Short communication

A Cobalt Nitrate/Hydrogen Peroxide System as an Efficient Reagent for the Synthesis of 2-Aryl Benzimidazoles and Benzothiazoles

**Pranav S. Chandrachood,[1] Dinesh R. Garud,[2] Tushar V. Gadakari,[1]
Rasika C. Torane,[1] Nirmala R. Deshpande[1] and Rajashree V. Kashalkar[1,*]**

[1] *T. R. Ingle Research Laboratory, Department of Chemistry, Sir Parashurambhau College, Pune 411030, India.*

[2] *Department of Chemistry, Sir Parashurambhau College, Pune 411030, India.*

** Corresponding author: E-mail: rvkashalkar@gmail.com*

Received: 19-12-2010

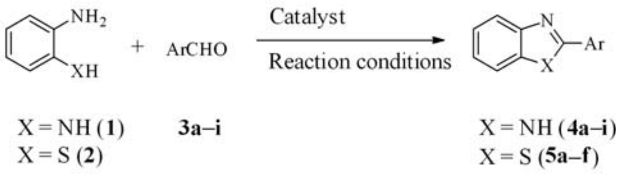
Abstract

Benzimidazoles and benzothiazoles show significant and promising activities against various viruses such as HIV and HCMV-1. Their synthesis using cobalt nitrate and hydrogen peroxide in *N*,*N*-dimethylformamide has been presented in the following study. The cobalt nitrate/H_2O_2 appears to be a smooth and efficient reagent system for the synthesis of 2-aryl substituted benzimidazoles and benzothiazoles. Simple and convenient reaction procedures and shorter reaction times are the salient features of the presented route.

Keywords: *o*-phenylenediamine, *o*-aminothiophenol, aldehyde, cobalt nitrate hexahydrate, hydrogen peroxide.

1. Introduction

Bezimidazole and benzothiazole derivatives show significant activities against various viruses such as human cytomegalovirus (HCMV),[1] herpes (HSV-1),[2,3] HIV,[4,5] influenza etc. Benzothizole nucleus has been a common pharmacophore in various antitumor and anticancer agents.[6,7] Consequently, the preparation of benzimidazole and benzothiazole derivatives with prominent biological activities has attracted tremendous attention nowadays, even though many routes are available for the synthesis of 2-aryl benzimidazoles and benzothiazoles, there are just two commonly used routes. The most commonly used method involves direct condensation of *o*-phenylenediamine or *o*-aminothiophenol with aldehyde to afford a Schiff base which then undergoes oxidative cyclisation to yield corresponding 2-subtituted benzimidazoles or benzothiazoles (Scheme 1). The oxidative cyclisation is catalyzed by various acidic reagents such as *p*-TsOH,[8] $FeCl_3 6H_2O$,[9] $In(OTf)_3$,[10] $Yb(OTf)_3$,[11] or oxidizing agents such as MnO_2,[12] I_2,[13] oxone,[14] ceric(IV) ammonium nitrate,[15] and silica supported sulfuric acid.[16] In another method, strongly acidic conditions are involved in coupling of *o*-phenylenediamines (or *o*-aminothiophenol) and carboxylic acids (or their derivatives, such as nitriles, orthoesters etc.). This route has a limited scope because of harsh conditions and formation of by-products, whereas milder reaction conditions make the previous route more attractive (Scheme 1). Many published routes use milder reagents, but suffer from disadvantages, such as prolonged reaction times, formation of numerous by-products, usage of toxic solvents etc. Therefore, to overcome these disadvantages, the search for a novel and milder reagent for the synthesis of 2-aryl benzimidazoles and benzothiazoles is the need of the day (Scheme 1).



Scheme 1

2. Experimental

Melting points were measured by using capillary tube method with MP-DS instrument. ^1H-NMR spectra were recorded on a Bruker 400 instrument using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as a solvent. The IR spectra were recorded on a Shimadzu 1600 instrument using KBr disks.

2. 1. General Procedure for the Synthesis of 2-aryl Substituted Benzimidazoles and Benzothiazoles

Aldehyde (1 mmol) and *o*-phenylenediamine (or *o*-aminothiophenol (1 mmol)) were mixed thoroughly in DMF in a round bottom flask. To this solution, cobalt nitrate hexahydrate (0.5 mmol, 146 mg) and aq. H_2O_2 (30%, 1 mmol, 0.8 mL) were added with continuous stirring. The reaction mixture was then heated to 80 °C using a paraffin oil bath with a magnetic stirrer and formation of product was monitored using TLC with hexane:ethyl acetate (8:2) as the mobile phase. After completion of the reaction, ethyl actate (30 mL) was added to the reaction mixture, and it was extracted with water (2 × 15 mL), brine (1 × 10 mL) and again with water (1 × 15 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain a crude mass. The solid mass was purified using column chromatography on silica gel (60–120) with hexane:ethyl acetate (8:2) as eluent. The pure compound was then recrystalized from chloroform.

2. 2. Spectral Data for Selected Compounds

2-(3-nitrophenyl) benzimidazole (4f): mp 198–200 °C. *m/z* = 240, $[M+1]^+$. ^{1}HNMR (400 MHz, DMSO-d_6): δ 12.7 (1H, brs, NH), 9.04 (1H, s, Ar-H), 8.67 (1H, d, Ar-H), 8.24 (1H, d, Ar-H), 7.8–7.59 (3H, m, Ar-H), 7.126 (2H, m, Ar-H).

2-(3-nitrophenyl) benzothiazole (5f): mp 182–184 °C. *m/z* = 257, $[M+1]^+$. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.94 (1H, s, Ar-H), 7.3–7.69 (4H, m, Ar-H), 7.93–8.44 (3H, m, Ar-H).

2-(4-chlorophenyl) benzothiazole (5e): mp 118–119 °C. *m/z* = 246, $[M+1]^+$. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.08–7.90 (4H, m, Ar-H), 7.53–7.39 (4H, m, Ar-H).

2-(2-chlorophenyl) benzothiazole (5d): mp 69–71 °C. *m/z* = 246, $[M+1]^+$. ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.12–7.53 (3H, m, ArH), 7.52–7.39 (5H, m, Ar-H).

3. Results and Discussion

The screening of the reagent system was done by carrying out the synthesis of 2-(4-chlorophenyl)benzothiazole (**5e**) using various reagents. The results revealed that when the reaction was carried out using silica as the catalyst, even after prolonged heating in dichloromethane it gave poor yields. When the reaction was carried out using silica in the absence of any solvent under microwave irradiation it gave only 33% yield of the desired product. A solvent free reaction was attempted under heating using silica supported sulfuric acid as a catalyst, which gave poor yields. These results promoted us to use metal nitrates (Co and Ni) for the reaction. The best results were obtained when the reaction was carried out using $Co(NO_3)_2/H_2O_2$ system in DMF as a solvent (Table 1).

In order to set the optimum reaction conditions in terms of solvent, temperature and reagent quantity, a reaction of *o*-aminothiophenol and *p*-chlorobenzaldehyde was carried out at two different temperatures, in various solvents ranging from nonpolar hexane to polar *N*,*N*-dimethylformamide (DMF) and by varying reagent quantities (Table 2).

3. 1. Effect of Change of Solvent Media and Temperature

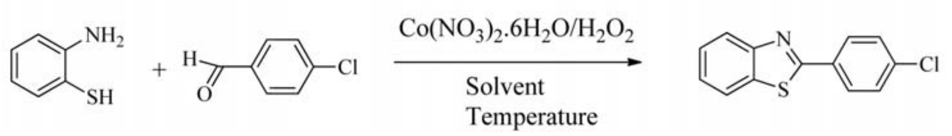
The selection of a proper solvent is an essential condition for synthesis of 2-substituted benzothiazoles and benzimidazoles in quantitative yields. In order to select a proper solvent, the reaction of *o*-aminothiophenol with *p*-chlorobenzaldehyde was carried out in various solvents. In nonpolar hexane, the yields were poor with longer reaction times. DMF as the solvent provided quantitative yields with shorter reaction times. To evaluate the effect of change in temperature, the reagent quantity was kept constant. The reaction was carried out at two different temperatures and moderate to excellent yields were obtained at 80 °C.

Table 1. Screening of catalyst for the synthesis of 2-(4-chlorophenyl) benzothiazole.

Entry	Catalyst	Time (Min)	Yield (%)[c]	Reaction Condition
1	Silica[a]	300	29	Dichloromethane/reflux
2	Silica[a]	10	33	Solvent free/microwave
3	Silica supported sulfuric acid[a]	120	58	Solvent free/heating at 90 °C
4	$Co(NO_3)_2\ 6H_2O$[b]	15	93	Dimethyl formamide/80 °C
5	$Co(NO_3)_2\ 6H_2O$[b]	45	77	Solvent free/room temp.
6	$Ni(NO_3)_2\ 6H_2O$[b]	90	85	Dimethyl formamide/80 °C

[a] Reaction conditions: **2** (1 mmol), **3**e (1 mmol), catalyst (100 mg). [b] Reaction conditions: **2** (1 mmol), **3**e (1 mmol), Metal nitrate hexahydrate (2 mmol), 30% aq. H_2O_2 (2 mmol). [c] Isolated yields.

Table 2. Effect of change in solvent, temperature and reagent quantity on the synthesis of 2-(4-chlorophenyl)benzothiazole[a]



Entry	Solvent	Temperature (°C)	$Co(NO_3)_2\ 6H_2O$ (Equiv.)	H_2O_2 (Equiv.)	Yield (%)	Time (min)
1	Hexane	25	2	2	49	90
2	Dichloromethane	25	2	2	55	60
3	Acetone	25	2	2	67	60
4	Methanol	25	2	2	70	40
5	DMF	25	2	2	79	30
6	Hexane	Reflux	2	2	54	80
7	Dichloromethane	Reflux	2	2	55	40
8	Acetone	Reflux	2	2	78	30
9	Methanol	Reflux	2	2	81	30
10	DMF	80	2	2	93	15
11	DMF	80	1	1	91	15
12	DMF	80	0	1	30	35
13	DMF	80	0.2	1	52	25
14	DMF	80	0.5	1	93	20

[a] Reaction conditions: **2** (1 mmol), **3e** (1 mmol), $Co(NO_3)_2\ 6H_2O$, 30% aq. H_2O_2, solvent
[b] Isolated yields.

Optimum reaction conditions were obtained when reaction was carried out at 80 °C and DMF as a solvent (Table 2).

3. 2. Effect of Change in Reagent Quantity

In order to optimize the reagent quantity, the reaction was carried out at 80 °C in DMF by varying the concentrations of cobalt nitrate hexahydrate and H_2O_2. Initially, 2 equiv. of cobalt nitrate were used along with equimolar proportion of H_2O_2. The yields were quantitative with shorter reaction times. Next, in order to find out optimal reagent concentration, it was gradually decreased from 2 equiv. to 1 equiv. and so on. In the absence of cobalt nitrate the yields were very poor (only 30% of the desired product was isolated). This confirms the essentiality of the cobalt nitrate in the synthesis of benzothiazole. The yields were only slightly increased when 0.2 equiv. of cobalt nitrate was used along with 2 equiv. of H_2O_2. To get the more satisfactory results, the quantity of cobalt nitrate was increased to 0.5 equiv. keeping the concentration of H_2O_2 constant. The best results were obtained when 0.5 equiv. of cobalt nitrate was used along with 1 equiv. of H_2O_2 as reported (Table 2).

The reagent system was tested by carrying out the reaction using aromatic aldehydes with varying substituents on the aromatic ring for generalization of reaction route. It was a delight to observe that the reaction of *o*-phenylenediamine (or *o*-aminothiophenol) worked well with a variety of the substituents on the aromatic ring ranging from electron withdrawing NO_2 to electron donating OMe. The above mentioned reagent system tolerated different substituents such as NO_2, Cl, Br, CH_3 and OMe. From the results can be concluded that compounds containing electron withdrawing substituents reacted relatively faster than those with electron donating substituents. This can be attributed to higher electrophilicity of the carbonyl carbon in the presence of electron withdrawing nitro substituent which is an essential condition for the first condensation step to take place. As expected, *o*-phenylenediamine reacted faster with increased yields than *o*-aminothiophenol due to the higher nucleophilicity of nitrogen than sulfur (Table 3).

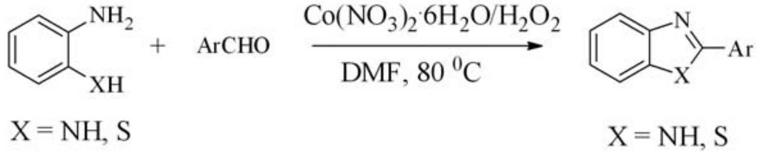
4. Conclusions

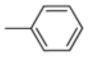
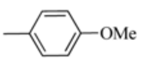
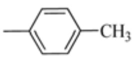
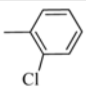
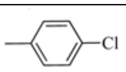
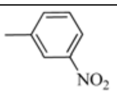
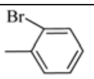
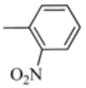
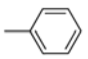
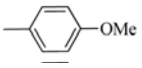
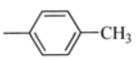
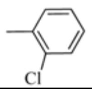
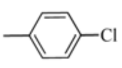
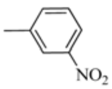
The $Co(NO_3)_2/H_2O_2$ presents a novel and efficient reagent system for the synthesis of 2-aryl benzimidazoles and benzothiazoles in moderate to excellent yields. Simple reaction conditions, simple workup procedures and easy availability of the reagents make this route more attractive and economically viable. Aliphatic aldehydes do not work well with this reagent.

5. Acknowledgements

The authors are grateful to The Principal, Sir Parashurambhau College, Pune, India, for providing necessary facilities and place of work.

Table 3. Synthesis of 2-aryl benzimidazoles and benzthiazoles using $Co(NO_3)_2/H_2O_2$ system[a]



Entry	X	Aldehyde	Ar	Product	Time (min)	Yield (%)[b]	m.p. (°C)	
							Lit [Ref]	Observed
1	NH	**3a**		**4a**	30	87	290–293[17]	288–291
2	NH	**3b**		**4b**	35	85	165–167[17]	168–169
3	NH	**3c**		**4c**	30	84	264–265[18]	260–261
4	NH	**3d**		**4d**	30	89	234–235[19]	229–231
5	NH	**3e**		**4e**	30	90	292–294[19]	290–291
6	NH	**3f**		**4f**	25	89	201–203[20]	198–200
7	NH	**3g**		**4g**	35	88	246–248[21]	244–245
8	NH	**3h**		**4h**	30	89	262–264[22]	258–260
9	NH	**3i**	$-CH_3$	**4i**	40	Trace	168–170[23]	170–171
10	S	**3a**		**5a**	35	88	112–114[24]	110–111
11	S	**3b**		**5b**	30	86	120–121[25]	120–122
12	S	**3c**		**5c**	25	87	84–86[26]	82–83
13	S	**3d**		**5d**	25	92	72–74[27]	69–71
14	S	**3e**		**5e**	15	93	115–117[28]	115–117
15	S	**3f**		**5f**	15	91	180–182[29]	182–184

[a] Reaction conditions: Amino compound (1 mmol), aldehyde (1 mmol), $Co(NO_3)_2\ 6H_2O$ (0.5 mmol), H_2O_2 (1 mmol) in DMF at 80 °C.
[b] Isolated yields.

6. References

1. A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1252–1262.
2. M. T. Migawa, J. L. Girardet, J. A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1242–1251.
3. L. Garuti, A. Ferranti, G. Giovanninetti, G. Scapini, L. Franchi, M. P. Landini, *Archiv der Pharmazie* **1982**, *315*, 1007–1013.
4. M. L. Morningstar, T. Roth, D. W. Farnsworth, M. K. Smith, K. Watson, R. W. Jr. Buckheit, K. Das, W. Zhang, E. Arnold, J. G. Julias, S. H. Hughes, C. J. Michejda, *J. Med. Chem.* **2007**, *50*, 4003–4015.
5. T. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Jr. Buckheit, C. J. Michejda, *J. Med. Chem.* **1997**, *40*, 4199–4207.
6. I. Hotchinson, T. D. Bradshaw, C. S. Matthews, M. F. G. Stevens, A. D. Westwell, *Bioorg. Med. Chem. Lett.* **2003,** *13*, 472–474.
7. S. T. Huang, I. J. Hesi, C. Chen, *Bioorg. Med. Chem.* **2006,** *14*, 6106–6119.
8. H. Xiangming, M. Huiqiang, W. Yulu, *Arkivoc* **2007**, (*viii*), 150–153.
9. M. P. Singh, S. Sasmal, W. Lu, M. N. Chatterjee, *Synthesis* **2000**, 1380–1390.
10. R. Trivedi, S. K. De, R. A. Gibbs, *J. Mol. Cat. A: Chem.* **2005**, *245*, 8–11.
11. C. Massimo, E. Francesco, M. Francesca, *Synth. Lett.* **2004**, 1832–1834.
12. I. Bhatnagar, M. V. George, *Tetrahedron* **1968**, *24*, 1293–1298.
13. P. Gogoi, D. Konwar, *Tetrahedron Lett.* **2006**, *47*, 79–82.
14. P. L. Beaulieu, B. Hache, E. Von Moos, *Synthesis* **2003**, 1683–1692.
15. F. Al-Qalaf, R. R. Mekheimer, K. U. Sadek, *Molecules* **2008**, *13*, 2908–2914.
16. I. M. Baltork, M. Moghadam, S. Tangestaninejad, V. Mirkhani, M. A. Zolfigol, S. F. Hojati, *J. Iran. Chem. Soc.* **2008**, *5*, S65–S70.
17. B. A. Abdelkrim, K. Bougrin, M. Soufiaoui, *Tetrahedron Lett*. **2003**, *44*, 5935–5937.
18. R. J. Perry, B. D. Wilson, *J. Org. Chem*. **1993**, *58*, 7016–7021.
19. B. A. Abdelkrim, S. Bakkas, M. Soufiaoui, *Tetrahedron Lett*. **1998,** *39*, 4481–4484.
20. M. R. DeLuca, S. M. Kerwin, *Tetrahedron* **1997**, *53*, 457–464.
21. M. Rope, R. W. Isensee, L. Joseph, *J. Am. Chem. Soc*. **1952**, *74*, 1095–1096.
22. K. Bourgin, A. Loupy, M. Soufiaoui, *Tetrahedron* **1998**, *54*, 8055–8064.
23. A. Harizi, H. Zantour, *Synth. Commun*. **2002**, *32*, 387–392.
24. X. G. Mu, J. P. Zou, R. S. Zeng, J. C. Wu, *Tetrahedron Lett*. **2005**, *46*, 4345–4347.
25. M. Okimoto, T. Yoshida, M. Hoshi, K. Hattori, M. Komata, K. Tomozawa, T. Chiba, *Heterocycles* **2008**, *75*, 35–42.
26. B. Maleki, H. Salehabadi, M. K. Moghadda, *Acta Chim. Slov*. **2010**, *57*, 741–745.
27. A. Q. Fawzia, R. A. Mekheimer, K. U. Sadek, *Molecules* **2008**, *13*, 2908–2914.
28. K. S. Niralwad, B. B. Shingate, M. S. Shingare, *Bull. Korean Chem. Soc*. **2010**, *31*, 981–983.
29. C. Praveen, K. H. Kumar, D. Muralidharan, P. T. Perumal, *Tetrahedron* **2008**, *64*, 2369–2374.

Povzetek

Benzimidazoli in benzotiazoli kažejo opazno in obetavno aktivnost proti različnim virusom, kot sta npr. HIV in HCMV-1. V tej študiji predstavljamo njihovo sintezo z uporabo kobaltovega nitrata in vodikovega peroksida v *N*,*N*-dimetilformamidu. Kobaltov nitrat/H_2O_2 se je izkazal kot učinkovit sistem reagentov za sintezo 2-aril substituiranih benzimidazolov in benzotiazolov. Enostavna in priročna izvedba reakcije ter kratki reakcijski časi so bistvene prednosti predstavljene sinteze.