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Mercury(II) *p*-toluenesulfonate mediated synthesis of oxazoles under microwave irradiation

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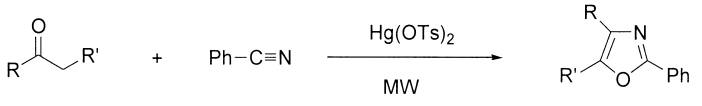
Abstract

Direct transformation of aromatic ketones into oxazoles in the presence of mercury(II) *p*-toluenesulfonate under microwave irradiation is described.

Keywords: ketones; oxazoles; mercury(II) *p*-toluenesulfonate; microwave.

Oxazole ring system is a basic building block of several biologically interesting compounds.[1,2] Although there are many indirect synthetic methods available for the formation of the oxazoles, general methods for the direct preparation of oxazoles are relatively rare.[3–6] Furthermore, there is no general literature method for the direct preparations of 4-aryl-2-phenyloxazoles and 5-alkyl-4-aryl-2-phenyloxazoles.[7–9] In this paper, we wish to report a direct and rapid preparation method for the 5-alkyl-4-aryl-2-phenyloxazoles and 4-aryl-2-phenyloxazoles, utilizing the reaction of aromatic ketones with benzonitrile in the presence of mercury(II) *p*-toluenesulfonate under microwave irradiation. To our knowledge, this is the first report of direct conversion of ketones to oxazoles under solventless reaction conditions.



Generally, a heterogeneous mixture of the aromatic ketone, $Hg(OTs)_2$ (1.0 equiv.), and benzonitrile (5.0 equiv.) was placed in a glass tube and the reaction mixture was exposed to microwave irradiation in a domestic microwave oven for 2–4 min. The best results were obtained by employing 5.0 equiv. of benzonitrile. The use of smaller amounts of benzonitrile gave reduced yields. A range of 5-alkyl-4-aryl-2-phenyloxazoles and 4-aryl-2-phenyloxazoles were prepared in

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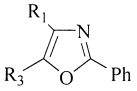
the yields of 47–86% as summarized in the Table 1. Reactions of mercury(II) *p*-toluenesulfonate with aromatic α-methylene ketones (entries 3–8) invariably provided better yields than in the case of aromatic α-methyl ketones (entries 1 and 2). In fact, for the reaction of aromatic α-methyl ketones, the addition of *p*-toluenesulfonic acid (1.0 equiv.) was necessary to improve the yields of oxazole formations. This result clearly indicates that higher enol content of ketones is important for successful reactions. To examine the feasibility of $Cu(OTf)_2$[5] in the oxazole forming reaction, the reactions were conducted with $Cu(OTf)_2$ at the same reaction conditions, by replacing $Hg(OTs)_2$. However, no oxazole formation was noticed and only the starting materials were recovered.

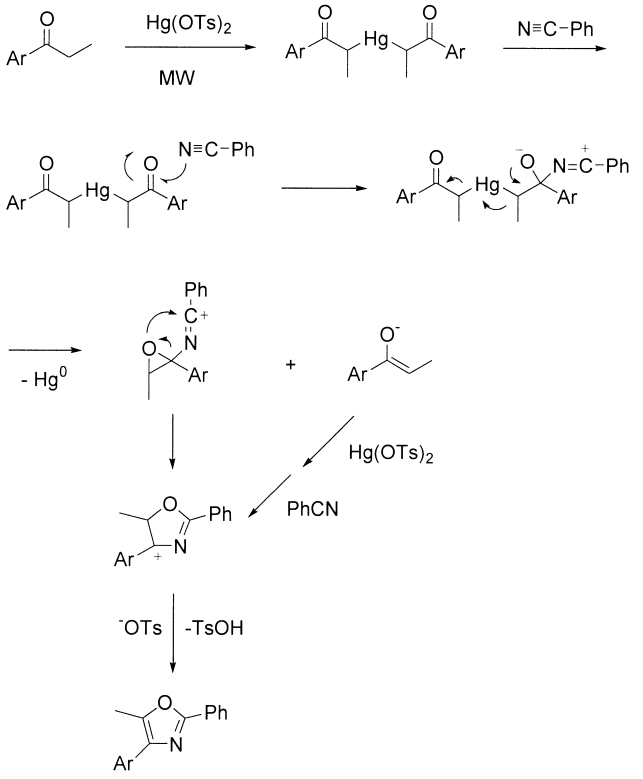
Table 1
Synthesis of 2,4- and 2,4,5-substituted oxazoles under microwave irradiation

Entry	Substrate	Product	Time (min)[a]	Yield (%)[b]
				
1	$R_1 = C_6H_5$; $R_2 = CH_3$	$R_1 = C_6H_5$; R_3= H	4	51
2	$R_1 = p\text{-}ClC_6H_4$; $R_2 = CH_3$	$R_1 = p\text{-}ClC_6H_4$; R_3 = H	4	50
3	$R_1 = C_6H_5$; $R_2 = CH_2CH_3$	$R_1 = C_6H_5$; $R_3 = CH_3$	2	85
4	$R_1 = p\text{-}CH_3C_6H_4$; $R_2 = CH_2CH_3$	$R_1 = p\text{-}CH_3C_6H_4$; $R_3 = CH_3$	2	83
5	$R_1 = p\text{-}ClC_6H_4$; $R_2 = CH_2CH_3$	$R_1 = p\text{-}ClC_6H_4$; $R_3 = CH_3$	3	86
6	$R_1 = p\text{-}FC_6H_4$; $R_2 = CH_2CH_3$	$R_1 = p\text{-}FC_6H_4$; $R_2 = CH_3$	3	85
7	$R_1 = C_6H_5$; $R_2 = CH_2CH_2CH_3$	$R_1 = C_6H_5$; $R_3 = CH_2CH_3$	2	79
8	$R_1 = p\text{-}ClC_6H_4$; $R_2 = CH_2CH_2CH_3$	$R_1 = p\text{-}ClC_6H_4$; $R_3 = CH_2CH_3$	3	71
9	R_1 = COOEt; $R_2 = CH_3$	R_1 = COOEt; R_3 = H	2	47
10	R_1 = COOEt; $R_2 = CH_2CH_3$	R_1 = COOEt; $R_3 = CH_3$	2	65

[a]Microwave irradiation time. [b]Isolated yields of pure products.

Recently, oxazole-4-carboxylates received much attention due to their growing interest as synthetic intermediates for the construction of naturally occurring oxazole systems.[10–12] Thus, we have examined the reaction of ethyl 2-oxoalkanoates under the same reaction conditions. The results were successful to give ethyl 2-phenyloxazole-4-carboxylate and ethyl 5-methyl-2-phenyl-oxazole-4-carboxylate in the yields of 47 and 65% respectively (entries 9 and 10). By analogy with the formation of di(α-phenacyl)Hg(II)[13,14] the ring formation process occurs probably through

initial formation of di(α-arylalkanoyl)Hg(II) by the reaction of mercury(II) tosylate with the enol tautomer of the ketones followed by attack of the nitrogen atom of benzonitrile to the carbonyl carbon of ketones (Scheme 1).



Scheme 1.

In conclusion, the short reaction time, the high yield, and the simple work-up offer significant advantages over existing methods for the multi-substituted oxazole ring formations.

Typical procedure: A mixture of propiophenone (1.0 mmol), $Hg(OTs)_2$ (1.0 mmol), and benzonitrile (5.0 mmol) was placed into a glass tube. The glass tube was placed in an alumina bath inside a domestic microwave oven and irradiated for 30 s intervals. After this heating, a period of 30 s was allowed for cooling to prevent excess heating. This process was repeated 4–8 times. After completion of the reaction, the product was extracted into dichloromethane (2×20 ml), which was washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using ethyl acetate/hexane (1:9) as the eluent to give 5-methyl-2,4-diphenyloxazole in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 3H), 7.31–7.46 (m, 6H), 7.72–7.75 (m, 2H), 8.06–8.10 (m, 2H); MS (EI, m/z): 235 (M^+).

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