ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 6, pp. 863–865. © Pleiades Publishing, Ltd., 2008.
Published in Russian in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 6, pp. 872–874.

A Simple and Efficient Synthesis of 2-Aryl-Substituted Benzimidazoles*

Xiangming Han[a,b], Huiqiang Ma[b], and Yulu Wang[a]

[a] *College of Chemistry and Environmental Science, Henan Normal University, Xinxiang, Henan, 453007 China*
e-mail: wyl@henannu.edu.cn

[b] *Department of Chemistry and Environmental Engineering, Pingyuan University, Xinxiang, Henan, 453003 China*

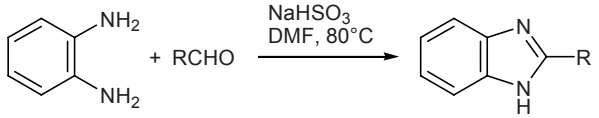
Received January 26, 2007

Abstract—Sodium hydrogen sulfite was used to promote condensation of *o*-phenylenediamine with aromatic aldehydes in dimethylformamide to obtain the corresponding 2-arylbenzimidazoles. The procedure is simple and convenient, and it implies inexpensive promoter and is characterized by short reaction time and easy purification of the final products.

DOI: 10.1134/S1070428008060146

Benzimidazoles are very useful intermediates for the synthesis of compounds of pharmaceutical or biological interest. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV [1], herpes (HSV-1) [2], RNA [3]. influenza [4], and human cytomegalovirus (HCMV) [1]. Strong interest in benzimidazole-containing structures has promoted extensive studies on their synthesis. Although many strategies are available for the synthesis of benzimidazole derivatives [7–16], there are only two general methods for the preparation of 2-substituted benzimidazoles. One of these is based on coupling of *o*-phenylenediamines with carboxylic acids [4] or their derivatives (nitriles, imidates, or ortho esters) [5], and it often requires strongly acidic conditions in combination with very high temperatures or the use of microwave irradiation [6]. The other method is a two-step procedure including oxidative cyclodehydrogenation of Schiff bases prepared in turn by condensation of *o*-phenylenediamines with aldehydes. Various oxidants and catalysts, such as sulfamic acid [7], molecular iodine [8], 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) [9], atmospheric air [10], Oxone [11], $FeCl_3 \cdot 6H_2O$ [12], $In(OTf)_3$ [13], $Yb(OTf)_3$ [14], $Sc(OTf)_3$ [15], $KHSO_4$ [16], and SO_2 [17], were used. Despite efficiency of some published methods, some of these suffer from one or more disadvantages such as high reaction temperature, prolonged reaction time, toxic solvents, etc. Therefore, development of mild and practical synthetic routes to 2-substituted benzimidazoles continues to attract researchers' attention.

Scheme 1.



For R, see Table 3.

The goal of the present work was to develop a simple and ecologically friendly procedure for the synthesis of benzimidazoles. It is known that the system urea–hydrogen peroxide is a stable, ecologically safe, and easy-to-handle reagent in organic synthesis.

Table 1. Variation of promoter in the condensation of *o*-phenylenediamine with 4-chlorobenzaldehyde

Promoter (mol %)	Time, min	Yield,[a] %
Urea–H_2O_2 (100)	20	Traces
Urea–H_2O_2 (200)	20	Traces
Urea–H_2O_2 (500)	20	Traces
Urea–H_2O_2+$NaHSO_3$ (100+30)	20	82
$NaHSO_3$ (30)	20	82
NaH_2PO_4 (30)	20	Traces
NaH_2PO_4 (100)	20	Traces
KH_2PO_4 (100)	20	Traces
Na_2HPO_4 (100)	20	Traces
$NaHCO_3$ (100)	20	Traces
None	20	Traces

* The text was submitted by the authors in English.

We tried to synthesize benzimidazoles using urea–hydrogen peroxide as oxidant, but failed. On the other hand, we found that sodium hydrogen sulfite is an effective promoter in the synthesis of 2-aryl-substituted benzimidazoles via condensation of aromatic aldehydes or cinnamaldehyde with *o*-phenylenediamine (Scheme 1). In order to find optimal conditions, various promoters and solvents were examined in the reaction of *o*-phenylenediamine with 4-chlorobenzaldehyde as model process. The reactions were carried out in dimethylformamide at 80°C, and the results are collected in Table 1. It is seen that addition of 30 mol % of $NaHSO_3$ ensures the best yield of the product. When the amount of $NaHSO_3$ was smaller than 30 mol %, the reaction took longer time, while larger amount of the promoter favored increased fraction of by-products. Next we examined the effect of solvent (Table 2). The yield of 2-(4-chlorophenyl)benzimidazole increased in parallel with the boiling point of the solvent, except for xylene. Good results were obtained in alcohols (methanol and ethanol) and DMSO. Clearly, the best solvent was DMF: it ensured fast conversion and high yield and is less toxic.

Table 2. Solvent effect on the condensation of *o*-phenylenediamine with 4-chlorobenzaldehyde (reaction time 20 min)

Solvent	Temperature, °C	Yield,[a] %
Methylene chloride	Reflux	20
Tetrahydrofuran	Reflux	35
Methanol	Reflux	58
Ethanol	Reflux	60
Water	80	55
Dimethyl sulfoxide	80	78
Xylene	80	26
Dimethylformamide	80	82

Table 3. Synthesis of benzimidazoles in dimethylformamide in the presence of $NaHSO_3$ (temperature 80°C)

R	Time, min	Yield,[a] %	mp, °C [17]
4-ClC_6H_4	20	82	284–286
Ph	20	84	289–290
4-MeC_6H_4	30	80	264–265
2-HOC_6H_4	45	75	234–236
3-$O_2NC_6H_4$	40	81	203–204
4-$MeOC_6H_4$	35	75	223–225
2-Furyl	20	78	285–287
PhCH=CH	20	70	199–202
4-$Me_2NC_6H_4$	45	72	264–266 [7]
$MeCH_2CH_2$	60	Traces	–
$Me(CH_2)_5$	60	Traces	–

[a] Isolated product.

The scope and versatility of the proposed procedure were determined using differently substituted benzaldehydes. In all cases the corresponding 2-arylbenzimidazoles were isolated in good to high yields. However, reactions of *o*-phenylenediamine with aliphatic aldehydes (butanal and heptanal) gave only traces of the corresponding 2-substituted benzimidazoles. The results are summarized in Table 3.

Thus we have developed a simple one-pot procedure for the synthesis of 2-arylbenzimidazoles by condensation of *o*-phenylenediamine with the corresponding substituted aromatic aldehyde in the presence of $NaHSO_3$. The procedure is advantageous due to mild conditions, simple manipulations, the use of inexpensive promoter, easy purification, and short reaction time.

EXPERIMENTAL

The melting points were determined on a Kofler micro melting point apparatus and were uncorrected. The ^1H NMR spectra were measured on a Bruker DPX-400M spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent.

Typical procedure for the synthesis of benzimidazoles. Equimolar amounts (0.5 mmol) of *o*-phenylenediamine and the corresponding aromatic aldehyde (0.5 mmol) were thoroughly mixed in 2 ml of DMF, 0.15 mmol of sodium hydrogen sulfite was added, and the mixture was stirred at 80°C until the reaction was complete according to the TLC data. The mixture was cooled to room temperature and added dropwise to 20 ml of water under vigorous stirring. If the product separated as a free flowing solid, it was collected by filtration, washed with water, and dried. If a gummy material separated, it was extracted into ethyl acetate, the extract was washed with water and a solution of sodium chloride, dried over sodium sulfate, and evaporated, and the residue was purified by column chromatography on silica gel using cyclohexane–ethyl acetate (3 : 1) as eluent.

2-(4-Chlorophenyl)-1*H*-benzimidazole. ^1H NMR spectrum, δ, ppm: 12.98 br.s (1H), 8.18 d (2H, J = 8 Hz), 7.63 d (2H, J = 8.4 Hz), 7.22–7.55 m (4H).

2-Phenyl-1*H*-benzimidazole. ^1H NMR spectrum, δ, ppm: 8.05–8.10 m (2H), 7.65 m (2H), 7.46–7.51 m (3H), 7.28 m (2H).

2-(4-Methylphenyl)-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 12.70 br.s (1H), 8.05 d (2H, *J* = 8 Hz), 7.35–7.56 m (4H), 87.15 m (2H), 2.37 s (3H).

2-(1*H*-Benzimidazol-2-yl)phenol. ^{1}H NMR spectrum, δ, ppm: 8.20 d (1H, *J* = 7.6 Hz), 7.40–7.60 m (3H), 7.12–7.30 m (3H), 7.10 d (1H, *J* = 8.0 Hz).

2-(3-Nitrophenyl)-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 8.42 s (1H), 8.29 d (1H, *J* = 7.6 Hz), 7.76–8.15 m (4H), 7.31 m (2H).

2-(4-Methoxyphenyl)-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 8.15 d (2H, *J* = 8.4 Hz), 87.70 m (2H), 87.42 m (2H), 87.26 d (2H, *J* =8.4 Hz), 4.06 s (3H).

2-(2-Furyl)-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 7.97 s (1H), 7.68 m (2H), 7.47 s (1H), 6.70–7.29 m (3H).

2-Styryl-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 7.2–7.8 m (11H).

2-(4-Dimethylaminophenyl)-1*H*-benzimidazole. ^{1}H NMR spectrum, δ, ppm: 7.96 d (2H, *J* = 8 Hz), 7.26–7.50 m (4H), 7.12–7.25 m (2H), 2.93 s (6H).

REFERENCES

1. Porcari, A.R., Devivar, R.V., Kucera, L.S., Drach, J.C., and Townsend, L.B., *J. Med. Chem*., 1998, vol. 41, p. 1252; Roth, T., Morningstar, M.L., Boyer, P.L., Hughes, S.H., Buckheit, R.W., Jr., and Michejda, C.J., *J. Med. Chem*., 1997, vol. 40, p. 4199.
2. Migawa, M.T., Girardet, J.L., Walker, J.A., Koszalka, G.W., Chamberlain, S.D., Drach, J.C., and Townsend, L.B., *J. Med. Chem*., 1998, vol. 41, p. 1242.
3. Tamm, L. and Seghal, P.B., *Adv. Virus Res*., 1978, vol. 22, p. 187.
4. Hisano, T., Ichikawa, M., Tsumoto, K., and Tasaki, M., *Chem. Pharm. Bull*., 1982, vol. 30, p. 2996.
5. Czarny, A., Wilson, W.D., and Boykin, D.W., *J. Heterocycl. Chem*., 1996, vol. 33, p. 1393; Tidwell, R.R., Geratz, J.D., Dann, O., Volz, G., Zeh, D., and Loewe, H., *J. Med. Chem*., 1978, vol. 27, p. 613.
6. Reddy, G.V., Rama Rao, V.V.V.N.S., Narsaiah, B., and Rao, P.S., *Synth. Commun*., 2002, vol. 32, p. 2467.
7. Chakrabarty, M., Karmakar, S., Mukherji, A., Arima, S., and Harigaya, Y., *Heterocycles*, 2006, vol. 68, p. 967.
8. Gogoi, P. and Konwar, D., *Tetrahedron Lett*., 2006, vol. 47, p. 79.
9. Lee, K.J., and Janda, K.D., *Can. J. Chem*., 2001, vol. 79, p. 1556.
10. Lin, S. and Yang, L., *Tetrahedron Lett*., 2005, vol. 46, p. 4315.
11. Beaulieu, P.L., Hache, B., and Von Moos, H., *Synthesis*, 2003, p. 1683.
12. Singh, M.P., Sasmal, S., Lu, W., and Chatterjee, M.N., *Synthesis*, 2000, p. 1380.
13. Nadaf, R.N., Siddiqui, S.A., Daniel, T., Lahoti, R.J., and Srinivasan, K.V., *J. Mol. Catal. A: Chem*., 2004, vol. 214, p. 155.
14. Massimo, C., Francesco, E., Francesca, M., Rosati, O., and Taccone, S., *Synlett*, 2004, no. 10, p. 1832.
15. Itoh, T., Nagata, K., Ishikawa, H., and Ohsawa, A., *Heterocycles*, 2004, vol. 63, p. 2769; Nagata, K., Itoh, T., Ishikawa, H., and Ohsawa, A., *Heterocycles*, 2003. vol. 61, p. 93.
16. Huiqiang Ma, Yulu Wang, and Jinye Wang, *Heterocycles*, 2006, vol. 68, p. 1669.
17. Ben-Alloum, A., Bougrin, K., and Soufiaoui, M., *Tetrahedron Lett*., 2003, vol. 44, p. 5935; DeLuca, M.R. and Kerwin, S.M., *Tetrahedron*, 1997, vol. 53, p. 457; Dubey, P.K., Kumar, R., Kumar, C. R., Grossert, J.S., and Hooper, D.L., *Synth. Commun*., 2001, vol. 31, p. 3439.