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Catalyst-free synthesis of aminothiazole derivatives in water

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

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

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities [1-3]. Moreover, they also contribute in the feld of material science, [4] dyes and pigment science [5] as well as agrochemistry [6]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [7, 8] Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [9] and could be performed in the presence of nanocatalyst and produce heterocyclic compounds.

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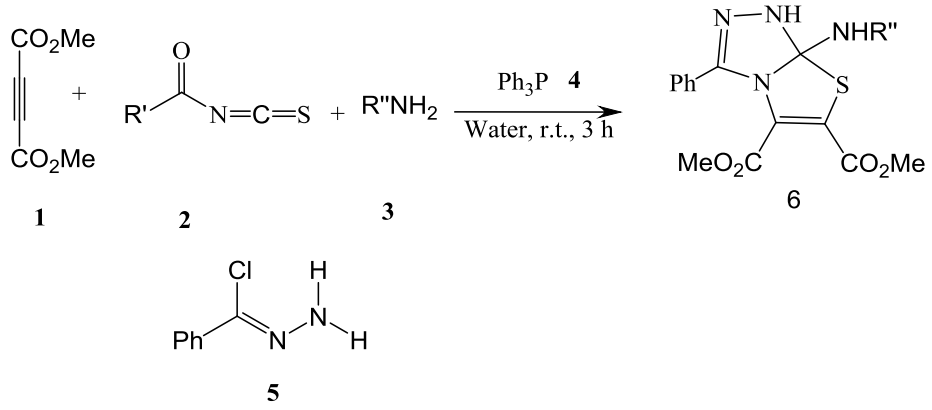
Thiazoles occupy a prominent position among heterocycles. In nature, the thiazolium ring is the chemically active in the coenzyme derived from vitamin B_1 (thiamin). A large number ofaminothiazole exhibit important biological activity such as antitumor, antifungal, antibiotic, and antiviral activities [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]. 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 imino-1,3-thiazolane derivatives **5** in good

yield *via* the reaction of dimethylacetylene dicarboxylate **1,** isothiocyanate **2** and primary amine **3** triphenylphosphine **4** and hydrazonoyl chloride **5** in water as green solvent at room temperature (Scheme **1**).

Results and discussion

As a shown in Scheme **1**, the reaction of dimethyl acetylenedicarboxylate **1**, benzoyl isothiocyanate **2**, primary amine **3** and triphenylphosphine **4** and hydrazonoyl chloride **5** in water as green solvent at room temperature lead to aminothiazole derivatives **5** in good yield.



1 **2** **3** **6**

5

6	R	R'	R"	Yield (%) of **6**
a	Me	^{t}Bu	Me	93
b	Me	Ph	Et	90
c	Et	4-MeO-C_6H_4	n-Bu	87
d	Et	4-Me-C_6H_4	^{t}Bu	87
e	Me	^{t}Bu	4-Me-benzyl	94

Scheme 1: Synthesis of imino thiazolane derivatives **5**

The structures of compound **6** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **6a** 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 **6a** 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 **7** formed from trialkyl phosphite **2** and dialkyl acetylenedicarboxylate **1** that is protonated by the thiourea **8** was generated *in situ* from primary amine **4** and benzoyl isothiocyanate **3**. Then by adding of intermediate **9** to **10** intermediates **11** and **9** are resulted *via* proton transformation process. In next step, nucleophilic attack of thiourea **9** to intermediate **12** leads to adduct **13** which undergoes intramolecular cyclization reaction and elimination of phosphate to produce intermediate **14**. Compound **14** by elimination of RCOOH group is produced **15**. Finally compound **6** is generated by oxidation process (Scheme **2**).

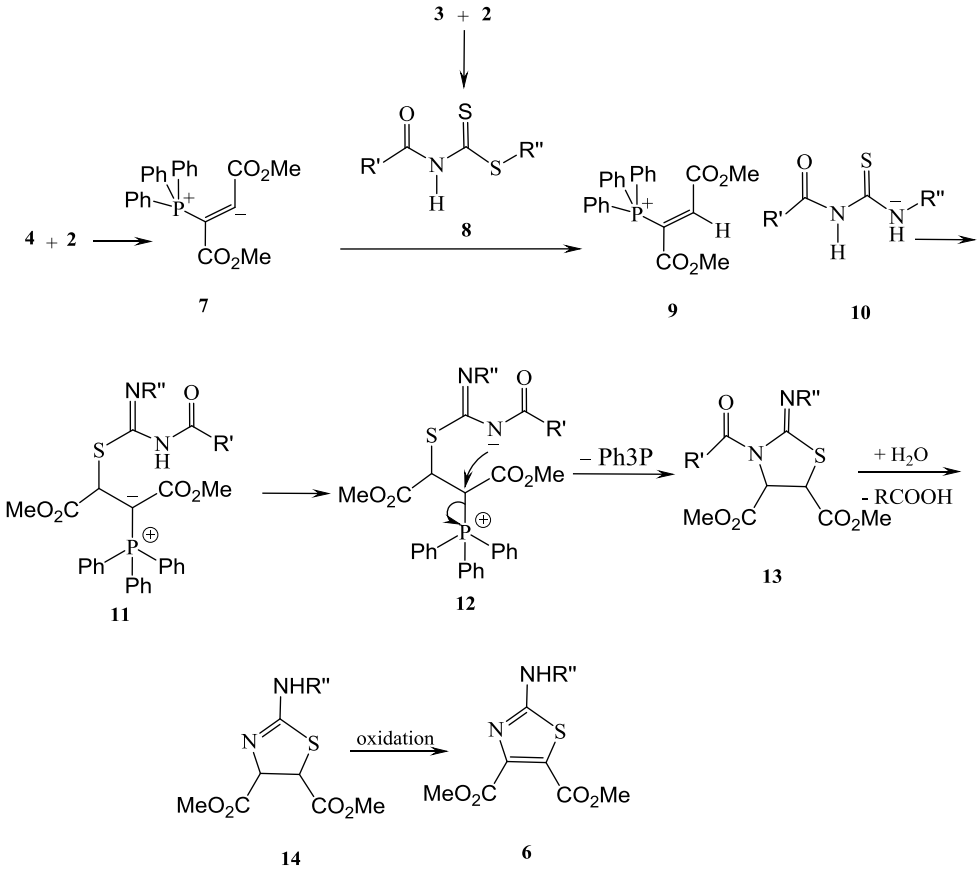
Conclusion

In conclusion, In conclusion, we reported a novel method for the synthesis ofaminothiazole derivatives *via* the reaction of dimethyl acetylenedicarboxylate, primary amines, isothiocyanate and trialkyl phosphites in green media.

Experimental

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.



Scheme 2: proposed mechanism for the formation of **6**

General procedure for preparation of compounds 5a-e:

To a stirred mixture of dimethyl acetylenedicarboxylate **1** (2 mmol) and triphenylphosphine **4** (2 mmol) was added mixture of benzoyl isothicyanate **2** and primary amine **3** (2 mmol) at room temperature after 5 min in water as green solvent. 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 **6**.

Dimethyl 2-(methylamino)-1,3-thiazole-4,5-dicarboxylate (6a):

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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 (6b):

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, $CDCl_3$): δ = 1.24 (3 H, t, ^3J = 7.3 Hz, Me), 3.25 (2 H, q, ^3J = 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 (125.7 MHz, $CDCl_3$): δ = 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 (6c):

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, $CDCl_3$): δ= 1.25 (3 H, t, ^3J = 7.4 Hz, Me), 1.75 (2 H, m, CH_2), 1.83 (2 H, m, CH_2), 3.12 (2 H, t, ^3J = 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, $CDCl_3$): δ = 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 (6d):

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, $CDCl_3$): δ = 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_3C), 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 (6e):

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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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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