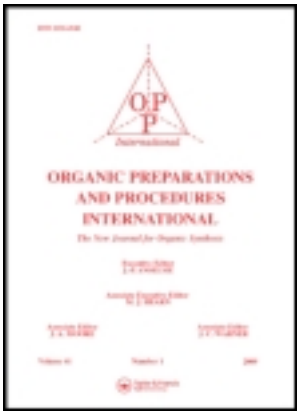
This article was downloaded by: [Laurentian University]
On: 06 April 2013, At: 08:23
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A Practical and Convenient Method for the Synthesis of Some Benzimidazoles

Babak Kaboudin [a], Minoo Khodamorady [a] & Yaghoub Abedi [a]

[a] Department of Chemistry, Institute for Advanced Studies in Basic Sciences, Gava Zang, Zanjan, 45137-66731, IRAN

Version of record first published: 20 Mar 2013.

To cite this article: Babak Kaboudin , Minoo Khodamorady & Yaghoub Abedi (2013): A Practical and Convenient Method for the Synthesis of Some Benzimidazoles, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 45:2, 162-167

To link to this article: http://dx.doi.org/10.1080/00304948.2013.765294

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Organic Preparations and Procedures International, 45:162–167, 2013
Copyright © Taylor & Francis Group, LLC
ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2013.765294

Downloaded by [Laurentian University] at 08:23 06 April 2013

OPPI BRIEF

A Practical and Convenient Method for the Synthesis of Some Benzimidazoles

Babak Kaboudin, Minoo Khodamorady, and Yaghoub Abedi

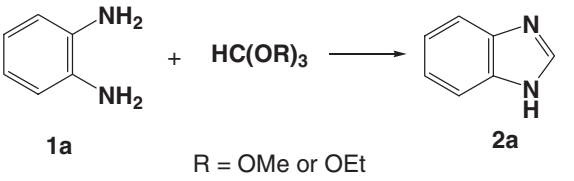
Department of Chemistry, Institute for Advanced Studies in Basic Sciences
Gava Zang, Zanjan 45137-66731, IRAN

Benzimidazole and its derivatives represent an important class of bioactive molecules.[1] Some benzimidazoles are potent antiparasitic agents,[2] topoisomerase I inhibitors,[3] selective neuropeptide Y Y1 receptor antagonists,[4] angiotensin II (AII) inhibitors,[5] inhibitors of human cytomegalovirus (HCMV) replication,[6] potential antitumour agents,[7] antimicrobial agents,[8] and inhibitors of the hepatitis C virus RNA polymerase.[9] They have also shown significant activity against several viruses including HIV,[10] herpes (HSV-1),[11] RNA,[12] and influenza.[13] Benzimidazoles can also act as ligands to transition metals for modeling biological systems[14] and have been widely used as carbon skeletons for *N*-heterocyclic carbenes.[15]

Many procedures have been reported for the synthesis of benzimidazoles[16–20] and some of these methods involve: 1) reaction of the appropriate *o*-phenylenediamines with carboxylic acids in the presence of a strong protic acid[21,22] or Lewis-acid catalysts,[23–25] 2) reaction of *o*-phenylenediamines with nitriles,[26] 3) the reaction between *N*-ethoxycarbonylthioamides [RC(S)NHCO$_2$Et] and aromatic 1,2-diamines,[27] and 4) palladium-catalyzed intramolecular arylamination of *o*-bromoarylamidines.[28] Recently Wang and co-workers developed a new procedure for the preparation of these compounds by the reaction of *o*-phenylenediamines with orthoesters in the presence of Lewis acids.[29] Although these methods are suitable for the synthesis of benzimidazoles, they have drawbacks, such as harsh reaction conditions, low yields, long reaction times, use of Lewis acids and formation of side-products; in some cases, more than one step is required. Therefore, the development of novel efficient, practical, economical, and environmentally benign methods for the synthesis of important and biologically active benzimidazoles remains an active research area.[30–32] We now report a new method for the synthesis of some benzimidazoles by the reaction of *o*-phenylenediamines with orthoesters under solvent-free conditions without any additives such as base, acid or catalyst.

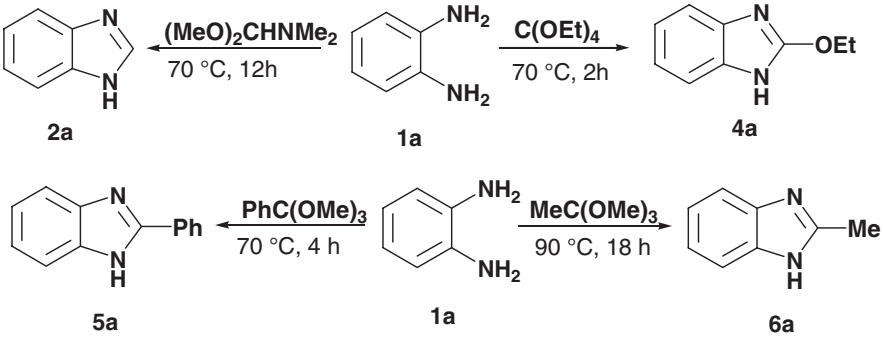
Submitted by 5, 2012.
Address correspondence to Babak Kaboudin, Department of Chemistry, Institute for Advanced Studies in Basic Sciences, Gava Zang, Zanjan 45137-66731, IRAN. E-mail: kaboudin@iasbs.ac.ir

Treatment of *o*-phenylenediamine (**1a**) with trimethyl orthoformate, as a model, was studied under various conditions in several solvents (EtOH, EtOAc, dichloromethane, chloroform, DMF, DMSO and water) and without any solvent. In water, the corresponding adduct **2a** was obtained in 30% yield after 24 hrs at ambient temperature while the yield increased to only 35% at reflux temperature (*Scheme 1*). While treatment of **1a** with trimethyl orthoformate under solvent-free conditions at room temperature for 24 h gives **2a** in only 35% yield, the same reaction proceeded smoothly under solvent-free conditions at 70°C for 12 h to give **2a** in 85% yield. The reaction with a number of *o*-phenylenediamines afforded the corresponding benzimidazoles in 57–85% yields (*Table 1*). 2,3-Diaminonaphthalene and 2,3-diaminopyridine gave the corresponding adducts **2e** and **2f** in 69% and 73% yield respectively. However, under the same conditions *cis*-1,2-diaminocyclohexane, gave a complex mixture of unknown products. The reaction of *o*-phenylenediamine with selected



Scheme 1

esters was also studied. Thus, similar treatment of **1a** with tetraethyl orthocarbonate and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) afforded 2-ethoxy-H-benzimidazole (**4a**) and **2a** in 93% and 86% yields respectively. Treatment of **1a** with trimethyl orthobenzoate under solvent-free conditions at 70°C for 4h gives **5a** in 90% yield but the same reaction of **1a** with trimethyl orthoacetate failed to give any product at 70°C for 24 h; the same reaction proceeded smoothly under solvent-free conditions at 90°C for 18 h, gave **6a** in 87% (*Scheme 2*)

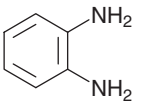
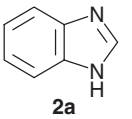
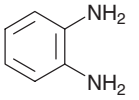
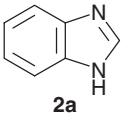
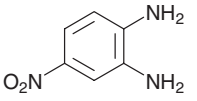
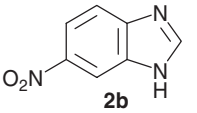
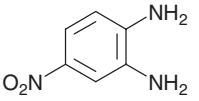
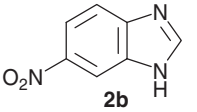
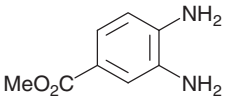
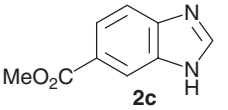
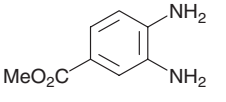
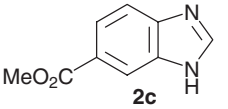
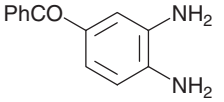
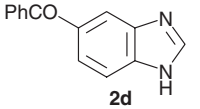
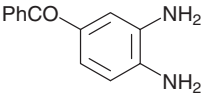
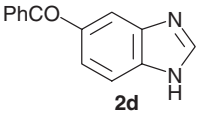
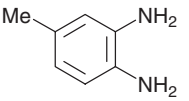
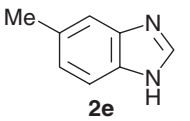
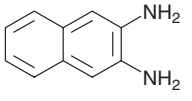
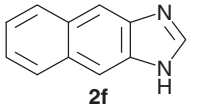
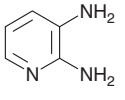
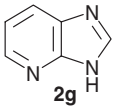


Scheme 2

In summary, we have developed a simple and practical process for the synthesis of benzimidazoles in moderate to good yields under solvent- and catalyst-free conditions.

Downloaded by [Laurentian University] at 08:23 06 April 2013

Table 1
Solvent- and catalyst-free synthesis of benzimidazoles (2)[a]

Entry	Cmpd	Product (**2**)	Time (hr)	Yield (%)	mp. (°C)	lit. mp. (°C)
1		 **2a**	12	85[b]	170–171	170–172[31]
2		 **2a**	12	82[c]	170–171	170—172[31]
3		 **2b**	24	66[b]	210–212	206–208[32]
4		 **2b**	24	68[c]	210–212	206–208[32]
5		 **2c**	18	50[b]	140–142	139–141[33]
6		 **2c**	14	80[c]	140–142	139–141[33]
7		 **2d**	18	51[b]	98–100	124–125[34]
8		 **2d**	14	62[c]	98–100	124–125[34]
9		 **2e**	14	83[c]	110–112	114–117[27]
10		 **2f**	16	69[c]	193–195	221[35]
11		 **2g**	18	73[c]	>300	>300[36]

a) At 70°C. b) Using $HC(OMe)_3$. c) Using $HC(OEt)_3$.

Downloaded by [Laurentian University] at 08:23 06 April 2013

Experimental Section

All chemicals were commercial products and were distilled or recrystallized before use. NMR spectra were taken with a 400 MHz Brucker Avance instrument with the chemical shifts being reported as δ and couplings expressed in Hertz. The chemical shift data for each signal in ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ 7.26) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance ($\delta = 77.0$). Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC.

Typical Procedure. Synthesis of Benzimidazole (2a)

A solution of *o*-phenylenediamine (5.40 g, 50 mmol) in trimethyl orthoformate (7.4 g, 70 mmol) (or orthocarbonate or DMFDMA) was stirred using magnetic stir bar for 12–24 h at 70°C (*Table 1*). The reaction mixture was then distilted under reduced pressure (to recover excess reagent) and the oily residue was chromatographed on silica gel [EtOAc/*n*-hexane (4:6)]; evaporation of the eluates (EtOAc and *n*-hexane) under reduced pressure gave pure benzimidazole (5.90 g, 85%). All products gave spectral data in accord with the assigned structures and literature data.[33–41]

2-Ethoxy-1H-benzimidazole (4a), mp.

165–167°C lit.[37] 166–167°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ1.49 (t, 3H, $J = 7.2$ Hz), 4.63 (q, 2H, $J = 7.2$ Hz), 7.10–7.20 (2H, m), 7.40–7.45 (2H, m), 8.50–9.50 (br, 1H); ^{13}C-NMR ($CDCl_3$,100 MHz): δ 14.6, 66.1, 112.1–114.1 (br), 121.5, 158.1.

2-Phenyl-1H-benzimidazole (5a), mp.

293–295°C lit.[38] 289–291°C; ^{1}H NMR (DMSO-d_6_400 MHz): δ 7.15–7.28 (2H, m), 7.48–7.58 (4H, m), 7.60–7.75 (1H, m), 8.11 (2H, d, $J = 7.2$ Hz), 9.8–10.20 (br, 1H); ^{13}C-NMR (DMSO-d $_6$-100 MHz): δ 111.7, 122.2, 126.9, 129.6, 130.5, 135.3, 144.2, 151.6.

2-Methyl-1H-benzimidazole (6a), mp.

179–180°C lit.[39] 177–178°C; ^{1}H NMR ($CDCl_3$-400 MHz): δ 2.67 (s, 3H), 7.15–7.28 (2H, m), 7.48–7.68 (2H, m), 8.0–9.1 (br, 1H); ^{13}C-NMR ($CDCl_3$_100 MHz): δ 15.0, 114.5, 122.2, 139.6, 151.3.

Acknowledgement

The authors gratefully acknowledge support by the Institute for Advanced Studies in Basic Sciences (IASBS) Research Council under grant No. G20109IASBS120.

Downloaded by [Laurentian University] at 08:23 06 April 2013

References

1. H. J. Roth and A. Kleemann, *Pharmaceutical Chemistry;* Vol. 1, *Drug Synthesis*. New York: Wiley, 1988, p 218.
2. J. Valdez, R. Cedillo,A. Hernandez-Campos, V. Yepez, F. Hernandez-Luis, G. Navarrete-Vazquez, A. Tapia, R. Cortes, M. Hernandez, and R. Castilloa, *Bioorg. Med. Chem. Lett.*, **12**, 2221 (2002).
3. J. S. Kim, B. Gatto, C. Yu, A. Liu, L. F. Liu and E. J. LaVoie, *J. Med. Chem.*, **39**, 992 (1996).
4. H. Zarrinmehr, A. M. Nunes, P. L. Ornstein, D. M. Zimmerman, B. Arnold, D. A. Schober, S. L. Gackenheimer, R. F. Bruns, P. A. Hipskind, T. C. Britton, B. E. Cantrell and D. R. Gehlert, *J. Med. Chem.*, **41**, 2709 (1998).
5. Y. Kohara, K. Kubo, E. Imamiya, T. Wada, Y. Inada and T. Naka, *J. Med. Chem.*, **39**, 5228 (1996).
6. A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, **41**, 1252 (1998).
7. W. A. Denny, W. Rewcastle and B. C. Baguley, *J. Med. Chem.*, **33**, 814 (1990).
8. T. Fonseca, B. Gigante and T. L. Gilchrist, *Tetrahedron*, **57**, 1793 (2001).
9. S. R. LaPlante, A. Jakalian, N. Aubry, Y. Bousquet, J. -M. Ferland, J. Gillard, S. Lefebvre, M. Poirier, Y. S. Tsantrizos, G. Kukolj and P. L. Beaulieu, *Angew. Chem. Int. Ed.*, **43**, 4306 (2004).
10. M. Rothe, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Buckheit Jr. and C. J. Michejda, *J. Med. Chem.*, **40**, 4199 (1997).
11. M. T. Migawa, J. –L. Girardet, J. A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, **41**, 1242 (1998).
12. I. Tamm and P. B. Sehgal, *Adv. Virus Res.*, **22**, 187 (1978).
13. I. Tamm, *Science*, **126**, 1235 (1957).
14. T. Fekner, J. Gallucci and M. K. Chan, *J. Am. Chem. Soc.*, **126**, 22 (2004).
15. H. V. Huynh, J. H. H. Ho, T. C. Ne Yo and L. L. Koh, *J. Organomet. Chem.*, **690**, 3854 (2005).
16. A. Ben Alloum, K. Bougrin and M. Soufiaoui, *Tetrahedron Lett*., **44**, 5935 (2003).
17. P. Gogi and D. Konwar, *Tetrahedron Lett*., **47**, 79 (2006).
18. H. Wang, R. E. Partch and Y. Li, *J. Org. Chem.*, **62**, 5222 (1997).
19. D. S. Van Vliet, P. Gillespie and J. J. Scicinski, *Tetrahedron Lett*., **46**, 6741 (2005).
20. J. T. Gupton, K. F. Correia and B. S. Foster, *Synth. Commun.*, **16**, 365 (1986).
21. D. W. Hein, R. S. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).
22. M. M. Heravi, N. Montazeri, M. Rahimizadeh, M. Bakavoli and M. Ghassemzadeh, *J. Chem. Res. (S)*, 584 **(2000)**.
23. L.-M. Wang, J. Sheng; H. Tian, C. -T. Qian, E. L. Hoiijes Jr. and E. W. C. Wagner, *Synth. Commun*., **34**, 4265 (2004).
24. B. Karami, V. Ghashghaee and S. Khodabakhshi, *Chin. J. Chem.*, **30**, 959 (2012). *Chem. Abstr.*, **157**, 165487 (2012).
25. S. Khaksar, A. Heydari, M. Tajbakhsh, and S. M. Vahdat, *J. Fluorine Chem.*, **131**, 1377 (2010)
26. C. H. Roeder and A. R. Day, *J. Org. Chem.*, **6**, 25 (1941).

Downloaded by [Laurentian University] at 08:23 06 April 2013

27. B. George and E. P. Papadopoulos, *J. Org. Chem.*, **42**, 441 (1977).
28. C. T. Brain and J. T. Steer, *J. Org. Chem.*, **68**, 6814 (2003).
29. Z.-H. Zhang, L. Yin and Y.-M. Wang, *Catal Commun.*, **8**, 1126 (2007).
30. B. Kaboudin and L. Malekzadeh, *Tetrahedron Lett*., **52**, 6424 (2011).
31. B. Kaboudin and L. Malekzadeh, *Synlett*, 2807 (**2011**).
32. B. Kaboudin, Y. Abedi and T. Yokomatsu, *Eur. J. Org. Chem.*, 6656 (**2011**).
33. E. C. Wagner, *J. Org. Chem.*, **5**, 136 (1940).
34. K. K. Donkor and B. Kratochvil, *J. Chem. Eng. Data*, **38**, 569 (1993).
35. K. J. Lee, and K. D. Janda, *Can. J. Chem.*, **79**, 1556 (2001).
36. Yu. V. Koshchienko, *Chem. Heterocycl. Compds*, **42**, 115 (2006).
37. K. Fries, R. Walter and K. Schilling, *Liebigs Ann. Chem.*, **516**, 248 (1935).
38. F. Perandones and J. L. Soto, *J. Heterocycl. Chem.*, **34**, 107 (1997).
39. D. J. Brown and R. K. Lynn, *J. Chem. Soc. Perkin Trans 1*, 349 (**1974**).
40. R. J. Perry and B. D. Wilson, *J. Org. Chem.*, **58**, 7016 (1993).
41. D. W. Hein, R. J. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).

Downloaded by [Laurentian University] at 08:23 06 April 2013