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.

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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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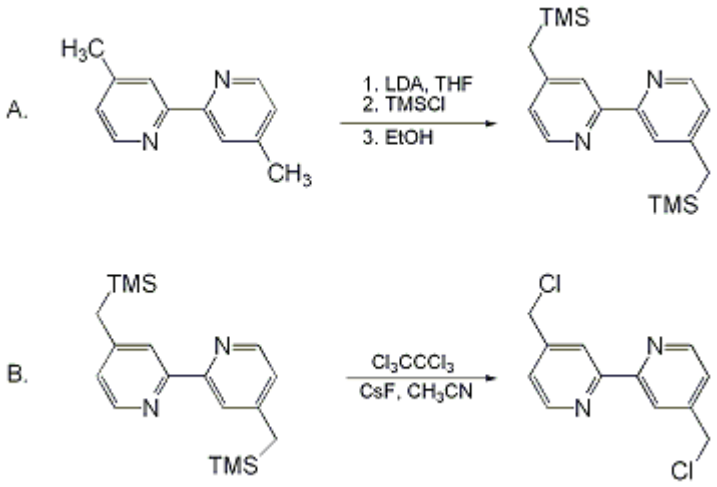
EFFICIENT SYNTHESIS OF HALOMETHYL-2,2'-BIPYRIDINES: 4,4'-BIS(CHLOROMETHYL)-2,2'-BIPYRIDINE

[2,2'-Bipyridine, 4,4'-bis(chloromethyl)-]



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Checked by Motoki Yamane and Koichi Narasaka.
Discussion Addendum *Org. Synth.* **2012**, *89*, 82

1. Procedure

A. 4,4'-Bis[(trimethylsilyl)methyl]-2,2'-bipyridine . A 500-mL, two-necked, round-bottomed flask (Note 1), equipped with a nitrogen inlet, magnetic stirrer, and rubber septum is charged with tetrahydrofuran (THF) (90 mL) (Note 2) and diisopropylamine (9.8 mL, 69.7 mmol) (Note 3). The reaction mixture is cooled to −78°C and a solution of butyllithium (n-BuLi) (1.7 M in hexanes, 36.0 mL, 61.4 mmol) (Note 4) is added. The solution is stirred at −78°C for 10 min, warmed to 0°C and stirred for 10 min, then cooled back to −78°C. A solution of 4,4'-dimethyl-2,2'-bipyridine (5.14 g, 27.9 mmol) (Note 5) in THF (130 mL) (Note 2), prepared in a 250-mL, two-necked, round-bottomed flask under a nitrogen atmosphere, is added via cannula to the cold lithium diisopropylamide (LDA) solution. The resulting maroon-black reaction mixture is stirred at −78°C for 1 hr, then chlorotrimethylsilane (TMSCl) (8.85 mL, 69.7 mmol) (Note 6) is rapidly added via syringe. After the solution becomes pale blue-green (≈10 sec after the TMSCl addition), the reaction is quenched by rapid addition of absolute ethanol (10 mL). (Note: the reaction should be quenched regardless of color change after a maximum of 15 seconds to avoid over silylation). The cold reaction mixture is poured into a separatory funnel (1 L) containing aqueous saturated sodium bicarbonate ($NaHCO_3$, ≈200 mL) and allowed to warm to ≈25°C. The product is extracted with dichloromethane (CH_2Cl_2, 3 × 300 mL); the combined organic fractions are shaken with brine (≈200 mL) and dried over sodium sulfate (Na_2SO_4). Filtration and concentration on a rotary evaporator affords 8.85 g (97%) of 4,4'-bis[(trimethylsilyl)methyl]-2,2'-bipyridine as a slightly off-white crystalline solid (Note 7).

B. 4,4'-Bis(chloromethyl)-2,2'-bipyridine . Into a 500-mL, two-necked, round-bottomed flask (Note 1) equipped with a magnetic stirring bar are placed 5.22 g (15.9 mmol) of 4,4'-bis[(trimethylsilyl) methyl]-2,2'-bipyridine , 15.1 g (63.6 mmol) of hexachloroethane (Cl_3CCCl_3, Note 8) and 9.65 g (63.6 mmol) of cesium fluoride (CsF, Note 9) at 25°C under a nitrogen atmosphere. Acetonitrile (260 mL) (Note 10) is added and the heterogeneous reaction mixture is stirred at 60°C for ≈3.5 hr (or until TLC indicates that all TMS starting material is consumed). After the mixture is cooled to 25°C, it is poured into a separatory funnel containing ethyl acetate (EtOAc) and water (H_2O, ≈100 mL each). The product is extracted with EtOAc (3 × 100 mL); the combined organic fractions are shaken with brine (≈200 mL) and dried over Na_2SO_4. Filtration and concentration on a rotary evaporator, followed by flash

chromatography using deactivated silica gel (60% EtOAc: 40% hexanes) (Note 11), gives 3.67 g (91%) of the chloride as a white solid (Note 12).

2. Notes

1. Before use, all glassware, needles, and syringes were dried overnight in a 120°C oven.
2. THF was dried and purified by passage through alumina solvent purification columns[2] or by distillation over sodium/benzophenone.
3. Diisopropylamine was purchased from Aldrich Chemical Company, Inc. , and distilled over calcium hydride (CaH_2) prior to use.
4. A 1.7 M solution of n-BuLi in hexanes was obtained from Aldrich Chemical Company, Inc. The n-BuLi is titrated prior to its use in each reaction using the following procedure.[3] To a 50-mL, round-bottomed flask (Note 1), equipped with nitrogen inlet and a magnetic stirrer is added N-benzylbenzamide (854 mg, 4.0 mmol) (as received from Aldrich Chemical Company, Inc.) and THF (40 mL) (Note 2). The solution is cooled to −42°C (acetonitrile/dry ice) and n-BuLi is added dropwise to the blue endpoint (color persists for >30 sec). The molarity is calculated using a 1:1 stoichiometric ratio of N-benzylbenzamide to n-BuLi. (Just greater than 1 equivalent of alkyllithium is needed to reach the endpoint).
5. 4,4'-Dimethyl-2,2'-bipyridine was obtained from GFS Chemicals, Inc. or Tokyo Chemical Industry Co. and used as received.
6. Chlorotrimethylsilane (TMSCl) was purchased from Aldrich Chemical Company, Inc. , and used as obtained.
7. The following characterization data was obtained: mp 90-92°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.04 (s, 18 H), 2.21 (s, 4 H), 6.94 (d, 2 H, J = 5.01), 8.05 (br s, 2 H), 8.46 (d, 2 H, J = 5.00) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: −2.2, 27.1, 120.4, 123.0, 148.3, 150.8, 155.5 . Anal. Calcd for $C_{18}H_{28}N_2Si_2$: C, 65.79; H, 8.59; N, 8.53. Found: C, 65.78; H, 8.43; N, 8.76. It has been noted that desilylation occurs after standing in deuterochloroform ($CDCl_3$) overnight. The resulting methyl derivatives have also been observed in certain purified TMS bipyridine samples when stored over time. Therefore, it is best to convert these intermediates to the corresponding halides in a timely fashion.
8. Hexachloroethane (Cl_3CCCl_3), obtained from Aldrich Chemical Company, Inc. , was used as received.
9. Cesium fluoride was purchased from Acros Organics, Inc. or Soekawa Chemicals Co. and stored in a dry box prior to use.
10. Acetonitrile was distilled over CaH_2 and stored in a 500-mL Kontes flask prior to use.
11. Silica gel used for flash chromatography (particle size 0.035-0.075 mm) was obtained from VWR Scientific Products . Silica chromatography columns were deactivated by flushing with 10% triethylamine in hexanes and then were washed with hexanes prior to use.
12. Spectral properties are as follows: mp 98-100°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.63 (s, 4 H), 7.38 (dd, 2 H, J = 1.9, 5.0), 8.43 (s, 2 H), 8.70 (d, 2 H, J = 4.6) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 43.9, 120.1, 122.8, 146.7, 149.4, 155.8 . Anal. Calcd for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 56.82; H, 4.04; N, 11.01.
13. In some cases, particularly if the solvent or reaction conditions are not thoroughly dry, 4,4'-dimethyl-2,2'-bipyridine is formed as a byproduct during the halogenation reaction. This compound may be separated from 4,4'-bis(chloromethyl)-2,2'-bipyridine by flash chromatography on silica gel (not deactivated with Et3N) using EtOAc as the mobile phase. Alternatively, 4,4'-bis(chloromethyl)-2,2'-bipyridine may be purified by recrystallization in hot/cold absolute EtOH, with no evidence of ether formation (e.g., 4,4'-di-Ethoxymethyl-2,2'-bipyridine) by 1H NMR.

Waste Disposal Information

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

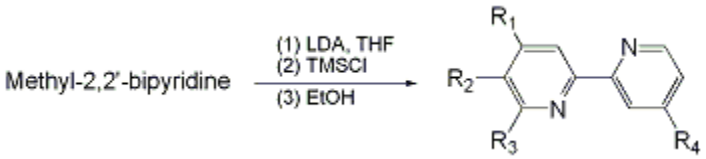
3. Discussion

Halomethylbipyridines, are typically synthesized either by radical halogenation[4] or from hydroxymethylbipyridine precursors.[5] Radical methods often give rise to mixtures of halogenated

species that are difficult to separate with flash chromatography. A solution to this problem, involving the selective reduction of polyhalogenated by-products with diisobutylaluminum hydride (DIBAL-H), has resulted in slight improvements in overall yields.[6] While the synthesis of halomethyl compounds from hydroxymethyl precursors is more efficient than radical halogenation, such procedures involve many steps, each of which give intermediates in moderate to high yields.[5] Direct trapping of bpy $(CH_2Li)_n$ with electrophiles has proved unsuccessful for the generation of halide products.[5a] The quenching of LDA-generated carbanions with TMSCl prior to halogenation as described here constitutes an efficient, high yield synthesis of halomethyl bpys substituted at various positions around the ring system.[7,8]

Currently, 2,2'-bipyridine derivatives figure prominently in supramolecular assembly,[9] in bioinorganic contexts,[10] in studies of redox electrocatalysis[4a] and in polymeric materials.[11] Halomethyl bpys and their various metal complexes have also been used as initiators for controlled polymerizations of several different monomers including styrene and 2-alkyl-2-oxazolines.[12]

TABLE I
SYNTHESIS OF (TRIMETHYLSILYL)METHYL-2,2'-BIPYRIDINES



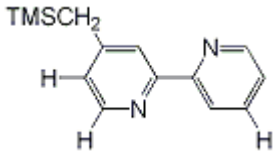
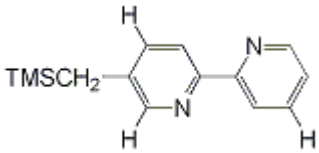
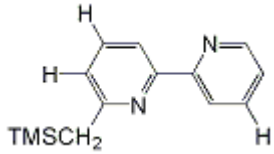
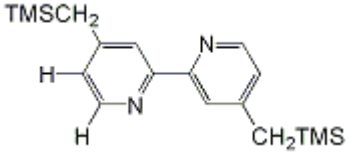
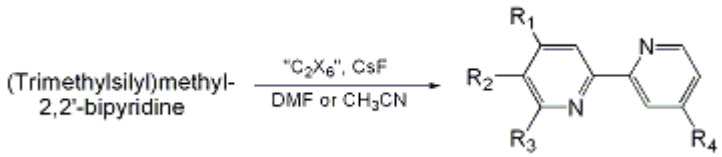
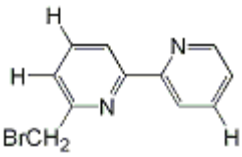
Product	R_1	R_2	R_3	R_4	Yield (%)
4-(Trimethylsilyl)-methyl-2,2'-bipyridine 	$TMSCH_2$	H	H	H	93
5-(Trimethylsilyl)-methyl-2,2'-bipyridine 	H	$TMSCH_2$	H	H	99
6-(Trimethylsilyl)-methyl-2,2'-bipyridine 	H	H	$TMSCH_2$	H	97
4,4'-Bis[(trimethylsilyl)-methyl]-2,2'-bipyridine 	$TMSCH_2$	H	H	$TMSCH_2$	97

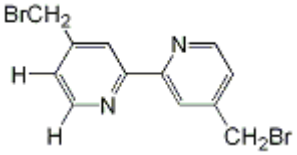
TABLE II
SYNTHESIS OF HALOMETHYL-2,2'-BIPYRIDINES



Product	R_1	R_2	R_3	R_4	Yield (%)
4-Chloromethyl-2,2'-bipyridine	$ClCH_2$	H	H	H	94
5-Chloromethyl-2,2'-bipyridine	H	$ClCH_2$	H	H	98
6-Chloromethyl-2,2'-bipyridine	H	H	$ClCH_2$	H	95
4,4'-Bis(chloromethyl)-2,2'-bipyridine	$ClCH_2$	H	H	$ClCH_2$	91
4-Bromomethyl-2,2'-bipyridine	$BrCH_2$	H	H	H	92
5-Bromomethyl-2,2'-bipyridine	H	$BrCH_2$	H	H	98
6-Bromomethyl-2,2'-bipyridine	H	H	$BrCH_2$	H	99



4,4'-Bis(bromomethyl)-2,2'-bipyridine



$BrCH_2$	H	H	$BrCH_2$	97

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

4,4'-Bis(chloromethyl)-2,2'-bipyridines:
2,2'-Bipyridine, 4,4'-bis(chloromethyl)- (13); (138219-98-4)

4,4'-Bis[(trimethylsilyl)methyl]-2,2'-bipyridine:
2,2'-Bipyridine, 4,4'-bis[(trimethylsilyl)methyl]- (14); (199282-52-5)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

4,4'-Dimethyl-2,2'-bipyridine:
2,2'-Bipyridine, 4,4'-dimethyl- (9); (1134-35-6)

Chlorotrimethylsilane:
Silane, chlorotrimethyl- (8,9); (75-77-4)

Hexachloroethane:
Ethane, hexachloro- (8,9); (67-72-1)

Cesium fluoride (8,9); (13400-13-0)

Acetonitrile: TOXIC (8,9); (75-05-8)

N-Benzylbenzamide:
Benzamide, N-benzyl- (8);
Benzamide, N-(phenylmethyl)- (9); (1485-70-7)