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A simple and eco-friendly process catalyzed by montmorillonite K-10, with air as oxidant, for synthesis of 2-substituted benzothiazoles

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Abstract Simple and eco-friendly synthesis of 2-substituted benzothiazoles is described. The reaction is performed in absolute ethanol at room temperature, using a catalytic amount of montmorillonite K-10, and with continuous bubbling of air as oxidant. Simplicity, ease of handling of the system, an environmentally friendly and reusable catalyst, a plentiful, inexpensive, and safe oxidant, and mild conditions are the main advantages of this procedure.

Keywords Benzothiazoles · *o*-Aminothiophenol · Aromatic aldehydes · Montmorillonite K-10 · Air oxidation

Introduction

Benzothiazole and its derivatives have been attracting increasing interest because of their biological and pharmaceutical activity. Applications in drug discovery are based on their antitumor [1–4], antimicrobial [5], and antiviral [6] activity. They are also used in the production of antioxidants, vulcanization accelerators, and organic

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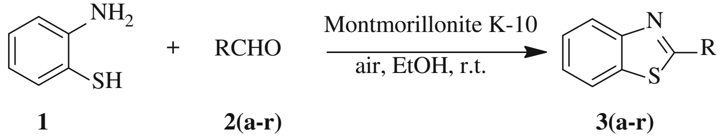
optoelectronic materials [7–9]. In recent years, because of their importance in bioorganic and medicinal chemistry, numerous methods have been developed for synthesis of benzothiazole and its derivatives. Among these, the most commonly used method involves condensation of *o*-aminothiophenol with substituted nitriles [10], carboxylic acids [11–14], acyl chlorides [15, 16], or esters [17]. These reactions are often accomplished under drastic reaction conditions. Aldehydes have recently become very popular starting materials for synthesis of 2-substituted benzothiazoles, because of their ready availability, low cost, relatively low toxicity and ease of transformation into a wide variety of functional groups. Several oxidants, for example 4-methoxy-TEMPO [18], H_2O_2/CAN [19], H_2O_2/HCl [20], poly(4-diacetoxyiodo)styrene [21], $Sc(OTf)_3$ [22], trichloroisocyanuric acid [23], I_2 [24], $HClO_4$/PANI [25], activated carbon–molecular oxygen [26], bakers' yeast [27], glucose oxidase–peroxidase [28], and $Fe(HSO_4)_3$ [29], among others, have been used in the cyclocondensation of *o*-aminothiophenol and aldehydes. Other methods include cyclization of thioformanilides [30, 31], copper-catalyzed coupling of 2-haloanilides with metal sulfides [32], palladium-catalyzed Suzuki biaryl coupling of 2-halobenzothiazole with arylboronic acids [33, 34], and coupling of benzothiazoles with aryl bromides [35]. We have recently reported the preparation of 2-substituted benzothiazoles promoted by $FeCl_3$–montmorillonite K-10 or silica–sulfuric acid [36, 37]. However, despite the merits of these procedures, many have one or more disadvantages, for example harsh reaction conditions, requirement for excess reagents or catalysts, prolonged reaction time, low yields of products, tedious work up procedures, and non-reusability of the catalysts. Development of a more efficient, convenient, and environmentally friendly methods for synthesis of 2-substituted benzothiazoles is, thus, still an important experimental challenge for chemists.

Environmentally friendly or "green" chemistry is becoming increasingly important in modern organic synthesis. This requires us to avoid the use of toxic and/or hazardous solvents and reagents, preferably eliminate the formation of waste, minimize the energy requirement, and utilize renewable raw materials where possible. Air and commercially available montmorillonite K-10 are materials that can fulfill these requirements. Montmorillonite K-10 has been widely used in synthetic organic chemistry because it is non-toxic, inexpensive, air and water-compatible, highly effective under mild reaction conditions, non-corrosive, and recyclable; use and work-up procedures are also convenient [38–42]. Recently, use of air as an oxidant has attracted much attention because it is inexpensive, readily available, simple to use, non-toxic, and safe [43–45].

As a part of our continuing attempts to develop green synthetic routes for biologically important heterocycles [44], we report here the use of montmorillonite K-10 as a reusable catalyst and continuous bubbling of air as oxidant for synthesis of 2-substituted benzothiazoles by condensation of *o*-aminothiophenol and a variety of aldehydes (Scheme 1).

Results and discussion

We have previously reported that synthesis of 2-substituted benzimidazoles in absolute ethanol at room temperature can be promoted by continuous bubbling of air



Scheme 1 Synthesis of 2-substituted benzimidazoles

[45]. In continuation of our interest in the use of air in useful synthetic methods, we attempted to synthesize 2-substituted benzothiazoles from *o*-aminothiophenol and aldehydes with use of air to improve the efficiency of the reaction. Initially, synthesis of 2-phenylbenzothiazole (**3a**) from benzaldehyde (**2a**) and *o*-aminothiophenol (**1**) was performed as model reaction. The results are listed in Table 1. The model reaction yielded 65.8 % **3a** after 10 h with continuous bubbling of air as oxidant, at room temperature, with stirring (Table 1, Entry 1). Similar results were observed in the presence of Na_2SO_4 and $MgSO_4$ (Table 1, Entries 2, 3). I_2 was also used as promoter in the model reaction under the same conditions, and **3a** was obtained in 79.6 % yield after 10 h at 25–30 °C in absolute ethanol (Table 1, Entry 4). The poor yield of **3a** inspired us to investigate this transformation further. When montmorillonite K-10 (25 mg) was added to the system as catalyst, the yield of **3a** was increased to 84.0 % (Table 1, Entry 5). Thus, montmorillonite K-10 has a definitive catalytic effect on benzothiazole formation. When 50, 75, and 100 mg montmorillonite K-10 were used, the yields were 80.4, 81.7 and 81.5 %, respectively (Table 1, Entries 6–8). From this, we concluded that 25 mg of montmorillonite K-10 was the optimum amount of catalyst for this reaction.

Post-treatment in this method is simple. After completion of the reaction (as indicated by TLC), the mixture was filtered and the ethanol was removed under reduced pressure to afford the crude product. The corresponding benzothiazoles were obtained by silica gel chromatography with petroleum ether or a mixture of petroleum ether and ethyl acetate as eluent.

To study the scope and limitations of this new procedure, a variety of aldehydes with electron-donating or electron-withdrawing groups were investigated. The results are listed in Table 2. A variety of substituents, for example *p*-methyl, *o*-chloro, *o*-methoxy, and *m*-chloro gave excellent yields (>80 %). The highest yield was obtained with *m*-chlorobenzaldehyde as starting material (Table 2, Entry 11). For *p*-hydroxy, 2,4-dichloro, 4-dimethylamino, *o*-hydroxy, 3-nitro, and 4-nitro as substituents, however, yields were <40 %. Of all aldehydes, 4-dimethylaminobenzaldehyde gave the lowest yield (17.6 %).

The procedure is, moreover, also applicable to heterocyclic aldehydes, for example furfural (**2q**), which produced the corresponding 2-(2-furanyl)benzothiazole (**3q**) smoothly in moderate yield (73.5 %) within 35 h (Table 2, Entry 18). Under the same reaction conditions, none of the desired products were obtained when aliphatic aldehydes, for example *n*-butyraldehyde and *n*-heptaldehyde, were used as substrates (Table 2, Entries 21, 22). The product was probably destabilized because the resulting benzothiazole cannot form a conjugated plane. The same

Table 1 Optimization of the conditions for synthesis of 2-phenylbenzothiazole (**3a**)[a]

Entry	Catalyst	Solvent	Time (h)	Isolated yield (%)[b]
1	None	EtOH	10	63.8
2	Na_2SO_4 (25 mg)	EtOH	10	71.0
3	$MgSO_4$ (25 mg)	EtOH	10	64.5
4	I_2 (25 mg)	EtOH	10	79.6
5	Montmorillonite K-10 (25 mg)	EtOH	10	84.0
6	Montmorillonite K-10 (50 mg)	EtOH	10	80.4
7	Montmorillonite K-10 (75 mg)	EtOH	10	81.7
8	Montmorillonite K-10 (100 mg)	EtOH	10	81.5

[a] Standard conditions: *o*-aminothiophenol (1.0 mmol), benzaldehyde (1.0 mmol), absolute ethanol (10 mL), continuous bubbling of air, room temp

[b] Isolated yield after silica gel column chromatography

Table 2 Synthesis of 2-substituted benzothiazole derivatives

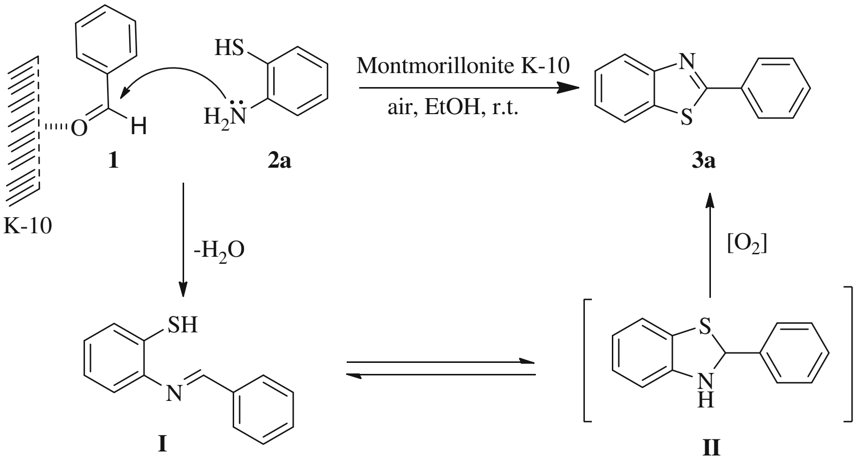
Entry	R	Product	Time (h)	Isolated yield (%)	m.p. (°C) (lit)
1	C_6H_5	**3a**	10	84.0	113–115 (112–113) [24]
2	C_6H_5	**3a**	10	77.0[a]	
3	$4\text{-}ClC_6H_4$	**3b**	15	55.2	118–120 (116–117) [25]
4	$4\text{-}CH_3C_6H_4$	**3c**	12	83.9	84–86 (83–85) [24]
5	$4\text{-}OHC_6H_4$	**3d**	40	23.8	226–228 (230–234) [36]
6	$4\text{-}CH_3OC_6H_4$	**3e**	40	47.1	123–124 (120–122) [24]
7	$4\text{-}(Me)_2NC_6H_4$	**3f**	14	17.6	172–175 (169–170) [25]
8	$2\text{-}ClC_6H_4$	**3g**	17	81.3	82–84 (80–82) [36]
9	$2\text{-}CH_3OC_6H_4$	**3h**	28	85.3	104–106 (110–112) [36]
10	$2\text{-}OHC_6H_4$	**3i**	13	38.3	134–136(129–131) [24]
11	$3\text{-}ClC_6H_4$	**3j**	9	88.3	99–100 (94–95) [25]
12	$3\text{-}NO_2C_6H_4$	**3k**	40	31.5	186–188 (183–185) [24]
13	$3,4\text{-}Cl_2C_6H_3$	**3l**	55	64.3	123-124 (123-124) [36]
14	$2,4\text{-}Cl_2C_6H_3$	**3m**	31	37.1	146–149 (150–152) [36]
15	$4\text{-}OH\text{-}3\text{-}MeOC_6H_3$	**3n**	40	47.1	176–178 (180–182) [36]
16	$2\text{-}OH\text{-}3\text{-}MeOC_6H_3$	**3o**	38	48.1	160–161 (162–163) [29]
17	$3,4\text{-}OCH_2OC_6H_3$	**3p**	39	53.2	126–128 (129–130) [36]
18	2-Furyl	**3q**	35	73.5	98–100 (102–104) [24]
19	$4\text{-}NO_2C_6H_4$	**3r**	28	19.4	232–234 (235) [26]
20	$2,4\text{-}(NO_2)_2C_6H_3$		40[b]	–	–
21	$CH_3CH_2CH_2$		15[b]	–	–
22	$CH_3(CH_2)_5$		15[b]	–	–

[a] The reaction was carried out on a 20 mmol scale

[b] No reaction

Table 3 Synthesis of 2-phenylbenzothiazole (3a) with recovered montmorillonite K-10

Number of cycles	Fresh	Recycle I	Recycle II	Recycle III	Recycle IV
Isolated yield (%)	84.0	79.5	75.5	75.4	74.0



Scheme 2 Proposed mechanism for the synthesis of 2-phenylbenzothiazole (**3a**)

situation was found when 2,4-dinitrobenzaldehyde was used as substrate (Table 2, Entry 20).

Recovery and reusability of the catalyst are among the most important features of this procedure. After completion of the reaction of **1** and **2a**, the catalyst was separated by simple filtration, washed successively with absolute ethanol to remove remaining organic compounds, dried at 120 °C for 1 h, and re-used. Recovered catalyst was reused for four consecutive runs under the same experimental conditions as for the initial run, and furnished the corresponding benzothiazole with isolated yields of 79.5, 75.5, 75.4 and 74.0 % (Table 3). These experimental results reveal that the catalyst can be reused accompanied by appreciable loss of its activity.

Montmorillonite K-10 has been widely used as an acidic catalyst for a variety of organic reactions because of its Brønsted and Lewis acidity [40, 41]. The mechanism proposed for synthesis of 2-phenylbenzothiazole catalyzed by montmorillonite K-10 with air as oxidant is shown in Scheme 2. First, the carbonyl oxygen of benzaldehyde is activated by the acid sites of montmorillonite K-10 and subsequently condenses with *o*-aminothiophenol to form a Schiff base of type (**I**) as intermediate. Intermediate (**I**) is converted to a five-membered ring intermediate (**II**) in either a sequential or concerted manner. Finally, elimination of hydrogen from intermediate (**II**), with air as oxidant, affords 2-phenylbenzothiazole (**3a**).

Finally, to show the potential of our procedure for large-scale synthesis of these heterocycles, condensation of **1** with **2a** was conducted on the 20 mmol scale, by use of the montmorillonite K-10–air system at room temperature. The reaction proceeded smoothly and the isolated yield of **3a** was 77.0 %, slightly less than that obtained on the smaller scale under these mild conditions.

Conclusion

In summary, a facile and green method catalyzed by montmorillonite K-10 at room temperature, with continuous bubbling of air as oxidant, has been developed for synthesis of 2-substituted benzothiazoles. Compared with methods reported previously, this procedure features mild reaction conditions, a practically inexhaustible oxidant, and easy separation and reuse of the catalyst. Also, the montmorillonite K-10–air system is inexpensive, safe, and environmentally benign.

Experimental

Apparatus, materials, and measurements

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Montmorillonite K-10 from Sigma–Aldrich was used without pretreatment. Before use in reactions, solvents were dried and freshly distilled by use of standard literature procedures. Reactions were monitored by use of thin-layer chromatography (TLC) on silica gel F254 plates. Melting points are uncorrected. ^{1}H NMR (600 MHz) spectra were recorded at room temperature on a Bruker Avance III 600 spectrometer with $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard.

General procedure for synthesis of 2-substituted benzothiazoles

Aldehyde (**2**, 1.0 mmol) and *o*-aminothiophenol (**1**, 1.0 mmol) were mixed in absolute ethanol (10 mL) in a 50-mL three-necked flask equipped with a water-cooled condenser and a gas inlet, as reported elsewhere [45]. The solution was stirred at room temperature, then montmorillonite K-10 (25 mg) was added. Air was bubbled continuously through the reaction system, at a speed of 60 bubbles per minute on average, by means of a small air pump. After completion of the reaction (monitored by TLC) the catalyst was recovered by filtration and washed with EtOH. The filtrate was concentrated and purified by short column chromatography on silica gel, with petroleum ether or a mixture of petroleum ether and ethyl acetate as eluent, to give the pure product. The products (**3a**–**r**) are all known compounds and were identified by ^{1}H NMR spectroscopy, by comparison of their melting points with those reported in the literature, and by comparison of their TLC R_f values with those of standards.

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References

1. D.F. Shi, T.D. Bradshaw, S. Wrigley, C.J. McCall, P. Lelieveld, I. Fichtner, M.F. Stevens, J. Med. Chem. **39**, 3375 (1996)
2. M.S. Chua, D.F. Shi, S. Wrigley, T.D. Bradshaw, I. Hutchinson, P.N. Shaw, D.A. Barrett, L.A. Stanley, M.F.G. Stevens, J. Med. Chem. **42**, 381 (1999)
3. I. Hutchinson, M.S. Chua, H.L. Browne, V. Trapani, T.D. Bradshaw, A.D. Westwell, M.F. Stevens, J. Med. Chem. **44**, 1446 (2001)
4. I. Hutchinson, S.A. Jennings, B.R. Vishnuvajjala, A.D. Westwell, M.F.G. Stevens, J. Med. Chem. **45**, 744 (2002)
5. M. Zajac, P. Hrobárik, P. Magdolen, P. Foltínová, P. Zahradník, Tetrahedron **64**, 10605 (2008)
6. A.D. Borthwick, D.E. Davies, P.F. Ertl, A.M. Exall, T.M. Haley, G.J. Hart, D.L. Jackson, N.R. Parry, A. Patikis, N. Trivedi, G.G. Weingarten, J.M. Woolven, J. Med. Chem. **46**, 4428 (2003)
7. S.C. Debnath, D.K. Basu, J. Appl. Polym. Sci. **52**, 597 (1994)
8. C.P. Ye, N.G. Wang, H.Q. Jia, X.J. Xu, Chin. J. Appl. Chem. **19**, 1008 (2002)
9. A. Heynderickx, R. Guglielmetti, R. Dubest, J. Aubard, A. Samat, Synthesis 1112 (2003)
10. R.H. Tale, Org. Lett. **4**, 1641 (2002)
11. S. Mourtas, D. Gatos, K. Barlos, Tetrahedron Lett. **42**, 2201 (2001)
12. A.K. Chakraborti, C. Selvam, G. Kaur, S. Bhagat, Synlett 851 (2004)
13. C.P. Chen, Y.J. Chen, Tetrahedron Lett. **45**, 113 (2004)
14. J.A. Seijas, M.P. Vazquez-Tato, M.R. Carballido-Reboredo, J. Crecente-Campo, L. Romar-Lopez, Synlett 313 (2007)
15. I.R. Laskar, T.M. Chen, Chem. Mater. **16**, 111 (2004)
16. R.N. Nadaf, S.A. Siddiqui, T. Daniel, R.J. Lahoti, K.V. Srinivasan, J. Mol. Catal. A: Chem. **214**, 155 (2004)
17. H. Matsushita, S.H. Lee, M. Joung, B. Clapham, K.D. Janda, Tetrahedron Lett. **45**, 313 (2004)
18. Y.X. Chen, L.F. Qian, W. Zhang, B. Han, Angew. Chem. Int. Ed. **47**, 9330 (2008)
19. K. Bahrami, M.M. Khodaei, F. Naali, J. Org. Chem. **73**, 6835 (2008)
20. H.Y. Guo, J.C. Li, Y.L. Shang, Chin. Chem. Lett. **20**, 1408 (2009)
21. A. Kumar, R.A. Maurya, P. Ahmad, J. Comb. Chem. **11**, 198 (2009)
22. T. Itoh, K. Nagata, H. Ishikawa, A. Ohsawa, Heterocycles **62**, 197 (2004)
23. H.L. Xiao, J.X. Chen, M.C. Liu, D.J. Zhu, J.C. Ding, H.Y. Wu, Chem. Lett. **38**, 170 (2009)
24. Y. Li, Y.L. Wang, J.Y. Wang, Chem. Lett. **35**, 460 (2006)
25. M. Abdollahi-Alibeik, S. Poorirani, Phosphorus Sulfur Silicon Relat. Elem. **184**, 3182 (2009)
26. Y. Kawashita, J. Yanagi, T. Fujii, M. Hayashi, Bull. Chem. Soc. Jpn. **82**, 482 (2009)
27. U.R. Pratap, J.R. Mali, D.V. Jawale, R.A. Mane, Tetrahedron Lett. **50**, 1352 (2009)
28. A. Kumar, S. Sharma, R.A. Maurya, Tetrahedron Lett. **51**, 6224 (2010)
29. H. Eshghi, M. Rahimizadeh, A. Shiri, P. Sedaghat, Bull. Korean Chem. Soc. **33**, 515 (2012)
30. D.S. Bose, M. Idrees, B. Srikanth, Synthesis 819 (2007)
31. Y. Cheng, J. Yang, Y. Qu, P. Li, Org. Lett. **14**, 98 (2012)
32. D.W. Ma, S.W. Xie, P. Xue, X.J. Zhang, J.H. Dong, Y.W. Jiang, Angew. Chem. Int. Ed. **48**, 4222 (2009)
33. V.J. Majo, J. Prabhakaran, J.J. Mann, J.S.D. Kumar, Tetrahedron Lett. **44**, 8535 (2003)
34. Y. Heo, Y.S. Song, B.T. Kim, J.N. Heo, Tetrahedron Lett. **47**, 3091 (2006)
35. D. Alagille, R.M. Baldwin, G.D. Tamagnan, Tetrahedron Lett. **46**, 1349 (2005)
36. G.F. Chen, H.M. Jia, L.Y. Zhang, B.H. Chen, J.T. Li, Ultrason. Sonochem. **20**, 627 (2013)
37. G.F. Chen, L.Y. Zhang, H.M. Jia, B.H. Chen, J.T. Li, S.X. Wang, G.Y. Bai, Res. Chem. Intermed. **39**, 2077 (2013)
38. S. Kanagasabapathy, A. Sudalai, B.C. Benicewicz, Tetrahedron Lett. **42**, 3791 (2001)
39. D. Habibi, O. Marvi, J. Serb. Chem. Soc. **70**, 579 (2005)

40. T.K. Huang, R. Wang, L. Shi, X.X. Lu, Catal. Commun. **9**, 1143 (2008)
41. M.V. Reddy, G.C.S. Reddy, Y.T. Jeong, Tetrahedron **68**, 6820 (2012)
42. T.R. Reddy, G.R. Reddy, L.S. Reddy, C.L.T. Meda, K.V.L. Parsa, K.S. Kumar, Y. Lingappa, M. Pal, Eur. J. Med. Chem. **62**, 395 (2013)
43. C. Zhang, L.R. Zhang, N. Jiao, Green Chem. **14**, 3273 (2012)
44. Y.Y. Ji, W.Z. Li, Y.X. Chen, C.Y. Yu, F.Y. Yu, H.Y. Xu. J. Nat. Gas Chem. **9**, 291 (2000)
45. G.F. Chen, H.D. Shen, H.M. Jia, L.Y. Zhang, H.Y. Kang, Q.Q. Qi, B.H. Chen, J.L. Cao, J.T. Li, Aust. J. Chem. **66**, 262 (2013)