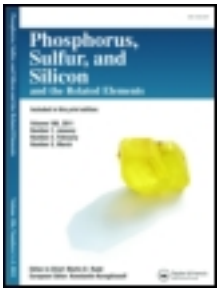


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

A Simple, Microwave-Assisted, and Solvent-Free Synthesis of 2-Arylbenzothiazoles by Acetic Acid-Promoted Condensation of Aldehydes with 2-Aminothiophenol in Air

Davood Azarifar [a], Behrooz Maleki [a] & Mehrnaz Setayeshnazar [a]

[a] Faculty of Chemistry, Bu-Ali Sina University, Hamadan, Iran

Version of record first published: 22 Jul 2009

To cite this article: Davood Azarifar, Behrooz Maleki & Mehrnaz Setayeshnazar (2009): A Simple, Microwave-Assisted, and Solvent-Free Synthesis of 2-Arylbenzothiazoles by Acetic Acid-Promoted Condensation of Aldehydes with 2-Aminothiophenol in Air, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:8, 2097-2102

To link to this article: http://dx.doi.org/10.1080/10426500802423933

Phosphorus, Sulfur, and Silicon, 184:2097–2102, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802423933

Taylor & Francis
Taylor & Francis Group

A Simple, Microwave-Assisted, and Solvent-Free Synthesis of 2-Arylbenzothiazoles by Acetic Acid–Promoted Condensation of Aldehydes with 2-Aminothiophenol in Air

Davood Azarifar, Behrooz Maleki, and Mehrnaz Setayeshnazar
Faculty of Chemistry, Bu-Ali Sina University, Hamadan, Iran

An efficient and simple procedure has been developed for the synthesis of various 2-arylbenzothiazoles by acetic acid–promoted condensation of 2-aminothiophenol with aromatic aldehydes under microwave irradiation and solvent-free conditions in high yields.

Keywords Aldehydes; 2-aminothiophenol; 2-arylbenzothiazoles; microwave irradiation

INTRODUCTION

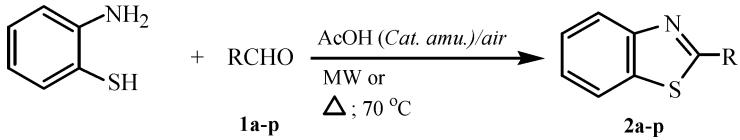
Among various benzazoles, 2-substituted benzothiazoles are an important class of biologically active compounds.[1–5] The 2-arylbenzothiazole nucleus exists as the core unit in a myriad of pharmaceutical agents, including antitumor drugs.[5,6] In addition, 2-arylbenzothiazoles have been used as fluorescent whiting agents[7] and photochromic compounds.[8] A number of such compounds play a prominent therapeutic role, for example, in the prevention of solid organ transplant rejection,[9] epilepsy,[10] amyotrophic lateral sclerosis,[11] analgesia,[12] and tuberculosis.[13] Benzothiazoles are also useful synthetic intermediates that are prone to various transformations and transition-metal–catalyzed cross-coupling reactions, such as Heck,[14] Negishi,[15] Stille,[16] and Sonogashira[17] couplings. Thus, synthesis of these heterocyclic systems is of much interest, and considerable research has been directed towards these compounds.[18] Two important methods reported

Received 18 March 2008; accepted 21 August 2008.
We wish to thank the Research Council of Bu-Ali Sina University, Hamedan, Iran, for financial support to carry out this research.
Address correspondence to Davood Azarifar, Faculty of Chemistry, Bu-Ali Sina University, Hamadan 65178, Iran. E-mail: azarifar@basu.ac.ir

for the synthesis of benzothiazoles are (i) condensation of aldehydes with 2-aminothiophenol[19] using DMSO/120°C,[19a] ionic liquid 1-phenyl-3-methylimidazoliumbromide ([pmIm]Br),[19b] scandium triflate,[19c] silica gel,[19d] MnO_2/SiO_2,[19e] molecular iodine,[19f] molecular oxygen promoted by activated carbon,[19g] *p*–TsOH,[19h] SiO_2/graphite,[19i] electrochemical synthesis in methanol containing sodium acetate as supporting electrolyte,[19j] water/110°C,[19k] carboxylic acids,[20] acid chlorides,[21] or esters[22]; and (ii) cyclization of thiobenzanilides.[23] Several other miscellaneous methods have been reported including microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes,[24] palladium-catalyzed Suzuki biaryl coupling of 2-bromobenzothiazoles with arylboronic acids,[25] coupling of benzothiazoles with arylbromides,[26] and reaction of thiophenol with aromatic nitriles.[27] However, many of these procedures are subject to certain disadvantages, such as the use of toxic and/or costly catalysts[18d,18f,19d]; hazardous and carcinogenic organic solvents such as nitrobenzene,[18c]acetonitrile,[26] and dioxane[18f]; and multistep process for reactions.[20a,20d] To eliminate the harmful effects of these organic solvents often used in large quantities for organic transformations, serious steps have been recently taken toward alternative green synthetic procedures.[1,2]

RESULTS AND DISCUSSION

To make a contribution towards the elimination of the above-mentioned drawbacks, we were prompted to report here a very simple, benign, and environmentally friendly procedure for the synthesis of 2-arylsubstituted benzothiazoles. In this report, we have employed a catalytic amount of glacial acetic acid as a very mild, inexpensive, and nontoxic catalyst when compared with the previously reported strong and non-green acids, such as *p*-TsOH,[19h] to effect the synthesis of a variety of 2-arylbenzothiazoles (**2a–p**) by direct and solvent-free condensation of arylaldehydes (**1a–p**) with 2-aminothiophenol under both microwave irradiation and conventional thermal heating in high yields (72–96%; Table I, Scheme 1). To obtain the best reaction temperature



SCHEME 1

TABLE I Synthesis of 2-Arylbenzothiazoles (2a–p) by Acetic Acid–Promoted Condensation of Aldehydes (1a–p) with 2-Aminothiophenol Under Both Microwave Irradiation and Conventional Heating Conditions[a]

				Mp (°C)	
Product[b]	R	Time (min)	Yield (%)[c]	Found	Reported
2a	4-$MeOC_6H_4$	15 (5)	90 (90)	119–121	120–121[19d]
2b	2-ClC_6H_4	20 (5)	70 (80)	81–83	84–85[19d]
2c	3-$O_2NC_6H_4$	15 (4)	86 (92)	182–184	181–182[19f]
2d	2-HOC_6H_4	25 (5)	75 (80)	122–124	125–126[19d]
2e	C_6H_5	15 (4)	90 (84)	110–112	112–113[19d]
2f	2-Furyl	20 (5)	80 (84)	100–103	103–104[19d]
2g	4-ClC_6H_4	20 (4)	84 (88)	116–117	115–117[19d]
2h	2-MeO C_6H_4	20 (6)	78 (80)	99–102	101–103[19d]
2i	4-NCC_6H_4	15 (3)	96 (92)	165–166	162–164[19i]
2j	4-MeC_6H_4	30 (8)	78 (72)	85–87	84–86[19d]
2k	4-HOC_6H_4	20 (5)	70 (70)	227–228	225–226[19d]
2l	2-$O_2NC_6H_4$	20 (4)	76 (79)	133–135	135–136[19d]
2m	2-MeC_6H_4	35 (10)	70 (70)	52–54	53–54[19d]
2n	4-BrC_6H_4	25 (4)	80 (74)	129–131	130–131[19i]
2o	4-FC_6H_4	20 (7)	74 (64)	98–100	101–103[19f]
2p	3-BrC_6H_4	15 (4)	80 (72)	84–86	84–86[19i]

[a]The reaction times and yields under microwave irradaiation condition are shown in the parenthesis.

[b]Products were characterized by their physical properties, comparison with authentic samples, and by their spectral (^{1}H-NMR, ^{13}C-NMR, IR) analysis.

[c]Isolated yields.

for thermal reactions or the best power level for microwave-irradiated reactions, optimization was carried out, for example, for the reaction of 4-methoxybenzaldehyde with 2-aminothiophenol at various temperatures or different power levels. It was noticed that 70°C was the best temperature for thermal reactions (15 min, 90%), and also the most convenient power level found to produce the highest yield in shortest time was 60%. It is noticed that the application of the microwave (MW) irradiation technique has a profound effect on the acceleration of these reactions, providing short reaction times without any considerable change in the yields of the products. The rate-enhancing role of microwave irradiation is now believed to be presumably due to the selective absorption of MW energy by polar molecules such as acetic acid or polar intermediates formed in the course of the reactions.[28] It is important to mention that when these reactions are carried out under

conventional heating conditions (70°C), much longer periods of time (15–35 min) are required.

When these reactions are run at room temperature, only a trace amount of benzothiazoles are formed, and the reactions are mainly ended with the formation of imines, as reported by others.[19b,19e] This implies that the mechanism of the reaction most likely involves the prior formation of an intermediate imine that undergoes cyclization with the –SH group under reflux conditions or microwave irradiation followed by dehydrative oxidation in air to yield benzothiazole.

In conclusion, the present work offers a simple procedure promoted by inexpensive and nontoxic glacial acetic acid as an efficient methodology for the synthesis of 2-substituted benzothiazoles through both thermal heating and microwave-assisted condensation of aromatic aldehydes with 2-aminothiophenol. The significant advantages of this procedure are (a) very fast reaction (3–10 min), (b) mild reaction conditions compatible with a variety of sensitive groups, (c) high yields, (d) low cost of AcOH as the catalyst, and (e) green aspects avoiding hazardous solvents, toxic catalysts, and waste.

EXPERIMENTAL

General Procedure for the Synthesis of 2-Arylbenzothiozoles

Microwave Irradiation

2-Aminothiophenol (1 mmol), aldehydes **1a–p** (1 mmol), and a catalytic amount of acetic acid (2 mmol) were thoroughly mixed in an open glass tube. The tube was placed in an alumina bath in a domestic microwave oven (model: Black & Decker, MX30PG 1000 watt) and irradiated for an appropriate time (3–10 min) (Table I) at power level of 60% with intermittent cooling after each 30 sec of irradiation. The progress of the reactions was monitored by TLC (*n*−hexane:ethyl acetate, 2:8), and the products were recrystallized from EtOH (96%) following their extraction from the reaction mixture (Table I).

Thermal Heating Condition

2-Aminothiophenol (1 mmol), aldehydes **1a–p** (1 mmol), and a catalytic amount of acetic acid (2 mmol) were thoroughly mixed in an open glass tube. The tube was placed in a water bath at 70°C for 15–35 min (Table I). After complete conversion of the substrates (as monitored by TLC using *n*-hexane:ethyl acetate, 2:8), the products **2a–p** were purified by recrystallization from EtOH (96%) following their extraction from the reaction mixture (Table I).

REFERENCES

[1] (a) J. S. Wikes, *Green Chem*., **4,** 73 (2002); (b) R. Sheldon, *Chem. Commun.*, 2399 (2001); (c) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, **39,** 3772 (2000); (d) T. Welton, *Chem. Rev.*, **99,** 2071, (1999).

[2] (a) H. M. Zerth, N. M. Leonard, and R. S. Mohan, *Org. Lett*., **5,** 55 (2003); (b) C. Su, Z.-C. Chen, and Q.-G. Zheng, *Synthesis*, 555 (2003); (c) T. Sima, S. Guo, F. Shi, and Y. Deng, *Tetrahedron Lett*., **43,** 8145 (2002); (d) C. E. Song, W. H. Shim, E. J. Roh, S.-G. Lee, and J. H. Choi, *Chem. Commun*., 1122 (2001); (e) G. Bar, A. F. Parsons, and C. B. Thomas, *Chem. Commun*., 1350 (2001); (f) J. N. Rosa, C. A. M. Afonso, and A. G. Santos, *Tetrahedron*, **57,** 4189 (2001); (g) G. L. Rebeiro and B. M. Khadilkar, *Synthesis*, 370 (2001).

[3] (a) B. C. Ranu and A. Hajra, *Tetrahedron*, **57,** 4767 (2001); (b) B. C. Ranu, A. Hajra, and S. S. Dey, *Org. Process Res. Dev*., **6,** 817 (2002); (c) B. C. Ranu and A. Hajra, *Green Chem*., **4,** 551 (2002); (d) B. C. Ranu, S. S. Dey, and A. Hajra, *Green Chem*., **5,** 44 (2003).

[4] (a) B. C. Ranu, A. Das, and S. Samanta, *J. Chem. Soc., Perkin Trans.* **1,** 1520 (2002); (b) B. C. Ranu, S. S. Dey, and A. Hajra, *Tetrahedron*, **59,** 2417 (2003); (c) B. C. Ranu and S. S. Dey, *Tetrahedron Lett*., **44,** 2865 (2003).

[5] L. W. Wattenberg, M. A. Page, and J. L. Leong, *Cancer Res*., **28,** 2539 (1968).

[6] (a) I. Hutchinson, M. S. Chua, H. L. Browne, and V. Trapani, *J. Med. Chem*., **44,** 1446 (2001); (b) T. D. Bradshaw and A. D. Westwell, *Curr. Med. Chem*., **11,** 1009 (2004).

[7] A. Reiser, L. J. Leyshon, D. Saunders, M. V. Mijovic, A. Bright, and J. Bogie, *J. Am. Chem. Soc.*, **94,** 2414 (1972).

[8] A. Heynderickx, R. Guglielmetti, R. Dubest, J. Aubard, and A. Samat, *Synthesis*, 1112 (2003).

[9] P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M. A. Coleno, A. Doble, G. Doerflinger, C. D. Huu, M. H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Ladurin, J. Le Blevec, M. Meunier, J. M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J. M. Stutzmann, and S. Mignani, *J. Med. Chem.*, **42,** 2828 (1999).

[10] (a) S. J. Hays, M. J. Rice, D. F. Ortwine, G. Johnson, R. D. Schwarz, D. K. Boyd, L. F. Copeland, M. G. Vartanian, and P. A. Boxer, *J. Pharm. Sci.*, **83,** 1425 (1994); (b) Y. He, A. Benz, T. Fu, M. Wang, D. F. Covey, C. F. Zormuski, and S. Mennerick, *Neuropharmacology*, **42,** 199 (2002).

[11] G. Bensimon, L. Lacomblez, and V. Meininger, *New Engl. J. Med.*, **330,** 585 (1994).

[12] G. Foscolos, G. Tsatsas, A. Champagnace, and M. Pommier, *Ann. Pharm. Fr*., **35,** 295 (1977).

[13] V. G. Srirke, A. S. Bobade, R. P. Bhamaria, B. G. Khadse, and S. R. Sengupta, *Indian Drugs*, **27,** 350 (1990).

[14] Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Konoh, R. Honma, Y. Akita, and A. Ohta, *Heterocycles*, **33,** 257 (1992).

[15] (a) M. Kosugi, M. Koshiba, A. Atoh, H. Sano, and T. Migita, *Bull. Chem. Soc. Jpn*., **59,** 677 (1986); (b) K. C. Molloy, P. C. Waterfield, and M. F. Mahon, *J. Organomet. Chem*., **365,** 61 (1989); (c) R. R. Hark, D. B. Hauze, O. Petrovskaia, M. M. Joullié, R. Jaouhari, and P. McComisky, *Tetrahedron*, **35,** 7719 (1994); (d) A. G. Birchler, F. Liu, and L. S. Liebeskind, *J. Org. Chem.*, **59,** 7737 (1994).

[16] (a) J. Schlegel and G. Maas, *Synthesis*, 100 (1999); (b) S. A. Nye and K. T. Potts, *Synthesis*, 375 (1988).
[17] (a) J.-P. Gillet, R. Sauvétre, and J.-F.Normant, *Tetrahedron Lett*., **26,** 3999 (1985); (b) F.-T. Luo and R.-T. Wang, *Heterocycles*, **31,** 1543 (1990).
[18] (a) A. Roe and W. P. Tucker, *J. Heterocycl. Chem*., **2,** 148 (1965); (b) M. J. Spitulnik, *Synthesis*, 730 (1976); (c) A. Ben-Alloum, S. Bakkas and M. Soufiaoui, *Tetrahedron Lett*., **38,** 6395 (1997); (d) K. Takagi, *Chem. Lett*., **15,** 265 (1986); (e) K. Bougrin, A. Loupy and M. Soufiaoui, *Tetrahedron*, **54,** 8055 (1998); (f) C. Benedi, F. Bravo, P. Uriz, E. Fernandez, C. Claver, and S. Castillon, *Tetrahedron Lett*., **44,** 6073 (2003); (g) S.-J. Choi, H. J. Park, S. K. Lee, S. W. Kim, G. Han, and H.-Y. P. Choo, *Biorg. Med. Chem.*, **14,** 1229 (2006).
[19] (a) R. M. Batista, S. P. G. Costa, and M. M. M. Raposo, *Tetrahedron Lett.*,**45,** 2825 (2004);(b) B. C. Ranu, R. Jana, and S. Dey, *Chem. Lett.*, **33,** 274 (2004); (c) T. Itoh, K. Nagata, H. Ishikawa, and A. Ohsawa, *Heterocycles*, **62,** 197 (2004); (d) M. Kodomari, Y. Tamaru, and T. Aoyama, *Synth. Commun.*, **34,** 3029 (2004); (e) K. Bougrin, A. Loupy, and M. Soufiaoui, *Tetrahedron*, **54,** 8055 (1998); (f) Y. Li, Y. L. Wang, and J. Y. Wang, *Chem. Lett.*, **35,** 460 (2006); (g) M. Hayashi and Y. Kawashita, *Lett. Org. Chem.*, **3,** 571 (2006); (h) R. Gupta, M. Gupta, and A. Paul, S*ynth. Commun*., **32,** 3541 (2002); (i) S. Rostamizadeh and S. A. G. Housaini, *Phosphorus, Sulfur, and Silicon*, **180,** 1321 (2005); (j) M. Okimoto, T. Yoshida, M. Hoshi, K. Hottori, M. Komata, K. Tomozawa, and T. Chiba, *Heterocycles*, **75,** 35 (2008); (k) A. K. Chakraborti, S. Rudrawar, K. B. Jadhav, G. Kuar, and S. V. Chankeshwara, *Greem Chem.,* **9,** 1335 (2007).
[20] (a) S. Mourtas, D. Gatos, and K. Barlos, *Tetrahedron Lett.*, **42,** 2201 (2001); (b) Y. Njoya, A. Gellids, M. Crozet, and P. Vanelle, *Sulfur Lett.*, **26,** 67 (2003); (c) A. K. Chakraborti, C. Selvam, G. Kaur, and S. Bhagat, *Synlett*, 851 (2004); (d) I. Yildiz-Oren, I. Yalcin, E. Aki-Sener, and N. Ucarturk, *Eur. J. Med. Chem.*, **39,** 291 (2004); (e) C. Chen and Y. J. Chen, *Tetrahedron Lett*., **45,** 113 (2004); (f) J. A. Seijas, M. P. Vazquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo, and L. Romar-Lopez, *Synlett*, 313 (2007).
[21] (a) I. R. Laskar and T. M. Chen, *Chem. Mater.*, **16,** 117 (2004); (b) R. N. Nadaf, S. A. Siddiqui, T. Daniel, R. J. Lahoti, and K. V. Srinivasan, *J. Mol. Catal. A: Chem*., **214,** 155 (2004).
[22] (a) H. Matsushita, S. H. Lee, M. Joung, B. Clapham, and K. D. Janda,*Tetrahedron Lett*., **45,** 313 (2004); (b) A. K. Chakraborti, C. Selvam, G. Kaur, and S. Bhagat, *Synlett*, 851 (2004).
[23] (a) L. L. Loyce, G. Evindar, and R. A. Batey, *Chem. Commun.,* 446 (2004); (b) X. J. Mu, J. P. Zou, R. S. Zeng, and J. C. Wu, *Tetrahedron Lett*., **46,** 4345 (2005); (c) F. M. Moghaddam and H. Z. Boeini, *Synlett*, 1612 (2005); (d) D. S. Bose and M. Idrees, *J. Org. Chem.*, **71,** 8261 (2006).
[24] S. Paul, M. Gupta, and R. Gupta, *Synth. Commun.*, **32,** 3541 (2002).
[25] V. J. Majo, J. Prabhakaram, J. J. Mann, and J. S. D. Kumar, *Tetrahedron Lett*.,**44,** 8535 (2003).
[26] D. Alagille, R. M. Baldwin, and G. D. Tamagnan, *Tetrahedron Lett*., **46,** 1349 (2005).
[27] R. H. Tale, *Org. Lett*., **4,** 1641 (2002).
[28] R. S. Varma, *Green Chem*., **1,** 43 (1999).