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One pot multicomponent reactions of hydrazonoyl chlorides for the green synthesis of substituted triazoles using diethyl oxalate

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Abstract: A novel, convenient and efficient approach to the synthesis of triazole derivatives *via* the reaction between primary amines, isocyanate, diethyl oxalate and hydrazonoyl chloride is described. The method offers several advantages including high yields of products and performing reaction under solvent-free conditions.

Keywords: Primary amines, Triazoles, Isocyanate, Alkyl propiolate, Diethyl oxalate, Hydrazonoyl chloride.

Introduction

Five membered heterocycles with a nitrogen atom, such as pyrroles and triazoles, are important building blocks in a wide number of biologically active compounds [1-6]. Among them, pyrroles are heterocycles of great importance because of their frequent presence in natural products similar to heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes [7]. Some recently isolated pyrrole-containing marine natural products have been found to display significant cytotoxicity and function as multidrug resistance (MDR) reversal agents [8]. Many of these biologically active compounds function as chemotherapeutic agents. Also, the triazoles system can be found in numerous medically relevant compounds, such as the fungicide Ketoconazole [9] and its family members, the benzodiazepine antagonist Flumazenil [10], the antineoplastic drug, Dacarbazine[11], the antibiotic Metronidazole [12], the antiulcerative agent Cimetidine [13], the antihyperthyroid drug Methimazole [14], the rohormone Thyroliberin [15], the muscarinic receptor agonist Pilocarpine [16] and the hypnotic agent Etomidate [17]. Our research group reported the synthesis of a series of triazoles using the reaction of primary amines **1** with isocyanates **2** in the presence of diethyl oxalate **3** and hydrazonoyl chloride **4** in water in good yields.

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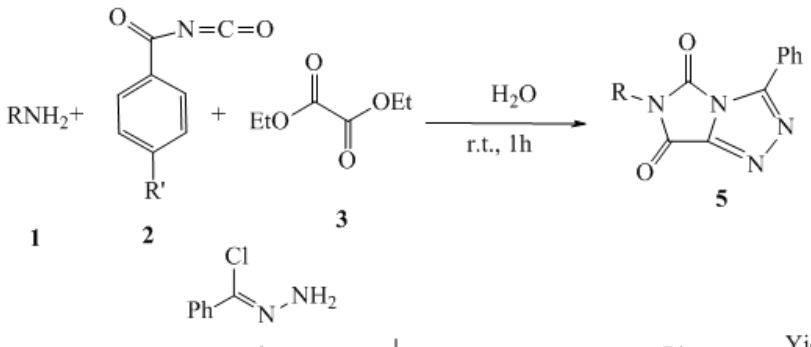
Results and discussion

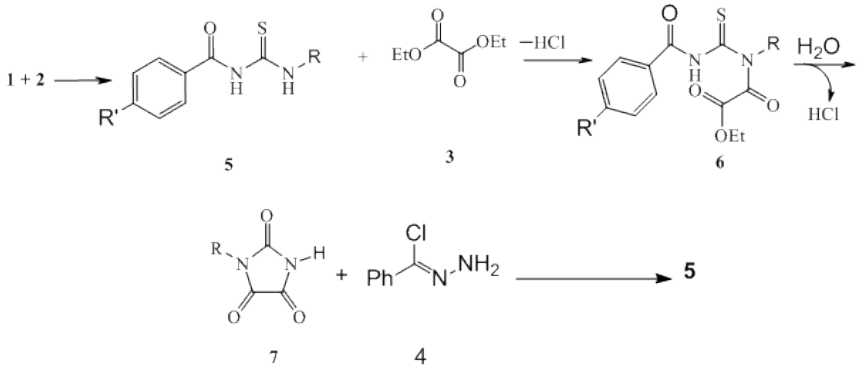
Three component reactions between primary amine **1**, arylisocyanate **2**, diethyl oxalate **3** and hydrazonoyl chloride **4** at room temperature in water produce triazole derivatives **5** in excellent yields (Scheme **1**).



5	R	R'	Yield (%) of **5**
a	Bn	Me	80
b	4-$MeC_6H_4CH_2$	OMe	78
c	4-$MeOC_6H_4CH_2$	Me	85
d	*n*-Bu	NO_2	70
e	Et	OMe	70

Scheme 1: Synthesis of compound **5** using primary amine, isocyanate and diethyl oxalate

The structures of compounds **5** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data, and these data were showed in supporting information. For example, the ^{1}H NMR spectrum of **5a** exhibited one singlet for methyl protons at (δ 2.35) and one singlet for NCH_2 protons at (δ 5.14) along with signals for an aromatic moiety. Three resonances at 154.3 (C=O), 156.7 (C=O), and 183.6 (C=O) ppm were observed in the ^{13}C NMR spectrum of **5a**, which is attributed to the carbonyl and thionyl groups, further confirming the proposed structure. Although we have not established the mechanism of the reaction between the amines and aryisocyanate in the presence of diethyl oxalate in an experimental manner, a possible explanation is proposed in Scheme **2**. Compound **5** result from the initial addition of the amine to isocyanate and subsequent attack of the resulting reactive compound **6** on the diethyl oxalate to yield intermediate **6**. Cyclization of the intermediate **6** by elimination of HCl leads to compound **7** which react with hydrazonoyle chloride **4** and produced compounds **5**.



Scheme 2: Proposed mechanism for the synthesis of compound **5**.

Conclusion

In conclusion, we reported a novel method involving primary amines and isothiocyanate in the presence of diethyl oxalate for the synthesis of triazoles derivatives. The advantages of our work are that the reaction is performed in water without using a catalyst.

Experimental Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, phenacyl bromide or its derivatives and triphenylphosphine were obtained from Fluka and were used without further purification.

General procedure for preparation of compounds 4a-e.

To a mixture of primary amine **1** (2 mmol) and arylisocyanate **2** (2 mmol) was added diethyl oxalate **3** (2.5 mmol) at room temperature. After 1 h hydrazonoyl chlorids **4** (2 mmol) was added and final mixture was then stirred for 3 h. After completion of the reaction [TLC (AcOEt/hexane, 1:4 v/v) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to afforded pure compounds **5** (Scheme **2**).

1-Benzyl-3-(4-methylphenyl)-2-thioxodihydro-1H-triazoles -4,5-dione (5a):

Yellow powder, m.p. 158-160°C, yield: 0.53g (85%), IR (KBr) (ν_{max}/cm^{-1}): 1764, 1735, 1666, 1441, 1340 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.35 (3 H, s, Me), 5.14 (2 H, s, N-CH_2), 7.28 (1 H, d, ^{3}J = 7.2 Hz, CH), 7.32 (2 H, t, ^{3}J = 7.6 Hz, 2 CH), 7.38 (2 H, d, ^{3}J = 7.3 Hz, 2 CH), 7.41 (2 H, d, ^{3}J = 7.3 Hz, 2 CH), 7.52 (2 H, d, ^{3}J = 7.4 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.4 (Me), 45.6 (N-CH_2), 117.5 (2 CH), 128.2 (CH), 129.0 (2 CH), 129.2 (2 CH), 132.4 (2 CH), 133.2 (C), 137.5 (C), 139.4 (C), 154.3 (C=O), 156.7 (C=O), 183.6 (C=S) ppm. MS: *m*/*z* (%) = 310 (M^+, 10), 219 (68), 91 (100), 77 (60). Anal. Calc. for $C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03. found: C, 65.83; H, 4.62; N, 9.14%.

1-(4-Methylbenzyl)-3-(4-methoxyphenyl)-2-thioxodihydro-1H-triazoles -4,5-dione (5b):

Pale yellow powder, m.p. 168-170°C, yield: 0.54g (80%), IR (KBr) (ν_{max}/cm^{-1}): 1759, 1748, 1667, 1443, 1347 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.34 (3 H, s, Me), 5.12 (2 H, s, N-CH_2), 7.15 (2 H, d, ^{3}J = 7.8 Hz, 2 CH), 7.24 (2 H, d, ^{3}J = 7.5 Hz, 2 CH),7.34 (2 H, d, ^{3}J = 7.8 Hz, 2 CH), 7.42 (2 H, d, ^{3}J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.5 (Me), 46.7 (N-CH_2), 55.3 (MeO), 114.6 (2 CH), 128.5 (2 CH), 129.4 (2 CH), 131.8 (C), 132.2 (2 CH), 136.4 (C), 139.3 (C), 155.2 (C=O), 155.8 (C=O), 160.4 (C), 180.4 (C=S) ppm. Anal. Calc. for $C_{18}H_{16}N_2O_3S$ (340.39): C, 63.51; H, 4.74; N, 8.23. found: C, 63.62; H, 4.83; N, 8.32%.

1-(4-Methoxybenzyl)-3-(4-methylphenyl)-2-thioxodihydro-1H-triazoles -4,5-dione (5c):

Yellow powder, m.p. 165-167°C, yield: 0.37g (87%), IR (KBr) (ν_{max}/cm^{-1}): 1764, 1735, 1670, 1445, 1340 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.36 (3 H, s, Me), 5.15 (2 H, s, N-CH_2), 7.18 (2 H, d, ^{3}J = 7.6 Hz, 2 CH), 7.28 (2 H, d, ^{3}J = 7.9 Hz, 2 CH), 7.38 (2 H, d, ^{3}J = 7.9 Hz, 2 CH), 7.45 (2 H, d, ^{3}J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.2 (Me), 47.3 (N-CH_2), 55.5 (MeO), 113.8 (2 CH), 128.8 (2 CH), 129.6 (2 CH), 132.3 (C), 132.8 (2 CH), 135.7 (C), 138.4 (C), 155.3 (C=O), 156.2 (C=O), 161.3 (C), 181.7 (C=S) ppm. Anal. Calc. for $C_{18}H_{16}N_2O_3S$ (340.39): C, 63.51; H, 4.74; N, 8.23. found: C, 63.65; H, 4.84; N, 8.30%.

1-butyl-3-(4-nitrophenyl))-2-thioxodihydro-1H-triazoles -4,5-dione (5d):

Yellow powder, mp: 137-139 °C, yield: 0.46g (75 %). IR (KBr) (ν_{max}/cm^{-1}): 1764, 1742, 1675, 1443, 1348 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 1.12 (3 H, t, ^{3}J = 7.4 Hz, CH_3), 1.38 (2 H, m, CH_2), 1.52 (2 H, m, CH_2), 4.58 (2 H, s, N-CH_2), 7.76 (2 H, d, ^{3}J = 7.8 Hz, 2 CH), 8.37 (2 H, d, ^{3}J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.4 (CH_3), 19.4 (CH_2), 28.4 (CH_2), 43.7 (N-CH_2), 118.7 (2 CH), 128.5 (2 CH), 140.2 (C), 142.3 (C), 155.2 (C=O), 155.4 (C=O), 178.6 (C=S) ppm. Anal. Calc. for $C_{13}H_{13}N_3O_4S$ (307.33): C, 50.81; H, 4.26; N, 13.67. found: C, 50.92; H, 4.36; N, 13.72%.

1-ethyl-3-(4-methoxyphenyl))-2-thioxodihydro-1H-triazoles -4,5-dione (5e):

Yellow powder, m.p. 140-142 °C, yield: 0.39g (75 %), IR (KBr) (ν_{max}/cm^{-1}): 1765, 1742, 1665, 1487, 1345 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 1.28 (3 H, t, ^{3}J = 7.3 Hz, CH_3), 3.85 (3 H, s, MeO), 3.87 (2 H, q, ^{3}J = 7.4 Hz, NCH_2), 7.24 (2 H, d, ^{3}J = 7.6 Hz, 2 CH), 7.35 (2 H, d, ^{3}J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.4 (CH_3), 36.7 (NCH2), 55.6 (MeO), 113.4 (2 CH), 132.4 (2 CH), 133.7 (C), 153.7 (C=O), 155.6 (C=O), 159.4 (C), 182.5 (C=S) ppm.

Anal. Calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C, 54.30; H, 4.58; N, 10.60. found: C, 54.42; H, 4.63; N, 10.70%.

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