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Microwave-assisted synthesis of 1,2-benzisoxazole derivatives in ionic liquid

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Abstract: A simple, highly efficient and environmentally benign method for the efficient conversion of 2-hydroxyalkyl/aryl ketoximes to 1,2-benzisoxazoles in the presence of catalytic amount of basic ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) carried out under the influence of microwave irradiation. This method gives remarkable advantages such as short reaction times (30-60 sec), simple work-up procedure and excellent yields (85-96%). The ionic liquid was successfully reused for four cycles without significant loss of activity.

Keywords: 1,2-Benzisoxazole ketoxime; ionic liquid; microwave irradiation.

1. Introduction

The growing interest in heterocyclic compounds is basically because of their raised biological activity and also they make possible development of novel materials with unique properties. One very interesting and promising class of heterocycle is the series of 3-substituted-1,2-benzisoxazole.[1] This type of heterocycle has significant pharmacological and biological activity such as anticonvulsant,[2] antipsychotic,[3] anticancer,[4] presented affinity for serotonergic and dopaminergic receptors.[5] In particular, 3-(*N*-benzylpiperidinylethyl)-1,2-benzisoxazoles inhibit acetyl cholinesterase, making them suitable candidates for the palliative treatment of Alzheimer's disease.[6]

Due to great importance, many synthetic strategies have been employed for the synthesis of 1,2-benzisoxazoles such as Ac_2O/K_2CO_3,[7] Ac_2O/pyridine,[4] $SOCl_2$/pyridine.[8] However, these methods usually carried out in two steps where first step involves the conversion of hydroxyl group of oxime to good leaving group and in second step cyclization occurs under basic condition. Very few methods described for the synthesis of 1,2-benzisoxazole in one step using trichloroacetyl isocyanate.[9] Recently, the microwave induced synthetic methods were reported.[10,11] However, some of these previous methods have suffered from one or more drawbacks like high temperature required, highly basic conditions and prolonged reaction times. Thus, the development of a new method for the synthesis of 3-substituted-1,2-benzisoxazole derivatives would be highly desirable.

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In recent years, application of ionic liquids in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, negligible vapor pressure, easy recycling, high thermal stability and rate enhancers.[12-14] Nowadays, much attention has been focused on organic reactions catalyzed by ionic liquids.[15-17] Particularly, imidazolium ionic liquids have been successfully used in many organic transformations includes Diels–Alder,[18] Wittig,[19]Hantzsch condensation.[20] The basic ionic liquid [bmim]OH used in various organic transformation such as Michael reaction,[21] Knoevenagel condensation.[22]

The science of green chemistry is developed to meet the increasing demand of environmentally benign chemical processes. Many application of microwaves, as an efficient heating source for organic reactions, has been reported in the literature.[23] The main advantage of microwave assisted organic synthesis is the shorter reaction time using only small amount of energy. Many microwave-assisted transformations offer additional convenience in the field of organic synthesis because of simple experimental procedure and high yields.

2. Results and Discussion

In continuation of our research interest in microwave-assisted synthesis[24-25] and the development of novel synthetic methodology,[26-32] herein, we would like to report a simple, efficient and rapid method for the synthesis of 3-substituted-1,2 benzisoxazoles (Scheme 1).

In order to find optimum reaction conditions and to investigate the effect of different amount of catalyst on the yield, compound **1a** and acetic anhydride (Ac_2O) under microwave irradiation was selected as model. The best result was obtained by carrying out the reaction with 1:1.2 mol ratios of 2-hydroxy phenyl methyl ketoxime: acetic anhydride and 2 mol% of [bmim]OH (Figure **1**) under microwave irradiation to give 3-methyl-1,2-benzisoxazole **2a** (96%) (Table **1**, entry **2**). The same reaction was carried out in the absence of catalyst, which resulted in acetate of oxime as a sole product instead of the desired product despite of a prolonged reaction time (Table **1**, entry **1**).

In view of economical and environmental friendly methodologies, recovery and reuse of the ionic liquid is highly preferable. As indicated in Table **2** (entry **2a**), recycled ionic liquid shows no loss of efficiency with regard to reaction time and yield after four successive runs.

The results of this study are summarized in Table **2**. As shown in this table, the use of basic ionic liquid [bmim]OH under microwave irradiation produces 1,2-benzisoxazoles as the sole products. With optimized reaction condition in hand, we have synthesized various 3-substituted 1,2-benzisoxazoles from substituted ketoximes in the presence of [bmim]OH under influence of microwave irradiation. The successful synthesis of 1,2-benzisoxazole derivatives *via* the cyclization of different 2-hydroxyalkyl/aryl ketoximes were perforemed in shorter reaction times (30-60 sec) with excellent yields (85-96%). This methodology avoids the use of strong base, hazardous solvents and requires only catalytic amount of the basic ionic liquid to promote the reaction.

In Table **3**, we have compared our result with results obtained by some other procedures for the synthesis of 1,2-benzisoxazole. The data presented in this table show the promising features of this method in terms of reaction rate and yield of the product.

3. Conclusion

In conclusion, we have reported a new and effective methodology for the synthesis of 1,2-benzisoxazole derivatives. The notable merits of the present method are short reaction times (30-60 sec), simple work-up procedure and excellent yield of products. Moreover, the [bmim]OH was successfully reused for four cycles without significant loss of activity. It is thus a rapid, convenient and environmentally benign method for the synthesis of compounds of type **2**(**a-s**). To the best of our knowledge this is first repot on synthesis of 1,2-benzisoxazole derivatives in basic ionic liquid.

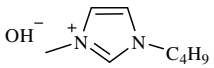
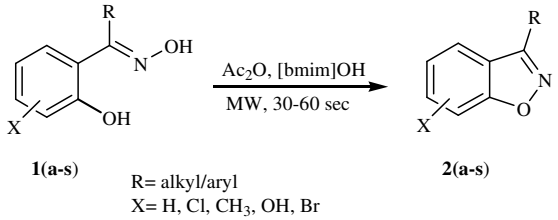


Figure 1. 1-butyl-3-methylimidazolium hydroxide ([bmim]OH)



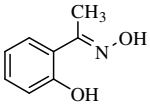
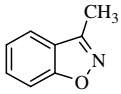
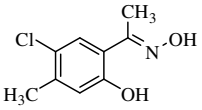
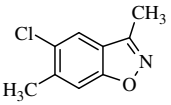
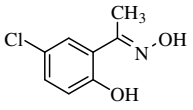
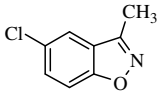
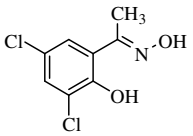
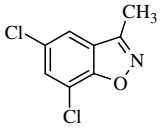
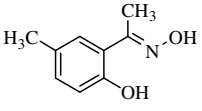
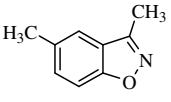
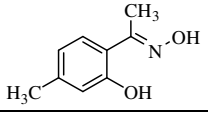
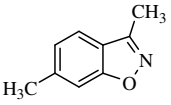
Scheme 1. Synthetic path way for compounds **2(a-s)**.

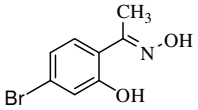
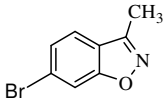
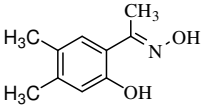
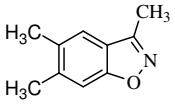
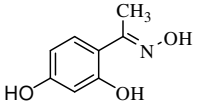
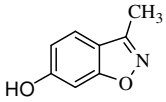
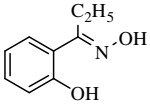
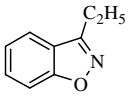
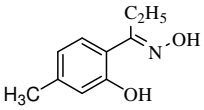
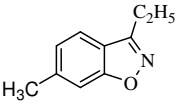
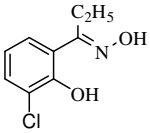
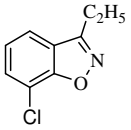
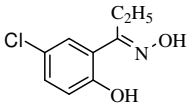
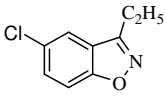
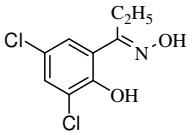
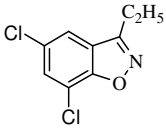
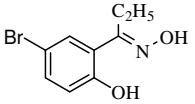
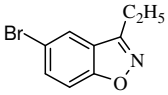
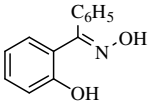
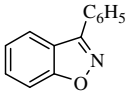
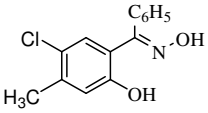
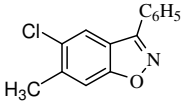
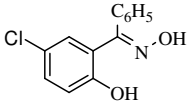
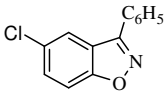
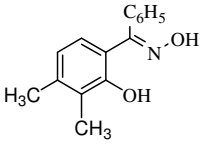
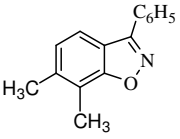
Table 1. Effect of Ionic Liquid on the Synthesis of 3-Methyl-1,2-benzisoxazole **2a**[a]

Entry	Ionic liquid	Time (sec)	Oxime acetate(%)[c]	1,2-Benzisoxazole (%)[c]
1	-	20[b]	90	-
2	[bmim]OH	50	-	96

[a]Reaction condition: **1a** (1 mmol) and Ac_2O (1.2 mmol) under microwave irradiation (180 W). [b]Reaction time in min. [c]Isolated yield.

Table 2. Synthesis of 3-Alkyl/Aryl 1,2-Benzissoxazoles **2**(**a-s**) Catalyzed by [bmim]OH under Microwave Irradiation[a]

Entry	Substrate	Product	Yield (%)[b]	m. p. (°C)	
				Found	Lit
2a			96 (92, 89, 88, 87)[c]	liquid	liquid[9]
2b			93	65-67[d]	67[8]
2c			95	50-52[d]	51[8]
2d			95	62-64[d]	65[8]
2e			94	liquid	liquid[10]
2f			92	liquid	liquid[1]

2g			95	42-44[d]	43[10]
2h			95	90-92[d]	90[8]
2i			89	164-176[d]	164[1]
2j			90	liquid	liquid[1]
2k			91	liquid	liquid[10]
2l			92	liquid	liquid[1]
2m			94	liquid	liquid[1]
2n			92	62-64[d]	64[10]
2o			94	liquid	liquid[1]
2p			90	83-84[d]	82[1]
2q			87	118-120[d]	119[10]
2r			91	88-90[d]	89[10]
2s			85	82-84[d]	83[10]

[a]Reaction time 30-60 sec. [b]Isolated yield. [c]The same ionic liquid was used for each of the runs. [d]Solid compound.

Table 3. Comparisons of Results of other Reported Procedures with the Present Method[a]

Entry	Reagent	Reaction condition	Time	Yield (%)	Reference
1	Ac_2O/K_2CO_3	C_6H_6/reflux	5 h	43-61	[4]
2	$Cl_3CCONCO$	THF/r.t	30 min	33-90	[9]
3	Silica gel/Na_2CO_3	MW	3-4 min	80-95	[10]
4	Ac_2O/[bmim]OH	MW	30-60 sec	85-96	Present

[a]Synthesis of 1,2-benzisoxazole

4. Experimental

The materials were obtained from commercial suppliers and were used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progresses of the reactions were monitored by TLC (Thin Layer Chromatography). ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Mass spectra MS(ESI) were recorded on a Water-Micro mass Quattro-II spectrophotometer. Microwave irradiation was carried out in a microwave oven (BPL, 800T, 2450 MHz) with power output of 800W.

4.1 General procedure for the synthesis of compounds 2(a-s):

A mixture of ketoxime (1 mmol), acetic anhydride (1.2 mmol) and [bmim]OH (2 mol%) were taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and irradiated for a period of 5 sec at a time. The total period of microwave irradiation (180W) was 30-60 sec. The progress of reaction was monitored by TLC. After completion of reaction, the reaction content cooled to room temperature. The product was extracted with diethyl ether (2 × 20 mL) and the insoluble ionic liquid [bmim]OH directly recycled in subsequent runs. The organic layer washed by brine (2 × 10 mL), dried over Na_2SO_4 and solvent removed on rotary evaporator under reduced pressure. The liquid compounds are obtained in pure form and solid compounds were recrystallized by aqueous ethanol to afford the desired products **2(a-s)**.

4.2. Spectral data of principle compound:

(2a): ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.26 (s, 4H), 2.37 (s, 3H).

(2b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (s, 1H), 7.00 (s, 1H), 2.30 (s, 3H), 2.50 (s, 3H).

(2c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 1H), 7.27 (d, 1H, *J*= 8.0 Hz), 7.20 (d, 1H, *J*= 8.0 Hz), 2.57 (s, 3H). MS (ESI): m/z = 197(M+1).

(**2d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 1H), 7.20 (s, 1H), 2.40 (s, 3H). MS (ESI): m/z = 231 (M+1).

(**2e**): ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 7.20 (d, 1H, *J*= 8Hz), 7.15 (d, 1H, *J*= 8.0 Hz), 7.10 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H). MS (ESI): m/z = 177 (M+1).

(2i): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, 1H, *J*= 8.0 Hz), 6.90 (d, 1H, *J*= 8Hz), 6.80 (s, 1H), 5.00 (s, 1H, OH), 2.40 (s, 3H).

(**2j**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, 1H, *J*= 7.5 Hz), 7.50-7.60 (m, 2H), 7.30 (m, 1H), 3.00 (q, 2H, *J*= 7.5 Hz), 1.50 (t, 3H, *J*= 7.5 Hz). MS (ESI): m/z = 148 (M+1).

(2l): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, 1H, *J*= 8.4 Hz), 7.30 (bt, J=8.0 Hz), 7.10 (d, 1H, *J*= 7.50 Hz), 2.60 (q, 2H, *J*= 7.5 Hz), 1.25 (t, 3H, *J*= 7.5 Hz),

(**2m**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, 1H, *J*= 8 Hz), 7.20 (d, 1H, *J*= 8 Hz), 7.15 (s, 1H), 2.60 (q, 2H, *J*= 7.5 Hz), 1.20 (t, 3H, *J*= 7.5 Hz). MS (ESI): m/z = 211 (M+1).

(2o): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 7.35 (d, 1H, *J*= 8 Hz), 7.10 (d, 1H, *J*= 8 Hz), 2.60 (q, 2H, *J*= 7.5 Hz), 1.24 (t, 3H, *J*= 7.5 Hz).

(**2p**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 2H, *J*= 8.0 Hz), 7.30 (t, 2H, *J*= 8.0 Hz), 7.25 (t, 1H, *J*= 8 Hz), 7.25 (d, 1H, *J*= 8 Hz), 7.20 (d, 1H, *J*= 8 Hz), 7.15 (t, 2H, *J*= 8.0 Hz), MS (ESI): m/z = 196 (M+1).

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