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.

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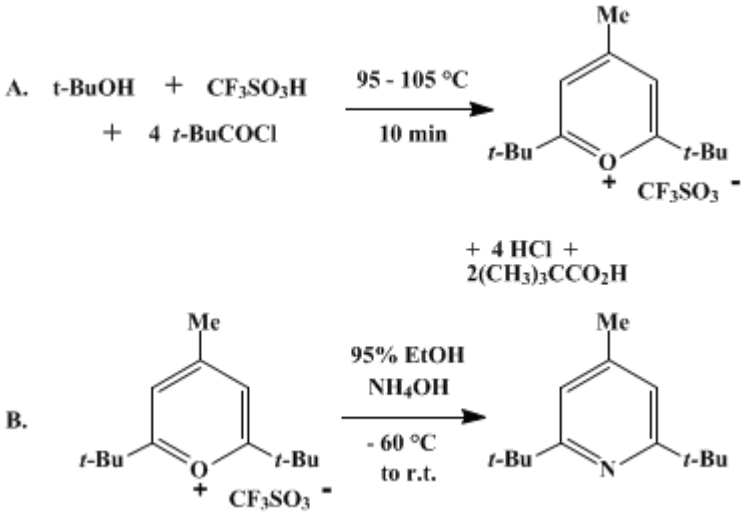
Organic Syntheses, Coll. Vol. 7, p.144 (1990); Vol. 60, p.34 (1981).

2,6-DI-*tert*-BUTYL-4-METHYLPYRIDINE

[Pyridine, 2,6-bis(1,1-dimethylethyl)-3-methyl-]



Submitted by Albert G. Anderson[1] and Peter J. Stang[2].
Checked by Mark T. DuPriest and George Büchi.

1. Procedure

Caution! The reaction described in Step A should be conducted in a hood, since some carbon monoxide is generated by partial decarbonylation of pivaloyl chloride.

A. *2,6-Di*-tert-*butyl-4-methylpyrylium trifluoromethanesulfonate* **(1)**. The center neck of a 5-L, three-necked, round-bottomed flask equipped with a thermometer port, magnetic stirrer bar coated with Teflon, and heating mantle is fitted with a 125-mL pressure-equalizing dropping funnel. The two side necks are fitted with 7 cm (diam) × 27 cm dry ice condensers vented through oil-filled bubblers into traps containing aqueous 1 *N* sodium hydroxide (Note 1). A thermometer is placed in the thermometer port to extend nearly to the bottom of the flask without contacting the stirrer bar. The apparatus is purged with dry nitrogen, the nitrogen flow is stopped, and to the flask are added 300 g (2.5 mol) of pivaloyl chloride and 46 g (0.62 mol) of anhydrous *tert*-butyl alcohol (Note 2). The condensers are charged with isopropyl alcohol-dry ice and, with stirring, the reaction mixture is warmed to 85°C. Heating is discontinued, and the mantle is allowed to remain in place. Then 187.5 g (109 mL, 1.25 mol) of trifluoromethanesulfonic acid is added with stirring during a period of 2–3 min (Note 3). After the addition is complete, the temperature is maintained at 95–105°C for 10 min with the heating mantle. The mantle is removed, and the brown reaction mixture is first allowed to spontaneously cool to 50°C and finally cooled to −10°C with an isopropyl alcohol-dry-ice bath. On addition of 1 L of cold diethyl ether (Note 4), a precipitate forms immediately and is collected, washed with three 300-mL portions of diethyl ether, and air-dried on a medium-porosity fritted-glass filter to give 118–137 g (53–62%) of light tan 2,6-di-*tert*-butyl-4-methylpyrylium trifluoromethanesulfonate, mp 153–164°C (Note 5).

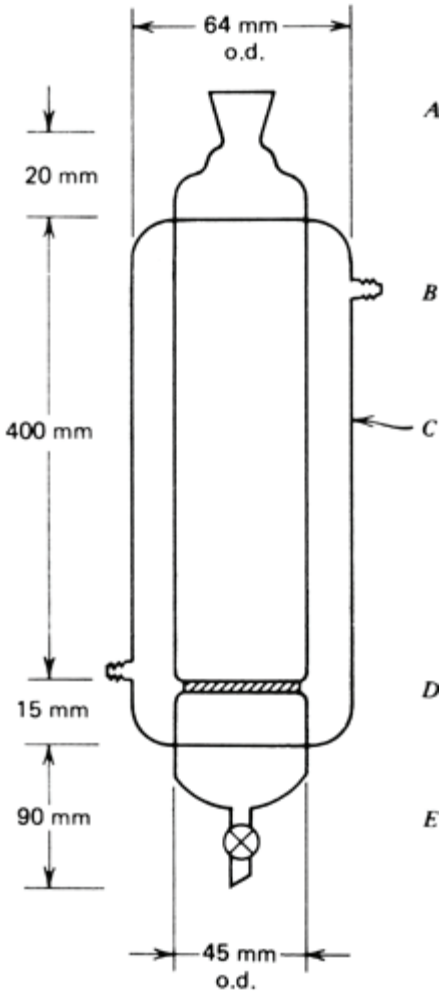
B. *2,6-Di*-tert-*butyl-4-methylpyridine* **(2)**. To 119–128 g (0.33–0.36 mol) of crude pyrylium salt in a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer is added 2 L of 95% ethanol. The mixture is cooled to −60°C with an isopropyl alcohol-dry ice bath and to the fine slurry is added, with stirring, in one portion 1 L of concentrated (*d* 0.90) ammonium hydroxide also cooled to −60°C. The yellow reaction mixture is held at −60°C for 30 min, then allowed to warm to −40°C and maintained at that temperature for 2 hr, during which time the slurry dissolves. The mixture is then allowed to spontaneously warm to room temperature (Note 6). The reaction mixture is divided into two portions. Each portion is poured into a 4-L separatory funnel, 1 L of aqueous 10% sodium hydroxide is

added, and the mixture is extracted with four 250-mL portions of pentane (Note 7). The extracts from both portions are combined and washed with 100 mL of saturated aqueous sodium chloride solution. The pentane is removed on the rotary evaporator (Note 8), leaving a residual light-yellow oil that is dissolved in 150 mL of pentane and introduced slowly during 20–30 min onto the top of a 40 × 4.5 cm water-jacketed chromatography column (Note 9) containing 300 g of activated alumina (Note 10). After the solution has been added, the column is filled with pentane and a 1-L constant-pressure addition funnel, also filled with pentane, is fitted to the top of the column to provide a slight head pressure. The elution is completed in ca. 90 min. All the pyridine is obtained in the first 2 L of eluant (Note 11). The pentane is removed on the rotary evaporator to yield 62.7–66.3 g (90–93%) of a colorless, odorless oil that solidifies on cooling or standing, mp 31–32°C (Note 12).

2. Notes

1. Since gas evolution at the onset of the reaction is quite vigorous, the operator should check to see that the passage of gas is unobstructed. Gas entering the sodium hydroxide trap should be passed over the solution, not bubbled through it, to guard against the possibility of sodium hydroxide solution being drawn back into the reaction flask.
2. *tert*-Butyl alcohol was obtained from Eastman Organic Chemicals and was used as received. The checkers also used *tert*-butyl alcohol freshly distilled from potassium with equal results. Pivaloyl chloride was obtained from Aldrich Chemical Company, Inc.
3. Trifluoromethanesulfonic acid FC-24 was obtained directly from the manufacturer, Minnesota Mining and Manufacturing Co. (3M), 15 Henderson Dr., West Caldwell, NJ 07006. Adherence to both the time and temperature during the addition is critical for best results.
4. The diethyl ether is conveniently cooled to −10°C by addition of some dry ice.
5. The crude salt darkens somewhat on standing because of further polymerization of impurities, but this does not affect the preparation of the base. It may be further purified by two recrystallizations at −30°C from isopropyl alcohol (8.7 mL/g) to give colorless needles (94% recovery), mp 168–169°C. The salt is not hygroscopic and may be stored indefinitely at room temperature. It is characterized by NMR [$(CD_3)_2SO$] δ: 1.45 (s, 18 H), 2.72 (s, 3 H), 8.10 (s, 2 H).
6. The submitters state that the reaction may be monitored by the formation of a brilliant-yellow intermediate that fades on completion of the reaction.[3] The checkers found it most convenient to remove the cold bath and allow the reaction to stir overnight at room temperature. If the reaction is worked up before completion, a yellow impurity is formed which cannot be removed by subsequent chromatography.
7. Phillips Petroleum Company pentane was used as received. Other brands required distillation to remove small amounts of higher-boiling compounds.
8. Ethanol should not be removed by distillation or use of a rotary evaporator since considerable amounts of product codistil with the ethanol.
9. The water-jacketed chromatography column shown in Figure 1 is useful when low-boiling solvents or heat-sensitive compounds are chromatographed. Considerable heat is generated when the pentane solution containing the pyridine is introduced onto the column. This may cause boiling of the pentane and separation of the alumina. A flow of cold water through the jacket avoids separation of the alumina. The column was packed by slowly adding the alumina to the column half filled with pentane.

Figure 1. Not drawn to scale. (*A*) 29/26 joint; (*B*) hose connection; (*C*) water jacket; (*D*) 40 mm Kimflow fritted disk, size 40-C (coarse), Lab Glass LG28280; (*E*) Teflon Stopcock 2-mm plug bore, Lab Glass LG9605T.



10. Aluminum oxide, activated, acidic, was obtained from Aldrich Chemical Company, Inc., and used as received.
11. The progress of the elution may be monitored by occasionally spotting a fluorescent TLC plate and examining the plate under short-wave UV light; the pyridine appears as a dark-blue spot. Attempts to completely remove colored impurities by distillation, acid-base extraction, or activated charcoal were unsuccessful.
12. Additional physical constants are bp 148–153°C (95 mm), 223°C (760 mm); $HPtCl_6$ salt mp 213–214°C (decomp), CF_3SO_3H salt mp 202.5–203.5°C (from CH_2Cl_2); NMR (CCl_4) δ: 1.29 (s, 18 H), 2.25 (s, 3 H), 6.73 (s, 2 H); pK_a in 50% ethanol: 4.41[4] vs. 4.38 for pyridine in the same solvent.[5] Approximately 0.1% of an impurity, identified by gas chromatography–mass spectrum as 2,6-di-*tert*-butyl-4-neopentylpyridine, is also present; this arises by acid-catalyzed dimerization of isobutylene generated in situ during formation of the pyrylium salt.

3. Discussion

2,6-Di-*tert*-butyl-4-methylpyrylium salts previously have been prepared in yields of 4–40% starting with the chloride or anhydride of pivalic acid and employing various counterions, such as ClO_4^-, $FeCl_4^-$, or $AlCl_4^-$.[6] A more recent multistep preparation yields 33% of the perchlorate.[7] The pyrylium salt has been used to prepare pyrylotrimethinecyanine compounds.[8] 2,6-Di-*tert*-butyl-4-methylpyridine has been prepared in 44% yield by treating 4-picoline with a 10 molar excess of *tert*-butyl lithium[4] or by an anionic condensation reaction.[9] The present procedure is essentially that of Anderson and Stang.[3]

The pyrylium trifluoromethanesulfonate salt is nonexplosive. The resulting pyridine possesses the ability to distinguish between Lewis and Brπnsted acids.[3,5] It will not react with metal cations[10] or BF_3.

The combination of 2,6-di-*tert*-butyl-4-methylpyridine and methyl trifluoromethanesulfonate results in improved yields under very mild conditions of methylated carbohydrates containing acid- or base-labile groups.[11] This pyridine was used as a hindered base in the synthesis of an antigenic bacterial hexasaccharide from *Salmonella newington*.[12] The base has also found use in silylation studies.[13,14] The hindered pyridine makes possible Friedel-Crafts alkylation of aromatic rings under basic conditons.[15,16] Substitution of pyridine by the hindered base results in substantially improved yields of a variety of vinyl esters.[16] The use of the sterically hindered base was essential for the preparation of 1-(ethynyl) vinyl trifluoromethanesulfonates.[17] After use the protonated base can be economically recovered in greater than 95% yield by addition of the pyridinium salt to a two-phase mixture of aqueous 50% sodium hydroxide and pentane followed by elution of the pentane solution through an unactivated silica gel column.[17]

Recently, 2,6,-di-*tert*-butyl-4-methylpyridine was incorporated into a polymer[18] via the 4-methyl group and the resulting polymer bound 2,6-di-*tert*-butylpyridine used in vinyl triflate synthesis. It has also been shown[19] that unlike 2,6-dimethyl and 2,4,6-trimethylpyridine, the 2,6-di-*tert*-butyl-4-methylpyridine does not react with triflic anhydride, $(CF_3SO_2)_2O$, and this might account for the advantageous use of this nonnucleophilic base when preparing reactive triflates.[20]

Because of its ease of preparation and ready availability in quantity 2,6-di-*tert*-butyl-4-methylpyridine continues to be the base of choice in variety of applications when nonnucleophilic basic reaction conditions are required.[21,22]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 506
- Org. Syn. Coll. Vol. 8, 97
- Org. Syn. Coll. Vol. 8, 126
- Org. Syn. Coll. Vol. 9, 67

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

alumina

pyrylium salt

chloride or anhydride of pivalic acid

1-(ethynyl)vinyl trifluoromethanesulfonates

2,6-dimethyl and 2,4,6-trimethylpyridine

ethanol (64-17-5)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

isopropyl alcohol (67-63-0)

ammonium hydroxide (1336-21-6)

potassium (7440-09-7)

Pentane (109-66-0)

aluminum oxide (1344-28-1)

isobutylene (9003-27-4)

tert-butyl alcohol (75-65-0)

trifluoromethanesulfonic acid (1493-13-6)

pivaloyl chloride (3282-30-2)

triflic anhydride (358-23-6)

4-picoline (108-89-4)

Pyridine, 2,6-bis(1,1-dimethylethyl)-3-methyl-

methyl trifluoromethanesulfonate (333-27-7)

tert-butyl lithium (594-19-4)

2,6-Di-tert-butyl-4-methylpyridine,
2,6,-di-tert-butyl-4-methylpyridine (38222-83-2)

2,6-Di-tert-butyl-4-methylpyrylium trifluoromethanesulfonate (59643-43-5)

2,6-di-tert-butyl-4-neopentylpyridine

2,6-di-tert-butylpyridine (585-48-8)