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One-pot green synthesis of oxazines using electron deficient acetylenic compounds

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Abstract: A one-pot synthesis of oxazines from dialkyl acetylenedicarboxylates and thiourea in the presence of Et_3N under solvent-free conditions is described.

Keywords: oxazines, *N*-formylmorpholine, Dialkyl acetylenedicarboxylates.

Introduction

The heterocyclic compounds containing spiro moiety because of their rigidity and considerable biological characteristics are particularly significant [1]. Making spiro heterocyclic compounds is significant and intriguing because this structure is also shown in natural alkaloids [2]. The heterocyclic compounds in among organic compounds have well-known position for showing many biological properties [3-15]. One strategy for the preparation of heterocyclic compounds is multicomponent reaction (MCRs), which could produce these compounds with significant biological activity in one pot and high yields compared with reactions with more stages [16, 17]. MCRs have many advantages over different process reactions, such as good product performance, easy removal and atom economy, and short reaction time [18-20]. We must take care of this that most MCRs cannot be done without a catalyst and must be performed in the presence of a catalyst. The synthesized compounds may have biological activity such as antioxidant and antimicrobial activity.

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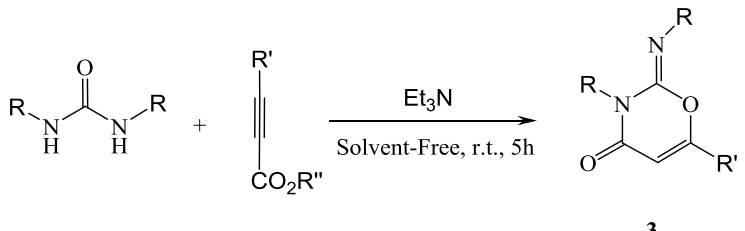
The antioxidant activity of organic compounds is attributed to having a chemical structure with reducing properties. The negative effect of free radicals could be eliminated by free radicals of DPPH. Also, organic compounds with antioxidant ability could prevent of some diseases [21-24]. Additionally, the produced compounds might have antimicrobial property which in this research was investigated this point. Drug-resistant bacteria are harmful and can cause a variety of disease in connection with numerous infectious diseases. Finding the best method for resolving or decreasing this process is important for several reasons. In our quest for developing new techniques to synthesize new heterocyclic compounds [25-33], we report a simple and environmentally benign strategy for the synthesis of functionalized 3,4-dihydro-2*H*-oxazines. Thus, the reaction of dialkylthioureas **1** with activated acetylenic esters **2** in the presence of Et_3N under solvent free conditions, produced functionalized oxazines **3** in good yields (Scheme **1**).

Results and discussion

The structures of compounds **3a**–**3f** were assigned by a consideration of their IR, ^{1}H NMR, ^{13}C NMR spectroscopic and mass spectrometric data. For example, the ^{1}H NMR spectrum of **3a** exhibited three

singlets for methyl proton at δ = 3.17, 3.19, and 3.75 ppm, together with characteristic signal for the methine protons at δ = 6.77 ppm. In the ^{13}C NMR spectrum of **3a**, the signals corresponding to carbonyl and thionyl groups were observed at δ = 150.6, 164.6, and 166.2 ppm. The mass spectrum of **3a** displayed the molecular ion peak at *m*/*z* = 214.

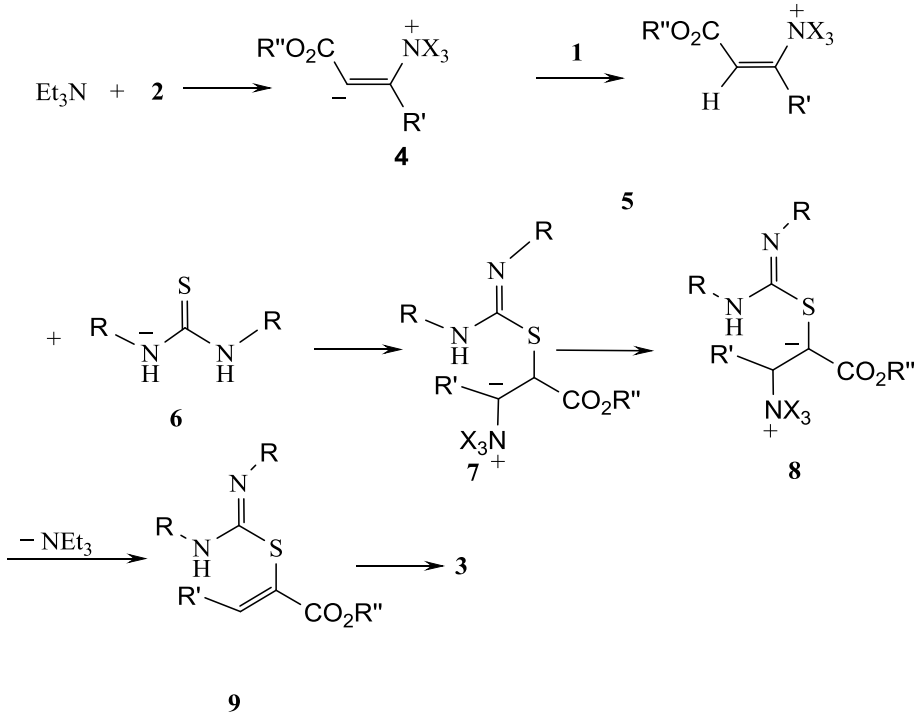
Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the reaction involves the initial formation of a 1:1 zwitterionic intermediate **4** between the activated acetylenes **2** and Et3N**,** which undergoes reaction with **1** to produce **5**. This intermediate is attacked by anion **6** to produce **7**. Intermediate **7** is converted to product **3** via elimination of Et_3N and cyclization (Scheme **2**).



1 **2** **3**

3	R	R'	R"	Yield/ % of **3**
a	Me	CO_2Me	Me	85
b	Me	CO_2Et	Et	80
c	Et	CO_2Me	Me	87
d	Et	H	Et	78
e	Ph	Me	Me	90
f	Ph	H	Et	87

Scheme 1: Synthesis of oxazin derivatives



Scheme 2: Proposed mechanism for the formation of **3.**

Conclusion

In conclusion, conclusion, the reaction between Et_3N and electron-deficient acetylenic esters, in the presence of thiourea leads to functionalized oxazines in good yields. This procedure has the advantage that the reaction is performed under neutral conditions, and the starting materials can be used without any pre activation or modification.

Experimental

Chemicals were purchased from Fluka and 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. The results agreed favorably with the calculated values. 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-, and ^{13}C-NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz.

General procedure for preparation of compound 3:

To a stirred mixture of thiourea**1** (2 mmol) and activated acetylenic compounds **2** (2 mmol) was added 0.21 g Et_3N (5 mL) at r.t. After completion of the reaction (1-3 h) as indicated by TLC (*n*-hexane/EtOAc 8:1), the resulting solid was filtered and dried.

Methyl 3-methyl-2-(methylimino)-4-oxo-3,4-dihydro-2H-1,3-oxazine-6-carboxylate (3a):

Pale yellow powder, yield: 0.37 g (87%), m.p. 98-100°C. IR (KBr) (ν_{max}/cm^{-1}): 1717, 1695, 1658, 1621, 1433, 1331, and 1211 cm^{-1}; EI-MS: 214 (M^+, 25); 199 (45); 186 (62); 155 (70); 144 (75); 69 (100); ^{1}H NMR: 3.17 (3 H, s, MeN), 3.19 (3 H, s, MeN), 3.75 (3 H, s, MeO), 6.77 (1 H, s, CH) ppm. ^{13}C NMR: 28.9 (MeN), 30.7 (MeN), 52.3 (MeO), 115.1 (CH), 141.1 (C), 150.6 (C=O), 164.6 (C=O), 166.2 (C=S) ppm. Anal.Calcd (%) for $C_8H_{10}N_2O_3S$ (214.24): C, 44.85, H, 4.70, N, 13.08. Found: C, 44.79, H, 4.63, N, 12.88.

Ethyl 3-methyl-2-(methylimino)-4-oxo-3,4-dihydro-2H-1,3-oxazine-6-carboxylate (3b):

Pale yellow powder, yield: 0.37 g (85%), m.p. 112-114°C. IR (KBr) (ν_{max}/cm^{-1}): 1714, 1692, 1657, 1613, 1423, and 1197 cm^{-1}; EI-MS: 228 (M^+, 15); 199 (68); 185 (76); 158 (68); 70 (100); 29 (65); ^{1}H NMR: 1.34 (3 H, t, ^{3}J = 7.2 Hz, Me), 3.28 (3 H, s, MeN), 3.29 (3 H, s, MeN), 4.30 (2 H, q, ^{3}J = 7.2 Hz, CH_2O), 6.89 (1 H, s, CH) ppm. ^{13}C NMR: 14.2 (Me), 29.1 (MeN), 38.9 (MeN), 61.6 (CH_2O), 115.8 (CH), 140.9 (C), 1150.9 (C=O), 164.9 (C=O), 166.0 (C=S) ppm. Anal. Calcd (%) for $C_9H_{12}N_2O_3S$ (228.26): C, 47.36, H, 5.30, N, 12.27. Found: C, 47.28, H, 5.12, N, 12.07.

Methyl 3-ethyl-2-(ethylimino)-4-oxo-3,4-dihydro 2H-1,3-oxazine-6-carboxylate (3c):

White powder, yield: 0.43 g (90%), m.p. 125-127°C. IR (KBr) (ν_{max}/cm^{-1}): 1712, 1643, 1610, 1434, 1392, and 1317 cm^{-1}; EI-MS: 242 (M^+, 10); 227 (56); 198 (56); 158 (68); 84 (100); 44 (58); ^{1}H NMR: 1.20 (3 H, t, ^{3}J = 7.3 Hz, Me), 1.24 (3 H, t, ^{3}J = 7.4 Hz, Me), 3.46 (2 H, q, ^{3}J = 7.3 Hz, CH_2N), 3.83 (3 H, s, MeO), 3.86 (2 H, q, ^{3}J = 7.4 Hz, CH_2N), 6.84 (1 H, s, CH) ppm. ^{13}C NMR: 12.6 (Me), 15.8 (Me), 37.9 (MeN), 47.3 (MeN), 52.3 (MeO), 114.8 (CH), 141.7 (C), 147.8 (C=O), 164.5 (C=O), 166.4 (C=S) ppm.

Ethyl 3-ethyl-2-(ethylimino)-4-oxo-3,4-dihydro-2H-1,3-oxazine-6-carboxylate (3d):

White powder, yield: 0.42 g (83%), m.p. 137-139°C. IR (KBr) (ν_{max}/cm^{-1}): 1718, 1693, 1643, 1434, 1313, and 1193 cm^{-1}; EI-MS: 256 (M^+, 15); 227 (66); 168 (68); 88 (100); 45 (88); ^{1}H NMR: 1.14 (3 H, t, ^{3}J = 7.2 Hz, Me), 1.19 (3 H, t, ^{3}J = 7.4 Hz, Me), 1.26 (3 H, t, ^{3}J = 7.3 Hz, Me), 3.40 (2 H, q, ^{3}J = 7.3 Hz, CH_2N), 3.80 (2 H, q, ^{3}J = 7.4 Hz, CH_2N), 4.20 (2 H, q, ^{3}J = 7.4 Hz, CH_2O), 6.77 (1 H, s, CH) ppm. ^{13}C NMR: 12.6 (Me), 14.1 (Me), 15.8 (Me), 37.8 (MeN), 47.2 (CH_2N), 61.4 (CH_2O), 115.3 (CH), 141.3 (C), 148.1 (C=O), 164.5 (C=O), 165.9 (C=S) ppm.

Methyl 3-phenyl-2-(phenylimino)-4-oxo-3,4-dihydro-2H-1,3-oxazine-6-carboxylate (3e):

Pale yellow powder, yield: 0.62 g (92%), m.p. 150-152°C. IR (KBr) (ν_{max}/cm^{-1}): 1714, 1692, 1657, 1612, 1424, 1323, and 1196 cm^{-1}; EI-MS: 338 (M^+, 10); 323 (45); 279 (65); 206 (68); 132 (100); 59 (88); ^{1}H NMR: 3.83 (3 H, s, MeO), 7.34 (2 H, t, ^{3}J = 7.2 Hz, 2 CH_m), 7.56 (1 H, t, ^{3}J = 7.2 Hz, CH_p), 6.94 (2 H, d, ^{3}J = 7.2 Hz, 2 CH_o), 7.01 (1 H, s, CH) ppm. ^{13}C NMR: 52.6 (MeO), 127.9 (C), 129.4 (CH), 134.0 (CH), 141.4 (CH), 147.3 (C), 151.6 (C=O), 164.6 (C=S), 166.4 (C=O) ppm. Anal.Calcd (%) for $C_{18}H_{14}N_2O_3S$ (338.38): C,

63.89, H, 4.17, N, 8.28. Found: C, 63.78, H, 4.13, N, 8.19.

Ethyl 3-phenyl-2-(phenylimino)-4-oxo-3,4-dihydro-2H-1,3-oxazine-6-carboxylate (3f):

Pale yellow powder, yield: 0.63 g (89%), m.p. 148-150°C. IR (KBr) (ν_{max}/cm^{-1}): 1728, 1691, 1612, 1590, 1489, and 1192 cm^{-1}; EI-MS: 352 (M^+, 15); 323 (68); 279 (52); 220 (68); 118 (100); 45 (88); ^{1}H NMR: 1.33 (3 H, t, ^{3}J = 7.2 Hz, Me), 4.30 (2 H, q, ^{3}J = 7.2 Hz, CH_2O), 6.94 (1 H, d, ^{3}J = 7.2 Hz, 2 CH_o), 7.01 (1 H, s, CH), 7.23 (2 H, t, ^{3}J = 7.2 Hz, 2 CH_m), 7.34 (1 H, t, ^{3}J = 7.2 Hz, CH_p) ppm. ^{13}C NMR: 14.2 (Me), 61.8 (CH_2O), 120.6 (CH), 127.9 (C), 115.3 (2 CH), 117.1 (2 CH), 125.3 (CH), 147.4 (C=O), 164.7 (C=S), 166.0 (C=O) ppm.

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