Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 5953–5955
Tetrahedron Letters

Aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β-cyclodextrin ☆

M. Narender, M. Somi Reddy, R. Sridhar, Y. V. D. Nageswar and K. Rama Rao*

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 13 May 2005; revised 17 June 2005; accepted 21 June 2005
Available online 14 July 2005

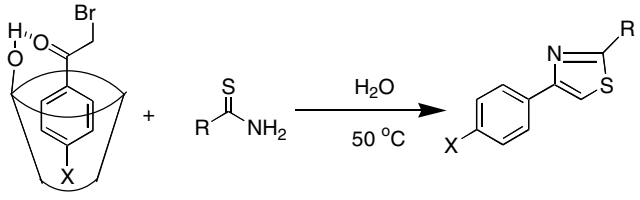
Abstract—A simple and practical procedure for the aqueous phase preparation of thiazoles and aminothiazoles has been developed from phenacyl bromides and thioamide/thiourea in the presence of β-cyclodextrin.

The thiazole ring system is a useful structural motif found in numerous biologically active molecules.[1] This structure has found applications in drug development for the treatment of allergies,[2] hypertension,[3] schizophrenia,[4] inflammation,[5] bacterial[6] and HIV[7] infections. Aminothiazoles are known to be ligands of estrogen receptors[8] as well as a novel class of adenosine receptor antagonists[9] whereas other analogues are used as fungicides, inhibiting in vivo growth of *Xanthomonas* and as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[10] Heterocycle-bearing substrates are particularly desirable structures for screening and are prevalent in drugs that have reached the market place.[11] Recently, organic reactions in aqueous media have acquired interest in organic synthesis as it overcomes the harmful effects of organic solvents and is also environmentally benign. These aqueous reactions are more sophisticated if they can be performed under supramolecular catalysis.

Amongst various methodologies reported for the synthesis of thiazoles, solid supported synthesis has been widely used to generate small organic molecule libraries[12] and solution phase preparation of 2-aminothiazole combinatorial libraries have been reported in DMF[13] as well as in 1,4-dioxane.[11c] These methods require high temperatures, long reaction times and hazardous solvents with low yields and the requirement for cleavage of the solid support using acids. In our efforts to develop biomimetic approaches through supramolecular catalysis[14] and also to overcome some of the drawbacks in the existing methodologies, we report for the first time, the aqueous phase synthesis of thiazoles and aminothiazoles from phenacyl bromides and thioamide/thiourea in the presence of β-cyclodextrin (Scheme 1).

Cyclodextrins, which are cyclic oligosaccharides, have generated interest as enzyme models due to their ability to bind substrates selectively and catalyze chemical reactions by supramolecular catalysis, involving the reversible formation of host–guest complexes with the substrates by non-covalent bonding, as seen in enzyme complexation processes.[15] Complexation depends on the size, shape and hydrophobicity of the guest molecule. Cyclodextrins have been utilized for biomimetic modelling of the synthesis of thiazoles in water.

Reactions were carried out by the in situ formation of the β-cyclodextrin complex of a phenacyl bromide in



X = H, CH_3, Cl, Br R = NH_2,CH_3,Ph-

Scheme 1.

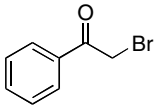
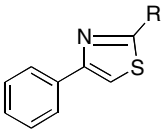
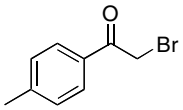
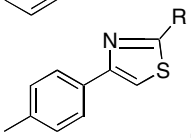
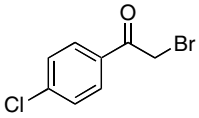
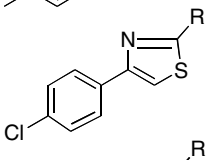
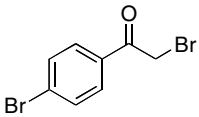
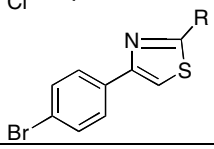
Keywords: Phenacyl bromide; Thioacetamide; Thiobenzamide; Thiourea; β-Cyclodextrin; Water.

☆ IICT communication number 050607.

* Corresponding author. Tel.: +91 4027193164; fax: +91 4027160512; e-mail: drkrrao@yahoo.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.130

Table 1. Thiazole ring formation in the presence of β-cyclodextrin in water from phenacyl bromide and thiourea or thioamide

Entry	Substrate	Product[a]		Time (h)	Yield[b] (%)
1			R = NH_2	1.0	88
2			R = CH_3	1.5	86
3			R = Ph	1.3	90
4			R = NH_2	1.3	85
5			R = CH_3	2.0	82
6			R = Ph	1.5	80
7			R = NH_2	1.5	92
8			R = CH_3	2.3	84
9			R = Ph	2.5	84
10			R = NH_2	1.5	87
11			R = CH_3	2.0	84
12			R = Ph	2.0	82

[a] All the products were identified by IR, NMR and mass spectroscopy.
[b] Yields of products isolated after column chromatography.

water followed by the addition of thioamide or thiourea to give the corresponding thiazole or aminothiazole respectively, in impressive yields (Table 1).[16] The reaction proceeds smoothly without the formation of any by-products or rearranged products. All the products were characterized by ^{1}H NMR, IR, mass spectroscopy and elemental analysis.

Here, the role of cyclodextrin appears to be to activate the phenacyl bromide, and solubilize and promote the reaction to completion in decreased reaction times. In the absence of β-cyclodextrin the reaction does take place but the yields were poor (20%) after long reaction times (12 h).

In conclusion, we have demonstrated for the first time that thiazole formation can be promoted by β-cyclodextrin in water. This methodology also overcomes the formation of unwanted by-products, low yields, slow reaction times, high temperatures and hazardous solvents, thus making it a more user-friendly procedure.

Acknowledgements

We thank CSIR New Delhi, India, for fellowships to M.N. and M.S.R.

References and notes

1. Lewis, J. R. *Nat. Prod. Rep.* **1999**, *16*, 389–416.
2. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158–1163.
3. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doharty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Bately, B. L.; Painchand, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olzon, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562–2572.
4. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 311–317.
5. (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719–1728; (b) Clemence, F.; Marter, O. L.; Delevalle, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453–1462.
6. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601–1606.
7. Bell, F. W.; Cantrell, A. S.; Hoberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929–4936.
8. Fink, B. A.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205–219.
9. Van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; Von Drabbe Kunzel, J. F.; De Groote, M.; Visser, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749–762.
10. Metzger, J. V. In *Comprehensive Heterocyclic Chemistry I*; Pergamon Press, 1984; Vol. 6, p 328.
11. (a) Baxter, A. D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 79–85; (b) Rich, D. H.; Wiley, R. A. *Med. Res. Rev.* **1993**, *13*, 327–384; (c) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *62*, 196–200; (d) Goff, D.; Fernandez, J. *Tetrahedron Lett.* **1999**, *40*, 423–426.
12. Kazzouli, S. EI.; Raboin, S. B.; Mouadbib, A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *43*, 3193–3196.
13. Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Stephen, P. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409–1414.
14. (a) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 9119–9121; (b) Surendra, K.; Krishnaveni, N. S.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 4994–4995; (c) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058–2059; (d) Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.*

2003, *68*, 2018–2019; (e) Narender, M.; Surendra, K.; Krishnaveni, N. S.; Reddy, M. S.; Rao, K. R. *Tetrahedron Lett.* **2004**, 7995–7997.
15. Szejtli, J.; Osa, T. In *Comprehensive Supramolecular Chemistry*; Pergamon Press, 1996; Vol. 3.
16. *General procedure*: β-Cyclodextrin (1.0 mmol) was dissolved in water (15 mL) at 60 °C. The phenacyl bromide (1.0 mmol) dissolved in acetone (1.0 mL) was added slowly, with stirring and the mixture cooled to 50 °C. To this solution, thioamide/thiourea (1.2 mmol) was added and stirring was continued at 50 °C. After completion of the reaction the organic material was extracted with ethyl acetate, the organic phase was separated and washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (1:9 for aminothiazoles and 0.2:9.8 for thiazoles) as eluent.