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Selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water at ambient temperature

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Abstract—A highly selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles from the reaction of *o*-phenylenediamines and aromatic aldehydes in the presence of silica sulfuric acid is reported. The reactions were performed in ethanol or water and the catalyst could be reused for several runs.

1. Introduction

The benzimidazole nucleus is of significant importance to medicinal chemistry. Several publications report benzimidazole-containing compounds showing biological activities such as selective neuropeptide YY1 receptor antagonism,[1] and as 5-lipoxygenase inhibitors for use as novel antiallergic agents,[2] factor Xa (FXa) inhibitors,[3] poly (ADP-ribose) polymerase (PARP) inhibitors[4] and as human cytomegalovirus (HCMV) inhibitors.[5] Substituted benzimidazole derivatives have found commercial applications in veterinarian medicine as anthelmintic agents and in diverse human therapeutic areas such as treatment of ulcers and as antihistaminics.[6] 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.[7]

The traditional synthesis of benzimidazoles involves the reaction between an *o*-phenylendiamine and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.[8] Benzimidazoles have also been prepared on solid-phase to provide a combinatorial approach.[9] The most popular strategies for their synthesis utilise *o*-nitroanilines as intermediates or resort to direct *N*-alkylation of an unsubstituted benzimidazole.[10] A number of synthetic protocols that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support.[11–17] Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions.[18–22]

In continuation of our interest in catalysed solid support reactions,[23] we report a selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in ethanol and water. When *o*-phenylenediamine derivatives **1** and aromatic aldehydes **2** in the presence of silica sulfuric acid[24] and different organic solvents, were allowed to react at room temperature, both expected products were obtained whose ratios depended on the nature of the solvent (Scheme 1, **3** and **4**). As can be seen in Table 1, the best overall yields and selectivities were obtained in ethanol, in which only *N*-substituted benzimidazoles **3** were produced. Consequently several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. In all cases the yields were high and **3** was formed selectively rather than **4** (Table 2).

Keywords: Heterocycles; Benzimidazole; Heterogenous catalysis; Water; Silica sulfuric acid.
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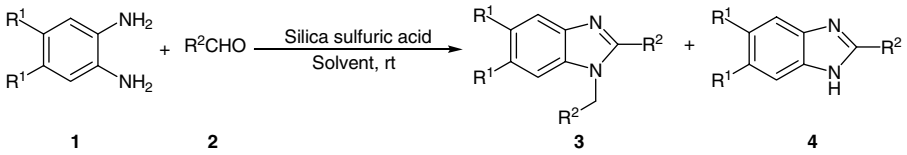

Scheme 1.

Table 1. Effect of solvent on the time and yield of the reaction of *o*-phenylenediamine and *p*-chlorobenzaldehyde in the presence of a catalytic amount of silica sulfuric acid

Solvent	Time (h)	Yield[a] (%)	
		3	**4**
EtOH	1	90	0
CH_3CN	2	78	2
CH_3OH	2.5	40	15
$C_6H_5CH_3$	4.5	30	10
H_2O	2	50	0
H_2O+LiCl[b]	1.5	85	0

[a] Isolated yield based on the aromatic aldehyde.
[b] Reaction was performed in 1 M aqueous LiCl.

There is an urgent need to develop alternative solvents and technologies due to pressure from governmental organisations and other regulatory bodies to protect the environment. Use of green solvents like water show both economical and synthetic advantages. To the best of our knowledge there is no pervious report on the synthesis of 1,2-disubstituted benzimidazoles in aqueous media at room temperature. Thus, we decided to investigate the reaction in water. Unfortunately, the yield was not satisfactory even at reflux, but the selectivity for the production of **3** was high. To increase the reaction yield in water, LiCl was added in order to increase the dielectric constant of the medium.[25] As expected the reaction time became shorter and yields were increased whilst maintaining the selectively.

As described before, compound **3** may be produced through a tandem sequence of reactions starting with the formation of dibenzylidene-*o*-phenylenediamine followed by ring closure.[22] Finally, aromatisation took place via deprotonation and 1,3-hydride transfer.

The production of monosubstituted benzimidazole **4** in some cases could be visualised to occur by condensation of *o*-phenylenediamine with the aldehyde followed by air oxidation of the dihydrobenzimidazole derivative, as previously reported.[26]

The recyclability of the catalyst was investigated using a model reaction between *o*-phenylenediamine and 4-chlorobenzaldehyde in the presence of 30 mol % of the catalyst in ethanol. After completion of the reaction, the mixture was filtered to separate the catalyst. The recycled catalyst was used for further runs and its activity did not show any significant decrease even after five runs.

In summary, we have reported a new and effective methodology for the eco-compatible preparation of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles. The easy purification of the products by simple filtration and crystallisation, the use of water as the solvent and silica sulfuric acid as a heterogeneous and reusable catalyst suggest good prospects for the applicability of this process. Also, the problem of obtaining two possible products was overcome using this new method.

2. General procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in organic solvents

Aromatic aldehyde (2 mmol), *o*-phenylenediamine derivative (1 mmol) and silica sulfuric acid (0.11 g equal to

Table 2. Reaction of aromatic aldehydes with *o*-phenylenediamines in the presence of silica sulfuric acid in water and ethanol

Product	R^1	R^2	Time (h)		Yield[b] (%)		Mp[c] (°C)
			Ethanol	Water[a]	Ethanol	Water[a]	
3a	H	C_6H_5	1.5	2	75	71	132[10]
3b	H	4-$MeOC_6H_4$	2	2.5	78	78	129–130[22]
3c	H	4-MeC_6H_4	1	1.5	95	90	128–130[10a]
3d	H	4-ClC_6H_4	1	2	90	82	136[10b]
3e	H	2-$MeOC_6H_4$	2	3	75	70	153[22]
3f	H	2-ClC_6H_4	1.5	2	67	60	163[10a]
3g	H	2-Furyl	2	2.5	88	75	94[22]
3h	H	4-$Me_2NC_6H_4$	1.5	3	70	72	255[10a]
3i	H	4-^{i}PrC_6H_4	1	2	94	85	176[10a]
3j	H	2-Pyridyl	1.5	3.5	75	71	130[22]
3k	CH_3	4-ClC_6H_4	1	2	84	78	190[27]
3l	CH_3	4-MeC_6H_4	1.5	3	78	75	177[27]

[a] Reactions were performed in 1 M aqueous LiCl.
[b] Isolated yield based on the aromatic aldehyde.
[c] The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures.

0.3 mmol H^+) were placed in a round bottomed flask. Then 5 mL of solvent was added and the mixture was stirred magnetically. After completion of the reaction (TLC, eluent, *n*-hexane/ethyl acetate, 3/1), the mixture was filtered, the solvent evaporated and the crude product was recrystallised from ethanol.

3. General procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water

Silica sulfuric acid (0.11 g equal to 0.3 mmol H^+), *o*-phenylenediamine (1 mmol), aromatic aldehyde (2 mmol) and 0.02 g of LiCl were added to 5 mL of water and the reaction stirred in a round bottomed flask for the appropriate time (see Table 2). The solvent was decanted, hot ethanol (5 mL) was added and the mixture was then filtered. The resulting solution was condensed under reduced pressure. Finally the crude product was recrystallised from ethanol.

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References and notes

1. Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. R. *J. Med. Chem.* **1998**, *41*, 2709–2719.
2. Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Matsumoto, H.; Taguchi, T.; Inagaki, N.; Nagai, H.; Satoh, T. *Bioorg. Med. Chem.* **2000**, *8*, 373–380.
3. Zhao, Z. S.; Arnaiz, D. O.; Griedel, B.; Sakata, S.; Dallas, J. L.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M. M.; Shaw, K. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 963–966.
4. White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. *J. Med. Chem.* **2000**, *43*, 4084–4097.
5. Zhu, Z.; Lippa, B.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2430–2437.
6. Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232–243.
7. (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; Dipardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S.; Chang, R. S. L.; Lotti, V. J.; Gerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246; (b) Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hume, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251–3264.
8. (a) Preston, P. N. In *Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons, 1981; Vol. 40; (b) Chi, Y.-C.; Sun, C.-M. *Synlett* **2000**, 591–594; (c) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668; (d) Dudd, L. M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake, A. J.; Wilson, C.; Poliakoff, M. *Green Chem.* **2003**, *5*, 187–192.
9. (a) Wu, Z.; Rea, P.; Wickam, G. *Tetrahedron Lett.* **2000**, *41*, 9871–9874, and references cited therein; (b) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67–70.
10. (a) Kim, B. H.; Han, R.; Kim, J. S.; Jun, Y. M.; Baik, W.; Lee, B. M. *Heterocycles* **2004**, *63*, 41–54; (b) Itoh, T.; Nagata, K.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2004**, *63*, 2769–2783.
11. Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67.
12. Tumelty, D.; Cao, K.; Holmes, C. P. *Org. Lett.* **2001**, *3*, 83–86.
13. Tumelty, D.; Schwarz, M. K.; Needels, M. C. *Tetrahedron Lett.* **1998**, *38*, 7467–7470.
14. Mayer, J. P.; Lewis, G. S.; Mc Gee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655–6658.
15. Huang, W.; Scarborogh, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668.
16. Smith, J. M.; Krchnak, V. *Tetrahedron Lett.* **1999**, *40*, 7633–7636.
17. Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2000**, *41*, 5419–5421.
18. Pertry, R. J.; Wilson, B. D. *J. Org. Chem.* **1993**, *58*, 7016–7021.
19. Esser, F.; Ehrengart, P.; Ignanatow, H. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1153–1154.
20. Anastasiou, D.; Campi, E. M.; Chaouk, H.; Jackson, W. R. *Tetrahedron* **1992**, *48*, 7467–7478.
21. Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893–1895.
22. Perumal, S.; Mariappan, S.; Selvaraj, S. *Arkivoc* **2004**, *8*, 46–51.
23. (a) Dabiri, M.; Salehi, P.; Mohammadi, A. A.; Baghbanzadeh, M. *Synth. Commun.* **2005**, *35*, 279–287; (b) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzadeh, M. *Synlett* **2005**, 1155–1157; (c) Dabiri, M.; Salehi, P.; Mohammadi, A. A.; Baghbanzadeh, M.; Kozehgiry, Gh. *J. Chem. Res. (S)* **2004**, 570–572.
24. (a) Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509–9511; (b) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghi Fard, M. A. *Tetrahedron Lett.* **2003**, *44*, 2889–2891; (c) Zolfigol, M. A.; Shirini, F.; Ghorbani Choghamarani, A.; Mohammadpoor Baltork, I. *Green Chem.* **2002**, *4*, 562–564; (d) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghi Fard, M. A. *J. Braz. Chem. Soc.* **2004**, *15*, 773–776; (e) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghi Fard, M. A. *Heterocycles* **2003**, *60*, 2435–2440; (f) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzadeh, M. *Tetrahedron Lett.* **2005**, *46*, 7051–7053.
25. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (b) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225; (c) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820; (d) Pratt, L. R.; Pohrille, A. *Chem. Rev.* **2002**, *102*, 2671–2692; (e) Ludwig, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1808–1827; (f) Berslow, R. *Acc. Chem. Res.* **2004**, *37*, 471–478; (g) Narayan, S.; Muldoon, J.; Fin, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
26. Curini, M.; Epifano, F.; Montanari, F.; Rosati, O.; Taccone, S. *Synlett* **2004**, 1832–1834.
27. Compound (**3k**) ($C_{22}H_{18}Cl_2N_2$): Pale yellow solid; mp 190 °C; IR (KBr) (ν_{max}, cm^{-1}): 3100, 2965, 1505, 1457, 1379; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.36$ (3H, s, CH_3), 2.40 (3H, s, CH_3), 5.43 (2H, s, CH_2), 7.00–7.72 (10H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.3$, 20.7, 48.0, 110.7, 118.9, 127.1, 129.4, 129.5, 130.5, 133.4, 134.6, 133.9, 134.1, 137.2, 150.7 ppm; MS (EI, 70 eV) (*m*/*z*, %): 381 (M^+, 2), 256 (20), 125 (100). Compound (**3l**) ($C_{24}H_{24}N_2$): White solid; mp 177 °C; IR (KBr) (ν_{max}, cm^{-1}): 3020, 2900, 1507, 1436, 1381; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 2.33$ (3H, s, CH_3), 2.36 (3H,

s, CH_3), 2.40 (3H, s, CH_3), 2.41 (3H, s, CH_3), 5.38 (2H, s, CH_2), 6.99–7.66 (10H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.3$, 20.6, 21.1, 21.4, 48.1, 110.6, 119.4, 125.7, 126.4, 129.1, 129.5, 129.7, 132.0, 132.4, 133.4, 134.3, 137.4, 140.2, 153.0 ppm; MS (EI, 70 eV) (*m*/*z*, %): 340 (M^+, 15), 236 (20), 105 (100).