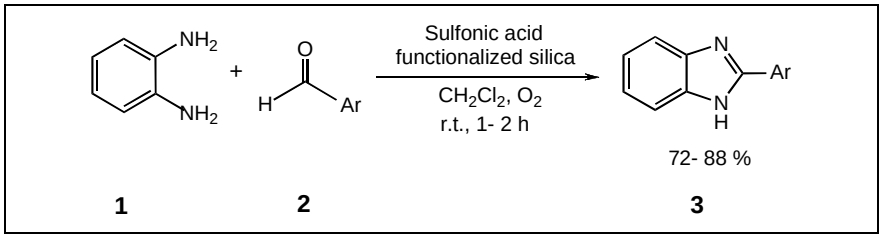
Sulfonic Acid Functionalized Silica as an Efficient Heterogeneous Recyclable Catalyst for One-Pot Synthesis of 2-Substituted Benzimidazoles

Biswanath Das,* Boddu Shashi Kanth, Kongara Ravinder Reddy and Avula Satya Kumar

Organic Chemistry Division – I
Indian Institute of Chemical Technology, Hyderabad – 500 007, India
Email: biswanathdas@yahoo.com

Received November 15, 2007



An efficient one-pot synthesis of 2-substituted benzimidazoles from o-phenylenediamine and aldehydes in the presence of sulfonic acid functionalized silica at room temperature is reported.

J. Heterocyclic Chem., **45**, 1499 (2008).

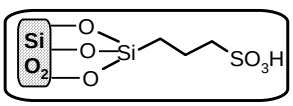
INTRODUCTION

Benzimidazole nucleus has a ubiquitous presence in several bioactive molecules and is considered to be the 'privileged sub-structure' for drug design [1]. Various benzimidazole derivatives have been found to possess anticancer, antiviral and antihypertension properties [1-3]. Benzimidazoles are also important intermediates in organic synthesis [4,5].

The general method for the preparation of 2-substituted benzimidazoles involves the treatment of *o*-phenylene-diamine with carboxylic acids or various derivatives in the presence of an acid or with aldehydes in the presence of an oxidant [6-11]. However, a number of earlier methods of the synthesis of benzimidazoles are associated with different drawbacks such as drastic reaction conditions, long conversion times and low yields.

RESULTS AND DISCUSSION

During the course of our studies [12-14] towards the development of useful synthetic methodologies we have discovered an efficient synthesis of benzimidazoles by reaction of *o*-phenylenediamine with aldehydes in the presence of a catalytic amount of sulfonic acid function-alized silica (Figure 1) at room temperature (Scheme 1).

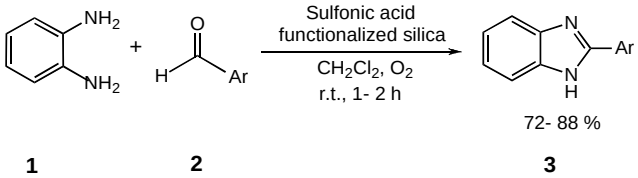


Sulfonic acid functionalized silica

Figure 1

A number of aldehydes (aromatic and aliphatic) were conveniently converted into the corresponding 2-substituted benzimidazoles in quite good yields (Table 1). Aromatic aldehydes bearing electron-donating and electron-withdrawing substituents underwent the conversion smoothly. Heteroaryl aldehydes (Table 1, entries n and p) were also applied for the preparation of the corresponding 2-substituted benzimidazoles. The reaction conditions were very mild and the conversion was complete within 1-2 h. When the reaction was carried out under nitrogen, only 2-substituted-2,3-dihydro-1*H*-benzoimidazoles were formed indicating that air is the possible oxidant here and sulfonic acid functionalized silica catalyses the oxidation at room temperature. The structures of the products were determined from their spectral (^{1}H nmr and ms) data.

Scheme I



The present catalyst, sulfonic acid functionalized silica [15-16] works as an organic-inorganic hybrid (interphase) heterogeneous catalyst wherein a Bronsted acid site has been selectively created. It catalyzes the formation of benzimidazoles facilely from *o*-phenylenediamine and aldehydes. It can easily be recovered and reused for three reaction cycles with almost similar reactivity.

Table 1

Synthesis of benzimidazoles using sulfonic acid functionalized silica.[†]

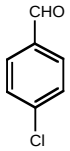
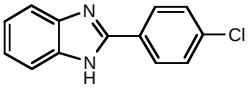
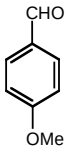
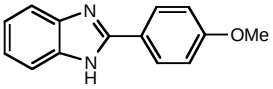
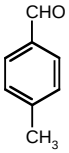
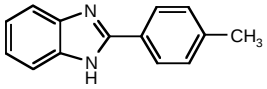
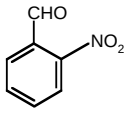
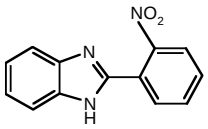
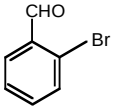
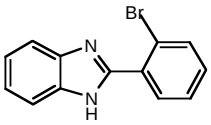
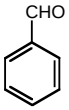
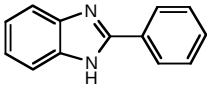
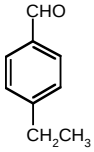
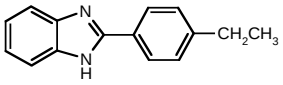
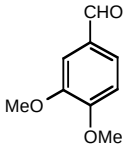
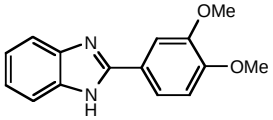
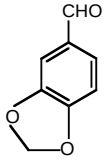
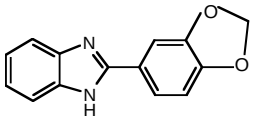
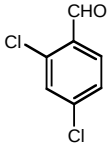
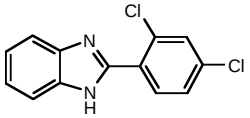
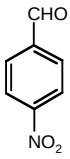
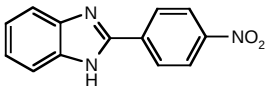
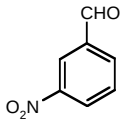
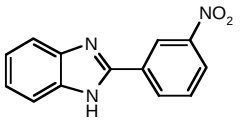
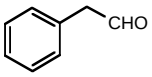
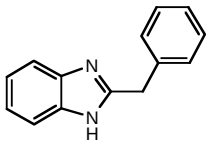
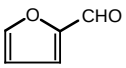
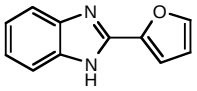
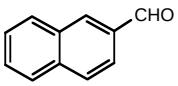
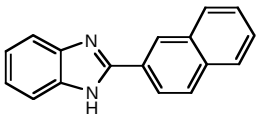
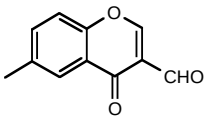
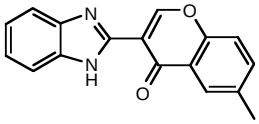
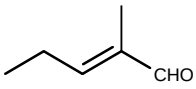
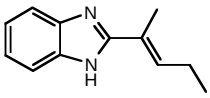
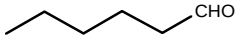
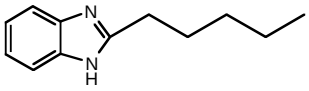
Entry	Aldehyde (**2**)	Product (**3**)	Time (h)	Isolated Yield (%)	Mp (°C) (reported[Ref])
a			1	84	288-290 289-291 [20]
b			1.5	78	222-224 224-225 [20]
c			1.5	81	267-269 268-270 [20]
d			1	83	211-213 210 [19]
e			1	81	245-247
f			1	82	290-292 292-293 [20]
g			1.5	79	144-146 143-145 [17]
h			2	74	236-238 235.5-236.7 [18]
i			2	73	245-247 246 [18]
j			1	86	230-232 228-231 [24]

Table 1 (continued)

Entry	Aldehyde (**2**)	Product (**3**)	Time (h)	Isolated Yield (%)	Mp (°C) (reported[Ref])
k			1	88	306-308 308-310 [23]
l			1	85	199-201 200-202 [23]
m			1.5	76	182-184 182-183 [21]
n			1.5	75	285-287 284-286 [23]
o			1	78	209-211 210-212 [18]
p			1	84	viscous
q			2	83	viscous
r			2	72	163-165 162-163 [22]

[†] The structures of the products were settled from their spectral (^{1}H nmr and ms) values.

EXPERIMENTAL

General experimental procedure. To a mixture of an aldehyde (0.5 mmol), and *o*-phenylenediamine (0.6 mmol) in CH_2Cl_2 (5 mL) sulfonic acid functionalized silica prepared by reported method [15,16] (10 mg) was added. The mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion the mixture was filtered and the catalyst was recovered. The filtrate was concentrated and a mixture of water and EtOAc (1:1) (10 mL) was added. The mixture was shaken and subsequently extracted with EtOAc (3 x 10 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography to obtain pure benzimidazole. The recovered catalyst was washed with $CHCl_3$ (2 × 5 mL), EtOH (2 × 5 mL) and Et_2O (2 × 5 mL) and subsequently dried at 80 °C for reuse. It was recycled three times with almost similar reactivity.

3d: ^{1}H nmr ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 12.18 (1H, brs), 7.42-7.34 (3H, m), 7.31-7.21 (5H, m); FABMS: *m/z* 240 [M + H]$^+$. *Anal*. Calcd. for $C_{14}H_9N_3O_2$: C, 65.27; H, 3.76; N, 17.57. Found: C, 65.35; H, 3.77; N, 17.60.

3h: ^{1}H nmr ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 7.81 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 8.0, 2.0 Hz), 7.58-7.50 (2H, m), 7.19-7.10 (2H, m), 6.95 (2H, d, J = 8.0 Hz), 3.97 (3H, m), 3.92 (3H, s); FABMS: *m/z* 255 [M + H]$^+$. *Anal*. Calcd. for $C_{15}H_{14}N_2O_2$: C, 80.41; H, 5.15; N, 14.43. Found: C, 80.44; H, 5.16; N, 14.48.

3p: ^{1}H nmr ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 11.77 (1H, brs), 9.27 (1H,s), 8.15 (1H, s), 7.67 (1H, m), 7.58-7.45 (2H, m), 7.22-7.18 (3H, m), 2.55 (3H, s); FABMS: *m/z* 277 $[M + H]^+$. *Anal*. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.91; H, 4.35; N, 10.14. Found: C, 73.96; H, 4.35; N, 10.19.

3q: ^{1}H nmr ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 11.80 (1H, brs), 7.61-7.22 (2H, m), 7.17-7.02 (2H, m), 6.44 (1H, t, J = 7.0 Hz), 2.28-2.23 (2H, m), 2.16 (3H, s), 1.07 (3H, t, J = 7.0 Hz); FABMS: *m/z* 187 $[M + H]^+$. *Anal*. Calcd. for $C_{12}H_{14}N_2$: C, 77.42; H, 7.53; N, 15.05. Found: C, 77.48; H, 7.60; N, 15.10.

REFERENCES

[1] Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; Mckinney, E.; Tang, C. J. *J. Med. Chem.* **1997**, *40*, 3937.

[2] Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H., Buckheit, R. W. Jr.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199.

[3] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *108*, 893.

[4] Hasegawa, E.; Yonenka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yangi, K. *Tetrahedron* . **1999**, *55*, 12957.

[5] Bai, Y.; Lu, J.; Shi, Z.; Yang, B. *Synlett* **2001**, 544.

[6] Fairley, T. A.; Tidwell, R. R.; Donkor, I.; Naiman, N. A.; Ohemeng, K. A.; Lombardy, R. J.; Bentley, J. A.; Cory, M. *J. Med. Chem.* **1993**, *36*, 1746.

[7] Czaray, A.; Wilson, W. D.; Boykin, D. W. *J. Heterocycl. Chem.* **1996**, *33*, 1393.

[8] Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823.

[9] Patzold, F.; Zeuner, F.; Heyer, T. H.; Niclas, H. J. *Synth. Commun.* **1992**, *22*, 281.

[10] Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell. R. R.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 1452.

[11] Beaulieu, P. L; Hache, B.; Van Moos, F. *Synthesis* ***2003***, 1683.

[12] Das, B.; Venkateshwarlu, K.; Mahender, G.; Mahender, I. *Tetrahedron Lett.* **2005**, *46*, 3041.

[13] Das, B.; Ramu, R.; Ravi Kanth, B.; Reddy, K. R. *Tetrahedron Lett.* **2006**, *47*, 779.

[14] Das, B.; Venkateshwarlu, K.; Suneel, K.; Majhi, A. *Tetrahedron Lett.* **2007**, *48*, 5371.

[15] Shylesh, A.; Sharma, S.; Mirajkar, S. P.; Sing, A. P. *J.Mol. Catal. A: Chem.* **2004**, *212*, 219.

[16] Karimi, B.; Khalkhali, M. *J.Mol. Catal. A: Chem.* **2005**, *232*, 113.

[17] Du, L- H.; Wang, Y- G. *Synthesis* **2007**, 675.

[18] Chakrabarty, M.; Karmakar, S.; Mukherji, A.; Arima, S.; Harigaya, Y. *Heterocycles* **2006**, *68*, 967.

[19] Alloum, A. B.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **2003**, *44*, 5935.

[20] Lu, J.; Yan, B.; Bai, Y. *Synth. Commun.***2002**, *32*, 3703.

[21] Chaudhury, S.; Debroy, A.; Mahajan, M. P. *Canad. J. Chem.* **1982**, *60*, 1122.

[22] Jing, X.; Zhu, Q.; Xu, F.; Ren, X.; Li, D.; Yan, C. *Synth. Commun.* **2006**, *36*, 2597.

[23] Xiangming, H.; Huiqiang, M.; Yulu, W. *Arkivoc* **2007** (xiii), 150.

[24] Jian, F- F.; Yu, H- Q.; Qiao, Y- B., Liang, T- L, Zhao. P- S. Acta Crystallographica, Section E, Structure Reports online **2007**, *63*, 321.