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Catalyst-free synthesis of iminothiazole using one-pot multicomponent reactions

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Abstract: The thiazolimide derivatives are obtained in good to excellent yields by proceeding through a simple, mild, and efficient procedure utilizing isothiocyanate, ammonium acetate and activated acetylenic compounds in the presence of triphenylphosphine in water at room temperature.

Keywords: Thiazolimide, Isothiocyanate, Activated acetylenic compounds, Triphenylphosphine.

Introduction

Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [1-3]. They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [4-7]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [8]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9]. Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [11].

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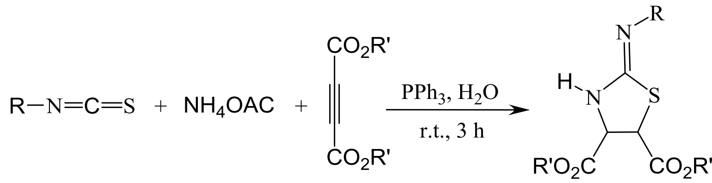
Hence, we investigated a simple three-component reaction between isothiocyanate, ammonium acetate and activated acetylenic compounds in the presence of triphenylphosphine in water at room temperature which afforded thiazolimide derivatives **4** in good isolated yields (Scheme **1**).

Results and discussion

The thiazolimide derivatives are obtained in good to excellent yields by proceeding through a simple, mild, and efficient procedure utilizing isothiocyanate, ammonium acetate and activated acetylenic compounds in the presence of triphenylphosphine in water at room temperature. The ^{1}H NMR spectrum of **4a** displayed signals for vicinal methine protons at δ = 4.78 and 4.92, which appeared as two set of doublets with $^{3}J_{HH}$ values of 12.4 Hz. The methoxy groups showed two separate singlet at δ = 3.78 and 3.85. Observation of $^{3}J_{HH}$ = 12.4 Hz for the vicinal methine protons in **4a** indicates the dominance of anti arrangement. The carbonyl groups resonances in the ^{13}C NMR spectra of **4a** are appeared at 172.5 (C=O), 173.7 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak in the appropriate m/z values. A proposed mechanism for the formation of compound **4** is shown in Scheme **2**.

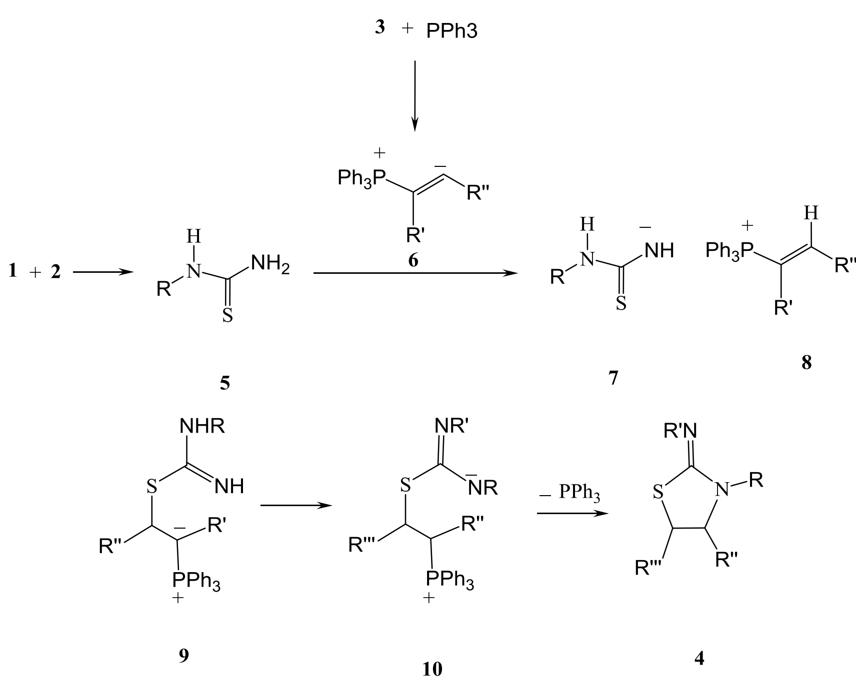


1 2 3 4

4	R	R'	Yield (%) of **4**
a	Ph	Me	85
b	4-MeO-C_6H_4	Me	92
c	4-MeO-C_6H_4	Et	90
d	4-Me-C_6H_4	Et	89
e	4-Br-C_6H_4	Me	85

Scheme 1: Reaction of isothiocyanate, ammonium acetate and activated acetylenic compounds

Apparently, the zwitterionic intermediate **6** which formed from the reaction of triphenylphosphine and electron deficient acetylenic ester **3** is protonated by the intermediate **5** that was generated in situ from the reaction of primary amine **2** and isothiocyanate **1**, produce intermediates **7** and **8**. Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9** which undergo proton shifts to afford new zwitterionic **10**. Finally, intramolecular cyclization of **10** with elimination of triphenylphosphine produces compound **4**.



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

Conclusion

In conclusion, we found that the reaction of activated acetylenic compounds with isothiocyanates and ammonium acetate in the presence of triphenylphosphine leads to a facile synthesis of some functionalized thiazolimide in water at room temperature without using any catalyst.

Experimental

All chemicals used in this work were prepared from Fluka (Buchs, Switzerland) and were used without further purification. Electrothermal 9100 apparatus is employed for measuring of melting points of products. Elemental analyses for C, H, and N were performed with Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. Measurement of IR spectra was performed by Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were evaluated with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

General procedure for preparation of compounds 4

To a magnetically stirred mixture of activated acetylenes **3** (2 mmol) and PPh3 (2 mmol) was added mixture of isocyanates **1** and ammonium acetate **2** at room temperature. The reaction mixture was then stirred. After completion of the reaction [TLC (AcOEt/hexane 1:7) monitoring], 15 mL H_2O was poured into the reaction mixture. The solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4**.

Dimethyl 2-(methylimino)-3-phenyl-1,3- imidazole -4,5-dicarboxylate (4a): Yellow powder, m.p. 156-158°C, yield: 0.46 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1738, 1698, 1657, 1574, 1467, 1382, 1215 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4S$ (308.35): C, 54.53; H, 5.23; N, 9.08. Found: C, 54.62; H, 5.34; N, 9.23%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.83 (3 H, s, NMe), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.78 (1 H, d, ^3J = 12.4, CH), 4.92 (1 H, d, ^3J = 12.4, CH), 7.23 (1 H, t, ^3J = 7.4, CH), 7.35 (2 H, d, ^3J = 7.6, 2 CH), 7.54 (2 H, t, ^3J = 7.6, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 34.6 (NMe), 42.7 (CH), 51.6 (MeO), 52.4 (MeO), 58.4 (CH), 122.8 (CH), 128.3 (2 CH), 129.6 (2 CH), 139.8 (C), 163.4 (C=N), 172.5 (C=O), 173.7 (C=O) ppm. MS, *m/z* (%): 308 (M$^+$, 15), 277 (86), 77 (64), 31 (100).

Dimethyl 2-(ethylimino)-3-(4-methoxyphenyl)-1,3-imidazole -4,5-dicarboxylate (4b): Pale yellow powder, m.p. 168-170 °C, yield: 0.59 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1736, 1686, 1632, 1525, 1487, 1325, 1219 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_5S$ (352.41): C, 54.53; H, 5.72; N, 7.95. Found: C, 54.64; H, 5.80; N, 8.10%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (3H, t, ^3J = 7.3, CH_3), 3.27 (2 H, q, ^3J = 7.3, CH_2), 3.70 (3 H, s, MeO), 3.76 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.75 (1 H, d, ^3J = 12.2, CH), 4.87 (1 H, d, ^3J = 12.2, CH), 7.14 (2 H, d, ^3J = 7.8, 2 CH), 7.28 (2 H, d, ^3J = 7.6, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (CH_3), 41.5 (CH_2), 43.7 (CH), 51.5 (MeO), 52.6 (MeO), 55.4 (MeO), 59.3 (CH), 111.2 (2 CH), 130.3 (2 CH), 134.8 (C), 154.2 (C), 160.7 (C=N), 171.8 (C=O), 172.6 (C=O) ppm. MS, *m/z* (%): 352 (M$^+$, 10), 321 (64), 108 (96), 31 (100).

Diethyl 2-(buthylimino)-3-(4-methoxyphenyl)-1,3-imidazole -4,5-dicarboxylate (4c): White powder, m.p. 162-164 °C, yield: 0.70 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1738, 1687, 1645, 1438, 1357, 1256 cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_5S$ (408.51): C, 58.80; H, 6.91; N, 6.86. Found: C, 58.92; H, 6.98; N, 6.90%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (3H, t, ^3J = 7.2, CH_3), 1.22 (3H, t, ^3J = 7.4, CH_3), 1.28 (3H, t, ^3J = 7.3, CH_3), 1.68 (2 H, q, ^3J = 7.3, CH_2), 1.78 (2 H, m, CH_2), 2.83 (2 H, t, ^3J = 6.8, NCH_2), 3.75 (3 H, s, MeO), 4.12 (2 H, q, ^3J = 7.3, CH_2O), 4.23 (2 H, q, ^3J = 7.3, CH_2O), 4.62 (1 H, d, ^3J = 11.7, CH), 5.02 (1 H, d, ^3J = 11.7, CH), 7.12 (2 H, d, ^3J = 7.6, 2 CH), 7.32 (2 H, d, ^3J = 7.6, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.3 (CH_3), 13.8 (CH_3), 14.3 (CH_3), 21.4 (CH_2), 32.5 (CH_2), 43.6 (CH), 54.8 (MeO), 59.5 (CH), 61.2 (CH_2O), 62.0 (CH_2O), 62.7 (NCH_2), 114.5 (2 CH), 130.8 (2 CH), 135.4 (C), 156.7 (C), 161.2 (C=N), 172.3 (C=O), 174.2 (C=O) ppm. MS, *m/z* (%): 408 (M$^+$, 8), 363 (84), 108 (68), 45 (100).

Diethyl 2-(tert-butylimino)-3-(4-methylphenyl)-1,3-imidazole-4,5-dicarboxylate (4d): yellow powder, m.p. 164-166 °C, yield: 0.59 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1732, 1694, 1587, 1467, 1346, 1238 cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_4S$ (392.51): C, 61.20; H, 7.19; N, 7.14. Found: C, 61.32; H, 7.25; N, 7.22%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, ^3J = 7.4, CH_3), 1.32 (3H, t, ^3J = 7.4, CH_3), 1.35 (9H, s, *Me*$_3$C), 2.28 (3 H, s, CH_3), 4.15 (2 H, q, ^3J = 7.4, CH_2O), 4.28 (2 H, q, ^3J = 7.4, CH_2O), 4.73 (1 H, d, ^3J = 11.5, CH), 4.96 (1 H, d, ^3J = 11.5, CH), 7.24 (2 H, d, ^3J = 7.5, 2 CH), 7.36 (2 H, d, ^3J = 7.6, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (CH_3), 14.2 (CH_3), 22.4

(CH_3), 28.7 (*Me*$_3$C), 44.3 (CH), 48.7 (Me_3*C*), 58.7 (CH), 61.4 (CH_2O), 62.3 (CH_2O), 129.4 (2 CH), 130.2 (C), 131.4 (2 CH), 140.7 (C), 160.4 (C=N), 172.5 (C=O), 175.3 (C=O) ppm. MS, *m/z* (%): 392 (M^+, 20), 377 (84), 91 (84), 45 (100).

Dimethyl 2-(methylimino)-3-(4-bromophenyl)-1,3-imidazole-4,5-dicarboxylate (4e): yellow crystals, m.p. 183-185 ^{o}C, yield: 0.62 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1732, 1695, 1587, 1485, 1436, 1342, 1225 cm^{-1}. Anal. Calcd for $C_{14}H_{15}BrN_2O_4S$ (387.25): C, 43.42; H, 3.90; N, 7.23. Found: C, 43.53; H, 3.95; N,7.32%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (3H, s, NMe), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.83 (1 H, d, ^3J = 11.8, CH), 4.92 (1 H, d, ^3J = 11.8, CH), 7.10 (2 H, d, ^3J = 7.8, 2 CH), 7.54 (2 H, d, ^3J = 7.8, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 34.5 (NCH_3), 44.2 (CH), 51.2 (MeO), 51.8 (MeO), 60.3 (CH), 116.7 (C), 129.7 (2 CH), 132.6 (2 CH), 139.4 (C), 162.3 (C=N), 172.4 (C=O), 173.8 (C=O) ppm. MS, *m/z* (%): 387 (M^+, 15), 356 (78), 156 (64), 31 (100).

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