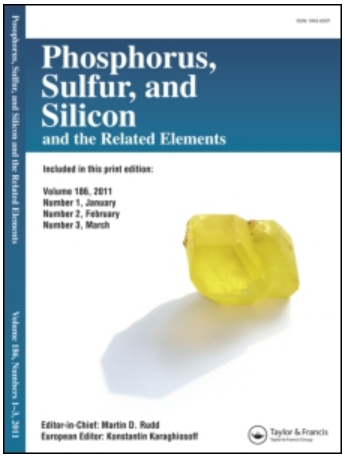

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Synthesis and Reactions of Some Pyrimidine Derivatives

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*Three different series of compounds including N-formylated thioxopyrimidines **3a-d**, thiazine derivatives **4a–c** and N-formylated oxopyrimidines **5a–d** were synthesized by reaction of an appropriate ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with DMF in the presence of $POCl_3$ under different conditions. Furtherer reaction of the thiazine derivatives **4a–c** with aqueous HCl under heating followed by neutralization with NaOH gave **7a–c**. IR and NMR spectroscopy, as well as elemental analysis were used for the identification of the new compounds.*

Keywords Carboxylate; formyl; pyrimidine; thiazine

INTRODUCTION

The first Biginelli compound was synthesized in 1893.[1] Recently this reaction has been extended for preparation of a large number of 3,4-dihydropyrimidines.[2] It is well known that a large number of 3,4-dihydropyrimidines show interesting pharmacological efficiencies such as antitumor, antiviral, and antibacterial activities.[2–9] In the past decade, 3,4-dihydropyrimidines with appropriate functional groups have emerged as antihypertensive agents[6–9] and potent calcium channel blockers.[4,5] Furthermore, several marine alkaloids with interesting biological activities contain the dihydropyrimidine-5-carboxylate moiety.[7] The most convenient preparation methods of these compounds include a one-pot reaction of β-ketoester or β-diketone, arylaldehyde and (thio)urea using photochemical[10] or microwave irradiation.[11–13] However, because of the incessant interest in this field, a new efficient synthesis of novel pyrimidine derivatives is desirable.

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RESULTS AND DISCUSSION

The starting pyrimidines **1** were synthesized according to literature procedures.[10–13] Compound **2**, which acts as an intermediate, was prepared by reacting ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1** with DMF and $POCl_3$ via a Vilsmeier formylation. The compounds **3a–d** was obtained by hydrolysis of the intermediate **2** at room temperature. However, hydrolysis of **2** under heating led to the formation of the thiazine carboxylates **4** and the 3-formyl-2-oxopyrimidines **5** as the major and the minor product, respectively. Compounds **5** are insoluble in an ice-cooled solution and can be easily isolated by filtration. Hydrolysis of **4** under dilute acidic conditions and heating afforded intermediately the hydrochloride **6**. Neutralization of the solution of **6** with 2 N NaOH gave **7**, which was isolated from an ice-cooled solution of $EtOH/H_2O$ (Scheme 1).

The ^1H NMR spectra of the *N*-formylated thioxopyrimidines **3a–d** and the *N*-formylated oxopyrimidines **5a–d** are very similar. The resonance of the formyl proton at low field and the absence of one of the NH proton resonances compared to the starting material support the structures of **3** and **5**. The H-6 proton of these compounds showed a downfield shift due to the adjacent electron withdrawing formyl group at the N-1 nitrogen atom. Thus, the rearranged products **4a–c** and **7a–c** were identified as 6*H*-1,3-thiazines.[14]

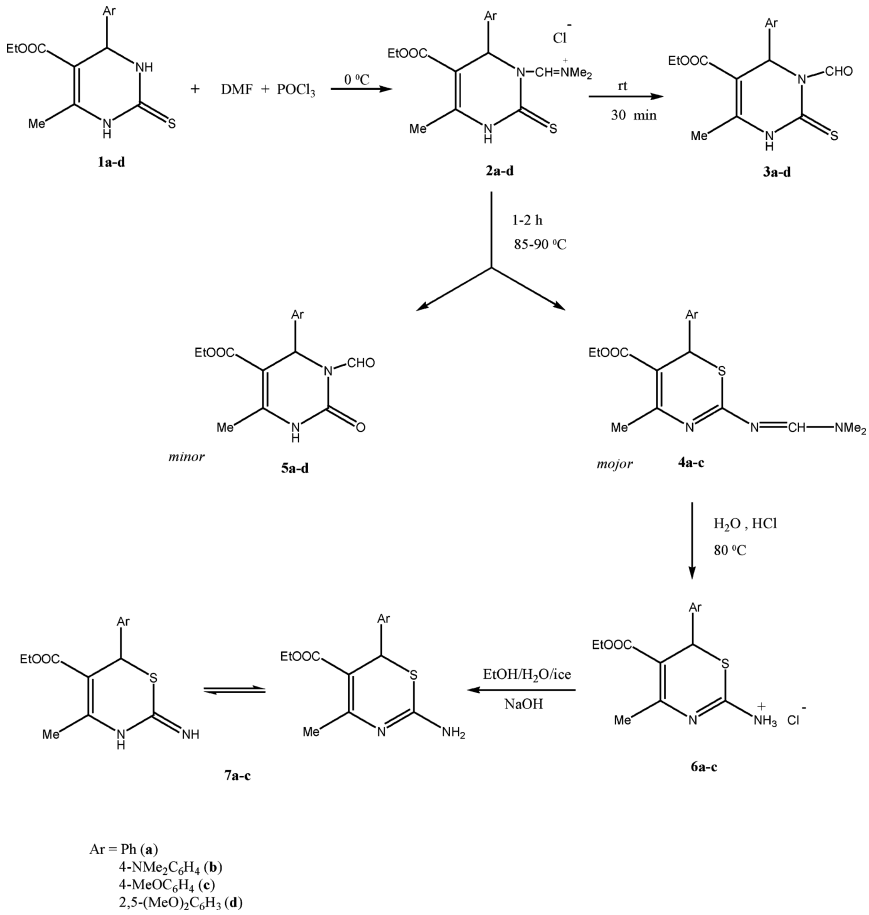
EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus Mettler Toledo Type FP62. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance (300 MHz) spectrometer. The IR spectra were recorded on Unicom Galaxy series FT-IR 5000 Spectrometer. Microanalyses were performed by the Microanalytical Lab at the Arak petrochemical company. Reactions were monitored by thin layer chromatography using silica gel F_{254} aluminum sheets (Merck). All materials were used as obtained without further purification.

GENERAL PROCEDURES

Synthesis of 3a–d

To a solution of the appropriate ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.001 mol) in DMF (10 mL) $POCl_3$(0.001 mol) was added dropwise at 0°C under stirring. Stirring was continued at room temperature for 30 min 10 mL of ice water was added to this solution and the precipitate was filtered to give the



SCHEME 1

N-formylated thioxopyrimidines **3a–d**, which were recrystallized from ethanol.

Synthesis of 4a–c and 5a–d

To a solution of the appropriate ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.001 mol) in DMF (10 mL) was added $POCl_3$(0.001 mol) under stirring at 0°C. The reaction mixture was heated at 85–90 °C for 1–2 h, allowed to cool to room temperature, and poured in 10 mL of ice-cooled water. The precipitate was separated by filtration and recrystallized from ethanol to give pure **5a–d**. The filtrate was made alkaline with NaOH (2N) to give **4a–c** as the major products.

Synthesis of 7a–c

A solution of **4** (0.001 mol) in 20 mL of HCl (37%) and 10 mL of water was heated at 80°C for 10 min. The precipitate was filtered to give the hydrochloride **6**. The ice-cooled solution of the precipitate in ethanol (10 mL) was neutralized with 2N NaOH to give the free amine **7**, which was precipitated by adding ice water.

Ethyl 1-Formyl-4-methyl-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3a)

Yield 76%, m.p. 165–166°C. IR (KBr): $\nu = 3213, 3153, 3009, 1712, 1645, 1630, 1520, 1498\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.23$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.46 (s, 1H, 4-H), 7.30 (m, 5H, arom-H), 9.71 (br s, 1H, NH), 11.10 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta = 14, 18, 52, 61, 107, 127, 128, 129, 139, 142, 163, 165, 178$. Anal. calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20%. Found: C, 59.48; H, 5.51; N, 9.61%.

Ethyl 6-[4-(Dimethylamino)phenyl]-1-formyl-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3b)

Yield 73%, m.p. 164–165°C. IR (KBr): $\nu = 3248, 3011, 2833, 1678, 1710, 1662, 1527\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.17$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.66 (s, 3H, NCH_3), 3.68 (s, 3H, NCH_3), 4.05 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.12 (s, 1H, 4-H), 6.84 (m, 4H, arom-H), 9.70 (br s, 1H, NH), 11.70 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta = 14, 18, 52, 56, 61, 105, 112, 118, 128, 152, 153, 163, 165, 178$. Anal. calcd. for $C_{17}H_{21}N_3O_3S$: C, 58.77; H, 6.09; N, 12.09%. Found: C, 59.10; H, 5.81; N, 12.28%.

Ethyl 1-Formyl-6-(4-methoxyphenyl)-4-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (3c)

Yield 33%, m.p. 112–113°C. IR (KBr): $\nu = 3267, 3155, 2974, 1707, 1658, 1610, 1512, 1236, 1095\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.52 (s, 3H, OCH_3), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.39 (s, 1H, 4-H), 7.10 (m, 4H, arom-H), 8.20 (br s, 1H, NH), 9.87 (s, 1H, CHO). Anal. calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38%. Found: C, 57.61; H, 5.46; N, 8.20%.

Ethyl 6-(2,5-Dimethoxyphenyl)-1-formyl-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3d)

Yield 86%, m.p. 163–164°C. IR (KBr): $\nu = 3383, 3100, 2941, 1678, 1610, 1512, 1207, 1066\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.21$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.71 (s, 6H, OCH_3), 4.11 (q, $J = 7.2$ Hz, 2H,

OCH_2), 6.24 (s, 1H, 4-H), 6.73 (m, 3H, arom-H), 8.21 (br s, 1H, NH), 9.30 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta = 14$, 17, 52, 55, 56, 61, 105, 112, 114, 118, 128, 141, 152, 153, 163, 165, 178. Anal. calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69%. Found: C, 56.29; H, 5.34; N, 7.48%.

Ethyl 2-{(Dimethylamino)methyleneamino}-4-methyl-6-phenyl-6H-1,3-thiazine-5-carboxylate (4a)

Yield 52%, m.p. 140–142°C. IR (KBr): $\nu = 2990$, 2930, 1687, 1615, 1580, 1471 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.23$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.00 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 4.18 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.37 (s, 1H, 4-H), 7.22 (m, 5H, arom- H), 8.11 (s, 1H, N=CH—). ^{13}C NMR ($CDCl_3$): $\delta = 14$, 24, 35, 41, 43, 60, 105, 126, 127, 128, 143, 158, 162, 165, 167. Anal. calcd. for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N, 12.68%. Found: C, 61.50; H, 6.49; N, 12.30%.

Ethyl2-{(Dimethylamino)methyleneamino}-6-[4-(dimethylamino)phenyl]-4-methyl-6H-1,3-thiazine-5-carboxylate (4b)

Yield 61%, m.p. 146–148°C. IR (KBr): $\nu = 2984$, 2918, 1685, 1610, 1479 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3), 4.11 (q, $J = 7.1$ Hz, 2H, OCH_2), 5.74 (s, 1H, 4-H), 6.70 (m, 4H, arom-H), 8.10 (s, 1H, N=CH—). Anal. calcd. for $C_{19}H_{26}N_4O_2S$: C, 60.94; H, 7.00; N, 14.96%. Found: C, 61.24; H, 7.15; N, 14.55%.

Ethyl 6-(2,5-Dimethoxyphenyl)-2-{(dimethylamino) methyleneamino}-4-methyl-6H-1,3-thiazine-5-carboxylate (4c)

Yield 61%, m.p. 132–133°C. IR (KBr): $\nu = 3074$, 2951, 1678 m 1645, 1610, 1531, 1493, 1276, 1053 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (t, $J = 7.0$ Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.12 (q, $J = 7.0$ Hz, 2H, OCH_2), 5.69 (s, 1H, 4-H), 6.71 (m, 3H, arom-H), 8.1 (s, 1H, N=CH—). Anal. calcd. for $C_{19}H_{25}N_3O_4S$: C, 58.29; H, 6.44; N, 10.73%. Found: C, 58.60; H, 6.62; N, 10.50%.

Ethyl 1-Formyl-4-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5a)

Yield 20%, m.p. 216–218°C. IR (KBr): $\nu = 3252$, 3147, 2980, 1704, 1652, 1492 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.15$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.35 (s,

3H, CH_3), 3.39 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.18 (s, 1H, 4-H), 7.43 (m, 5H, arom-H), 9.25 (br s, 1H, NH), 10.35 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ = 14, 18, 53, 61, 105, 127, 128, 129, 140, 145, 152, 161, 165. Anal. calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%. Found: C, 62.31; H, 5.66; N, 9.79%.

Ethyl 6-[4-(Dimethylamino)phenyl]-1-formyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5b)

Yield 20%, m.p. 171–172°C. IR (KBr): $\nu = 3369, 3054, 2951, 1678, 1610, 1512$ cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.21$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.67 (s, 3H, NCH_3), 3.69 (s, 3H, NCH_3), 4.11 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.60 (s, 1H, 4-H), 6.79 (m, 4H, arom-H), 9.19 (br s, 1H, NH), 10.11 (s, 1H, CHO). Anal. calcd. for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68%. Found: C, 61.94; H, 6.48; N, 12.80%.

Ethyl 1-Formyl-6-(4-methoxyphenyl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5c)

Yield 42%, m.p. 118–119°C. IR (KBr): $\nu = 3252, 3136, 2955, 1705, 1649, 1512, 1248, 1082$ cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.13$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.01 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.21 (s, 1H, 4-H), 6.99 (m, 4H, arom-H), 8.64 (br s, 1H, NH), 9.21 (s, 1H, CHO). Anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80%. Found: C, 60.55; H, 5.91; N, 8.63%.

Ethyl 6-(2,5-Dimethoxyphenyl)-1-formyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5d)

Yield 20%, m.p. 165–167°C. IR (KBr): $\nu = 3379, 3074, 2951, 1678, 1610, 1512, 1238, 1053$ cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.25$ (t, $J = 7.1$ Hz, CH_3), 2.38 (s, 3H, CH_3), 3.75 (s, 6H, OCH_3), 4.11 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.22 (s, 1H, 4-H), 6.91 (m, 3H, arom-H), 8.16 (br s, 1H, NH), 9.29 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ = 14, 18, 53, 55, 56, 60, 102, 112, 114, 118, 128, 144, 151, 152, 153, 163, 165. Anal. calcd. for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04%. Found: C, 58.51; H, 5.90; N, 7.82%.

Ethyl 2-Imino-4-methyl-6-phenyl-3,6-dihydro-2H-1,3-thiazine-5-carboxylate (7a)

Yield 85%, m.p. 122–124°C. IR (KBr): $\nu = 3200, 3184, 2972, 1732, 1690, 1610, 1581$ cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.04$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.11 (q, $J = 7.1$ Hz, 2H, OCH_2), 5.68 (s, 1H, 4-H), 7.32

(m, 5H, arom-H), 9.33 (br s, 1H, NH), 10.35 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 14, 20, 42, 62, 106, 127, 128, 129, 139, 145, 164, 167$. Anal. calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.84; N, 10.14%. Found: C, 60.57; H, 6.16; N, 10.36%.

Ethyl 2-Amino-6-[4-(dimethylamino)phenyl]-4-methyl-6H-1,3-thiazine-5-carboxylate (7b)

Yield 90%, m.p. 161–163°C. IR (KBr): $\nu = 3377, 3360, 3090, 2955, 1678, 1650, 1520, 1496$ cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.71 (s, 3H, NCH_3), 3.87 (s, 3H, NCH_3) 4.13 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.69 (s, 1H, 4-H), 6.69 (m, 4H, arom-H), 7.28 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): $\delta = 14, 23, 36, 56, 60, 102, 111, 112, 114, 130, 150, 153, 167$. Anal. calcd. for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16%. Found: C, 60.55; H, 6.19; N, 13.32%.

Ethyl 2-Amino-6-(2,5-dimethoxyphenyl)-4-methyl-6H-1,3-thiazine-5-carboxylate (7c)

Yield 90%, m.p. 207–209°C. IR(KBr): $\nu = 3232, 3134, 2980, 1710, 1643, 1504, 1230, 1087$ cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.71 (s, 6H, OCH_3) 4.13 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.69 (s, 1H, 4-H), 6.67 (m, 3H, arom-H), 7.21 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): $\delta = 14, 23, 36, 55, 56, 60, 101, 111, 112, 113, 114, 115, 130, 150, 153, 166$. Anal. calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33%. Found: C, 57.35; H, 5.61; N, 8.37%.

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