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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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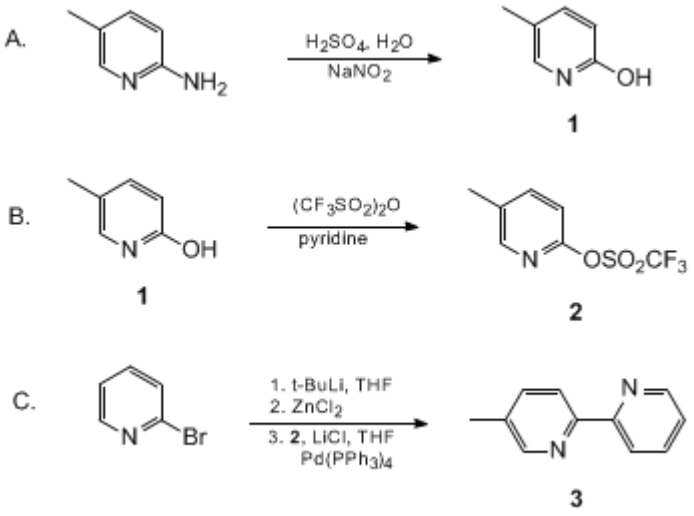
SYNTHESIS OF 4-, 5-, and 6-METHYL-2,2'-BIPYRIDINE BY A NEGISHI CROSS-COUPLING STRATEGY: 5-METHYL-2,2'-BIPYRIDINE

[2,2'-Bipyridine, 5-methyl-]



Submitted by Adam P. Smith, Scott A. Savage, J. Christopher Love, and Cassandra L. Fraser[1] . Checked by Erik Kuester and Louis S. Hegedus.
Discussion Addendum *Org. Synth.* **2012**, *89*, 76

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-Hydroxy-5-methylpyridine (**1**) (Note 1). A 500-mL, two-necked, round-bottomed flask (Note 2) equipped with an internal thermometer and egg-shaped, Teflon-coated magnetic stirrer is charged with 150 mL of water (H_2O) and 40 g of concentrated sulfuric acid (H_2SO_4). This aqueous solution is cooled below 0°C by immersion in an acetone/ice bath, and 2-amino-5-methylpyridine (18.2 g, 168 mmol) is added (Note 3). The reaction mixture is treated with an aqueous solution of sodium nitrite ($NaNO_2$) (15.4 g, 223 mmol in 30 mL of H_2O) (Note 4) at a rate sufficient to maintain a reaction temperature of 0-5°C. After addition of the $NaNO_2$ solution is complete, the resulting mixture is stirred at 0°C for 45 min, and then heated to 95°C for 15 min. The reaction mixture is allowed to cool to room temperature and a 50% w/w aqueous sodium hydroxide (NaOH) solution is added until a pH of 6.5-7.0 is achieved (≈30 mL) (Note 5). After the reaction mixture is heated to 60°C, the hot solution is extracted with ethyl acetate (EtOAc) (4 × 100 mL). The combined organic fractions are dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated on a rotary evaporator to yield a pale-yellow solid. Purification by recrystallization from hot/cold ethyl acetate (EtOAc) (≈300 mL) gives 2-hydroxy-5-methylpyridine (11.2 g, 61%) as white crystalline needles (Note 6).

B. 5-Methyl-2-(trifluoromethanesulfonyl)oxypyridine (**2**). The following procedure for the preparation of the 5-methyl-2-pyridyl triflate may also be used to synthesize the 4- and 6-methyl derivatives. A 200-mL Schlenk flask (Note 2) containing a Teflon-coated, magnetic stirring bar and capped with a rubber septum is flushed with nitrogen. The flask is charged with 2-hydroxy-5-methylpyridine (**1**) (4.85 g, 44.4 mmol) and dry pyridine (140 mL) (Note 7). After the reactant dissolves, the flask is cooled to −12°C by immersion in an acetone/ice bath. Trifluoromethanesulfonic anhydride (15.1 g, 53.5 mmol) (Note 8) is added rapidly to the flask via syringe through the rubber septum. The solution is stirred at 0°C for 30 min and poured into a separatory funnel containing H_2O (150 mL). The mixture is extracted with dichloromethane (CH_2Cl_2) (3 × 100 mL) and the combined organic fractions are dried over anhydrous Na_2SO_4. Filtration and concentration on a rotary evaporator, followed by flash chromatography on 375 g of deactivated silica gel (Note 9) with 20% EtOAc:80% hexanes, gives 9.89 g (92%) of 5-methyl-2-(trifluoromethanesulfonyl)oxypyridine as a clear, colorless oil

(Note 10).

C. 5-Methyl-2,2'-bipyridine (**3**). The 4- and 6-methyl-2,2'-bipyridines may also be prepared using the following procedure. A 500-mL, two-necked, round-bottomed flask (Note 2) with a Teflon-coated magnetic stirrer is placed in a dry ice/acetone bath (−78°C), then 80 mL of tetrahydrofuran (THF) (Note 11) and tert-butyllithium (tert-BuLi) (1.75 M in pentane, 52 mL, 91.0 mmol) (Note 12) are added to it, followed by dropwise addition of 2-bromopyridine (7.13 g, 4.3 mL, 45.1 mmol) (Note 13). The canary yellow THF solution becomes reddish-brown upon addition of the pyridyl bromide. After the solution is stirred at −78°C for 30 min, anhydrous zinc chloride ($ZnCl_2$) (13.3 g, 97.4 mmol) (Note 14) is added, and the reaction is stirred at 25°C for 2 hr. The 5-methylpyridyl triflate (**2**) (8.95 g, 37.1 mmol) , lithium choride (LiCl) (3.18 g, 75.2 mmol) (Note 15), and tetrakis(triphenylphosphine) palladium ($Pd(PPh_3)_4$) (1.75 g, 1.5 mmol) (Note 16) are then added. The brownish-yellow reaction mixture is heated at reflux (Note 17) for 18 hr. After the solution is cooled, an aqueous solution of ethylenediaminetetraacetic acid (EDTA) (55 g, 148 mmol in 400 mL) (Note 18) is added and the pH is adjusted to ≈8 with saturated aqueous sodium bicarbonate ($NaHCO_3$). The solution is stirred for 15 min then poured into a separatory funnel. The product is extracted with CH_2Cl_2 (3 × 200 mL). The combined organic fractions are dried over anhydrous Na_2SO_4 , filtered, and concentrated using a rotary evaporator. Flash chromatography on 275 g of deactivated silica gel (Note 9) (20% EtOAc:80% hexanes) affords 5.94 g (94%) of 5-methyl-2,2'-bipyridine as a very pale yellow oil (Note 19).

2. Notes

1. This procedure is a modification of that reported by Adger and co-workers.[2] Both 2-hydroxy-4-methylpyridine and 2-hydroxy-6-methylpyridine can be obtained from Aldrich Chemical Company, Inc. However, it is more economical to prepare them in large quantities using this procedure from 2-amino-4-methylpyridine and 2-amino-6-methylpyridine, respectively.

2. Before use, all glassware, needles, and syringes were dried overnight in a 120°C oven.

3. 2-Amino-5-methylpyridine was purchased from Aldrich Chemical Company, Inc. and used as received. (Aldrich name: 2-Amino-5-picoline.)

4. Sodium nitrite was purchased from Aldrich Chemical Company, Inc. and used as obtained.

5. Sodium hydroxide pellets from Mallinckrodt Inc. were used as received.

6. The following characterization data was obtained: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.99 (s, 3 H), 6.43 (d, 1 H, J = 8.8), 7.06 (s, 1 H), 7.23 (dd, 1 H, J = 2.2, 9.5), 13.48 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.1, 116.2, 119.8, 132.5, 144.4, 164.9 . Anal. Calcd for C_6H_7NO: C, 66.04; H, 6.46; N, 12.84. Found: C, 66.09; H, 6.31; N, 13.05.

7. Pyridine (99.9+% HPLC grade) was purchased from Aldrich Chemical Company, Inc. , and used without further purification.

8. Trifluoromethanesulfonic anhydride, obtained from Aldrich Chemical Company, Inc. , was used as received and weighed in a syringe inside a dry box. The checkers measured the anhydride volumetrically in a dry syringe, in a hood using a density of 1.68. Transfer in a dry box proved unnecessary.

9. 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 (Et_3N) in hexanes and then were washed with hexanes prior to use.

10. The product has the following properties: TLC R_f = 0.54 (20% EtOAc:80% hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.37 (s, 3 H), 7.06 (d, 1 H, J = 8.1), 7.67 (dd, 1 H, J = 2.4, 8.5), 8.17 (s, 1 H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.9, 114.9, 118.8 (q, J_{CF} = 320.3), 134.7, 141.6, 148.8, 154.2 . Anal. Calcd for $C_7H_6F_3NO_3S$: C, 34.86; H, 2.51; N, 5.81. Found: C, 34.99; H, 2.19; N, 5.70.

11. THF was dried and purified by passage through alumina solvent purification columns[3] or by distillation over sodium/benzophenone.

12. A 1.6 M solution of tert-BuLi in pentane was obtained from Aldrich Chemical Company, Inc. It is crucial to have at least 2 equiv of tert-BuLi for the lithium-halogen exchange. Depressed yields (25-60%) were obtained when less than 2 equiv were used. The tert-BuLi is titrated prior to its use in each reaction using the following procedure.[4] To a 50-mL Schlenk flask is added N-benzylbenzamide (274 mg, 1.3 mmol) (as received from Aldrich Chemical Company, Inc.) and THF (10 mL) (Note 11). The solution is cooled to −43°C (acetonitrile/dry ice) and tert-BuLi is added dropwise to the blue endpoint (color persists for >30 s). The molarity is calculated using a 1:1 stoichiometric ratio of N-benzylbenzamide to tert-BuLi (just greater than 1 equivalent of alkyllithium needed to reach the endpoint).

13. 2-Bromopyridine was purchased from Aldrich Chemical Company, Inc. , and used as received.

14. Zinc chloride, obtained from Strem Chemicals Inc. , was flame-dried to remove excess H_2O and stored in a dry box prior to use. Weighing out flame-dried zinc chloride on the bench rather than in a dry box resulted in reduced yields. When a 1M solution of the above flame-dried zinc chloride was prepared in THF and transferred by syringe,

the published yields were obtained.

15. Granular lithium chloride from Mallinckrodt, Inc. was stored in a dry box prior to use. The checkers stored the LiCl in a desiccator before use.

16. The $Pd(PPh_3)_4$ catalyst can be purchased from Aldrich Chemical Company, Inc., or Strem Chemicals Inc. However, it was easily prepared using the procedure of Coulson[5] for the synthesis delineated here.

17. Pentane is removed by distillation (bp 36°C). A reflux temperature of 70-75 is required for the reaction to proceed to completion.

18. Ethylenediaminetetraacetic acid, disodium salt dihydrate, 99+% was obtained from Aldrich Chemical Company, Inc. and used as received. The EDTA mixture was heated gently to facilitate dissolution and was allowed to cool to room temperature prior to use.

19. The analytical data for 5-methyl-2,2'-bipyridine are as follows: TLC R_f = 0.46 (20% EtOAc:80% hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.43 (s, 3 H), 7.35 (dd, 1 H, J = 4.6, 7.7), 7.71 (d, 1 H, J = 7.7), 7.87 (t, 1 H, J = 7.3), 8.39 (d, 1 H, J = 7.7), 8.48 (d, 1 H, J = 7.3), 8.55 (s, 1 H), 8.70 (d, 1 H, J = 4.6) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.7, 120.0, 120.2, 122.8, 132.8, 136.2, 136.8, 148.5, 149.1, 153.0, 155.7 . Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.66; H, 5.98; N, 16.37.

Waste Disposal Information

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

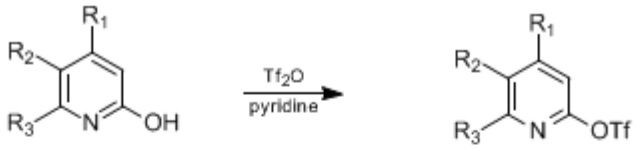
3. Discussion

As ligands for metal ions, 2,2'-bipyridines find wide application in chemistry. They have been used in studies of supramolecular assembly,[6] in bioinorganic contexts,[7] and in polymeric materials,[8] as well as in discrete small-molecule analogues.

Traditionally, methyl-2,2'-bipyridines (methyl bpys) have been prepared by the Kröhnke method, which involves reaction of pyridinium salts with α,β-unsaturated ketones followed by treatment with ammonium acetate to effect cyclization.[9] They have also been made by coupling pyridyllithium reagents with pyridyl sulfoxides,[10] by Ni and other metal-catalyzed cross-coupling reactions,[11] by the Ullman reaction[9] and by use of α-oxoketene dithioacetals among a variety of other routes.[12] Many methods lead to mixtures of isomers or they produce dimethyl byproducts. Nearly all of them afford products in moderate yields at best. The cross-coupling of a pyridyl zinc reagent and a pyridyl triflate in the presence of a catalytic amount of palladium by the Negishi method [13] as described here constitutes an efficient, large scale, high yield synthesis of 4-, 5-, and 6-methyl-2,2'-bipyridine. These methyl bpys are readily converted to bromomethyl and chloromethyl analogues,[14] which are valuable starting materials for further derivatization.[15] Moreover, the halomethyl bipyridines have been used as ligand initiators in controlled polymerizations.[16]

TABLE I

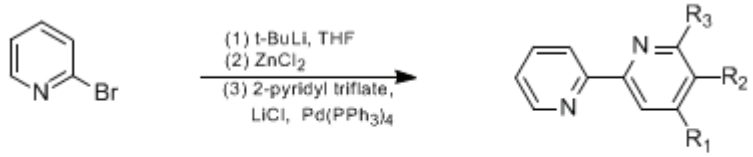
SYNTHESIS OF 2-PYRIDYL TRIFLATES



Product	R_1	R_2	R_3	Yield (%)
4-Methyl Triflate	CH_3	H	H	95
5-Methyl Triflate	H	CH_3	H	95
6-Methyl Triflate	H	H	CH_3	94

TABLE II

SYNTHESIS OF METHYL-2,2'-BIPYRIDINES



Product	R_1	R_2	R_3	Yield (%)
4-Methyl-2,2'-bipyridine	CH_3	H	H	96
5-Methyl-2,2'-bipyridine	H	CH_3	H	94
6-Methyl-2,2'-bipyridine	H	H	CH_3	93

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

2-Hydroxy-5-methylpyridine:
2(1H)-Pyridinone, 5-methyl- (8,9); (1003-68-5)

2-Amino-5-methylpyridine: Aldrich Name:
2-Amino-5-picoline: HIGHLY TOXIC:
3-Picoline, 6-amino- (8);
2-Pyridinamine, 5-methyl- (9); (1603-41-4)

Sodium nitrite:
Nitrous acid, sodium salt (8,9); (7632-00-0)

5-Methyl-2-(trifluoromethanesulfonyl)oxypyridine:
Methanesulfonic acid, trifluoro-, 5-methyl-2-pyridinyl ester (13); (154447-03-7)

4-Methyl-2-pyridyl triflate:
Methanesulfonic acid, trifluoro-, 4-methyl-2-pyridinyl ester (13); (179260-78-7)

6-Methyl-2-pyridyl triflate:
Methanesulfonic acid, trifluoro-, 6-methyl-2-pyridinyl ester (13); (154447-04-8)

Trifluoromethanesulfonic anhydride:
Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

5-Methyl-2,2'-bipyridine:
2,2'-Bipyridine, 5-methyl- (9); (56100-20-0)

4-Methyl-2,2'-bipyridine:
2,2'-Bipyridine, 4-methyl- (9); (56100-19-7)

6-Methyl-2,2'-bipyridine:
2,2'-Bipyridine, 6-methyl- (9); (56100-22-2)

tert-Butyllithium:
Lithium, tert-butyl- (8);
Lithium, (1,1-dimethylethyl)- (9); (594-19-4)

2-Bromopyridine: HIGHLY TOXIC:
Pyridine, 2-bromo- (8,9); (109-04-6)

Zinc chloride (8,9); (7646-85-7)

Lithium chloride (8,9); (7447-41-8)

Tetrakis(triphenylphosphine)palladium(0):
Palladium, tetrakis(triphenylphosphine)- (8);
Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

Ethylenediaminetetraacetic acid, disodium salt dihydrate:
Acetic acid (ethylenedinitrilo)tetra-, disodium salt, dihydrate (8);
Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, disodium salt, dihydrate (9); (6381-92-6)

2-Hydroxy-4-methylpyridine:
2(1H)-Pyridinone, 4-methyl- (9); (13466-41-6)

2-Hydroxy-6-methylpyridine:
2(1H)-Pyridinone, 6-methyl- (9); (3279-76-3)

2-Amino-4-methylpyridine: Aldrich Name:
2-Amino-4-picoline: HIGHLY TOXIC:
4-Picoline, 2-amino- (8);
2-Pyridinamine, 4-methyl- (9); (695-34-1)

2-Amino-6-methylpyridine: Aldrich Name:
2-Amino-6-picoline: HIGHLY TOXIC:
2-Picoline, 6-amino- (8);
2-Pyridinamine, 6-methyl- (9); (1824-81-3)

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