclizations do take place in nucleophilic solvents such as H_2O[4] or in non-nucleophilic solvents when a strong nucleophile is present.[3]

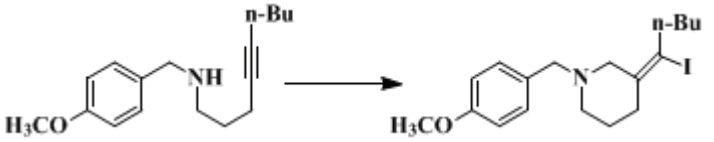
The present procedure illustrates the use of added iodide anion to promote the Mannich cyclization of an alkyne to afford 3-alkylidenepiperidines. As illustrated in Table I a variety of nonbasic nucleophiles with nucleophilic constants[5] η-CH_3I >5.8 are useful promoters of formaldiminium ion-alkyne cyclizations.[3] Piperidines containing both endocyclic and exocyclic allylic unsaturation can be efficiently assembled in this way from readily available alkynol precursors (see Table I).[3] To the limits of ^1H NMR detection at 500 MHz all nucleophile-promoted cyclizations that form 3-alkylidenepiperidines occur with complete anti-stereoselectivity.

TABLE I
NUCLEOPHILE-PROMOTED IMINIUM ION-ALKYNE CYCLIZATIONS[3]

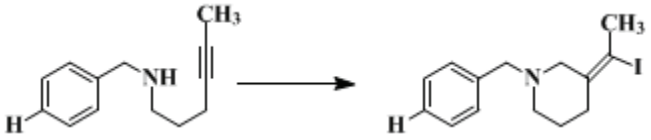


R'	R	X	Yield
OCH_3	CH_3	Br	 89%
OCH_3CH_3	CH_3	I	 80%
OCH_3	n-Bu	Br	

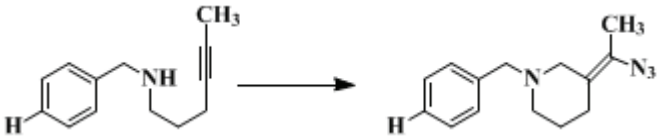
63%[6]

OCH_3 n-Bu I 

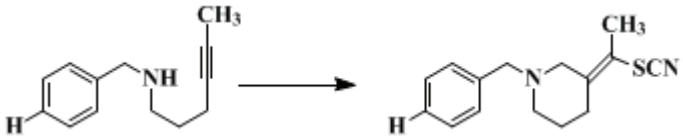
76%[6]

H CH_3 I 

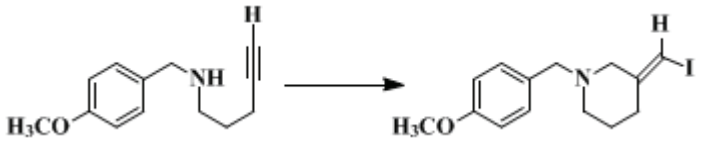
81-90%

H CH_3 N_3 

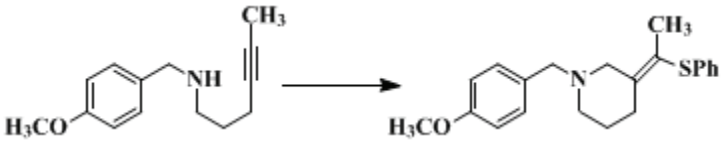
72%

H CH_3 SCN 

82%

OCH_3 H I 

56%

OCH_3 CH_3 SPh 

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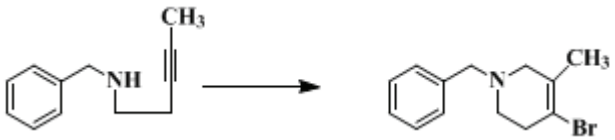
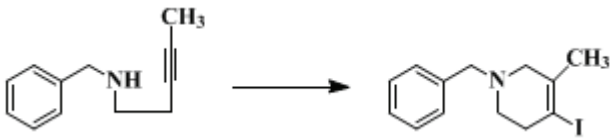
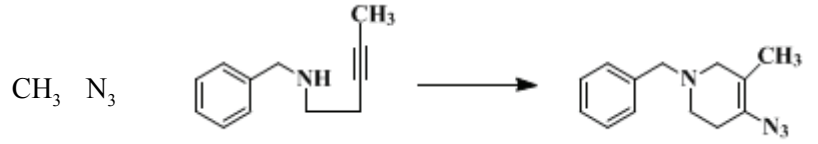
CH_3 Br 

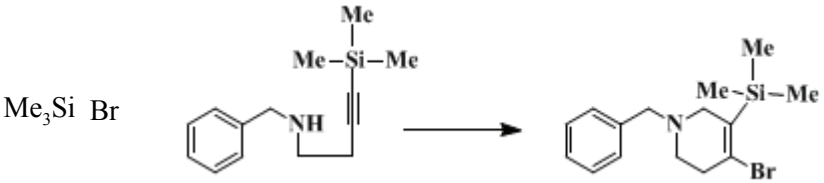
75%

CH_3 I 

90%



40%



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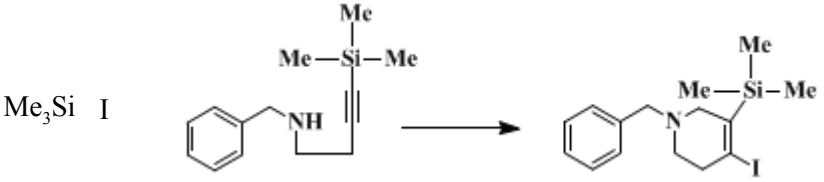

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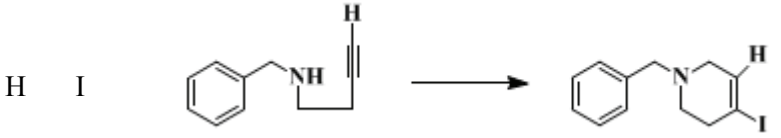
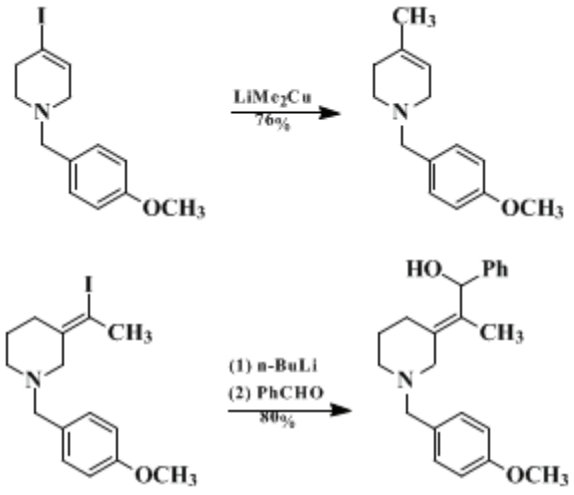
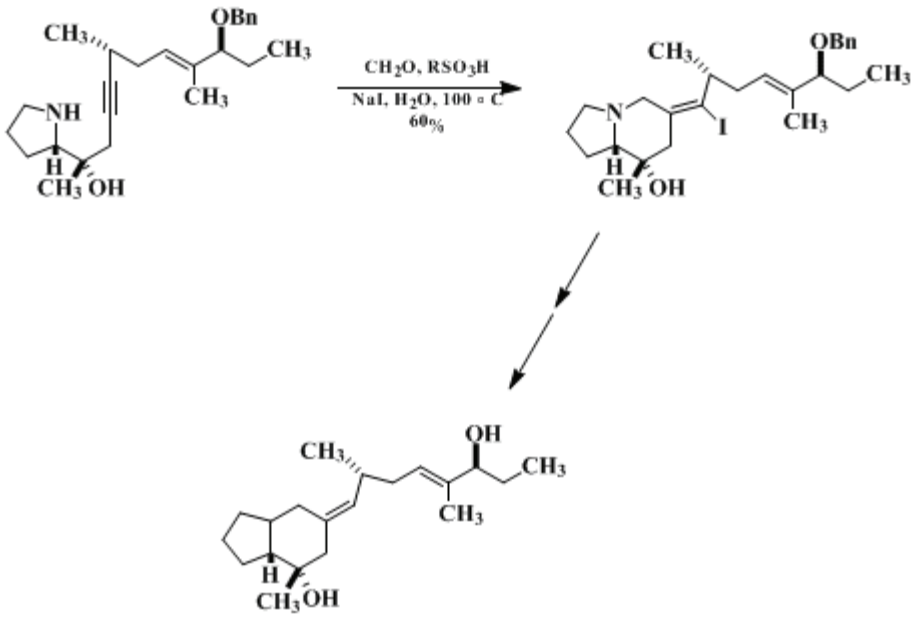


87%

The usefulness of nucleophile-promoted iminium ion-alkyne cyclizations derives from the ready availability of alkynylamines and the subsequent transformations of the cyclization products made possible because of their vinylic functionality (e.g., equations 1 and 2). Equation 2 illustrates use of this chemistry to elaborate an exocyclic tetrasubstituted double bond with complete stereocontrol. Net "reductive" iminium ion alkyne cyclizations can be accomplished by dehalogenation of vinyl halide cyclization products. The conversion illustrated in equation 3 is a key step in an efficient, practical synthesis of the cardiotonic frog alkaloid pumiliotoxin A.[7]





References and Notes

1. Department of Chemistry, University of California, Irvine, CA 92717.
2. Negishi, E.-i.; Chiu, K.-W. *J. Org. Chem.* **1976**, *41*, 3484.
3. Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612, 5934.
4. Ahmad, V. U.; Feuerherd, K. H.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 3624.
5. Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968** *90*, 319.
6. Sharp, M. J. unpublished examples.
7. Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.

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

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

formaldehyde (50-00-0)

sodium bicarbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

potassium hydroxide (1310-58-3)

iodomethane (74-88-4)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

Methanesulfonyl chloride (124-63-0)

mesylate (75-75-2)

4-Pentyn-1-ol (5390-04-5)

camphorsulfonic acid (5872-08-2)

p-toluenesulfonic acid (104-15-4)

(E)-1-Benzyl-3-(1-iodoethylidene)piperidine (146980-71-4)

Piperidine, 3-(iodoethylidene)-1-(phenylmethyl)-(E)

4-Hexyn-1-yl methanesulfonate (68275-05-8)

4-hexyn-1-ol (928-93-8)

N-Benzyl-4-hexyn-1-amine (112069-91-7)

camphorsulfonic acid monohydrate (5872-08-2)

tetrahydro-2-(4-pentynyloxy)-2H-pyran (62992-46-5)

iodoamine

4-hexynylamine