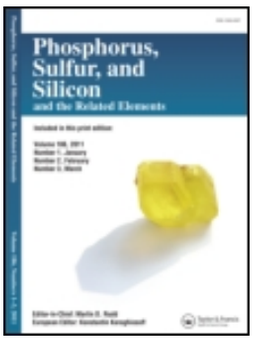

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ONE-POT SYNTHESIS OF FUNCTIONALIZED PYRIMIDO[2,1-B][1,3]THIAZIN-6-ONES VIA A MULTICOMPONENT REACTION

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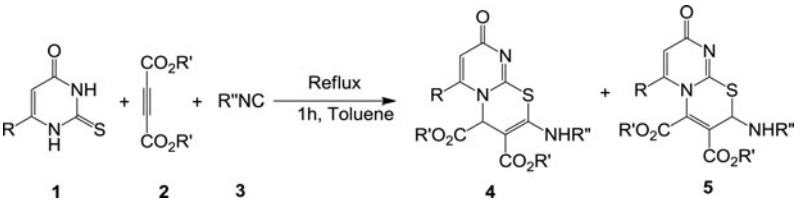
GRAPHICAL ABSTRACT



Abstract *A facile and direct synthesis of pyrimido[2,1-b][1,3]thiazin-6-ones via a one-pot, three-component reaction of dialkyl acetylenedicarboxylates with alkyl or aryl isocyanides and 2-thioxopyrimidin-4-ones in good overall yields.*

Keywords 2-Thioxopyrimidin-4-one; pyrimido[2; 1-b][1; 3]thiazin-6-one; isocyanide; acetylenedicarboxylates

INTRODUCTION

Pyrimidines and related fused heterocyclic derivatives are of great biological interest due to their anti-inflammatory, analgesic, antimicrobial, antileishmanial, and therapeutic properties and especially their antiviral, antithyroid, and antitumor activities.[1–7] Several methods have been reported for the synthesis of some fused pyrimidine derivatives.[8] Drawbacks of some of these methods include multistep reactions,[8f] long reaction times,[8g] production of mixture products,[8h] the use of catalysts[8j] and modest yields.[8l] Therefore, the further development of synthetic methods to produce a variety of these templates remains an important task.

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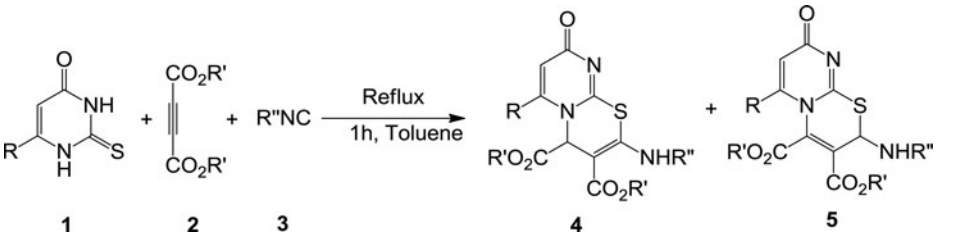
The reaction of isocyanide nucleophiles with activated acetylenic compounds such as dialkyl acetylenedicarboxylates leads to activated zwitterions. These types of zwitterions can be trapped by a variety of electrophiles such as activated carbonyl compounds or reagents containing NH, OH, CH, and SH acidic groups to afford highly functionalized novel aminofurans and iminolactones in good yields.[9]

As part of our current studies on the development of new routes in heterocyclic synthesis,[10] this work reports the results of our studies involving the reaction of the zwitterionic intermediates derived from alkyl isocyanides **3** and acetylenic esters **2** with 2-thiouracils **1**, which constitutes a synthesis of pyrimido[2,1-b][1,3]thiazine derivatives **4** and **5** in 85–96% yields (Scheme 1). The optimized results are summarized in Table 1.



Scheme 1 Synthesis of pyrimido[2,1-b][1,3]thiazin-6-ones

RESULTS AND DISCUSSION

The reaction of 2-thiouracils **1** with dialkyl acetylenedicarboxylates **2** in the presence of isocyanides **3** proceeded in refluxing toluene, over 1 h to give dialkyl 4-(alkylamino)-2,6-dihydro-6-oxo-8-alkylpyrimido[2,1-b][1,3]thiazine-2,3-dicarboxylate **4** and dialkyl 4-(arylamino)-4,6-dihydro-6-oxo-8-alkylpyrimido[2,1-b][1,3]thiazine-2,3-dicarboxylate **5**. The structures of compounds **4a–4h** and **5a-5d** were deduced from their elemental analyses and IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these stable compounds displayed molecular ion peaks at the appropriate *m/z* values. Any initial fragmentation involves loss from, or complete loss of the side chains and scission of the heterocyclic

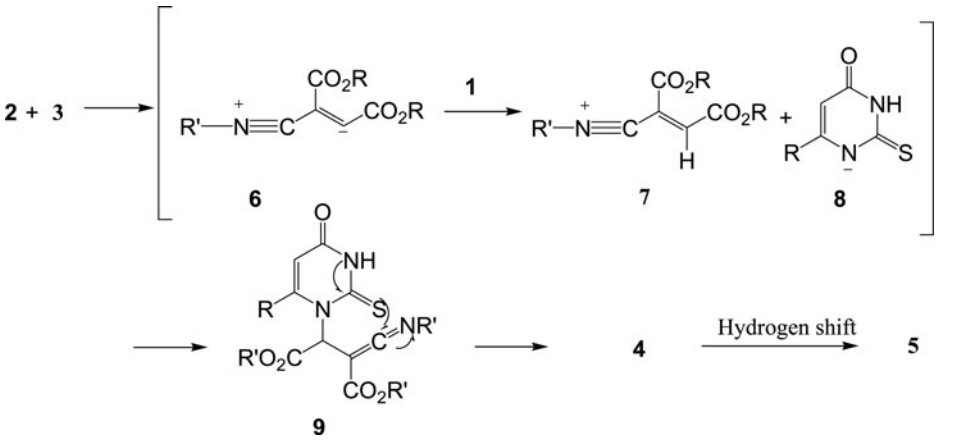
Table 1 Synthesis of pyrimido[2,1-b][1,3]thiazin-6-ones

Entry	R	R′	R″	Product	Yield%
1	H	Me	Cyclohexyl	**4a**	91
2	H	Et	Cyclohexyl	**4b**	87
3	n-Pr	Me	Cyclohexyl	**4c**	94
4	n-Pr	Et	Cyclohexyl	**4d**	87
5	H	Me	1,1,3,3-Tetramethylbutyl	**4e**	93
6	H	Et	1,1,3,3-Tetramethylbutyl	**4f**	86
7	n-Pr	Me	1,1,3,3-Tetramethylbutyl	**4g**	93
8	n-Pr	Et	1,1,3,3-Tetramethylbutyl	**4h**	85
9	H	Me	2,6-Dimethyl phenyl	**5a**	94
10	H	Et	2,6-Dimethyl phenyl	**5b**	96
11	n-Pr	Me	2,6-Dimethyl phenyl	**5c**	92
12	n-Pr	Et	2,6-Dimethyl phenyl	**5d**	93

ring system. The ^{1}H NMR spectrum of **4a** displayed cyclohexyl ($\delta = 1.27$–2.01 ppm), two methoxy ($\delta = 3.57$ and 3.75 ppm), and methine ($\delta = 7.11$ ppm) protons. The adjacent alkene protons were exhibited as two doublets at $\delta = 6.42$ and 7.83 ppm, along with a broad singlet at $\delta = 9.67$ ppm for the NH group. The proton decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the proposed structure.

The ^{1}H NMR spectrum of **5a** exhibited five singlets identified as methyl ($\delta = 1.91$ and 2.43 ppm), methoxy ($\delta = 3.73$ and 3.87 ppm), and methine ($\delta = 4.96$ ppm) protons. Two doublets were observed at $\delta = 5.45$ and 7.45 ppm for the adjacent alkene protons, aromatic protons ($\delta = 6.87$–7.06 ppm) and a broad singlet at $\delta = 10.57$ ppm for the NH group. The proton decoupled ^{13}C NMR spectrum of **5a** showed 19 distinct resonances in agreement with the proposed structure.

Although we have not yet established the mechanism of formation of **4** and **5** in an experimental manner, a plausible rationalization for the formation of functionalized pyrimido[2,1-b][1,3]thiazin-6-ones **4a–4h** and **5a-5d** is shown in Scheme 2. Presumably, the zwitterionic intermediate,[11] formed from **2** and **3**, is protonated by the NH acidic compound **1**. Then, the positively charged ion **7** undergoes an intramolecular reaction with compounds **8** to produce the ketenimines **9**, which apparently isomerize under the reaction conditions employed to produce the final products **4** in excellent yields. Finally, a hydrogen shift produces the final products **5** in good yields (Scheme 2). The absence of the strong ketenimine absorption bands at about 2050 cm^{-1} in the IR spectra of compounds **4** and **5**, excludes the conjugate addition of the anion **8** to the intermediate **7**.



Scheme 2 Proposed mechanism.

CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of functionalized pyrimido[2,1-b][1,3]thiazin-6-ones derivatives of potential synthetic and pharmacological interest. The one-pot nature of the present procedure makes it an acceptable method for the preparation of target molecules with variable functionalities. The advantages of the present method include good functional group tolerance, high yields of products, simple experimental procedure and purification, no need for dry solvent, no catalyst and

no prior activation, no mixture product, short reaction times and the starting materials and reagents can be mixed without any activation or modification. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

EXPERIMENTAL

2-Thioxopyrimidin-4-ones, acetylenic esters and isocyanides were obtained from Fluka and were used without further purification. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were measured with a Bruker DRX-300 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were obtained with a Finnigan-MAT-8430 mass spectrometer, in *m/z*. The Supplemental Materials contain sample ^{1}H and ^{13}C NMR spectra of 4e and 5a (Figures S–S4).

General Procedure for the Preparation of Compounds 4, 5

To a stirred solution of **1** (1 mmol) and **2** (1 mmol) in 5 mL toluene was added a mixture of (**3**, 1 mmol) in 2 mL toluene. The reaction mixture was heated for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; *n*-hexane/AcOEt = 3/1)

Typical procedure for the preparation of dimethyl 2-(cyclohexylamino)-4,8-dihydro-6-methyl-8-oxopyrimido[2,1-b][1,3]thiazine-3,4-dicarboxylate (4a): To a stirred solution of 2-Thioxopyrimidin-4-one (**1**, 1 mmol) and DMADs (**2**, 1 mmol) in toluene (5 mL) was added a drop wise solution of cyclohexylisocyanide (**3**, 1 mmol) in toluene (2 mL). The reaction mixture was heated for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; n-hexane/AcOEt = 3/1) to afford the pure adducts. **4a** as a White powder; m.p: 145–147 °C; yield: 0.35 g (91%). IR (KBr) (ν_{max}/cm^{-1}): 3211, 1741, 1690, 1241 cm^{-1}. ^{1}H NMR: 1.27–2.01 (10 H, m, 5 CH_2), 3.58 (1 H, m, CH), 3.75 (3 H, s, CH_3O), 3.81 (3 H, s, CH_3O), 6.42 (1 H, d, $^{3}J_{HH}$ = 6.7, CH), 7.11 (1 H, s, CH), 7.83 (1 H, d,$^{3}J_{HH}$ = 6.7, CH), 9.32 (1 H, br s, NH). ^{13}C NMR: 24.7 (CH_2), 25.5 ($2CH_2$), 33.8 (CH_2), 34.3 (CH_2), 51.9 (CH–N), 53.0 (CH_3O), 54.1 (CH_3O), 54.7 (CH), 85.6 (C), 113.4 (CH),152.9 (CH), 156.0 (C), 156.4 (C=N), 160.4 (C=O), 167.2 (C=O), 168.9 (C=O). EI-MS, m/z (%): 379 (M+, 13), 320 (17), 253 (100), 83 (13), 59 (15); Anal. Calcd for $C_{17}H_{21}N_3O_5S$ (379.12); C, 53.81; H, 5.58; N, 11.07; Found: C, 54.01; H, 5.48; N, 10.97.

Diethyl2-(cyclohexylamino)-4,8-dihydro-8-oxopyrimido[2,1-b][1,3]thiazine3,4-dicarboxylate (4b): White powder; m.p: 161–163 °C; yield: 0.36 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3223, 1735, 1691, 1241 cm^{-1}. ^{1}H NMR: 1.27–2.01 (10 H, m, 5 CH_2), 1.26 (3 H, t, $^{3}J_{HH}$ = 7.1, CH_3), 1.42 (3 H, t, $^{3}J_{HH}$ = 7.1, CH_3), 3.58 (1 H, m, CH), 4.15 (2 H, dq, $^{2}J_{HH}$ = 11.6, $^{3}J_{HH}$ = 7.1, CH_2O), 4.53 (2 H, dq, $^{2}J_{HH}$ = 11.6, $^{3}J_{HH}$ = 7.1, CH_2O), 6.45 (1H, d,$^{3}J_{HH}$ = 6.7, CH), 7.03 (1 H, s, CH), 7.88 (1 H, d,$^{3}J_{HH}$ = 6.7, CH), 9.32 (1 H, br s, NH). ^{13}C NMR: 14.3 (CH_3), 14.8 (CH_3), 24.4 (CH_2), 25.5 (2 CH_2), 33.7 (CH_2), 34.4 (CH_2), 51.7 (CH–N), 54.7 (CH), 61.0 (CH_2O), 61.7 (CH_2O), 86.6 (C), 113.5 (CH), 152.6 (CH), 156.2 (C), 157.4 (C = N), 160.4 (C = O), 167.2 (C = O), 168.9 (C = O).

EI-MS, *m/z* (%):407 (M+, 13), 334 (17), 267 (100), 83 (13), 59 (47); Anal. Calcd for $C_{19}H_{25}N_3O_5S$ (407.15) C, 56.00; H, 6.18; N, 10.31; Found: C, 56.52; H, 6.76; N, 10.01.

Dimethyl2-(cyclohexylamino)-4,8-dihydro-8-oxo-6-propylpyrimido[2,1-b][1,3] thiazine-3,4-dicarboxylate(4c): White powder; m.p: 155–157 °C; yield: 0.39 g (94%). IR (KBr) (ν_{max}/cm^{-1}): 3120, 1739, 1691, 1241 cm^{-1}. ^{1}H NMR: 0.89 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.25–2.06 (10 H, m, 5 CH_2), 1.54 (quin, $^3J_{HH}$ = 7.4, CH_2), 2.27 (2 H, t, $^3J_{HH}$ = 7.4, CH_2), 3.58 (1H, m, CH), 3.71 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 5.98 (1H, s, CH), 7.14 (1H, s, CH), 9.37 (1H, br s, NH). ^{13}C NMR: 13.8 (CH_3), 21.3 (CH_2), 24.7 (CH_2), 25.3 (2 CH_2), 33.8 (CH_2), 34.1 (CH_2), 39.2 (CH_2), 51.4 (CH–N), 53.0 (CH_3O), 53.9 (CH_3O), 54.6 (CH), 85.6 (C), 113.4 (CH), 152.9 (C), 156.0 (C), 156.3 (C=N), 160.4 (C=O), 167.6 (C=O), 168.9 (C=O). EI-MS, *m/z* (%): 421 (M+, 13), 362 (17), 320 (15), 253 (100), 83 (15), 59 (47); Anal. Calcd for $C_{20}H_{27}N_3O_5S$ (421.16) C, 56.99; H, 6.46; N, 9.97; Found: C, 57.39; H, 6.96; N, 8.87.

Diethyl2-(cyclohexylamino)-4,8-dihydro-8-oxo-6-propylpyrimido[2,1-b][1,3] thiazine-3,4-dicarboxylate(4d): White powder; m.p: 142–145 °C; yield: 0.39 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 3330, 1745, 1681, 1222 cm^{-1}. ^{1}H NMR: 0.88 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.27–2.01 (10 H, m, 5 CH_2), 1.25 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.41 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.52 (2H, quin, $^3J_{HH}$ = 7.4, CH_2), 2.28 (2H, t, $^3J_{HH}$ = 7.4, CH_2), 3.58 (1H, m, CH),), 4.14 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.51 (2H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 6.46 (1H, s, CH), 7.01 (1H, s, CH), 9.32 (1 H, br s, NH). ^{13}C NMR:13.3 (CH_3), 14.3 (CH_3), 14.3 (CH_3), 20.2 (CH_2), 24.7 (CH_2), 25.5 (CH_2), 33.9 (2 CH_2), 34.3 (CH_2), 37.5 (CH_2), 51.9 (CH-N), 54.7 (CH), 61.0 (CH_2O), 61.7 (CH_2O), 86.6 (C), 113.1 (CH), 152.5 (C), 156.2 (C), 157.4 (C=N),160.4 (C=O), 167.2 (C=O), 168.9 (C=O). EI-MS, *m/z* (%):449 (M+, 13), 376 (18), 334 (15), 267 (100), 83 (15), 59 (45); Anal. Calcd for $C_{22}H_{31}N_3O_5S$ (449.19) C, 58.78; H, 6.95; N, 9.35; Found C, 58.62; H, 6.95; N, 9.34.

Dimethyl 2-(2,4,4-trimethylpentan-2-ylamino)-4,8-dihydro-8-oxopyrimido[2,1-b][1,3]thiazine-3,4-dicarboxylate(4e):145–147 °C; yield: 0.38 g (93%). IR (KBr) (ν_{max}/cm^{-1}): 3220, 1745, 1691, 1241 cm^{-1}. ^{1}H NMR: 1.02 (9 H, s, 3 CH_3), 1.51 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 1.62 (1 H, d, $^2J_{HH}$ = 15.3, CH), 1.92 (1 H, d, $^2J_{HH}$ = 15.3, CH), 3.72 (3 H, s, CH_3O), 3.80 (3 H, s, CH_3O), 6.42 (1 H, d, $^3J_{HH}$ = 6.6, CH), 7.15 (1 H, s, CH), 7.83 (1 H, d, $^3J_{HH}$ = 6.6, CH), 9.67 (1 H, br s, NH). ^{13}C NMR: 31.3 (CH_3), 31.7 (3 CH_3), 32.1 (C), 39.5 (CH_3), 51.9 (CH_2), 52.7 (CH_3O), 53.1 (C), 53.6 (CH_3O), 58.4 (CH), 86.8 (C), 110.3 (CH), 154.4 (CH), 157.0 (C), 160.8 (C=N), 167.4 (C=O), 167.6 (C=O), 169.2 (C=O). EI-MS, *m/z* (%):409 (M+, 13), 350 (18), 283 (100), 113 (16), 59 (34); Anal. Calcd for $C_{19}H_{27}N_3O_5S$ (409.16); C, 55.73; H, 6.65; N, 10.26. Found: C, 55. 37; H, 6.05; N, 10.36.

Diethyl2-(2,4,4-trimethylpentan-2-ylamino)-4,8-dihydro-8-oxopyrimido[2,1-b] [1,3]thiazine-3,4-dicarboxylate(4f):White powder; m.p: 149–151 °C; yield: 0.40 g (86%). IR (KBr) (ν_{max}/cm^{-1}): 3232, 1735, 1696, 1221 cm^{-1}. ^{1}H NMR: 1.02 (9 H, s, 3 CH_3), 1.23 (3 H, t, $^3J_{HH}$ = 7.1 CH_3), 1.43 (3 H, t,$^3J_{HH}$ = 7.1, CH_3), 1.54 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 1.71 (1 H, d, $^2J_{HH}$ = 15.3, CH), 1.90 (1 H, d, $^2J_{HH}$ = 15.3, CH), 4.05 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.41 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 6.44 (1 H, d, $^3J_{HH}$ = 6.7, CH), 7.13 (1 H, s, CH), 7.83 (1 H, d, $^3J_{HH}$ = 6.7, CH), 9.52 (1 H, br s, NH). ^{13}C NMR: 14.3 (CH_3), 14.8 (CH_3), 30.2 (CH_3), 32.1 (3 CH_3), 32.8 (C), 33.1 (CH_3), 52.9 (CH_2), 53.6 (C), 60.1 (CH_2O), 62.1 (CH_2O), 64.4 (CH), 87.2 (C), 111.4 (CH), 153.9 (CH), 156.1(C), 160.8 (C=N), 165.8 (C=O), 167.4 (C=O), 169.1 (C=O). EI-MS, *m/z* (%):437 (M+, 13), 364 (18), 297 (100), 113 (15), 59 (45); Anal. Calcd for $C_{21}H_{31}N_3O_5S$ (437.19) C, 57.64; H, 7.14; N, 9.60; Found: C, 58.04; H, 6.89; N, 9.34.

Dimethyl2-(2,4,4-trimethylpentan-2-ylamino)-4,8-dihydro-8-oxo-6-propyl pyrimido[2,1-b][1,3]thiazine-3,4-dicarboxylate(4g):White powder; m.p: 153–157 °C; yield: 0.38 g (93%). IR (KBr) (ν_{max}/cm^{-1}): 3220, 1745, 1691, 1241 cm^{-1}. ^{1}H NMR: 0.88 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.02 (9 H, s, 3 CH_3), 1.51 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.57 (quin, $^3J_{HH}$ = 7.4, CH_2), 1.70 (1 H, d, $^2J_{HH}$ = 15.3, CH), 1.92 (1 H, d, $^2J_{HH}$ = 15.3, CH), 2.27 (2H, t, $^3J_{HH}$ = 7.4, CH_2), 3.72 (3 H, s, CH_3O), 3.81 (3 H, s, CH_3O), 5.46 (1 H, s, CH), 7.05 (1 H, s, CH), 9.67 (1 H, br s, NH). ^{13}C NMR: 13.9 (CH_3), 21.5 (CH_2), 31.3 (CH_3), 31.7 (3 CH_3), 31.9 (C), 32.0 (CH_3), 39.5 (CH_2), 51.9 (CH_2), 52.7 (CH_3O), 53.1 (C), 53.6 (CH_3O), 58.4 (CH), 86.8 (C), 110.3 (CH), 154.4 (C), 157.0 (C), 161.8 (C = N), 167.4 (C=O), 167.6 (C=O), 169.2 (C=O). EI-MS, *m/z* (%):451 (M+, 13), 392 (18), 350 (17), 283 (100), 113 (17), 59 (34); Anal. Calcd for $C_{22}H_{33}N_3O_5S$ (451.21); C, 58.51; H, 7.37; N, 9.31; Found: C, 58.42; H, 7.07; N, 8.91.

Diethyl2-(2,4,4-trimethylpentan-2-ylamino)-4,8-dihydro-8-oxo-6-propyl pyrimido [2,1-b][1,3]thiazine-3,4-dicarboxylate(4h): White powder; m.p: 144–146 °C; yield: 0.41 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 3232, 1741, 1687, 1237 cm^{-1}. ^{1}H NMR: 0.87 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.09 (9 H, s, 3 CH_3), 1.23 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.44 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.53(3 H, s, CH_3), 1.57 (2 H, quin, $^3J_{HH}$ = 7.4, CH_2), 1.58 (3 H, s, CH_3), 1.72 (1 H, d, $^2J_{HH}$ = 15.3, CH), 1.95 (1 H, d, $^2J_{HH}$ = 15.3, CH), 2.26 (2 H, t, $^3J_{HH}$ = 7.4, CH_2), 4.04 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.41 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 5.48 (1 H, s, CH), 7.11 (1 H, s, CH), 9.52 (1H, br s, NH). ^{13}C NMR: 13.9 (CH_3), 14.3 (CH_3), 14.8 (CH_3), 21.5 (CH_2), 30.2 (CH_3), 32.1 (3 CH_3), 32.9 (C), 33.1(CH_3), 39.6 (CH_2), 52.9 (CH_2), 53.6 (C), 60.1 (CH_2O), 62.1 (CH_2O), 64.4 (CH), 87.2 (C), 111.4 (CH), 153.9 (C), 156.1 (C), 160.8 (C=N), 165.8 (C=O), 167.4 (C=O), 169.1 (C=O). EI-MS, *m/z* (%):479 (M+, 12), 406 (15), 364 (17), 297 (100), 113 (15), 59 (41); Anal. Calcd for $C_{24}H_{37}N_3O_5S$ (479.24); C, 60.10; H, 7.78; N, 8.76; Found: C, 61.32; H, 7.12; N, 7.96.

Typical procedure for the preparation of dimethyl 2-(2,6-dimethyl phenyl amino)-2,8-dihydro-8-oxopyrimido[2,1-b][1,3]thiazine-3,4-dicarboxylate (5a): To a stirred solution of 2-Thioxopyrimidin-4-one (1, 1 mmol) and DMADs (2, 1 mmol) in toluene (5 mL) was added, drop wise, a solution of 2,6-dimethylphenylisocyanide (3, 1 mmol) in toluene (2 mL). The reaction mixture was heated for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; n-hexane/AcOEt = 3/1) to afford the pure adducts.

5a as Yellow powder; m.p: 162–165 °C; yield: 0.38 g (94%). IR (KBr) (ν_{max}/cm^{-1}): 3220, 1745, 1691, 1241 cm^{-1}. ^{1}H NMR: 1.91 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 3.71 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.94 (1H, s, CH), 5.65 (1H, d, $^3J_{HH}$ = 6.7, CH), 6.87 (1H, d, $^3J_{HH}$ = 7.3, CH), 7.01 (1H, d, $^3J_{HH}$ = 7.3, CH), 7.06 (1 H, t, $^3J_{HH}$ = 7.3), 7.45 (1 H, d, $^3J_{HH}$ = 6.7, CH), 10.57 (1H, brs, NH). ^{13}C NMR: 19.1 (CH_3), 20.9 (CH_3), 40.2 (CH), 52.4 (CH_3O), 53.7 (CH_3O), 88.2 (C), 109.5 (CH), 127.2 (CH), 128.5 (CH), 128.9 (CH), 132.8 (C), 135.4 (C), 136.2 (C), 152.7 (CH), 158.3 (C), 159.5 (C=N), 164.9(C=O), 167.8 (C=O), 169.9 (C=O). EI-MS, *m/z* (%): 401 (M+, 13), 342 (17), 274 (100), 149 (13), 105 (15), 57 (47); Anal. Calcd for $C_{19}H_{19}N_3O_5S$ (401.10) C, 56.85; H, 4.77; N, 10.47; Found: C, 57.12; H, 4.07; N, 9.86.

Diethyl2-(2,6-dimethylphenylamino)-2,8-dihydro-8-oxopyrimido[2,1-b][1,3] thiazine-3,4-dicarboxylate(5b): Yellow powder; m.p: 145–147 °C; yield: 0.41 g (96%). IR (KBr) (ν_{max}/cm^{-1}): 3220, 1745, 1691, 1241 cm^{-1}. ^{1}H NMR: 1.23 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.41 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.96 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 4.15 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.51 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.94 (1H, s, CH), 5.65 (1H, d, $^3J_{HH}$ = 6.7, CH), 6.87 (1 H, d, $^3J_{HH}$ = 7.3, CH), 7.02

(1 H, d, $^3J_{HH}$ = 7.3, CH), 7.06 (1 H, t, $^3J_{HH}$ = 7.3, CH), 7.33 (1 H, d, $^3J_{HH}$ = 6.7, CH), 10.57 (1H, br s, NH). ^{13}C NMR: 14.4 (CH_3), 14.4 (CH_3), 19.6 (CH_3), 21.0 (CH_3), 40.5 (CH), 61.5 (CH_2O), 62.6 (CH_2O), 86.8 (C), 109.1 (CH), 127.8 (CH), 128.5 (CH), 128.8 (CH), 132.5 (C), 135.5 (C), 136.0 (C), 152.3(CH), 157.0 (C), 159.8 (C=N), 164.4 (C=O), 167.6 (C=O), 169.3 (C=O). EI-MS, *m/z* (%):429 (M+, 13), 401 (14), 342(100), 274 (15), 105 (12), 57 (44); Anal. Calcd for $C_{21}H_{23}N_3O_5S$ (429.13); C, 58.73; H, 5.40; N, 9.78; Found: C, 58.45; H, 5.37; N, 9.72.

Dimethyl2-(2,6-dimethylphenylamino)-2,8-dihydro-8-oxo-6-propylpyrimido [2,1-b][1,3]thiazine-3,4-dicarboxylate (5c):Yellow powder; m.p: 159–161 °C; yield: 0.40 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 3320, 1745, 1694, 1231 cm^{-1}. ^{1}H NMR: 0.88 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.57 (2 H, quin, $^3J_{HH}$ = 7.4, CH_2), 1.92 (3 H, s, CH_3), 2.27 (2 H, t, $^3J_{HH}$ = 7.4, CH_2), 2.33 (3 H, s, CH_3), 3.71 (3 H, s, CH_3O), 3.87 (3 H, s, CH_3O), 4.95 (1 H, s, CH), 5.46 (1 H, s,CH), 6.87 (1 H, d, $^3J_{HH}$ = 7.3, CH), 7.00 (1 H, d, $^3J_{HH}$ = 7.3, CH), 7.05 (1 H, t, $^3J_{HH}$ = 7.3), 10.47 (1 H, br s, NH). ^{13}C NMR: 13.6 (CH_3), 17.9 (CH_2), 19.2 (CH_3), 21.0 (CH_3), 38.6 (CH_2), 40.5 (CH), 52.7 (CH_3O), 53.6 (CH_3O), 86.8 (C), 109.3 (CH), 127.1 (CH), 128.7 (CH), 128.8 (CH), 132.6 (C), 135.3 (C), 136.0 (C), 152.4 (C), 158.0 (C),159.8 (C=N),164.4 (C=O), 167.6 (C=O), 169.2 (C=O). EI-MS, *m/z* (%):443 (M+, 13), 384 (15), 274 (100), 149 (14), 105 (13), 57 (44); Anal. Calcd for $C_{22}H_{25}N_3O_5S$ (443.15) C, 59.58; H, 5.68; N, 9.47; Found: C, 59.83; H, 5.23; N, 9.34.

Diethyl 2-(2,6-dimethylphenylamino)-2,8-dihydro-8-oxo-6-propylpyrimido [2,1-b][1,3]thiazine-3,4-dicarboxylate(5d):Yellow powder; m.p: 148–150 °C; yield: 0.42 g (93%). IR (KBr) (ν_{max}/cm^{-1}): 3210, 1732, 1686, 1241 cm^{-1}. ^{1}H NMR: 0.89 (3 H, t, $^3J_{HH}$ = 7.4, CH_3), 1.54 (2H, quin, $^3J_{HH}$ = 7.4, CH_2), 1.26 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.41 (3 H, t, $^3J_{HH}$ = 7.1, CH_3), 1.93 (3H, s, CH_3), 2.27 (2H, t, $^3J_{HH}$ = 7.4, CH_2), 2.42 (3 H, s, CH_3), 4.13 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.58 (2 H, dq, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 7.1, CH_2O), 4.84 (1 H, s, CH), 5.43 (1 H, s, CH), 6.87 (1 H, d, $^3J_{HH}$ = 7.3, CH), 7.00 (1 H, d, $^3J_{HH}$ = 7.3, CH), 7.06 (1H, t, $^3J_{HH}$ = 7.3, CH), 10.54 (1H, br s, NH). ^{13}C NMR: 13.8 (CH_3), 14.1 (CH_3), 14.8 (CH_3), 17.4 (CH_2), 19.6 (CH_3), 21.0 (CH_3), 38.1 (CH_2), 40.3 (CH), 61.6 (CH_2O), 62.6 (CH_2O), 86.8 (C), 109.1 (CH), 127.2 (CH), 128.5 (CH), 128.8 (CH), 132.8 (C), 135.5 (C), 136.0 (C), 152.4 (C), 158.0 (C), 159.6 (C=N),164.3 (C=O), 167.1 (C=O), 169.6 (C=O). EI-MS, *m/z* (%): 471 (M+, 13), 398 (14), 289 (100), 149 (15), 105 (12), 57 (44); Anal. Calcd for $C_{24}H_{29}N_3O_5S$ (471.18) C, 61.13; H, 6.20; N, 8.91; Found: C, 61.23; H, 6.34; N, 8.54.

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SUPPLEMENTARY MATERIAL

Supplemental data for this article can be accessed on the publisher's website at http://dx.doi.org/10.1080/10426507.2015.1050015.

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