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MINI REVIEW

Synthesis of Tertiary Amine *N*-Oxides-A Review

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Oxidation reactions with environmentally acceptable oxidants such as molecular oxygen and hydrogen peroxide have been intensively studied. Recently, catalytic H_2O_2 oxidations of aromatic *N*-heterocyclic compounds to their corresponding *N*-oxides employing a biomimetic manganese porphyrin or methyltrioxorhenium as catalyst were reported. Other oxidants employed in the oxidation of tertiary amines include peracids, magnesium monoperphthalate, 2-sulfonyloxaziridines, dioxiranes, *etc*.

Key Words: Tertiary amine, Oxidant, Tertiary amine oxide, Catalyst, Molecular oxygen.

INTRODUCTION

Amine *N*-oxides are synthetically important building blocks and are extensively used as oxidants, for example in osmium-catalyzed dihydroxylation of olefins[1-3], in ruthenium-catalyzed oxidation of alcohols[4,5] and in a mild procedure for conversion of halides to aldehydes[6-8]. Amine oxides are also compounds of increasing interest as potential cytoximes which are hypoxia-selective for the treatment of solid tumors[9]. Aliphatic *tert*-amine *N*-oxides are essential and major components for ubiquitously used materials such as hair conditioners, shampoos, toothpaste, laundry detergent powders, fabric softeners, toilet soaps and cosmetics as well as in biomedical applications[10]. A variety of stoichiometric as well as catalytic methods are reported in the literature for the oxidation of tertiary nitrogen compounds to *N*-oxides.

Oxidation methods

Oxidation of amines with 2-sulfonyloxaziridines (Davis' reagents): This is easy to prepare and handle solids are useful aprotic and neutral oxidizing reagents, which have been employed for the oxidation of a wide variety of functionalities. The disadvantage is that the initial materials are not readily available.

General procedure[11]: To a solution of the amine (1 mmol) in 3 mL of $CDCl_3$ was added in a single portion 2-(phenylsulfonyl)-3-phenyloxaziridine (**1**) (1 mmol). The reaction mixture was stirred for 1 h. Any solid that precipitated was removed by filtration and a ^{13}C NMR spectrum of the filtrate was obtained. After the spectrum had been recorded the $CDCl_3$ solution was evaporated and the residue was either

recrystallized or chromatograpahed. The yields of the tertiary amine oxidations of triethylamine, *N*-methylpiperidine and 1-azabicyclo[2.2.2]octane are all more than 95 %. The preparation method of **1** are shown in **Scheme-I**[12].
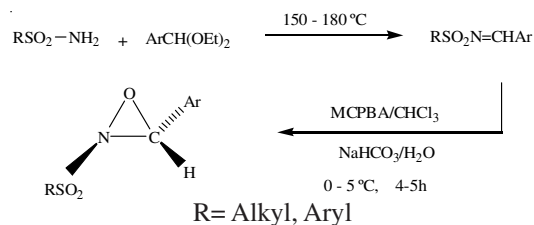
Scheme-I: Preparation of 2-(phenylsulfonyl)-3-phenyloxaziridine (**1**)

Using dioxiranes: Treatment of tertiary amines with DMD at 0 °C afforded the corresponding *N*-oxides in quantitative conversion yields (in all cases less than 1 h), although reaction conditions, in particular regarding the amount of DMD required (1.0-2.0 DMD molar equiv were used), depended on each substrate. In addition, the oxidation was chemoselective in the presence of carbon-carbon double bonds[13]. In conclusion, preparation of amine *N*-oxides by using DMD is a simple and valuable procedure. A convenient preparation of acetone solutions of dimethyldioxirane was developed (**Scheme-II**), but the yeild of DMD is so low, which is not more than 5 %[14].
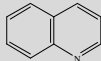
Molecular oxygen is an attractive oxidant and development of synthetic methodologies using molecular oxygen as the sole oxidant is a rewarding goal both from environmental and economic points of view[15-18]. The following three methods show easy accesses to *N*-oxides.

$$CH_3COCH_3 + KHSO_5 \xrightarrow[\text{pH=7.4, 5 -10 °C}]{\text{H}_2\text{O, NaHCO}_3}$$
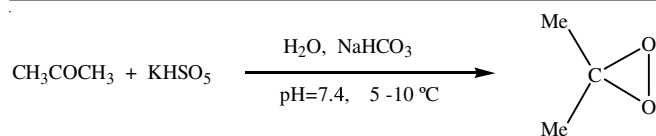
Scheme-II: Preparation of acetone solutions of dimethyldioxirane

Cobalt-catalyzed aerobic oxidation: A wide variety of tertiary nitrogen compounds were oxidized to give their corresponding *N*-oxides in nearly quantitative yields by simpl bubbling molecular oxygen into a solution of the tertiary nitrogen compound in 1,2-dichloroethane at room temperature in the presence of 5-Å molecular sieves and with the cobalt(II) Schiff base complex as the catalyst (**Scheme-III**). These results are summarized in Table-1[19]. This is an environmentally friendly method. However, the preparation of cobalt(II) Schiff base complex should be under nitrogen atmosphere in anhydrous system for long time nearly 40 h[20], so the catalyst can not be easily achieved.
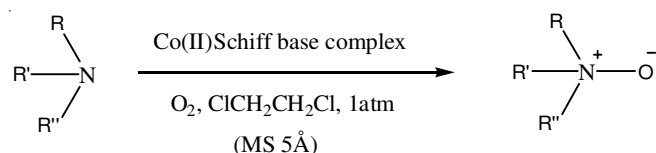
Scheme-III: Oxidation of tertiary nitrogen compounds to *N*-oxides catalyzed by a cobalt(II) Schiff base.
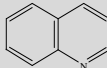
TABLE-1
OXIDATION OF TERTIARY NITROGEN COMPOUNDS TO *N*-OXIDES

Entry	Substrate	t(h)	Yield (%)
1	Pyridine	8	80
2	4-Picoline	8	85
3	2-Picoline	10	75
4	Nicotinamide	14	55
5	Isonicotinonitrile	12	50
6	3-Picoline	10	65
7	(quinoline)	12	50
8	*N,N*-Diethylaniline	6	92
9	*N,N*-Dimethylaniline	6	90
10	Triethylamine	5	92

Ruthenium catalyzed oxidation with molecular oxygen: A simple and convenient ruthenium catalyzed oxidation of tertiary nitrogen compounds to their *N*-oxides in near quantitative yields using molecular oxygen as the sole oxidant[21]. The substrates tested are 4-picoline, 2-picoline, 3-picoline, pyridine, *N,N*-dimethylaniline, *N,N*-diethylaniline and triethylamine, yields of their corresponding *N*-oxides were 95, 94, 90, 85, 98, 94 and 98 %. All the substrates and solvents are commercially available.
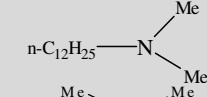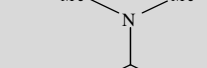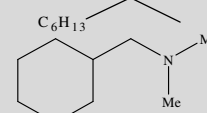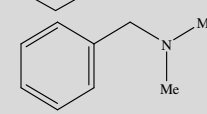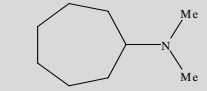
Bromamine-T/RuCl₃ as an efficient system: A variety of tertiary amines were efficiently and selectively oxidized to the corresponding *N*-oxides by bromamine-T using ruthenium trichloride as catalyst in alkaline (pH 8.4) acetonitrile/water (1:1) at 80 °C. The results are summarized in Table-2[22].
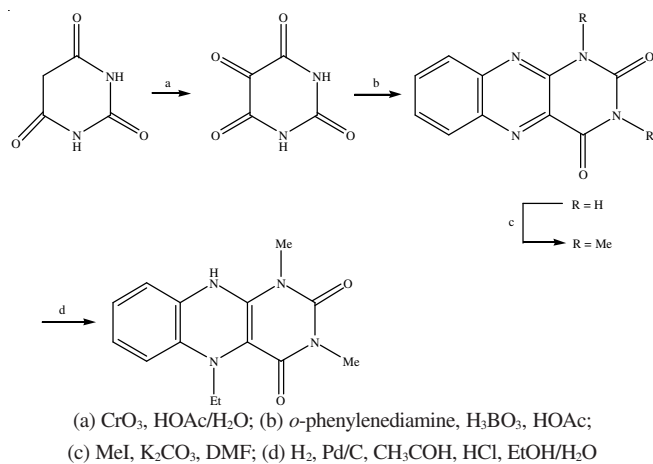
This is a simple reaction under mild conditions. However, compared to the above described ruthenium catalyzed oxidation with molecular oxygen, this method is less efficient and needs more harsh conditions.

TABLE-2
OXIDATION OF TERTIARY NITROGEN COMPOUNDS TO *N*-OXIDES

Entry	Substrate	Time (h)	Yield (%)
1	Pyridine	3.0	75
2	4-Picoline	2.5	85
3	2-Picoline	3.0	80
4	Nicotinamide	6.0	50
5	Isonicotinonitrile	4.5	65
6	3-Picoline	10	65
7	(quinoline)	12	50
8	*N,N*-Diethylaniline	2.5	92
9	*N,N*-Dimethylaniline	2.5	90
10	$(C_2H_5)_3N$	5	92

Flavin-catalyzed H₂O₂ oxidation: A mild and highly effective H₂O₂ oxidation of tertiary amines has been developed by using flavin catalysis. Eight aliphatic amines were oxidized to their corresponding N-oxides in fast and selective reactions[23].

Amine was stirred in MeOH, to this mixture the flavin catalyst and H₂O₂ were added. After several hours stirring at room temperature, excess H₂O₂ was destroyed by addition of solid MnO₂. Filtration through celite, followed by evaporation of the solvents under reduced pressure, gave the crude product, which was purified on basic Al₂O₃. Immediate evaporation of the solvents afforded the *N*-oxide. For all substrates a considerable rate enhancement was observed compared to the non-catalyzed reactions (Table-3). However, it was found to be crucial to carry out the workup under a strictly inert atmosphere for a successful preparation of flavin analogue (**Scheme -IV**). Besides, the catalyst seemed to be extremely air sensitive, so they should be stored at -30 °C under argon.

TABLE-3
OXIDATION OF TERTIARY AMINES EMPLOYING THE FLAVIN-HYDROGEN PEROXIDE SYSTEM AS OXIDANT[23]

Entry	Amine	Time (> 85 % conv.) (min)	Rate enhancement cat. : non-cat.
1	4-Methylmorpholine	60	61:1
2	$n\text{-}C_{12}H_{25}\text{—}N(Me)_2$	27	49:1
3	(amine structure)	25	51:1
4	(amine structure)	50	83:1
5	(amine structure)	31	67:1
6	(amine structure)	32	27:1
7	*N*-Methyl piperidine	55	39:1
8	Triethylamine	54	27:1

(a) CrO₃, HOAc/H₂O; (b) *o*-phenylenediamine, H₃BO₃, HOAc;
(c) MeI, K₂CO₃, DMF; (d) H₂, Pd/C, CH₃COH, HCl, EtOH/H₂O

Scheme-IV: Synthesis of the flavin catalyst

Methyltrioxorhenium-hydrogen peroxide system:
Methyltrioxorhenium catalyzes the reaction of hydrogen peroxide with organonitrogen compounds. Methyltrioxorhenium forms two adducts with H_2O_2 (**Scheme-V**), both of which will be expected to undergo rapid reaction with nucleophilic nitrogen. The reactions are facile and high yield at room temperature or below (Table-4)[24].
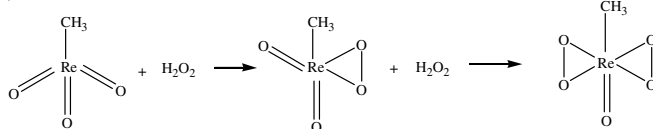
Scheme-V: Methyltrioxorhenium forms two adducts with H_2O_2

TABLE-4
OXIDATION OF AMINES WITH H_2O_2-
METHYLTRIOXORHENIUM

Entry	Amines	Reaction time (h)	Conditions temp (°C)	Product	Yield (%)
1	Pyridine	1	RT		100
2		1	0		100

Typical reaction: Methyltrioxorhenium was added to a solution of H_2O_2 in ethanol. This solution was then added to the amine substrate. After stirring for the appropriate time, water was added to the reaction mixture. The reaction was then extracted witn CH_2Cl_2. The observed chemistry is similar to the previously described method, which uses dimethyl-dioxirane as the oxidant.

Hydrogen peroxide in the presence of TS-1: TS-1 was prepared according to the method of Taramasso *et al*.[25] and calcined at 550 °C immediately prior to use. Reactions were carried out using the heterocyclic substrate (0.05 mol), aqueous hydrogen peroxide (0.05 mol) and TS-1 (200 mg).

Two procedures were investigated: In method A, the reaction was initiated by adding the premixed reactants to the catalyst, while in method B the catalyst and heterocycle were stirred together for 5 min after, which addition of the oxidant

started the reaction. The reaction mixtures were stirred at 60 °C for a period of 24 h (Table-5)[26]. It took long time and the yield was not very good.

TABLE-5
OXIDATION OF PYRIDINE AND PICOLINES
USING H_2O_2 AS OXIDANT

Catalyst/method	*N*-oxide product yield (%)			
	Pyridine	2-picoline	3-picoline	4-picoline
Non-catalyzed	35.5	28.4	15.9	9.6
TS-1 method A	95.3	84.7	42.4	34.7
TS-1 method B	96.0	88.0	51.9	53.2

Sulfonic peracid[27,28]**:** The sulfonic peracid (**2**) was generated *in situ* by the reaction of *p*-toluenesulfonylimidazole with H_2O_2 in the presence of aqueous NaOH (**Scheme-VI**). As expected, the oxidation of tertiary amines with the oxidation system 1/H_2O_2/NaOH leads to the formation of the corresponding *N*-oxides depending on the type of amine introduced. The yields are not very good. Yields of *N*-oxides of *N,N*-dimethylaniline, *N*-Methyl piperidine, *N*-ethyl-*N*-isopropyl-propan-2-amine, pyridine and 2,4,6- trimethylpyri-dine are 95, 70, 40, 60 and 55 %, respectively.
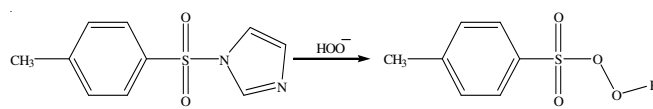
Scheme-VI: Preparation of sulfonic peracid (**2**)

Tungstate-exchanged Mg-Al layered double hydroxide in water: A green process, using a recyclable tungstate-exchanged Mg-Al layered double hydroxide (LDH-WO4²⁻) heterogenized catalyst and aqueous H_2O_2 oxidant in water, leads to *N*-oxidation of aliphatic *tert*-amines to amine *N*-oxides in quantitative yields, at a high rate at room temperature (**Scheme-VII**)[29]. The potential for its commercial application is strengthened by the high throughput of the product, lower process inventories and use of an aqueous phase reaction system. The Mg-Al LDH (3:1) tungstate was prepared according to the reported procedure[30], which is very easy. The exchanged LDH catalyst was evaluated in oxidation of aliphatic *tert*-amines with H_2O_2 (Table-6), the catalyst can be reused for six cycles (Table-6, entry 9) without loss of activity and selectivity.
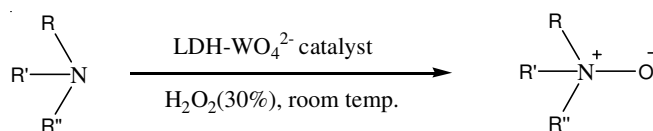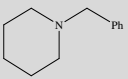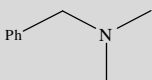

R,R',R" = alkyl, cyclohexyl or cyclic

Scheme-VII: Oxidation of *tert*-amines to amine *N*-oxides catalyzed by tungstate- exchanged Mg-Al LDH.

Pyrazine-based polymeric complex of oxodiperoxo-chromium(VI) compound: The coordination polymer of pyrazine and oxodiperoxochromium(VI) compound as a new stable form of CrO_5 was found to be an efficient oxidizing agent for tertiary amines. For example, with this reagent triehyl-amine and *N,N'*-dimethyl- aniline were changed to the *N*-oxides

quantitatively (nearly 100 % yield)[31]. Both reactions were performed in CH_2Cl_2 at room temperature with oxid./subst. = 2/1.

TABLE-6
OXIDATION OF ALIPHATIC *tert*-AMINES WITH H_2O_2
USING EXCHANGED LDH CATALYST[29]

Entry	Amine	Procedure	Time (h)	Yield (%)
1	4-Methylmorpholine	I	1.0	96
2		II	1.0	96
3	Triethylamine	I	3.0	96
4		II	1.5	96
5		I	3.0	97
6		II	1.0	97
7		I	1,5	95
8		II	1.0	96

Using magnesium monoperphthalate: A comparison with *m*-chloroperoxybenzoic acid.

The oxidation of a wide variety of functional groups using peracids has been much investigated, but established methods suffer from a number of disadvantages. In many cases, the reagent has to be prepared as required using high-strength hydrogen peroxide and may well be strongly acidic as well as being unstable. *m*-Chloroperoxybenzoic acid (MCPBA) is one peracid that is widely used, but safety and cost considerations frequently discourage its use for large-scale syntheses. The *m*-chloroperoxybenzoic in its pure form is both shock-sensitive and potentially explosive in the condensed phase. Commercial forms of *m*-chloroperoxybenzoic acid normally contain *m*-chlorobenzoic acid as a contaminant, this leads to some reduction in the hazardous nature of the product, but it is still shock-sensitive and capable of deflagration. Magnesium monoperoxyphthalate hexahydrate (MMPP), by comparision, is non-shock-sensitive and non-deflagrating. Consequently, the product is much safer to use in both small- and large-scale operations. Magnesium monoperoxyphthalate has a number of other properties that make it an attractive alternative to *m*-chloroperoxybenzoic acid. Typical experimental procedures using different solvent systems are given below (Table-7). Reaction of pyridine is also given below (**Scheme-VIII**)[32].

TABLE-7
OXIDATION REACTIONS USING MAGNESIUM
MONOPERPHTHALATE[32]

Substrate	Mol ratio Substrate: MMPP	Solvent	Temp (°C)	Time (h)	Yield (%)
Pyridine	1:0.55	H_2O	45	1.5	92
Pyridine	1:0.5	AcOH	85	2.0	88
2-Methylpyridine	1:0.5	AcOH	85	2.0	86
2-Chloropyridine	1:0.5	AcOH	85	2.0	69
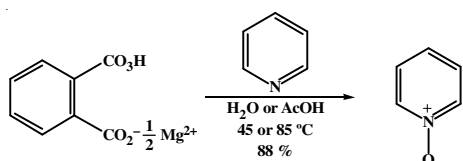
Scheme-VIII: Reaction of magnesium monoperphthalate and pyridine

Conclusion

Generally two process routes are used for synthesis of tertiary amine oxides, one of which directly uses molecular oxygen as oxidant while another uses other oxidants. The route used molecular oxygen as oxidant needs lower cost and achieves quantative products, but needs higher equipments and reaction conditions. Another route usually applys hydrogen peroxide as oxidant, which is widely used at home and abroad. The advantages of this method are simple to operate, easy to control and requires no special equipment. In recent years the oxidation of tertiary nitrogen compounds with hydrogen peroxide using methyltrioxorhenium, manganese porphyrin, flavin, TS-1, molecular sieves, or tungstate-exchanged Mg-Al layered double hydroxide as catalysts has been reported in pursuit to the development of ecofriendly synthetic methodologies.

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