Synthesis of Nitrones by Methyltrioxorhenium Catalyzed Direct Oxidation of Secondary Amines

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Abstract: Oxidation of secondary amines catalyzed by methyltrioxorhenium (MTO) with H_2O_2 or urea-hydrogen peroxide complex (UHP) at room temperature gives the corresponding nitrones in good yields. Copyright © 1996 Elsevier Science Ltd

We have recently reported two new procedures for the oxidation of secondary amines to imines[1] and of *N,N*-disubstituted hydroxylamines to nitrones[2] by catalysis of tetra-*n*-propylammonium perruthenate (TPAP). In continuation of these studies we were interested to develop a new, catalytic oxidation of secondary amines directly to nitrones, highly valuable synthetic intermediates.[3] The methods available for this transformation need the use of aqueous hydrogen peroxide in water or biphasic systems,[4] or employ toxic materials[4d] or expensive and not commercially available oxidants in stoichiometric (2 equivalents) amounts.[5] Recently, a method has been developed which prevents most of these shortcomings by the use of the urea-hydrogen peroxide complex (UHP) in the presence of sodium wolframate or molybdate or selenium dioxide.[6] However, in our hands the selenium or wolframate catalyzed oxidation has proven unreliable in some particular cases.[7]

In consideration of Murahashi's generalization that oxo metal complexes catalyze the oxidation of secondary amines to imines, while hydroperoxy metal species catalyze their transformation into the corresponding nitrones,[8] we envisaged methyltrioxorhenium (MTO, **1**) as a potential candidate for the desired oxidation, on the basis of the ascertained formation of peroxy species **2** and **3** from MTO and hydrogen peroxide (Scheme 1).[9]

Scheme 1
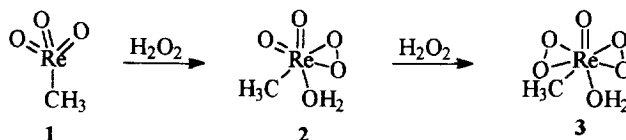
MTO has emerged during the last five years as a versatile catalyst for the oxidation of a number of functionalized compounds, including alkenes,[10] alkynes,[10a] arenes,[11] phenols,[12] benzaldehydes,[13] sulfides,[14] anilines,[15] phosphines,[16] as well as for insertion into C-H bonds,[17] by using hydrogen peroxide, preferably in high concentrations, as the stoichiometric oxidant.

We have initially performed the oxidation reaction in several conditions on dibenzylamine (4) as a representative substrate, in order to define the best method for the desired conversion to nitrone 5 (Table 1).

Table 1. Methyl Trioxorhenium (MTO) Catalyzed Oxidation of Dibenzylamine (4).[a]

$$Ph\diagup N(H)\diagdown Ph \xrightarrow[\text{rt, 24 h}]{H_2O_2,\ MTO} Ph\diagup N^{+}(O^-)\diagdown Ph \ + \ Ph\diagup N(OH)\diagdown Ph$$

Entry	MTO (eq %)	Oxidant (eq)	Solvent	Conversion (%)[b]	5:6 Ratio[b]
1	1.6	35% aq H_2O_2 (3.3)	CH_2Cl_2	50	0.50
2	3	35% aq H_2O_2 (4)	CH_2Cl_2	59	0.43
3	3	35% aq H_2O_2 (4)	CH_3OH[c]	98	2.45
4	5	35% aq H_2O_2 (4)	CH_3OH[c]	100	>50
5	2	4.3 M H_2O_2 in EtOH[d] (2)	CH_3OH[c]	100	1.34
6	2	4.3 M H_2O_2 in EtOH[d] (4)	CH_3CH_2OH[c]	100	1.35
7	2	UHP (4)	CH_2Cl_2[c]	79	0.27
8	2	UHP (4)	CH_3OH[c]	100 .	30
9	2	UHP (3)	CH_3OH	100	>50

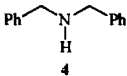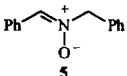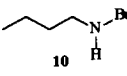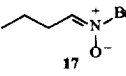[a]Reactions carried out on a 0.5 mmol scale. [b]Calculated by integration of the ^{1}H NMR spectra of the crude mixture. [c]Anhydrous sodium sulfate (100 mg) was added to the reaction mixture. [d]Prepared according to ref. 17.
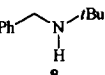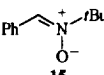
The reactions were carried out at rt for 24 h, after which time the reaction mixtures were analyzed by ^{1}H NMR. The spectra showed essentially the peaks of the starting amine 4 and of the oxidation products 5 and 6 and allowed calculation of conversion and nitrone/hydroxylamine ratio. Commercial 35% aqueous hydrogen peroxide was employed in order to avoid the hazards connected with the use of more concentrated solutions. With this oxidant, methanol as the solvent and at least 3% equivalents of MTO were required for practical conversion, but still relevant amounts of hydroxylamine 6 were present (entry 3). Only the use of 5% of MTO allowed the nitrone 5 to be the exclusive reaction product (entry 4), apart minor amounts of benzaldehyde always present in the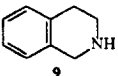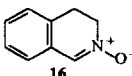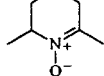 reaction mixture (<5%). The use of an ethanolic solution of H_2O_2[17] gave total conversion already with only 2% of MTO (entries 5 and 6), but with a low 5/6 ratio, independently on the amount of oxidant used. Finally, the urea-hydrogen peroxide complex (UHP) was tested as the oxidant (entries 7-9). Once again, the use of the alcoholic solvent was essential for attaining good conversions and complete oxidation to nitrone (cfr. entries 7 and 8). In these conditions, 2% of MTO and 3 equivalents of UHP were sufficient for the practical transformation of dibenzylamine (4) to the nitrone 5 (entry 9). Addition of anhydrous Na_2SO_4 to the reaction mixture (entries 3-8) for remotion of water proved to be not essential and, on the contrary, appeared to have an unfavorable effect on the reaction rate (cfr. entries 8 and 9), as previously observed.[18] On the other hand, the increase of hydrolysis products (benzaldehyde) in absence of the drying agent was very limited.

While this work was in progress, two communications have reported the convenient use of MTO with UHP in chlorinated solvents for the epoxidation of alkenes.[18,19] One more communication has appeared, dealing with the MTO catalyzed oxidation of nitrogen containing compounds, but a single example of a secondary amine (4) as a substrate was reported and the oxidation afforded mainly the corresponding hydroxylamine 6 after short reaction times (15 min) at 0 °C.[20] Since ethanolic H_2O_2 was used in that work, this result is consistent with those reported in entries 5 and 6.

On the basis of the results reported in Table 1, the conditions of entry 9 were chosen for demonstrating the synthetic utility of this new method. Therefore, the secondary amines 4 and 7-13 were oxidized[21] and the corresponding nitrones 5 and 14-20 isolated by purification of the crude mixture by flash column chromatography or distillation (Table 2).

Table 2. Catalytic Oxidation of Secondary Amines to Nitrones with Methyltrioxorhenium and UHP.[a]

Entry	Amine	Nitrone	Yield (%)	Entry	Amine	Nitrone	Yield (%)
1	4	5	95	5[c]	10	17	60[d]
2	7	14	70	6	11	18	65
3[b]	8	15	86	7	12	19	60[e]
4	9	16	82	8	13	20	91

[a]See ref. 21 for reaction conditions. [b]With 5 eq UHP. [c]On a 1 mmol scale and 3 h reaction time (conversion was complete, but formation of an unidentified side-product also occurred). [d]Isolated by Kugelrohr distillation. [e]About 10% of the regioisomeric aldonitrone was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

The amines 4 and 7-13 are efficiently oxidized to give the corresponding nitrones in good yields (60-95%) (Table 2). The sterically congested amine 8 (entry 3) required more oxidant (5 eq) for completion of oxidation of the intermediate hydroxylamine. Unsymmetrically substituted secondary amines 7, 9, 11 and 12 gave the more stable nitrone, albeit in some cases (e.g. entry 7) the regioisomer has been observed in the crude mixture.

In summary, this novel direct oxidation method of secondary amines gives good yields of nitrones, employing only commercially available and non toxic or dangerous materials, mild reaction conditions in non aqueous medium, and quick and simple work-up procedures. For these reasons, it is expected to be employed as an useful alternative to the existing procedures for the same transformation. Methyltrioxorhenium, which can be used in limited amount, confirms its high versatility and broadens its applicability as catalyst in oxidation procedures of organic compounds.

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21. Typical procedure. A 10 mL reaction flask was charged sequentially with MTO (0.01 mmol), CH_3OH (1 mL), and UHP (1.5 mmol). The stirred solution became yellow due to formation of peroxy species and, after 10 min, was cooled to 0 °C and the amine (0.5 mmol) was added. The reaction mixture was stirred under N_2 at room temperature for 24 h. The solvent was removed under vacuum. The crude reaction mixture was added with CH_2Cl_2 and the undissolved urea filtered off. The pure nitrones were collected by chromatography on silica gel using the appropriate eluent.