Organic Syntheses

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.

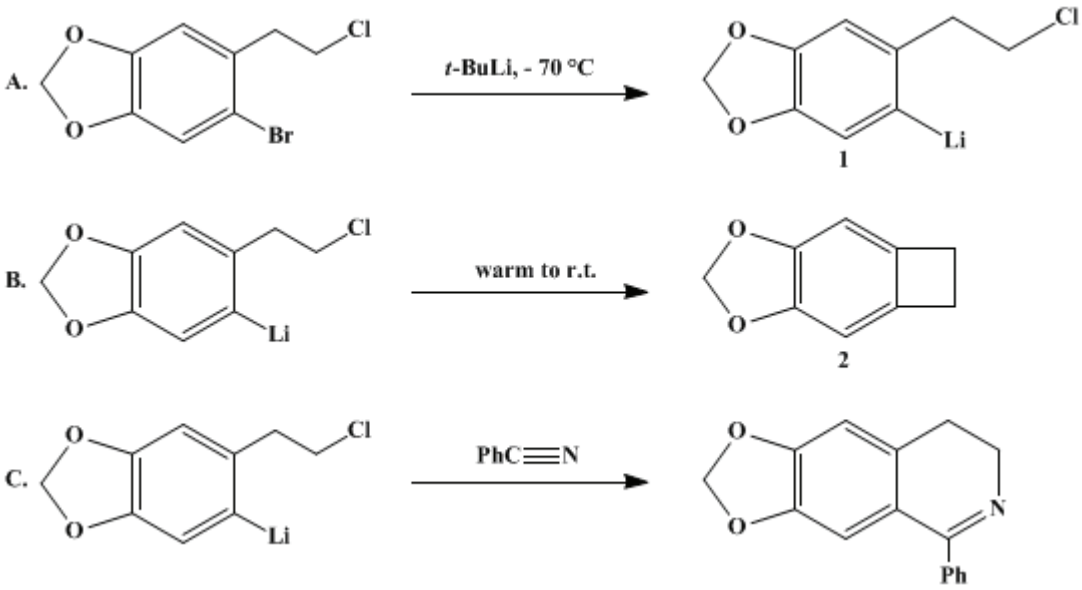
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.062.0074

Organic Syntheses, Coll. Vol. 7, p.326 (1990); Vol. 62, p.74 (1984).

SELECTIVE HALOGEN-LITHIUM EXCHANGE REACTIONS OF 2-(2'-HALOPHENYL)ETHYL HALIDES: SYNTHESIS OF 4,5-METHYLENEDIOXYBENZOCYCLOBUTENE AND 1-PHENYL-3,4-DIHYDRO-6,7-METHYLENEDIOXYISOQUINOLINE

[Cyclobuta[*f*]-1,3-benzodioxole, 5,6-dihydro- and 1,3-dioxolo [4,5-*g*]isoquinoline, 7,8-dihydro-5-phenyl-]



Submitted by Dennis J. Jakiela, Paul Helquist[1], and Lawrence D. Jones[2].
Checked by Neville D. Emslie and Ian Fleming.

1. Procedure

Caution! tert-Butylithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].

A. *2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, 50-mL pressure-equalizing addition funnel (Note 1), low-temperature thermometer, and a three-way stopcock having a vertically oriented tube capped with a rubber septum and a horizontal tube connected to a source of dry nitrogen and vacuum, is charged with 10.0 g (37.9 mmol) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride (Note 2). The assembled apparatus is evacuated and refilled with nitrogen three times. Freshly distilled diethyl ether (200 mL) (Note 3) is added to the flask by means of a double-ended needle (0.5 m in length) inserted through the vertical tube of the stopcock while a slight vacuum is applied to the apparatus. A slightly positive pressure of nitrogen is then maintained in the apparatus throughout the course of the reaction. The solution is cooled in a dry ice–acetone bath (Note 4). The glass jacket (or styrofoam cup) (Note 1), which surrounds the addition funnel, is filled with powdered dry ice, and 33 mL of a 2.3 *M* solution of *tert*-butyllithium (76 mmol) in pentane (Note 5) is added to the addition funnel by means of a syringe. After 10 min the lithium reagent is added dropwise to the flask over a period of 1 hr, while the temperature of the reaction mixture is maintained below −60°C. The solution of the resulting aryllithium reagent **1** is then used in either of the two reactions described below.

B. *4,5-Methylenedioxybenzocyclobutene*. The reaction mixture from Step A is simply allowed to warm to room temperature over a period of several hours, during which time a white precipitate forms. After 18 hr, 100 mL of water is slowly added and the mixture is transferred to a 500-mL separatory funnel. As the mixture is shaken, the solid dissolves in

the aqueous phase, which becomes light brown. The aqueous layer is extracted with two 75-mL portions of diethyl ether, and the combined organic layers are reduced in volume to 150 mL by rotary evaporation, washed with 75 mL of water and then 75 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to dryness by rotary evaporation to give 5.6 g of pale-yellow solid (Note 6). This crude product is transferred to a large, dry ice-cooled sublimation apparatus (Note 7) and sublimed over a 6-hr period at 35°C (0.07 mm), at which time a dark-brown oil remains in the bottom of the apparatus. The vacuum is released by filling the apparatus with nitrogen, and the cooled portion of the apparatus is allowed to warm to room temperature. Pure 4,5-methylenedioxybenzocyclobutene, **2** (5.1–5.2 g, 91–93%) is obtained as colorless crystals, mp 60–62°C (Note 8).

C. *1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline*. The reaction mixture containing the aryllithium intermediate is stirred for 15 min (internal temperature −65 to −68°C), and then 4.3 mL (42 mmol) of distilled benzonitrile is added quickly. The mixture is allowed to warm gradually to room temperature and the stirring is continued overnight. The yellow solution (Note 9) is diluted with 25 mL of ether, the mixture is poured into a 1-L separatory funnel, and the reaction flask is rinsed with an additional 75 mL of ether. The combined ether solutions are washed with 150 mL of water and then extracted with three 75-mL portions of 10% (w / w) hydrochloric acid. The combined acid extracts are rendered basic by the addition of 100 mL of 20% (w / w) aqueous sodium hydroxide solution, and the resulting milky white mixture is extracted with three 75-mL portions of dichloromethane. The combined organic extracts are washed with 50 mL of water and 50 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness by rotary evaporation, to give 8.96 g (94% crude yield) of orange-tan solid. This material is purified by recrystallization from ethyl acetate : acetone 2 : 1 (v : v) to give a first crop (6.8 g), and by flash chromatography[3] of the residue from the mother liquor, using 150 g of 230–400-mesh silica gel (Merck), a 40-mm diameter column, and elution with 10 : 1 (v : v) ethyl acetate : methanol. A fast-moving orange band and a slower moving lemon–yellow band can be seen clearly on the column. The lemon-yellow band is collected from the column and evaporation gives a second crop (1.4 g) of comparably pure material. The total yield of the pale-yellow isoquinoline is 8.2 g (86%), mp 135–137°C (Note 10).

2. Notes

1. The checkers used a home-made, glass-jacketed funnel sealed with a rubber septum. The submitters cut one side and part of the bottom of a styrofoam cup and held this in place with tape around the lower part of the addition funnel.

2. This starting material is prepared in three steps from commercially available (from Research Organic/Inorganic Chemical Corp., Belleville, NJ) 3,4-methylenedioxyphenylacetic acid according to well-established procedures that have been applied to similar compounds.[4 5 6 7 8 9] As an alternative starting material that could be used in a closely related fashion, 3,4-methylenedioxyphenylacetonitrile is available from Aldrich Chemical Company, Inc. First, 16.0 g (88.8 mmol) of the acid, recrystallized from chloroform, is dissolved in 50 mL of tetrahydrofuran, and the solution is added to a suspension of 5.98 g (158 mmol) of lithium aluminum hydride powder in 225 mL of distilled diethyl ether (Note 3) at 0°C. *(Caution: Lithium aluminum hydride is very sensitive to mechanical shock and very reactive toward moisture and other protic substances; its dust is very irritating to skin and mucous membranes. It should not be allowed to come into contact with metallic species of apparatus, including metal spatulas, because of the potential danger of metal ion-promoted detonation.)* The mixture is stirred at 25°C for 16 hr and is then quenched[10] by the careful, dropwise addition of 6 mL of 15% aqueous sodium hydroxide, and finally 18 mL of water. *(Caution: The reaction of excess lithium aluminum hydride with water is very exothermic and produces a large volume of hydrogen gas.)* The resulting mixture is stirred for 1 hr and is then subjected to vacuum filtration. The white solid that is retained is washed with three 50-mL portions of diethyl ether, and the combined filtrates are concentrated by rotary evaporation to give 13.1 g (89%) of 2-(3',4'-methylenedioxyphenyl)ethanol as a clear yellow oil, bp 136–140°C (0.003 mm). Next, 12.7 g (76.5 mmol) of this compound and 7.4 mL (91.5 mmol) of pyridine are dissolved in 200 mL of dichloromethane at 0°C, and 4.3 mL (83.9 mmol) of neat bromine is added to the solution over a 4-min period. After the solution has been stirred at 25°C for 16 hr, it is washed with three 50-mL portions of 2 *N* hydrochloric acid, two 50-mL portions of saturated aqueous sodium sulfite, two 50-mL portions of water, and 50 mL of saturated aqueous sodium chloride. The organic layer is then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to give 18.6 g (99.5%) of yellow solid. Recrystallization from a mixture of 160 mL of hexane and 60 mL of ethyl acetate gives 14.6 g (78%) of 2-(2'-bromo-4',5'-methylenedioxyphenyl)ethanol as light yellow needles, mp 93–94°C. Finally, 9.95 mL (123 mmol) of distilled pyridine and 8.75 mL (120 mmol) of distilled thionyl chloride are added separately to a solution of 14.4 g (58.8 mmol) of the preceding product and 180 mL of chloroform at 25°C. The mixture is heated at reflux for 18 hr, cooled to 25°C, washed with 40 mL *N* hydrochloric acid, 40 mL of 5% aqueous sodium carbonate, two 40-mL portions of water, and 40 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation to give 14.0 g (90%) of brown crystals. Distillation gives 13.0 g (84%) of an oil (bp 130–134°C at 0.006 mm), which solidifies to give the final product as colorless crystals: ^{1}H-NMR ($CDCl_3$) δ: 3.08 (t, 2 H, J = 6.8),

3.67 (t, 2 H, J = 6.8), 5.95 (s, 2 H), 6.74 (s, 1 H), and 6.98 (s, 1 H); mp 47.0–47.5°C (corrected).

3. Commercially available anhydrous diethyl ether is distilled under nitrogen from a solution of the sodium benzophenone radical anion generated by treating a solution of 10 g of benzophenone and 1 L of ether with 10 g of sodium ribbon until a dark-blue or purple color persists.

4. Although the dry ice–acetone bath itself attains a temperature of −78°C, the lowest temperature achieved by the solution within the flask is only −68°C.

5. *Caution: tert-Butyllithium is pyrophoric in air; excess quantities of the reagent in the syringe should be discarded very carefully.* The checkers used the reagent available from Aldrich Chemical Company Ltd., England and standardized it by double titration with ethylene dibromide and hydrochloric acid.[11]

6. The submitters also ran the reaction on smaller scales using from 0.5 to 5.0 g of starting material and regularly obtained a crude yield of 98–105% at this stage.

7. The sublimation apparatus should have a least a 1-cm separation between the upper surface of the crude solid to be sublimed and the bottom of the cooling surface in order to avoid splattering of the oily residue onto the purified product near the end of the sublimation procedure.

8. The product showed the following spectral properties: ^{1}H NMR ($CHCl_3$) δ: 3.00 (s, 4 H), 5.75 (s, 2 H), and 6.50 (s, 2 H).

9. At this stage, the submitters had a brick-red reaction mixture that became yellow on dilution with ether.

10. The product showed the following spectral properties: ^{1}H-NMR ($CDCl_3$) δ: 2.67 (t, 2 H, J = 7.5), 3.73 (t, 2 H, J = 7.5), 5.83 (s, 2 H), 6.63 (s, 2 H), and 7.37 (m, 5 H).

3. Discussion

The halogen–metal exchange reaction was pioneered by Gilman and coworkers,[12] who established that substituted aryl bromides would exchange efficiently with butyllithium and that the reaction was of synthetic value provided the substituent was not reactive toward alkyl- or aryllithium reagents. More recently, Parham[8,13 14 15] and others[9,16 17 18 19 20 21 22] further defined the scope and limitations of this reaction by demonstrating that haloarenes substituted with electron-withdrawing (CO_2H, CN, CO_2R) or electron-donating [OR, OCH_2O, $(-CH_2-)_nX$, where X = Br, Cl] functional groups would selectively exchange with alkyllithium reagents at low temperature. While a detailed mechanistic evaluation is not within the scope of this discussion, the halogen–metal exchange reaction has been shown to be reversible and rapid at −75°C, and in the exchange of alkyllithium with a haloarene, the equilibrium reaction favors formation of the lithioarene.[12,23,24]

As exemplified in the present procedure, the reaction has been optimized and extended in scope; it affords functionalized benzocyclobutenes as well as substituted isoquinolines in high yields. Benzocyclobutenes have been used as intermediates in the synthesis of many naturally occurring alkaloids,[25] steroids,[26 27 28 29 30] polycyclic terpenoids,[31] and anthracycline antibiotics.[32] The traditional routes leading to the preparation of benzocyclobutenes have been reviewed[33] and have involved (1) Cava's cyclization of *o*-quinodimethane intermediates (via reaction of sodium iodide with α,α,α',α'-tetrabromo-*o*-xylene) (2) thermal extrusion of sulfur dioxide from 1,3-dihydroisothianaphthene 2,2-dioxide, (3) dehydrogenation of the Diels–Alder adducts of 1,4-butadienes and cyclobutenes, and (4) Wolff rearrangement of α-diazoindanones. More recent methods include (1) thermal rearrangement of *p*-tolylcarbene,[34] (2) thermal decomposition of 3-isochromanones,[25] and (3) cobalt-catalyzed cyclizations of acetylenic compounds.[35] Many of these methods for synthesizing functionalized benzocyclobutenes involve (a) multistep routes, (b) unusual or relatively unavailable starting materials, (c) low overall yields, or (d) special apparatus. The method of halogen–metal exchange demonstrates a high degree of selectivity for formulation of the lithioarene intermediate, is broad in scope without loss of procedural simplicity, and provides a high-yield route to benzocyclobutenes of general synthetic utility by direct cyclization of readily available 2-(2'-lithiophenyl)ethyl chlorides.[8,9,17]

The lithioarene intermediate has also been shown to be of use in the synthesis of the isoquinoline ring system. This ring system is common to a variety of natural products that possess useful physiological activity. Several methods have been developed for the synthesis of isoquinolines; the most commonly used routes are the Bischler–Napieralski and the Pictet–Spengler reactions.[36 37 38 39 40,41 42 43 44] These methods involve electrophilic, aromatic substitution in the key ring-forming steps with the limitation that best results are obtained only when the aromatic ring bears electron-donating substituents. The present method permits use of substrates either with or without electron-donating groups on the aromatic nucleus since generation of the lithioarene has been shown to be relatively independent of the nature of the substituents.[13,d]

References and Notes

1. Department of Chemistry, State University of New York, Stony Brook, NY 11794. Partial support was provided by the National Institutes of Health (Grant No. CA22741). Present address of Paul Helquist: Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.
2. Johnson Matthey Inc., Wayne, PA 19087; formerly of FMC Corporation, Princeton, NJ 08540, which we acknowledge for partial support of this work.
3. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
4. Bickelhaupt, F.; Stach, K.; Thiel, M. *Chem. Ber*. **1965**, *98*, 685;
5. Gilman, H.; Marrs, O. L. *J. Org. Chem*. **1965**, *30*, 325;
6. Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem*. **1974**, *39*, 3052
7. Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc*. **1975** *97*, 2507–2516;
8. Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem*. **1976**, *41*, 1184;
9. Bradsher, C. K.; Hunt, D. A. *Org. Prep. Proc. Int*. **1978**, *10*, 267.
10. Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p. 584.
11. Whitesides, G. M.; Casey, C. P.; Kreiger, J. K. *J. Am. Chem. Soc*. **1971**, *93*, 1379.
12. Jones, R. G.; Gilman, H. *Org. React*. **1951**, *6*, 339.
13. Parham, W. E.; Sayed, Y. A. *J. Org. Chem*. **1974**, *39*, 2053;
14. Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem*. **1975**, *40*, 2394;
15. Parham, W. E.; Jones, L. D. *J. Org. Chem*. **1976**, *41*, 2704.
16. Hergrueter, C. A.; Brewer, P. D.; Tagat, J.; Helquist, P. *Tetrahedron Lett*. **1977**, 4145;
17. Brewer, P. D.; Tagat, J.; Hergrueter, C. A.; Helquist, P. *Tetrahedron Lett*. **1977**, 4573;
18. Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem*. **1981**, *46*, 118;
19. Parham, W. E.; Bradsher, C. K.; Hunt, D. A. *J. Org. Chem*. **1978**, *43*, 1606; Bradsher, C. K.; Reames, D. C. *J. Org. Chem*. **1978**, *43*, 3800;
20. Bradsher, C. K.; Hunt, D. A. *J. Org. Chem*. **1980**, *45*, 4248;
21. Reames, D. C.; Hunt, D. A.; Bradsher, C. K. *Synthesis* **1980**, 454;
22. Toth, J. E.; Fuchs, P. L. *J. Org. Chem*. **1987**, *52*, 473.
23. Gilman, H.; Jones, R. G. *J. Am. Chem. Soc*. **1941**, *63*, 1441.
24. The use of two equivalents of alkyllithium reagent to effect lithium–halogen exchange reactions most efficiently was developed by Seebach and Neuman; see Neuman, H.; Seebach, D. *Chem. Ber*. **1978**, *111*, 2785.
25. Spangler, R. J.; Bechmann, B. G.; Kim, J. H. *J. Org. Chem*. **1977**, *42*, 2989 and references cited therein.
26. Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc*. **1978**, *100*, 6218;
27. Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Chem. Commun*. **1979**, 1119;
28. Oppolzer, W.; Roberts, D. A. *Helv. Chim Acta* **1980**, *63*, 1703;
29. Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem*. **1980**, *45*, 2247;
30. Kametani, T.; Suzuki, K.; Nemoto, H. *J. Org. Chem*. **1980**, *45*, 2204.
31. Kametani, T.; Hirai, Y.; Shiratori, Y.; Fukumoto, K.; Satoh, F. *J. Am. Chem. Soc*. **1978**, *100*, 554.
32. Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G.; *Tetrahedron Lett*. **1978**, 3765.
33. Klundt, I. L. *Chem. Rev*. **1970**, *70*, 471; see also Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc*. **1960**, *82*, 2524 and references cited therein; Thummel, R. P.; Nutakul, W. *J. Org. Chem*. **1977**, *42*, 300; Radlick, P.; Brown, L. R. *J. Org. Chem*. **1973**, *38*, 3412.
34. Hedaya, E.; Kent, M. E. *J. Am. Chem. Soc*. **1971**, *93*, 3283.
35. Vollhardt, K. P. C. *Acc. Chem. Res*. **1977**, *10*, 1.
36. For extensive discussions concerning the synthesis, pharmacology, and other properties of isoquinolines, see: (a) McCorkindale, N. J. In "The Alkaloids," Grundon, M. F., Senior Reporter; The Chemical Society: London, 1976; Vol. 6, Chapter 8, and the earlier volumes in this series;
37. "The Alkaloids: Chemistry and Physiology"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. XV, Chapters 3 and 5, and the earlier volumes of this series;
38. Kametani, T. "The Chemistry of the Isoquinoline Alkaloids"; Hirokawa Publishing Co, Inc.; Tokyo, 1969; Vol. 1, Kinkodo Publishing Co.: Sendai 1974; Vol. 2;
39. Shamma, M. "The Isoquinoline Alkaloids"; Academic Press: New York, 1972;
40. Kametani, T. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. 3, pp. 1–272.
41. For other more recent methods for the synthesis of isoquinolines, see [36] and [38] and other works cited therein, in addition to: (a) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun*. **1978**, 379;
42. Barrett, A. G. M.; Barton, D. H. R.; Falck, J. R.; Papaioannou, D.; Widdowson, D. A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 652;
43. Kozikowski, A. P.; Ames, A. *J. Org. Chem*. **1980**, *45*, 2548;
44. Mendelson, W. L.; Spainhour, C. B.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett*. **1980**, *21* 1393.

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

silica gel

2-(2'-Lithio-4',5'-methylenedioxyphenyl)ethyl chloride

2-(2'-bromo-4',5'-methylenedioxyphenyl)ethyl chloride

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

benzonitrile (100-47-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sulfur dioxide (7446-09-5)

nitrogen (7727-37-9)

acetone (67-64-1)

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium ribbon (13966-32-0)

ethylene dibromide (106-93-4)

sodium iodide (7681-82-5)

Pentane (109-66-0)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride,
lithium aluminum hydride powder (16853-85-3)

hexane (110-54-3)

isoquinoline (119-65-3)

4,5-Methylenedioxybenzocyclobutene

1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline,
1,3-dioxolo [4,5-g]isoquinoline, 7,8-dihydro-5-phenyl- (55507-10-3)

3,4-methylenedioxyphenylacetic acid (2861-28-1)

3,4-methylenedioxyphenylacetonitrile (4439-02-5)

tert-Butyllithium (594-19-4)

1,3-dihydroisothianaphthene 2,2-dioxide

Cyclobuta[f]-1,3-benzodioxole, 5,6-dihydro- (61099-23-8)

o-quinodimethane

p-tolylcarbene

α,α,α',α'-tetrabromo-o-xylene (13209-15-9)