Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5171–5172
Tetrahedron Letters

Microwave promoted synthesis of functionalized 2-aminothiazoles

George W. Kabalka* and Arjun R. Mereddy

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37966-1600, USA

Received 6 December 2005; revised 9 May 2006; accepted 10 May 2006

Abstract—Microwave irradiation promotes the rapid one-pot synthesis of 2-aminothiazoles fromed via the condensation of α-bromoketones with thiourea.

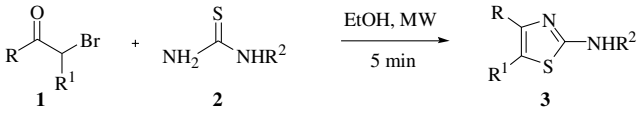
The biological activity of aminothiazoles has been well documented.[1] They have broad application in the treatment of allergies,[2] hypertension,[3] schizophrenia,[4] inflammation,[5] bacterial infections,[6] and HIV.[7] Recently they have been utilized for the treatment of pain,[8] as fibrinogen receptor antagonists with anti-thrombotic activity,[9] as inhibitors of bacterial DNA gyrase B,[6] and in the development of cyclin-dependent kinase (CDK) inhibitors.[10]

Among the various methodologies reported for the preparation of thiazoles, solid supported syntheses have been used to generate small organic libraries[11] and solution phase preparations of combinatorial libraries have been prepared in DMF[12] as well as in 1,4-dioxane.[13] These methods require high temperatures, long reaction times, hazardous solvents, and often produce low yields.

The use of microwaves in organic synthesis has recently gained in importance.[14] Microwave systems provide the opportunity to complete complex reactions in minutes. In this letter, we report the use of microwave irradiation to enhance condensation reactions between α-bromoketones and thiourea. We have found that the condensation of α-bromoketones with thioureas furnish the desired products within 5 min under microwave (MW) irradiation in the absence of catalysts. The results of the study are summarized in the Table 1.

In a typical procedure, a mixture of α-bromoketone **1** (1.0 mmol) and a thiourea **3** (1.0 mmol) were placed in a MW test tube (10 mL) containing a magnetic stirring bar, rubber cap, and 4 mL of ethanol. The test tube was placed in the microwave cavity (CEM, Discover) and subjected to MW irradiation at 50 °C (100 W) for 5 min. After completion of the reaction, the tube was removed, cooled to room temperature, and the contents added to water (10 mL). The product **3** was extracted

Table 1. Synthesis of 2-(*N*-substituted)aminothiazoles from α-bromoketones[a]



Substrates **1** and **2**			Yield[b] (%)
R	R^1	R^2	
C_6H_5	C_6H_5	H	98
C_6H_5	C_6H_5	CH_3	96
C_6H_5	C_6H_5	C_6H_5	98
C_6H_5	CH_3	H	96
C_6H_5	CH_3	CH_3	88
C_6H_5	CH_3	C_6H_5	97
C_6H_5	H	H	99
C_6H_5	H	CH_3	98
C_6H_5	H	C_6H_5	98
$CH_3C_6H_4$	H	H	98
$CH_3C_6H_4$	H	CH_3	98
$CH_3C_6H_4$	H	C_6H_5	98
$NO_2C_6H_4$	H	H	98
$NO_2C_6H_4$	H	CH_3	97
$NO_2C_6H_4$	H	C_6H_5	97
$CH_3SC_6H_4$	H	H	95
$CH_3SO_2C_6H_4$	H	H	87

[a] All products were identified by ^1H, ^{13}C NMR, and comparison with authentic samples.
[b] Isolated yields.

Keywords: Microwave; Aminothiazole; Green chemistry; α-Bromo ketone; Thiourea.
* Corresponding author. Tel.: +1 865 974 3260; fax: +1 865 974 2997; e-mail: kabalka@utk.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.053

into methylene chloride (15 mL), which was filtered though a short silica column to afford the 2-aminothiazole after the solvent was removed under reduced pressure.

In conclusion, microwave irradiation promotes the condensation of α-bromoketones with thioureas to provide an excellent route to highly functionalized 2-aminothiazoles.

Acknowledgements

We wish to thank the US Department of Energy and the Robert H. Cole foundation for support of this research.

References and notes

1. (a) Barone, R.; Chanon, M.; Gallo, R. Aminothiazoles and their derivatives. In *The Chemistry of Heterocyclic Compounds, Part 2*; Metzger, J. V., Ed.; Wiley: New York, 1979; Vol. 34, (b) Gorczynski, M. J.; Leal, R. M.; Mooberry, S. L.; Bushweller, J. H.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 1029.
2. Ohkubo, M.; Kuno, A.; Nakanishi, I.; Takasugi, H. *Chem. Pharm. Bull.* **1995**, *43*, 1497.
3. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562.
4. Hallas, G.; Choi, J. *Dyes Pigments* **1999**, *42*, 249.
5. Jayashree, B. S.; Anuradha, D.; Venugopala, N. K. *Asian. J. Chem.* **2005**, *17*, 2093.
6. Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F.-U. *J. Med. Chem.* **2001**, *44*, 619.
7. Venkatachalam, T. K.; Sudbeck, E. A.; Mao, C.; Uckum, F. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 523.
8. Wilson, K. J.; Illig, C. R.; Subasinghe, N.; Hoffman, J. B.; Jonathan Rudolph, M.; Soll, R.; Molloy, C.; Bone, R.; Green, D.; Randall, T.; Zhang, M.; Lewandowski, F. A.; Zhou, Z.; Sharp, C.; Maguire, D.; Grasberger, B.; DesJarlais, R. L.; Spurlino, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 915.
9. Badorc, A.; Borders, M.-F.; Cointet, P. de.; Savi, P.; Bernat, A.; Lale, A.; Petitou, M.; Maffrand, J.-P.; Herbert, J.-M. *J. Med. Chem.* **1997**, *40*, 3393.
10. (a) Kim, K. S.; Kimball, S. D.; Misra, R. N.; Rawlins, D. B.; Hunt, J. T.; Xiao, H.-Y.; Lu, S.; Qian, L.; Han, W.-C.; Shan, W.; Mitt, T.; Cai, Z.-W.; Poss, M. A. .; Zhu, H.; Sack, J. S.; Tokarski, J. S.; Chang, C. Y.; Pavletich, N.; Kamath, A.; Humphreys, W. G.; Marathe, P.; Bursuker, I.; Kellar, K. A.; Roongta, U.; Batorsky, R.; Mulheron, J. G.; Bol, D.; Fairchild, C. R.; Lee, F. Y.; Webster, K. R. *J. Med. Chem.* **2002**, *45*, 3905; (b) Misra, R. N.; Xiao, H.-Y.; Kim, K. S.; Lu, S.; Han, W.-C.; Barbosa, S. A.; Hunt, J. T.; Rawlins, D. B.; Shan, W.; Ahmed, S. Z.; Qian, L.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Kellar, K. A.; Mulheron, J. G.; Batorsky, R.; Roongta, U.; Kamath, A.; Marathe, P.; Ranadive, S. A.; Sack, J. S.; Tokarski, J. S.; Pavletich, N. P.; Lee, F. Y. F.; Webster, K. R.; Kimball, S. D. *J. Med. Chem.* **2004**, *47*, 1719.
11. Kazzouli, S. EI.; Raboin, S. B.; Mouadbib, A.; Guillaumet, G. *Tetrahedron Lett.* **1999**, *40*, 423.
12. Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Stephen, P. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409.
13. Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *62*, 196.
14. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9925.