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Chinese Chemical Letters 22 (2011) 1151–1154
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester a recyclable catalyst for the synthesis of 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazole derivatives

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Received 10 January 2011
Available online 18 July 2011

Abstract

A highly selective synthesis of 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazoles from the reaction of *o*-phenylene-diamine and aromatic aldehydes in the presence of sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE) in water and at 80 °C in good to excellent yields.

Keywords: Sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester; 2-Aryl-1-arylmethyl-*1H*-1,3-benzimidazoles; Aldehydes; *o*-Phenylenediamine; Water

The benzimidazole nucleus is of significant importance to medicinal chemistry. Benzimidazoles are a component of vitamin B12 and are related to the DNA base purine and the stimulant caffeine [1]. Interest in benzimidazole-containing structures stems from their widespread occurrence in molecules that exhibit significant activity [2,3]. In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as 'privileged sub-structures' for drug design [4,5].

The traditional synthesis of benzimidazoles involves the reaction between an *o*-phenylenediamines and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions [6,7]. Benzimidazoles have also been prepared on solid-phase to provide a combinatorial approach [8]. The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct *N*-alkylation of an unsubstituted benzimidazole [9]. A number of synthetic protocols that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support [10]. Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamines with aldehydes in the presence of acidic catalysts under various reaction conditions [11–19].

Recently we prepared sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE) and used as a catalyst for the formylation and acetylation of hydroxyl groups [20] (Scheme 1).

During the course of our studies towards the development of new routes to the synthesis of highly substituted heterocycles and using solid acid catalysts [21–26], herein we wish to report a valid and an efficient procedure for the

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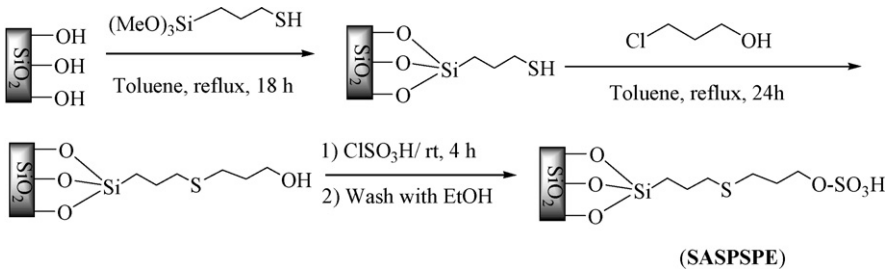
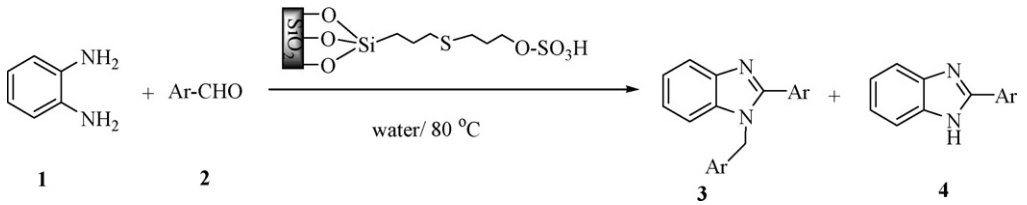
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.04.012



Scheme 1. Preparation of sulfuric acid {[3-(3-silicapropyl)sulfanyl]propyl}ester (SASPSPE).



Scheme 2. Condensation of *o*-phenylenediamine with aromatic aldehydes catalyzed by SASPSPE.

Table 1
The reaction of *o*-phenylenediamine with 4-methylbenzaldehyde in the presence of different amounts of SASPSPE at 80 °C in water.[a]

Entry	The amount of catalyst (g)	Product	Time (min)	Yield (%)[b]
1	–	–	180	–
2	0.01	**3**	50	70
3	0.03	**3**	40	80
3	0.05	**3**	30	90
4	0.1	**3**	30	90

[a] The molar ratios of 1,2-phenylenediamine and aldehyde were used as followed 1:2 respectively at 80 °C in water (5 mL).
[b] Isolated yield.

synthesis of 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazoles *via* one-pot condensation of *o*-phenylenediamine and aldehydes in the presence of SASPSPE as an inexpensive solid acid catalyst (Scheme 2).

To study the effect of catalyst loading on the condensation of *o*-phenylenediamine, aldehydes as the corresponding 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazoles, the reaction of *o*-phenylenediamine and 4-methylbenzaldehyde was chosen as a model reaction in water under reflux conditions (Table 1).

The results show clearly that SASPSPE is an effective catalyst for this transformation and in the absence of SASPSPE, the reaction did not take place, even after 3 h (Table 1, entry 1). As indicated in Table 1, the best result has been obtained with an amount of 0.05 g (1.7 mol%) SASPSPE in terms of reaction time and isolated yield.

Several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. As Table 2 shows, arylaldehydes without substituents gave the desired benzimidazoles in excellent yields (**3a**, **3i**). Aromatic aldehydes bearing electron-donating substituents gave the desired benzimidazoles (**3b**–**3d**) in a short reaction times (20–25 min) and very good to excellent yields (Table 2). Arylaldehydes with electron-withdrawing substituents such as 4-cyano- and 4-fluorobenzaldehyde gave the corresponding benzimidazoles **3g**, and **3h** in very good yields. To extend the scope of this method, we also examined the condensation of alkyl aldehydes such as butanal and octanal with *o*-phenylenediamine, but failed. In addition, the condensation reaction of cyclohexanone with *o*-phenylenediamine failed (Table 2, entries 10–12).

The possibility of recycling the catalyst was examined. For this reason, the reaction of *o*-phenylenediamine with 4-methylbenzaldehyde in the presence of SASPSPE was studied at 80 °C in water. Upon completion, the reaction mixture was filtered and washed with warm ethanol. The product was recrystallized from hot water–ethanol (1:1).

Table 2
Synthesis of 2-aryl-1-arylmethyl-*1H*-1,3-benzimidazoles catalyzed by SASPSPE at 80 °C in water.[a]

Entry	Aldehyde	Product	Time (min)	Yield (%)[b]	M_p (°C)
1	C_6H_5CHO	**3a**	25	87	130–132
2	4-$CH_3C_6H_4CHO$	**3b**	25, 25, 30, 35, 35[c]	90, 88, 89, 86, 85[c]	128–130
3	4-$CH_3OC_6H_4CHO$	**3c**	20	93	129–131
4	2-$CH_3OC_6H_4CHO$	**3d**	25	91	150–151
5	4-ClC_6H_4CHO	**3e**	30	90	135–137
6	2-ClC_6H_4CHO	**3f**	35	89	161–163
7	4-FC_6H_4CHO	**3g**	35	85	82–84
8	4-NCC_6H_4CHO	**3h**	35	93	190–192
9	2-Furyl-CHO	**3i**	30	75	92–94
10	$CH_3(CH_2)_2$–CHO	**3j**	45	Trace	–
11	$CH_3(CH_2)_6$–CHO	**3k**	45	Trace	–
12	Cyclohexanone	**3l**	45	–	–

[a] The molar ratios of 1,2-phenylenediamine:aldehyde:SASPSPE were used as followed 1:2: and 0.05 (g) respectively at 80 °C in water (5 mL).
[b] Isolated yield.
[c] The recycled catalyst was used.

The recycled catalyst could be reused four times without any treatment. No observation of appreciable loss in its catalytic activities was shown (Table 2, entry 2).

In conclusion, heterogeneous conditions, green solvent, easy and clean work-up, high yields and recovery of the catalyst makes this method practical for the synthesis of benzimidazole derivatives.

General procedure, synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles

In a round bottomed flask to a mixture of *o*-phenylenediamine (1 mmol), aromatic aldehyde (2 mmol) in water (5 mL), SASPSPE (0.05 g, 1.7 mol%) were added and the reaction mixture stirred in an oil bath at 80 °C for the appropriate time (see Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was filtered and the precipitates were solved in hot ethanol (3× 10 mL) and filtered to afford the desired product. Finally the crude product was recrystallized from water–ethanol (1:1). The recovered catalyst was dried and reused for subsequent runs.

Compound **3a**: mp 130–132 °C, Lit. [11] 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (s, 2H), 7.02 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.11–7.17 (m, 2H), 7.21–7.27 (m, 4H), 7.33–7.39 (m, 3H), 7.59–7.62 (m, 2H), 7.79 (dd, 1H, J_1 = 8.7 Hz, J_2 = 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.42, 110.59, 120.02, 122.73, 123.09, 126.01, 127.82, 128.80, 129.11, 129.30, 129.97, 130.09, 136.09, 136.42, 143.20, 154.22.

Compound **3b**: mp 128–130 °C, Lit. [19] 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.40 (s, 3H), 5.41 (s, 2H), 6.99 (d, 2H, J = 7.8 Hz), 7.13 (d, 2H, J = 7.8 Hz), 7.19–7.26 (m, 4H), 7.30 (t, 1H, J = 7.3 Hz), 7.59 (d, 2H, J = 7.8 Hz), 7.86 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.50, 21.85, 48.65, 110.96, 120.18, 123.06, 123.33, 126.32, 127.44, 129.61, 129.88, 130.13, 133.81, 136.45, 137.90, 140.55, 154.68.

Compound **3c**: mp 129–131 °C, Lit. [19] 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.88 (s, 3H), 5.41 (s, 2H), 6.89 (dt, 2H, J_1 = 6.9 Hz, J_2 = 2.4 Hz), 7.01 (dt, 2H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 7.06 (d, 2H, J = 8.7 Hz), 7.24–7.26 (m, 2H), 7.31–7.34 (m, 1H), 7.68 (dt, 2H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 7.88 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.33, 55.71, 55.80, 110.85, 114.63, 114.86, 120.09, 122.75, 123.00, 123.20, 127.64, 128.86, 131.15, 136.46, 154.47, 159.56, 161.37.

Compound **3d**: mp 150–151 °C, Lit. [19] 149–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.59 (s, 3H), 3.77 (s, 3H), 5.24 (s, 2H), 6.70 (d, 1H, J = 6.8 Hz), 6.76 (t, 1H, J = 7.4 Hz), 6.83 (d, 1H, J = 8.2 Hz), 6.96 (d, 1H, J = 8.3 Hz), 7.05 (t, 1H, J = 7.5 Hz), 7.17–7.28 (m, 4H), 7.45 (dt, 1H, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 7.54 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.6 Hz), 7.86 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.07, 55.59, 55.63, 110.40, 111.25, 111.31, 120.07, 120.83, 121.25, 122.56, 123.03, 124.83, 127.26, 128.23, 128.89, 131.98, 132.82, 156.96, 158.04.

Acknowledgment

We are thankful to the Islamic Azad University Research Council for the partial support of this work.

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