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ORIGINAL PAPER

Ph_3P-mediated one-pot synthesis of functionalized 3,4-dihydro-2*H*-1,3-thiazines from *N*,*N*′-dialkylthioureas and activated acetylenes in water

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Abstract A one-pot synthesis of alkyl 3,4-dihydro-4-oxo-2*H*-1,3-thiazine-6-carboxylates from dialkyl acetylenedicarboxylates and *N*,*N*′-dialkylthioureas in the presence of triphenylphosphine (20 mol%) is described.

Keywords 1,3-Thiazines · Dialkylthiourea · Acetylenic ester · Triphenylphosphine

Introduction

1,3-Thiazines and their derivatives possess remarkable biological activity, for example antibacterial, antitumor, insecticidal, and fungicidal [1–5]. They are also known as anti-radiation agents and used as radiation-sickness drugs [6]. Furthermore, the antibiotic activity of cephalosporins is because of the presence of the 1,3-thiazine nucleus [7]. Also, 1,3-thiazines are important synthetic intermediates in organic synthesis [8]. Transformation of 1,3-thiazines into 6-alkyluracils and dihydropyrimidines has also been reported [2, 9]. Owing to their chemical and biological importance, syntheses of various 1,3-thiazine derivatives have been reported [1, 2, 10–22].

Water is an ideal solvent and reagent for biochemical transformations. In the past, water was not used as solvent for synthetic organic chemistry because of 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 the insolubility of the final products facilitates their isolation [23, 24].

As part of our current studies on the development of new routes in heterocyclic synthesis [25–27], we report a simple and environmentally benign strategy for synthesis of functionalized 3,4-dihydro-2*H*-1,3-thiazines. Thus, reaction of dialkylthioureas **1** with activated acetylenic esters **2** in the presence of 20 mol% of triphenylphosphine (Ph_3P) in water as a solvent produced functionalized 2*H*-1,3-thiazines **3** in good yields (Scheme 1). Organophosphorus compounds have been used in organic synthesis as useful reagents, and as ligands in a number of transition metal catalysts [28, 29]. However, there are few reactions in which organophosphorus(III) species work as catalysts [30–38].

The structures of compounds **3a**–**3f** were assigned by consideration of their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic and mass spectrometric data. For example, the ^{1}H NMR spectrum of **3a** contained three singlets for methyl protons at $\delta = 3.17$, 3.19, and 3.75 ppm, together with a characteristic signal for the methine proton at $\delta = 6.77$ ppm. In the ^{13}C NMR spectrum of **3a**, signals corresponding to carbonyl and thionyl groups were observed at $\delta = 150.6$, 164.6, and 166.2 ppm. The mass spectrum of **3a** contained 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 Ph_3P, which undergoes reaction with **1** to produce the salt pair **5**. Combination of this salt pair will produce **6**. This intermediate is converted to product **3** via elimination of Ph_3P and cyclization (Scheme 2).

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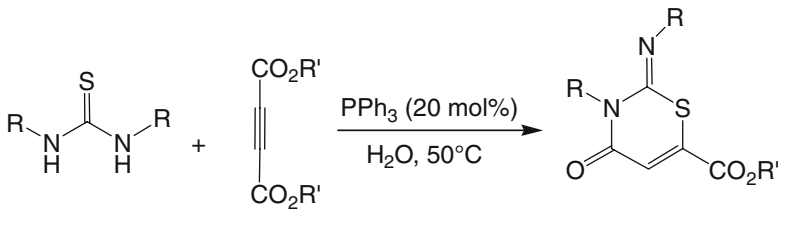
Scheme 1

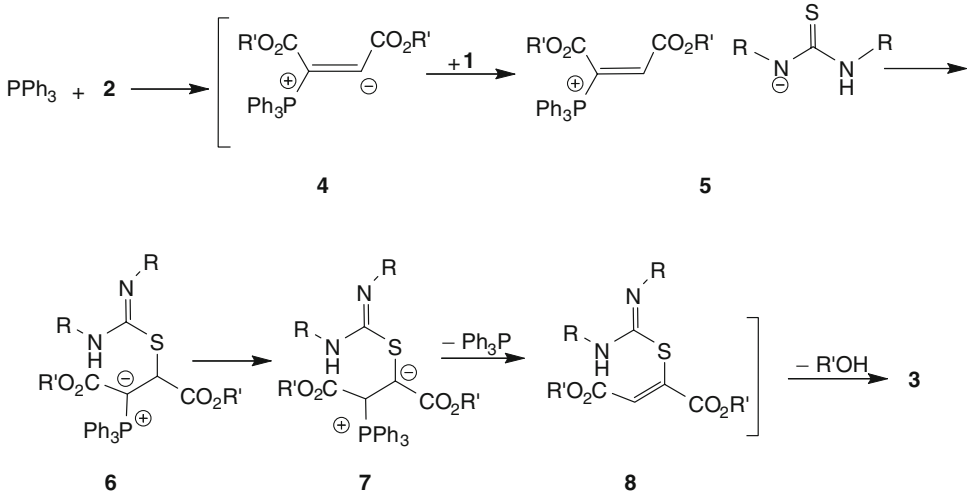


1	R
a	Me
b	Et
c	Ph

2	R'
a	Me
b	Et

3	R	R'	Yield (%)
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 2



When these reactions were performed in the absence of Ph_3P or in the presence of Et_3N, the starting materials were recovered unchanged.

In conclusion, the reaction between *N*,*N*′-dialkylthioureas 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 preactivation or modification.

Experimental

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer, and the results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 spectrometer at 500.1 and 125.8 MHz, respectively.

General procedure for the preparation of ***3***

To a stirred mixture of **1** (2 mmol) and **2** (2 mmol) in 5 cm^3 water was added 0.21 g Ph_3P (20 mol%) at 50 °C. After completion of the reaction (1–3 h) as indicated by TLC (*n*-hexane–EtOAc 8:1), the resulting solid was isolated by filtration and dried.

Methyl 3,4-dihydro-3-methyl-2-(methylimino)-4-oxo-2H-1,3-thiazine-6-carboxylate (**3a**, $C_8H_{10}N_2O_3S$)
Pale yellow powder, yield 0.37 g (87%); m.p.: 98–100 °C; IR (KBr): $\bar{\nu}$ = 1,717, 1,695, 1,658, 1,621, 1,433, 1,331, 1,211 cm^{-1}; EI-MS: *m/z* = 214 (M^+, 25), 199 (45), 186 (62), 155 (70), 144 (75), 69 (100); ^1H NMR ($CDCl_3$): δ = 3.17 (3H, s, MeN), 3.19 (3H, s, MeN), 3.75 (3H, s, MeO), 6.77 (1H, s, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 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.

Ethyl 3,4-dihydro-3-methyl-2-(methylimino)-4-oxo-2H-1,3-thiazine-6-carboxylate (**3b**, $C_9H_{12}N_2O_3S$)
Pale yellow powder, yield 0.37 g (85%); m.p.: 112–114 °C; IR (KBr): $\bar{\nu}$ = 1,714, 1,692, 1,657, 1,613, 1,423, 1,197 cm^{-1}; EI-MS: *m/z* = 228 (M^+, 15), 199 (68), 185 (76), 158 (68), 70 (100), 29 (65); ^1H NMR ($CDCl_3$): δ = 1.34 (3H, t, ^3J = 7.2 Hz, Me), 3.28 (3H, s, MeN), 3.29 (3H, s, MeN), 4.30 (2H, q, ^3J = 7.2 Hz, CH_2O), 6.89 (1H, s, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.2 (Me), 29.1 (MeN), 38.9 (MeN), 61.6 (CH_2O), 115.8 (CH), 140.9 (C), 150.9 (C=O), 164.9 (C=O), 166.0 (C=S) ppm.

Methyl 3-ethyl-2-(ethylimino)-3,4-dihydro-4-oxo-2H-1,3-thiazine-6-carboxylate (**3c**, $C_{10}H_{14}N_2O_3S$)
White powder, yield 0.43 g (90%); m.p.: 125–127 °C; IR (KBr): $\bar{\nu}$ = 1,712, 1,643, 1,610, 1,434, 1,392, 1,317 cm^{-1}; EI-MS: *m/z* = 242 (M^+, 10), 227 (56), 198 (56), 158 (68), 84 (100), 44 (58); ^1H NMR ($CDCl_3$): δ = 1.20 (3H, t, ^3J = 7.3 Hz, Me), 1.24 (3H, t, ^3J = 7.4 Hz, Me), 3.46 (2H, q, ^3J = 7.3 Hz, CH_2N), 3.83 (3H, s, MeO), 3.86 (2H, q, ^3J = 7.4 Hz, CH_2N), 6.84 (1H, s, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.6 (Me), 15.8 (Me), 37.9 (CH_2N), 47.3 (CH_2N), 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)-3,4-dihydro-4-oxo-2H-1,3-thiazine-6-carboxylate (**3d**, $C_{11}H_{16}N_2O_3S$)
White powder, yield 0.42 g (83%); m.p.: 137–139 °C; IR (KBr): $\bar{\nu}$ = 1,718, 1,693, 1,643, 1,434, 1,313, 1,193 cm^{-1}; EI-MS: *m/z* = 256 (M^+, 15), 227 (66), 168 (68), 88 (100), 45 (88); ^1H NMR ($CDCl_3$): δ = 1.14 (3H, t, ^3J = 7.2 Hz, Me), 1.19 (3H, t, ^3J = 7.4 Hz, Me), 1.26 (3H, t, ^3J = 7.3 Hz, Me), 3.40 (2H, q, ^3J = 7.3 Hz, CH_2N), 3.80 (2H, q, ^3J = 7.4 Hz, CH_2N), 4.20 (2H, q, ^3J = 7.4 Hz, CH_2O), 6.77 (1H, s, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.6 (Me), 14.1 (Me), 15.8 (Me), 37.8 (CH_2N), 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 3,4-dihydro-4-oxo-3-phenyl-2-(phenylimino)-2H-1,3-thiazine-6-carboxylate (**3e**, $C_{18}H_{14}N_2O_3S$)
Pale yellow powder, yield 0.62 g (92%); m.p.: 150–152 °C; IR (KBr): $\bar{\nu}$ = 1,714, 1,692, 1,657, 1,612, 1,424, 1,323, 1,196 cm^{-1}; EI-MS: *m/z* = 338 (M^+, 10), 323 (45), 279 (65), 206 (68), 132 (100), 59 (88); ^1H NMR ($CDCl_3$): δ = 3.83 (3H, s, MeO), 7.34 (2H, t, ^3J = 7.2 Hz, 2 CH_m), 7.56 (1H, t, ^3J = 7.2 Hz, CH_p), 6.94 (2H, d, ^3J = 7.2 Hz, 2 CH_o), 7.01 (1H, s, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 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.

Ethyl 3,4-dihydro-4-oxo-3-phenyl-2-(phenylimino)-2H-1,3-thiazine-6-carboxylate (**3f**, $C_{19}H_{16}N_2O_3S$)
Pale yellow powder, yield 0.63 g (89%); m.p.: 148–150 °C; IR (KBr): $\bar{\nu}$ = 1,728, 1,691, 1,612, 1,590, 1,489, 1,192 cm^{-1}; EI-MS: *m/z* = 352 (M^+, 15), 323 (68), 279 (52), 220 (68), 118 (100), 45 (88); ^1H NMR ($CDCl_3$): δ = 1.33 (3H, t, ^3J = 7.2 Hz, Me), 4.30 (2H, q, ^3J = 7.2 Hz, CH_2O), 6.94 (1H, d, ^3J = 7.2 Hz, 2 CH_o), 7.01 (1H, s, CH), 7.23 (2H, t, ^3J = 7.2 Hz, 2 CH_m), 7.34 (1H, t, ^3J = 7.2 Hz, CH_p) ppm; ^{13}C NMR ($CDCl_3$): δ = 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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