Microwave-assisted synthesis of benzothiazole derivatives using glycerol as green solvent

Xia-Zhong Zhang[a], Wen-Jun Zhou*[a], Min Yang[a], Jin-Xian Wang[b], and Lin Bai[c]

[a]*Key Laboratory of Fruit Waste Treatment and Resource Recycling of the Sichuan Provincial College & College of Chemistry and Chemical Engineering, Neijiang Normal University, Sichuan 641112, P. R. China*

[b]*Institute of Chemistry and Chemical Engineering, Northwest Normal University, 967 Anning Road (E), Lanzhou 730070, P. R. China.*

[c]*Institute of Green Chemistry Experiment and Teaching, Lanzhou City University, Lanzhou, P. R. China*

A rapid method has been developed for the synthesis of benzothiazoles *via* the condensation of 2-aminothiophenol with aldehydes under CEM-focused microwave irradiation conditions. The reaction used glycerol as a green solvent without any catalyst, rendering this methodology valuable from both economic and environmental points of view.

Keywords: microwave irradiation, glycerol, benzothiazole, green chemistry

Five-membered heterocyclic rings, such as benzothiazole derivatives, are present in natural products, in synthetic agrochemical and pharmaceutical compounds and in organic synthetic intermediates. They have been widely used in therapeutic areas including anti-tumour agents, Gram-positive selective antibacterials, HIV reverse transcriptase inhibitors, and orexin-1 receptor antagonists.[1–3] Classical methods for the synthesis of benzothiazoles involve the condensation of *o*-aminothiophenols with substituted nitriles, aldehydes, carboxylic acids, acyl chlorides, or esters using strong oxidants as catalysts, such as animal bone meal (ABM) and Lewis acids doped ABMs,[4] $FeCl_3{\cdot}6H_2O$,[5] mesoporous mixed metal oxide nanocrystals,[6] Lawesson's reagent,[7] $H_2O_2/Fe(NO_3)_3$,[8] $Na_2S_2O_5$,[9] and other methods.[10–13] Although successful, many of these processes suffer from drawbacks such as drastic reaction conditions, low yields, tedious work-up procedures or using toxic metal salts as catalysts. The main disadvantages are the use of toxic organic solvents and catalysts that are destroyed in the work-up and cannot be recovered or reused. Hence, the search for the better method is still being actively pursued.

Recently, due to environmental and safety considerations, reduction of costs and the simplicity of the process, attention has been drawn to reactions using green solvents.[14–16] Glycerol is usually produced as a major by-product of the biodiesel industry. Indeed, glycerol is abundant, biodegradable, cheap, non-toxic, non-flammable and has a very high boiling point.[17] It is highly polar and immiscible with hydrocarbons and ethers. It is suitable for biphasic catalysis and for product isolation by liquid–liquid extraction. All of these properties indicated that glycerol meets the requirements for consideration as a green solvent.[18,19]

Microwave-assisted organic synthesis has had a profound impact on the way that chemists approach organic synthesis.[20–22] This enabling technology has now been generally accepted in industrial research laboratories and is no longer an academic curiosity. Several organic transformations have been successfully realised employing this technique. In contrast to conventional heating, microwave-assisted organic synthesis has proven to dramatically shorten reaction times, to deliver cleaner reaction mixtures and hence increases overall yields. In many instances, CEM focused microwave heating under sealed vessel conditions has had a dramatic influence on reducing reaction times, increasing product yields, improving selectivity, using less solvent, and enhancing product purities by reducing unwanted side reactions compared to conventional synthetic methods.[23–25]

To the best of our knowledge, the synthesis of benzothiazole derivatives in glycerol under microwave radiation conditions has not so far been reported. In our search for developing efficient protocols for green synthesis,[26,27] we describe here the use of glycerol as a green solvent for the synthesis of benzothiazole derivatives in good yields *via* the condensation of *o*-aminothiophenols with substituted aldehydes under microwave radiation conditions.

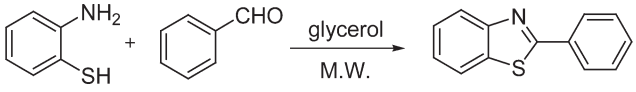
* Correspondent. E-mail: zhouwj@njtc.edu.cn

Results and discussion

As a starting point for the development of the microwave-promoted synthesis of benzothiazole derivatives, we initially studied the condensation of 2-aminothiophenol and benzaldehyde using glycerol as solvent in a CEM focused microwave. We examined the effects of temperature and power on the yields of the reaction.

It can be seen from Table 1 that a poor yield of the desired product was obtained when the temperature was 100 °C at low power (Table 1, entries 1 and 2). Fortunately, 180 W is the appropriate power for the reaction and a 92% yield of the corresponding 2-phenylbenzothiazole was obtained (Table 1, entries 1–5). Furthermore, lowering or raising the reaction temperature had no positive effect, and 100 °C was the best temperature for the condensation (Table 1, entries 4–7). Comparative reactions were also carried out with conventional heating condition and an improved reflux microwave oven which cannot control the temperature.[28] The results were not positive (Table 1, entries 8–10). In contrast to the improved reflux microwave oven, CEM Focused Microwave can increase

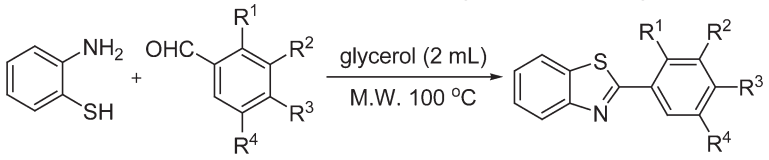
Table 1 Optimised conditions *via* the condensation of 2-aminothiophenol and benzaldehyde[a]

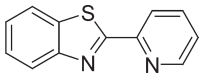
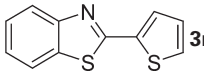
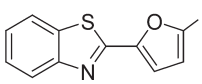


Entry	Power/W	Temp/°C	Time/min	Yield/%[b]
1	80	100	8	26
2	100	100	8	42
3	120	100	4	67
4	180	100	4	92
5	200	100	4	89
6	180	110	4	90
7	180	90	4	82
8	180	–	4	Trace[c]
9	600	–	4	64[c]
10	–	100	8 h	56[d]

[a]Reaction conditions: 2-aminothiophenol (1.0 mmol), benzaldehyde (1.0 mmol), glycerol (2 mL), irradiating under CEM Focused Microwave. [b]Isolated yield. [c]Reactions were performed with an improved reflux microwave oven. [d]Conventional heating was used and the reaction was stirred in an oil bath at 100 °C.

Table 2 Synthesis of benzothiazole *via* the condensation of 2-aminothiophenol and aldehydes[a]



Entry	Products	Time/min	Yield/%[b]	M.p./°C	
				Found	Lit.
1	$R^1 = R^2 = R^3 = R^4 = H$ for **3a**	4	92	113–114	110–111[29]
2	$R^1 = R^3 = Cl$, $R^2 = R^4 = H$ for **3b**	4	96	123–124	121–122[30]
3	$R^1 = Cl$, $R^2 = R^3 = R^4 = H$ for **3c**	4	94	95–96	97–98[31]
4	$R^2 = Cl$, $R^1 = R^3 = R^4 = H$ for **3d**	4	92	96–97	97–98[31]
5	$R^3 = Cl$, $R^1 = R^2 = R^4 = H$ for **3e**	4	96	188–189	187–189[30]
6	R^3= Br, $R^1 = R^2 = R^4 = H$ for **3f**	5	94	147–148	144–145[29]
7	$R^3 = NO_2$, $R^1 = R^2 = R^4 = H$ for **3g**	5	91	246–247	244–245[30]
8	$R^1 = OH$, $R^4 = Br$, $R^2 = R^3 = H$ for **3h**	8	86	167–168	165–166[32]
9	$R^3 = OH$, $R^1 = R^2 = R^4 = H$ for **3i**	8	90	226–227	228–229[33]
10	$R^3 = CH_3$, $R^1 = R^2 = R^4 = H$ for **3j**	4	94	85–86	85–86[29]
11	$R^3 = OCH_3$, $R^1 = R^2 = R^4 = H$ for **3k**	4	95	121–122	120–121[28]
12	 **3l**	8	82	135–136	137–138[29]
13	 **3m**	8	80	100–101	100–101[34]
14	 **3n**	8	78	131–132	125–126[35]

[a] Reaction conditions: 2-aminothiphenol (1.0 mmol), aldehyde (1.0 mmol) and glycerol (2 mL), P = 180 W at 100 °C for the appropriate time. [b] Isolated yields.

the yield because it can efficiently stir the substrates and accurately control the temperature and power.

In order to study the generality of this procedure, the applicability of this green system was then examined for the reactions of a series of aromatic aldehydes with 2-aminothiophenol under the optimized reaction conditions. As shown in Table 2, all of the substrates afforded the corresponding benzothiazoles with good to excellent yields. The reaction of a variety of aromatic aldehydes bearing electron-withdrawing substituents, such as chloro, bromo and nitro groups, afforded high yields of the products (Table 2, entries 2–7). In addition, a hydroxy group can be tolerated under these condition, and good yields of the desired products were obtained (Table 2, entries 8 and 9). Further study indicated that reaction of heterocyclic aldehydes also provided the 2-heterocyclic-substituted benzothiazoles in good yields (Table 2, entries 12–14).

Conclusions

In summary, glycerol was found to be an effective and environmentally benign medium for the synthesis of 2-substituted benzothiazoles under CEM-focused microwave-irradiation conditions. Excellent yields, short reaction times, mild reaction conditions and easy work-up procedures make this a green, facile and superior method for the synthesis of benzothiazole derivatives.

Experimental

The melting points were determined on a WRS-1 A digital melting point apparatus. IR spectra were measured for KBr discs using an Alpha Centauri FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Mercury plus 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ with TMS as an internal standard using a Mercury plus 400 MHz spectrometer. EI-MS were measured on an HP5988A mass spectrometer.

Microwave reactions were conducted using a CEM Focused Microwave Synthesis System (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. The pressure control system uses a load cell for an indirect measurement of the reaction vessel contents. The load cell is connected to a 10-mL vessel and senses changes in the external deflection of the septa on top of the sealed pressure vessel. The temperature control system uses a non-contact, IR sensor to measure temperature. It is located below the microwave cavity floor and measures the temperature on the bottom of the vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Synthesis of benzothiazole derivatives; general procedure

A mixture of 2-aminothiophenol (1.0 mmol) and the aldehydes (1.0 mmol) and a magnetic stirrer were placed in a 10 mL glass tube. Then the vessel was sealed with a septum and placed into the microwave cavity. With the irradiation of 180W, the temperature was ramped from room temperature to 100 °C where the mixture was vigorously stirred. After completion of the reaction, the mixture was cooled, quenched with water (10 mL) and extracted with ethyl acetate (2× 10 mL). The organic layer was dried over anhydrous Mg_2SO_4 and evaporated under reduced pressure to give the crude product. The pure product was obtained by column chromatography on silica gel using petroleum ether and acetone (10:1 v:v) as the eluent.

2-Phenylbenzothiazole (**3a**): M.p. 113–114 °C, (lit.[16] 110–111 °C). IR (υ/cm^{-1}): 3240, 2965, 1655, 1526, 1260. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.07 (m, 3H), 7.90 (d, J = 7.6 Hz, 1H), 7.50–7.48 (m, 4H), 7.41–7.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 154.1, 135.0, 133.6, 130.9, 129.0, 127.5, 126.3, 125.1, 123.2, 121.6. MS *m*/*z* (%): 211 (M^+, 100), 134 (81).

The work was supported by the project of Sichuan Province Education Office (No. 12ZB074).

Received 17 April 2012; accepted 23 May 2012
Paper 1201269 doi: 10.3184/174751912X13400085970187
Published online: 8 August 2012

References

1 E. Oksuzoglu, O. Temiz-Arpaci, B. Tekiner-Gulbas, H. Eroglu, G. Sen, S. Alper, I. Yildiz, N. Diril, E. Aki-Sener and I. Yalcin, *Med. Chem. Res*., 2008, **16**, 1.
2 M. Hranjec, M. Kralj, I. Piantanida, M. Sedic, L. Suman, K. Pavelic and G. Karminski-Zamola, *J. Med. Chem*., 2007, **50**, 5696.
3 J.A. Grobler, G. Dornadula, M.R. Rice, A.L. Simcoe, D.J. Hazuda and M.D. Miller, *J. Biol. Chem*., 2007, **282**, 8005.
4 Y. Riadi, R. Mamouni, R. Azzalou, M. El Haddad, S. Routier, G. Guillaumet and S. Lazar, *Tetrahedron Lett.*, 2011, **52**, 3492.
5 X. Fan, Y. He, Y. Wang, Z. Xue, X. Zhang and J. Wang, *Tetrahedron Lett.*, 2011, **52**, 899.
6 P. Bandyopadhyay, M. Sathe, G.K. Prasad, P. Sharma and M.P. Kaushik, *J. Mol. Catal. A: Chem.* 2011, **341**, 77.
7 J.A. Seijas, M.P. Vázquez-Tato, M.R. Carballido-Reboredo, J. Crecente-Campo and L. Romar-López, *Synlett*, 2007, 313.
8 K. Bahrami, M.M. Khodaei and F. Naali, *Synlett*, 2009, 569.
9 K.M. Khan, F. Rahim, S.A. Halim, M. Taha, M. Khan, S. Perveen, M.A. Mesaik and M.I. Choudhary, *Bioorg. Med. Chem*., 2011, **19**, 4286.
10 V.I. Cohen and S. Pourabass, *J. Heterocycl. Chem.*, 1977, **14**, 1321.
11 D.E. Boger, *J. Org. Chem.*, 1978, **43**, 2296.
13 A. Abbotto, S. Bradnmante, A. Facchetti and G.A. Pagani, *J. Org. Chem.*, 2002, **67**, 5753.
14 N.R. Candeias, L.C. Branco, P.M.P. Gois, C.A.M. Afonso and A.F. Trindade, *Chem. Rev*., 2009, **109**, 2703.
15 P.J. Walsh, H. Li and C.A. De Parrodi, *Chem. Rev*., 2007, **107**, 2503.
16 M.A.P. Martins, C.P. Frizzo, D.N. Moreira, L. Buriol and P. Machado, *Chem. Rev*., 2009, **109**, 4140.
17 M. Pagliaro, and M. Rossi, *The future of glycerol: new usages for a versatile raw material*, RSC Publishing, Cambridge, 2008.
18 Y. Gu and F. Jérôme, *Green Chem*., 2010, **12**, 1127.
19 A. Díaz-Álvarez, J. Feancos, B. Lastra-Barreira, P. Crochet and V. Cadierno, *Adv. Synth. Catal*., 2011, **47**, 6208.
20 P. Appukkuttan, V.P. Mehta and P. Van der Eycken, *Chem. Soc. Rev*., 2010, **39**, 1467.
21 V. Polshettiwar and R.S. Varma, *Green Chem*., 2010, **12**, 743.
22 C.O Kappe and E. Van der Eycken, *Chem. Soc. Rev*., 2010, **39**, 1280.
23 L. Bai and J.-X. Wang, *Adv. Synth. Catal*., 2008, **350**, 315.
24 C. Henry, A. Haupt and S.C. Turner, *J. Org. Chem*., 2009, **74**, 1932.
25 S. Caddick and R. Fitzmaurice, *Tetrahedron*, 2009, **65**, 3325.
26 W.-J. Zhou, K.-H. Wang and J.-X. Wang, *J. Org. Chem.*, 2009, **74**, 5599.
27 W. Shi and J.-X. Wang, *J. Chem. Res.*, 2008, 270.
28 J.-X. Wang, Y. Xi, X. Wu, Y. Hu and Z. Du, *Synth. Commun*., 1998, **28**, 4619.
29 G. Evindar and R.A. Batey, *J. Org. Chem.*, 2006, **71**, 1802.
30 E. Belgodere, R. Bossio, S. Chimichi, V. Parrini and R. Pepino, *Dyes Pigments*, 1983, **1**, 59.
31 A. Brembilla, D. Roizard and P. Lochon,*Synth. Commun.*,1990, **21**, 3379.
32 K. Anthony, R.G. Brown, J.D. Hepworth, K.W. Hodgson, B. May and M.A. West, *J. Chem. Soc. Perkin Trans.*, 1984, 2111.
33 M.T. Bogert and H.B. Corbitt, *J. Am. Chem. Soc*., 1926, **48**, 783.
34 B. Maleki, *Collect. Czech. Chem. Commun.*, 2011, **76**, 27.
35 E.B. Melnikova, M.M. Elchaninov, A.A. Milov and B.S. Lukyanov, *Chem. Heterocylic. Comp.*, 2008, **44**, 1070.