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.

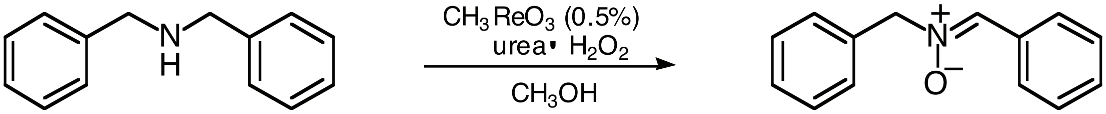
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.081.0204

Organic Syntheses, Vol. 81, p. 204-212 (2005); Coll. Vol. 11, p. 114-120 (2009).

METHYLTRIOXORHENIUM CATALYZED OXIDATION OF SECONDARY AMINES TO NITRONES: *N*-BENZYLIDENE-BENZYLAMINE *N*-OXIDE

[Benzenemethanamine, (*N*-phenylmethylene)-, *N*-oxide]



Submitted by Andrea Goti,[1] Francesca Cardona, and Gianluca Soldaini.
Checked by Xiaowu Jiang and Marvin J. Miller.

1. Procedure

A. 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirbar, thermometer, and a reflux condenser fitted with a rubber septum and balloon of argon is charged with a solution of methyltrioxorhenium (MTO) (0.013 g, 0.05 mmol, 0.1% mol equiv) in 100 mL of methanol (Note 1). Urea hydrogen peroxide (UHP) (14.3 g, 152 mmol) is added (Notes 1, 2, 3, 4), the flask is cooled in an ice bath, and dibenzylamine (9.7 mL, 50.7 mmol) is then added dropwise via syringe over 10 min (Notes 1, 5). After completion of the addition, the ice bath is removed and the mixture is stirred at room temperature (Note 6). A white precipitate forms after approximately 5 min (Note 7) and the yellow color disappears within 20 min (Note 8). Another four portions of MTO (0.1% mol equiv, 0.013 g each) are added at 30-min intervals (2.5 hr total reaction time). After each addition, the reaction mixture develops a yellow color, which then disappears; only after the last addition does the mixture remain pale yellow (Note 9). The reaction flask is cooled in an ice bath and solid sodium thiosulfate pentahydrate (12.6 g, 50.7 mmol) is added in portions over 20 min in order to destroy excess hydrogen peroxide (Note 10). The cooled solution is stirred for 1 h further, at which point a KI paper assay indicates that the excess oxidant has been completely consumed. The solution is decanted into a 500-mL flask to remove small amounts of undissolved thiosulfate. The solid is washed with 50 mL of MeOH and the methanol extract is added to the reaction solution which is then concentrated under reduced pressure by rotary evaporation. Dichloromethane (250 mL) is added to the residue and the urea is removed by filtration through cotton and celite. Concentration of the filtrate affords 10.3 g (97%) of the nitrone as a yellow solid (Note 11).

If desired, the nitrone can be recrystallized from diisopropyl ether (200 mL) (Notes 12, 13), affording 9.0 g (84%) of a white solid (Note 14). Concentration of the mother liquor and recrystallization of the residue from 40 mL of diisopropyl ether provides 0.600 g of additional nitrone. Total yield: 9.6 g (89%) of the nitrone as a white solid (Note 15).

2. Notes

1. Dibenzylamine, MTO, and UHP were purchased from Aldrich Chemical Company and used as received.

2. *Caution:* Potential hazards are associated with the use of the urea hydrogen peroxide complex (UHP). Due to the relatively high hydrogen peroxide content (ca. 36%) of this reagent, care should be exercised in its use. Additionally, concentrated solutions of H_2O_2 are potentially explosive, especially when contaminants such as metals are present. However, it has been reported that UHP is a safe source of hydrogen peroxide,[2] which makes it a good alternative to anhydrous or highly concentrated aqueous solutions of H_2O_2. UHP has been judged stable by negative impact and pressure-time tests for explosiveness on small samples[2] and the submitters have never experienced problems in its use.

3. Although the oxidation requires 2 mol equiv of oxidant with respect to amine, use of 3 mol equiv of UHP is advised in order to speed up the reaction and to reduce the amount of catalyst required. For example, use of a smaller excess of UHP (2.5 mol equiv) required an increase to 0.7% mol equiv of MTO and a 4 h reaction time in order for the oxidation to proceed to completion.

4. Immediately upon addition of the urea-hydrogen peroxide adduct to the solution containing methyltrioxorhenium, a yellow color develops due to formation of the catalytically active rhenium peroxo complexes.[3]

5. The internal temperature of the solution rises from ca. 4 °C to 12-13 °C after all of the amine has been added.

6. The internal temperature varies from 24 °C to 32 °C during the whole reaction time, with the highest values being reached after each addition of the catalyst.

7. The white precipitate is presumably *N*,*N*-dibenzylhydroxylamine, an intermediate oxidation product, which disappears after the third catalyst addition.

8. The disappearance of the yellow color indicates a low concentration of the active catalytic species due to loss in efficiency of the cycle.

9. Monitoring of the reaction by TLC on silica gel showed complete consumption of the starting amine (elution with 20:1 CH_2Cl_2/CH_3OH, visualization by UV and by iodine; dibenzylamine: $R_f = 0.4$, nitrone: $R_f = 0.7$).

10. The submitters found that on small scale (1 mmol) this treatment is unnecessary. On a larger scale, it is recommended to destroy excess hydrogen peroxide for safety, although oxidations on larger scale without this treatment have been carried out without experiencing any problem. It was also observed that product of higher purity is obtained when hydrogen peroxide is destroyed.

11. The crude nitrone has the following physical data: mp 75-77 °C; Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.39; H, 6.18; N, 6.78.

12. *Caution:* Use of diisopropyl ether from a freshly opened bottle is advised, due to possible formation of peroxides in aged ethereal solvents. Other solvents were less effective for this recrystallization.

13. The crude solid is readily dissolved in a smaller amount of solvent, but employing the indicated volumes is recommended in order to achieve better yields of recrystallization. With this volume of solvent, heating at 74 °C is sufficient to have complete solubilization of the solid.

14. The nitrone exhibits the following spectral and physical data: mp (uncorr.) 79-81 °C (lit.[4] 81-83 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.09 (s, 2 H), 7.38-7.49 (m, 9 H), 8.17-8.20 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 71.29, 128.41, 128.57, 128.93, 129.17, 130.35, 130.51, 133.35, 134.11; IR (KBr) cm^{-1}: 3061, 3030, 2995, 1581, 1497, 1459, 1153; MS (EI, 70 eV) m/z (%): 211 ($M^{+\cdot}$, 27), 195 (7), 181 (16), 91 (100), 83 (78), 66 (70), 65 (52);

exact mass (FAB): Calcd $(M+H)^+$ 212.1075, found 212.1064. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.57; H, 5.92; N, 6.51.

15. The submitters report a yield of 86% and the checkers obtained the product in 85-90% yield in several runs.

Waste Disposal Information

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

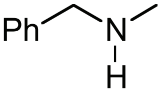
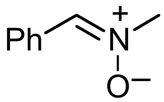
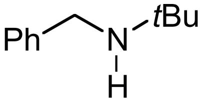
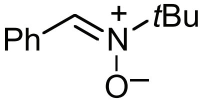
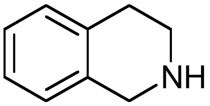
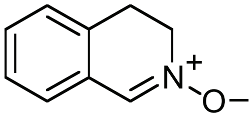
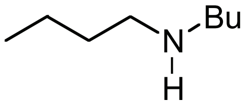
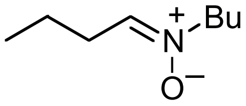
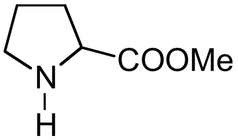
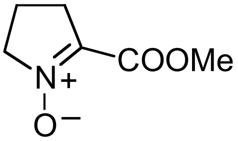
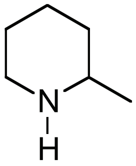
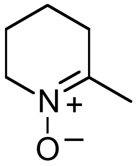
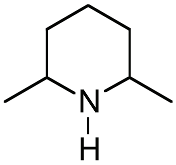
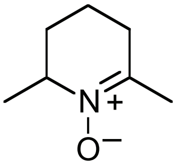
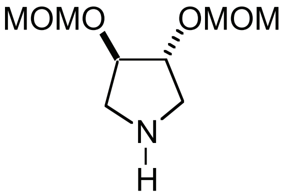
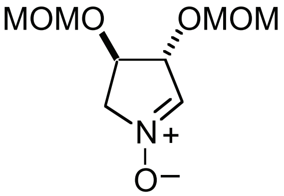
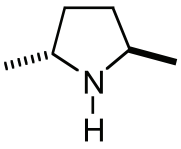
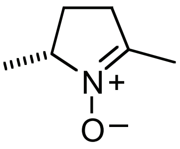
3. Discussion

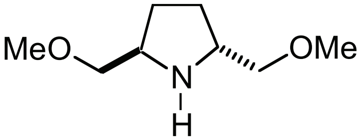
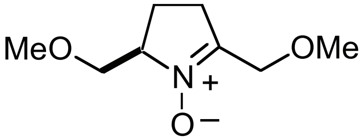
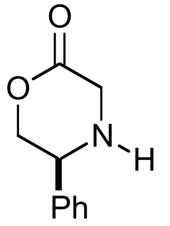
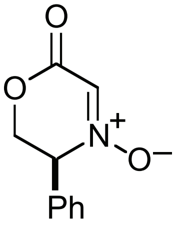
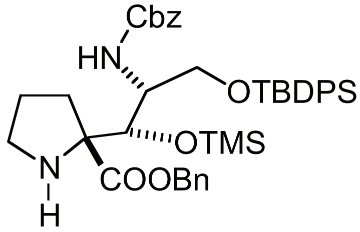
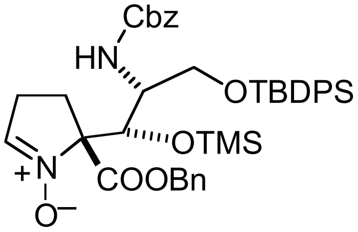
Nitrones are very useful tools in the construction of structurally complex molecules and particularly nitrogen-containing biologically active compounds, usually allowing a high degree of diastereocontrol. In this context, both the [3+2] cycloaddition of nitrones to alkenes[5,6] and the alkylation of nitrones by organometallic reagents[7] have been extensively developed and have become extremely reliable synthetic procedures. In addition, nitrones are useful spin trap reagents, widely employed in biological systems.[8]

The most widely employed methods for the synthesis of nitrones are the condensation of carbonyl compounds with *N*-hydroxylamines[5] and the oxidation of *N*,*N*-disubstituted hydroxylamines.[5,9] Practical and reliable methods for the oxidation of more easily available secondary amines have become available only recently.[10-13] These include reactions with stoichiometric oxidants not readily available, such as dimethyldioxirane[10] or *N*-phenylsulfonyl-*C*-phenyloxaziridine,[11] and oxidations with hydrogen peroxide catalyzed by Na_2WO_4[4,12] or SeO_2.[13] All these methods suffer from limitations in scope and substrate tolerance. For example, oxidations with dimethyldioxirane seem to be limited to arylmethanamines and the above mentioned catalytic oxidations have been reported (and we have experienced as well) to give somewhat erratic and unreproducible results in some cases. Particularly, functionalized pyrrolidines and piperidines behaved as capricious substrates in those protocols. For example, a chiral optically active pyrrolidine underwent racemization to variable degrees upon oxidation to the corresponding nitrone with H_2O_2 catalyzed by Na_2WO_4[14] and oxidation with dimethyldioxirane of a chiral 2-morpholinone gave scarcely reproducible results.[15] In these cases, the described oxidation method using methyltrioxorhenium/urea·H_2O_2 complex was demonstrated to be a better alternative, furnishing consistently good and reproducible yields (see Table, entries 9 and 11, respectively), without loss of enantiomeric purity, also on multi-gram scale. The examples reported in the Table are illustrative of the scope of the oxidation method described here. Most of the reactions reported in the Table have been carried out on a 0.5-1 mmol scale and are unoptimized, with a 2% mol equiv of MTO being employed. The procedure described above has been scaled-up and optimized, also in terms of minimal catalyst use. The amount of catalyst to be used in order to achieve complete conversion is not greatly influenced by the reaction scale. Indeed, essentially the same results as those reported above have been obtained on a 10 mmol scale with 0.4% mol equiv of MTO and in a further scale-up of the process on 0.1 mol of dibenzylamine with a minimal increase to 0.6% mol equiv of MTO. On a 10-12 mmol scale, 0.7% mol equiv of MTO were necessary for oxidizing completely dibutylamine and 1% mol equiv was sufficient to oxidize the more sterically congested *N*-(*tert*-butyl)-*N*-benzylhydroxylamine.

Due to its broad scope, as well as to its favorable features (commercial availability of the catalyst, use of a “green” oxidant, economy, extremely simple procedure and work-up), this method has been rapidly accepted, as demonstrated by its use by several different research groups, despite its recent disclosure.[16,17] This procedure employing CH_3ReO_3 and UHP appears to be the method of choice when optically active nitrones are prepared by oxidation of the corresponding amines.[14,15,18, 19]

Table

Entry	Amine	Nitrone	Yield (%)
1[a]			70
2[a]			86
3[a]			82
4[a]			60
5[a]			65
6[a]			60[b]
7[a,c]			91
8[d]			80
9[e]			51[f]

10[g]			94[h]
11[i]			70-80[l]
12[m]			85

[a] Reference 16.
[b] About 10% of the regioisomeric aldonitrone was observed in the ^1H NMR spectrum of the crude mixture.
[c] Reference 18a.
[d] Reference 17a.
[e] Reference 14.
[f] Calculated over two steps starting from the *N*-benzylamine derivative.
[g] Reference 18b.
[h] Yield of crude product, used without further purification.
[i] Reference 15.
[l] On multigram scale.
[m] Reference 18c.

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19. It has been recently discovered that imines also undergo oxidation to nitrones under similar conditions: Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-Benzylidene-benzylamine *N*-oxide; Benzenemethanamine,
    N-(phenylmethylene)-, *N*-oxide; (3376-26-9)
Methyltrioxorhenium: Rhenium, methyltrioxo-, (T-4); (70197-13-6)
Urea hydrogen peroxide: Urea, compd. with hydrogen peroxide (H_2O_2)
    (1:1); (124-43-6)
Dibenzylamine: Benzenemethanamine, *N*-(phenylmethyl)-; (103-49-1)

xwj-orgsyn

Pulse Sequence: s2pul