

HETEROCYCLES, Vol. 81, No. 12, 2010, pp. 2849 - 2854. © The Japan Institute of Heterocyclic Chemistry
Received, 18th September, 2010, Accepted, 25th October, 2010, Published online, 4th November, 2010
DOI: 10.3987/COM-10-12067

A RAPID AND HIGH-YIELDING SYNTHESIS OF THIAZOLES AND AMINOTHIAZOLES USING TETRABUTYLAMMONIUM SALTS

Erdal Kocabas,* Ahmet Burak Sariguney, and Ahmet Coskun

Department of Chemistry, Selcuk University, Konya 42099, Turkey

ekocabas50@gmail.com, absariguney@gmail.com, acoskun42@gmail.com

Abstract – A convenient method for the synthesis of thiazoles and aminothiazoles by treatment of phenacyl bromides with thioamides/thiourea in the presence of tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) at room temperature was developed. The products having high yields were formed rapidly (within 15 min). The method is simple, rapid and practical, generating thiazole derivatives in excellent isolated yields. The structures of the newly synthesized products were identified by FT-IR, ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis data.

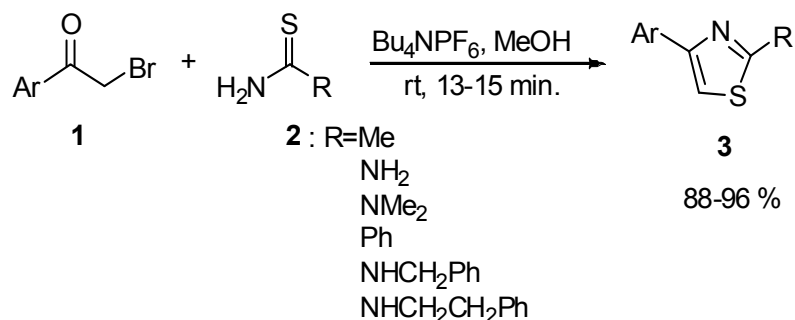
Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B₁ serves as an electron sink, and its coenzyme form is important for the decarboxylation of α -keto acids.¹ This heterocyclic system has a broad application in drug developments for the treatment of inflammation,² hypertension,³ bacterial,⁴ and HIV infections.⁵ Especially, aminothiazoles are known to be ligands of estrogen receptors⁶ as well as a novel class of adenosine receptor antagonists.⁷

In view of the importance of thiazole and its derivatives, several methods for the synthesis of thiazole derivatives were developed. The most widely used method is Hantzsch synthesis,^{8,9} involving the reactions of α -halo carbonyl compounds with thiourea or thioamide derivatives. Recently, many improved methods have been reported for the synthesis of thiazoles by using catalysts such as ammonium-12-molybdophosphate in methanol,¹⁰ β -cyclodextrin in water,¹¹ iodine,¹² 1,3-di-alkylimidazolium salts¹³ and by the use of microwave in ethanol.¹⁴ However, in spite of their potential utility, some of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields and often expensive catalysts.

We, herein, present an improved method for the synthesis of thiazoles, 2-amino and 2-alkyl derivatives, from treatments of phenacyl bromides with thioamide/thiourea derivatives by using Bu_4NPF_6 as a catalyst.

The reactions were carried out at room temperature and the high yield products were formed within 15 min. The obtained structures were settled from their spectral (^1H and ^{13}C NMR) data.

Thiazole derivatives in high yield were obtained from the treatments of phenacyl bromides and thiourea/thioamide derivatives with Bu_4NPF_6 at ambient temperature (Scheme 1).



Scheme 1. Synthesis of thiazole derivatives in the presence of catalyst

The catalyzed reaction time and yield, and also melting points of the obtained products are given in Table 1.

Table 1. Synthesis of 2-amino-4-arylthiazoles and 2-methyl-4-arylthiazoles catalyzed by Bu_4NPF_6

Entry	Ar	R	Thiazole	Yield ^a	Time (min)	Mp (°C)	Lit. mp (°C)
1	C ₆ H ₅	NH ₂	3a	96	14	150-151	150 ¹⁵
2	C ₆ H ₅	Me	3b	95	15	67-68	67 ¹⁶
3	<i>p</i> -F-C ₆ H ₄	NH ₂	3c	94	13	101-102	102-103 ¹⁷
4	<i>p</i> -F-C ₆ H ₄	Me	3d	93	14	184-185	185 ¹⁸
5	<i>p</i> -Cl-C ₆ H ₄	NH ₂	3e	93	15	163-164	163-164 ¹⁶
6	<i>p</i> -Cl-C ₆ H ₄	Me	3f	89	14	111-112	111 ¹⁹
7	<i>p</i> -Br-C ₆ H ₄	NH ₂	3g	94	15	179-181	180-181 ¹⁶
8	<i>p</i> -Br-C ₆ H ₄	Me	3h	88	13	130-131	130 ²⁰
9	<i>p</i> -Me-C ₆ H ₄	NH ₂	3i	91	15	124-125	124-125 ²¹
10	<i>p</i> -Me-C ₆ H ₄	Me	3j	92	15	58-60	58-59 ¹⁹
11	<i>p</i> -MeO-C ₆ H ₄	NH ₂	3k	89	14	202-203	200-203 ¹⁹
12	<i>p</i> -MeO-C ₆ H ₄	Me	3l	95	15	66-67	67-68 ¹⁹
13	C ₆ H ₄ -O-C ₆ H ₄	NH ₂	3m	94	15	65-67	-
14	C ₆ H ₄ -O-C ₆ H ₄	Me	3n	92	14	67-68	-
15	C ₆ H ₄ -O-C ₆ H ₄	NMe ₂	3p	89	13	154-155	-
16	C ₆ H ₄ -O-C ₆ H ₄	Ph	3r	93	15	127-128	-
17	C ₆ H ₄ -O-C ₆ H ₄	NHCH ₂ Ph	3s	94	14	137-138	-
18	C ₆ H ₅	NHCH ₂ CH ₂ Ph	3t	92	15	116-117	116-117 ²²

^a Isolated yield after column chromatography.

We also examined various tetrabutylammonium salts given in Table 2 to investigate the efficiency of the catalyst. When tetrabutylammonium hexafluorophosphate was used, it was observed that conversion of phenacyl halides into thiazoles occurred in a shorter reaction time and higher yield according to other tetrabutylammonium salts.

The significant enhancement in the rate of reaction has been attributed to basicity of anions as depicted in the previous study.²² Indeed, the nature of the anion governing the electrophilicity of the tetrabutylammonium cation led to the remarkable rate accelerations.

The amount of catalysts used in the reaction did not have any significant influence on the overall rate of the reaction and yields of products. This was confirmed by scaling up the concentration from the present 10% solids (w/v) to 15% and 20% solids (w/v) in the case of **3m** and **3n** compounds, respectively. The reactions went to completion in identical times and with the same isolated yields as for the diluted reaction mixture.

Table 2. Conversion of phenacyl bromide using different tetrabutylammonium salts as catalyst

Catalyst	Thiazole 3a		Thiazole 3c		Thiazole 3h		Thiazole 3k		Thiazole 3n	
	<i>t</i>	<i>y</i>	<i>t</i>	<i>y</i>	<i>t</i>	<i>y</i>	<i>t</i>	<i>y</i>	<i>t</i>	<i>y</i>
Bu ₄ NPF ₆	14	96	13	94	13	88	14	89	14	92
Bu ₄ N BF ₄	22	89	21	86	25	81	26	80	28	83
Bu ₄ NCl	22	88	23	88	23	83	24	82	25	81
Bu ₄ NBr	23	86	22	85	24	82	25	81	27	85
Bu ₄ NI	21	89	24	87	23	80	22	83	24	82

* *t*= time (min), *y*= yield (%)

Several phenacyl bromides given in Table 2 exhibited smooth reactions with thiourea and thioacetamide to give substituted 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole, respectively. As can be seen in Table 2, the reactions were efficiently completed at ambient temperature under mild conditions to afford the corresponding thiazoles in excellent yields in all cases. Also, we did not obtain any difference among the phenacyl bromides substituted by electron-donating or electron-withdrawing groups. The obtained products were characterized by ¹H and ¹³C NMR spectroscopy, FT-IR, melting point and elemental analyses.

The ¹H NMR spectra of **3s** and **3m** compounds show peaks as broad singlets at δ 5.04 and 5.12 ppm respectively, which correspond to the amino group. The characteristic peaks appearing at δ 6.48–6.62 ppm correspond to C5–H of the thiazole ring for all compounds. In the ¹³C NMR spectra, the peaks appearing in the range of δ 169–171 ppm correspond to C2 of the thiazole ring. The FT-IR spectra of **3m** and **3s** compounds show peaks at 3448 and 3459 cm⁻¹ corresponding to the amino group. In the case of **3n**

and **3p** compounds, the peaks corresponding to the methyl group appeared at 3019-2835 cm^{-1} . For the compounds synthesized previously (compounds **3a-3l** and **3t** in Table 1), the obtained values were in agreement with those reported in the literature.

Methanol was chosen as the most available solvent for the catalyzed reactions among the polar solvents, because the reaction was sluggish in the others, such as dichloromethane and chloroform. It was also noted that the reaction did not proceed in nonpolar solvents such as hexane and toluene even after stretching the reaction time (24 h).

N-Phenethyl-4-phenylthiazol-2-amine, commonly known as fanetizole is an anti-inflammatory agent that was reported to have reached phase II clinical trials for the treatment of rheumatoid arthritis.²³ Generally, fanetizole has been synthesized by using stringent reaction conditions such as microreactors and heating in solvents, such as DMF and NMP. We presented a novel procedure for the synthesis of the anti-inflammatory drug fanetizole (compound **3t**). In this procedure, we treated phenacyl bromide with 2-phenylethyl thiourea in methanol by using Bu_4NPF_6 as a catalyst to afford fanetizole in 92% yield in 15 min at ambient temperature.

EXPERIMENTAL

Materials and methods

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in CDCl_3 using TMS as internal standard. Infrared spectra were recorded with Perkin-Elmer 1605 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a LECO-CHNS-932 instrument. Melting points were measured by using a EZ-Melt Automated MPA 120 melting point apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck, Fluka and Sigma. Column chromatography was performed using silica gel (60–120 mesh size).

General procedure for the synthesis of thiazole derivatives

A mixture of phenacyl bromide **1** (1 mmol), thioamide/thiourea **2** (1.2 mmol) and Bu_4NPF_6 (10 mol%) was stirred in MeOH (5 mL) at room temperature under vigorous magnetic stirring. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using hexane-EtOAc (4:1) as eluent to afford pure product.

4-(4-Phenoxyphenyl)thiazol-2-amine (3m)

White solid; mp 65–67 °C; FT-IR (KBr): 3459, 3244, 3016, 2202, 2048, 1673, 1626, 1543, 1522, 1491, 1456, 1329, 973, 761 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ = 5.12 (br s, 2H, NH_2), 6.55 (s, 1H, thiazole H), 7.14-7.72 (m, 9H, Ar-H); ^{13}C NMR (CDCl_3 , 100 MHz): δ = 98.6, 119.2, 119.7, 124.0, 125.6, 127.9, 130.2,

145.6, 156.4, 158.5, 171.3. Anal. Calcd for C₁₅H₁₂N₂OS: C, 67.14; H, 4.51; N, 10.44%. Found: C, 67.49; H, 4.72; N, 10.34%.

2-Methyl-4-(4-phenoxyphenyl)thiazole (3n)

Yellow solid; mp 67–68 °C; FT-IR (KBr): 3235, 3017, 2835, 2200, 1669, 1619, 1541, 1488, 1461, 1301, 977, 756 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ= 2.77 (s, 3H, CH₃), 6.51 (s, 1H, thiazole H), 7.17-7.64 (m, 9H, Ar-H); ¹³C NMR (CDCl₃, 100 MHz): δ= 19.7, 108.4, 118.0, 118.8, 121.9, 124.1, 126.2, 127.1, 128.5, 153.4, 157.0, 169.2. Anal. Calcd for C₁₆H₁₃NOS: C, 71.88; H, 4.90; N, 5.24%. Found: C, 71.76; H, 4.77; N, 5.09%.

N,N-Dimethyl-4-(4-phenoxyphenyl)thiazol-2-amine (3p)

White solid; mp 154–155 °C; FT-IR (KBr): 3209, 3019, 2837, 1605, 1565, 1548, 1488, 1461, 1313, 759 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ= 3.12 (s, 6H, CH₃), 6.48 (s, 1H, thiazole H), 7.11-7.66 (m, 9H, Ar-H); ¹³C NMR (CDCl₃, 100 MHz): δ= 41.0, 105.0, 117.6, 117.9, 121.5, 124.0, 125.4, 127.2, 127.9, 150.2, 157.0, 170.1. Anal. Calcd for C₁₇H₁₆N₂OS: C, 68.89; H, 5.44; N, 9.45%. Found: C, 69.09; H, 5.06; N, 9.13%.

4-(4-Phenoxyphenyl)-2-phenylthiazole (3r)

Yellow solid; mp 127-128 °C; FT-IR (KBr): 3221, 3009, 1611, 1543, 1521, 1479, 1449, 759 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ= 6.46 (s, 1H, thiazole H), 7.09-7.69 (m, 14H, Ar-H); ¹³C NMR (CDCl₃, 100 MHz): δ= 100.3, 111.4, 118.7, 119.6, 123.9, 125.4, 127.6, 129.1, 130.8, 144.9, 153.2, 156.1, 158.2, 170.4. Anal. Calcd for C₂₁H₁₅NOS: C, 76.57; H, 4.59; N, 4.25%. Found: C, 76.35; H, 4.83; N, 4.03%.

N-Benzyl-4-(4-phenoxyphenyl)thiazol-2-amine (3s)

Yellow solid; mp 137-138 °C; FT-IR (KBr): 3448, 3196, 3010, 2824, 1618, 1552, 1539, 1477, 1454, 1318, 753 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ= 4.41 (s, 2H, CH₂), 5.04 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 6.89-7.46 (m, 14H, Ar-H); ¹³C NMR (CDCl₃, 100 MHz): δ= 49.0, 114.3, 116.1, 118.7, 121.4, 126.8, 128.4, 139.9, 152.4, 152.6, 157.1, 170.2. Anal. Calcd for C₂₂H₁₈N₂OS: C, 73.71; H, 5.06; N, 7.82%. Found: C, 73.34; H, 4.99; N, 7.39%.

ACKNOWLEDGEMENTS

The authors are please to acknowledge the Scientific Research Projects (BAP) of Selcuk University for grant with grant number (No. 2008/08401063).

REFERENCES

1. R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.
2. F. Haviv, J. D. Ratajczyk, R. W. DeNet, F. A. Kerdesky, R. L. Walters, S. P. Schmidt, J. H. Holms, P. R. Young, and G. W. Carter, *J. Med. Chem.*, 1988, **31**, 1719.

3. W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Taylor, C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, and S. C. J. Olson, *J. Med. Chem.*, 1992, **35**, 2562.
4. K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1601.
5. F. W. Bell, A. S. Cantrell, M. Hoegberg, S. R. Jaskunas, N. G. Johansson, C. L. Jordon, M. D. Kinnick, P. Lind, J. M. Morin, R. O. B. Noreen, J. A. Palkowitz, C. A. Parrish, P. Pranc, C. Sahlberg, R. J. Ternansky, R. T. Vasileff, L. Vrang, S. J. West, H. Zhang, and X.-X. Zhou, *J. Med. Chem.*, 1995, **38**, 4929.
6. B. A. Fink, D. S. Mortensen, S. R. Stauffer, Z. D. Aron, and J. A. Katzenellenbogen, *Chem. Biol.*, 1999, **6**, 205.
7. J. E. van Muijlwijk-Koezen, H. Timmerman, R. C. Vollinga, J. F. von Drabbe Künzel, M. de Groote, S. Visser, and A. P. Ijzerman, *J. Med. Chem.*, 2001, **44**, 749.
8. A. Hantzsch and J. H. Weber, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 3118.
9. J. V. Metzger In: R. Katritzky and C. W. Rees, Editors, *Comprehensive Heterocyclic Chemistry Vol. 6*, Pergamon, New York, NY (1984), pp. 235–332.
10. B. Das, V. Saidi Reddy, and R. Ramu, *J. Mol. Catal. A: Chem.*, 2006, **252**, 235.
11. M. Narender, M. S. Reddy, R. Sridhar, Y. V. D. Nageswar, and K. R. Rao, *Tetrahedron Lett.*, 2005, **46**, 5953.
12. H. L. Siddiqui, A. Iqbal, S. Ahmed, and G. Weaver, *Molecules*, 2006, **11**, 206.
13. T. M. Potewar, S. A. Ingale, and K. V. Srinivasan, *Tetrahedron*, 2007, **63**, 11066.
14. W. K. George and R. M. Arjun, *Tetrahedron Lett.*, 2006, **47**, 5171.
15. T. Aoyama, S. Murata, I. Arai, N. Araki, T. Takido, Y. Suzuki, and M. Kodomari, *Tetrahedron*, 2006, **62**, 3201.
16. S. Balalaie, S. Nikoo, and S. Haddadi, *Synth. Commun.*, 2008, **38**, 2521.
17. T. M. Potewar, S. A. Ingale, and K. V. Srinivasan, *Tetrahedron*, 2008, **64**, 5019.
18. K. C. Joshi, V. N. Pathak, and P. Arya, *Agric. Biol. Chem.*, 1979, **43**, 199.
19. M. Ueno and H. Togo, *Synthesis*, 2004, **16**, 2673.
20. C. R. Barbarín, S. Bernès, F. Sánchez-Viesca, and M. Berros, *Acta Cryst. C*, 2003, **59**, 360.
21. L. C. King and R. J. Hlavacek, *J. Am. Chem. Soc.*, 1950, **72**, 3722.
22. M. P. Taterao, A. I. Sachin, and V. S. Kumar, *Tetrahedron*, 2007, **63**, 11066.
23. E. Garcia-Egido, S. Y. F. Wong, and B. H. Warrington, *Lab Chip.*, 2002, **2**, 31.