

**IMPROVED OXIDATION OF ACTIVE METHYL GROUP OF
N-HETEROAROMATIC COMPOUNDS BY SELENIUM DIOXIDE IN
THE PRESENCE OF *tert*-BUTYL HYDROPEROXIDE**

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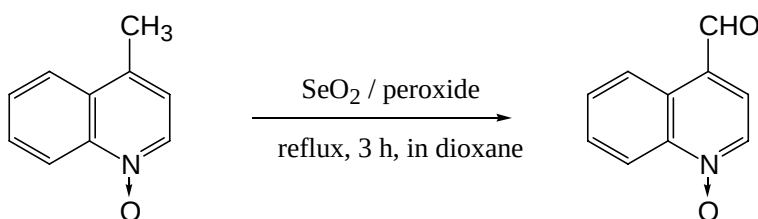
Abstract – The oxidation of active methyl group of *N*-heteroaromatic compounds including both of bicyclic and monocyclic compounds using SeO₂ was considerably improved in the presence of *tert*-butyl hydroperoxide in dioxane to give the corresponding aldehyde or carboxylic acid in the moderate to good yields. The present oxidation proceeds more mildly and more selectively to form aldehyde rather than carboxylic acid, compared with conventional SeO₂ oxidation without *tert*-butyl hydroperoxide.

Selenium dioxide (SeO₂) oxidation has been well-documented as mild and selective oxidation and SeO₂ is particularly used for oxidation of active methyl, methylene and methine groups, alcohols and unsaturated bonds and for dehydrogenation of ethylene compounds.¹ Active methyl group of aromatic and *N*-heteroaromatic compounds is oxidized by SeO₂ to give the corresponding aldehydes or carboxylic acids, but in some cases the oxidation has resulted in the low yield of the corresponding aldehydes and carboxylic acids and the formation of undesired by-products.¹

In order to improve such an inefficient SeO₂ oxidation we examined SeO₂ oxidation of active methyl group of *N*-heteroaromatic compounds in the presence of *t*-butyl hydroperoxide (TBHP)² and revealed in this report that SeO₂ oxidation of active alkyl compounds proceeds in the presence of TBHP more smoothly at lower temperature to afford the corresponding aldehyde or carboxylic acid than the traditional SeO₂ oxidation without TBHP. The general procedure of the present oxidation is as follows : To a solution of SeO₂ (23 mmol) in solvent (20 mL) was added dropwise 70%TBHP (10 mmol) and the mixture was stirred for 0.5 h at room temperature to form the complex. After the starting material (SM) (10 mmol) was added to the mixture, the resulting solution was heated or refluxed according to Tables.

The reaction mixture was filtered and the solvent was evaporated to give the residue which was, after addition of a little amount of water, extracted with CHCl_3 . The CHCl_3 fraction was purified with silica gel column chromatography to afford the product as shown in Tables. The oxidation³ of lepidine 1-oxide by SeO_2 / peroxide in search of the optimal reaction conditions was at first investigated in terms of choosing solvent, peroxide and the molar ratio of SM, peroxide and SeO_2 to give the results as shown in Table 1, 2, and 3.

Table 1 Effect of peroxide on the yield of aldehyde



SM ^{a)}	Solvent	Peroxide	Temp.(°C)	Time(h)	Yield(%)
lepidine 1-oxide	dioxane	70%TBHP ^{b)}	reflux	3	55
		MCPBA ^{c)}	reflux	3	46
		30%H ₂ O ₂	reflux	3	7
		-	reflux	3	45
		80%TBHP	reflux	3	55

a) starting material

c) *m*-chloroperbenzoic acid

Table 2 Effect of molar ratio on the yield of aldehyde

SM ^{a)}	Solvent	Molar ratio of			Temp.(°C)	Time(h)	Yield(%)
		SM :	TBHP ^{b)} :	SeO ₂			
lepidine 1-oxide	dioxane	1 :	1 :	2.3	reflux	3	55
		1 :	0 :	2.3	reflux	3	45
		1	0	4	reflux	3	44
		1 :	1 :	1	reflux	3	25
		1 :	2 :	1	reflux	3	28

a) starting material

Table 3 Effect of solvent on the yield of aldehyde

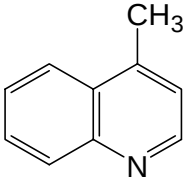
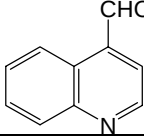
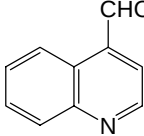
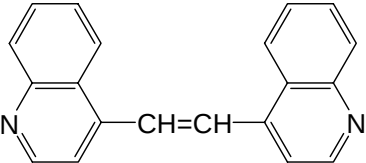
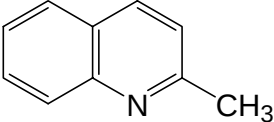
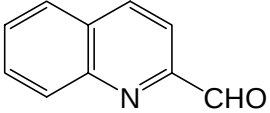
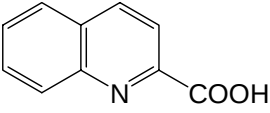
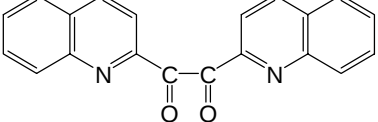
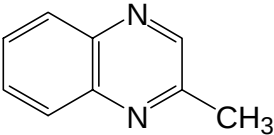
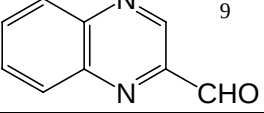
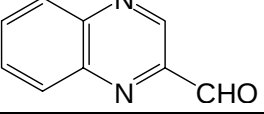
SM ^{a)}	Solvent	Molar ratio of			Temp.(°C)	Time(h)	Yield(%)
		SM	: TBHP ^{b)}	: SeO ₂			
lepidine 1-oxide	dioxane	1	:	1 : 2.3	reflux	3	55
	acetone	1	:	1 : 2.3	reflux	3	0
	THF	1	:	1 : 2.3	reflux	3	4
	DME ^{c)}	1	:	1 : 2.3	reflux	3	17
	dichloromethane	1	:	1 : 2.3	reflux	3	0

a) starting material

c) 1,2-dimethoxyethane

Judging from these experimental results, we adopted TBHP (70%) as a peroxide, dioxane as a solvent, and the molar ratio of 1 : 1 : 2.3 (= SM : TBHP : SeO₂). Using the above-mentioned reaction conditions we carried out the oxidation of active methyl group on the various types of *N*-heteroaromatic compounds (Table 4 and 5).

Table 4 Oxidation of active methyl group on bicyclic *N*-heteroaromatic compound

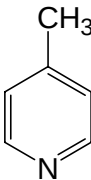
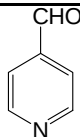
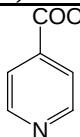
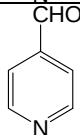
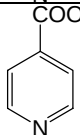
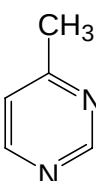
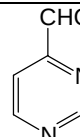
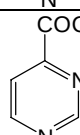
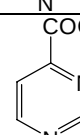
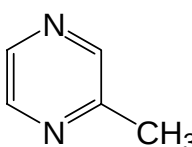
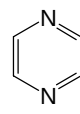
SM ^{a)}	Reaction Conditions	Product (%)
	A, 1.5 h, 50 °C	 85
	B, 1.5 h, 50 °C	no reaction
	SeO ₂ , AcOH-Ac ₂ O ⁴ 1.5 h, 85-90 °C or SeO ₂ , xylene, 1 h, 135 °C ⁵	 50-60
	SeO ₂ , H ₂ O-dioxane ⁶ 1 h, reflux	 89
	A, 1 h, 50 °C	 80
	B, 1 h, 50 °C	no reaction
	SeO ₂ , pyridine ⁷ 70 min, 115 °C	 75
	SeO ₂ , H ₂ O-dioxane ⁸ 1 h, reflux	 91
	A, 1 h, 50 °C	 ⁹ quant.
	B, 1 h, 50 °C	 33

a) starting material

A : SM : 70%TBHP : SeO₂ = 1 : 1 : 2.3 and dioxane as a solvent.

B : SM : SeO₂ = 1 : 2.3 and dioxane as a solvent.

Table 5 Oxidation of active methyl group on monocyclic *N*-heteroaromatic compound

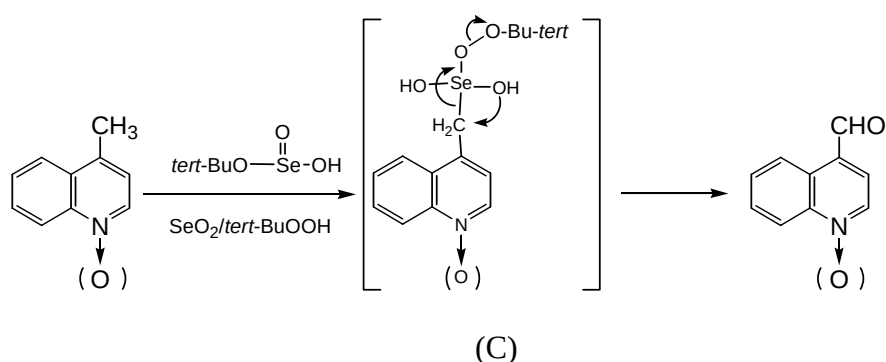
SM ^{a)}	Reaction Conditions	Product (%)			
	A , reflux , 24 h	 CHO	34	 COOH	11
	B , reflux , 24 h	 CHO	2	 COOH	19
	A , 50 °C , 0.5 h	 CHO	10		72
	B , 50 °C , 0.5 h	 COOH	11		18
	SM : 70% TBHP : SeO ₂ = 1 : 10 : 2.3 , 50 °C , 0.5 h dioxane	 COOH			72
	A , reflux , 3 h	 CHO	b), 12		11
	B , reflux , 3 h	no reaction			

a) starting material

b) The aldehyde was obtained as 2,4-dinitrophenylhydrazone.

A : SM : 70%TBHP : SeO₂ = 1 : 1 : 2.3 and dioxane as a solvent.B : SM : SeO₂ = 1 : 2.3 and dioxane as a solvent.

Table 4 and 5 show that the oxidation of active methyl group on both of monocyclic and bicyclic *N*-heteroaromatic compounds proceeds more smoothly under reaction conditions A (with TBHP) than the oxidation under reaction conditions B (without TBHP) to give the corresponding aldehydes and carboxylic acids in better yields. Furthermore, reaction conditions A is much milder one than conditions B to give larger amount of aldehyde than carboxylic acid and facilitated selective oxidation suppressing the formation of by-products. We suggest the plausible mechanism shown in the Scheme.

**Scheme**

Selenium *tert*-butyl peroxy complex reacts with active methyl group to form the intermediate C which rearrange to aldehyde¹³. This mechanism is supported by the fact that the gelatinous precipitate obtained by the reaction of 4-methyl pyridine with SeO₂ / TBHP at 50 °C showed CH₂ proton and carbon signals in the NMR spectrum and that it was transformed into the corresponding aldehyde when it was refluxed for a few hours.

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