Novel Direct Synthesis of Multi-Substituted Oxazoles from Ketones

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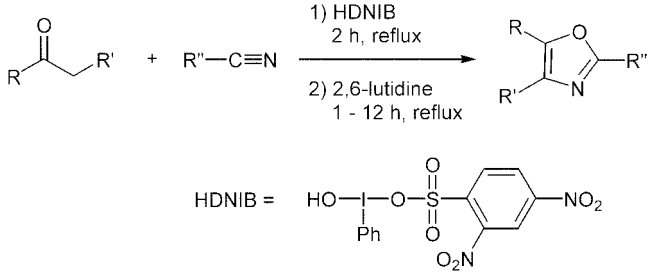
Oxazoles are well known as important structural units in a wide variety of biologically active natural products as well as useful synthetic intermediates.[1] In particular, many efforts have been focused for synthesis of 2,5- and 2,4,5-substituted oxazoles, due to their existence in substructures of many pharmaceuticals.[1-3] The most common methods for the preparation of 2,5- and 2,4,5-substituted oxazoles include dehydration of α-acylaminocarbonyl compounds,[4] catalytic decomposition of α-diazocarbonyl compounds in nitriles,[5-7] reaction of β-(acyloxy)vinyl azides with triethyl phosphite,[8] reaction of benzoin carboxylates with formamide,[9] and decarboxylation of *N*-acylisoxazol-5-ones by means of photolysis or pyrolysis.[10,11] However, these methods suffer from one or more drawbacks that include use of reactive starting materials, long reaction times, low yields, and harsh reaction conditions. Furthermore, until very recently, direct conversion of ketones to the corresponding oxazoles has received little attention and there are only few studies in the literature. For example, 2-alkyl-5-aryloxazoles were prepared by the direct reactions of aromatic α-methyl ketones with thallium(III) acetate[12] or iodobenzene diacetate[13] in the presence of trifluoromethanesulfonic acid (TfOH) in various nitriles. In addition, 2-alkyl(aryl)-4,5-diaryloxazoles have been prepared by the reaction of deoxybenzoin with nitriles in the presence of TfOH-H_2SO_4.[14] However, these methods have invariably utilized very strong acidic conditions and have been applied only for aromatic α-methyl ketones or reactive deoxybenzoin derivatives, which limit their practical applications. Therefore, development of a facile and efficient method for the direct conversion of ketones into the corresponding 2,5-disubstituted oxazoles or 2,4,5-trisubstituted oxazoles under non-acidic conditions would be highly desirable.

Hypervalent iodine(III) sulfonates have been gained increasing popularity in last two decades because of their valuable utilities in many organic transformations.[15] We recently reported an efficient method for α-sulfonyloxylation of various carbonyl compounds with [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) in acetonitrile at room temperature.[16] The required HDNIB can be easily obtained from the reaction of iodobenzene diacetate and 2,4-dinitrobenzenesulfonic acid in excellent yield (90%).[17] In the course of our attempts to apply this protocol to synthesis of heterocylic compounds, we observed unexpected formation of oxazoles when the same reactions were performed at refluxing acetonitriles in the presence of catalytic amount of 2,6-lutidine. This observation led us to develop a new and efficient method for the preparation of oxazoles by conducting reaction of ketones with HDNIB in various nitriles. Treatment of ketones with HDNIB in nitriles with reflux for 2 h and subsequent addition of catalytic amount of 2,6-lutidine (0.1 equiv.) with prolonged reactions for 1-12 h at reflux afforded the corresponding oxazoles in high yields. The reactions apparently involved nucleophilic reaction of nitriles on the alpha carbon of preformed α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone intermediates followed by 2,6-lutidine promoted dehydration reactions.



Scheme 1

Both aromatic α-methyl ketones and α-methylene ketones reacted equally well with alkyl nitriles or benzonitrile to provide 2-alkyl(aryl)-5-aryloxazoles and 2-alkyl(aryl)-4-alkyl(aryl)-5-aryloxazoles in high yields as shown in Table 1. Extension of this method for the reaction of alkyl pyruvates in acetonitriles under the same reaction conditions also provided corresponding 2-methyloxazole-5-carboxylates in good yields (entries **7** and **8**). In addition, reaction of 3-pentanone with acetonitrile provided the corresponding oxazole in high yield (entry **9**).

It is noteworthy that the use of 2,6-lutidine in dehydration step is necessary for the success of the reactions, otherwise the yields of reactions were reduced significantly. No isomeric oxazole products were observed in all of the reactions investigated. The advantage of present method over the known direct methods in the literature becomes evident upon comparison with the reaction of acetophenone by benzonitrile, which provided much higher yield (72%) of 2,5-diphenyloxazole than the reported ones (35-37%).[12,13] General experimental procedure is as follows: To a solution of ketone (1.00 mmol) and HDNIB (0.562 g, 1.20 mmol) in 20 mL of nitrile was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature, 2,6-lutidine (0.011 g, 0.10 mmol) was added. The reaction mixture was further refluxed for additional 1-12 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The resulting residue

Table 1. Synthesis of multi-substituted oxazoles

Entry	R	R'	R"	Yield (a)[a]
1	C_6H_5	H	CH_3	72
2	C_6H_5	H	CH_3CH_2	74
3	C_6H_5	H	$CH_3CH_2CH_2$	71
4	*p*-$CH_3C_6H_4$	H	CH_3	70
5	*p*-ClC_6H_4	H	CH_3	71
6	C_6H_5	H	C_6H_5	72
7	CH_3OOC	H	CH_3	62
8	CH_3CH_2OOC	H	CH_3	67
9	CH_3CH_2	CH_3	CH_3	74
10	C_6H_5	CH_3	CH_3	78
11	C_6H_5	CH_3	CH_3CH_2	74
12	C_6H_5	CH_3	$CH_3CH_2CH_2$	75
13	C_6H_5	CH_3	C_6H_5	72
14	*p*-$CH_3C_6H_4$	CH_3	CH_3	73
15	*p*-ClC_6H_4	CH_3	CH_3	65
16	C_6H_5	CH_3CH_2	CH_3	71
17	C_6H_5	C_6H_5	CH_3	75
18	C_6H_5	C_6H_5	CH_3CH_2	68
19	C_6H_5	C_6H_5	$(CH_3)_2CH$	65
20	C_6H_5	C_6H_5	C_6H_5	76

[a]Isolated yields.

was taken up in 50 mL of dichloromethane, washed with water (20×2 mL), and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by flash column chromatography on SiO_2 (ethyl acetate : hexane = 1 : 2) to give desired pure oxazole .

In summary, we have developed the first direct and convenient method for the synthesis of multi-substituted oxazoles starting from ketones under non-acidic conditions. The convenience and efficiency of the present method should make it a useful complement to the existing methods for synthesis of the multi-substituted oxazoles.

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