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A green synthesis of functionalized thiazol-2(3H)-imine *via* a three-component tandem reaction in ionic liquid media

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Abstract

In this research, an efficient synthesis toward *2-(2-((4-Methoxybenzoyl)imino)-4-(4-methoxyphenyl)thiazol-3(2H)-yl)-2-phenylacetic acid* has been described *via* a three-component tandem reaction using aroylisothiocyanate, phenyl glycine, and 4-methoxyphenacylbromide in an ionic liquid (IL). 1-Methyl-3-pentylimidazoliumbromide(IL) has been employed as a recyclable green solvent. The work-up procedure was fairly simple and the product did not require further purification. The influence of various reaction parameters such as solvent, temperature, and time was examined and among the various solvents such as ethanol, acetonitrile, n-hexane, water, and ionic liquid for synthesis of the final product, the best result was obtained in 1-methyl-3-pentylimidazolium bromide at 50 ^{o}C for 1 h.

Keywords: Thiazol-2(3H)-imine; α-bromoketone; ionic liquid; phenyl glycine; tandem reacrion; aroylisothiocyanate.

Introduction

Among the different aromatic heterocycles, thiazoles occupy a prominent role in the drug discovery process and this ring structure is found in several marketed drugs [1]. Thiazoles and their derivatives have been often discovered as a vital part of novel and structurally diverse natural products that show a variety of biological activities [2]. Thiazole derivatives display a range of biological activities such as cardiotonic [3], fungicidal [4], sedative [5], anaesthetic [6], antibacterial [7] and anti-inflammatory [8].

The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties [9]. They can be also used as ionophore in ion-selective membrane electrodes. These electrodes are often applied within the determination and detection of some heavy metals [10-12]. Several methods for the synthesis of thiazole derivatives have been developed, among them, Hantzsch's synthesis (reaction between *α*-halocarbonyl compounds and thioamides, thioureas, thiocarbamic acids, or dithiocarbamic acids) is the most widely used method [13]. 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, immiscibility with bothorganic compounds and water, high thermal stability, non-flammability, and recyclability. Room

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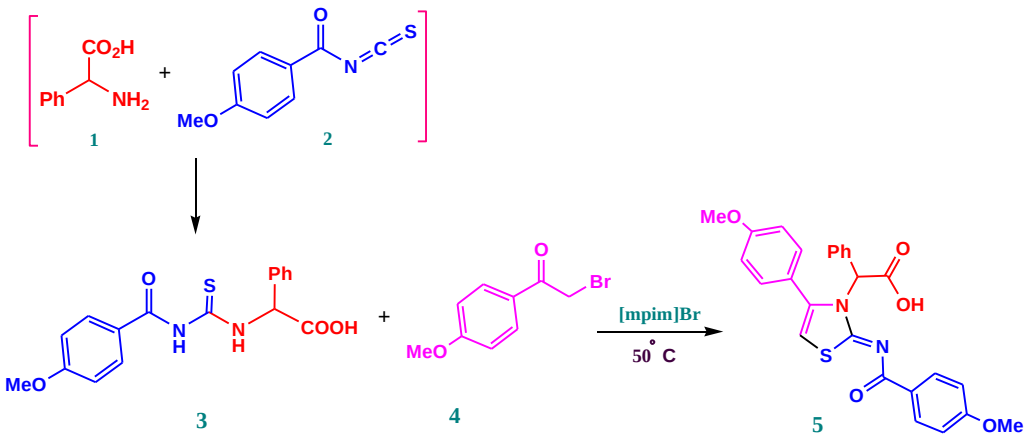
temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazelium salts, have shown great promise as attractive alternatives to the conventional solvents[14-16].As part of our current studies on the development of new routes in heterocyclic synthesis [17-19], herein, we report an efficient one-pot synthesis of functionalized thiazol-2(3H)-imine5 in good yield by a three-component tandem reaction between aroylisothiocyanate, a-amino acid, and a-bromoketonein 1-methyl-3-pentylimidazolium bromide[mpim]Br as a recyclable, green solvent at 50 ^{0}C (Scheme 1).The synthesized product is characterized by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy.



Scheme 1. Synthesis of thiazol-2(3H)-imine **5**

Experimental

Materials and measurements

Phenyl glycine, p-methoxybenzoylisothio- cyanates, and a-bromoketone were obtained from Fluka and were used without further purification. Ionic liquid [mpim]Br was synthesized from the reaction of *N*-methylimidazole and *n*-pentyl bromide [20].The structure of the [mpim] Br, used in this study, is shown in Figure 1. Melting points were obtained on an Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer,^{1}H and ^{13}C NMR spectra: Bruker DRX-300AVANC instrument, in $CDCl_3$ at 300 MHz and 75 MHz, respectively, δ in ppm *J* in Hz, EI-MS (70 eV): Finningan-MAT-8430 mass spectro- meter, in *m/z*. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. The mass and analyses data were in agreement with the proposed structures.

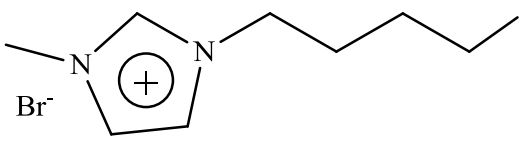


Figure 1. Chemical structure of [mpim]Br

Synthesis of compound 5

Equimolarquantitiesof 4-methoxybenzoyl-isothiocyanate(1 mmol) and phenyl glycine (1 mmol) were mixed in1-methyl-3-pentylimidazolium bromide (1 mL) in 50 °C for 1 h. Then4-methoxyphenacylbromide(1 mmol) was added to it. The progress of the reaction was monitored by TLC analysis. After stirring for 1 h and completing the reaction, 5 mL of water was added and the mixture was extracted with ethyl acetate. The organic phase was evaporated under reduced pressure to leave a crude solid**5**. The final product was purified by recrystallization from ethyl acetate/n-hexane (1:3) (Scheme 1).

Spectrum data of the product 5

*2-(2-((4-Methoxybenzoyl)imino)-4-(4-methoxyphenyl)thiazol-3(2H)-yl)-2-phenylacetic acid***(5)**

Pale yellow powder, yield: 0.46 g (97%), mp.110-112°C. IR (KBr) (ν_{max}/cm^{-1}): 2800-3500 (COOH), 1718, 1678, 1598, 1462, 1364, 1247, 1168 cm^{-1}.^{1}HNMR (300.1 MHz, $CDCl_3$): δ = 3.81 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.13 (1 H, s, CH), 6.84 (1 H, s, CH), 6.90 (2 H, d, ^3J 8.9, 2 CH), 7.04 (2 H, d, ^3J 8.7, 2 CH), 7.21-7.32 (5 H, m, 5 CH-Ph),7.35 (2 H, d, ^3J 8.7, 2 CH), 8.12 (2 H, d, ^3J8.9, 2 CH),11.29 (1 H, br-s, COOH)ppm.^{13}CNMR (75.4 MHz, $CDCl_3$): δ =55.6 (OMe), 60.9 (OMe), 107.5 (CH), 110.9 (CH), 113.9 (2 CH), 115.2 (2 CH), 123.2 (C), 125.6 (C), 128.5 (CH), 128.8 (2 CH), 129.5 (2 CH), 131.9 (2 CH), 132.0 (2 CH), 135.2 (C), 138.1 (C), 148.2 (C), 158.9(N-C=N), 161.4 (C), 163.4 (C=O), 172.6 (C=O)ppm.EI-MS: 474 (M^+, 7), 365 (14), 337 (21), 135 (13), 105 (100), 77 (48), 41 (44). Anal. Calcd for $C_{26}H_{22}N_2O_5S$ (474.53): C, 65.81; H, 4.67; N, 5.90%; Found: C, 65.96; H, 4.96; N, 6.04%.

Results and discussion

The reaction of *N*-protected-amino acid **3**, prepared from α-amino acid **1** andaroylisothiocyanate **2**, with *α*-bromoketones **4** proceeds smoothly in [pmim]Br at 50 ºC to produce functionalized thiazole-2(3*H*)-imines **5** in good yield. The structure of compound **5** was assigned based on its IR, ^{1}H-NMR, and^{13}C-NMR spectral data. The ^{1}H NMR spectrum of **5** exhibited five singlets for 2 OMe (δ = 3.81, 3.87), NCH (δ = 6.13), CHS (δ = 6.84), and CO_2H (δ = 11.29) protons, along with characteristic signals for 3 phenyl groups. In the ^{13}C-NMR spectrum, the signals corresponding to the carbonyl groups of 5 were observed at δ = 163.4, and 172.6 ppm, while the C=N appeared at δ = 158.9 ppm. The mass spectrum of **5** displayed the molecular ion peak at *m*/*z* = 474.

The recyclability of ionic liquid [mpim]Br was examined in synthesis of thiazole-2(3*H*)-imine **5**. It was recovered from the reaction mixture by extraction with water. After evaporating of water under reduced pressure, it was reused three times for the synthesis of **5**. In second run, **5** was obtained in 89% yield that reduced to 85% in third run. The influence of various reaction parameters such as solvent, temperature, and time was examined. Initially, we have screened various solvents such as ethanol, acetonitrile, n-hexane, water, and ionic liquid for synthesis of thiazole-2(3*H*)-imine **5** under reflux and room temperature (Table 1).

It was observed that the reaction proceeded very slowly and the product yield is very low at the room temperature. As can be seen, the best result was obtained in 1-methyl-3-pentylimidazolium bromide at 50 ºC.

Table 1. Effect of solvent and temperature on the synthesis of thiazole **5**

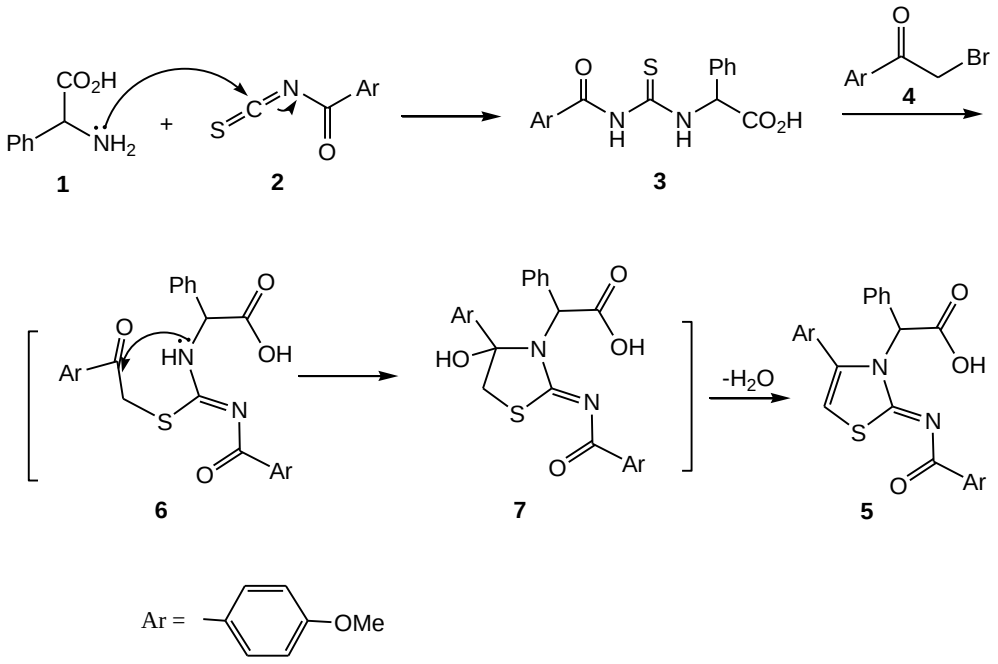
Entry	Solvent	Time	Temperature	Yield (%)
1	Ethanol	24 h	Reflux	70
2	Ethanol	72 h	25°C	30
3	CH_3CN	24 h	Reflux	78
4	CH_3CN	72 h	25°C	35
5	n-Hexane	72 h	Reflux	Trace
6	Water	72 h	Reflux	NR
7	[mpim]Br	1 h	50°C	97[a]

[a]5, yield 97% in [mpim]Br for the first time, 89% in the second run, and 85% in the third run with recycled il.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. 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 **5** by elimination of H_2O (Scheme 2).

Conclusion

In conclusion, we have described a one-pot three component tandem reaction for the synthesis of functionalized thiazol-2(3H)-imine, named *2-(2-((4-Methoxybenzoyl)imino)-4-(4-methoxyphenyl)thiazol-3(2H)-yl)-2-phenylacetic acid*, using aroylisothiocyanate,α-amino acid, and α-bromoketone in an ionic liquid as environmentally friendly media.The work-up procedure was fairly simple and the products did not require further purification.



Scheme 2. Proposed mechanism for the formation of compounds **5**

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