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Efficient synthesis of 2,4-disubstituted thiazoles using ionic liquid under ambient conditions: a practical approach towards the synthesis of Fanetizole

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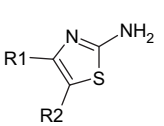
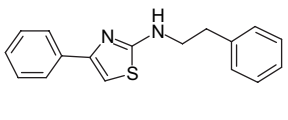
Abstract—A highly efficient and rapid synthesis of 2-amino-4-arylthiazoles and 2-methyl-4-arylthiazole from α-bromoketone and thiourea/thioamide is described using room temperature ionic liquid at ambient conditions. The method is simple, rapid and practical, generating thiazole derivatives in excellent isolated yields. This protocol is utilized for a commercially feasible synthesis of an anti-inflammatory agent, Fanetizole.

1. Introduction

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 $\mathbf{B}_1$ serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids.[1] This heterocyclic system has found broad application in drug development for the treatment of inflammation,[2] hypertension,[3] bacterial[4] and HIV infections.[5] Aminothiazoles are known to be ligands of estrogen receptors[6] as well as a novel class of adenosine receptor antagonists.[7] Other analogues are used as fungicides, inhibiting in vivo growth of *Xanthomonas*, as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[8] Fanetizole, a derivative of 2-aminothiazole is an anti-inflammatory agent. In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.



2-Aminothiazole



Fanetizole

In view of the importance of thiazoles and their derivatives, several methods for the synthesis of thiazole derivatives were developed by Hantzsch, Tchernic, Cook-Heilborn, Gabriel and other groups. The most wildly used method is Hantzsch synthesis,[9,10] who originated it in 1887, involving the reaction of α-halo carbonyl compounds with thioureas or thioamides. Recently, thiazole derivatives were synthesized by using catalyst such as ammonium 12-molybdophosphate,[11] cyclodextrin,[13] iodine[14a] and silica chloride[14b] in organic solvents at elevated temperature and solvents such as 1-methyl-2-pyrrolidinone,[12] and with the use of microwave.[15] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction time, cumbersome product isolation procedures, polar, volatile and 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 development of efficient and environmentally friendly chemical processes for the preparation of biologically active molecules constitutes a major challenge for chemists in organic synthesis. In this context, in recent times, room temperature ionic liquids (RTIL), especially those based on the 1,3-di-alkylimidazolium salts, have shown great promise as an attractive alternative to conventional solvents. They possess the unique advantages of high thermal stability, negligible vapour pressure, immiscibility with a number of organic solvents and recyclability.[16] In many cases, the products are weakly soluble in the ionic phase so that the products can be easily separated by simple extraction. We have recently shown that they can promote and catalyze organic transformations particularly heterocyclization. The various

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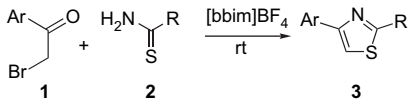
heterocyclization reactions investigated by us include regioselective synthesis of 1,5 benzodiazepines,[17] substituted quinoline and fused polycyclic quinolines using the Friedlander heteroannulation[18] and 2-aryl-4(3*H*)-quinazolinone.[19]

2. Result and discussion

As a continuation of our research devoted to the development of green organic processes through performing reactions in green solvents such as ionic liquids, herein we report a versatile, environmentally friendly synthesis of 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole in ionic liquid (IL). The treatment of phenacyl bromides and thiourea or thioamides in the IL 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4) at ambient temperature afforded the corresponding 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole derivative **3** in excellent yields (Scheme 1).



Scheme 1.

Ionic liquids (ILs) based on 1,3-di-*n*-butylimidazolium salts [bbim]X with varying basicity of anions such as BF_4, Cl, Br and ClO_4 were studied in the typical reaction of phenacyl bromide and thiourea to afford 2-amino-4-phenylthiazole **3a**. The efficacy of the ILs to promote these heterocyclization reactions was correlated to the basicity of the anions. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield. Thus the yield of 2-amino-4-phenylthiazole (**3a**) was compared against the pK_a values of the corresponding acid of the anion (Table 1). Among these ionic liquids, ([bbim])BF_4 was found to be superior in terms of yields and reaction rates. The reaction goes to completion in just 15 min, giving rise to an excellent yield of 2-amino-4-phenylthiazole (96%). Consequently, all further studies were conducted using this IL as the reaction medium.

Table 1. Synthesis of 2-amino-4-phenylthiazole (**3a**) in different ILs

Sr. No.	Ils	pK_a[a]	Yield[c] (%)
1	[bbim]ClO_4	−11	48[b]
2	[bbim]Br	−9	57[b]
3	[bbim]Cl	−7	71[b]
4	[bbim]BF_4	0.5	96[d]

[a] The pK_a values of the parent acid of the anions.[25]
[b] The reaction was stirred upto 2 h.
[c] Isolated yield after column chromatography.
[d] The reaction was completed in 15 min.

Similarly, several phenacyl bromides reacted smoothly with thiourea and thioacetamide to give substituted 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole, respectively, in 87–96% yield in short reaction times. The results are summarized in Table 2. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in the phenacyl bromide. In all cases, the reactions proceeded efficiently at ambient temperature under mild conditions to afford the corresponding thiazoles in excellent yields. All the products were characterized by ^1H and ^{13}C NMR spectroscopy, IR, melting point and elemental analyses.

In all the case, some common features were obtained for ^1H and ^{13}C NMR chemical shift and IR frequencies, which are as follows. The ^1H NMR spectra of 2-amino-4-arylthiazoles show a peak as a broad singlet at δ 5.29–6.31 ppm, which corresponds to the amino–NH group. Furthermore the characteristic peak appearing at δ 5.99–6.70 ppm corresponds to C_5–H of the thiazole ring. However, in the case of 2-methy-4-aryllthiazole, C_5–H of the thiazole ring appears at δ 7.13–7.31 ppm. In the ^{13}C NMR spectrum, the peak appearing in the range of δ 165–170 ppm corresponds to C_2 of the thiazole ring. The IR spectra of 2-amino-4-arylthiazole shows peak at 3450–3200 cm^{-1} corresponding to the amino group while in the case of 2-methyl-4-arylthiazole, the peak corresponding to the methyl group appeared at 2970–2850 cm^{-1}. For the known compounds, the values were in agreement with those reported in the literature.

The experimental procedure is very simple. A mixture of phenacyl bromide, thiourea (or thioacetamide) and ionic liquid, [bbim]BF_4 was stirred at room temperature until completion of the reaction. The progress of the reaction was monitored by thin-layer Chromatography. On completion, the reaction mixture was extracted with a mixture of petroleum ether and ethyl acetate (4:6). The product was pure enough (single spot on TLC) for all practical purposes, however, for characterization purposes it was further purified by

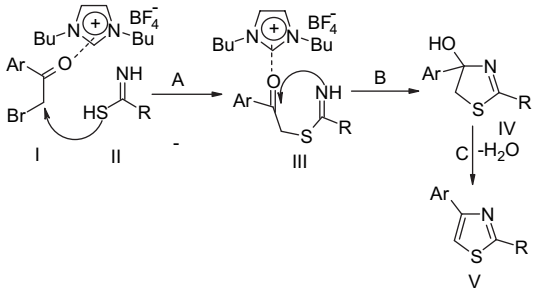
Table 2. Synthesis of 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole

Entry	Ar	R	Thiazole	Time (min)	Yield[a] (%)	Mp (°C)	Lit. mp (°C)
1	C_6H_5	NH_2	**3a**	15	96	150–151	150[23]
2	C_6H_5	Me	**3b**	10	94	67–68	67[22]
3	C_6H_5	$NHCH_2Ph$	**3c**	20	92	100–101	101–102[21]
4	*p*-Me-C_6H_4	NH_2	**3d**	15	93	125–126	124–125[24]
5	*p*-Me-C_6H_4	Me	**3e**	20	89	60–61	58–59[21]
6	*p*-Me-C_6H_4	$NHCH_2Ph$	**3f**	10	93	111–112	—
7	*p*-OMe-C_6H_4	NH_2	**3g**	15	88	202–203	200–203[21]
8	*p*-OMe-C_6H_4	Me	**3h**	15	96	66–67	67–68[21]
9	*p*-OMe-C_6H_4	$NHCH_2Ph$	**3i**	15	95	83–84	—
10	*p*-Cl-C_6H_4	NH_2	**3j**	10	94	163–164	163–164[24]
11	*p*-Cl-C_6H_4	Me	**3k**	10	87	111–112	111[21]
12	*p*-Cl-C_6H_4	$NHCH_2Ph$	**3l**	15	90	114–115	—
13	C_6H_5	$NHCH_2CH_2Ph$	**3m**	15	93	116–117	—

[a] Isolated yield after column chromatography.

column chromatography. The advantage of the use of ionic liquids as novel reaction media for this transformation is that these ionic liquids can be easily recovered and recycled in subsequent reactions. All reactions are general, clean and very fast, almost completed in just 10–20 min. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with a mixture of petroleum ether and ethyl acetate (4:6). The rest of the viscous ionic liquid was thoroughly washed with ether and reused in subsequent reactions without further purification. The recovered IL was used three times without loss in yield.

The role of the IL may be postulated in terms of some Lewis/Brønsted acidity of the imidazolium cation leading to its interaction with the carbonyl oxygen of ketone I and III resulting in its increased polarization leading to increased electrophilicity of the carbocation, thus promoting condensation step A and cyclization step B to give five membered ring IV, which on dehydration afforded thiazole V (Scheme 2). Furthermore, high polarity of ionic liquid helps to solubilize the starting materials, thus obviating the necessity of using any additional solvents.



Scheme 2.

2-Phenylethylamino-4-phenylthiazole, commonly known as Fanetizole is an anti-inflammatory agent that has been reported to have reached phase II clinical trails for the treatment of rheumatoid arthritis.[12,20] Fanetizole has been synthesized by using stringent reaction conditions such as microreactors and heating in solvents such as DMF and 1-methyl-2-pyrrolidinone (NMP). The developed protocol is successfully utilized for a practical synthesis of this anti-inflammatory agent Fanetizole **3m** from phenacyl bromide and 2-phenylethylthiourea in 93% yield (Table 2, entry 13). As compared to reported conditions, we have synthesized this molecule under ambient conditions in excellent yield using the recyclable IL as a reaction medium and promoter.

3. Conclusion

In conclusion, we have described a novel and efficient method for the synthesis of 2-amino-4-arylthiazole and 2-alkyl-4-arylthiazole using ionic liquid as reaction medium as well as a promoter. The important features of this procedure are enhanced reaction rate, mild reaction conditions, high yields and green aspects such as avoiding hazardous organic solvents, toxic catalysts and waste, ease of recovery and reuse of this novel reaction medium. This methodology is successfully applied for a practical synthesis of an anti-inflammatory agent, Fanetizole.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 200 MHz on a Bruker AV-200 spectrometer and chemical shifts (δ) are recorded in parts per million relative to internal standard TMS (δ=0.00). ^{13}C NMR spectra were recorded at 50 MHz and chemical shift (δ) are recorded in parts per million relative to $CDCl_3$ (δ=77.0). 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. The ILs were prepared as per the procedure reported by us earlier.[18]

4.2. General experimental procedure for thiazole synthesis

A mixture of phenacyl bromide (1 mmol), thiourea or thioacetamide (1 mmol) in 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 (2 mL) was stirred at ambient temperature for the appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with a mixture of petroleum ether and ethyl acetate (4:6) (3×10 mL). The combined solvent extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate:petroleum ether to afford pure thiazoles **3**. The immiscible ionic liquid was separated, further washed with ether and dried at 80 °C under reduced pressure, which was reused for subsequent reactions.

4.2.1. 2-Benzylamino-4-(*p*-methylphenyl)thiazole (3f). Yellow solid; mp 111–112 °C; IR (KBr) 3226, 3018, 1546, 1528, 1492, 1453, 1329, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.50 (s, 2H, $ArCH_2$), 6.08 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 7.15–7.18 (d, *J*=8.1 Hz, 2H, ArH), 7.31–7.39 (m, 5H, ArH), 7.66–7.70 (d, *J*=8.2 Hz, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 49.7, 100.0, 125.8, 127.5, 128.6, 129.1, 132.0, 137.4, 137.6, 151.2, 169.5. Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99%. Found: C, 72.53; H, 5.89; N, 10.11%.

4.2.2. 2-Benzylamino-4-(*p*-methoxyphenyl)thiazole (3i). Yellow solid; mp 83–84 °C; IR (KBr) 3214, 3017, 2838, 1610, 1577, 1546, 1492, 1464, 1301, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.49 (s, 2H, $ArCH_2$), 6.13 (br s, 1H, NH), 6.54 (s, 1H, thiazole H), 6.87–6.91 (d, *J*=8.8 Hz, 2H, ArH), 7.31–7.39 (m, 5H, ArH), 7.69–7.74 (d, *J*=8.8 Hz, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 49.8, 55.1, 98.9, 113.7, 127.2, 127.4, 127.4, 127.6, 128.5, 137.6, 150.8, 159.1, 169.8. Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45%. Found: C, 68.79; H, 5.37; N, 9.56%.

4.2.3. 2-Benzylamino-4-(*p*-chlorophenyl)thiazole (3l). White solid; mp 114–115 °C; IR (KBr) 3240, 3019, 1547, 1477, 1328, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.45 (s, 2H, $ArCH_2$), 6.06 (br s, 1H, NH), 6.60 (s, 1H, thiazole H), 7.19–7.31 (m, 7H, ArH), 7.62–7.68 (m, 2H, ArH);

^{13}C NMR (50 MHz, $CDCl_3$): δ 49.7, 101.2, 127.2, 127.5, 127.7, 128.6, 128.6, 133.1, 133.2, 137.4, 150.0, 169.6. Anal. Calcd for $C_{16}H_{13}ClN_2S$: C, 63.89; H, 4.36; N, 9.31%. Found: C, 63.72; H, 4.53; N, 9.47%.

4.2.4. Fanetizole (3m). White crystal; mp 116–117 °C; IR (KBr) 3196, 3016, 2975, 1602, 1584, 1552, 1495, 1463, 1335, 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.94–3.01 (t, J=7.0 Hz, 2H, CH_2), 3.52–3.62 (q, J=7.0 Hz, 2H, N–CH_2), 5.24 (br s, 1H, NH), 6.70 (s, 1H, thiazole H), 7.24–7.37 (m, 8H, ArH), 7.76–7.80 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.4, 47.5, 100.7, 126.03, 126.59, 127.59, 128.51, 128.66, 134.96, 138.46, 151.5, 169.4. Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99%. Found: C, 72.68; H, 5.81; N, 10.04%.

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **3a–m** are given as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.036.

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