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Simple and efficient synthesis of substituted pyrimido[2,1-b][1,3]thiazines

Abstract: Simple and efficient synthesis of a novel fused bicyclic heterocyclic compound 3 by the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate and thiourea in the presence of potassium carbonate in dimethylformamide under reflux conditions is reported. The optimized molar ratio of the substrates is 2:1. The parent compound was used for further derivatization by using a synthetic strategy that is based on suitability of the substituted pyrimido[2,1-b][1,3]thiazine system to react as a bis-electrophilic species with various nucleophiles. Products 4a–e and 5a–e were obtained in good yields (65–76%).

Keywords: bis-electrophilic species; 2-cyano-3,3-bis(methylthio) acrylate; Michael type reaction; oxopyrimidothiazine.

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Introduction

The synthesis of fused bicyclic heterocyclic compounds possessing a pyrimido[2,1-b][1,3]thiazine central core is described herein. Several synthetic routes to this class of compounds have been reported previously [1–7]. These types of compounds show a wide range of biological properties such as antibacterial, antiallergic, anti-inflammatory and antitumor activity; some of them are phosphodiesterase inhibitors and drugs against parkinsonism [1–7]. In the literature, there are many reports on the synthesis of related 1,3-thiazines compounds [8, 9]. The thiazine derivatives exhibit a variety of biological activities [10, 11]. The physiologically active thiazine derivatives can be prepared starting with an α,β-unsaturated carbonyl system [12, 13]. The reaction of thiourea with the α,β-unsaturated system (Michael acceptor) yields oxopyrimido-1,3-thiazine compounds [14, 15].

The present report is related to other work described in the literature [16–22]. In the present study, the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate (1) and thiourea (2) was carried out in the presence of potassium carbonate in dimethylformamide (DMF) under reflux conditions to obtain 2,6-dihydro-4,8-bis(methylthio)-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (3) in excellent yield. Compound 3 was used as a substrate for the preparation of its derivatives in a manner previously described for its analogs [23–28].

Results and discussion

The fused heterocyclic compound 3 was prepared by the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate (1) and thiourea (2) in the presence of a catalytic amount of potassium bicarbonate in DMF under reflux conditions. The optimized molar ratio of these substrates is 2:1. The proposed mechanistic pathway is depicted in Scheme 1.

Scheme 1
Compound 3 contains methylthio groups (-SMe) at positions 4 and 8 that are activated by adjacent ring nitrogen atoms and electron-withdrawing groups towards a nucleophilic displacement. Compound 3 was allowed to react with various selected nucleophiles including arylamines and phenols. The successful synthesis of products 4a–e and 5a–e is shown in Scheme 2.

Conclusion
A new pyrimido[2,1-b][1,3]thiazine 3 and its derivatives 4 and 5 were synthesized by using simple and efficient chemistry.

Experimental
Melting points were determined in open capillary tubes and are uncorrected. The silica gel F<sub>254</sub> plates were used for thin layer chromatography (TLC); the spots were examined under UV light and then developed in an iodine vapor. Column chromatography was performed with silica gel (BDH 100–200 mesh). Solvents were purified according to standard procedures. The spectra were recorded as follows: IR, KBr pellets, a Perkin-Elmer RX1 FT-IR spectrophotometer; <sup>1</sup>H NMR, CDCl<sub>3</sub>, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

2,6-Dihydro-2,6-dioxo-4,8-bis(methylthio)-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (3) A mixture of 2-cyano-3,3-bis(methylthio)acrylate (1, 2 mmol) and thiourea (2, 1 mmol), DMF (10 mL) and anhydrous potassium carbonate (10 mg) were heated under reflux for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, washed with water (3 × 10 mL) and extracted with ethyl acetate (3 × 10 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, hexane-ethyl acetate) to obtain pure solid compound 3: Yield 86%; mp 135–136 °C, IR: 2250, 1690, 1610, 1590 cm<sup>–1</sup>; <sup>1</sup>H NMR: δ 3.35 (s, 6H, SMe); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 190.2, 115.1, 135.9, 132.6, 52.0, 51.9; ESI-MS: m/z 323 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>11</sub>H<sub>6</sub>N<sub>4</sub>S<sub>3</sub>O<sub>2</sub>: C, 41.00%; H, 1.90%; N, 17.36%; S, 29.82. Found: C, 41.01%; H, 1.93%; N, 17.40%; S, 29.79%.

2,6-Dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitriles 4a–e and 5a–d A mixture of 3 (1 mmol), a substituted aromatic amine or a substituted aromatic phenol (2 mmol), DMF (10 mL) and anhydrous potassium carbonate (10 mg) was heated under reflux for 6 h, then cooled to room temperature and poured into ice-cold water. The separated solid product 4 or 5 was filtered, washed with water and crystallized from ethyl alcohol.

2,6-Dihydro-2,6-dioxo-4,8-bis(phenylamino)pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4a) Colorless solid; yield 52%; mp 143–144°C; IR: 2240, 1695, 1615, 1595 cm<sup>–1</sup>; <sup>1</sup>H NMR: δ 4.15 (s, 2H), 6.90–7.70 (m, 10H); ESI-MS: m/z 413 [M + H]<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>12</sub>N<sub>6</sub>O<sub>2</sub>S: C, 61.18; H, 2.94; N, 20.36; S, 7.75. Found: C, 61.20; H, 2.97; N, 20.36; S, 7.80.

4,8-Disubstituted 2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitriles 4a–e and 5a–d A mixture of 3 (1 mmol), a substituted aromatic amine or a substituted aromatic phenol (2 mmol), DMF (10 mL) and anhydrous potassium carbonate (10 mg) was heated under reflux for 6 h, then cooled to room temperature and poured into ice-cold water. The separated solid product 4 or 5 was filtered, washed with water and crystallized from ethyl alcohol.
4,8-Bis(4-methoxyphenylamino)-2,6-dihydro-2,6-dioxo
pyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4d) Colorless solid; yield 68%; mp 155–156°C; IR: 2245, 1698, 1627, 1590 cm⁻¹; ¹H NMR: δ 3.60 (s, 6H), 4.80 (s, 2H), 7.62 (m, 8H); ESI-MS: m/z 473 [M+H]⁺. Anal. Calcd for C₂₇H₁₇N₄O₄S: C, 52.20; H, 1.72; N, 11.68; S, 6.38. Found: C, 52.22; H, 1.72; N, 11.65; S, 6.38.

4,8-Bis(3-nitrophenoxy)-2,6-dihydro-2,6-dioxopyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (4c) Yellow solid; yield 70%; mp 145–147°C; IR: 2235, 1690, 1620, 1590 cm⁻¹; ¹H NMR: δ 3.68 (s, 6H), 5.23 (s, 2H); ESI-MS: m/z 473 [M+H]⁺. Anal. Calcd for C₂₇H₁₇N₄O₄S: C, 52.20; H, 1.72; N, 11.68; S, 6.38. Found: C, 52.22; H, 1.72; N, 11.65; S, 6.38.

2,6-Dioxo-4,8-diphenoxypyrimido[2,1-b][1,3]thiazine-3,7-dicarbonitrile (5b) Yellow solid; yield 73%; mp 165–167°C; IR: 2235, 1690, 1620, 1590 cm⁻¹; ¹H NMR: δ 7.55 (d, 8H, J = 8.0 Hz); ESI-MS: m/z 505 [M+H]⁺. Anal. Calcd for C₂₇H₁₇N₄O₄S: C, 50.07; H, 1.68; N, 16.68; S, 6.34. Found: C, 50.07; H, 1.68; N, 16.72; S, 6.38.

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