Efficient Oxidative Conversion of Aldehydes to 2-Substituted Oxazolines and Oxazines Using (Diacetoxyiodo)benzene

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Abstract: An efficient synthesis of 2-substituted oxazolines from aldehydes and 2-amino alcohol using (diacetoxyiodo)benzene as an oxidant, is reported. (Diacetoxyiodo)benzene acts as a mild dehydrogenating agent to convert the initially formed oxazolidine from aldehyde and 2-amino alcohol to furnish 2-substituted oxazoline. Similarly, 3-aminopropanol and aldehydes gives the corresponding 2-substituted oxazines.

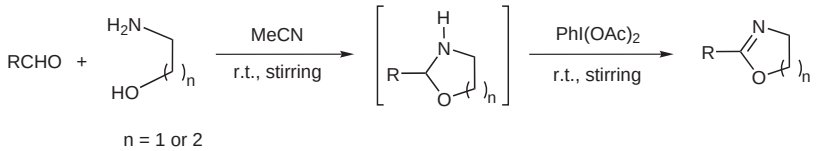
Key-words: hypervalent iodine, oxazolines, oxazines, oxidation, aldehydes

The substructural units of oxazoline heterocycle exist in a variety of naturally occurring iron chelators,[1a] cytotoxic cyclic peptides[1b] and antimitotic[1c] and neuroprotective agents.[1d] They also contribute to the flavors of a variety of foods.[2] The 2-substituted oxazolines can also be used as a robust protecting group for carboxylic acids resisting the attack of nucleophiles, bases ,and radicals.[3] In synthetic chemistry, Meyers and others have found that 2-aryl-2-oxazolines can be used as highly regio- and enantioselective directing groups for the *ortho* lithiation of aryl rings.[4] In addition, the recent intense study of chiral oxazolines as ligands in enantioselective Lewis acid catalysis is particularly significant area of research within heterocyclic chemistry and organic synthesis in general.[5]

There are several synthetic methods for the preparation of 2-substituted oxazolines mainly from carboxylic acids[6] using different reagents such as $SOCl_2$,[6a,b] PPh_3/DEAD,[6c] DAST[6d] and Burgess reagent.[6e] Other starting materials such as carboxylic esters,[7] 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 are fewer 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-azido alcohols in presence of $BF_3{\cdot}OEt_2$ 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,[6] high reaction temperature (200–220 °C),[6c] 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 methods for the synthesis of 2-oxazoline compounds from a readily available precursor such as aldehyde.

Recently, hypervalent iodine reagents are gaining increasing popularity as versatile oxidizing agents in modern organic synthesis.[16] (Diacetoxyiodo)benzene (DIB) is the most extensively utilized parent hypervalent iodine(III) reagent which is easy to handle, nontoxic, commercially available, and similar in reactivity to heavy metal reagents and anodic oxidations.[17] In continuation of our interest in hypervalent iodine reagents,[18] we wish to report herein a mild and facile synthesis of 2-substituted oxazolines and oxazines from aldehydes using DIB as an oxidant (Scheme 1).

To study this process, we have examined the model reaction of 4-tolualdehyde (1.0 mmol) with 2-aminoethanol (1.0 mmol) in acetonitrile (15 mL). This reaction mixture was stirred for four hours and then (diacetoxyiodo)benzene (1.2 mmol) was added consecutively. The resulting mixture was again stirred at room temperature for another



Scheme 1

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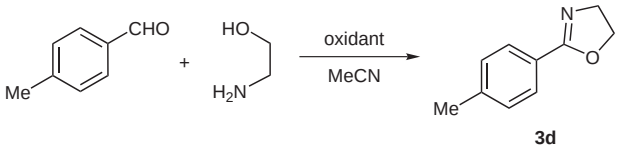
three hours. After completion of reaction, the corresponding 2-(4-tolyl)-4,5-dihydrooxazole was established as the final product, mp 143–144 °C (lit.[8d] 144–145 °C) in 72% yield.[19]

Apart from (diacetoxyiodo)benzene, we have also examined different sources of electrophilic iodine as oxidizing agents such as I_2 and I_2/K_2CO_3 and the results are summarized in Table 1 with respect to the formation of 2-(4-tolyl)-4,5-dihydrooxazole. It follows from Table 1 that the molecular iodine with moderate oxidizing capacity was insufficient to produce **3d** in any appreciable quantity. The combination of I_2 and K_2CO_3 only resulted in the formation of **3d** in a poor yield. The electrophilic DIB was, however, found to be, above all, an excellent oxidizing agent to yield **3d** in reasonably good yield under very mild conditions.

Table 1 Study of Different Iodine Related Oxidizing Agents for the Formation of 2-(4-Tolyl)-4,5-dihydrooxazole



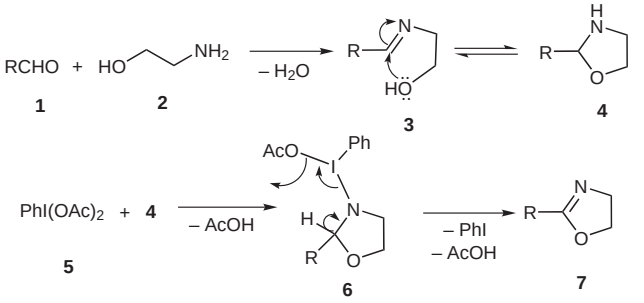
3d

Entry	Oxidizing agent	Quantity of the catalyst (equiv)	Reaction time and conditions	Yield of **3d** (%)[a]
1	I_2	1	24 h and reflux	0
2	I_2/K_2CO_3	1:1	10 h and reflux	18
3	$PhI(OAc)_2$	1.2	7 h and r.t. stirring	72

[a] Isolated yields.

A possible mechanism for the reaction is depicted in Scheme 2. Reaction of aldehyde with 2-amino alcohol gives open-chain imine **3** which can exist in equilibrium with oxazolidines **4**.[20] In support of this fact, we have isolated the intermediate 2-styryloxazolidine resulting from the reaction of cinnamaldehyde and 2-amino-2-methyl-1-propanol and analyzed by LCMS analysis (M + 1 = 204).[21] Ligand-exchange reaction between electrophilic DIB and **4** will generate the putative intermediate **6**. The overwhelming tendency of iodobenzene for reductive elimination from the intermediate **6** will promote the concomitant oxidation of the oxazolidine **4** to yield 2-substituted oxazolines **7**.

In order to assess the generality of the methodology, we synthesized several 2-substituted oxazolines from a range of aldehydes and appropriate amino alcohols (Table 2). In all the reactions, good to excellent yields of the products were observed with 1.2 equivalents of DIB as the mild oxidant. Aliphatic aldehydes were also transformed to the respective oxazolines with good yields. The yields of reactions were relatively less dependent on the substituents present on the aromatic rings. The use of (*R*)-2-amino-1-butanol in place of 2-aminoethanol was also studied, since



Scheme 2

the applications of chiral oxazolines as chiral ligands have been recently increasing. Thus, the aromatic (Table 2, entry i) and aliphatic aldehydes (Table 2, entry j) afforded the corresponding chiral oxazolines in high yields. Having succeeded with 2-oxazoline formation, we then attempted the reaction of 3-aminopropanol with 4-methoxybenzaldehyde using (diacetoxyiodo)benzene under similar reaction conditions to afford 2-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,3-oxazine in 67% yield. Thus the present protocol also permits the one-pot oxidative conversion of aldehydes directly to 2-substituted oxazines (Table 2, entries k–m).

In conclusion, we have developed a transition-metal-free protocol for the oxidative conversion of aldehydes to 2-substituted oxazolines and oxazines using DIB as an oxidant. This reaction is a useful entry in demonstrating the role of DIB as a versatile dehydrogenating reagent. The other advantages of the present reaction are mild reaction conditions, short reaction time, easy work-up, and high yields of the products.

Acknowledgment

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References and Notes

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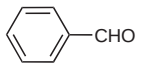
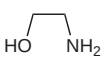
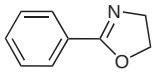
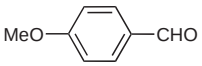
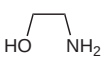
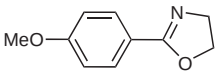
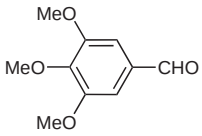
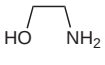
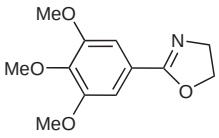
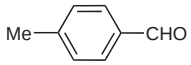
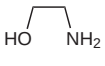
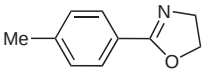
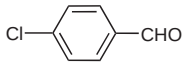
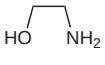
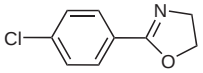
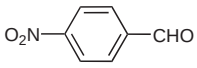
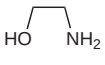
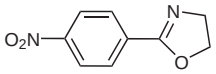
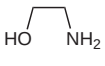
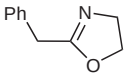
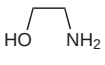
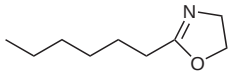
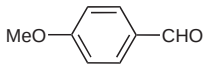
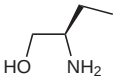
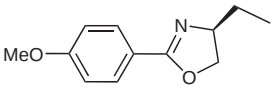
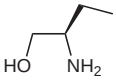
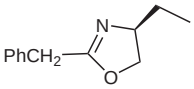
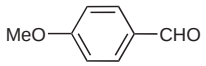
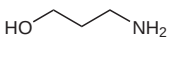
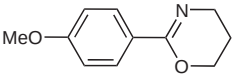
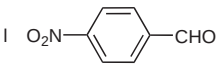
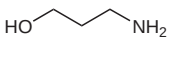
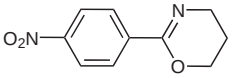
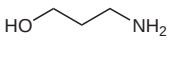
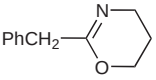
Table 2 Formation of 2-Substituted Oxazolines and Oxazines from Aldehydes and Amino Alcohol Using (Diacetoxyiodo)benzene in Acetonitrile at Room-Temperature Stirring

Entry	Aldehyde **1**	Amino alcohol **2**	Product **3**	Reaction time (h)	Yield (%)[a]
a				7	63
b				7	70
c				9	69
d				7	72
e				8	65
f				9	52
g	$PhCH_2CHO$			9	70
h	$Me(CH_2)_5CHO$			10	62
i				8	68
j	$PhCH_2CHO$			8	65
k				7	67
l				7	71
m	$PhCH_2CHO$			8	69

[a] Isolated yields.

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(19) **Typical Experimental Procedure**

A mixture of an aldehyde (1.0 mmol) and an appropriate 2-amino alcohol (1.0 mmol) was stirred for 4 h at r.t. (Diacetoxyiodo)benzene (1.2 mmol) was then added to the above mixture and the resulting reaction mixture was again subjected for stirring for another 3–6 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, H_2O (15 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over anhyd Na_2SO_4, concentrated in vacuo, and chromatographed to give 2-substituted oxazolines/oxazines.

Spectroscopic Data of Selected Products

2-(4-Nitrophenyl)-4,5-dihydrooxazole

Mp 157–159 °C. IR (KBr): 3028, 2971, 2894, 1649, 1602, 1528, 1464, 1349, 1268, 1092, 952, 861, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.12 (t, *J* = 9.6 Hz, 2 H), 4.50 (t, *J* = 9.6 Hz, 2 H), 8.14 (d, *J* = 8.3 Hz, 2 H), 8.24 (d, *J* = 8.3 Hz, 2 H). LCMS [M + 1]: *m/z* = 193.

2-(4-Chlorophenyl)-4,5-dihydrooxazole

Mp 116–118 °C (lit.[8d] mp 118–119 °C). IR (KBr): 3062, 2964, 2891, 1724, 1638, 1590, 1474, 1280, 1073, 933, 824, 763 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.72 (t, *J* = 9.4 Hz, 2 H), 3.97 (t, *J* = 9.4 Hz, 2 H), 7.40 (d, *J* = 7.9 Hz, 2 H), 7.68 (d, *J* = 7.9 Hz, 2 H). LCMS [M + 1]: *m/z* = 182.

2-(4-Methoxyphenyl)-4,5-dihydrooxazole

Mp 138–139 °C. IR (KBr): 2958, 2849, 1711, 1620, 1505, 1255, 1158, 1024, 842, 775 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.71 (s, 3 H), 3.76 (t, *J* = 9.2 Hz, 2 H), 3.91 (t, *J* = 9.2 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 6.87 (d, *J* = 7.6 Hz, 2 H). LCMS [M + 1]: *m/z* = 178.

2-(3,4,5-Trimethoxyphenyl)-4,5-dihydrooxazole

Mp 83–85 °C. IR (KBr): 2940, 2849, 1711, 1638, 1584, 1407, 1225, 1128, 988, 769 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.89 (m, 9 H), 4.07 (t, *J* = 9.3 Hz, 2 H), 4.43 (t, *J* = 9.3 Hz, 2 H), 6.97 (s, 1 H), 7.13 (s, 1 H). LCMS [M + 1]: *m/z* = 238.

2-(4-Tolyl)-4,5-dihydrooxazole

Mp 143–144 °C (lit.[8d] mp 144–145 °C). IR (KBr): 2928, 2879, 2855, 1650, 1596, 1389, 1286, 1055, 969, 811 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.46 (s, 3 H), 3.75 (t, *J* = 9.3 Hz, 2 H), 3.91 (t, *J* = 9.3 Hz, 2 H), 7.63 (d, *J* = 7.4 Hz, 2 H), 7.22 (d, *J* = 7.6 Hz, 2 H). LCMS [M + 1]: *m/z* = 162.

4-Ethyl-4,5-dihydro-2-(4-methoxyphenyl)oxazole

Liquid. IR (KBr): 3068, 2964, 2873, 2855, 1645, 1489, 1268, 1085, 818 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.92 (t, *J* = 9.1 Hz, 3 H), 1.36 (m, 2 H), 3.86 (s, 3 H), 3.97 (d, *J* = 9.2 Hz, 2 H), 4.14 (m, 1 H), 6.91 (d, *J* = 7.5 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 2 H). LCMS [M + 1]: *m/z* = 206.

2-(4-Methoxyphenyl)-5,6-dihydro-4*H*-[1,3]-oxazine

Liquid. IR (KBr): 3012, 2958, 1637, 1602, 1510, 1358, 1307, 1283, 1273, 1256 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.96 (quin, *J* = 5.8 Hz, 2 H), 3.58 (t, *J* = 5.4 Hz, 2 H), 3.81 (s, 3 H), 4.37 (t, *J* = 5.4 Hz, 2 H), 6.89 (d, *J* = 9.4 Hz, 2 H), 7.87 (d, *J* = 9.4 Hz, 2 H). LCMS [M + 1]: *m/z* = 192.

2-(4-Nitrophenyl)-5,6-dihydro-4*H*-[1,3]-oxazine

Mp 143–144 °C (lit.[22] mp 145–146 °C). ^1H NMR ($CDCl_3$): δ = 1.99 (quin, *J* = 5.8 Hz, 2 H), 3.66 (t, *J* = 5.6 Hz, 2 H), 4.37 (t, *J* = 5.6 Hz, 2 H), 8.07 (d, *J* = 9.2 Hz, 2 H), 8.22 (d, *J* = 9.3 Hz, 2 H). LCMS [M + 1]: *m/z* = 207.

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(21) When the reaction mixture of cinnamaldehyde and 2-amino-2-methyl-1-propanol was stirred in the absence of DIB, the immediate precipitation of 2-styryloxazolidine was observed. This product was recrystallized from PE and subjected to LCMS analysis which showed a molecular ion peak [M + 1] at 204 corresponding to the formation of 4,4-dimethyl-2-styryloxazolidine. The reaction of 4,4-dimethyl-2-styryloxazolidine (1 mmol) with DIB (1.2 mmol) in $CHCl_3$ (10 mL) was independently carried out at r.t. stirring for another 3 h. After usual reaction workup, the formation of 4,5-dihydro-4,4-dimethyl-2-styryloxazole was realized in 38% yield.

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