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Efficient synthesis of multi-substituted oxazoles under solvent-free microwave irradiation

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Abstract—A new and efficient method for the synthesis of multi-substituted oxazoles from various carbonyl compounds has been developed using sequential treatment of carbonyl compounds with HDNIB and amides such as acetamide or benzamide under solvent-free microwave irradiation conditions.

Oxazoles have attracted great interest due to their appearance as subunit of various biologically active natural products as well as their utilities as valuable precursors in many useful synthetic transformations.[1] Oxazoles are commonly prepared from methods utilizing synthetic intermediates such as α-halo ketones,[2] α-diazo ketones,[3] α-acyloxy ketones,[4] and α-acylamino ketones.[5] However, preparations of these reactive intermediates are not always straightforward to carry out because of various drawbacks involved in these reactions, such as long reaction times, low yields, and forced reaction conditions. Although there are many useful synthetic methods reported for the substituted oxazoles, practical and convenient methods for the synthesis of 2,4,5-trisubstituted oxazoles, which are widely found in the skeleton of oxazole containing natural products, have been quite limited.[6] In addition, only a few synthetic methods for the direct and convenient conversion of ketones to substituted oxazoles, without isolation of the reactive intermediates, have been known. These include the reaction of ketones with nitriles as solvents in the presence of copper(II) triflate,[7] thallium(III) triflate,[8] and iodobenzene diacetate.[9] Furthermore, although there have been a couple of methods reported on the conversion of 2-halo-1,3-dicarbonyl compounds to oxazoles in modest yields utilizing the reaction with amide in refluxing carboxylic acid media,[10] there have been no examples to date for a convenient approach for the preparation of substituted oxazoles directly from 1,3-dicarbonyl compounds. Therefore, development of a more convenient and efficient method is required for the conversion of carbonyl compounds to multi-substituted oxazoles.

Recently organic transformations accelerated under solvent-free microwave irradiation conditions gained wide popularity due to many practical advantages associated with enhanced reaction rates, high yields, improved selectivity, and environment-friendly reaction conditions.[11]

In conjunction with our program to utilize hypervalent iodine(III) sulfonates in microwave promoted chemistry, we wish to report herein a novel and efficient one-pot method for the synthesis of multi-substituted oxazoles by the reaction of amides with intermediary α-[(2,4-dinitrobenzene)sulfonyl]oxy carbonyl compounds, formed in situ from the reaction of [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) with carbonyl compounds, under solvent-free microwave irradiation (MWI) conditions. The required HDNIB was prepared in satisfactory yields from the reaction of 2,4-dinitrobenzenesulfonic acid with iodobenzene diacetate.[12] Initial reaction of aromatic ketones with 1.2 equiv. of HDNIB under microwave irradiation for 20–40 s provided α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone intermediates which were then converted to oxazoles by subsequent treatment with acetamide or benzamide (2.0 equiv.) under microwave irradiation for 1–2 min (Scheme 1). In all cases investigated, the oxazole formation reactions proceeded efficiently with high to excellent yields in short reaction times. We have also examined the scope of this protocol for the oxazole formation reactions of 1,3-dicarbonyl compounds under the same reaction conditions.

Keywords: amides; carbonyl compounds; hypervalent elements; microwave heating; oxazoles.

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Table 1. Preparation of oxazoles from ketones under microwave irradiation

Entry	R_1	R_2	R_2	Yield (%)[a]
1	Ph	H	Me	92 (78)[b]
2	Ph	Me	Me	94 (72)[b]
3	*p*-MeC_6H_4	Me	Me	94
4	*p*-ClC_6H_4	Me	Me	83
5	Me	COMe	Me	82
6	Me	COOEt	Me	58
7	Ph	COOEt	Me	91
8	Me	$CONEt_2$	Me	82
9	Ph	Ph	Me	70
10	Ph	Ph	Ph	68
11	Ph	H	Ph	77 (63)[b]
12	Ph	Me	Ph	85 (62)[b]
13	*p*-MeC_6H_4	Me	Ph	80
14	*p*-ClC_6H_4	Me	Ph	87
15	Me	COMe	Ph	87
16	Me	COOEt	Ph	74
17	Ph	COOEt	Ph	90
18	Me	$CONEt_2$	Ph	63

[a] Isolated yields of pure products.
[b] Yields obtained from replacing HDNIB by HTIB under the same reaction conditions.

To our satisfaction, the reactions proceeded well not only for 1,3-diketone (entries 5 and 15) but also for β-keto ester (entries 6, 7 and 16, 17) and β-keto amide (entries 8 and 18) to give the corresponding oxazoles in high yields. Results of the reactions of several substrates are listed in Table 1. Under present reaction conditions, the oxazole formation reactions were highly regioselective to give only a single oxazole product without any regioisomeric oxazoles, as determined by GC–MS analysis.[13] When the oxazole forming reaction of aromatic ketones attempted in the presence of [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB),[14] instead of HDNIB, the yields of the corresponding oxazoles were invariably reduced, as demonstrated in Table 1. Moreover, in the cases of the sequential reactions between 1,3-dicarbonyl compounds with HTIB and amides under solvent-free microwave irradiation failed to give the corresponding oxazoles and the starting 1,3-dicarbonyl compounds remained mostly unchanged. These observations clearly demonstrated the leaving ability of -ODNs superior to -OTs in nucleophilic substitution reactions.

The oxazole formation reactions were carried out in the following general way: ketone (1.0 mmol) and HDNIB (0.562 g, 1.2 mmol) were mixed thoroughly and placed in a 50 mL of glass tube. The reaction mixture was inserted in an alumina bath inside a household microwave oven and irradiated (850 W) twice for a period of 20 s with a 10 s interval. After the reaction mixture was cooled to room temperature, an amide (2.0 mmol) was added and irradiated an additional three times for a period of 20 s with 10 s intervals. The reaction mixture was extracted with dichloromethane (2×25 mL) and washed with water (40 mL). The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, ethyl acetate:hexane = 1:2) to afford pure oxazole.

In conclusion, we have described a rapid and highly efficient method for the synthesis of multi-substituted oxazoles starting from carbonyl compounds under solvent-free microwave irradiation reaction conditions. With such successful results of the otherwise difficult oxazole formation reaction of 1,3-dicarbonyl compounds, this convenient and efficient oxazole ring forming protocol should provide a superior alternative of the existing methods because of its fast and clean reactions and high yields.

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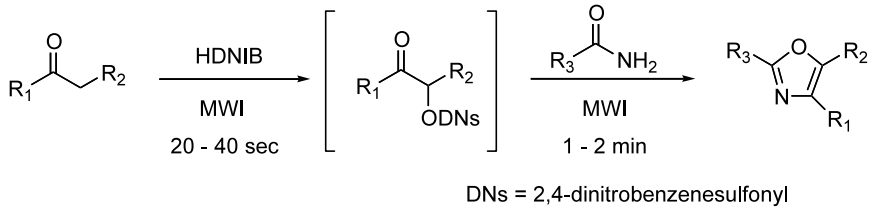

Scheme 1.

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