Chinese Chemical Letters 25 (2014) 119–122

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Formation of thiazol-2(3*H*)-imines by reaction of α-amino acids, aroylisothiocyanates, and α-bromoketones in an ionic liquid

Ashraf S. Shahvelayati [a,*], Issa Yavari [b], Akram S. Delbari [c]

[a] Department of Chemistry, Shahr-e Ray Branch, Islamic Azad University, Tehran 18155-144, Iran
[b] Department of Chemistry, Tarbiat Modares University, Tehran 14115-175, Iran
[c] Department of Chemistry, Islamshahr Branch, Islamshahr 33135-369, Iran

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form 15 October 2013
Accepted 25 October 2013
Available online 7 December 2013

Keywords:
Aroylisothiocyanate
α-Amino acids
S-Nucleophile
α-Bromoketones
Ionic liquid

ABSTRACT

An efficient one-pot synthesis of functionalized thiazol-2(3*H*)-imines by a three-component reaction between aroylisothiocyanates, α-amino acids, and α-bromoketones in an ionic liquid is described.

1. Introduction

Thiazoles are an important group of heterocyclic compounds, several derivatives of which have been found to possess useful bioactivity such as anti-tumor [1], anti-fungal [2], anti-inflammatory, and anti-microbial properties [3]. In recent years, thiazole derivatives have attracted considerable attention because of their bioactivity and many applications in organic and medicinal chemistry [4,5]. A number of thiazolidenebenzenesulfonamide derivatives are reported as a novel class of non-nucleoside HIV-1RT inhibitors [6]. Thiazole-5-hydroxamic acids have been described as novel histone deacetylase inhibitors [7].

Although the Hantzsch process, in which an α-halocarbonyl compound is condensed with a thioamide, has been for decades the method of choice for the synthesis of thiazoles [8], great effort has been dedicated to more flexible procedures, and particularly to that of thiazole ring formation in novel reaction media [9,10].

Ionic liquids (ILs) have attracted considerable attention as a novel media in recent years due to their unique properties, such as lack of measurable vapor pressure, non-flammability and recyclability. Their high polarity and ability to dissolve both inorganic and organic materials can result in enhanced rates of chemical processes and can provide higher selectivity compared to conventional solvents. Thus, as a result of their 'green' credentials and potential to enhance rate and selectivity, ILs have been used as solvents in chemical transformations [11–13].

As part of our current studies on the development of new routes in heterocyclic synthesis [14–17], we report an efficient one-pot synthesis of functionalized thiazol-2(3*H*)-imines **4**a–**l** in good yields by a three-component reaction between aroylisothiocyanates **1**, α-amino acids **2**, and α-bromoketones **3** in 1-butyl-3-methylimidazolium bromide [bmim]Br as a solvent at 50 °C (Scheme 1).

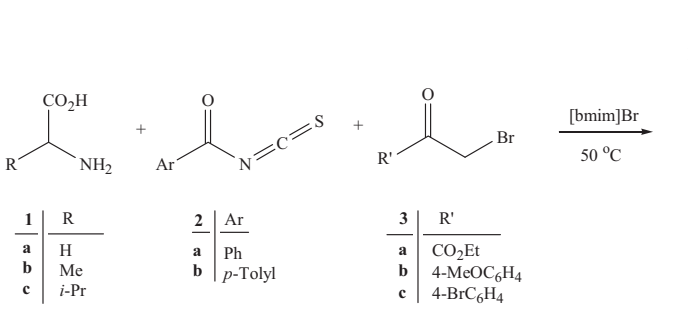
2. Experimental

α-Amino acids, aroylisothiocyanates, and α-bromoketones were obtained from Fluka and were used without further purification. Melting points were obtained on an Electrothermal-9100 apparatus. IR Spectra were recorded with a *Shimadzu IR-460* spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-300 Avance instrument using $CDCl_3$ as the deuterated solvent containing tetramethylsilane as internal standard, at 300 MHz and 75 MHz, respectively; δ in parts per million, *J* in hertz. EIMS (70 eV): Mass spectra were obtained with a Finnigan-MAT-8430 mass spectrometer, in *m*/*z*. Elemental analyses (C, H, N) were obtained with a Heraeus CHN-O-Rapid analyzer.

General procedure for the preparation of compounds **4**: A mixture of α-amino acid **1** (1 mmol) and aroylisothiocyanate **2** (1 mmol) was stirred in 1 mL of [bmim]Br for 1 h at 50 °C, and then

* Corresponding author.
E-mail address: avelayati@yahoo.com (A.S. Shahvelayati).

1001-8417/$ – see front matter
http://dx.doi.org/10.1016/j.cclet.2013.11.009



1	R
a	H
b	Me
c	*i*-Pr

2	Ar
a	Ph
b	*p*-Tolyl

3	R'
a	CO_2Et
b	4-$MeOC_6H_4$
c	4-BrC_6H_4

4	R	Ar	R'	Yiled (%)
a	H	Ph	CO_2Et	76
b	H	Ph	4-$MeOC_6H_4$	79
c	H	Ph	4-BrC_6H_4	86
d	Me	Ph	CO_2Et	96[a]
e	Me	Ph	4-$MeOC_6H_4$	94
f	Me	Ph	4-BrC_6H_4	97
g	*i*-Pr	Ph	CO_2Et	92
h	*i*-Pr	Ph	4-$MeOC_6H_4$	89
i	*i*-Pr	Ph	4-BrC_6H_4	96
j	Me	*p*-Tolyl	CO_2Et	80
k	Me	*p*-Tolyl	4-$MeOC_6H_4$	85
l	Me	*p*-Tolyl	4-BrC_6H_4	83

[a] **4 d**, yiled 96% in [bmim]Br for the first time, 90% in the second run, and 88% in the third run with recycled il; yiled 95% in [omim]Br

Scheme 1. Synthesis of compounds **4**a–**l**.

α-bromo-carbonyl compound **3** (1 mmol) was added. After stirring for 3 h, 5 mL of water was added and the mixture was extracted with Et_2O (3×10 mL). The solvent from the mixture was evaporated under reduced pressure to leave a residue that was purified by column chromatography (SiO_2; hexane/EtOAc = 4/1) to afford pure **4**. The ionic liquid can be reused after extraction from the aqueous phase.

2-[4-(Ethoxycarbonyl)-2-(benzoylimino)thiazol-3(2*H*)-yl]acetic acid (**4a**): Cream powder, yield: 0.25 g (76%); mp 176–178 °C; IR (KBr, cm^{-1}): ν_{max} 3610–2950 (CO_2H), 1752, 1721, 1666, 1601, 1220, 1107. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, ^3J = 7.0 Hz, CH_3), 4.34 (q, ^3J = 7.0 Hz, CH_2), 5.62 (s, CH_2), 7.44 (t, ^3J = 7.1 Hz, 2 CH), 7.50 (t, ^3J = 7.1 Hz, CH), 7.65 (s, CH), 8.30 (d, ^3J = 7.1 Hz, 2 CH), 11.29 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (Me), 49.2 (CH_2), 62.4 (OCH_2), 121.1 (CH), 128.8 (2 CH), 129.0 (CH), 129.7 (2 CH), 132.6 (C), 136.8 (C), 158.8 (C=N), 169.4 (C=O), 169.7 (C=O), 174.1 (C=O). MS: *m*/*z* (%) 334 (M^+, 7), 276 (52), 261 (23), 105 (100), 77 (34), 45 (47). Anal. Calcd. for $C_{15}H_{14}N_2O_5S$ (334.35): C, 53.88; H, 4.22; N, 8.38; Found: C, 53.6; H, 4.3; N, 8.5.

2-[2-(Benzoylimino)-4-(4-methoxyphenyl)thiazol-3(2*H*)-yl]acetic acid (**4b**): Pale yellow crystals, yield: 0.29 g (79%); mp 200–202 °C; IR (KBr, cm^{-1}): ν_{max} 3250–2700 (CO_2H), 1741, 1680, 1609, 1365, 1102. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, OMe), 4.82 (s, CH_2), 6.98 (s, CH), 7.08 (d, ^3J = 8.7 Hz, 2 CH), 7.40 (d, ^3J = 8.7 Hz, 2 CH), 7.45–7.54 (m, 3 CH), 8.19 (d, ^3J = 7.0 Hz, 2 CH), 11.12 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.2 (CH_2), 56.2 (OMe), 107.3 (CH), 115.3 (2 CH), 122.6 (C), 129.1 (2 CH), 129.6 (2 CH), 131.5 (CH), 132.5 (2 CH), 137.3 (C), 139.4 (C), 161.1 (C), 168.9 (C=N), 169.7 (C=O), 173.4 (C=O). MS: *m*/*z* (%) 368 (M^+, 2), 310 (35), 105 (100), 77 (28), 59 (28), 45 (19). Anal. Calcd. for $C_{19}H_{16}N_2O_4S$ (368.41): C, 61.94; H, 4.38; N, 7.60. Found: C, 61.7; H, 4.5; N, 7.5.

2-[2-(Benzoylimino)-4-(4-bromophenyl)thiazol-3(2*H*)-yl]acetic acid (**4c**): Pale yellow crystals, yield: 0.36 g (86%); mp 211–212 °C; IR (KBr, cm^{-1}): ν_{max} 3320–2800 (CO_2H), 1733, 1747, 1554, 1343, 1178. ^1H NMR (300 MHz, $CDCl_3$): δ 4.78 (s, CH_2), 6.56 (s, CH), 7.28 (d, ^3J = 7.2 Hz, 2 CH), 7.38 (t, ^3J = 8.0 Hz, 2 CH), 7.46 (t, ^3J = 8.0 Hz, CH), 7.56 (d, ^3J = 8.0 Hz, 2 CH), 8.27 (d, ^3J = 7.2 Hz, 2 CH), 11.06 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.1 (CH_2), 107.6 (CH), 127.7 (C), 128.5 (CH), 128.8 (2 CH), 129.7 (2 CH), 131.4 (2 CH), 132.2 (C), 132.8 (2 CH), 136.8 (C), 138.7 (C), 155.6 (C=N), 169.5 (C=O), 174.4 (C=O). MS: *m*/*z* (%) 418 (M^++2, 1.2), 416 (M^+, 1.2), 360 (34), 358 (34), 323 (10), 321 (10), 105 (100), 77 (36). Anal. Calcd. for $C_{18}H_{13}BrN_2O_3S$ (417.28): C, 51.81; H, 3.14; N, 6.71. Found: C, 51.3; H, 3.3; N, 6.8.

2-[4-(Ethoxycarbonyl)-2-(benzoylimino)thiazol-3(2*H*)-yl]propanoic acid (**4d**): Cream powder, yield: 0.33 g (96%); mp 175–177 °C; IR (KBr, cm^{-1}): ν_{max} 3600–3000 (CO_2H), 1749, 1716, 1650, 1605, 1203, 1106. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, ^3J = 7.2 Hz, CH_3), 1.85 (d, ^3J = 6.9 Hz, CH_3), 4.34 (q, ^3J = 7.2 Hz, CH_2), 6.42 (q, ^3J = 6.9 Hz, CH), 7.42 (t, ^3J = 7.5 Hz, 2 CH), 7.50 (t, ^3J = 7.5 Hz, CH), 7.66 (s, CH), 8.22 (d, ^3J = 7.5 Hz, 2 CH), 11.21 (s, COOH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.5 (Me), 15.7 (Me), 56.2 (CH), 62.7 (OCH_2), 121.5 (CH), 127.9 (2 CH), 128.5 (2 CH), 129.8 (CH), 132.5 (C), 136.3 (C), 159.0 (C=N), 168.2 (C=O), 174.2 (C=O), 174.8 (C=O). MS: *m*/*z* (%) 348 (M^+, 4), 276 (81), 105 (100), 77 (19), 73 (43), 45 (56). Anal. Calcd. for $C_{16}H_{16}N_2O_5S$ (348.37): C, 55.16; H, 4.63; N, 8.04. Found: C, 55.5; H, 4.8; N, 8.2.

2-[2-(Benzoylimino)-4-(4-methoxyphenyl)thiazol-3(2*H*)-yl]propanoic acid (**4e**): White powder, yield: 0.36 g (94%); mp 202–203 °C; IR (KBr, cm^{-1}): ν_{max} 3300–2800 (CO_2H), 1738, 1650, 1614, 1370, 1152. ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (d, ^3J = 6.6 Hz, CH_3), 3.90 (s, CH_3), 4.92 (q, ^3J = 6.6 Hz, CH), 6.60 (s, CH), 7.03 (d, ^3J = 8.1 Hz, 2 CH), 7.35 (d, ^3J = 8.1 Hz, 2 CH), 7.40–7.49 (m, 3 CH), 8.22 (d, ^3J = 7.4 Hz, 2 CH), 10.98 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5 (Me), 55.9 (OMe), 57.7 (CH), 107.6 (CH), 115.1 (2 CH), 122.0 (C), 128.6 (2 CH), 129.6 (2 CH), 131.2 (2 CH), 132.3 (CH), 136.3 (C), 139.4 (C), 161.4 (C–OMe), 168.1 (C=N), 173.2 (C=O), 173.7 (C=O). MS: *m*/*z* (%) 382 (M^+, 3), 310 (45), 105 (100), 77 (31), 73 (48), 45 (18). Anal. Calcd. for $C_{20}H_{18}N_2O_4S$ (382.43): C, 62.81; H, 4.74; N, 7.33. Found: C, 62.4; H, 4.8; N, 7.5.

2-[2-(Benzoylimino)-4-(4-bromophenyl)thiazol-3(2*H*)-yl]propanoic acid (**4f**): Pale yellow crystals, yield: 0.33 g (85%); mp 223–224 °C; [α]D = - 43.5; IR (KBr, cm^{-1}): ν_{max} 3400–2900 (CO_2H), 1739, 1700, 1592, 1381, 1203. ^1H NMR (300 MHz, $CDCl_3$): δ 1.68 (d, ^3J = 6.9 Hz, CH_3), 4.70 (q, ^3J = 6.9 Hz, CH), 6.56 (s, CH), 7.27–7.41 (m, 3 CH), 7.34 (d, ^3J = 8.1 Hz, 2 CH), 7.59 (d, ^3J = 8.1 Hz, 2 CH), 8.18 (d, ^3J = 7.2 Hz, 2 CH), 11.56 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6 (Me), 56.8 (CH), 108.9 (CH), 124.3 (C), 129.0 (2 CH), 129.7 (2 CH), 130.0 (C), 132.3 (2 CH), 132.6 (C), 133.0 (2 CH), 137.4 (C), 138.4 (C), 167.7 (C=N), 171.3 (C=O), 173.2 (C=O). MS: *m*/*z* (%) 432 (M^++2, 1), 430 (M^+, 1), 358 (31), 360 (31), 321 (12), 323 (12), 105 (100), 77 (29). Anal. Calcd. for $C_{19}H_{15}BrN_2O_3S$ (431.30): C, 52.91; H, 3.51; N, 6.50. Found: C, 53.2; H, 3.6; N, 6.6.

2-[4-(Ethoxycarbonyl)-2-(benzoylimino)thiazol-3(2*H*)-yl]-3-methylbutanoic acid (**4g**): Cream powder, yield: 0.34 g (92%); mp 183–184 °C; IR (KBr, cm^{-1}): ν_{max} 3500–2900 (CO_2H), 1750, 1720, 1670, 1601, 1235, 1100. ^1H NMR (300 MHz, $CDCl_3$): δ 0.69 (d, ^3J = 6.5 Hz, CH_3), 1.33 (d, ^3J = 6.5 Hz, CH_3), 1.42 (t, ^3J = 7.0 Hz, CH_3), 3.22 (m, CH), 4.40 (q, ^3J = 7.0 Hz, CH_2), 6.06 (d, ^3J = 9.3 Hz, CH), 7.48 (t, ^3J = 7.2 Hz, 2 CH), 7.53 (t, ^3J = 7.2 Hz, CH), 7.72 (s, CH), 8.19 (d, ^3J = 7.2 Hz, 2 CH), 11.09 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5 (Me), 19.3 (Me), 21.7 (Me), 28.1 (CH), 62.8 (OCH_2), 66.8 (CH), 121.6 (CH), 128.7 (2 CH), 129.0 (CH), 129.7 (2 CH), 132.7 (C), 135.8 (C), 158.9 (C=N), 164.8 (C=O), 172.4 (C=O), 174.3 (C=O). MS: *m*/*z* (%) 376 (M^+, 4), 303 (29), 276 (59), 105 (100), 77 (38), 45 (67). Anal. Calcd. for $C_{18}H_{20}N_2O_5S$ (376.43): C, 57.43; H, 5.36; N, 7.44. Found: C, 57.7; H, 5.2; N, 7.6.

2-[2-(Benzoylimino)-4-(4-methoxyphenyl)thiazol-3(2*H*)-yl]-3-methylbutanoic acid (**4h**): White powder, yield: 0.36 g (89%); mp 169–171 °C; IR (KBr, cm^{-1}): ν_{max} 3300–2750 (CO_2H), 1742,

1664, 1609, 1378, 1162. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.51 (d, ^3J = 6.6 Hz, CH_3), 1.05 (d, ^3J = 6.6 Hz, CH_3), 3.25 (m, CH), 3.89 (s, CH_3), 4.46 (d, ^3J = 10.5 Hz, CH), 6.64 (s, CH), 7.04 (d, ^3J = 8.7 Hz, 2 CH), 7.35 (d, ^3J = 8.7 Hz, 2 CH), 7.48 (t, ^3J = 8.3 Hz, 2 CH), 7.54 (t, ^3J = 8.3 Hz, CH), 8.17 (d, ^3J = 8.3 Hz, 2 CH), 10.89 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$):δ 19.3 (Me), 20.15 (Me), 27.7 (CH), 55.8 (OMe), 71.9 (CH), 108.0 (CH), 115.2 (2 CH), 121.8 (C), 129.0 (2 CH), 129.3 (2 CH), 131.6 (2 CH), 132.8 (CH), 135.5 (C), 142.0 (C), 161.4 (C–OMe), 169.1 (C=N), 170.5 (C=O), 172.8 (C=O). MS: *m*/*z* (%) 410 (M^+, 2), 310 (39), 105 (100), 101 (19), 77 (38), 45 (15). Anal. Calcd. for $C_{22}H_{22}N_2O_4S$ (410.49): C, 64.37; H, 5.40; N, 6.82. Found: C, 64.7; H, 5.5; N, 7.0.

2-[2-(Benzoylimino)-4-(4-bromophenyl)thiazol-3(2*H*)-yl]-3-methylbutanoic acid (**4i**): Pale yellow crystals, yield: 0.44 g (96%); mp 171–173 °C; IR (KBr, cm^{-1}): ν_{max} 3400–2900 (CO_2H), 1739, 1700, 1592, 1381, 1203. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.53 (d, ^3J = 6.6 Hz, CH_3), 1.08 (d, ^3J = 6.6 Hz, CH_3), 3.28 (m, CH), 4.38 (d, ^3J = 9.0 Hz, CH), 6.75 (s, CH), 7.32 (d, ^3J = 8.1 Hz, 2 CH), 7.49 (t, ^3J = 7.5 Hz, 2 CH), 7.53 (t, ^3J = 7.5 Hz, CH), 7.71 (d, ^3J = 8.1 Hz, 2 CH), 8.18 (d, ^3J = 7.5 Hz, 2 CH), 11.08 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$):δ 19.4 (Me), 19.9 (Me), 27.6 (CH), 72.6 (CH), 109.3 (CH), 125.5 (C), 128.7 (C), 129.1 (2 CH), 129.3 (2 CH), 131.5 (2 CH), 133.0 (2 CH), 133.1 (CH), 135.2 (C), 141.0 (C), 169.5 (C=N), 169.9 (C=O), 172.9 (C=O). MS: *m*/*z* (%) 460 (M^++2, 1), 458 (M^+, 2), 360 (26), 358 (24), 323 (10), 321 (10), 105 (100), 77 (33). Anal. Calcd. for $C_{21}H_{19}BrN_2O_3S$ (459.36): C, 54.91; H, 4.17; N, 6.10. Found: C, 54.5; H, 4.1; N, 6.2.

2-[4-(Ethoxycarbonyl)-2-(4-methylbenzoylimino)thiazol-3(2*H*)-yl]propanoic acid (**4j**): Cream crystals, yield: 0.29 g (80%); mp 165–167 °C; IR (KBr, cm^{-1}): ν_{max} 3650–3000 (CO_2H), 1752, 1720, 1660, 1610, 1250, 1105; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, ^3J = 7.1 Hz, CH_3), 1.83 (d, ^3J = 6.8 Hz, CH_3), 2.40 (s, CH_3), 4.33 (q, ^3J = 7.1 Hz, CH_2), 6.40 (q, ^3J = 6.8 Hz, CH), 7.19 (d, ^3J = 7.9 Hz, 2 CH), 7.63 (s, CH), 8.10 (d, ^3J = 7.9 Hz, 2 CH), 11.17 (s, COOH); ^{13}C NMR (75 MHz, $CDCl_3$):δ 14.5 (Me), 15.6 (Me), 22.1 (Me), 56.3 (CH), 62.6 (OCH_2), 121.5 (CH), 128.0 (C), 129.3 (2 CH), 129.9 (2 CH), 133.6 (C), 143.0 (C), 158.9 (C=N), 168.0 (C=O), 174.8 (C=O), 174.9 (C=O). MS: *m*/*z* (%) 362 (M^+, 12), 290 (68), 119 (100), 91 (56), 73 (24), 45 (50). Anal. Calcd. for $C_{17}H_{18}N_2O_5S$ (362.40): C, 56.34; H, 5.01; N, 7.73. Found: C, 56.7; H, 4.9; N, 7.8.

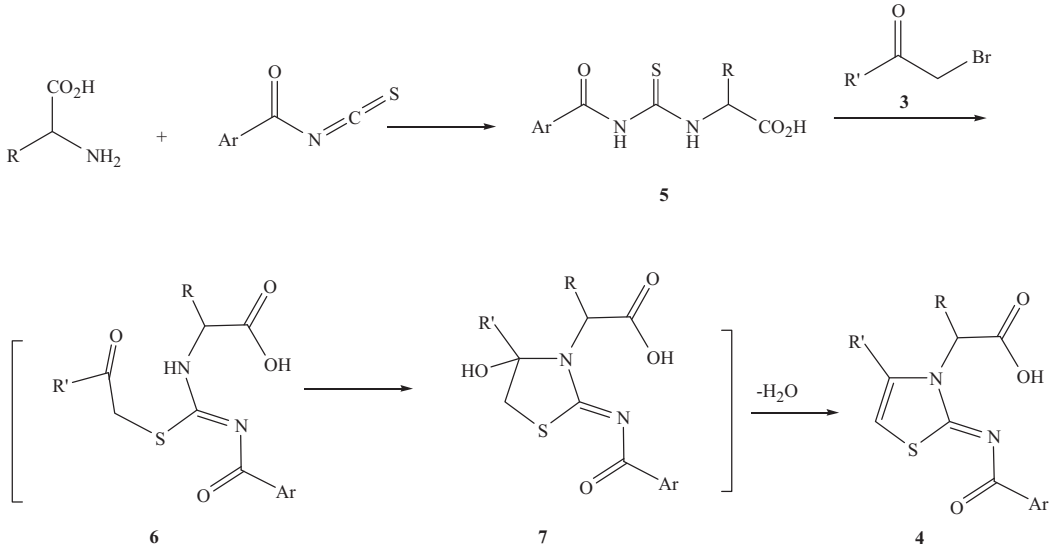
2-[2-(4-Methylbenzoylimino)-4-(4-methoxyphenyl)thiazol-3(2*H*)-yl]propanoic acid (**4k**): Colorless crystals, yield: 0.33 g (85%); mp 197–198 °C; IR (KBr, cm^{-1}): ν_{max} 3330–2700 (CO_2H), 1742, 1673, 1612, 1375, 1163. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (d, ^3J = 6.8 Hz, CH_3), 2.37 (s, CH_3), 3.83 (s, CH_3), 4.81 (q, ^3J = 6.8 Hz, CH), 6.94 (s, CH), 7.12 (d, ^3J = 8.6 Hz, 2 CH), 7.27 (d, ^3J = 8.1 Hz, 2 CH), 7.43 (d, ^3J = 8.6 Hz, 2 CH), 8.06 (d, ^3J = 8.1 Hz, 2 CH), 10.85 (s, COOH). ^{13}C NMR (75 MHz, $CDCl_3$):δ 15.5 (Me), 22.0 (Me), 56.2 (OMe), 60.6 (CH), 107.5 (CH), 115.4 (2 CH), 122.8 (C), 129.6 (2 CH), 129.8 (2 CH), 131.7 (2 CH), 134.9 (CH), 139.3 (C), 142.5 (C), 161.2 (C–OMe), 167.3 (C=N), 171.4 (C=O), 173.2 (C=O). MS: *m*/*z* (%) 396 (M^+, 3), 324 (33), 119 (100), 91 (42), 73 (47), 45 (20). Anal. Calcd. for $C_{21}H_{20}N_2O_4S$ (396.46): C, 63.62; H, 5.08; N, 7.07. Found: C, 63.2; H, 4.9; N, 6.9.

2-[2-(4-Methylbenzoylimino)-4-(4-bromophenyl)thiazol-3(2*H*)-yl]propanoic acid (**4l**): Pale yellow crystals, yield: 0.37 g (83%); mp 186–188 °C; $[\alpha]_D$ = −28.6; IR (KBr, cm^{-1}): ν_{max} 3430–2950 (CO_2H), 1743, 1710, 1605, 1376, 1213. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (d, ^3J = 6.8 Hz, CH_3), 2.37 (s, CH_3), 4.84 (q, ^3J = 6.8 Hz, CH), 7.06 (s, CH), 7.27 (d, ^3J = 8.0 Hz, 2 CH), 7.45 (d, ^3J = 8.4 Hz, 2 CH), 7.77 (d, J = 8.4 Hz, 2 CH), 8.05 (d, ^3J = 8.0 Hz, 2 CH), 10.92 (s, COOH). ^{13}C-NMR (75 MHz, $CDCl_3$):δ 15.6 (Me), 22.0 (Me), 56.7 (CH), 108.8 (CH), 124.3 (2 CH), 129.7 (C), 129.8 (2 CH), 130.0 (2 CH), 132.3 (C), 133.0 (2 CH), 134.3 (C), 138.3 (C), 142.6 (C), 167.5 (C=N), 171.3 (C=O), 173.3 (C=O). MS: *m*/*z* (%) 446 (M^++2, 1.5), 444 (M^+, 1.4), 374 (29), 372 (29), 119 (100), 91 (49). Anal. Calcd. for $C_{20}H_{17}N_2O_3S$ (445.33): C, 53.94; H, 3.85; N, 6.29. Found: C, 54.3; H, 3.9; N, 6.4.

3. Results and discussion

The structures of compounds **4**a–**l** were assigned based on their IR, ^{1}H NMR, ^{13}C NMR spectral data [14]. For example, the ^{1}H NMR spectrum of **4**a exhibited three singlets for CH_2N (δ 5.62), CHS (δ 7.65), and CO_2H (δ 11.29) protons, along with characteristic signals for the ethyl and phenyl groups. In the ^{13}C NMR spectrum, the signals corresponding to the carbonyl groups of **4**a were observed at δ 169.4, 169.7, and 174.1, while the C=N appeared at δ 158.8. The mass spectrum of **4**a displayed the molecular ion peak at *m*/*z* 334. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**l** were similar to those for **4**a except for the alkyl and aryl moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

The recyclability of ionic liquid [bmim]Br was examined in synthesis of thiazole-2(3*H*)-imine **4d**. It was recovered from the reaction mixture by extraction with water. After evaporation of the water under reduced pressure, it was reused three times for the



Scheme 2. Proposed mechanism for the formation of compounds **4**.

synthesis of **4d**. In the second run, **4d** was obtained in 90% yield, and that reduced to 88% in the third run.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme 2) [9]. Presumably, the reaction starts with the formation of thiourea derivative **5**, followed by its alkylation by **3** to generate intermediate **6**. This intermediate undergoes a cyclization reaction to afford **7**, which is converted to product **4** by elimination of H_2O.

In order to confirm that the chiral center present in the amino acid component **3** remains intact under the reaction conditions, we measured the optical activities of compounds **4f** and **4l**, obtained from *S*-(+)-alanine, for solutions containing about 1 g of the samples in 5 mL of dimethylformamide. The specific rotation for **4f** and **4l** were $[\alpha]_D = -43.5$ and $[\alpha]_D = -28.6$, respectively. Thus, we conclude that the configurations of the amino acid components remain unchanged in these reactions.

4. Conclusion

In conclusion, we have developed a convenient, one-pot method for the synthesis of functionalized thiazol-2(3*H*)-imines using aroylisothiocyanates and α-amino acids in the presence of α-bromoketones in an ionic liquid. The present method may be considered as a practical route for the synthesis of thiazole-ring systems.

Acknowledgment

We are grateful to Dr. Mina Ghiasi, Az-Zahra University, Tehran, Iran, for polarimetric measurements.

References

[1] R. Pereira, C. Gaudon, B. Iglesias, et al., Synthesis of the PPARβ/δ-selective agonist GW501516 and C_4-thiazole-substituted analogs, Bioorg. Med. Chem. Lett. 16 (2006) 49–54.
[2] S.K. Bharti, G. Nath, R. Tilak, S.K. Sing, Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring, Eur. J. Med. Chem. 45 (2010) 651–660.
[3] B.S. Holla, K.V. Malini, B.S. Rao, B.K. Sarojini, N.S. Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, Eur. J. Med. Chem. 38 (2003) 313–318.
[4] G.B. Zhou, Y.Q. Guan, C. Shen, et al., A novel and convenient synthesis of thiazol-2(3H)-imine-linked glycoconjugates, Synthesis 13 (2008) 1994–1996.
[5] A.A. Zambon, G. Borsato, S. Brussolo, P. Frascella, V. Lucchini, Efficient access to 5-substituted thiazoles by a novel metallotropic rearrangement, Tetrahedron Lett. 49 (2008) 66–69.
[6] N. Masuda, O. Yamamoto, M. Fujii, T. Ohgami, et al., Studies of non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 2: synthesis and structure–activity relationships of 2-cyano and 2-hydroxy thiazolidenebenzenesulfonamide derivatives, Bioorg. Med. Chem. 13 (2005) 949–961.
[7] S.K. Anandan, J.S. Ward, R.D. Brokx, et al., Design and synthesis of thiazole-5-hydroxamic acids as novel histone deacetylase inhibitors, Bioorg. Med. Chem. Lett. 17 (2007) 5995–5999.
[8] S.E. Bramley, V. Dupplin, D.G.C. Goberdhan, G.D. Meakins, The Hantzsch thiazole synthesis under acidic conditions, J. Chem. Soc. Perkin. Trans. 1 (1987) 639–643.
[9] T.M. Potewar, S.A. Ingale, K.V. Srinivasan, Efficient synthesis of 2,4-disubstituted thiazoles using ionic liquid under ambient conditions: a practical approach towards the synthesis of Fanetizole, Tetrahedron 63 (2007) 11066–11069.
[10] D.V. Jawale, D.L. Lingampalle, U.R. Pratap, R.A. Mane, One-pot synthesis of 2-aminothiazoles in PEG-400, Chin. Chem. Lett. 21 (2010) 412–416.
[11] P. Wasserscheid, T. Welton, Ionic Liquids in Synthesis, 2nd ed., Wiley-VCH, Weinheim, Germany, 1987.
[12] M.A. Martins, C.P. Frizzo, D.N. Moreira, N. Zanatta, H.G. Bonacorso, Ionic liquids in heterocyclic synthesis, Chem. Rev. 108 (2008) 2015–2050.
[13] I. Yavari, E. Kowsari, Ionic liquids as novel and recyclable reaction media for N-alkylation of amino-9,10-anthraquinones by trialkyl phosphites, Tetrahedron Lett. 48 (2007) 3753–3756.
[14] I. Yavari, S. Souri, Efficient synthesis of functionalized 2-pyridones from malonyl dichloride, alkylamines and dimethyl acetylenedicarboxylate, Synlett 19 (2007) 2969–2970.
[15] I. Yavari, M. Sabbaghan, K. Porshamsian, et al., Efficient synthesis of alkyl 2-[2-(arylcarbonylimino)-3-aryl-4-oxo-1,3-thiazolan-5-ylidene]-acetates, Mol. Divers. 11 (2007) 81–85.
[16] I. Yavari, A.S. Shahvelayati, A. Malekafzali, Efficient synthesis of functionalized 2,4-diaminothiazoles from tetramethylguanidine, isothiocyanates, and α-bromoketones, J. Sulfur Chem. 31 (2010) 499–508.
[17] I. Yavari, S. Nasiri-Gheidari, A. Mirzaei, Isoquinoline-mediated S-vinylation and N-vinylation of benzo[d]oxazole-2-thiol and benzo[d]thiazole-2-thiol, Chin. Chem. Lett. 23 (2012) 5–8.