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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Fan Wang , Hao Zhang , Guoqiang Song And & Xiaoling Lu (1999) A New Method for Oxidation of Tertiary Amine by Molecular Oxygen/Aldehyde/Fe203 System, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:1, 11-14, DOI: <u>10.1080/00397919908085728</u>

To link to this article: http://dx.doi.org/10.1080/00397919908085728

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A NEW METHOD FOR OXIDATION OF TERTIARY AMINE BY MOLECULAR OXYGEN/ALDEHYDE/Fe₂O₃ SYSTEM

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Abstract: Oxidation of tertiary amines to tertiary amine N-oxides was achieved in moderate to high yields, by using Fe₂O₃ as catalyst, with molecular oxygen in the presence of isovaleraldehyde under mild conditions.

Oxidation is one of the most important reactions in organic synthesis. Although catalytic oxidation of organic compounds can be accomplished with a wide variety of oxidants, much effort has been made to seek after a method for direct oxidation by use of molecular oxygen (1 atm) under mild reaction conditions. Recently, the system consisting of molecular oxygen, aldehyde and catalyst has proved to be an efficient reagent for the oxidation of some organic compounds.¹ Several metal catalysts are effective for the system and have been studied for oxidation of alkane, epoxidation of olefins and Baeyer-Villiger oxidation of ketones etc.¹⁻³ Transformations of this type avoid the use of highly oxidized reagents such as peroxides which are potentially explosive,⁴ reducing the possibility of side reactions. In this communication, we would like to for the first time report our study on the efficient oxidation of tertiary amines to tertiary amine N-oxides by the O₂/RCHO/Fe₂O₃ system, this system is in a safe and very convenient method for the oxidation reaction of tertiary amines, compared with usual oxidizing reagents.

$$R^{\frac{1}{2}} - R^{\frac{3}{2}} + RCHO + O_2 \xrightarrow{cat.} R^{\frac{1}{2}} - R^{\frac{3}{2}} + RCOOH$$

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A typical reaction procedure for the oxidation of tertiary amines is as follows. A mixture of catalyst (0.1mmol), aldehyde (30mmol) and 1,2-dichloroethane (40ml) was placed into a four-necked flask with a reflux condenser and a thermometer, was vigorously stirred. Oxygen was bubbled into the stirred solution at 50°C for a while until the peroxide was produced (starch-iodide paper). Then tertiary amine (10mmol) was added to the above system, the resulting mixture was continuously stirred under bubbling of oxygen (1 atm) at 50°C until the starting material was consumed (monitoring by TLC, petroleum ether/acetone: 2/1). The catalyst was removed by filtration. Evaporation followed by column chromatography gave the corresponding product which was identified by ¹H-NMR, MS and IR.

At first, the importance of the aldehyde component in the oxidation system was examined in Fe₂O₃-catalyzed oxidation of pyridine at 40°C. It was found that the oxidation was strongly dependent on the kinds of aldehydes used and isovaleraldehyde is the most effective. With respect to the amount of isovaleraldehyde, the use of three equivalents' aldehyde led to complete conversion. However, the yield of pyridine N-oxide decreased to 49% by decreasing its amount to two equivalents and to 29% by using one equivalent of isovaleraldehyde, respectively. Raising reaction temperature to 50°C had positive effect on pyridine N-oxide formation. In the scrutiny of solvents in the pyridine oxidation with isovaleraldehyde, the solvent effect is remarkable and 1,2-dichloroethane has proved to be an excellent solvent. The representative results of Fe₂O₃-catalyzed aerobic oxidation of tertiary amines in 1,2-dichloroethane using the above combined system are summarized in Table 1 and 2.

Entry	Aldehyde	Yield (%)
1	Me ₂ CHCH ₂ CHO	49
2	Me ₂ CHCHO	35
3	Me(CH ₂) ₅ CHO	21
4	PhCHO	31
5		9

Table 1Effect of various aldehydes onFe2O3-catalyzed aerobic oxidation of pyridinea

^a Reaction temperature: 40°C, aldehyde: 20 mmol

E nt ry	Substrate	Product	Yield ^b (%)
1	< <u>∑</u> N	N-0	89
2			53
3	ON-Me	ON-Me	70

 Table 2
 Oxidation of tertiary amine by

 Op/MeaCHCHaCHO/FeaOa System^a

^a Reaction time: 3h. ^b Isolated yield.

Table 3Aerobic oxidation of pyridine catalyzedby transition metal salts in the presence of isovaleraldehydea

Entry	Catalyst	Yield (%)
1	Fe ₂ O ₃	49
2	Cu(OH) ₂	48
3	Co ₂ O ₃	16
4	CoCl ₂	11
5	Co(AcO) ₂	8

a Reaction temperature: 40°C, aldehyde: 20 mmol

Next, the catalytic activities of several transition metal salts have been examined, as shown in Table 3. Fe₂O₃ and Cu(OH)₂ have proved to be effective. the catalytic activity of them was much higher than that of cobalt salts.

The present procedure was also successfully applied to the oxidation of methyl phenyl sulfide, as shown in the following equation.

PhrS-Me + Me₂CHCH₂CHO + O₂ $\xrightarrow{\text{Fe}_2O_3 (1\%\text{mol})}{40^{\circ}\text{C}_1\text{h}, \text{OCH}_2\text{CH}_2\text{C}}$ $\begin{array}{c} P \\ PhrS-Me + PhrS-Me + Me_2\text{C}HCH_2\text{COOH} \\ O \\ 81\% & 8\% \end{array}$ Although it is premature to explain clearly the mechanism of this valuable transformation at the stage, the oxidation might occur mainly by an organic peracid generated from the reaction of an aldehyde with molecular oxygen in the presence of Fe₂O₃, the peracid subsequently react with the catalyst to afford active species.^{2b} Further work on the precise mechanism and other applications of the present oxidation is actively in progress in our laboratory.

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Accepted May 22, 1998