$ZNCL_2$ - PROMOTED SYNTHESIS OF BENZIMIDAZOLES UNDER MICROWAVE IRRADIATION

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Abstract : Benzimidazoles **3a-f** have been prepared in a few seconds from the reaction of *o*-phenylene-diamine **1** and *β*-ketoesters **2** on the surface of silica gel and $ZnCl_2$ under microwave irradiation in excellent yield. The reaction has also gone very well in MeOH and in the presence of $ZnCl_2$ under reflux condition.

Introduction

Microwave technology is emerging as an alternative energy source, powerful enough to accomplish chemical transformation in minutes, instead of hours or even days. For this reason, the number of publications related to microwave assisted organic synthesis (MAOS) has therefore increased dramatically (1).

Solid state chemistry or (solvent free technique) has been found to enhance many reactions in organic synthesis (2) and use of solid supports such as clays, aluminum oxides, silica gel etc. has also been claimed to be particularly environmentally friendly. In addition, the absence of solvent offers a simpler method of work up. Interest in benzimidazoles can be attributed to their diverse biological properties. These compounds are a unique, potent and broad spectrum class of biologically active compounds. They have shown antihelminthic (3), anticancer (4), antiviral (5), antibacterial, antifungal and antimicrobial activity (6). They also exhibit significant activity against several viruses including HIV (5), and influenza (7).

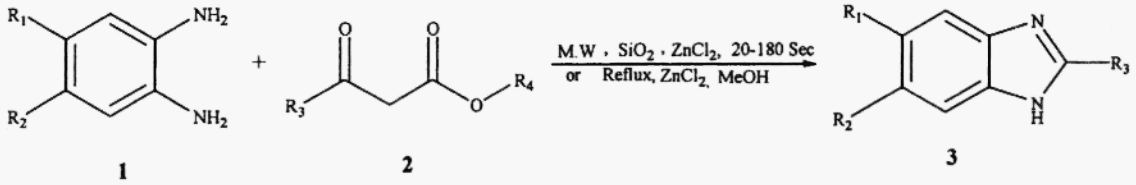
As a result, research in this area is still very popular and is directed toward the synthesis of compounds with enhanced pharmacological activity. In the past few years, there has been considerable interest in the search for new routes to benzimidazoles. Different synthetic methods to these compounds have been reported in the literature. The most common routes to 2-substituted benzimidazoles involve condensation of *o*-phenylenediamine with carboxylic acids and their derivatives, (8-12,13) aldehydes, (14,15) *S*-methylisothioamide hydroiodide, (16) and iminoethers (17,18). They have also been prepared from the reduction of *o*-nitro aniline derivatives (19). Recently synthesis of these compounds on solid supports and under microwave irradiation (20-23), as well as by employing infrared light as the energy source, (24) has also been reported in the literature.

Results and Discussions

Among the methods mentioned in the literature, formation of benzimidazoles from *o*-phenylenediamine and *β*-ketoesters (25-27), has received special attention in view of its final products. It has been shown that the progress of the reaction depends in a great part on the experimental conditions. Different products (benzimidazole and benzodiazepinone) were obtained under acidic, basic and neutral media. (18, 27, 28) Also change of solvent and catalyst (27, 29) resulted in the formation of different products. As reported by Soufiaoui and his co-workers reaction of *o*-phenylenediamine and ß-ketoesters in xylene under microwave irradiation resulted in formation of benzodiazepinone (27).

In view of different reports on the products obtained from the reaction of o-phenylenediamine and *β*-ketoesters which one of them is benzimidazole and also the importance of this heterocyclic nucleus which has been used extensively in medicinal chemistry, we decided to investigate further this reaction and find out what would be the product under our conditions.

In the present work, we have obtained 2- substituted benzimidazoles (**3a-f**) from the reaction of *o*-phenylenediamines **1** and *β*-ketoesters **2** in the presence of $ZnCl_2$ in refluxing MeOH as well as on the surface of silica gel and $ZnCl_2$ under microwave irradiation in excellent yield (**Scheme1 Table1**).



1 2 3

Scheme-1

Table-1 : Reaction of *o*-phenylenediamine with *β*-ketoesters in the presence of $ZnCl_2$ on the surface of silica gel and in refluxing MeOH [a]

Product	R^1	R^2	R^3	R^4	M.W		Reflux		M.p	Lit.M.p.
					Time (Sec)°C	Yield (%)	Time (Min)°C	Yield (%)		
3a	H	H	Me	Et	40	96	120	92	176	176-178 [21b, 16]
3b	Me	Me	Me	Et	40	96	150	87	237-239	239-241 [21b]
3c	H	H	Et	Me	20	96	60	96	177	179 [30]
3d	H	Me	Ph	Et	180	80	150	78	239-240	239 [16]
3e	H	H	Ph	Et	40	93	90	86	291-292	290-292 [30 16]
3f	Me	Me	Ph	Et	60	95	140	88	257-259	258-260 [21b]
3g	Me	Me	Me	CH_2Ph	60	96	210	92	240-242	239-241 [21b, 30]
3h	H	H	Me	Me	40	95	90	92	176	176 -178 [21b, 16]
3i	H	H	Me	CH_2Ph	60	96	60	96	175	176 [21b, 30]

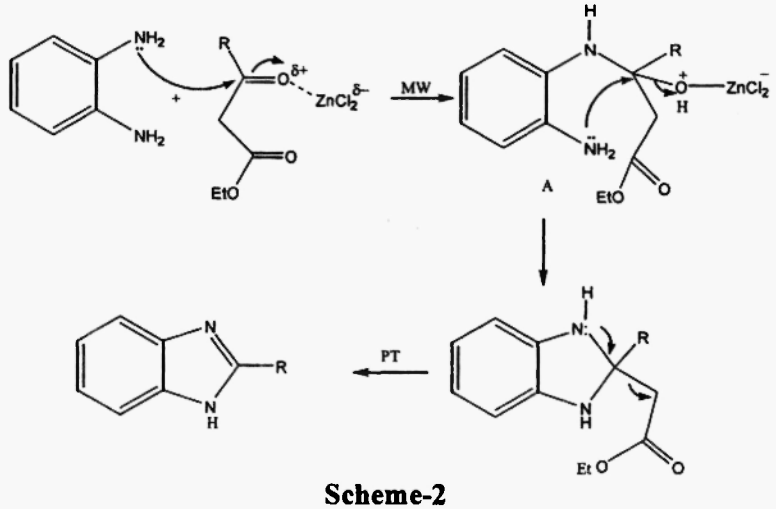
[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by our previous method [16] and other reported procedures.

In order to obtain the optimum condition, the reaction of o-phenylenediamine and ethyl acetoacetate **2a** was examined with different acidic reagents (H_2SO_4, PTSA, and $ZnCl_2$), among which $ZnCl_2$ gave the best result. Various amounts of $ZnCl_2$ were then used and (1g) proved to be the most efficient.

Therefore benzimidazoles **3b-f** were prepared in the same way by refluxing the starting materials in MeOH in the presence of $ZnCl_2$. When the reaction of o-phenylenediamine and ethyl acetoacetate **2a** was repeated in the absence of solvent on the surface of silica gel and $ZnCl_2$ the reaction went to completion within 40 seconds. Thus benzimidazoles **3b-f** were prepared under the same condition and the results are summarized in **Table-1**.

It seems that protic acids diminish the reactivity of *o*-phenylenediamine. $ZnCl_2$ on the other hand, by activating the carbonyl oxygen, makes it more prone toward a nucleophilic attack by phenylenediamine. One probable mechanism for these quick reactions is depicted in (**Scheme-2**). Since the intermediate **A** becomes a dipolar adduct which is more susceptible to microwave irradiation by dipole-dipole interactions and also because $ZnCl_2$ is a microwave active solid support, the higher yield and shortened reaction time are observed. However in order to find out whether the ester part of *β*-ketoesters is responsible for the rate of the reaction, different *β*-ketoesters (2a, 2h, 2i) and (2b, 2g) were also used and compared with each other. As indicated in **Table-1** there is not much difference in the yield of the products (3a, 3h, 3i), and (3b, 3g) which probably means separation of the ester part is not in the rate determining step.

High yield, short reaction time, formation of only one product and easy work up are advantages of this procedure in comparison to other methods reported in the literature.



Scheme-2

Experimental

Melting points were taken on an Electrothermal 9100 melting point apparatus.

IR spectra were taken with a Shimadzu IR-408 spectrometer (KBr). The ^{1}HNMR spectra were determined in methanol-d_4 and DMSO-d_6 solution on a Bruker DRX-500 Avance (500 MHz). Microwave irradiation was carried out using Moulinex, AET 5 microwave oven. Merck silica gel 60GF254 was used for preparative TLC.

General procedure for the synthesis of benzimidazole derivatives under M.W.

The mixture of SiO_2 (1gr), $ZnCl_2$ (1gr), *o*-phenylenediamine (1 mmol), and *β* -keto esters (1mmol) was ground in a mortar. The resulting mixture was then subjected to microwave irradiation in an open Pyrex beaker at appropriate power (750 Watt) and time (**Table-1**). The progress of reaction was monitored by TLC. After completion of the reaction, ethylacetate (100 ml) was added to the mixture, stirred for 20 minutes and the solid SiO_2 was filtered off. The filtrate was then washed with saturated $NaHCO_3$ (50 ml) and water. The precipitated solids which formed were filtered off and the filtrate was then evaporated *in vacuo*. The resulting oil or solids were further purified by recrystallization from appropriate solvent.

General procedure for the synthesis of benzimidazole derivatives under reflux

To the mixtures of *o*-phenylenediamine (1 mmol), and *β* -keto esters (1 mmol) in methanol (15 ml), $ZnCl_2$ (1g) was added and were refluxed in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction (**Table-1**), the mixture was extracted with ethylacetate (100 ml). The extracts were then combined and evaporated *in vacuo*. The resulting oil or solid was washed with saturated $NaHCO_3$ and water. The precipitate solids which formed, were filtered off and the filtrate was then evaporated *in vacuo*. The resulting oil or solids were further purified by recrystallization from appropriate solvent.

Conclusions

In conclusion, we have reported a convenient and easy method for the synthesis of benzimidazoles from *o*-phenylenediamine and *β* –ketoesters in a few seconds on the surface of silica gel by using $ZnCl_2$ which acts both as a lewis acid and as a microwave active solid support. Therefore, once more showed that combination of microwave energy together by using solid supports makes a powerful technique for the preparation of organic compounds. In this procedure we avoid using protic acids which lower the yield of products by protonation of *o*-phenylenediamine.

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