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A novel synthesis of 2-substituted oxazolines from aldehydes using $NaBrO_3/NaHSO_3$

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ABSTRACT

An efficient synthesis of 2-substituted oxazolines from aldehydes and 2-amino alcohol using the combination of $NaBrO_3$ with $NaHSO_3$ is reported. The *in situ* generated HOBr acts as dehydrogenating agent to convert the initially formed oxazolidine from aldehyde and 2-amino alcohol to furnish 2-substituted oxazolines. This one-pot synthesis is characterized by mild reaction condition, broad scope, high yields, and its preparative simplicity.

INTRODUCTION

Oxazolines, along with their oxidized oxazole relatives, are present in a wide variety of naturally occurring iron chelators, cytotoxic cyclic peptides, antimitotic and neuroprotective agents[1]. For example, Patellamide A is a cytotoxic peptide isolated from a tunicate *Lissoclinum patella*[2]. Optically active oxazolines have been extensively used as valuable auxiliaries in asymmetric synthesis[3]. For example; semicorrin, aryl mono-oxazoline as well as C_2-symmetric bis-oxazoline and pybox are chiral oxazolinyl ligand systems developed in the last few years. These are proved as extremely efficient chiral auxiliaries for a whole range of transition metal catalyzed enantioselective transformations[4]. Oxazolines are also used for the regioselective ortho-alkylation of aromatic carboxylic acids[5] and as protecting groups for carboxylic acids[6].

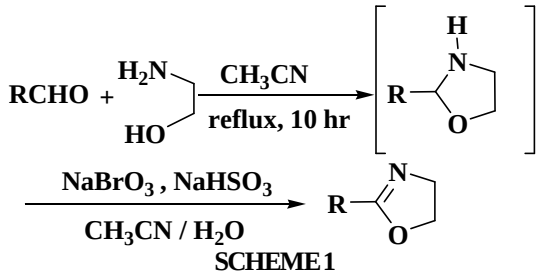
There are several synthetic methods for the preparation of 2-substituted oxazolines mainly from carboxylic acids[7] using different reagents such as $SOCl_2$ [7a-b], PPh_3/DEAD[7c], DAST[7d] and Burgess reagent[7e]. Other starting materials such as carboxylic esters[4], nitriles[8], imidates[9], amido alcohols[10] and olefins[11] can also be used for the synthesis of 2-substituted oxazolines. The literature survey has revealed that there is relatively little number of methods for the direct one-pot conversion of aldehydes to 2-substituted oxazolines. In one report, it has been shown that the reaction of aldehydes with rather less readily available 2-azidoalcohols in presence of $BF_3.OEt_2$ gives 2-substituted oxazolines in good yields[12]. However, the reaction outcome of 2-azidoethanol and aliphatic aldehyde is found to be dependent on the catalyst and the structure of the azido alcohol[13]. Recently, the N-bromosuccinimide[14] and pyridinium hydrobromide perbromide[15] have been reported for the oxidative conversion of aldehydes to corresponding 2-substituted oxazolines. Although all of these methods afford 2-oxazolines in good yields, some of them suffer from drawbacks such as difficulty in multistep manipulation[9,10], utilization of toxic reagents[7], high reaction temperature (200-220^{0}C)[7c], more than stoichiometric use of reagents[12,15] and stringent reaction parameters with occasional low yields of the products. Thus, there is still a need for the development of new, mild and effective method for the synthesis of 2-oxazoline compounds from the readily available precursor such as aldehyde.

The chemistry of the $NaBrO_3$/$NaHSO_3$ reagent has been widely studied because it can be utilized in several useful oxidative transformations[16-19]. It is reasoned that $NaBrO_3$ in combination with $NaHSO_3$ generates *in situ* hypobromous acid, HOBr which acts as a prominent reagent for inducing various oxidation reactions.

$$NaBrO_3 + NaHSO_3 \rightarrow HOBr + Na_2SO_3 + O_2$$

Hypobromous acid, HOBr is a source of electro phonic bromine which can induce transformations such as bromohydroxylatin of alkenes[16], oxidative esterification of primary alcohols[17], oxidation of diols[18], synthesis of γ - lactones[19]. Based upon these literature report, herein we wish to exploit $NaBrO_3$ / $NaHSO_3$ combination for the oxidative synthesis of 2-oxazolines and aromatization of 1,4-dihydropyridines.

Literature survey has revealed that the oxidative synthesis of 2-oxazolines can be achieved from aldehyde and 2-aminoalcohol using brominating agents such as NBS and pyridinium hydrobromide perbromide (PHPD). Both these reagents are the sources of electrophilic bromine. We came across another important literature report related to $NaBrO_3$/$NaHSO_3$ combination which is again known as the source of electrophilic bromine. Prompted by these literature reports, we decided to experiment the combination of $NaBrO_3$/ $NaHSO_3$ system for the oxidative synthesis of 2-oxazolines from aldehydes. Herein, we report that synthesis of 2-oxazolines can be achieved from a readily available aldehyde and 2-aminoalcohol using $NaBrO_3$/ $NaHSO_3$ system in CH_3CN-H_2O solvent (SCHEME 1).

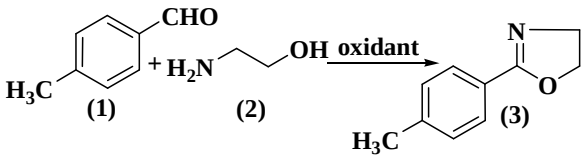


SCHEME 1

In order to confirm the optimum reaction conditions, *p*-tolylaldehyde was chosen as a model substrate and allowed to react with 2-aminoalcohol in presence of $NaBrO_3$/$NaHSO_3$ system under various reaction conditions (TABLE 1).

The success of oxidative conversion of aldehydes

TABLE 1: Optimizing the reaction conditions



Entry	$NaBrO_3$	$NaHSO_3$	Solvent	Reaction time (h)[a]	Yield of 3 (%)[b]
1	1 equiv.	-	CH_3CN	48	00
2	1 equiv.	-	CH_3CN-H_2O (1:1)	48	00
3	1 equiv.	1 equiv.	CH_3CN-H_2O (2:1)	27	34
4	2 equiv.	2 equiv.	CH_3CN-H_2O (2:1)	24	51
5	3 equiv.	3 equiv.	CH_3CN-H_2O (2:1)	22	69

[a]Refluxing conditions, [b]Isolated yields

to corresponding 2-oxazolines depends exclusively on the formation of open chain imine **(2)**. It is well established fact in the literature that aldehyde reacts with 2-amino alcohol to yield open chain imine **(2)** which exists in equilibrium with oxazolidines **(3)**[20]. This is truly an un-catalyzed reaction. The *in situ* generated oxazolidine **(3)** is then, supposed to undergo dehydrogenation using suitable oxidant. Based upon this hypothesis, we initially carried out the reaction of p-tolylaldehyle (5 mmol) with 2-aminoethanol (5 mmol) in CH_3CN under refluxing conditions for the duration of 10 hours. As shown in TABLE 1, $NaBrO_3$ alone did not produce 2-oxazoline product. However, the combination of $NaBrO_3$ and $NaHSO_3$ can induce oxidative transformation of *p*-tolylaldehyde to the corresponding 2-(4-tolyl)-4,5-dihydrooxazole in 69% yield.

In order to establish the scope of this novel oxidation protocol, we tested the reactions of a variety of aromatic aldehyde with 2-aminoethanol and 2-amino-2-methyl-1-propanol and the results are summarized in TABLE 2. As shown in TABLE 2, both electron donating and withdrawing substituents on the aromatic aldehyde afforded the corresponding 2-substituted oxazoline in good to excellent yields.

The tentative mechanism of the reaction is depicted in SCHEME 2. The literature survey has revealed that the uncatalysed reaction of aldehyde with 2-aminoalcohol gives open chain imine **(3)** which exists in equilibrium with oxazolidines **(4)**[20].

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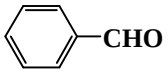
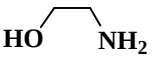
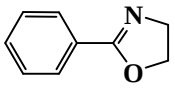
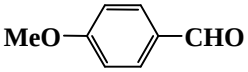
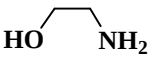
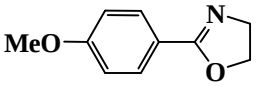
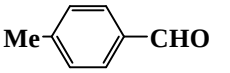
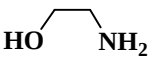
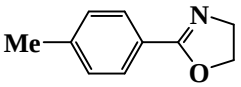
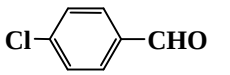
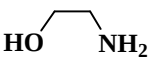
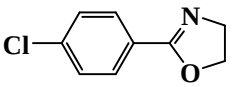
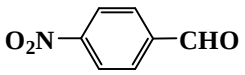
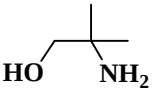
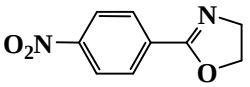
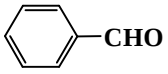
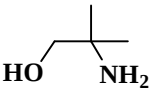
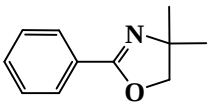
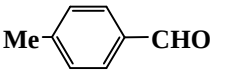
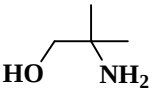
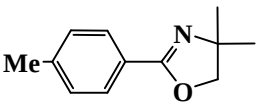
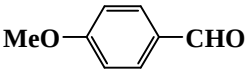
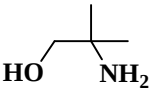
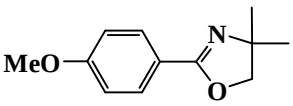
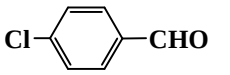
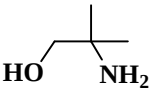
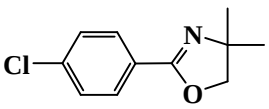
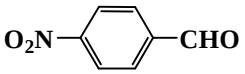
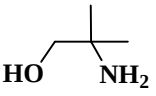
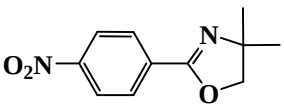
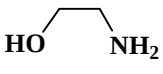
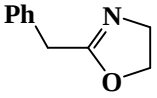
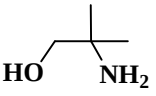
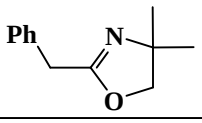
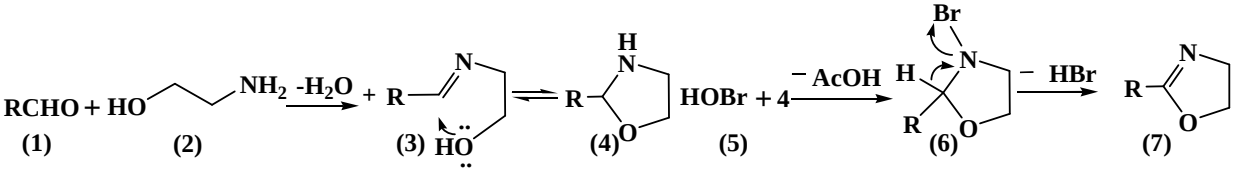
TABLE 2: Formation of 2-substituted oxazolines from aldehyde and 2-aminoalcohol using $NaBrO_3$/$NaHSO_3$ combination in CH_3CN-H_2O system

Entry	Aldehyde	Amino alcohol	Product	Reactin time(h)	Yield (%)
a				22	69
b				27	73
c				23	68
d				24	71
e				27	73
f				27	76
g				23	68
h				28	72
i				30	70
j				24	67
k	$PhCH_2CHO$			29	67
l	$PhCH_2CHO$			29	64

[a]**Isolated yields**



SCHEME 2

The reaction of $NaBrO_3$ with $NaHSO_3$ will generate hypobromous acid (HOBr) **(5)** which is an active source of electrophilic bromine[16-19]. Oxazolidines **(4)** will then react with electrophilic hypobromous acid to form the intermediate **(6)** involving N-Br bond formation. Finally, the concomitant oxidative dehydrogenation of **(6)** will take place to yield 2-substituted oxazolines **(7)**.

EXPERIMENTAL

A mixture of an aldehyde (5 mmol) and 2-amino alcohol (6 mmol) in CH_3CN (30 mL) was initially refluxed for 10 hours. Then a solution of $NaBrO_3$ (15 mmol) in H_2O (10 mL) was added to the above reaction mixture at room temperature. The resulting reaction mixture was stirred and a solution of $NaHSO_3$ (15 mmol) in H_2O (10 mL) was again added. The reaction mixture was further refluxed for the time period as shown in **TABLE 2**. The progress of the reaction was monitored by TLC. After the completion of reaction, CH_2Cl_2 (50 mL) was added and extracted the organic layer, dried over anhydrous Na_2SO_4 and reduced under vacuum to get crude product which was subsequently purified by column chromatography over silica gel using petroleum ether and ethyl acetate.

There is less number of methods (NBS and PHPD)[14-15] available in the literature for the oxidative transformations of aldehydes to substituted oxazolines. Therefore, the combination of $NaBrO_3$/$NaHSO_3$ is a novel oxidising system for the synthesis of 2-oxazolines from aldehydes and 2-amino alcohol. The important features of the methodology are as follows: (a) easy handling, low cost and less toxicity of $NaBrO_3$/$NaHSO_3$ system, (b) good to excellent yields of the products, (c) easy work-up, (d) use of water as co-solvent.

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