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Catalyst-free efficient synthesis of 2-aminothiazoles in water at ambient temperature

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ABSTRACT

A highly efficient and facile method has been described for the synthesis of substituted 2-aminothiazoles in water without any added catalyst or co-organic solvent. The reaction was carried out at ambient temperature and the products were obtained in excellent isolated yields. The developed protocol is successfully applied for the preparation of an anti-inflammatory drug, fanetizole.

1. Introduction

The thiazole ring system is a useful structural motif found in numerous biologically active molecules. Thiazole ring is a structural component of natural compounds such as vitamin B1 (thiamine), penicillin, and carboxylase. The 2-aminothiazole ring system is a useful structural element in medicinal chemistry having application in drug development for the treatment of allergies,[1] hypertension,[2] inflammation,[3] schizophrenia,[4] bacterial,[5] and HIV[6] infections. Aminothiazoles are known to be ligands of estrogen receptors[7] as well as a novel class of adenosine receptor antagonists[8] whereas other analogues are used as fungicides, inhibiting in vivo growth of *Xanthomonas*, and as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[9]

In view of the importance of 2-aminothiazole and its derivatives, several methods were reported in the literature. Hantzsch reaction of α-halocarbonyl compounds with thioureas or thioamides provides a useful method for the synthesis of thiazoles.[10] Solid supported synthesis have been used to generate small organic libraries[11] and solution phase preparation of combinatorial libraries have been prepared in DMF[12] as well as in dioxane.[13] Recently, many improved methods have been reported for the synthesis of thiazoles using catalyst such as ammonium-12-molybdophosphate (AMP) in methanol,[14] β-cyclodextrin in water,[15] iodine,[16] and by the use of microwave in ethanol.[17] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedures, polar/volatile/hazardous organic solvents, and often expensive catalysts. These processes also generate waste-containing solvent and catalysts, which have to be recovered, treated, and disposed of.

The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvent but also because water exhibits unique reactivity and selectivity, which is different from those obtained in conventional organic solvents. Thus, elements of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[18] The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding.[19] Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry.[20] Our recent results obtained during the synthesis of benzodiazepines promoted by water[21] prompted us to investigate the heterocyclization reaction for the synthesis of biologically active heterocycles using water as a solvent. In continuation to our research devoted to development of green organic processes for the synthesis of biologically active heterocycles, herein we report an efficient and facile method for the synthesis of 2-aminothiazoles in water.

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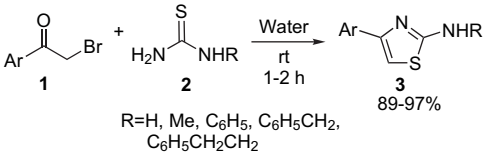
2. Result and discussion

When phenacyl bromide was treated with thiourea in water at room temperature, to our surprise, the reaction occurred affording 4-phenylthiazol-2-amine **3a** in 97% yield in just 1.5 h (Scheme 1).



Scheme 1. Synthesis of 2-aminothiazoles in water.

To investigate the advantageous role of water as a solvent for this method, comparative reactions were carried out in other solvents. The reaction of phenacyl bromide and thiourea was carried out in CH_2Cl_2 and toluene under similar reaction conditions where it furnished the desired 4-phenylthiazol-2-amine (**3a**) in yields of only 48 and 12%, respectively. When the same reaction was carried out in more polar solvents such as THF, MeCN, and MeOH under identical conditions, **3a** was obtained in yield of 68, 73, and 72%, respectively. It is remarkable that the reaction carried out in water afforded 4-phenylthiazol-2-amine (**3a**) in excellent yield (97%), which is significantly higher than those obtained for the volatile/toxic/polar organic solvents. The structure of **3a** was assigned on the basis of ^{1}H and ^{13}C NMR spectral data and by comparison with authentic samples prepared by literature procedure as well as by our methods.[22] The ^{1}H NMR spectra of **3a** shows a characteristic peak at δ 6.48 ppm corresponding to the hydrogen of thiazole ring, whereas in the ^{13}C NMR spectrum, the peak appearing of δ 101.4 and 167.8 ppm corresponds to C-5 and C-2, respectively, of the thiazole ring.

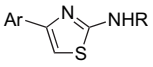
After optimizing the conditions, we next examined the scope and generality of this method to other substrates using different substituted phenacyl bromides and substituted thioureas. The results are summarized in Table 1. The phenacyl bromide with electron-rich functionality (entries 5–8) as well as electron-poor functionality (entries 14–17) undergoes condensation reaction with thiourea/substituted thiourea equally well to afford the corresponding 2-aminothiazoles in excellent isolated yields. Furthermore, α-bromo-2-acetonaphthone smoothly reacted with thiourea and substituted thiourea affording the corresponding products **3r**–**v** in excellent yields (Table 1, entries 18–22).

The experimental procedure is very simple and easy to carry out. A mixture of phenacyl bromide and thiourea was vigorously stirred in water at room temperature until completion of the reaction. Progress of reaction was monitored by thin layer chromatography using ethyl acetate/petroleum ether in appropriate proportions as eluent. Extraction in ethyl acetate followed by evaporation of solvent gave crude products, which were purified by column chromatography to yield pure products in excellent yields. All the products were characterized by IR, melting point, ^{1}H and ^{13}C NMR spectral analyses, and elemental analyses. The structure of all the known compounds were further confirmed by comparing their melting points with those reported in the literature. Complete characterization data for all the new compounds are given in Section 4.

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 applied our protocol for the synthesis of the anti-inflammatory drug fanetizole **3d**. For this, we treated phenacyl bromide with 2-phenylethyl thiourea in water as reaction medium under similar conditions to afford fanetizole in 92% yield in 1.5 h at ambient temperature (Table 1, entry 4).

Despite the various methods reported for the synthesis of the 2-aminothiazoles by using various organic solvents such as ethanol, methanol, DMF, acetone, etc. with or without catalyst, there has been considerable interest in the development of alternative approaches avoiding the use of volatile polar organic solvents and expensive catalyst. An alternative to this is the use of water as reaction medium since water has emerging as one of the 'Green solvents' in organic synthesis. To the best of our knowledge, this is the first approach for the synthesis of 2-aminothiazoles carried out in water at ambient temperature. It can be observed that almost all

Table 1
Synthesis of 2-aminothiazoles in water



Entry	Ar	R	Product **3**	Time (h)	Yield[a] (%)	Mp (°C)	Lit. mp (°C)
1	C_6H_5	H	**3a**	1.5	97	150–151	150–151[24]
2	C_6H_5	CH_3	**3b**	2	94	136–137	135–136[24]
3	C_6H_5	C_6H_5	**3c**	1	96	135–136	136–137[24]
4	C_6H_5	$C_6H_5CH_2CH_2$	**3d**	1.5	92	116–117	116–117[22]
5	*p*-CH_3–O–C_6H_4	H	**3e**	1	89	206–207	204–205[26]
6	*p*-CH_3–O–C_6H_4	CH_3	**3f**	1	93	138–139	138–139[24]
7	*p*-CH_3–O–C_6H_4	C_6H_5	**3g**	1	96	138–139	139–140[24]
8	*p*-CH_3–O–C_6H_4	$C_6H_5CH_2CH_2$	**3h**	1.5	97	121–122	—
9	*p*-F–C_6H_4	H	**3i**	2	93	102–103	—
10	*p*-F–C_6H_4	CH_3	**3j**	2	93	136–137	137–138[25]
11	*p*-F–C_6H_4	C_6H_5	**3k**	1	96	110–111	111–112[25]
12	*p*-F–C_6H_4	$C_6H_5CH_2$	**3l**	1	96	109–110	—
13	*p*-F–C_6H_4	$C_6H_5CH_2CH_2$	**3m**	1	95	108–109	—
14	*m*-O_2N–C_6H_4	H	**3n**	2	97	189–190	188–190[26]
15	*m*-O_2N–C_6H_4	CH_3	**3o**	2	92	156–157	—
16	*m*-O_2N–C_6H_4	C_6H_5	**3p**	1.5	90	122–124	—
17	*m*-O_2N–C_6H_4	$C_6H_5CH_2$	**3q**	2	91	102–103	—
18	β-$C_{10}H_7$	H	**3r**	1	94	153–154	152–153[24]
19	β-$C_{10}H_7$	CH_3	**3s**	2	89	123–124	121–122[24]
20	β-$C_{10}H_7$	C_6H_5	**3t**	2	90	149–150	147–148[24]
21	β-$C_{10}H_7$	$C_6H_5CH_2$	**3u**	2	93	131–132	—
22	β-$C_{10}H_7$	$C_6H_5CH_2CH_2$	**3v**	2	92	125–126	—

[a] Isolated yield after column chromatography.

reactions were complete in 1–2 h in water without the need of any added catalyst or co-organic solvents at ambient temperature. Water itself promotes the reactions. The use of water as a clean, inexpensive, and universal solvent combines features of both economic and environmental advantages. The amount of water 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 2% solids (w/v) to 20% solids (w/v) in the case of 4-phenyl-2-aminothiazole and fanetizole, respectively. The reactions went to completion in identical times and with the same isolated yields as for the diluted reaction mixture. This observation assumes great significance for optimizing reactor volumes during scale-up operations. A highly efficient stirring is required for the success of these reactions. The role of water as the reaction medium and its mechanism are still not clear. Water, probably due to its unique abilities such as hydrogen bonding, high dielectric constant, and polarity appears to be more efficient medium for this reaction. The good results obtained following our simple procedure are a pleasant surprise in view of the numerous catalysts employed in organic solvents to synthesize this class of compounds.

3. Conclusion

In conclusion, we have described a simple, highly efficient, and facile protocol for the synthesis of 2-aminothiazole derivatives in water as reaction medium at ambient temperature. This process avoids the use of highly polar and toxic volatile organic solvents such as DMF, dioxane, and methanol, and catalyst, with the water itself playing the dual role of a solvent and promoter. Furthermore, the procedure offers several advantages including improved yields, simple experimental procedure, cleaner reactions, and low cost, which makes it a useful and attractive strategy in view of economic and environmental advantages. The successful application of this protocol for the preparation of the anti-inflammatory drug fanetizole is a significant contribution for the development of a green commercial process for the same.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-200 spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as internal standard. Infrared spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a flash EA 1112 thermofinnigan instrument. Melting points were recorded in open capillary on Buchi melting Point B-540 apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster. Column chromatography was performed using silica gel (60–120 mesh size). Tap water (pH=6.7) was used for the reaction.

4.2. General procedure for the synthesis of 2-aminothiazoles

A mixture of phenacyl bromide **1** (1 mmol) and thiourea **2** (1.1 mmol) was stirred in water (5 mL) at room temperature under vigorous magnetic stirring for the specified time as mentioned in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted using ethyl acetate (2×15 mL). The organic layer was separated from aqueous layer. The combined organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to obtain the crude solid product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the pure product **3**.

4.2.1. 4-(4-Methoxyphenyl)-N-phenethylthiazol-2-amine (**3h**)

White solid; mp 121–122 °C; R_f (15% ethyl acetate/petroleum ether) 0.31; IR (KBr): 3228, 3019, 2958, 1549, 1492, 1333, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.93–3.0 (t, J=6.9 Hz, 2H, CH_2), 3.51–3.60 (q, J=6.9 Hz, 2H, CH_2N), 3.82 (s, 3H, OMe), 5.32 (br s, 1H, NH), 6.56 (s, 1H, thiazole H), 6.87–6.92 (d, J=8.9 Hz, 2H, ArH), 7.21–7.37 (m, 5H, ArH), 7.69–7.74 (d, J=8.9 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=35.3, 47.1, 55.2, 98.8, 113.8, 126.5, 127.2, 127.8, 128.6, 128.7, 138.4, 151.1, 159.1, 169.5. Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02%. Found: C, 69.42; H, 5.95; N, 9.11%.

4.2.2. 4-(4-Fluorophenyl)thiazol-2-amine (**3i**)

Yellow solid; mp 102–103 °C; R_f (40% ethyl acetate/petroleum ether) 0.52; IR (KBr): 3489, 3019, 1601, 1537, 1490, 1333, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=5.04 (br s, 2H, NH_2), 6.64 (s, 1H, thiazole H), 7.01–7.09 (m, 2H, ArH), 7.70–7.77 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=102.1, 115.3, 115.5, 127.6, 127.6, 130.9, 150.1, 161.3, 163.3, 167.6. Anal. Calcd for $C_9H_7FN_2S$: C, 55.65; H, 3.63; N, 14.42%. Found: C, 55.73; H, 3.56; N, 14.53%.

4.2.3. N-Benzyl-4-(4-fluorophenyl)thiazol-2-amine (**3l**)

White solid; mp 109–110 °C; R_f (15% ethyl acetate/petroleum ether) 0.42; IR (KBr): 3213, 3019, 2977, 1578, 1546, 1490, 1336, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=4.49–4.51 (d, J=5.0 Hz, 2H, CH_2), 5.69 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 6.98–7.09 (m, 2H, ArH), 7.29–7.40 (m, 5H, ArH), 7.71–7.81 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=49.7, 100.4, 115.1, 115.5, 127.4, 127.5, 127.6, 127.7, 128.6, 131.08, 131.1, 137.5, 150.3, 159.8, 164.7, 169.7. Anal. Calcd for $C_{16}H_{13}FN_2S$: C, 67.58; H, 4.61; N, 9.85%. Found: C, 67.72; H, 4.49; N, 9.72%.

4.2.4. 4-(4-Fluorophenyl)-N-phenethylthiazol-2-amine (**3m**)

White solid; mp 108–109 °C; R_f (15% ethyl acetate/petroleum ether) 0.46; IR (KBr): 3209, 3019, 2959, 1578, 1551, 1491, 1327, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.94–3.01 (t, J=6.9 Hz, 2H), 3.52–3.62 (q, J=6.9 Hz, 2H), 5.21 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 6.99–7.10 (m, 2H, ArH), 7.21–7.37 (m, 5H, ArH), 7.70–7.80 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=35.3, 47.0, 100.2, 115.1, 115.5, 126.6, 127.5, 127.7, 128.6, 128.7, 131.1, 131.2, 138.3, 150.5, 159.8, 164.7, 169.4. Anal. Calcd for $C_{17}H_{15}FN_2S$: C, 68.43; H, 5.07; N, 9.39%. Found: C, 68.32; H, 5.18; N, 9.51%.

4.2.5. N-Methyl-4-(3-nitrophenyl)thiazol-2-amine (**3o**)

Orange needles; mp 156–157 °C; R_f (20% ethyl acetate/petroleum ether) 0.28; IR (KBr): 3431, 3019, 2923, 1591, 1565, 1534, 1517, 1353, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=3.02–3.04 (d, J=5.12 Hz, 3H, Me), 5.39 (br s, 1H, NH), 6.86 (s, 1H, thiazole H), 7.48–7.56 (t, J=7.9 Hz, 1H, ArH), 8.09–8.13 (dd, J=1.9 and 7.9 Hz, 2H, ArH), 8.63–8.65 (t, J=1.9 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=32.1, 103.0, 120.8, 122.1, 129.4, 131.7, 136.5, 148.5, 149.2, 170.8. Anal. Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86%. Found: C, 51.13; H, 3.77; N, 17.92%.

4.2.6. 4-(3-Nitrophenyl)-N-phenylthiazol-2-amine (**3p**)

Yellow solid; mp 122–124 °C; R_f (20% ethyl acetate/petroleum ether) 0.42; IR (KBr): 3019, 1602, 1543, 1519, 1498, 1352, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=6.96 (s, 1H, thiazole H), 7.08–7.17 (m, 1H), 7.37–7.42 (m, 4H, ArH), 7.52–7.60 (t, J=7.8 Hz, 1H, ArH), 7.94 (br s, 1H, NH), 8.12–8.20 (m, 2H), 8.66–8.88 (t, J=1.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=103.7, 118.6, 120.8, 122.3, 123.5, 129.4, 129.5, 131.8, 135.7, 139.8, 148.0. Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13%. Found: C, 60.48; H, 3.81; N, 14.21%.

4.2.7. N-Benzyl-4-(3-nitrophenyl)thiazol-2-amine (**3q**)

Yellow solid; mp 102–103 °C; R_f (20% ethyl acetate/petroleum ether) 0.43; IR (KBr): 3227, 3020, 2977, 1548, 1518, 1495, 1351,

755 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ=4.53–4.55 (d, J=5.5 Hz, 2H, CH_2Ar), 5.67 (br s, 1H, NH), 6.85 (s, 1H, thiazole H), 7.29–7.41 (m, 5H, ArH), 7.47–7.55 (t, J=8.0 Hz, 1H, ArH), 8.08–8.13 (m, 2H, ArH), 8.63–8.64 (t, J=1.9 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=49.7, 103.2, 120.8, 122.0, 127.6, 127.7, 128.7, 129.3, 131.6, 136.4, 137.3, 148.5, 148.9, 169.5. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50%. Found: C, 61.83; H, 4.13; N, 13.39%.

*4.2.8. N-Benzyl-4-(naphthalen-2-yl)thiazol-2-amine (**3u**)*

Yellow solid; mp 131–132 °C; R_f (15% ethyl acetate/petroleum ether) 0.46; IR (KBr): 3205, 3019, 2976, 1601, 1549, 1515, 1490, 1350, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ=4.54–4.56 (d, J=4.7 Hz, 2H, CH_2Ar), 5.73 (s, 1H, NH), 6.83 (s, 1H, thiazole H), 7.29–7.45 (m, 7H, ArH), 7.78–7.90 (m, 4H, ArH), 8.33 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=49.8, 101.6, 124.0, 124.9, 125.8, 126.1, 127.5, 127.6, 128.0, 128.3, 128.6, 132.1, 132.9, 133.6, 137.5, 151.3, 169.5. Anal. Calcd for $C_{20}H_{16}N_2S$: C, 75.92; H, 5.10; N, 8.85%. Found: C, 75.81; H, 5.23; N, 8.72%.

*4.2.9. 4-(Naphthalen-2-yl)-N-phenethylthiazol-2-amine (**3v**)*

Yellow solid; mp 125–126 °C; R_f (15% ethyl acetate/petroleum ether) 0.39; IR (KBr): 3201, 3019, 2965, 1583, 1556, 1496, 1357, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ=2.96–3.03 (t, J=6.9 Hz, 2H, CH_2), 3.56–3.66 (q, J=6.9 Hz, 2H, CH_2), 5.32 (br s, 1H, NH), 6.83 (s, 1H, thiazole H), 7.20–7.50 (m, 7H, ArH), 7.77–7.89 (m, 4H, ArH), 8.32 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ=35.4, 47.2, 101.3, 124.0, 124.9, 125.8, 126.1, 126.6, 127.6, 128.0, 128.3, 128.6, 128.7, 132.1, 132.9, 133.6, 138.3, 151.4, 169.5. Anal. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48%. Found: C, 76.43; H, 5.35; N, 8.57%.

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Supplementary data

^1H and ^{13}C NMR spectra associated with this article are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.082.

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