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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.

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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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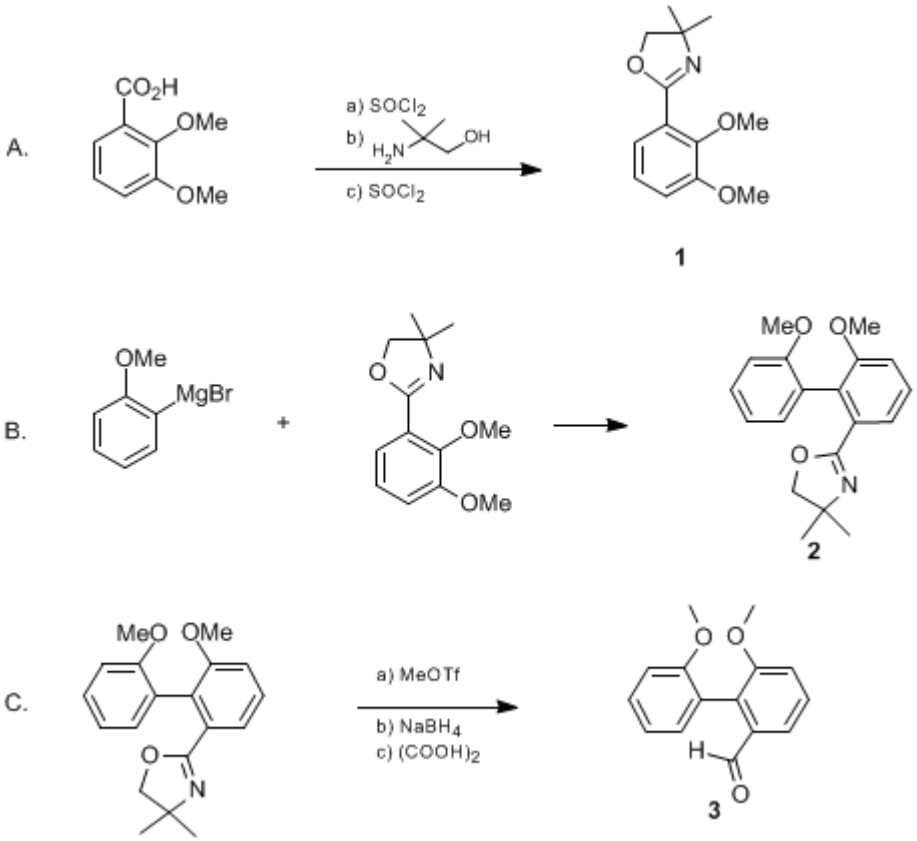
2,2'-DIMETHOXY-6-FORMYLBIPHENYL

[(1,1'-Biphenyl)-2-carboxaldehyde, 2',6-dimethoxy-]



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Checked by Chris H. Senanayake and Ichiro Shinkai.

1. Procedure

Caution! This procedure should be performed in a well-ventilated hood.

A. *2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline*. To a 100-mL, round-bottomed flask, fitted with a magnetic stirring bar and a reflux condenser and placed in an ice-water bath, is added 24.5 g (0.206 mol) of thionyl chloride (Note 1). To this is added 12.2 g (0.067 mol) of 2,3-dimethoxybenzoic acid (Note 2). The resulting mixture is stirred at 0°C for 1 hr and then at room temperature for 24 hr. Excess thionyl chloride is removed by rotary evaporation (HOOD!) and the residue is distilled using a Kugelrohr apparatus at 105°C (0.05 mm) to give 12.7–13.1 g of 2,3-dimethoxybenzoyl chloride, which crystallizes on cooling (Note 3).

The acid chloride, 12.7 g, is dissolved in 60 mL of dichloromethane and transferred to a 300-mL, round-bottomed flask fitted with a magnetic stirring bar and a 100-mL, pressure-equalizing dropping funnel. The solution is cooled to 0°C in an ice bath. 2-Amino-2-methyl-1-propanol (12.5 g, 0.140 mol) dissolved in 50 mL of dichloromethane is added dropwise to the cold solution over 15 min. The reaction mixture is allowed to warm to room temperature and stirring is continued for 2 hr. The white precipitate (Note 4) is removed by filtration and the mother liquor is removed by rotary evaporation to afford 15.7 g of the amido alcohol (Note 5). The amido alcohol is redissolved in 100 mL of dichloromethane and added to a 300-mL round-bottomed flask fitted with a reflux condenser and a magnetic stirring bar.

Thionyl chloride (24.5 g, 0.206 mol) is added dropwise and the resulting mixture is stirred at room temperature for 1.5 hr (Note 6). The reaction mixture is cooled to 0°C (ice-water bath) and to it is added slowly 50 mL of cold water followed by approximately 50 mL of aqueous 40% sodium hydroxide solution, which basifies the reaction mixture to approximately pH 11. Saturated sodium chloride solution (approximately 50 mL) is added and the contents of the flask are transferred to a 1-L separatory funnel. The lower phase (CH_2Cl_2 solution) is removed and set aside while the upper, aqueous phase is extracted once with 50 mL of dichloromethane. The dichloromethane extracts are combined and dried over magnesium sulfate. The solution is then filtered through Celite and concentrated under reduced pressure to leave crude 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline **(1)**. The latter is distilled in a Kugelrohr apparatus at 110°C (0.05 mm) to give 12.7–13.3 g (81–85%) (Note 7).

B. *2,2'-Dimethoxy-6-(4",4"-dimethyloxazolinyl)biphenyl*. Magnesium turnings (3.3 g, 0.14 g-atom, (Note 8)) and 100 mL of dry ether (Note 9) are added to a flame-dried, 1-L, round-bottomed flask under a nitrogen atmosphere. The flask is fitted with a 250-mL addition funnel, reflux condenser, and magnetic stirring bar, and placed under a slow nitrogen flow. A few crystals of iodine are added to the reaction vessel followed by dropwise addition of 18 g (0.12 mol) of 2-bromoanisole (Note 10) in 150 mL of anhydrous ether (Note 11). When the addition is complete, the reaction mixture is stirred for 2 hr at room temperature. When it is apparent that formation of the Grignard solution has consumed most of the magnesium turnings, a solution of the dimethoxyphenyloxazoline, 11.2 g (0.048 mol) in 300 mL of anhydrous tetrahydrofuran (Note 12), is added dropwise at room temperature to the stirred Grignard solution. After addition is complete, stirring of the dark solution is continued for 24 hr or until reaction is complete (Note 13). The reaction mixture is quenched by careful addition of saturated ammonium chloride (50 mL) followed by addition of 50 mL of water. The contents are transferred to a 1-L separatory funnel and the lower aqueous phase is separated while the upper organic phase is set aside. The aqueous phase is returned to the separatory funnel and extracted once with 50 mL of ether; both ethereal phases are then combined, dried over magnesium sulfate, and filtered and concentrated under reduced pressure. There is obtained 19.2 g of a yellow solid that contains, in addition to the biphenyl, some anisole and other contaminants (e.g., starting materials). The volatile impurities are removed by Kugelrohr or other short path distillation (105°C, 0.05 mm, 15 min) to leave 14.2 g (96%) of crude biphenyl product. Purification is performed by recrystallization from ethyl acetate-hexane (1:1) to give 12.2–13.0 g (80–85%) of pure material (Note 14), (Note 15).

C. *2,2'-Dimethoxy-6-formylbiphenyl*. To a flame-dried, 1-L, round-bottomed flask, under nitrogen, and fitted with a magnetic stirring bar is added 12.2 g (0.039 mol) of pure biphenyloxazoline **2** in 300 mL of dry dichloromethane (Note 16). To this is added 7.9 g (0.048 mol) of methyl trifluoromethanesulfonate (Note 17) and the chilled solution is stirred at room temperature for 2–3 hr (Note 18). The solution of quaternized oxazoline is cooled to 0°C in an ice-water bath. Separately, 3.3 g (0.87 mol) of sodium borohydride is slurried at 0°C with 125 mL of absolute ethanol. The chilled slurry is added slowly, to control foaming, to the reaction mixture. When the addition is complete, the mixture is stirred at 0°C for 45 min and the contents of the flask are evaporated under reduced pressure. The resulting solid residue is dissolved in 400 mL of 4:1 tetrahydrofuran-water and 19.5 g (0.217 mol) of oxalic acid is added in portions (exotherm). The mixture is stirred at room temperature for 16–18 hr (Note 19). Tetrahydrofuran is removed under rotary evaporation to leave behind an aqueous slurry that is washed in a separatory funnel with pentane-ether (1:1, 2 × 100 mL). The upper layer is removed and the aqueous layer is extracted again with 50 mL of pentane-ether. The organic layers are combined and washed with 50 mL of aqueous 10% sodium bicarbonate and then with 50 mL of saturated brine. The aqueous washes are also back-extracted with pentane-ether which is combined with the other organic solutions. The organic layers are dried over sodium sulfate (anhydrous) and the solution is filtered through Celite. Concentration of the solution under reduced pressure gives 7.5 g (75–83%) of the final biphenyl aldehyde, mp 65–67°C. Recrystallization from 2-propanol gives 6.5 g of pure material (Note 20), (Note 21).

2. Notes

1. Thionyl chloride was purchased from Fisher Scientific Company.
2. 2,3-Dimethoxybenzoic acid was used as received from Aldrich Chemical Company, Inc.
3. The melting point was 53–54°C.

4. This is the hydrochloride of 2-amino-2-methyl-1-propanol.
5. The melting point was 77–80°C after air drying for several hours.
6. The formation of the 2,3-dimethoxyphenyloxazoline **(1)** can be readily followed by removing aliquots, neutralizing with aqueous sodium hydroxide, and checking on TLC using silica gel and eluting with hexane-acetone, 85:15; R_f is 0.29.
7. The physical properties are as follows: mp 44–46°C, ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.36 (s, 6 H), 3.83 (s, 6 H), 4.08 (s, 2 H), 6.96 (dd, 1 H, J = 8.2, 1.9), 7.02 (dd, 1 H, J = 8.2, 7.5), 7.29 (dd, 1 H, J = 7.5, 1.9).
8. Magnesium turnings were purchased from J. T. Baker Chemical Company.
9. Ether was distilled from benzophenone ketyl under nitrogen. The checkers used ether dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.
10. 2-Bromoanisole was purchased, and used without further purification, from Aldrich Chemical Company, Inc.
11. Warming of the reaction vessel with a water bath (~30°C) tends to expedite the initiation of the Grignard reagent.
12. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone ketyl under nitrogen. The checkers used THF dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.
13. The reaction is followed by TLC (silica, hexane-acetone, 85:15) and shows the disappearance of the dimethoxyphenyloxazoline **1** at R_f 0.29 and the appearance of the biphenyl **2** at R_f 0.18.
14. The physical properties are as follows: mp 127–129°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (s, 3 H), 1.19 (s, 3 H), 3.59 (d, 1 H, J = 8.1), 3.72 (d, 1 H, J = 8.1), 3.75 (s, 6 H), 6.98 (om, 2 H), 7.05 (dd, 1 H, J = 7.1, 2.4), 7.15 (dd, 1 H, J = 7.4, 1.7), 7.29 (dd, 1 H, J = 7.6, 1.8), 7.34–7.39 (om, 2 H).
15. If crude material is used in Step C, the yield of final product is approximately 50–58%.
16. Dichloromethane was dried by distilling from calcium hydride. The checkers used dichloromethane (reagent grade) kept over 4 Å molecular sieves for 2 days to obtain the same results.
17. Methyl trifluoromethanesulfonate was purchased from Aldrich Chemical Company, Inc.
18. Stirring is continued until quaternization of the oxazoline **2** is complete. This is easily monitored by TLC which shows only baseline salt (silica, hexane-acetone) and complete absence of the biphenyloxazoline at R_f 0.18.
19. The checkers report that the reaction can be followed by TLC, indicating disappearance of starting material and appearance of the aldehyde (R_f = 0.75, hexane-ethyl acetate, 75:25).
20. The physical properties are as follows: mp 75–76°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.74 (s, 3 H), 3.78 (s, 3 H), 7.01 (d, 1 H, J = 8.3), 7.06 (m, 1 H), 7.22 (dd, 1 H, J = 7.9, 17), 7.23 (dd, 1 H, J = 7.4, 1.8), 7.39–7.49 (om, 2 H), 7.63 (dd, 1 H, J = 7.8, 1.0), 9.68 (d, 1 H, J = 0.8).
21. The submitters report that this procedure can also produce the corresponding biphenyl carboxylic acid by omitting the quaternization-reduction step and subjecting the biphenyloxazoline **2** to hydrolysis as follows:
A slurry of **2** (0.1 M) in 4 M hydrochloric acid is heated at reflux for 16 hr. The solution is concentrated to dryness by rotary evaporation and the crude carboxylic acid, derived from **2**, is recrystallized from hexane-ethyl acetate-isopropyl alcohol (2:1:1) furnishing pure material in 80% yield, mp 196–197°C.

Waste Disposal Information

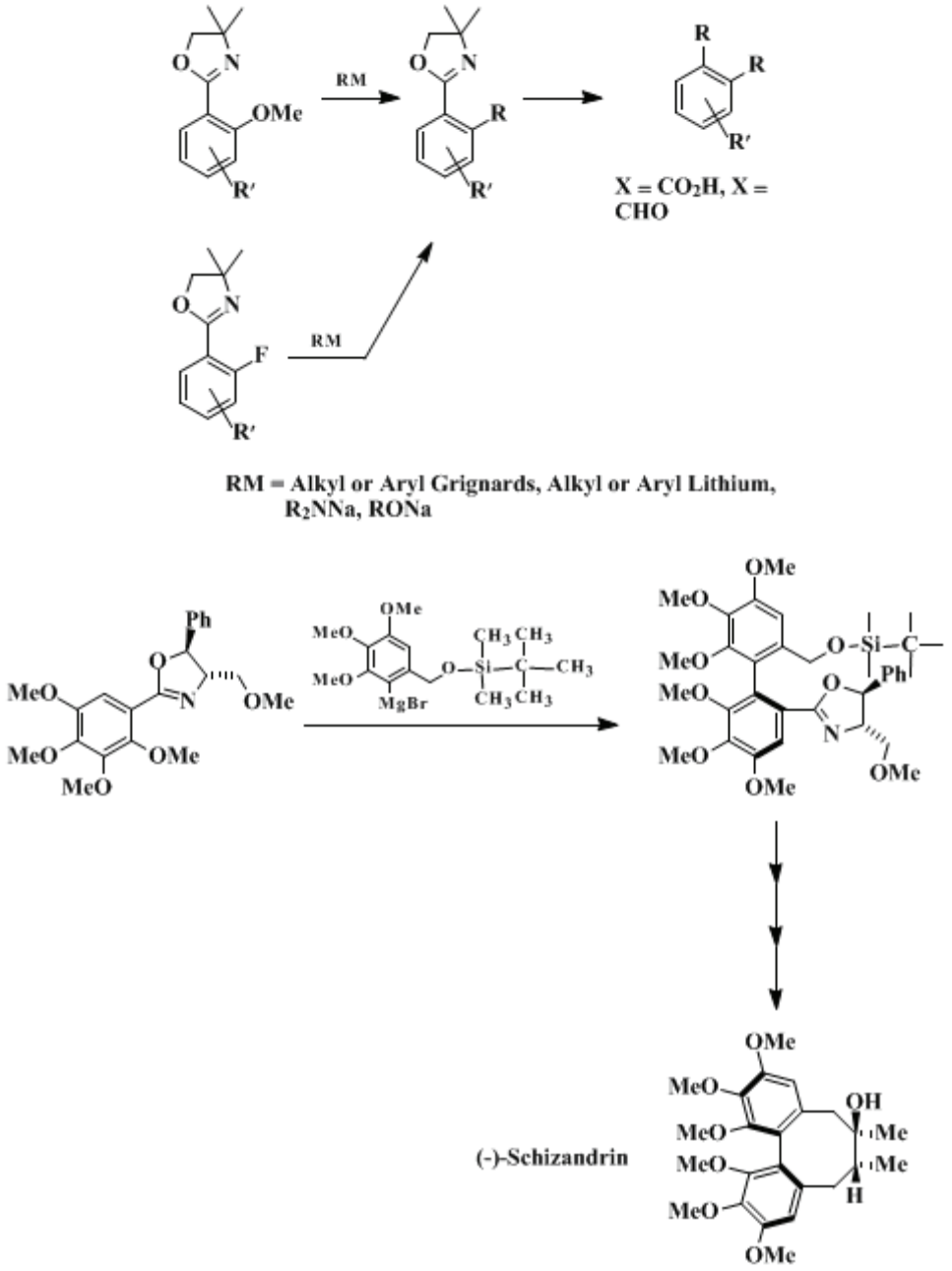
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The use of oxazolines in aromatic substitution is a valuable synthetic tool.[2] The o-methoxy- or o-fluorophenyloxazoline reacts readily with a variety of organolithium or Grignard reagents to displace only the ortho substituent. In this fashion a number of ortho-substituted benzoic acids, benzaldehydes, and unsymmetrical biphenyls are accessible. The reaction takes place under very mild conditions, usually at or below room temperature, and thus allows a number of other sensitive groups to be present.

In addition to the simple substitutions shown in Scheme 1, this reaction has been used in a variety of complex systems as a route to optically active substances. For example, use of chiral oxazolines in this

coupling process has led to an asymmetric synthesis of (−)-steganone,[3] podophyllotoxin,[4] (−)-schizandrin,[5] and (+)-phylictralin.[6] The synthesis of (−)-schizandrin is sketched in Scheme 2.



This method described here for preparing unsymmetrical biphenyls compares favorably with other recent and classical routes.[7,8,9,10]

References and Notes

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

silica gel

benzophenone ketyl

silica

brine

2,2'-Dimethoxy-6-(4",4"-dimethyloxazolinyl)biphenyl

o-methoxy- or o-fluorophenyloxazoline

(−)-steganone

podophyllotoxin

(−)-schizandrin

(+)-phylictralin

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

iodine (7553-56-2)

acetone (67-64-1)

isopropyl alcohol,
2-propanol (67-63-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

2-amino-2-methyl-1-propanol (124-68-5)

hexane (110-54-3)

calcium hydride (7789-78-8)

sodium borohydride (16940-66-2)

ethyl acetate-hexane (2639-63-6)

2,3-dimethoxybenzoic acid (1521-38-6)

methyl trifluoromethanesulfonate (333-27-7)

2,2'-Dimethoxy-6-formylbiphenyl,
(1,1'-Biphenyl)-2-carboxaldehyde, 2',6-dimethoxy- (87306-84-1)

2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (57598-32-0)

2,3-dimethoxybenzoyl chloride

2-bromoanisole (578-57-4)