Alumina-Supported Synthesis of Aminoazoles Using Microwaves

M. KIDWAI*, B. DAVE, and K. R. BHUSHAN

Department of Chemistry, University of Delhi, Delhi-110007, India

Received 22 September 1999

Alumina-supported synthesis of 2-aminothiazoles and α-oxazoles from halo carbonyl compounds and substituted thiourea/urea under "solvent-free conditions" using microwaves is described.

Microwave irradiation (MWI) as efficient thermal energy is becoming a standard technique in various fields of chemistry [1]. Nevertheless, it is only recently that microwave ovens have been applied to the synthesis of oxazoles [2] and various other organic compounds [3, 4]. These procedures are strongly limited by the presence of solvents which reach their boiling points within very short times (≈ 1 min) of exposure to microwaves [5]. Consequently, high pressures are developed, thus leading to damages to vessels, materials and occasionally to explosions [5]. Using reagents supported on inorganic solid materials in the absence of solvent (solvent-free conditions) [6] is not only advantageous from environmental point of view, but they also offer the further benefit of shorter reaction times, especially if microwaves are used [7]. Solvent-free conditions coupled with MWI lead to reaction rate enhancement, improved yields, and safe conditions which make this technique economical and indispensable for organic synthesis.

2-Aminothiazoles and -oxazoles are useful structural elements in medicinal chemistry. These structures have found application in drug development for treatment of allergies [8], hypertension [9], inflammation [10], schizophrenia [11], bacterial [12] and HIV infections [13]. Substituted thiazoles and oxazoles have been prepared by condensation of substituted acetophenone/benzylidene—acetone dibromide and thiourea/urea in the presence [14, 15] or absence [16] of iodine. These procedures are very expensive, require longer reaction time periods and have difficult work up with low yields.

Keeping in view the importance of 2-aminothiazoles and -oxazoles and advantages of solvent-free microwave-induced reactions, it was thought worthwhile to synthesize 2-aminothiazoles and -oxazoles (*IIIa—IIIr*) using solvent-free microwave technique.

EXPERIMENTAL

Melting points were determined using a Thomas Hoover melting point apparatus. IR (KBr) spectra were obtained on a Perkin—Elmer FTIR-1710 spectrophotometer. ^{1}H NMR spectra were recorded at 90 MHz on a Perkin—Elmer R-32 spectrometer using TMS as internal standard (chemical shifts in δ). Elemental analysis was performed on a Heraeus CHN-Rapid Analyser. A Padmini Essentia (model Brownie at 2450 MHz) unmodified household microwave oven (using every output 0.56 KW) was used for all experiments. The average bulk temperature at the end of reaction was measured by inserting a thermometer in the reaction mixture.

2-Aminothiazoles and -oxazoles (*IIIa—IIIr*)

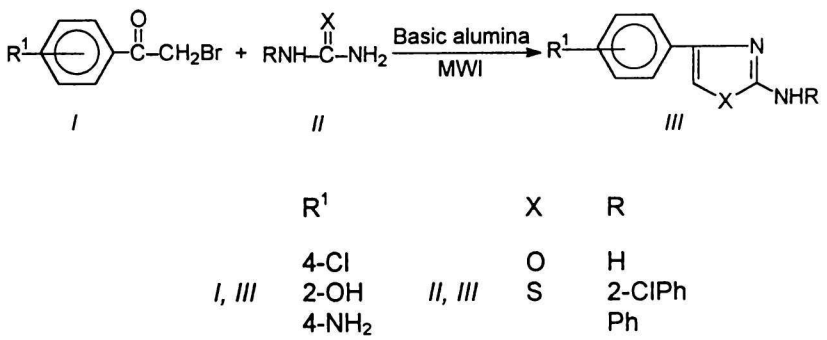
MWI Method

Basic alumina (40 g) was added to the solution of phenacyl bromide [17] (0.01 mol) and *N*-substituted thiourea [18] (urea [19]) (0.01 mol) dissolved in dichloromethane (methanol) (10 cm^3) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was dried in air (beaker) and placed in an alumina bath [20] inside microwave oven and irradiated (intermittently at 0.5 min intervals; 140 °C) for a specified time (Table 1). On completion of reaction as followed by TLC examination, the mixture was cooled to room temperature and then the product was extracted into dichloromethane (4 × 15 cm^3). Recovering the solvent under reduced pressure yielded the product which was purified by recrystallization from the mixture dichloromethane—acetone (Table 2).

*The author to whom the correspondence should be addressed.

Table 1. Comparison of Reaction Time and Yield

Compound	X	R	R^1	Conventional t/h (yield/%)	MWI t/s (yield/%)
IIIa	S	H	4-Cl	28 (60)	120 (95)
IIIb	S	Ph	4-Cl	29 (62)	120 (96)
IIIc	S	2-ClPh	4-Cl	30 (59)	150 (94)
IIId	O	H	4-Cl	33 (58)	150 (96)
IIIe	O	Ph	4-Cl	32 (60)	120 (95)
IIIf	O	2-ClPh	4-Cl	34 (58)	150 (96)
IIIg	S	H	4-NH_2	31 (61)	120 (94)
IIIh	S	Ph	4-NH_2	35 (62)	120 (93)
IIIi	S	2-ClPh	4-NH_2	18 (60)	180 (96)
IIIj	O	H	4-NH_2	30 (61)	165 (92)
IIIk	O	Ph	4-NH_2	32 (57)	120 (90)
IIIl	O	2-ClPh	4-NH_2	30 (60)	165 (91)
IIIm	S	H	2-OH	30 (61)	165 (94)
IIIn	S	Ph	2-OH	35 (59)	180 (95)
IIIo	S	2-ClPh	2-OH	36 (63)	150 (90)
IIIp	O	H	2-OH	32 (62)	180 (93)
IIIq	O	Ph	2-OH	34 (60)	180 (92)
IIIr	O	2-ClPh	2-OH	35 (58)	165 (89)



Scheme 1

Conventional Method

The reaction mixture prepared as in earlier method was placed in a preheated oil bath (at temperature 140°C) for a specified time (Table 1), and on completion of reaction as followed by TLC examination, the reaction mixture was worked up as in MWI method.

RESULTS AND DISCUSSION

α-Halo carbonyl compounds were condensed with substituted thiourea/urea to obtain corresponding 2-aminothiazoles and -oxazoles (Scheme 1). The formation of 2-aminothiazoles and -oxazoles (Table 2) is evidenced by the disappearance of a band due to the $COCH_2$ of α-halo carbonyl compounds and C=S (C=O) of thiourea (urea) at 1150 cm^{-1} (1650 cm^{-1}) and 1680 cm^{-1}, respectively, and appearance of a band due to C=N of thiazole (oxazole) ring at 1640 cm^{-1} in the IR spectra. The formation of 2-*N*-substituted thiazoles and -oxazoles is evidenced by the disappearance of a band due to $COCH_2$ of α-halo carbonyl compounds, C=S (C=O) of substituted thiourea (urea) and NH_2 at 1140 cm^{-1} (1640 cm^{-1}), 1690 cm^{-1}, and 3200 cm^{-1}, respectively, and the appearance of a band due to C=N of thiazole (oxazole) ring at 1630 cm^{-1} in the IR spectra. In ^1H NMR the signal for the $COCH_2$ protons was missing at $\delta = 7.9$ and the signal for CH proton of thiazole (oxazole) ring appeared at $\delta = 6.3$—6.6.

The observation that in the MWI method the reaction time has been drastically reduced with improved yield as compared to conventional method (see Table 1), reason is not purely thermal [21]. This difference was observed probably due to strong microwave effect and the high enhancement of the reaction rate.

CONCLUSION

This is the first report on the synthesis of 2-aminothiazoles and -oxazoles on alumina as a solid inorganic support using MWI. In short, the salient feature of our approach is the usage of microwaves without any volatile and toxic solvents, which makes

Table 2. Physical, Spectral, and Analytical Data of Compounds *IIIa*—*IIIr*

Compound	Formula	M_r	w_i(found)/% w_i(calc.)/%			M.p.	^{1}H NMR (DMSO-d_6 + $CDCl_3$), δ
			C	H	N	°C	
IIIa	$C_9H_7ClN_2S$	210	51.1	3.34	13.35	163—165 (m.p. = 163—164 °C [23])	
			51.4	3.33	13.33		
IIIb	$C_{15}H_{11}ClN_2S$	286	82.92	3.81	9.80	170—172	5.2 (br s, 1H, NH-2), 6.3 (s, 1H, H-5),
			82.93	3.84	9.79		7.2—7.6 (m, 9H, H_{arom})
IIIc	$C_{15}H_{11}Cl_2N_2S$	320	56.21	3.10	8.77	168—170	5.0 (br s, 1H, NH-2), 6.4 (s, 1H, H-5),
			56.25	3.12	8.75		7.1—7.4 (m, 8H, H_{arom})
IIId	$C_9H_7ClN_2O$	194	55.65	3.63	14.40	165—167	5.2 (br s, 2H, NH-2), 6.6 (s, 1H, H-5),
			55.67	3.60	14.43		7.1—7.5 (m, 4H, H_{arom})
IIIe	$C_{15}H_{11}ClN_2O$	270	66.63	4.10	10.38	158—160	5.3 (br s, 1H, NH-2), 6.5 (s, 1H, H-5),
			66.66	4.07	10.37		7.2—7.7 (m, 9H, H_{arom})
IIIf	$C_{15}H_{10}Cl_2N_2O$	304	55.69	3.59	14.41	140—143	5.1 (br s, 1H, NH-2), 6.4 (s, 1H, H-5),
			55.67	3.60	14.43		7.3—7.8 (m, 8H, H_{arom})
IIIg	$C_9H_9N_3S$	191	56.56	4.70	21.99	174—175 (m.p. = 174—175 °C [23])	
			56.54	4.71	21.98		
IIIh	$C_{15}H_{13}N_3S$	267	67.40	4.88	15.70	169—171	5.2 (br s, 1H, NH-2), 5.7 (br s, 2H, NH_2-4′),
			67.41	4.86	15.73		7.2—7.6 (m, 9H, H_{arom})
IIIi	$C_{15}H_{12}ClN_3S$	301	59.82	3.96	13.97	144—146	5.3 (br s, 1H, NH-2), 5.6 (br s, 2H, NH_2-4′),
			59.80	3.98	13.95		6.5 (s, 1H, H-5), 7.2—7.6 (m, 8H, H_{arom})
IIIj	$C_9H_9N_3O$	175	61.70	5.16	24.02	150—152	5.2 (br s, 2H, NH_2-2), 5.8 (br s, 2H, NH_2-4′),
			61.71	5.14	24.00		6.6 (s, 1H, H-5), 7.2—7.6 (m, 4H, H_{arom})
IIIk	$C_{15}H_{13}N_3O$	251	71.73	5.16	16.73	157—159	5.2 (br s, 1H, NH-2), 5.7 (br s, 2H, NH_2-4′),
			71.71	5.17	16.73		6.5 (s, 1H, H-5), 7.2—7.7 (m, 9H, H_{arom})
IIIl	$C_{15}H_{12}ClN_3O$	285	63.17	4.20	14.75	144—146	5.3 (br s, 1H, NH-2), 5.6 (br s, 2H, NH_2-4′),
			63.15	4.21	14.73		6.6 (s, 1H, H-5), 7.2—7.7 (m, 8H, H_{arom})
IIIm	$C_9H_8N_2OS$	192	56.24	4.18	14.55	138—140 (m.p. = 139—140 °C [23])	
			56.25	4.16	14.58		
IIIn	$C_{15}H_{12}N_2OS$	268	67.19	4.46	10.45	135—136	5.3 (br s, 1H, NH-2), 6.5 (s, 1H, H-5),
			67.16	4.47	10.44		6.9 (s, 1H, OH-2′), 7.0—7.4 (m, 9H, H_{arom})
IIIo	$C_{15}H_{11}ClN_2OS$	302	59.62	3.62	9.26	139—141	5.3 (br s, 1H, NH-2), 6.4 (s, 1H, H-5),
			59.60	3.64	9.27		6.8 (s, 1H, OH-2′), 7.3—7.7 (m, 8H, H_{arom})
IIIp	$C_9H_8N_2O_2$	176	61.39	4.55	15.89	173—174	5.2 (br s, 1H, NH_2-2), 6.6 (s, 1H, H-5),
			61.36	4.54	15.90		7.0 (s, 1H, OH-2′), 7.2—7.5 (m, 4H, H_{arom})
IIIq	$C_{15}H_{12}N_2O_2$	252	71.40	4.78	11.13	179—180	5.3 (br s, 1H, NH-2), 6.4 (s, 1H, H-5),
			71.42	4.76	11.11		7.1 (s, 1H, OH-2′), 7.3—7.8 (m, 9H, H_{arom})
IIIr	$C_{15}H_{12}ClN_2O_2$	286	62.91	3.86	9.81	180—182	5.3 (br s, 1H, NH-2), 6.5 (s, 1H, H-5),
			62.93	3.89	9.79		6.9 (s, 1H, OH-2′), 7.2—7.7 (m, 8H, H_{arom})

it a clean, efficient, and economical technology to obtain various useful heterocyclic compounds for organic synthesis. In our approach on solid support, less reaction time and better yield of products are found as compared with conventional heating [22].

REFERENCES

1. Thurey, J., *Les microoudes et leurs effects sur lamatiere, Technique et Documentation.* Lavoiser, Paris, 1989.
2. Brain, C. T. and Paul, J. M., *Synlett 1999,* 1642.
3. Caddick, S., *Tetrahedron 51,* 10403 (1995).
4. *a*) Kidwai, M. and Misra, P., *Synth. Commun. 29* (18) 3237 (1999).
   b) Kidwai, M. and Kumar, R., *Org. Prep. Proced. Int. 30,* 451 (1998).
5. Gedye, R. N., Smith, F. E., Westway, K. C., Ali, H., Baldisera, L., Laberge, L., and Rousell, J., *Tetrahedron Lett. 27,* 279 (1986).
6. Kidwai, M. and Bhushan, K. R., *Chem. Pap. 53,* 114 (1999).
7. Loupy, A., Petit, A., Hamelin, J., Texier-Boullet, F., Jacqualt, P., and Mathe, D., *Synthesis 1998,* 1213.
8. Hargrave, K. D., Hess, F. K., and Oliver, J. T., *J. Med. Chem. 26,* 1158 (1983).
9. Patt, W. C., Hamilton, H. W., Taylor, M. D., Connolly, C. J. C., Doherty, A. M., Batley, B. C., and Olson, S. C. J., *J. Med. Chem. 35,* 2562 (1992).
10. Havin, F., Ratajczyk, J. D., DeNet, R. W., Kerdesky, F. A., Waters, R. L., Young, P. R., and Carter, G. W., *J. Med. Chem. 31,* 1719 (1988).
11. Jaen, J. C., Wise, L. D., Caparthe, B. W., Tecle, H., Bergmeir, S., Meltzner, C. T., and Pugsley, T. A., *J. Med. Chem. 33,* 311 (1990).
12. Tsuji, K. and Ishikawa, H., *Bioorg. Med. Chem. Lett. 4,* 1601 (1994).

13. Bell, F. W., Cantrell, A. S., Hoberg, M., Jaskanas, S. R., Kinnick, M. D., Zhang, H., and Zhou, X.-X., *J. Med. Chem. 38*, 4929 (1995).
14. Das, B. and Rout, M. K., *J. Indian Chem. Soc. 32*, 663 (1955).
15. Mahapatra, G. N., *J. Indian Chem. Soc. 33*, 527 (1956).
16. Hantzsch, A. R. and Weber, J. H., *Ber. 20*, 3118 (1887).
17. Cowper, R. M. and Davidson, L. H., *Org. Synth. 2*, 480 (1943).
18. Poss, M. A., Iwanowicz, E., Reid, J. A., Lin, J., and Gu, Z., *Tetrahedron Lett. 40*, 5933 (1992).
19. Blanchand, D., *Org. Synth. 3*, 95 (1923).
20. Bram, G., Loupy, A., and Majdoub, M., *Tetrahedron 46*, 5167 (1990).
21. Raner, K. D., Strauss, C. R., Vysok, F., and Mokbel, L., *J. Org. Chem. 58*, 950 (1993).
22. Bram, G. and Decodts, G., *Tetrahedron Lett. 21*, 5011 (1980).
23. King, L. C. and Hlaveck, R. J., *J. Am. Chem. Soc. 72*, 3722 (1950).