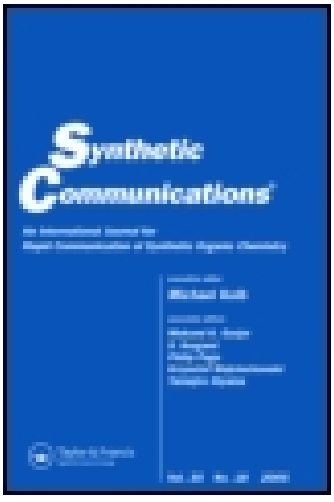

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Synthesis of 2-Substituted 4,5-Diphenyloxazoles under Solvent-Free Microwave Irradiation Conditions

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Abstract: A novel method for the direct conversion of deoxybenzoin into 2-alkyl-4,5-diphenyloxazoles and 2-aryl-4,5-diphenyloxazoles has been developed using treatment of HTIB and nitriles under solvent-free microwave irradiation conditions.

Keywords: hypervalent iodine, microwave, oxazole, solvent-free

Oxazoles, important heterocycles in organic chemistry, have received great attention because of their useful, biologically important properties.[1–3] In particular, in the past decade, synthesis of 2,4,5-trisubstituted oxazoles received increasing attention because of their common existence in naturally occurring compounds.[4,5] Among other 2,4,5-trisubstituted oxazoles, 2-substituted 4,5-diphenyloxazoles recently received substantial interest because of thier usefulness as synthetic scaffolds. The preparation of 2-substituted 4,5-diphenyloxazoles can be achieved by various methods, which include the reaction of benzoins with nitriles in the presence of triflic acid/H_2SO_4,[6] the reaction of benzoin carboxylates with formamide in the presence of H_2SO_4,[5] the coupling reaction of 2-methylthio-4,5-diphenyloxazole with Grignard reagents/nickel-bidentate phosphine complexes,[7] and the reaction of oxazolone template with aromatic solvents in the presence of aluminum chloride and triflic acid.[8] However, all of these methods generally use very strong acidic or basic conditions, which limit their further practical

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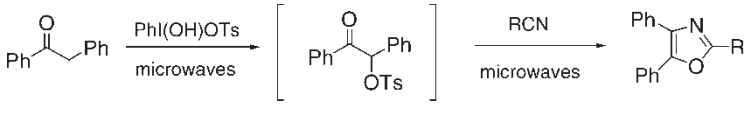
applications. Furthermore, there have been far fewer methods that describe the preparation of multisubstituted oxazoles starting directly from ketones.[6,9]

Recently, we reported the successful results of the preparation of multisubstituted oxazoles by the reaction of ketones with [hydroxyl(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) and amides under microwave irradiation conditions.[10] However, in this method, replacement of amides by nitriles mostly gave far inferior yields of oxazoles, and a majority of undesirable side products was obtained. In the course of our program, we needed an efficient method for the direct preparation of 2-substituted 4,5-diphenyloxazoles using the reaction of deoxybenzoin with easily available nitrile reagents. To the best of our knowledge, there was no report utilizing nitriles in the direct preparation of oxazoles from ketones under solvent-free microwave irradiation conditions. The Koser's reagent, [hydroxy(tosyloxy)iodo]benzene (HTIB), is one of the most versatile and readily available hypervalent iodine compounds, and its use in organic transformations is well documented.[11,12] Therefore, it is highly desirable to develop a new method for the synthesis of oxazoles starting from ketones using a reagent combination of HTIB and nitriles. Herein, we report a novel and facile method for the synthesis of 2-substituted 4,5-diphenyl oxazoles from the reaction of deoxybenzoin with HTIB and various nitriles under microwave irradiation conditions. Thus, sequential treatment of deoxybenzoin with HTIB (1.2 equiv.) and nitriles (1.0 equiv.) for 2–5 min under microwave irradiation in solvent-free conditions provided the corresponding 2-substituted 4,5-disubstituted oxazoles in high yields (Scheme 1). Both aliphatic and aromatic nitriles gave satisfactory yields of 2-alkyl-4,5-diphenyloxazoles and 2-aryl-4,5-diphenyloxazoles as shown in Table 1. The yields obtained in this study are comparable or superior to the previous results obtained from the reported methods for the direct synthesis of oxazoles from ketones. Therefore, this method can serve as a useful alternative to the existing methods because of the rapid, neutral, and ecofriendly nature of the reaction conditions. Apparently, the present protocol proceeded by the Ritter-type reactions of α-tosyloxydeoxybenzoin intermediates with nitriles lead to smooth formation of substituted oxazoles. Application of this protocol to the other ketones such as acetophenone and propiophenone provided only α-tosyloxy ketones without formation of oxazoles.

In summary, we have developed a new and efficient method for the preparation of 2-substituted 4,5-diphenyloxazoles from the microwave-promoted reactions of deoxybenzoin with HTIB/nitriles.



Scheme 1.

Table 1. Preparation of 2-substituted 4,5-diphenyloxazoles

Entry	Nitriles	Oxazoles	Yield (%)[a]
1	CH_3CN	R = CH_3	72
2	CH_3CH_2CN	R = CH_3CH_2	82
3	$CH_3CH_2CH_2CN$	R = $CH_3CH_2CH_2$	60
4	C_6H_5CN	R = C_6H_5	75
5	*p*-$CH_3C_6H_4CN$	R = *p*-$CH_3C_6H_4$	67
6	*p*-$CH_3OC_6H_4CN$	R = *p*-$CH_3OC_6H_4$	66
7	*p*-BrC_6H_4CN	R = *p*-BrC_6H_4	83
8	*p*-ClC_6H_4CN	R = *p*-ClC_6H_4	92
9	*p*-FC_6H_4CN	R = *p*-FC_6H_4	71

[a]Isolated yield.

EXPERIMENTAL

A commercial domestic microwave oven (Samsung RE-21C) with an 850-W power output was used for the all reactions.

General Procedure for 2-Substituted 4,5-Diphenyloxazoles

Deoxybenzoin (1.0 mmol) and HTIB (1.2 mmol) were mixed thoroughly and placed in a 50 mL glass tube. The reaction mixture was placed in a domestic microwave oven and irradiated three times for a period of 30 s with 10-s intervals. Then nitrile (1.0 mmol) was added to the reaction mixture, which was irradiated one to seven times for a period of 30 s with 10-s intervals. The reaction mixture was extracted with dichloromethane (2 × 30 mL) and washed with water. The organic layer was dried with magnesium sulfate. After evaporation of the solvent, the residue was purified by silica-gel column chromatography using dichloromethane as eluent to give the pure 2-substituted 4,5-diphenyloxazole.

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