Monatsh Chem (2009) 140:1471–1473
DOI 10.1007/s00706-009-0209-4

ORIGINAL PAPER

PTSA catalyzed simple and green synthesis of benzothiazole derivatives in water

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Received: 21 July 2009 / Accepted: 11 October 2009 / Published online: 11 November 2009

Abstract *p*-Toluenesulfonic acid (10 mol%) was found to be an effective and efficient catalyst for the synthesis of 2-substituted benzothiazoles from aromatic aldehydes and 2-aminothiophenol in moderate to excellent yields in water. This method provides a simple and efficient protocol in terms of mild reaction conditions, clean reaction profiles, small quantity of catalyst, and simple workup procedure.

Keywords Aldehydes · Aminothiophenol · Catalysis · Water chemistry · Green chemistry

Introduction

Benzothiazole derivatives are an important class of heterocyclic compounds that exhibit a wide range of biological properties in medicinal and agricultural chemistry [1–5]. Further industrial applications as antioxidants [6, 7], vulcanization accelerators [8, 9], and a dopant in a light-emitting organic electroluminescent devices [10] have also been reported.

Many reports have appeared in the literature describing the formation of benzothiazoles via one of the two major routes. The most commonly used method involves the condensation of *o*-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters in the presence of a catalyst such as *p*-toluenesulfonic acid (PTSA) in an organic solvent [11–19]. Another route is based on oxidative cyclization of thiobenzanilides using various oxidants [20–27]. However, these methodologies suffer from one or more disadvantages, such as tedious workup, high temperature, prolonged reaction time, and toxic organic solvents such as DMF and DMSO.

Carrying out organic reactions in water has become highly desirable in recent years to meet environmental considerations. The use of water as a sole medium of organic reactions would greatly contribute to the development of environmentally friendly processes. It would be even more desirable to carry out catalytic organic reactions in water, which normally require delicate reaction conditions in order for the catalyst to be stable and yet reactive. In this context, in recent years much attention has been focused on Lewis acid-catalyzed organic reactions in water, and several reactions of this type have been already identified [28–30].

Results and discussion

As a continuation of our research into developing green organic chemistry by using water as a reaction medium or by performing organic transformations under solvent-free conditions [31, 32], herein we report an efficient and environmentally benign synthesis of benzothiazole under mild conditions. Simple mixing of aromatic aldehydes and *o*-aminothiophenol was carried out under clean reaction conditions in the presence of a small amount of PTSA at 70 °C in water. This reduced the amount of waste by omitting organic solvents. We succeeded in obtaining high yields of the products with a very simple workup procedure (Scheme 1).

The literature survey reveals that there are so far few papers on synthesizing benzothiazoles under solvent-free conditions [33, 34] or in water [35–37]. Therefore, we were

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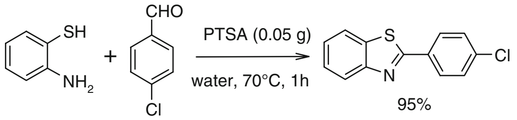
Scheme 1



Catalyst	Pd(OAc)$_2$	NiCl$_2$	Co(OAc)$_2$	CuCl$_2$	FeCl$_3$	ZrCl$_4$	H$_3$PW$_{12}$O$_{40}$	H$_3$PMo$_{12}$O$_{40}$	Bi(NO$_3$)$_2$
Yields (%)^a	78	80	70	68	60	80	84	82	78

Catalyst	I$_2$	CAN	NBS	HCl	H$_2$SO$_4$	H$_3$PO$_4$	NaHSO$_4$	NH$_4$MoO$_4$	La$_2$O$_3$	WO$_3$	PTSA
Yields (%)^a	60	80	75	73	72	78	80	80	88	92	95

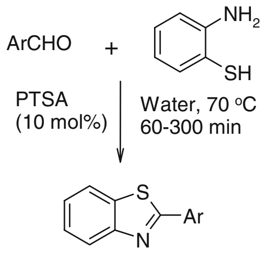
^{a} NMR yields; NBS: *N*-bromosuccinimide, CAN: ceric ammonium nitrate, PTSA: *p*-toluenesulfonic acid

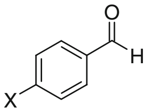
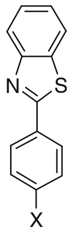
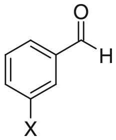
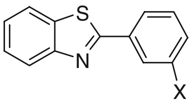
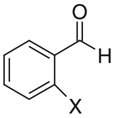
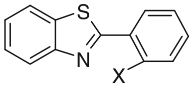
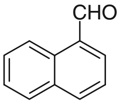
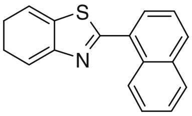
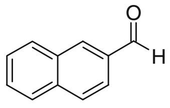
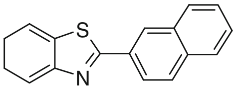
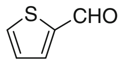
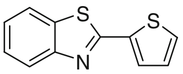
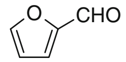
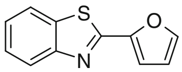
particularly interested in the use of simple starting materials such as aldehydes and *o*-aminothiophenol, which are easily available and inexpensive (Table 1). Thus, *o*-aminothiophenol was treated with 4-chlorobenzaldehyde with various catalysts at various temperatures. The results of this extensive catalyst screening and optimization of several reaction conditions at room temperature are shown in Scheme 1. It was found that both the yields and the rates of the reactions were improved when various acids were used under these conditions. Furthermore, a slight improvement in yields was observed when the reaction was carried out in the presence of a heteropoly acid, such as H$_3$PMo$_{12}$O$_{40}$ and H$_3$PW$_{12}$O$_{40}$, and metal oxides, such as WO$_3$ and La$_2$O$_3$, in water. After a survey of different reaction conditions, the reaction was best carried out by using one equivalent of *o*-aminothiophenol and one equivalent of 4-chlorobenzaldehyde in the presence of 10 mol% PTSA in water for 60 min at 70 °C. The crude product was isolated after washing with water and ethanol and afforded the corresponding benzothiazoles in 95% yield.

Encouraged by the remarkable results obtained with these conditions, to show the generality and scope of this new protocol, we turned our attention to various aldehydes, and the results (Table 1) clearly demonstrate that PTSA is an excellent catalyst in water. Thus, a variety of aromatic aldehydes, including electron-withdrawing and electron-donating groups, were tested using the new method in water in the presence of PTSA. The results are shown in Table 1. Generally, excellent yields of benzothiazoles were obtained under the optimized reaction conditions with aromatic aldehydes. The reaction worked well with a variety of aldehydes, including those bearing an electron-withdrawing group as well as heterocyclic aldehydes. Several electron-rich aromatic aldehydes led to the desired products in good yields. However, under the same reaction conditions, aliphatic aldehydes such as isobutyraldehyde and 3-phenylpropionaldehyde did not give the desired products.

In summary, we have described a simple system that is quite effective and an entirely green procedure for the

Table 1 Synthesis of benzothiazole in water



Entry	Aldehydes	Products		Yields (%)^a	Ref.
1			X= H	97	[32]
2			X= Cl	95	[32]
3			X= Br	92	[32]
4			X= F	80	[32]
5			X= CH$_3$	85	[32]
6			X= C$_2$H$_5$	82	[34]
7			X= OMe	70	[32]
8			X= NO$_2$	82	[32]
9			X= OH	74	[31]
10			X= Cl	80	[30]
11			X= Br	82	[30]
12			X= F	78	[33]
13			X= OMe	80	[33]
14			X= NO$_2$	84	[32]
15			X= Cl	74	[31]
16			X= OMe	64	[31]
17			X= Me	78	[31]
18			X= OH	60	[31]
19			X= NO$_2$	72	[31]
20				70	[33]
21				74	[33]
22				80	[33]
23				68	[33]

^{a} NMR yields

synthesis of benzothiazoles in water. Due to the mild reaction conditions, enhanced reaction rates, clean reaction profiles, operational and experimental simplicity, and with options of further transformations of the resulting benzothiazoles into synthetically interesting biologically active compounds, this synthetic methodology is ideally suited for automated applications in organic synthesis.

Experimental

General procedure for the synthesis of benzothiazoles in water

To a mixture of an aromatic aldehyde (3 mmol) and 2-aminothiophenol (3 mmol) in 2 cm^3 water, PTSA (10 mol%) was added and the reaction mixture stirred at 70 °C for 60–300 min. After the reaction was completed, pure products were isolated by filtration and washing with hot water and ethanol. In some examples the aqueous mixture was extracted with 10 cm^3 of diethyl ether or ethyl acetate and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give the desired products. The crude product was analyzed by ^1H and ^{13}C NMR. Further purification was carried out by short column chromatography on silica gel (hexane/diethyl ether) or crystallization.

Acknowledgments Financial support of this work by Chemistry and Chemical Research Center of Iran is gratefully appreciated.

References

1. Kashiyama E, Hutchinson I, Chua MS, Stinson SF, Phillips LR, Kaur G, Sausville EA, Bradshaw TD, Westwell AD, Stevens MFG (1999) J Med Chem 42:4172
2. Henriksen G, Hauser AI, Westwell AD, Yousefi BH, Schwaiger M, Drzezga A, Wester H-J (2007) J Med Chem 50:1087
3. Hutchinson I, Chua MS, Browne HL, Trapani V, Bradshaw TD, Westwell AD, Stevens MFG (2001) J Med Chem 44:1446
4. Sato G, Chimoto T, Aoki T, Hosokawa S, Sumigama S, Tsukidate K, Sagami F (1999) J Toxicol Sci 24:165
5. Phoon CW, Ng PY, Ting AE, Yeo SL, Sim MM (2001) Bioorg Med Chem Lett 11:1647
6. Ivanov SK, Yuritsyn VS (1971) Neftekhimiya 11:99
7. Ivanov SK, Yuritsyn VS (1971) Chem Abstr 74:124487m
8. Monsanto Co. Brit. Pat. 1,106,577, 1968
9. Monsanto Co. Brit. Pat. (1968) Chem Abstr 68: 96660t
10. Zhang XH, Wong OY, Gao ZQ, Lee CS, Kwong HL, Lee ST, Wu SK (2001) Mater Sci Eng B 85:182
11. Cohen VI, Pourabass SJ (1997) J Heterocycl Chem 14:1321
12. Ben-Alloum A, Bakkas S, Soufiaoui M (1997) Tetrahedron Lett 38:6395
13. Abbotto A, Bradamante S, Facchetti A, Pagani GA (2002) J Org Chem 67:5753
14. Rudrawar S, Kondaskar A, Chakraborti AK (2005) Synthesis 2521
15. Shi DF, Bradshaw TD, Wrigley S, McCall CJ, Lelieveld IF, Stevens MFG (1996) J Med Chem 39:3375
16. Xiao H-L, Chen JX, Liu M-C, Zhu DJ, Ding JC, Wu HY (2009) Chem Lett 38:170
17. Chen YX, Qian LF, Zhang W, Han B (2008) Angew Chem Int Ed 47:9330
18. Chang W-C, Hu AT, Duan JP, Rayabarapu DK, Cheng CH (2004) J Organomet Chem 689:4882
19. Rostamizadeh S, Housaini S (2005) Phosphorus Sulfur Silicon Relat Elem 180:1321
20. Metzger J (1984) In: Katritzky AR, Rees CW (eds) Comprehensive heterocyclic chemistry, vol 6. Pergamon Press, Oxford, pp 322–326
21. Thiel OR, Bernard C, King T, Dilmeghani-Seran M, Bostick T, Larsen RD, Faul MM (2008) J Org Chem 73:3508
22. Bose DS, Idrees M, Srikanth B (2007) Synthesis 819
23. Wang M, Gao M, Mock BH, Miller KD, Sledge GW, Hutchins GD, Zheng QH (2006) Bioorg Med Chem 14:8599
24. Mu XJ, Zou JP, Zeng RS, Wu JC (2005) Tetrahedron Lett 46:4345
25. Joyce LL, Evindar G, Batey RA (2004) Chem Commun 446
26. Evindar G, Batey RA (2006) J Org Chem 71:1802
27. Inamoto K, Hasegawa C, Hiroya K, Doi T (2008) Org Lett 10:5147
28. Das B, Holla H, Venkateswarlu K, Majhi A (2005) Tetrahedron Lett 46:8895
29. Ranu BC, Mandal T (2006) Tetrahedron Lett 47:6911
30. Firouzabadi H, Iranpoor N, Khoshnood A (2008) Catal Commun 9:529
31. Azizi N, Aryanasab F, Torkiyan L, Ziyaei A, Saidi MR (2006) J Org Chem 71:3634
32. Azizi N, Torkiyan L, Saidi MR (2006) Org Lett 6:2079
33. Kodomari M, Tamaru Y, Aoyama T (2004) Synth Commun 34:3029
34. Bahrami K, Khodaei MM, Naali F (2008) J Org Chem 73:6835
35. Chakraborti AK, Rudrawar S, Jadhav KB, Kaur G, Chankeshwara SV (2007) Green Chem 9:1335
36. Itoh T, Nagata K, Miyazaki M, Ohsawa A (2000) Heterocycles 52:1037
37. Mukhopadhyay C, Datta A (2009) J Heterocycl Chem 46:91