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

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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, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis data.

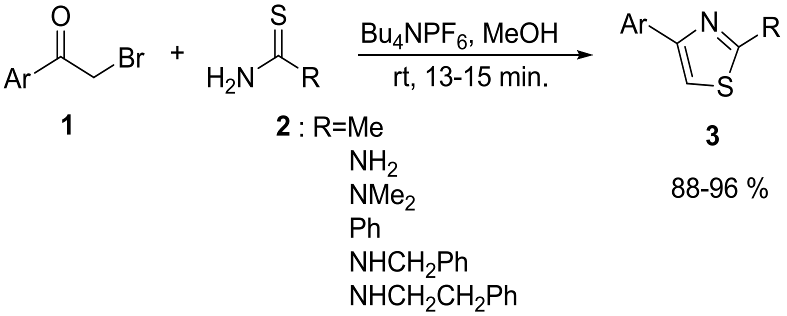
Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids.[1] This heterocyclic 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 receptors[6] 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 salts[13] 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 (^{1}H 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_6H_5	NH_2	**3a**	96	14	150-151	150[15]
2	C_6H_5	Me	**3b**	95	15	67-68	67[16]
3	*p*-F-C_6H_4	NH_2	**3c**	94	13	101-102	102-103[17]
4	*p*-F-C_6H_4	Me	**3d**	93	14	184-185	185[18]
5	*p*-Cl-C_6H_4	NH_2	**3e**	93	15	163-164	163-164[16]
6	*p*-Cl-C_6H_4	Me	**3f**	89	14	111-112	111[19]
7	*p*-Br-C_6H_4	NH_2	**3g**	94	15	179-181	180-181[16]
8	*p*-Br-C_6H_4	Me	**3h**	88	13	130-131	130[20]
9	*p*-Me-C_6H_4	NH_2	**3i**	91	15	124-125	124-125[21]
10	*p*-Me-C_6H_4	Me	**3j**	92	15	58-60	58-59[19]
11	*p*-MeO-C_6H_4	NH_2	**3k**	89	14	202-203	200-203[19]
12	*p*-MeO-C_6H_4	Me	**3l**	95	15	66-67	67-68[19]
13	C_6H_4-O-C_6H_4	NH_2	**3m**	94	15	65-67	-
14	C_6H_4-O-C_6H_4	Me	**3n**	92	14	67-68	-
15	C_6H_4-O-C_6H_4	NMe_2	**3p**	89	13	154-155	-
16	C_6H_4-O-C_6H_4	Ph	**3r**	93	15	127-128	-
17	C_6H_4-O-C_6H_4	$NHCH_2Ph$	**3s**	94	14	137-138	-
18	C_6H_5	$NHCH_2CH_2Ph$	**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. Convertion of phenacyl bromide using different tetrabutylammonium salts as catalyst

Catalyst	Thiazole **3a**		Thiazole **3c**		Thiazole **3h**		Thiazole **3k**		Thiazole **3n**	
	t	*y*	*t*	*y*	*t*	*y*	*t*	*y*	*t*	*y*
Bu_4NPF_6	14	96	13	94	13	88	14	89	14	92
$Bu_4N\ BF_4$	22	89	21	86	25	81	26	80	28	83
Bu_4NCl	22	88	23	88	23	83	24	82	25	81
Bu_4NBr	23	86	22	85	24	82	25	81	27	85
Bu_4NI	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 ^{1}H and ^{13}C NMR spectroscopy, FT-IR, melting point and elemental analyses.

The ^{1}H 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 ^{13}C 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 trails 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

^{1}H 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}; ^{1}H 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 $C_{15}H_{12}N_2OS$: 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 ($CDCl_3$, 400 MHz): δ= 2.77 (s, 3H, CH_3), 6.51 (s, 1H, thiazole H), 7.17-7.64 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 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 $C_{16}H_{13}NOS$: 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 ($CDCl_3$, 400 MHz): δ= 3.12 (s, 6H, CH_3), 6.48 (s, 1H, thiazole H), 7.11-7.66 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{16}N_2OS$: 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 ($CDCl_3$, 400 MHz): δ= 6.46 (s, 1H, thiazole H), 7.09-7.69 (m, 14H, Ar-H); ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{15}NOS$: 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 ($CDCl_3$, 400 MHz): δ= 4.41 (s, 2H, CH_2), 5.04 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 6.89-7.46 (m, 14H, Ar-H); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{18}N_2OS$: C, 73.71; H, 5.06; N, 7.82%. Found: C, 73.34; H, 4.99; N, 7.39%.

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