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Silica Sulfuric Acid Catalyzed Synthesis of Benzoxazoles, Benzimidazoles and Oxazolo[4,5-*b*]pyridines Under Heterogeneous and Solvent-Free Conditions

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This paper is dedicated to Professor H. Firouzabadi for his great contribution to the development of organic chemistry in the country in the occasion of his 65th birthday and also his retirement.

A simple, rapid and efficient method for the preparation of benzoxazoles, benzimidazoles and oxazolo[4,5-*b*]pyridines from the reaction of orthoesters with *o*-aminophenols, *o*-phenylenediamine and 2-amino-3-hydroxypyridine in the presence of silica sulfuric acid under heterogeneous and solvent-free conditions is reported. The significant features of this method are short reaction times, high yields of the products, mild reaction conditions, solvent free reaction, cheapness, non-toxicity and reusability of the catalyst.

Keywords: Benzoxazole, Benzimidazole, Oxazolo[4,5-b]pyridine, Orthoester, Silica sulfuric acid, Solvent-free.

INTRODUCTION

Benzoxazole, benzimidazole and oxazolo[4,5-*b*]pyridine moieties have attracted special attention in chemistry [1] and biochemistry [2-8]. These heterocycles show various pharmaceutical properties such ac antiviral [2], antibiotic [3], antibacterial [4], antifungal [5], anticancer [6], antitumor [7] and anti-inflammatory [8] activities. Furthermore, some of them have found applications as fluorescent whitening agents, in dye laser and as dye releaser in instant color chromatography [9]. They have been also used as ligands in asymmetric synthesis [10]. The extensive applications of these heterocycles have prompted wide studies for their synthesis. A number of methods have been reported for the preparation of these heterocycles including the condensation of carboxylic acids [11], orthoesters [12], acid chlorides [13], nitriles [14], amides [15], aldehydes [16] and esters [17] with *o*-substituted amino aromatics. However, most of these procedures have some drawbacks such as long reaction times, low yields of products, the use of expensive, toxic or non-reusable catalysts, high temperatures, harsh reaction conditions and use of toxic solvents and/or co-occurrence of several side reactions. In some cases more than one step is required for the synthesis of these heterocycles. Therefore, it is necessary to find a better catalyst for the synthesis of benzoxazoles, benzimidazoles and oxazolo[4,5-*b*]pyridines in terms of operational simplicity, non-toxicity, reusability and environmental and economical acceptability. In continuation of our works on the synthesis of heterocyclic compounds [18], we now report on the use of silica sulfuric acid as a heterogeneous and recoverable catalyst for the preparation of benzoxazole, benzimidazole and oxazolo[4,5-*b*]pyridine derivatives from orthoesters. Silica sulfuric acid is an inorganic acidic catalyst which has recently

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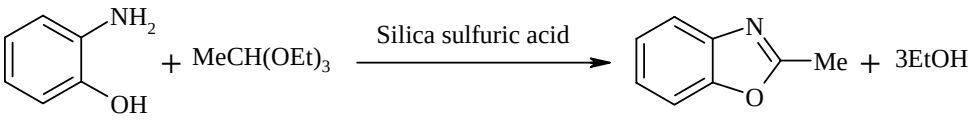


Scheme 1

attracted some interests in organic transformations [19]. This catalyst is simply prepared by the treatment of chlorosulfonic acid with silica gel at ambient temperature [20]. Easy handling, cheapness, efficiency, non-toxicity, recoverability and reusability make this catalyst eco-friendly, synthetically acceptable and economically viable.

EXPERIMENTAL

General Procedure for the Synthesis of Benzoxazoles, Benzimidazoles and Oxazolo[4,5-b]pyridines

A mixture of trialkyl orthoester (1.1 mmol), *o*-aminophenol, *o*-phenylenediamine or 2-amino-3-hydroxypyridine (1 mmol) and silica sulfuric acid (50 mg) was stirred at room temperature or at 85 ^{o}C for the appropriate time according to Tables 1-3. The progress of the reaction was monitored by TLC (eluent: *n*-hexane: ethyl acetate, 2:1). After completion of the reaction, the mixture was diluted with $CHCl_3$ (10 ml) and filtered. The solid material was washed with $CHCl_3$ and dried at 60 ^{o}C. The filtrate was evaporated and the residue was purified by recrystallization in *n*-hexane or by column chromatography on neutral alumina (Tables 1-3).

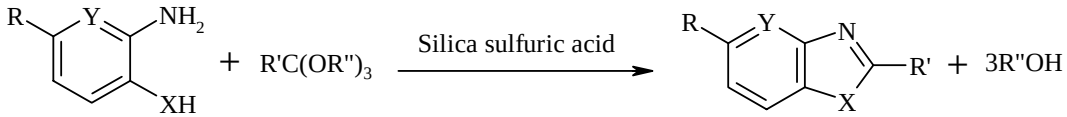
RESULTS AND DISCUSSION

In order to optimize the reaction conditions, at first, triethyl orthoacetate reacted with *o*-aminophenol in the presence of silica sulfuric acid (Scheme 1).

Different molar ratios of substrates and the catalyst, different solvents, absence of solvent and various temperatures were examined in the model reaction. The best result was obtained in the reaction of 1 mmol *o*-aminophenol with 1.1 mmol triethyl orthoacetate in the presence of 50 mg silica sulfuric acid at room temperature under solvent-free conditions, and 2-methylbenzoxazole was obtained in 95% yield after 2 min (Table 1, entry **d**). In order to show the catalytic effect of silica sulfuric acid, triethyl orthoacetate (1.1 mmol) reacted with *o*-aminophenol (1 mmol) in the absence of catalyst and solvent at room temperature. A analysis of the reaction mixture after 20 minutes illustrated that only 5% 2-methylbenzoxazole has been formed.

Under the optimized reaction conditions, a series of triethyl orthoesters reacted with *o*-aminophenols, *o*-phenylenediamine and 2-amino-3-hydroxypyridine (Scheme 2) and the corresponding benzoxazoles, benzimidazoles and oxazolo[4,5-*b*]pyridines were obtained in high to excellent yields (Tables 1-3).

As shown in Table 1, trialkyl orthoacetates and trialkyl orthopropionates reacted with *o*-aminophenols at room temperature successfully (Table 1, entries **a**-**i**). The reactions of trialkyl orthoformetes with *o*-aminophenols did not produce benzoxazoles at all at room temperature, but at 85 ^{o}C the corresponding benzoxazoles were obtained in high yields (Table1, entries **j**-**o**).

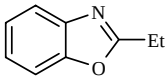
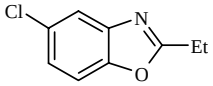
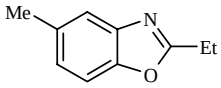
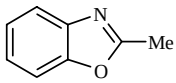
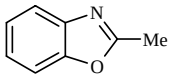
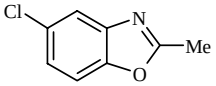
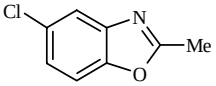
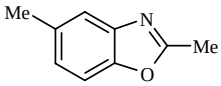
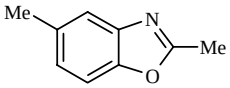
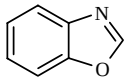
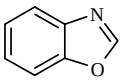
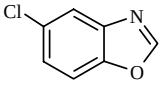
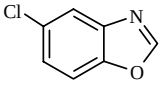
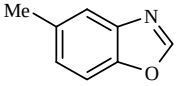
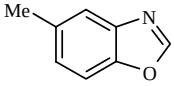


1 **2** **3-5**

X = O, NH R' = H, Me, Et
Y = C, N R" = Me, Et
R = H, Cl, Me

Scheme 2

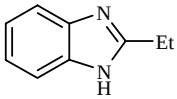
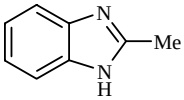
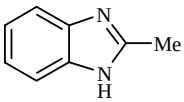
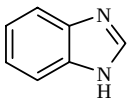
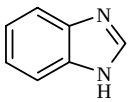
Table 1. Synthesis of Benzoxazoles from Orthoesters and *o*-Aminophenols in the Presence of Silica Sulfuric Acid

Entry	Orthoester (**2**)	Benzoxazole[a] (**3**)	Time (min)	Yield (%)[b]	M.p. (°C)[c]
a	$EtC(OEt)_3$		1.5	97	Oil [12c]
b	$EtC(OEt)_3$		3	95	59-61 [21a]
c	$EtC(OEt)_3$		8	92	29-31 [21a]
d	$MeC(OEt)_3$		2	95	Oil [12c]
e	$MeC(OMe)_3$		3	95	Oil [12c]
f	$MeC(OEt)_3$		5	96	53-55 [21a]
g	$MeC(OMe)_3$		5	93	53-55 [21a]
h	$MeC(OEt)_3$		4	95	Oil [21a]
i	$MeC(OMe)_3$		5	90	Oil [21a]
j[d]	$HC(OEt)_3$		8	90	Oil [12c]
k[d]	$HC(OMe)_3$		10	90	Oil [12c]
l[d]	$HC(OEt)_3$		5	92	36-38 [21b]
m[d]	$HC(OMe)_3$		5	90	36-38 [21b]
n[d]	$HC(OEt)_3$		8	92	42-44 [21c]
o[d]	$HC(OMe)_3$		10	85	42-44 [21c]

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples. [b] Isolated yields. [c] References for known compounds. [d]The reaction was performed at 85 °C.

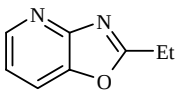
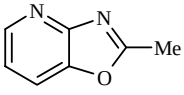
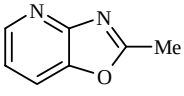
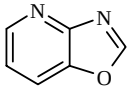
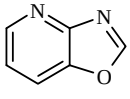
The reactions of trialkyl orthoesters with *o*-phenylenediamine and 2-amino-3-hydroxypyridine did not occur at room temperature but the corresponding benzimidazoles and oxazolo[4,5-*b*]pyridines were obtained at 85 °C in high yields (Tables 2 and 3).

Table 2. Synthesis of Benzimidazoles from Orthoesters and *o*-Phenylenediamine in the Presence of Silica Sulfuric Acid[a]

Entry	Orthoester (**2**)	Benzimidazole[b] (**4**)	Time (min)	Yield (%)[c]	M.p. (°C)[d]
a	$EtC(OEt)_3$		5	90	163-165 [21d]
b	$MeC(OEt)_3$		5	90	172-174 [21e]
c	$MeC(OMe)_3$		5	88	172-174 [21e]
d	$HC(OEt)_3$		5	90	170-172 [12a]
e	$HC(OMe)_3$		6	90	170-172 [12a]

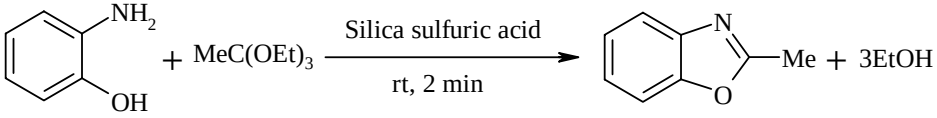
[a]The reaction was performed at 85 °C. [b] Products were identified by comparison of their physical and spectral data with those of authentic samples. [c] Isolated yields. [d] References for known compounds.

Table 3. Synthesis of Oxazolo[4,5-*b*]pyridines from Orthoesters and 2-Amino-3-hydroxypyridine in the Presence of Silica Sulfuric Acid[a]

Entry	Orthoester (**2**)	Oxazolo[4,5-*b*]pyridines[b] (**5**)	Time (min)	Yield (%)[c]	M.p. (°C)[d]
a	$EtC(OEt)_3$		5	90	51-53 [12b]
b	$MeC(OEt)_3$		7	88	70-72 [21f]
c	$MeC(OMe)_3$		10	86	70-72 [21f]
d	$HC(OEt)_3$		15	86	69-72 [12b]
e	$HC(OMe)_3$		15	70	69-72 [12b]

[a]The reaction was performed at 85 °C. [b]Products were identified by comparison of their physical and spectral data with those of authentic samples. [c]Isolated yields. [d]References for known compounds.

Table 4. Investigation of Reusability of Silica Sulfuric Acid in the Synthesis of 2-Methylbenzoxazole



Run no.	1	2	3	4	5
Yield (%)[a]	95	95	90	90	90

[a] Isolated yields.

The reusability of the catalyst is an important factor from economical and environmental point of views and has attracted much attention in recent years. Therefore, the reusability of silica sulfuric acid was examined in the reaction of triethyl orthoecetate with *o*-aminophenol under optimized reaction conditions. As silica sulfuric acid is a heterogeneous catalyst, it was separated by simple filtration after dilution of the reaction mixture with $CHCl_3$, dried at 60 ^oC and reused (Table 4). The results showed that the catalyst can be used 5 times without loss of its activity

.

CONCLUSIONS

In conclusion, we have developed an efficient method for the synthesis of benzoxazoles, benzimidazoles and oxazolo[4,5-*b*]pyridines from orthoesters. The use of silica sulfuric acid as a highly efficient, inexpensive, easy handling, non-toxic and reusable catalyst makes the present procedure eco-friendly and economically acceptable. Furthermore, short reaction times, high yields of products, mild reaction conditions, solvent free conditions and easy work-up are other noteworthy advantages which make this method a valid contribution to the existing methodologies.

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