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Green and catalyst-free synthesis of thiazole-imin derivatives

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Abstract: Functionalized thiazoles are generated from the reaction of dimethyl acetylenedicarboxylate, benzoylisothiocyanates and primary amines and trialkyl phosphite in water. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time and straightforward procedure.

Keywords: Thiazoles, Phosphonate, Primary amines, Phosphites, Activated acetylenic compound, Benzoylisothiocyanates.

Introduction

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [1-4]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [5-9]. Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active in the coenzyme derived from vitamin B_1 (thiamin). A large number of thiazoles exhibit important biological activity such as antitumor, antifungal, antibiotic, and antiviral activities [10]. Water is an ideal solvent and reagent for biochemical transformations. In the past, water was not used as a solvent for synthetic organic chemistry due to the poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Insolubility of the final products facilitates their isolation [11].

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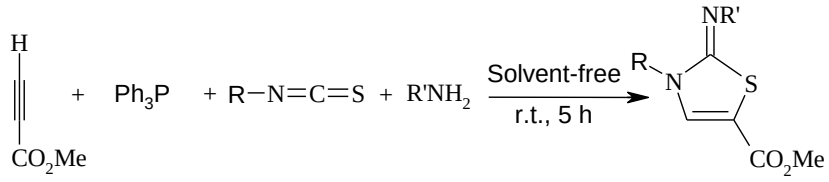
One of the useful strategies used to connect economic features with environmental concerns is performing organic reactions in water. This tactic is consisted of two or more synthetic steps, which are carried out in water as an inexpensive, nontoxic and environmentally friendly solvent in a one-step reaction. Performing reactions in water as green solvent is money, time and energy efficient as well as easy to work-up without separating any intermediates [12]. Herein, we display an efficient synthesis of thiazol derivatives **5** in good yield *via* the reaction of methyl propiolate **1,** triphenylphosphine **2**, isothiocyanate **3** and primary amine **4** under solvent-free condition at room temperature (Scheme **1**).

Results and discussion

As a shown in Scheme **1**, methyl propiolate **1,** triphenylphosphine **2**, isothiocyanate **3** and primary amine **4** under solvent-free condition at room temperature lead to thiazole derivatives **5** in good yield.

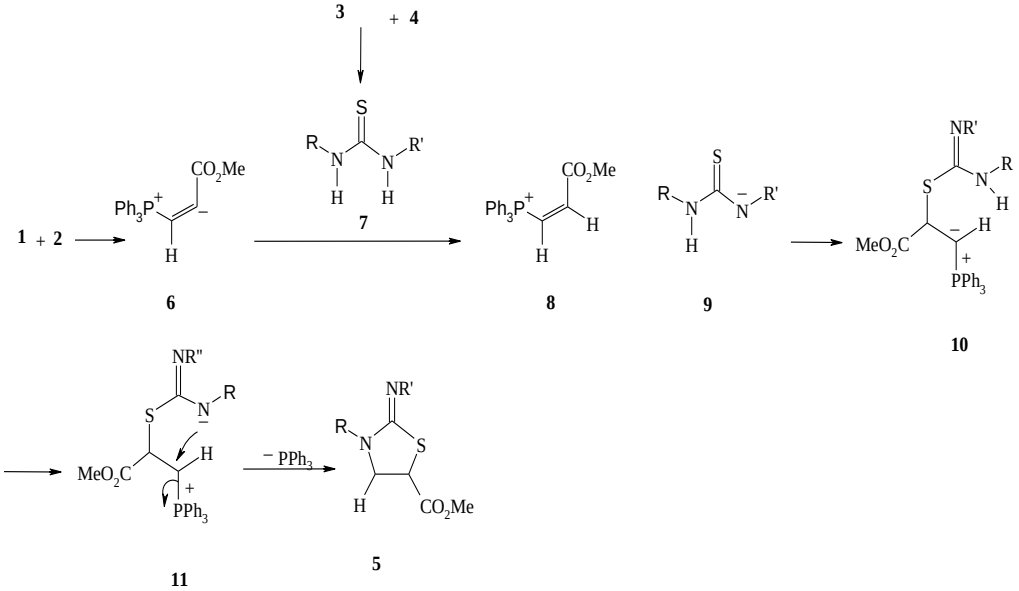


1 **2** **3** **4** **5**

2, 4, 5	R	R'	Yield (%) of **5**
a	^{t}Bu	Me	93
b	Ph	Et	90
c	4-MeO-C_6H_4	n-Bu	87
d	4-Me-C_6H_4	^{t}Bu	87
e	^{t}Bu	4-Me-benzyl	94

Scheme 1: Synthesis of thiazole derivatives **5**

The structures of compound **5** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **5a** exhibited one singlet for NMe protons at (δ 3.22 ppm), two singlets for methoxy protons at (δ = 3.85 and 3.92 ppm) and one singlet for NH proton at = 6.52ppm). The ^{13}C NMR spectrum of **5a** showed two carbonyl resonances at 163.4, 165.2 and one resonance for C=N group at 171.2 ppm which further confirmed the proposed structure. A proposed mechanism is shown in Scheme 2 in agreement with the predicted structure. The zwitterionic intermediate **6** formed from triphenylphosphin **2** and methyl propiolate **1** that is protonated by the thiourea **7** was generated *in situ* from primary amine **4** and isothiocyanate **3**. Then by adding of intermediate **6** to **7** intermediates **8** and **9** are resulted *via* proton transformation process. In next step, nucleophilic attack of thiourea **9** to intermediate **8** leads to adduct **10** which undergoes intramolecular cyclization reaction and elimination of phosphate to produce compound **5** (Scheme **2**).



Scheme 2: Proposed mechanism for generation of thiazole derivatives **5**

Conclusion

In conclusion, In conclusion, we reported a novel method for the synthesis of thiazole derivatives *via* the reaction of dimethyl acetylenedicarboxylate, primary amines, isothiocyanate and trialkyl phosphites in the presence of ZnO-NR as the catalyst in green media.

Eperimental

All chemicals that are used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, ^{13}C, and ^{31}P spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1, 125.8, and 202.4 MHz, respectively. ^{1}H, ^{13}C, and ^{31}P 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 5a-e:

To a stirred mixture of dimethyl acetylenedicarboxylate **1** (2 mmol) and trialkyl phosphite **2** (2 mmol) was added mixture of benzoyl isothicyanate **3** and primary amine **4** (2 mmol) at room temperature after 45 min under solvent-free conditions. The reaction mixture was then stirred for 5h. After completion of the reaction [TLC (AcOEt/hexane 1:6) monitoring], the solid residue was filtered and washed with ethyl acetate to afforded pure compounds **5**.

Dimethyl 2-(methylamino)-1,3-thiazole-4,5-dicarboxylate (5a):

Yellow powder; 114-116 °C, yield 0.43 g (93%) IR (KBr) (ν_{max}/cm^{-1}) = 1742, 1737, 1564, 1487, 1352, 1294 cm^{-1}. MS: *m/z* (%) = 230 (M^{+}, 15), 199 (82), 31 (100). Anal. Calcd (%) for $C_8H_{10}N_2O_4S$ (230.24): C, 41.73; H, 4.38; N, 12.17. Found: C, 41.84; H, 4.46; N, 12.28. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 3.22 (3 H, s, NMe), 3.85 (3 H, s, MeO), 3.92 (3 H, s, MeO), 6.52 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 29.2 (NMe), 51.2 (MeO), 52.6 (MeO), 114.2 (C), 137.2 (C), 163.4 (C=O), 165.2 (C=O), 171.2 (C=N) ppm.

Dimethyl 2-(methylamino)-1,3-thiazole-4,5-dicarboxylate (5b):

Yellow powder; 128-130 °C, yield 0.44 g (90%) IR (KBr) (ν_{max}/cm^{-1}) = 1738, 1735, 1698, 1575, 1438, 1375, 1286 cm^{-1}. MS: *m/z* (%) = 244 (M^{+}, 15), 213 (78), 31 (100). Anal. Calcd (%) for $C_9H_{12}N_2O_4S$ (244.27): C, 44.25; H, 4.95; N, 11.47. Found: C, 44.36; H, 5.12; N, 11.62. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 1.24 (3 H, t, ^{3}J = 7.3 Hz, Me), 3.25 (2 H, q, ^{3}J = 7.3 Hz, CH_2), 3.75 (3 H, s, MeO), 3.87 (3 H, s, MeO), 6.58 (1 H, s, NH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): □ = 14.5 (Me), 41.2 (CH_2), 51.6 (MeO), 52.8 (MeO), 114.3 (C), 136.4 (C), 163.4 (C=O), 165.2 (C=O), 169.4 (C=N) ppm.

Dimethyl 2-(butylamino)-1,3-thiazole-4,5-dicarboxylate (5c):

Yellow powder; 134-136 °C, yield 0.47 g (87%) IR (KBr) (ν_{max}/cm^{-1}) = 1742, 1740, 1686, 1582, 1447, 1362, 1293 cm^{-1}. MS: *m/z* (%) = 272 (M^{+}, 10), 241 (76), 31 (100). Anal. Calcd (%) for $C_{11}H_{16}N_2O_4S$ (272.32): C, 48.52; H, 5.92; N, 10.29. Found: C, 48.63; H, 6.04; N, 10.38. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 1.25 (3 H, t, ^{3}J = 7.4 Hz, Me), 1.75 (2 H, m, CH_2), 1.83 (2 H, m, CH_2), 3.12 (2 H, t, ^{3}J = 6.8 Hz, CH_2), 3.88 (3 H, s, MeO), 3.92 (3 H, s, MeO), 6.62 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 13.4 (Me), 20.7 (CH_2), 32.4 (CH_2), 47.2 (NCH_2), 51.5 (MeO), 52.6 (MeO), 114.3 (C), 137.4 (C), 163.7 (C=O), 164.8 (C=O), 166.7 (C=N) ppm.

Dimethyl 2-(tert-butylamino)-1,3-thiazole-4,5-dicarboxylate (5d):

Yellow powder; 142-144 °C, yield 0.47 g (87%) IR (KBr) (ν_{max}/cm^{-1}) = 1735, 1732, 1692, 1594, 1485, 1372, 1283 cm^{-1}. MS: *m/z* (%) = 272 (M^{+}, 15), 241 (68), 31 (100). Anal. Calcd (%) for $C_{11}H_{16}N_2O_4S$ (272.32): C, 48.52; H, 5.92; N, 10.29. Found: C, 48.64; H, 6.07; N, 10.38. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 1.28 (9 H, s, Me_3C), 3.74 (3 H, s, MeO), 3.83 (3 H, s, MeO), 6.65 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 31.5 (Me_3C), 50.8 (Me$_3$*C*), 51.6 (MeO), 53.4 (MeO), 114.8 (C), 135.6 (C), 163.7 (C=O), 165.2 (C=O), 167.3(C=N) ppm.

Dimethyl 2-(4-methylbenzylamino)-1,3-thiazole-4,5-dicarboxylate (5e):

Yellow powder; 162-168 °C, yield 0.57 g (94%) IR (KBr) (ν_{max}/cm^{-1}) = 1745, 1738, 1695, 1586, 1474, 1382, 1295 cm^{-1}. MS: *m/z* (%) = 306 (M^{+}, 15), 275(82), 31 (100). Anal. Calcd (%) for $C_{14}H_{14}N_2O_4S$ (306.34): C, 54.89; H, 4.61; N, 9.14. Found: C, 54.98; H, 4.74; N, 9.27. ^{1}H NMR (500.1 MHz, $CDCl_3$): □ = 2.52 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.85 (3 H, s,

MeO), 4.92 (2 H, s, CH_2), 6.68 (1 H, s, NH), 7.28 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.34 (2 H, d, ^3J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): □ = 21.2 (Me), 50.4 (CH_2N), 51.7 (MeO), 53.6 (MeO), 114.6 (C), 127.3 (2 CH), 130.6 (2CH), 132.6 (C), 136.8 (C), 138.6 (C), 163.4 (C=O), 164.7 (C=O), 168.2 (C=N) ppm.

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