Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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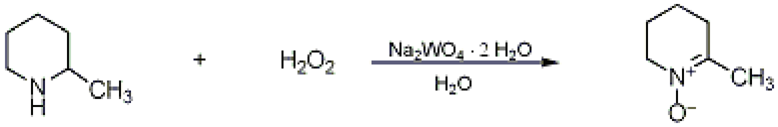
OXIDATION OF SECONDARY AMINES TO NITRONES: 6-METHYL-2,3,4,5-TETRAHYDROPYRIDINE N-OXIDE

[Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide]



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Checked by Gary C. Look and Larry E. Overman.

1. Procedure

In a 500-mL, three-necked, round-bottomed flask equipped with a 100-mL pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar is placed 2.64 g (8.00 mmol) of sodium tungstate dihydrate (Note 1). After the flask is flushed with nitrogen, 40 mL of water and 23.5 mL (200 mmol) of 2-methylpiperidine (Note 2) are added. The flask is cooled with an ice-salt bath to −5°C (internal temperature) and 45.0 mL (440 mmol) of 30% aqueous hydrogen peroxide solution (Note 3) is added dropwise over a period of ca. 30 min. During the period of addition the reaction mixture should be carefully kept at a temperature below 20°C (Note 4). The cooling bath is removed, and the mixture is stirred for 3 hr (Note 5). Excess hydrogen peroxide is decomposed by adding ca. 3 g of sodium hydrogen sulfite with ice cooling (Note 6). The solution is saturated by adding ca. 25 g of sodium chloride and extracted with ten 200-mL portions of dichloromethane (Note 7). Combined organic extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration, and the solvent is removed by a rotary evaporator keeping the temperature at 40°C (Note 8) to give a pale yellow oil (20.0–22.0 g), which may be sufficiently pure for some applications (Note 9). Purification of the nitrone is achieved by column chromatography on 300 g of silica gel packed in 97:3 chloroform/methanol in a 4.8-cm × 70-cm column (Note 10). The product is applied to the column in 10 mL of chloroform and the column is eluted with 97:3 chloroform/methanol. After twenty 100-mL fractions are collected, the eluent is changed to 8:2 chloroform/methanol, and another ten 100-mL fractions are collected and analyzed by thin layer chromatography (Note 11). Combination of fractions 16–30 and evaporation provides 14.0–15.7 g (62–70%) of pure 6-methyl-2,3,4,5-tetrahydropyridine N-oxide as a pale yellow oil (Note 12) and (Note 13).

2. Notes

1. Sodium tungstate dihydrate was purchased from Wako Pure Chemical Ind., Ltd. and used without further purification. The checkers employed material purchased from Mallinckrodt, Inc.
2. 2-Methylpiperidine purchased from Nacalai Tesque, Inc. was distilled prior to use (bp 119–120°C). The checkers employed 2-methylpiperidine purchased from Aldrich Chemical Company, Inc.
3. The 30% aqueous solution of hydrogen peroxide was purchased from Mitsubishi Gas Chemical Company, Inc. or Fisher Scientific. Ten percent excess of hydrogen peroxide is used to complete the reaction within an appropriate time.
4. This is an exothermic reaction. Higher reaction temperatures cause partial decomposition of the product.
5. The reaction mixture consists of the desired nitrone and 6–15% of isomeric 2-methyl-2,3,4,5-tetrahydropyridine N-oxide: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (d, 3 H, J = 6.9, $-CH_3$), 7.14 (t, 1 H, J = 3.9, -CH=N-).
6. The presence of hydrogen peroxide is detected with potassium iodide-starch test paper.
7. Extraction with five 200-mL portions of dichloromethane gives 20–21 g of the product. Oxidation of secondary amines which have low molecular weights requires water as solvent. The nitrones thus obtained are highly soluble in water, and many extractions are required. However, other nitrones can be

isolated easily by simple extraction.

8. Higher temperatures cause decomposition of the desired product, and lower temperatures retard the decomposition of the undesired nitrone to give the dimeric compound.

9. The crude nitrone consists of the desired nitrone (85–70%), the 1:1 adduct of the less substituted nitrone with the desired nitrone [(3,14-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (15–30%), R_f = 0.39 (TLC glass plate silica gel 60 F_{254}, obtained from E. Merck, 9:1 chloroform/methanol); m/e = 226.1681 ($C_{12}H_{22}N_2O_2$)], and the dimer of the desired nitrone [(3,10-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane) (< 1%), mp 87.5–88.0°C; R_f = 0.46 (under the same conditions); m/e = 226.1664]. The checkers found that the crude product decomposed noticeably when stored overnight at −20°C.

10. Silica gel 60 (70-230 mesh) was purchased from E. Merck. The checkers employed flash chromatography using a 20-cm × 7-cm column and 230-400 mesh EM silica gel 60. With this silica gel it is essential to have 1% triethylamine in the eluent.

11. The R_f value of the nitrone is 0.37 (under the same conditions described above).

12. The product has the following spectral characteristics: IR (neat) cm^{-1}: 2945, 1627, 1448, 1190, 1165, 951, 872, 750, a strong OH stretch at 3400 cm^{-1} is also apparent; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.71-1.77 (m, 2 H, H-4), 1.92–1.97 (m, 2 H, H-3), 2.11 (overlapping tt, 3 H, J = 1.5, 1.0, CH_3), 2.42–2.47 (m, 2 H, H-5), 3.78–3.83 (m, 2 H, H-2); ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 18.0 (CH_3), 18.2, 22.7, 30.0 (C-5), 57.3 (C-2), 145.1 (C-6); UV (EtOH) 235 nm (e 6910).

13. The nitrone slowly dimerizes at room temperature. It should be stored as a solution in a solvent such as dichloromethane to prevent dimerization.

Waste Disposal Information

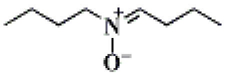
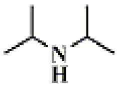
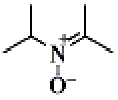
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

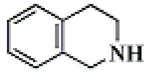
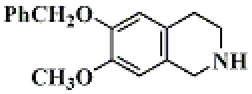
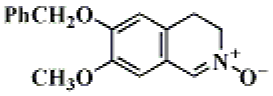
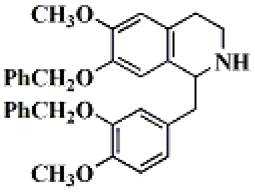
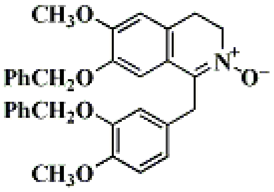
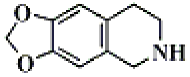
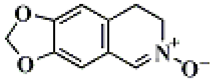
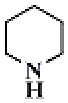
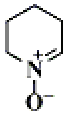
3. Discussion

Nitrones are highly versatile synthetic intermediates and excellent spin trapping reagents.[2] [3] [4] In particular, nitrones are excellent 1,3-dipoles[5] [6] [7] and have been used for the synthesis of various nitrogen-containing biologically active compounds.[5,6] The preparation of nitrones has been performed either by condensation of aldehydes or ketones with hydroxylamines,[8] or by oxidation of the corresponding hydroxylamines.[9] The difficulty of these methods is in the preparation of the starting hydroxylamines. For example, cyclic hydroxylamines are prepared from the corresponding cyclic amines via thermal decomposition of the corresponding tertiary amine N-oxides.[10] [11]

The present procedure provides a single step synthesis of nitrones from secondary amines.[12] Typical results of the preparation of nitrones are summarized in Table I. If necessary, the nitrones are easily purified by distillation, recrystallization, or column chromatography. Selenium dioxide is also an effective catalyst for the oxidation of secondary amines with hydrogen peroxide to give nitrones.[13] 1,3-Dipolar cycloadducts are obtained directly by the oxidation of secondary amines in the presence of alkenes.

TABLE I
CATALYTIC OXIDATION OF SECONDARY AMINES WITH HYDROGEN PEROXIDE

Amine	Solvent	Product	Yield %
	CH_3OH		89
	CH_3OH		74

	CH_3OH		85
	CH_3OH		85
	CH_3OH		86
	CH_3OH		60
	CH_3OH		62
	H_2O		44
	H_2O		40

The reaction of nitrones with various nucleophiles provides a powerful strategy for the introduction of a substituent at the α-position of secondary amines.[14] [15] The reaction of nitrones with Grignard reagents or organolithium compounds affords various α-substituted hydroxylamines, which can be converted into α-substituted secondary amines by catalytic hydrogenation. The nucleophilic reaction with potassium cyanide gives α-cyanohydroxylamines which are useful precursors for amino acids and N-hydroxyamino acids.[16]

References and Notes

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

silica gel

methanol (67-56-1)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

sodium hydrogen sulfite (7631-90-5)

selenium dioxide (7446-08-4)

hydrogen peroxide (7722-84-1)

dichloromethane (75-09-2)

triethylamine (121-44-8)

sodium tungstate dihydrate (10213-10-2)

6-Methyl-2,3,4,5-tetrahydropyridine N-oxide,
Pyridine, 2,3,4,5-tetrahydro-6-methyl-, 1-oxide (55386-67-9)

2-methylpiperidine (109-05-7)

2-methyl-2,3,4,5-tetrahydropyridine N-oxide

3,14-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane

3,10-dimethyl-2,9-dioxa-1,8-diazatricyclo[8.4.0.0^{3,8}]tetradecane