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Short Communication

A Highly Effective Sulfamic Acid/Methanol Catalytic System for the Synthesis of Benzimidazole Derivatives at Room Temperature

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Summary. Sulfamic acid/methanol was found to be an efficient catalytic system for the synthesis of benzimidazole compounds through the condensation of *o*-phenylenediamine with orthoester in high yields at room temperature.

Keywords. Benzimidazole; *o*-Phenylenediamines; Orthoesters; Sulfamic acid/methanol system; Synthesis.

Introduction

The synthesis of benzimidazole compounds has received significant attention because of the broad spectrum of their biological and pharmaceutical properties. This class of molecules has found commercial applications in several therapeutic areas such as antiparasitic [1], antitumor [2], antimicrobial [3], and anti-inflammatory [4] agents as well as antihelminthic agents in veterinarian medicine [5]. Furthermore, these compounds can act as ligands to transition metals for modeling biological systems [6].

Due to their great importance, many synthesis strategies have been developed. The most popular synthesis approaches generally involve the condensation of an arylenediamine with a carboxylic acid or its derivative under harsh dehydrating reaction conditions [7]. Another method is the condensation of an aldehyde with arylenediamine [8]. Some methods using transition metal catalyzed coupling reactions to construct the benzimidazole nucleus have also been reported. Those

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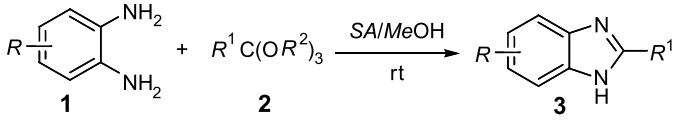

Scheme 1

involved a palladium-catalyzed intramolecular N-arylation of (*o*-bromophenyl)-amidine [9]. A method starting from arylenediamine and orthoester in the presence of Yb(O*Tf*)$_3$ [10], Zeolite [11], or KSF clay [12] at high temperature was also used for the synthesis of benzimidazole derivatives. However, many of these methodologies suffer from one or more disadvantages, such as low yields, lack of easy availability of the starting materials, prolonged reaction time, high temperature, requirement of excess of catalysts, special apparatus, and harsh reaction conditions. Thus, there is a need for simple and efficient processes for the synthesis of benzimidazole derivatives.

Recently, sulfamic acid (*SA*) has been introduced as a promising solid-acid catalyst for various organic transformations [13]. It is a nonvolatile, non-hygroscopic, odorless, uncorrodible, crystalline solid with outstanding physical stability and is a commercially available, cheap material [14]. The use of *SA* as a catalyst makes the process convenient, economic, and environmentally benign, its further exploration for other organic transformations will be quite useful. During the course of our recent studies directed at the development of practical, safe, and environmentally friendly procedures for important transformations [15], we wish to report an efficient, convenient, and facile method for the condensation of *o*-phenylenediamine with orthoester to the corresponding benzimidazole derivatives using a catalytic amount of *SA* at room temperature (Scheme 1).

Results and Discussion

Initially, the condensation of *o*-phenylenediamine as a model substrate was investigated by using triethyl orthoformate at room temperature in the presence of *SA*. For the typical experiment, first *o*-phenylenediamine (1 mmol) and then *SA* (0.05 mmol) were added to a solution of triethyl orthoformate (1.2 mmol) in *Me*OH at room temperature. The condensation was completed after 1 h (Table 1, entry 3). The effect of the relative amounts of *SA* on the outcome of the reaction was also studied. It should be pointed out that in the absence of *SA* the reactions did not

Table 1. *SA*-catalyzed synthesis of benzimidazole at room temperature

Entry	*SA* (mol%)	Time/h	Solvent	Yield/%
1	20	1	*Me*OH	96
2	10	1	*Me*OH	95
3	5	1	*Me*OH	95
4	1	1	*Me*OH	75
5	0	10	*Me*OH	0
6	10	1	*Et*OH	89
7	10	2	CH_2Cl_2	36

proceed in *Me*OH even after prolonged reaction times thus confirming the effectiveness of *SA* as catalyst. A catalytic amount of SA (5 mol%) is sufficient to obtain the desired product in high yields. No significant improvement in the yields was observed on increasing the catalyst loading further. The reaction was also carried out in some other organic solvents. Methanol was found to give the best yield of product in comparison with ethanol and dichloromethane. The remarkable efficiency of the *SA*/*Me*OH system can be explained by a better synergetic effect of SA in its zwitterionic form with *Me*OH. In the light of this, subsequent studies were carried out under following optimized conditions, that is, with 5 mol% *SA* at room temperature in *Me*OH.

Having established the optimized experimental conditions, various arylenediamines **1** were subjected to react with orthoesters **2** in order to investigate the reaction scope and several representative results are summarized in Table 2. As shown in Table 2, various types of *o*-diaminobenzene derivatives (**1a**–**1t**) with electron-donating and -withdrawing substituents on the aromatic ring were readily and rapidly converted to the corresponding substituted benzimidazoles in the presence of 5 mol% of *SA*. The electronic nature of the substituents on the aromatic ring of *o*-diaminobenzene was relevant to the yield of **3**. In general, when *R* represented electron-withdrawing groups such as chloro (Table 2, entries q and r) and nitro (Table 2, entries s and t), the yields and purities of the products were obviously worse, and long reaction times were required. The substituent R^2 in the orthoester has no influence on the reaction course (Table 2, entries a and b). Many

Table 2. *SA*/*Me*OH-catalyzed synthesis of benzimidazoles at room temperature

Entry	Arylenediamine **1**	Orthoesters **2**	Time/h	Yield/% of **3**[a]
a	*o*-phenylenediamine	$HC(OMe)_3$	1.0	96
b	*o*-phenylenediamine	$HC(OEt)_3$	1.0	98
c	*o*-phenylenediamine	$CH_3C(OMe)_3$	0.8	95
d	*o*-phenylenediamine	$CH_3CH_2C(OEt)_3$	0.8	92
e	*o*-phenylenediamine	$CH_3(CH_2)_3C(OMe)_3$	0.9	95
f	4-methylbenzene-1,2-diamine	$HC(OEt)_3$	0.5	93
g	4-methylbenzene-1,2-diamine	$CH_3C(OMe)_3$	0.5	92
h	4-methylbenzene-1,2-diamine	$CH_3CH_2C(OEt)_3$	0.6	92
i	4-methylbenzene-1,2-diamine	$CH_3(CH_2)_3C(OMe)_3$	0.6	91
j	3-methylbenzene-1,2-diamine	$HC(OEt)_3$	0.8	88
k	3-methylbenzene-1,2-diamine	$CH_3C(OMe)_3$	0.8	86
l	3-methylbenzene-1,2-diamine	$CH_3(CH_2)_3C(OMe)_3$	0.9	85
m	4,5-dimethylbenzene-1,2-diamine	$HC(OEt)_3$	1.0	94
n	4,5-dimethylbenzene-1,2-diamine	$CH_3C(OMe)_3$	0.7	93
o	4,5-dimethylbenzene-1,2-diamine	$CH_3CH_2C(OEt)_3$	0.7	95
p	4,5-dimethylbenzene-1,2-diamine	$CH_3(CH_2)_3C(OMe)_3$	0.8	92
q	4-chlorobenzene-1,2-diamine	$HC(OEt)_3$	2.0	89
r	4-chlorobenzene-1,2-diamine	$CH_3CH_2C(OMe)_3$	2.0	87
s	4-nitrobenzene-1,2-diamine	$HC(OEt)_3$	5.0	85
t	4-nitrobenzene-1,2-diamine	$CH_3CH(OMe)_3$	4.0	86

[a] Isolated yield

of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced by using this procedure. In all cases, the reaction proceeded efficiently at room temperature without the formation of any by-products. All of the products were characterized by IR, NMR, and mass spectral analysis and also by comparison with authentic samples [10].

In conclusion, sulfamic acid/*Me*OH is introduced as an excellent catalytic system for the synthesis of benzimidazole compounds. In comparison with the previously reported methods, this novel and practical method has the advantages of mild reaction conditions, short reaction times, excellent yields of products, simple workup procedure, and low cost of catalyst.

Experimental

Melting points were recorded on a X-4 apparatus. IR spectra were obtained using a Bruker-TENSOR 27 spectrometer instrument. NMR spectra were taken with a varain Mercury Plus 400 spectrometer. Mass spectra were performed on a ThermoFinnigan LCQ Advantage instrument with an ESI source (4.5 keV). Elemental analyses were carried out on an elementar vario EL analyzer. Their results agreed favourably with the calculated values.

General Procedure for the Synthesis of Benzimidazoles ***3***

A mixture of 1.0 mmol *o*-phenylenediamine, 1.2 mmol triethyl orthoformate, and 2 cm^3 *Me*OH was stirred at room temperature in the presence of a catalytic amount of sulfamic acid (0.05 mmol). The reaction was monitored by TLC. At completion of the reaction, the mixture was distilled under vacuum to remove the solvent and then diluted with 5 cm^3 H_2O. After extraction with 3×10 cm^3 ethyl acetate, the combined organic layers were washed with brine and dried ($MgSO_4$). The residue was concentrated to afford the crude product. The crude product was purified by recrystallization from diethyl ether or by silica gel column chromatography (20% ethyl acetate in *n*-hexane as eluent).

The compounds **3a** [10], **3c** [10], **3d** [10], **3e** [16], **3f** [10], **3g** [10], **3h** [10], **3j** [17], **3k** [17], **3m** [18], **3n** [18], **3p** [19], **3q** [10], **3r** [11], **3s** [10], and **3t** [10] are known, their identity was proven by means of IR, NMR, and mass spectra. Herein we give melting points and spectral data for **3i**, **3l**, and **3o**, which could not be found in literature.

2-Butyl-5-methylbenzimidazole (**3i**, $C_{12}H_{16}N_2$)

Pale yellow solid, mp 94–95°C; IR (KBr): $\bar{\nu}=3413$, 2955, 1634, 1548, 1425, 1325, 1281, 1090, 858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.90$ (t, $J=7.2$ Hz, 3H), 1.39 (sext, $J=7.2$ Hz, 2H), 1.82 (quin, $J=7.2$ Hz, 2H), 2.44 (s, 3H), 2.91 (t, $J=7.2$ Hz, 2H), 7.02 (d, $J=8.0$ Hz, 1H), 7.31 (s, 1H), 7.43 (d, $J=8.0$ Hz, 1H), 8.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.90$, 21.80, 22.63, 29.25, 30.75, 114.40, 114.66, 123.60, 131.96, 137.32, 138.76, 155.78 ppm; ESI-MS: $m/z=189$ $(M+1)^+$.

2-Butyl-4-methylbenzimidazole (**3l**, $C_{12}H_{16}N_2$)

Pale yellow solid, mp 130–131°C; IR (KBr): $\bar{\nu}=3414$, 2957, 2934, 1619, 1545, 1440, 1278, 1232, 1104, 880 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.86$ (t, $J=7.2$ Hz, 3H), 1.37 (sext, $J=7.2$ Hz, 2H), 1.82 (quin, $J=7.2$ Hz, 2H), 2.57 (s, 3H), 2.96 (t, $J=7.2$ Hz, 2H), 7.03 (d, $J=7.6$ Hz, 1H), 7.12 (t, $J=7.6$ Hz, 1H), 7.38 (d, $J=7.6$ Hz, 1H), 9.86 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.90$, 17.38, 22.66, 29.04, 30.76, 112.10, 122.70, 123.30, 124.86, 137.52, 154.85 ppm; ESI-MS: $m/z=189$ $(M+1)^+$.

2-Ethyl-5,6-dimethylbenzimidazole (**3o**, $C_{11}H_{14}N_2$)

Pale yellow solid, mp 229–231°C; IR (KBr): $\bar{\nu}=3405$, 1636, 1540, 1449, 1308, 1216, 1104, 1025, 860 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): $\delta=1.35$ (t, $J=7.6$ Hz, 3H), 2.28 (s, 6H), 2.92 (q,

$J = 7.6$ Hz, 2H), 7.30 (s, 2H), 9.71 (s, 1H) ppm; ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 11.90$, 19.63, 21.84, 114.69, 130.86, 136.35, 155.45 ppm; ESI-MS: $m/z = 175$ $(M + 1)^+$.

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