HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 953 - 957
Received, 24th December, 2002, Accepted, 6th February, 2003, Published online, 10th February, 2003

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

Yoshinobu Tagawa, Katsuya Yamashita, Yoshitaka Higuchi, and Yoshinobu Goto*

Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma 8-19-1, Jonan-ku, Fukuoka 814-0180, Japan

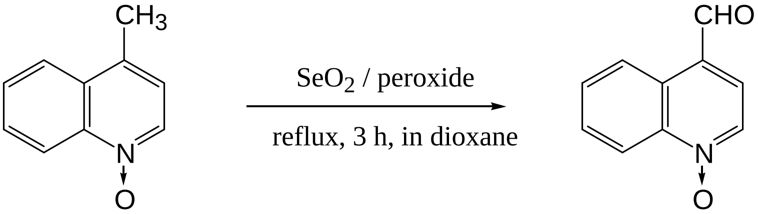
Abstract – The oxidation of active methyl group of *N*-heteroaromatic compounds including both of bicyclic and monocyclic compounds using SeO_2 was considerably improved in the presence of *tert*-butyl hydroperoxde in dioxane to give the corresponding aldehyde or carboxylic acid in the moderate to good yields. The present oxidation proceeds more mildly and more selectively to form aldehyde rather than carboxylic acid, compared with conventional SeO_2 oxidation without *tert*-butyl hydroperoxide.

Selenium dioxide (SeO_2) oxidation has been well-documented as mild and selective oxidation and SeO_2 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*-heteroaromaic compounds is oxidized by SeO_2 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 SeO_2 oxidation we examined SeO_2 oxidation of active methyl group of *N*-heteroaromatic compounds in the presence of *t*-butyl hydroperoxide (TBHP)[2] and revealed in this report that SeO_2 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 SeO_2 oxidation without TBHP. The general procedure of the present oxidation is as follows : To a solution of SeO_2 (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 oxidation[3] 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.(℃)	Time(h)	Yield(%)
lepidine 1-oxide	dioxane	70%TBHP[b)]	reflux	3	55
		MCPBA[c)]	reflux	3	46
		30%H_2O_2	reflux	3	7
		-	reflux	3	45
		80%TBHP	reflux	3	55

a) starting material b) *tert*-butyl hydroperoxide c) *m*-chloroperbenzoic acid

Table 2 Effect of molar ratio on the yield of aldehyde

		Molar ratio of							
SM[a)]	Solvent	SM	:	TBHP[b)]	:	SeO_2	Temp.(℃)	Time(h)	Yield(%)
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 b) 70% *tert*-butyl hydroperoxide

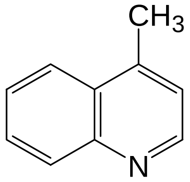
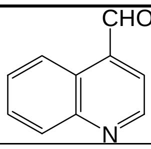
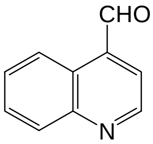
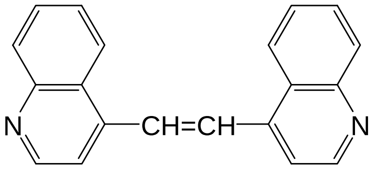
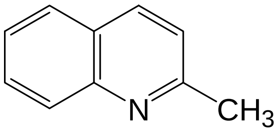
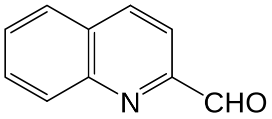
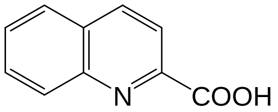
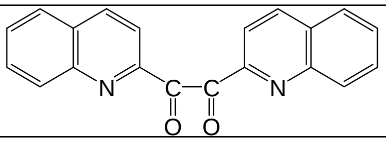
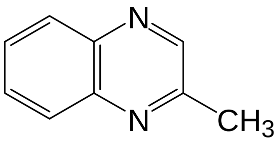
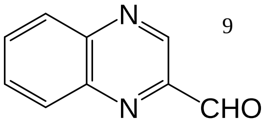
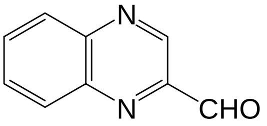
Table 3 Effect of solvent on the yield of aldehyde

		Molar ratio of							
SM[a)]	Solvent	SM	:	TBHP[b)]	:	SeO_2	Temp.(℃)	Time(h)	Yield(%)
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 b) 70% *tert*-butyl hydroperoxide c) 1,2-dimethoxyethane

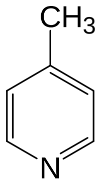
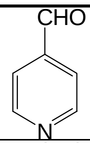
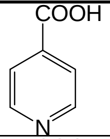
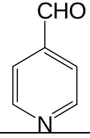
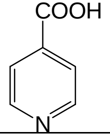
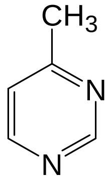
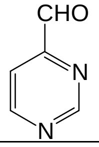
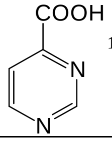
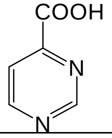
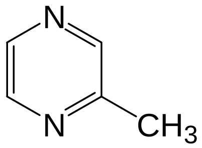
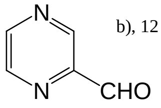
Judging from these experimental results, we adopted TBHP (70%) as a peroxide, dioxane as a solvent, and the molar ratio of 1 : 1 : 2.3 (= SM : TBHP : SeO_2). Using the above-mentioned reaction conditions we carried out the oxidation of active methyl group on the various types of *N*-heteroaromatic compounds (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 ℃		85
	B , 1.5 h , 50 ℃	no reaction	
	SeO_2 , AcOH-Ac_2O [4] 1.5 h , 85-90 ℃ or SeO_2 , xylene , 1 h , 135 ℃ [5]		50-60
	SeO_2 , H_2O-dioxane [6] 1 h , reflux		89
	A , 1 h , 50 ℃		80
	B , 1 h , 50 ℃	no reaction	
	SeO_2 , pyridine [7] 70 min , 115 ℃		75
	SeO_2 , H_2O-dioxane [8] 1 h , reflux		91
	A , 1 h , 50 ℃	 [9]	quant.
	B , 1 h , 50 ℃		33

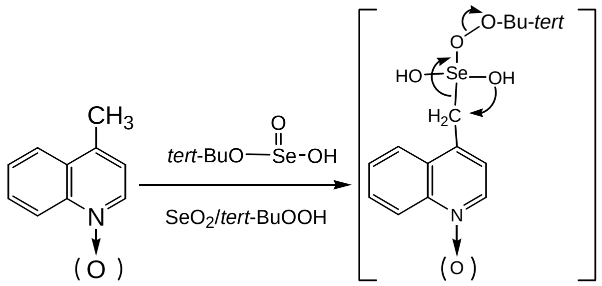
a) starting material
A : SM : 70%TBHP : SeO_2 = 1 : 1 : 2.3 and dioxane as a solvent.
B : SM : SeO_2 = 1 : 2.3 and dioxane as a solvent.

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

SM a)	Reaction Conditions	Product (%)			
	A , reflux , 24 h		34		11
	B , reflux , 24 h		2		19
	A , 50 ℃ , 0.5 h	 [10]	72		
	B , 50 ℃ , 0.5 h	 [11]	18		
	SM : 70% TBHP : SeO_2 = 1 : 10 : 2.3 , 50 ℃ , 0.5 h dioxane		72		
	A , reflux , 3 h	 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 : SeO_2 = 1 : 1 : 2.3 and dioxane as a solvent.
B : SM : SeO_2 = 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.



(C)

Scheme

Selenium *tert*-butyl peroxo complex reacts with active methyl group to form the intermediate C which rearrange to aldehyde[13]. This mechanism is supported by the fact that the gelatinous precipitate obtained by the reaction of 4-methyl pyridine with SeO_2 / TBHP at 50 ℃ showed CH_2 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.

REFERENCES

1. N. Rabjohn, *Org. React.*, 1976, **24**, 261.
2. K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.
3. M. Katada, *J. Pharm. Soc. Japan*, 1948, **68**, 123.
4. C. E. Kwartler and H. G. Lindwall, *J. Am. Chem. Soc.*, 1937, **59**, 524.
5. S. F. MacDonald, *ibid.*, 1947, **69**, 1219.
6. H. Kaplan, *ibid.*, 1941, **63**, 2654.
7. D. Jerchel , J. Heider, and H. Wagner, *Liebigs Ann. Chem.*, 1958, **613**, 153.
8. F. Linsker and R. L. Evans, *J. Am. Chem. Soc.*, 1946, **68**, 947.
9. J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 1956, 2052.
10. J. L. Wong, M. S. Brown, and H. Rapoport, *J. Org. Chem.*, **30**, 2398.
11. G. A. Archer, R. I. Kalish, R. Y. Ning, B. C. Sluboski, A. Stempel, T. V. Steppe, and L. H. Sternbach, *J. Med. Chem.*, 1977, **20**, 1312.
12. H. Rutner and P. E. Spoerri, *J. Org. Chem.*, 1963, **28**, 1898.
13. M. Haruna and K. Ito, *J. Chem. Soc., Chem. Commun.*, 1981, 483.