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of Reliable Methods
for the Preparation
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Working with Hazardous Chemicals

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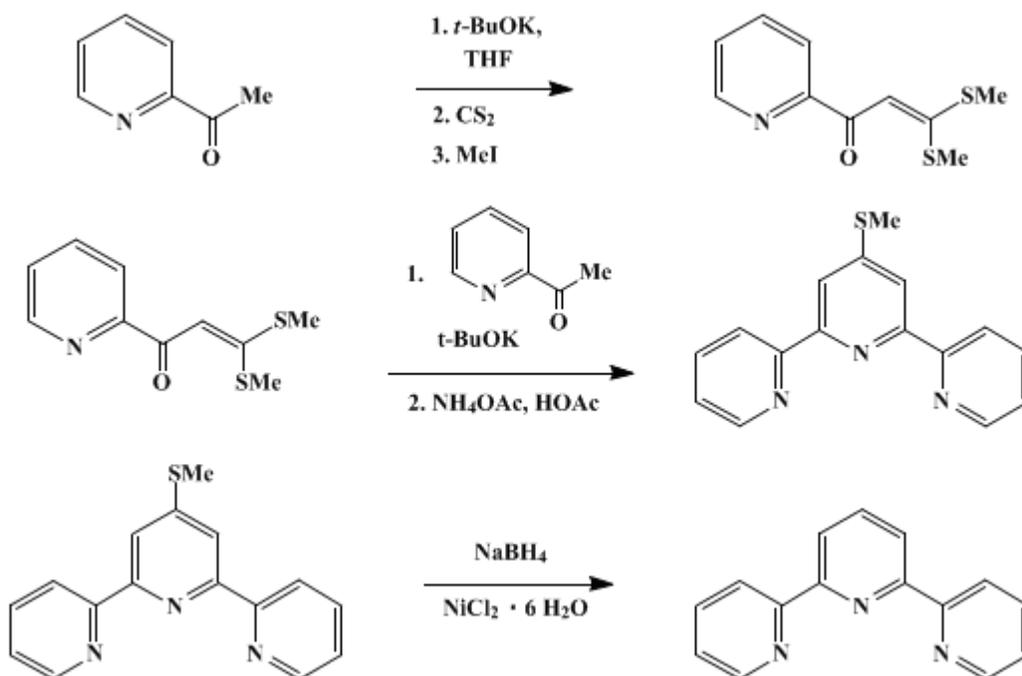
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2,2' : 6',2' -TERPYRIDINE



Submitted by Kevin T. Potts, Philip Ralli, George Theodoridis, and Paul Winslow¹.
Checked by B. L. Chenard and Bruce E. Smart.

1. Procedure

A. *3,3-Bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one*. A 3-L, three-necked flask is equipped with an efficient mechanical stirrer, pressure-equalizing dropping funnel with needle valve, and a reflux condenser fitted with a nitrogen gas inlet tube that is attached to a mineral oil bubbler. The system is flushed with nitrogen, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 1000 mL of dry tetrahydrofuran (Note 1) and 96.5 g (0.86 mol) of potassium *tert*-butoxide (Note 2). Freshly distilled 2-acetylpyridine (50.0 g, 0.41 mol) (Note 3) is then added dropwise over a period of 5–10 min (Note 4). To the resulting reaction mixture 32.7 g (0.43 mol) of carbon disulfide is added over a period of 30–35 min. After the addition is completed, 122.1 g (0.86 mol) of methyl iodide is added over 1 hr to the viscous, heterogeneous orange reaction mixture. After the tan reaction mixture is stirred for 12 hr at room temperature, it is poured into 2 L of iced water and allowed to stand for 4 hr. The solid that precipitates is collected by filtration and air-dried to give 56 g (61%) of yellow crystals, mp 106–107°C. The filtrate is diluted with water to a total volume of 4 L, and chilled to afford an additional 16.5 g (18%) of product, mp 104–107°C (Note 5).

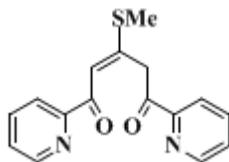
B. *4-(Methylthio)-2,2' : 6',2'-terpyridine* (Note 6). A 1-L, three-necked round-bottomed flask fitted with a mechanical stirrer and a gas inlet tube is flushed with nitrogen and charged with 500 mL of anhydrous tetrahydrofuran and 22.4 g (0.20 mol) of potassium *tert*-butoxide. Freshly distilled 2-acetylpyridine (12.1 g, 0.10 mol) (Note 3) is added, the solution is stirred for 10 min, and 22.5 g (0.1 mol) of 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one is then added. The mixture is stirred for 12 hr at room temperature, during which time it turns bright red and a red solid precipitates (Note 7). The mixture is next treated with 77 g (1.0 mol) of ammonium acetate and 250 mL of glacial acetic acid. A distillation head fitted with a thermometer is attached to the flask and the tetrahydrofuran is removed by distillation over a 2-hr period. The residual brown solution is chilled to 15°C, treated with 400 g of ice, and allowed to stand for 3 hr. Water (400 mL) is added, the mixture is chilled to 15°C, and the gray material that precipitates is collected by filtration, washed with iced water (3 × 200 mL), and air-dried. The crude product is taken up in 250 mL of boiling ethanol and filtered. The filtercake is rinsed with 50

mL of hot **ethanol**, and the hot filtrates are combined, diluted with 150 mL of water, concentrated to a volume of 400 mL, and allowed to cool to room temperature. After the mixture is thoroughly chilled in an ice bath, the precipitate is collected by filtration, washed with 50% aqueous **ethanol**, and dried under reduced pressure (23°C, 0.1 mm) to give 20.6–21.4 g (74–77%) of **4'-(methylthio)-2,2' : 6',2''-terpyridine** as gray needles, mp 118–119°C (**Note 8**). This material is sufficiently pure for use in the following step.

C. **2,2' : 6',2''-Terpyridine**. A 1-L, four-necked flask equipped with a mechanical stirrer, pressure-equalizing dropping funnel, thermometer, and a condenser fitted with a nitrogen gas inlet tube is flushed with **nitrogen** and charged with 300 mL of **ethanol**, 5.0 g (0.018 mol) of **4'-(methylthio)-2,2' : 6',2''-terpyridine** and 42.8 g (0.180 mol) of finely ground **nickel chloride hexahydrate** (**Note 9**). The resultant green heterogeneous mixture is chilled in an ice bath while the system is maintained under a static pressure of nitrogen. To this chilled (0–5°C) mixture, a solution of 20.4 g (0.54 mol) of **sodium borohydride** in 128 mL of 40% aqueous **sodium hydroxide** is added dropwise over 4 hr (**Note 10**). After the addition is completed and the evolution of **hydrogen** subsides, the dark reaction mixture is refluxed for 12 hr. The hot mixture is then filtered through a Celite pad, and the pad is washed with hot **ethanol** (3 × 100 mL). The filtrates are combined and evaporated to dryness under reduced pressure to yield a gray solid residue (**Note 11**). This solid is suspended in 300–400 mL of water and chilled in an ice bath for 4 hr. The cold suspension is filtered and the gray solid is air-dried. The crude product is taken up in 100 mL of boiling **hexane** and filtered. The filtrate is concentrated to 50 mL, chilled in an ice bath, and filtered to give 2.48–2.53 g (59–60%) of **2,2' : 6',2''-terpyridine** as cream-colored prisms, mp 84–86°C [lit.² mp 85–86°C] (**Note 12**) and (**Note 13**). The mother liquor is concentrated to 10 mL to give a second crop of 0.37–0.40 g (8.8–9.5%), mp 81–84°C.

2. Notes

1. The checkers used **tetrahydrofuran** that was distilled from **lithium aluminum hydride** (*Caution: See Org. Synth., Coll. Vol. V 1973, 976*) and stored with a chip of **sodium** metal. Distillation from **sodium/benzophenone** is preferable.
2. **Potassium tert-butoxide** was obtained from the Aldrich Chemical Company, Inc.
3. The checkers obtained **2-acetylpyridine** from the Aldrich Chemical Company, Inc. The submitters thank Reilly Tar & Chemical Corp. for a generous gift of **2-acetylpyridine** used in their work.
4. A light yellow solid precipitates during this addition.
5. The product is pure by ¹NMR (CDCl₃) δ: 2.55 (s, 3 H), 2.65 (s, 3 H), 7.40 (d of d of d, 1 H, *J* = 1.5, 5.6, 7.5), 7.65 (s, 1 H), 7.85 (d of t, 1 H, *J* = 7.5, 2.0), 8.20 (d of t, 1 H, *J* = 7.5, 1.5), 8.65 (d of m, 1 H, *J* = 7.5); IR (KBr) cm⁻¹: 1484, 1471. Analytically pure material, mp 108–109°C, may be obtained by recrystallization from **ethanol**.
6. Recently, it has been shown that this product may be prepared without isolation of the precursors obtained in Step A.³
7. This solid is the potassium salt of the enedione intermediate.



8. The checkers also obtained material with mp 116–118°C. The submitters report product of unspecified purity with mp 120–122°C. The material obtained by the checkers shows the following ¹H NMR (CDCl₃) δ: 2.0 (s, impurity), 2.67 (s, 3 H), 7.30 (d of d of d, 2 H *J* = 1.8, 5.6, 8.0), 7.80 (d of t, 2 H, *J* = 1.8, 8.0), 8.35 (s, 2 H), 8.4–8.78 (m, 4 H). Mass spectrum *m/e* calculated: 279.0830. Found: 279.0815. IR (KBr) cm⁻¹: 1558, 1390. The combustion analyses for the products obtained by the checkers were within accepted limits for H, but off about 2% for C, and 0.6–0.8% for N.
9. **Nickel chloride hexahydrate** was obtained from the Fisher Scientific Company.
10. This reaction, which generates nickel boride,⁴ is exothermic and evolves **hydrogen**. Frothing is prevented by keeping the reaction mixture at 0–5°C during addition of the **sodium borohydride**.
11. The submitters report obtaining tan material.

12. This material is analytically pure. Anal. calcd. for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found C: 76.82; H, 4.69; N, 18.17. The product shows 1H NMR ($CDCl_3$) δ : 7.33 (d of d of d, 2 H $J = 1.5, 5.0, 8.0$), 7.86 (d of t, 2 H, $J = 2.0, 8.0$), 7.96 (t, 1 H, $J = 8.0$ H), 8.45 (d, 2 H $J = 8.0$), 8.62 (d, 2 H, $J = 8.0$), 8.71 (d of m, 2 H).

13. The submitters report that 4'-(methylthio)-2,2' : 6',2''-terpyridine also can be conveniently reduced to 2',2'' : 6',2''-terpyridine with Raney nickel in ethanol. The checkers found, however, that this procedure invariably gave product contaminated with 4'-ethoxy-2,2' : 6',2''-terpyridine. Raney nickel which was exhaustively washed with water to remove base still gave 15% of this by-product.

3. Discussion

The procedure described here is by far the most efficient synthesis of terpyridine.⁵ Previous preparations include the dehydrogenation of pyridine with ferric chloride,² the Ullman reaction of 2-bromopyridine and 2,6-dibromopyridine,⁶ the action of copper on 2-bromopyridine and 6-bromo-2,2'-dipyridyl,⁶ the reaction of iodine or ferric chloride with 2,2'-bipyridyl,⁶ and the reaction of 2,2'-bipyridyl with 2-lithiopyridine (40% yield).⁷

Terpyridine is a very effective chelating agent.

References and Notes

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Appendix

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

sodium/benzophenone

nickel boride

2',2'' : 6',2''-terpyridine

6-bromo-2,2'-dipyridyl

ethanol (64-17-5)

acetic acid (64-19-7)

ammonium acetate (631-61-8)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

copper (7440-50-8)

nickel (7440-02-0)

iodine (7553-56-2)

pyridine (110-86-1)

sodium (13966-32-0)

carbon disulfide (75-15-0)

ferric chloride (7705-08-0)

Methyl iodide (74-88-4)

nickel chloride hexahydrate (7791-20-0)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

2-Bromopyridine (109-04-6)

hexane (110-54-3)

sodium borohydride (16940-66-2)

2,2'-bipyridyl (366-18-7)

TERPYRIDINE

2-acetylpyridine (1122-62-9)

3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (78570-34-0)

2,6-dibromopyridine (626-05-1)

2-lithiopyridine

potassium tert-butoxide (865-47-4)

2,2' : 6',2' -TERPYRIDINE,
2,2' : 6',2''-Terpyridine (1148-79-4)

4'-(Methylthio)-2,2' : 6',2''-terpyridine (78570-35-1)