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Der Chemica Sinica, 2015, 6(8):14-18

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

An efficient one-pot synthesis of 2-aminothiazole derivatives

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ABSTRACT

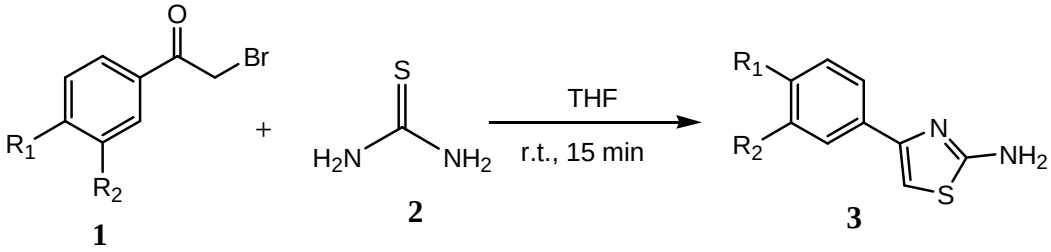
A highly efficient, rapid and catalyst free protocol has been developed for the synthesis of 2-aminothiazoles in tetrahydrofuran (THF). Reaction was carried out at room temperature and the products were obtained in high yields without further purification.

Keywords: Thiazole, Thiourea, Phenacyl bromide, Tetrahydrofuran, 2-Aminothiazole.

INTRODUCTION

Thiazole structural motifs represent one of the most biologically active classes of compounds [1,2]. They possess wide spectrum of biological activities and prove to be an important intermediate for the synthesis of biological active compounds [1,2]. 2-Amino-1,3-thiazole scaffolds have found to be useful as antibacterial [3], antitumor [4], antifungal [4], VGEF-A inhibiting [5], anti-allergic [6], anti-hypertension [7], anti-inflammatory [8], anti-viral [9] etc agents. They are also known to bind with estrogen receptors [10], behave as adenosine receptor antagonists [11] and are effective against schizophrenia [12]. Thus, synthesis of thiazole derivatives with the aim to develop new drug molecules has been an active area of research [1,2,13-15].

Various synthetic methods have been reported for the construction of thiazole ring among which Hantzsch synthesis is the most common method which involves cyclization of haloketones with thioamide [16]. Using this approach several synthetic methodology have been adopted including use of solid supported synthesis [17] and solution phase preparation using various solvents such as DMF [18], dioxane [19], PEG-400 [20], glycerine [21]. Other methods include synthesis through usage of catalyst such as using β-cyclodextrin [22], ammonium-molybdophosphate (AMP) [23], iodine [24], silica-chloride [25] as well as ionic liquids [26] and microwave irradiation [27]. However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, long reaction times, unsatisfactory yields, tedious product isolation procedures and use of expensive catalysts. So development of an improved protocol is of considerable interest. As a part of our ongoing effort towards the synthesis of biologically active compounds [28-30], we herein developed an efficient high yielding synthetic protocol for 2-amino-1,3-thiazoles (Scheme 1).



Scheme 1: Synthesis of 2-amino-1,3-thiazoles

MATERIALS AND METHODS

All the chemicals used in the synthesis were purchased from Sigma-Aldrich and used as received. Thin-layer chromatography was used to monitor reaction progress. Compounds were purified by crystallization. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer and the values are expressed in cm^{-1}. The ^1H NMR spectra were recorded on Bruker Spectrospin spectrometer at 400 MHz using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hz. Elemental analysis were performed on a Carlo Erba Model EA-1108 elemental analyzer.

General procedure for the synthesis of 4-phenylthiazol-2-amines: In a 50 mL round bottom flask, substituted phenacyl bromide was dissolved using THF. The thiourea was added in 1: 1.2 molar ratios to the reaction mixture and stirred at room temperature (r.t.) for 15 minutes. After completion, the reaction mixture was filtered and washed with water. The precipitate was dried and the product was obtained as solid powder. The separated solid was recrystallized using ethanol.

4-Phenyl-1,3-thiazol-2-amine (3a). IR: 3435, 3252, 3154, 2920, 2852, 1600, 1520, 1481, 1440 1333, 1215, 1072, 912, 846, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.12 (2H, bs), 6.75 (1H, s), 7.33 (1H, d, *J* = 7.6 Hz), 7.42-7.38 (2H, m), 7.80 (2H, d, *J* = 7.2 Hz); Anal. calc. for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90; found C, 61.44; H, 4.60; N, 15.94.

4-(4-Chlorophenyl)-1,3-thiazol-2-amine (3b). IR: 3436, 3243, 3145, 2920, 2850, 1599, 1522, 1482, 1440 1336, 1216, 1071, 912, 846, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.04 (2H, bs), 6.74 (1H, s), 7.35 (2H, d, *J* = 8.4 Hz), 7.72 (2H, d, *J* = 8.4 Hz); Anal. calc. for $C_9H_7N_2SCl$: C, 51.31; H, 3.35; N, 13.30; found C, 51.41; H, 3.40; N, 13.36.

4-(4-Fluorophenyl)-1,3-thiazol-2-amine (3c). IR: 3434, 3243, 3150, 2928, 2857, 1590, 1520, 1482, 1440 1333, 1216, 1073, 911, 846, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (2H, bs), 6.67 (1H, s), 7.11 (2H, d, *J* = 8.1 Hz), 7.78 (2H, d, *J* = 8.1 Hz); Anal. calc. for $C_9H_7N_2SF$: C, 55.65; H, 3.63; N, 14.42; found C, 55.56; H, 3.70; N, 14.41.

4-(4-Bromophenyl)-1,3-thiazol-2-amine (3d). IR: 3427, 3282, 3106, 2924, 1530, 1466, 1390, 1334, 1065, 1032, 1001, 820, 727, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.02 (2H, bs), 6.75 (1H, s), 7.50 (2H, d, *J* = 8.4 Hz), 7.66 (2H, d, *J* = 8.8 Hz); Anal. calc. for $C_9H_7N_2SBr$: C, 42.37; H, 2.77; N, 10.98; found C, 42.43; H, 2.72; N, 10.92.

4-(3-Bromophenyl)-1,3-thiazol-2-amine (3e). IR: 3440, 3281, 3126, 2924, 1530, 1466, 1350, 1334, 1065, 1033, 1021, 822, 729, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.02 (2H, bs), 7.15 (1H, s), 7.23-7.35 (3H, m, Ar-H), 7.65 (1H, d, *J* = 1.8Hz); Anal. calc. for $C_9H_7N_2SBr$: C, 42.37; H, 2.77; N, 10.98; found C, 42.41; H, 2.70; N, 10.92.

4-(4-Nitrophenyl)-1,3-thiazol-2-amine (3f). IR: 3430, 3243, 3091, 2933, 1572, 1514, 1377, 1360, 1310 1216, 1071, 915, 846, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.23 (2H, bs), 7.41 (1H, s), 8.03 (2H, d, *J* = 8.0 Hz), 8.25 (2H, d, *J* = 8.8 Hz); Anal. calc. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; found C, 48.90; H, 3.14; N, 18.92.

4-(3-Nitrophenyl)-1,3-thiazol-2-amine (3g). IR: 3429, 3240, 3071, 2933, 1570, 1514, 1373, 1360, 1312 1213, 1074, 915, 846, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.11 (2H, bs), 7.67 (1H, s), 7.73-7.78 (3H, m, Ar-H), 7.88 (1H, d, *J* = 1.8 Hz); Anal. calc. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; found C, 48.81; H, 3.25; N, 19.07.

4-(4-Methoxyphenyl)-1,3-thiazol-2-amine (3h). IR: 3434, 3253, 2948, 1524, 1482, 1336, 1216 , 1071, 910, 846, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s) 5.01 (2H, bs), 6.58 (1H, s), 6.81 (2H, dd, *J* = 8.2 Hz, *J* = 1.8 Hz) 7.72 (2H, dd, *J* = 8.4 Hz, *J* = 1.6 Hz); Anal. calc. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58; found C, 58.29; H, 4.70; N, 13.49.

4-(3-Methoxphenyl)-1,3-thiazol-2-amine (3i). IR: 3453, 3278, 2918, 2855, 1599, 1440, 1240, 1171, 908, 856, 780 cm.-1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (3H, s), 5.18 (2H, bs), 6.71 (1H, s), 6.86 (1H, d, *J* = 1.8 Hz), 7.34-7.25 (3H, m); Anal. calc. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58; found C, 58.19; H, 4.80; N, 13.49.

4-(4-Methylphenyl)-1,3-thiazol-2-amine (3j). IR: 3427, 3216, 3128, 2945, 2821, 1588, 1509, 1451, 1341, 1221, 1078, 918, 836, 763 cm.-1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 5.09 (2H, bs), 6.68 (1H, s), 7.19 (2H, d, *J* = 7.6 Hz), 7.67 (2H, d, *J* = 8.0 Hz); Anal. calc. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; found C, 63.11; H, 5.40; N, 14.77.

4-(3-Methylphenyl)-1,3-thiazol-2-amine (3k). IR: 3429, 3213, 3120, 2941, 2821, 1583, 1509, 1450, 1341, 1223, 1077, 918, 836, 663 cm^{-1}; ^1H NMR (400 MHz; DMSO): δ 2.33 (3H, s), 6.98 (1H, s), 7.02 (2H, bs), 7.16-7.23 (2H, m), 7.58 (1H, d, *J* = 7.8 Hz), 7.66 (1H, d, *J* = 1.6 Hz); Anal. calc. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; found C, 63.15; H, 5.37; N, 14.77.

4-(3,4-Dichlorophenyl)-1,3-thiazol-2-amine (3l). IR: 3425, 3235, 3144, 2919, 2864, 1517, 1486, 1423, 1316, 1096, 1062, 907, 834, 753 cm.-1 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$): δ 5.02 (2H, bs), 6.75 (1H, s), 7.47 (1H, d, *J* = 8.1 Hz), 7.61-7.58 (1H, dd, *J* = 8.4 Hz, *J* = 2.1 Hz), 7.89 (1H, d, *J* = 2.1 Hz); Anal. calc. for $C_9H_6N_2SCl_2$: C, 44.10; H, 2.47; N, 11.43; found C, 44.15; H, 2.40; N, 11.41.

4-(4-Cyanophenyl)-1,3-thiazol-2-amine (3m). IR: 3420, 3227, 3167, 2812, 2237, 1599, 1472, 1440 1339, 1211, 1042, 915, 856, 783 cm.-1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (2H, bs), 6.78 (1H, s), 8.03 (2H, d, *J* = 8.0 Hz), 8.25 (2H, d, *J* = 8.8 Hz); Anal. calc. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; found C, 59.60; H, 3.57; N, 20.81.

RESULTS AND DISCUSSION

Careful literature analysis revealed that a variety of solvents have been used for the reaction of haloketones with thioamide [18-21]. Our focus was to develop a synthetic protocol which can give high yield with easy work up. We have tried the reaction in various solvent systems (Table 1). Tetrahydrofuran (THF) gave maximum yield in minimum time with easy workup procedure. The reaction of phenacyl bromide (**1**) and thiourea (**2**) was carried out in the presence of THF (Scheme 1, Table 2). The phenacyl bromides carrying different functional groups were subjected to the reaction as presented in table 2. The reaction protocol gave high yields (83-95%) in a short reaction time of 15 minutes. All the used functionalities were found to be compatible under the reaction condition. We have also explored the possibility of using other solvent systems as the reaction media but the yield of the product was not appreciable even after refluxing for about 3-6 hours (Table 1).

To assess the feasibility of the methodology on higher scale under identical reaction conditions, we carried out the reaction on a 50 gm scale twice for compound **3a** and it was observed that the reaction proceeded smoothly and the desired product was isolated in 94% and 93% yields. The structures of all of the compounds were identified by their mp and spectral data.

Table 1: Reaction of 1 and 2 in various solvent systems

Solvent system	Time of reaction	Isolated Yield %
H_2O:DMF	4 h (Reflux)	60
Benzene	6 h (Reflux)	62
Dioxane	3 h (Reflux)	58
H_2O:Dioxane	3 h (Reflux)	63
H_2O:Toluene	4 h (Reflux)	65
Tetrahydrofuran (THF)	10 min (Room Temp.)	95

Table 2: One-pot synthesis of substituted 2-amino-1,3-thiazoles *via* Scheme 1

Comp. No. 3	R_1	R_2	Isolated Yield (%)	Mp (°C) Found	Mp (°C) Reported [ref]
a	H	H	95	147-148	150-151 [31]
b	Cl	H	83	162-164	167-168 [20]
c	F	H	85	105-108	102-103 [32]
d	Br	H	92	180-181	176-177 [33]
e	H	Br	89	132-135	-
f	NO_2	H	94	280-284	284-286 [34]
g	H	NO_2	90	190-192	189-190 [32]
h	OCH_3	H	92	204-206	208-209 [20]
i	H	OCH_3	89	99-100	98-100 [35]
j	CH_3	H	87	134-136	135-136 [34]
k	H	CH_3	85	59-60	56-58 [35]
l	Cl	Cl	92	190-195	-
m	CN	H	93	259-265	257-268 [36]

CONCLUSION

In conclusion, we have developed a novel synthetic methodology for the synthesis of 2-aminothiazole derivatives using phenacyl bromides and thiourea in tetrahydrofuran (THF). The short reaction times, high yields and easy workup are the main advantages of this process.

Acknowledgements
The authors AF and RS are thankful to Council of Scientific & Industrial Research (CSIR), New Delhi, India and DM to University Grant Commission (UGC) India for financial support.

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