SHORT PAPER

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Synthesis of functionalised pyrimidin-2-one derivatives†

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Pyrimidin-2-one and pyrimidine-2-thione derivatives **5** and **7** are obtained in 40-65% and 60-75% yields when 4-ethoxycarbonyl-5-phenylfuran-2,3-dione (**1**) react with semicarbazones, thiosemicarbazones **2a–f**, urea and thiourea derivatives **6a–d** through loss of water and carbon dioxide.

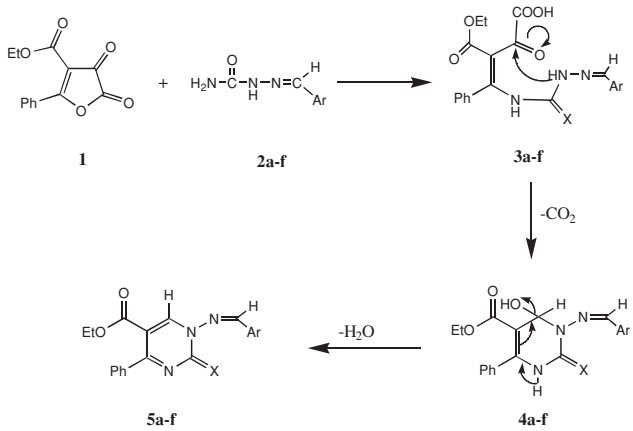
Keywords: pyrimidinones, furan-2,3-diones, semicarbazones, thiosemicarbazones, ureas, thioureas

In the course of a study to gain more insight into the chemical behaviour of five-membered heterocyclic 2,3-diones towards cycloaddition,[1,2] thermolysis reactions[3,4] and NH-nucleophiles,[5-7] affording various mono- and bicyclic systems,[8–10] we now report a simple and direct synthesis of functionalised pyrimidine derivatives **5a–f** and **7a–d** from the reactions of the furan-2,3-dione derivative **1**[11] with several semicarbazones, thiosemicarbazones **2a–f**, ureas and thioureas **6a–d**. Pyrimidines have found much interest for biological and medicinal reasons. Their chemistry has been investigated extensively[12,13] as well as their biological activity as possessing effective antibacterial, antifungal, antiviral, insecticidal and miticidal activities.[14-16]

The reaction of furan-2,3-dione **1** with semicarbazones or thiosemicarbazones **2a–f** resulted in the formation of the 1*H*-pyrimidin-2-ones **5** in 40–65% yields. The structural analogy of all compounds **5** is evident from the 1R, ^{1}H NMR and mass spectrometric data. The IR spectrum of **5a** shows characteristic absorption bands at 3050, 2980, 1740, 1720 and 1645 cm^{-1} for aromatic CH, aliphatic CH, ester CO and C=N groups respectively. The ^{1}H NMR spectrum of **5a** shows a singlet at 1.39 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 7.23–8.00 (m, 10H, aromatic-H), 8.7 (s, 1H, 6-H) and 10.2 (s, 1H, =CH-Ar). The mass spectrum was in accordance with the proposed structure.

The formation of the pyrimidines **5** is outlined briefly in Scheme 1. It is assumed that the amino group of semicarbazones **2a** attacks the C-5 position of the furan-2, 3-dione ring[3] leading to ring opening similar to a Michael-type addition. Synthesis of pyrimidine systems via Michael-type addition of ureas, thioureas, amidines and similar compounds of this type onto α,β-unsaturated carbonyls are well established.[17] Decarboxylation of an α-oxocarbonic acid intermediate **3**, initiated by the ring closure through addition of the NH to the CO moiety,[18] and finally loss of water via a fragmentation process,[19] led to the products (Scheme 1).

Similarly, trisubstituted pyrimidinones **7a–d** were obtained, in 60–75% yields, from the cyclization reaction of the furan-2,3-dione[11] derivatives **1** and the urea or thiourea derivatives **6a–d** (Scheme 2). Structural identification of **7** was established on the basis of elemental analysis and spectral data. The IR spectrum of **7a** showed characteristic absorption bands at 1740 and 1650 cm^{-1} for ester and CO group respectively, while its ^{1}H NMR spectrum showed signals at 1.29 (t, 3H, CH_3), 3.45 (s, 3H, NCH_3), 4.17 (q, 2H, CH_2), 7.34–7.92 (m, 5H, arom.) and 8.29 (s, 1H, C6-H), ^{13}C NMR spectrum showed signals at 175.7 (C-2), 166.6 (COO), 162.5

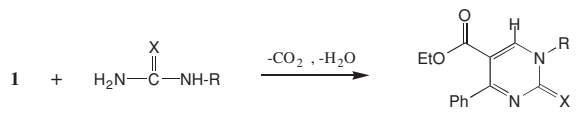


2-5	X	Ar
a	O	C_6H_5
b	O	*p*-CH_3-C_6H_4
c	O	*p*-CH_3O-C_6H_4
d	O	*p*-Cl-C_6H_4
e	S	*p*-Cl-C_6H_4
f	S	*p*-$(CH_3)_2N$-C_6H_4

Scheme 1

(C-4), 114.9 (C-5), 61.1 (CH_2), 41.4 (NCH_3) and 13.9 (CH_3). The C6-H proton of **7a–d** appeared in the region 8.2-8.7 ppm which was similar to that in analogues **5**. This is additional support for the proposed structure **7**.

The formation of the compounds **7a–d** should proceed via analogous key intermediates and subsequent elimination of CO_2 and H_2O as shown in Scheme 1.



6, 7	X	R
a	O	CH_3
b	O	C_6H_5
c	S	CH_3
d	S	C_6H_5

Scheme 2

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

All melting points were determined on a Gallenkamp melting point apparatus. Infrared spectra were measured as KBr pellets on a Perkin-Elmer Model 298 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer in $CDC1_3$ or DMSO as solvent with TMS as internal reference; chemical shifts are expressed as δ ppm units. Mass spectra were determined on a JEOL JMS 600 spectrometer operating at 70 eV. Analytical data were performed on CHN-Elemental Analyzer Carlo Erba 1106.

Synthesis of the pyrimidine derivatives 5a–f and 7a–d. General procedure: An equimolar mixture of **1**[11] and the corresponding semicarbazone, thiosemicarbazone **2a–f**, urea or thiourea **6a–d** respectively were refluxed in boiling toluene for 4–5 h. After evaporation of the solvent the oily residue was treated with dry ether and the so formed crude product crystallised from ethanol or acetic acid to give **5a–f** in 40–65% yields or **7a–d** in 60-75% yields respectively.

Ethyl 2-oxo-4-phenyl-1-[(phenylmethylidene)amino]-1,2-dihydro-5-pyrimidinecarboxylate (**5a**): (65%) had m.p.188–190 °C; IR (KBr): ν_{max}/ cm^{-1} 3050, 2980, 1740, 1720 and 1645 cm^{-1} for arom. CH, aliph. CH, ester CO, ring CO and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.39 (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 7.23–8.00 (m, 10H, arom.), 8.70 (s, 1H, C6-H). and 10.20 (s, 1H, CH=N). MS: *m*/*z* 347 (7%). (Found: C, 68.95; H, 4.86; N, 11.92. $C_{20}H_{17}N_3O_3$ requires C, 69.15; H, 4.93; N, 12.10).

Ethyl 1-[(4-methylphenyl)methylideneamino]-2-oxo-4-phenyl-1,2-dihydro-5-pyrimidinecarboxylate (**5b**): (57%) had m.p.170–172 °C; IR (KBr): ν_{max}/cm^{-1} 3050, 2980, 1745, 1720 and 1640 cm^{-1} for arom. CH, aliph. CH, ester CO, ring CO and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.40 (t. 3H, CH_3), 2 .53 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 7.25–8.12 (m, 9H, arom.), 8.80 (s, 1H, C6-H) and 10.22 (s, 1H CH=N). MS: *m*/*z* 361 (3%). (Found: C, 69.61; H, 5.24; N, 11.41. $C_{21}H_{19}N_3O_3$ requires C, 69.79; H. 5.30; N, 11.63).

Ethyl 1-[(4-methoxyphenyl)methylideneamino]-2-oxo-4-phenyl-1,2-dihydro-5-pyrimidinecarboxylate (**5c**): (60%) had m.p. 175–177 °C, IR (KBr): ν_{max}/ cm^{-1} 3050, 2980, 1740, 1720 and 1640 cm^{-1} for arom. CH, aliph. CH, ester CO, ringCO and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3H. CH_3), 3.75 (s, 3H, OCH_3), 4.35 (q, 2H, CH_2), 7.30–8.21 (m, 9H, arom.). 8.85 (s, 1H, C6-H). and 10.20 (s, 1H, CH= N). (Found: C, 66.63; H, 4.88; N, 10.87. $C_{21}H_{19}N_3O_4$ requires C, 66.83; H. 5.07; N, 11.14).

Ethyl 1-[(4-chlorophenyl)methylidene]amino-2-oxo-4-phenyl-1,2-dihydro-5-pyrimidinecarboxylate (**5d**): (51%) had m.p. 200–202 °C; IR (KBr): ν_{max}/ cm^{-1} 3050, 2980, 1735, 1710 and 1635 cm^{-1} for arom. CH, aliph. CH, ester CO, ring CO and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3H, CH_3),4.30 (q, 2H. CH_2), 7.20–8.00 (m, 9H, arom.), 8.80 (s, 1H, C6-H) and 10.25 (s, 1H, CH=N). MS: *m*/*z* 383 (7%). (Found: C, 62.77; H, 4.01; Cl, 8.98; N, 10.85. $C_{20}H_{16}ClN_3O_3$ requires C, 62.91; H, 4.22; Cl, 9.29; N, 11.01).

Ethyl 1-[(4-chlorophenyl)methylideneamino]-4-phenyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate (**5e**): (45%) had m.p. 230–233 ºC; IR (KBr): ν_{max}/ cm^{-1} 3050, 2980, 1730, 1685 and 1635 cm^{-1} for arom. CH, aliph. CH, ester C=O, C=S and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3H, CH_3), 4.28 (q. 2H, CH_2), 7.25–7.95 (m, 9H, arom.), 8.80 (s, 1H, C6-H) and 10.11 (s, 1H, CH=N). (Found: C, 60.12; H, 4.00; N, 10.29; S, 7.82. $C_{20}H_{16}ClN_3O_2S$ requires C, 60.38; H, 4.05; N, 10.56; S, 8.06).

Ethyl 1-[[(4-(dimethylamino)phenyl]methylideneamino]-4-phenyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate(**5f**): (40%) had m.p. 188–189 °C; IR (KBr): ν_{max}/cm^{-1} 3050, 2980, 1680, 1710 and 1635 cm^{-1} for arom. CH, aliph. CH, ester, C=S and C=N respectively. ^{1}H NMR (DMSO-d_6): δ 1.40 (t, 3H, CH_3), 3.10 (s, 6H, $N(CH_3)_2$), 4.25 (q, 2H, CH_2). 6.95–8.00 (m, 9H, arom.), 8.80 (s, 1H, C6-H) and 9.95 (s, 1H, CH=N). (Found: C, 64.75; H, 5.30; N, 13.59; S, 7.67. $C_{22}H_{22}N_4O_2S$ requires C, 65.00; H, 5.45; N, 13.78; S 7.89).

Ethyl 1-methyl-2-oxo-4-phenyl-1,2-dihydro-5-pyrimidine-carboxylate (**7a**): (75%) had m.p. 185–186 °C; IR (KBr): ν_{max}/cm^{-1} 2980, 1740 and 1650 cm^{-1} for aliph. CH, ester C=O and ring C=O respectively. ^{1}H NMR (DMSO-d_6): δ 1.29 (t, 3H, CH_3), 3.45 (s, 3H. NCH_3), 4.17 (q, 2H, CH_2), 7.34–7.92 (m, 5H, arom.) and 8.29 (s, 1H, C6-H). ^{13}C NMR (DMSO-d_6): δ 166.6 (COO), 162.5 (C-4), 157.7 (C-2). 156.9 (C-6), 135.2, 130.31, 128.9, 128.1 for aromatic carbons, 114.9 (C-5), 61.1 (CH_2), 41.4 (NCH_3) and 13.9 (CH_3). (Found: C, 64.89; H, 5.33; N, 10.73. $C_{14}H_{14}N_2O_3$ requires C. 65.11; H, 5.46; N, 10.85).

Ethyl 2-oxo-1,4-diphenyl-1,2-dihydro-5-pyrimidinecarboxylate (**7b**): (68%) had m.p. 210–212 °C; IR (KBr): ν_{max}/cm^{-1} 2980, 1735 and 1650 cm^{-1} for aliph. CH, ester C=O and ring C=O respectively. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3H, CH_3), 4.17 (q, 2H, CH_2), 7.17–7.93 (m, 10H, arom.) and 8.74 (s, 1H, C6-H). ^{13}C NMR (DMSO-d_6): δ 167.33 (COO), 163.3 (C-4), 156.70 (C-2), 157.4 (C-6), 115.7 (C-5), 142.7, 135.6, 130.2, 130.4, 129.6, 128.7, 128.1, 126.9 for aromatic carbons, 60.8 (CH_2), 14.2 (CH_3). (Found: C, 70.97; H, 4.93; N, 8.62. $C_{19}H_{16}N_2O_3$ requires C, 71.24; H, 5.03; N, 8.74).

Ethyl 1-methyl-4-phenyl-2-thioxo-1,2-dihydro-5-pyrimidine carboxylate (**7c**): (60%) had m.p.225–227 °C; IR (KBr): ν_{max}/cm^{-1} 2980, 1740 and 1640 cm^{-1} for aliph. CH, ester C=Oand C=S respectively. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3H, CH_3), 4.02 (s, 3H, NCH_3), 4.17 (q, 2H, CH_2), 7.51-7.94 (m, 5H, arom.) and 8.45 (s. 1H, C6-H). ^{13}C NMR (DMSO): δ 182.5 (C-2), 166.4 (COO), 162.9 (C-4), 156.4 (C-6), 136.4, 130.6, 129.1, 128.2 for aromatic carbons, 116.1 (C-5), 61.4 (CH_2), 40.1 (NCH_3) and 13.9 (CH_3). (Found: C. 61.02; H, 5.01; N, 9.98; S, 11.48. $C_{14}H_{14}N_2O_2S$ requires C, 61.29; H, 5.14;N, 10.21; S, 11.69).

Ethyl 1,4-diphenyl-2-thioxo-1,2-dihydro-5-pyrimidinecarboxylate (**7d**): (72%) had m.p. 216–218 °C; IR (KBr): ν_{max}/cm^{-1} 2980, 1740 and 1640 cm^{-1} for aliph. CH, ester C=O, and C=S respectively. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3H, CH_3). 4.21 (q, 2H, CH_2), 7.04–7.94 (m, 10H, arom.) and 8.33 (s, 1H, C6-H). ^{13}C-NMR (DMSO): δ 181.7 (C-2), 165.6 (COO), 162.7 (C-4), 155.1 (C-6), 143.1, 136.45, 130.6, 130.3, 129.1, 128.22, 127.7, 127.0 for aromatic carbons, 116.5 (C-5), 61.8 (CH_2), 14.2 (CH_3). (Found: C, 67.58; H, 4.53; N, 8.04; S, 9.24. $C_{19}H_{16}N_2O_2S$ requires C. 67.84; H, 4.79; N, 8.33; S, 9.53).

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