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Synthesis of 1,3-thiazines using *N*-formylmorpholine as a green solvent

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Abstract: A one-pot synthesis of 1,3-thiazines from dialkyl acetylenedicarboxylates and thiourea in the presence of *N*-formylmorpholine as green solvent is described.

Keywords: 1,3-Thiazines, *N*-formylmorpholine, Dialkyl acetylenedicarboxylates.

Introduction

1,3-Thiazines and their derivatives possess remarkable biological activities such as antibacterial, antitumour, insecticidal and fungicidal [1-3]. These are also known as anti-radiation agents and used as radiation-sickness drugs [4]. Furthermore, the antibiotic activity of cephalosporins is due to the presence of 1,3-thiazine nucleus [5]. As regards chemical viewpoint, 1,3-thiazines are important synthetic intermediates in organic syntheses [6]. Transformation of 1,3-thiazines into 6-alkyluracils and dihydropyrimidines has also been reported [1b, 7]. Owing to their chemical and biological interest, syntheses of various 1,3-thiazine derivatives have been reported [1, 8-18]. Also, 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. Now, it has been recognized that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and often the insolubility of the final products facilitates their isolation [19, 20].

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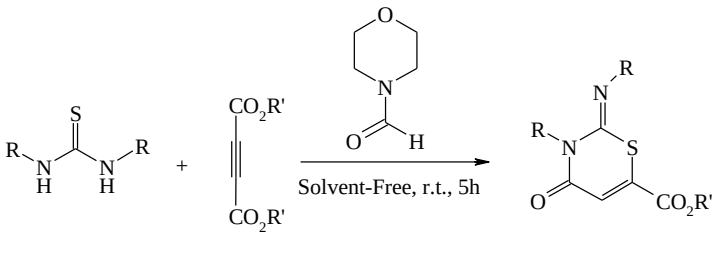
As part of our current studies on the development of new routes in heterocyclic synthesis [21-23], we report a simple and environmentally benign strategy for the synthesis of functionalized 3,4-dihydro-2*H*-1,3-thiazines. Thus, the reaction of dialkylthioureas **1** with activated acetylenic esters **2**, in the presence of *N*-formylmorpholine as a solvent, produced functionalized 1,3-thiazines **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 NFM**,** which undergoes reaction with **1** to produce **5**. This intermediate is

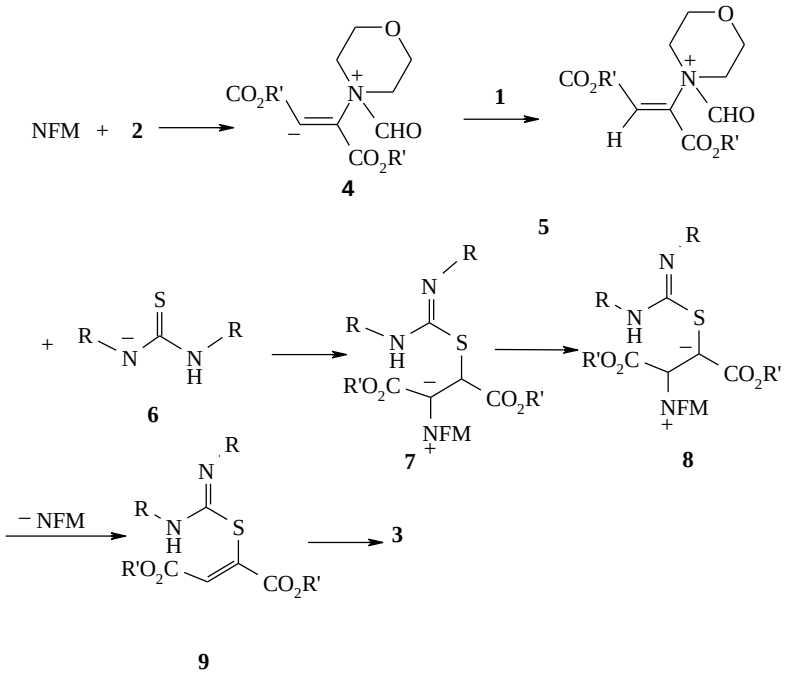
attacked by anion **6** to produce **7**. Intermediate **7** is converted to product **3** via elimination of NFM and cyclization (Scheme **2**).



1 **2** **3**

3	R	R'	Yield/ % of **3**
a	Me	Me	87
b	Me	Et	85
c	Et	Me	90
d	Et	Et	83
e	Ph	Me	92
f	Ph	Et	89

Scheme 1: Reaction of activated acetylenes and *N-formylmorpholine*



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

Conclusion

In conclusion, conclusion, the reaction between *N-formylmorpholine* and electron-deficient acetylenic esters, in the presence of Ph_3P leads to functionalized 3,4-dihydro-2*H*-1,3-thiazines 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 compounds 3:

To a stirred mixture of **1** (2 mmol) and **2** (2 mmol) was added 0.21 g NFM (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-thiazine-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-thiazine-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-thiazine-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-thiazine-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-thiazine-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-thiazine-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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