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Facile Entries for Regioselective Synthesis of [1,2,4]Triazolo-[4,3-a]pyrimidin-5(1H)-ones from 2-Thiouracil

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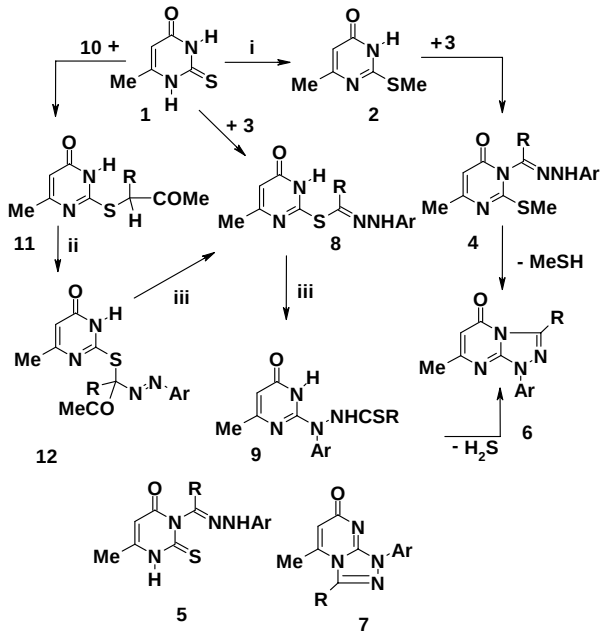
Three new alternative synthetic strategies based on reactions of hydrazonoyl halides **3** with 2-methylthiouracil **2** and treatment of either 2-pyrimidinyl thiohydrazonates **8** or the diazonium coupling products of active (pyrimidin-2-ylthio)methylene compounds **12** with sodium ethoxide in ethanol are described for the title compounds. The mechanisms and regiochemistry of the studied reactions are discussed.

Keywords: Heterocycles, Hydrazones, Rearrangement, Synthetic methods, 1,2,4-Triazolo-pyrimidine

INTRODUCTION

In continuation of our systematic studies on the use of hydrazonoyl halides devoted to the various aspects of their chemistry [1] we have decided to explore their potential as precursors for one-pot synthesis of [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-ones ring system incorporating different functionalities. At present, the general synthetic strategy for such compounds depends on cyclization of the appropriate 2-hydrazinopyrimidines with one carbon inserting agents [2,3]. The starting 2-hydrazinopyrimidines are usually prepared by nucleophilic displacement of the SH or MeS group at C-2 of the respective 2-thiouracil derivatives [3]. The interest in the synthesis of derivatives of such ring system is due to that many of them were reported to possess a wide range of pharmacological activities [2]. For example, many of such compounds are useful as calcium-channel blocking vasodilators and have antihypertensive [4], cardiovascular [5,6] and anxiolytic [7] activities as well as components in photographic materials [8]. In the present contribution, we describe three facile and short alternative routes for the synthesis of the title compounds starting from either 2-thiouracil **1** or its 2-methylthio derivative **2** and hydrazonoyl chlorides **3** (Scheme 1).



Scheme 1

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EXPERIMENTAL

The melting points were determined on an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a PU 9712 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Joel JNM-EX 270 FT NMR spectrometer and a Bruker spectrometer model 250. ^{13}C NMR spectra were measured on a Joel 68.5 MHz instrument. Mass spectra were obtained with a 75 eV Kratos spectrometer. Elemental analyses were carried out at the Microanalytical Center at Cairo University, Giza, Egypt.

The starting compounds 6-methyl-2-thiouracil **1** [9] 6-methyl-2-methylthiouracil **2**, [10] and the hydrazonoyl chlorides **3** [11] were prepared as previously reported.

Synthesis of 1,2,4-Triazolo [4,3-a]pyrimidin-5(1H)-ones 6

Method A. To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mg atom) and absolute ethanol (20 ml), was added 6-methyl-2-methylthiopyrimidin-4(3H)-ones **2** (1.56 g, 10 mmoles). To the resulting solution was added the appropriate hydrazonoyl chloride **3** (10 mmoles) portionwise while stirring the mixture. After the addition was complete, the reaction mixture was refluxed for 2 h, then cooled. The solid that precipitated was filtered off, washed with water, air dried and finally crystallized from the appropriate solvent to give the respective triazolopyrimidine **6** in 80-85% yield. The compounds prepared, together with their physical constants are given below.

Method B. To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mg atom) and absolute ethanol (20 ml), was added the appropriate thiohydrazonate ester **8** and the mixture was refluxed till all hydrogen sulfide ceased to evolve (2 h) while being stirred. The mixture was then cooled and poured onto water. The solid that precipitated was filtered off, washed with water and air dried. Crystallization from the appropriate solvent gave the respective product **6** in 68 - 80% yield. The latter products proved identical in all respects with those obtained above.

Method C. To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mg atom) and absolute ethanol (20 ml), was added the appropriate arylazo derivative **12** and the mixture was refluxed till all hydrogen sulfide ceased to evolve (2 h) while being stirred. The mixture was then cooled and poured onto water. The solid that precipitated was filtered off, washed with water and air dried. Crystallization from the appropriate solvent gave the respective product **6** in 60- 67% yield. The latter products proved identical in all respects with those obtained above.

N-Phenyl 7-methyl-1-phenyl[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one-3-carboxamide (**6Aa**)**:** Yield 70%, Mp. 162 °C (EtOH); ν (cm^{-1}) 3120, 1687, 1660; ^{1}H NMR ($CDCl_3$) δ_H 2.35 (s, 3H), 5.95 (s, 1H), 7.1-8.1(m, 10H), 8.65(s, 1H); δ_C ($CDCl_3$) 168, 162, 158.2, 150.3, 146.6, 138, 131.2, 130.4, 130, 129.7, 128, 126.1, 122, 102.4, 25.5; MS m/z (%) 346 (M^++1, 34), 345 (M^+, 95), 316 (27), 301 (39), 252 (13), 225 (30), 185 (21), 145 (26), 109 (9), 91 (48), 77 (100); Anal. Calcd. for $C_{19}H_{15}N_5O_2$ (345.3): C, 66.08; H, 4.38; N, 20.28; Found C, 66.0; H, 4.3; N, 20.2%.

N-Phenyl 7-methyl-1-(4-methylphenyl) [1,2,4] triazolo [4,3-a]pyrimidin-5(1H)-one-3-carboxamide (**6Ab**)**:** Yield 69%, Mp. 110 °C (EtOH), ν (cm^{-1}) 3167, 1700, 1640; ^{1}H NMR ($CDCl_3$) δ_H 2.25 (s, 3H), 2.4 (s, 3H), 6.1 (s, 1H), 7.0-8.1 (m, 9H), 8.5 (s, 1H); Anal. Calcd. for $C_{20}H_{17}N_5O_2$ (359.4): C, 66.84; H, 4.77; N, 19.49; Found C, 66.8; H, 4.8; N, 19.4%.

N-Phenyl 7-methyl-1-(4-chlorophenyl) [1,2,4] triazolo [4,3-a]pyrimidin-5(1H)-one-3-carboxamide (6Ac): Yield 69%, Mp. 191 °C (EtOH), ν (cm^{-1}) 3107, 1699, 1629; ^{1}H NMR ($CDCl_3$) δ_H 2.45 (s, 3H), 6.1 (s, 1H), 7.0-8.1 (m, 9H), 8.2 (s, 1H); Anal. Calcd. for $C_{19}H_{14}ClN_5O_2$ (379.8): C, 60.09; H, 3.72; N, 18.44; Found C, 60.2; H, 3.7; N, 18.5%.

Ethyl 7-methyl-1-phenyl[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one-3-carboxylate (6Ba): Yield 68%, Mp. 121 °C (pet.ether), ν (cm^{-1}) 1751, 1693; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t,3H), 2.25 (s, 3H), 4.6 (q, 2H), 6.0 (s, 1H), 7.3-8.4 (m, 5H); δ_C ($CDCl_3$) 167.1, 158.2, 154.3, 150.5, 146.7, 131.2, 126.4, 122.1, 102.2, 63.5, 25.1, 13.4; MS m/z (%) 299 (M^+ +1, 36), 298 (M^+, 100), 270 (14), 253 (5), 225 (18), 198 (10), 170 (10), 142 (5), 91 (6), 77 (5); Anal. Calcd. for $C_{15}H_{14}N_4O_3$ (298.3): C, 60.40; H, 4.73; N, 18.78; Found C, 60.3; H, 4.6; N, 18.8%.

Ethyl 7-methyl-1-(4-methylphenyl)[1,2,4]triazolo[4, 3-a]pyrimidin-5(1H)-one-3-carboxylate (**6Bb**)**:** Yield 70%, Mp. 157 °C (pet. ether), ν (cm^{-1}) 1750, 1700; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t, 3H), 2.25 (s, 3H), 2.4 (s, 3H), 4.55 (q, 2H), 5.9 (s, 1H), 7.3-8.0 (m, 4H); δ_C ($CDCl_3$) 167.5, 156.7, 155.2, 146.9, 137.8, 135.4, 133.8, 129.7, 120.8, 100.9, 63.7, 24.7, 21.0, 13.8; Anal. Calcd. for $C_{16}H_{16}N_4O_3$ (312.3): C, 61.53; H, 5.16; N, 17.94; Found C, 61.5; H,

5.1; N, 18.0%.

Ethyl 7-methyl-1-(4-chlorophenyl) [1,2,4] triazolo [4,3-a] pyrimidin-5(1H)-one-3-carboxylate (**6Bc**)**:** Yield 72%, Mp. 123 °C (pet. ether), ν (cm^{-1}) 1746, 1704; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t, 3H), 2.45 (s, 3H), 4.6 (q, 2H), 6.0 (s,1H), 7.5-8.3 (m, 4H); δ_C ($CDCl_3$) 167.0,156.0, 154.6, 146.4,135.3, 134.4, 132.7, 128.9, 121.2, 101.0, 63.5, 24.2, 13.4; Anal. Calcd. for $C_{15}H_{13}ClN_4O_3$ (332.7): C, 54.15; H, 3.94; N, 16.84; Found C, 54.2; H, 4.0; N, 16.8%.

3-Acetyl-7-methyl-1-phenyl[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one (**6Ca**)**:**Yield 68%, Mp. 181 °C (EtOH), ν (cm^{-1}) 1677; ^{1}H NMR ($CDCl_3$) δ_H 2.35 (s, 3H),2.4 (s, 3H), 6.0 (s, 1H), 7.0-7.6(m, 5H); δ_C ($CDCl_3$) 192.1, 167.7, 158.2, 150.2, 146, 138.1, 131.2, 126, 122.2, 102.4, 28.3, 24.5; MS m/z (%) 269 (M^++1, 21), 268 (M^+, 22), 267 (32), 242 (7), 185 (16), 142 (100), 114 (14); Anal. Calcd. for $C_{14}H_{12}N_4O_2$ (268.3): C, 62.68; H, 4.51; N, 20.88; Found C, 62.4; H, 4.6; N, 20.8%.

3-Acetyl-7-methyl-1-(4-methylphenyl) [1,2,4] triazolo[4,3-a]pyrimidin-5(1H)-one (**6Cb**) **:** Yield 69%, Mp. 158 °C (EtOH), ν (cm^{-1}) 1649; ^{1}H NMR ($CDCl_3$) δ_H 2.25 (s, 3H), 2.3 (s, 3H), 2.5 (s, 3H), 6.0 (s, 1H), 7.1-7.3(m, 4H); Anal. Calcd. for $C_{15}H_{14}N_4O_2$ (282.3): C, 63.82; H, 5.00; N, 19.85; Found C, 63.6; H, 4.7; N, 19.8%.

3-Acetyl-7-methyl-1-(4-chlorophenyl) [1,2,4] triazolo [4,3-a]pyrimidin-5(1H)-one (**6Cc**)**:** Yield 70%, Mp. 181 °C (EtOH), ν (cm^{-1}) 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.3 (s, 3H), 2.5 (s, 3H), 6.0 (s, 1H), 7.1-7.3 (m, 4H); Anal. Calcd. for $C_{14}H_{11}ClN_4O_2$ (302.7): C, 55.55; H, 3.66; N, 18.51; Found C, 55.4; H, 3.9; N, 18.3%.

1,3-Di(phenyl)-7-methyl[1,2,4]triazolo [4,3-a] pyrimidin-5(1H)-one (**6Da**) **:** Yield 75%, Mp. 180 °C (EtOH); ν 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 2.35 (s, 3H), 5.9 (s, 1H), 7.4-8.2 (m, 10H); δ_C ($CDCl_3$) 167.8, 158.1, 150.2, 146.0, 138.5, 132.4, 132.2, 131.1, 129.3, 129.0, 126.1, 122.6, 102.0, 25.6; MS m/z (%) 303 (M^++1, 20), 302 (M^+, 100), 273 (10), 236 (7), 187 (14), 170 (10), 129 (10), 109 (23), 91 (100), 77(16); Anal. Calcd. for $C_{18}H_{14}N_4O$ (302.3): C, 71.51; H, 4.67; N, 18.53; Found C, 71.4; H, 4.6; N, 18.4%.

Synthesis of (6-Methylpyrimidin-2-yl) N-aryl thiohydrazonates 8

General procedure. To a mixture of the appropriate hydrazonoyl chloride **3** and 6-methyl-2-thiouracil **1** (10 mmoles each) in absolute ethanol (30 ml) was added triethylamine (1.4 ml, 10 mmoles). The mixture was then stirred for 12 h at room temperature. During this period, the reactants dissolved and the crude product precipitated. The latter was collected by filtration, dried and finally crystallized from the appropriate solvent to give the corresponding thiohydrazonate ester **8**. The compounds prepared are listed together with their physical constants below.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-phenyl 2-oxo-2-(phenylamino)-ethanethiohydrazonate (**8Aa**)**:** Yield 78%, Mp. 197 °C (MeOH), ν (cm^{-1}) 3350, 3180, 1640; ^{1}H NMR ($CDCl_3$) δ_H 2.5 (s, 3H), 6.1 (s, 1H), 7.1-7.8 (m, 10H), 8.3 (s, 2H), 13.5 (s, 1H) ; MS m/z (%) 380 (M^++1, 22), 379 (M^+, 68), 336 (63), 277 (100), 259 (32), 187 (68), 142 (54), 109 (27), 91 (50), 77 (90); Anal. Calcd. for $C_{19}H_{17}N_5O_2S$ (379.4): C, 60.14; H, 4.52; N, 18.46; Found C, 60.2; H, 4.5; N, 18.4%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-methyl phenyl) 2-oxo-2- (phenylamino) ethanethiohydrazonate (**8Ab**)**:** Yield 75%, Mp. 207 °C (EtOH), ν (cm^{-1}) 3380, 3180, 1660; ^{1}H NMR ($CDCl_3$) δ_H 2.3 (s, 3H), 2.5 (s, 3H), 6.0 (s, 1H), 7.1-7.9 (m, 9H), 8.5 (s,1H), 8.55 (s, 1H),13.5 (s, 1H); Anal. Calcd. for $C_{20}H_{19}N_5O_2S$ (393.4): C, 61.05; H, 4.87; N, 17.80; Found C, 61.0; H, 4.9; N, 17.8%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-chloro phenyl) 2-oxo-2-(phenylamino)ethanethiohydrazonate (**8Ac**)**:** Yield 72%, Mp. 202 °C (EtOH), ν (cm^{-1}) 3400, 3180, 1660; ^{1}H NMR ($CDCl_3$) δ_H 2.55 (s, 3H), 6.2 (s, 1H), 7.1-8.0 (m, 9H), 8.5 (s,1H), 8.6 (s, 1H),11.7 (s, 1H); Anal. Calcd. for $C_{19}H_{16}ClN_5O_2S$ (413.9): C, 55.14; H, 3.90; N, 16.92; Found C, 55.4; H, 4.0; N, 16.9%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-phenyl 2-oxo-2-ethoxyethane thiohydrazonate (**8Ba**)**:** Yield 72%, Mp. 120 °C (pet.ether), ν (cm^{-1}) 3160, 1750, 1690; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t, 3H), 2.4 (s, 3H), 4.6 (q, 2H), 6.0 (s, 1H), 7.3-7.6 (5H), 8.15 (s, 1H), 11.3 (s, 1H); δ_C ($CDCl_3$) 167.2, 156.2, 154.8, 146.6, 135.8, 135.2, 128.8, 127.3, 120.4, 100.8, 63.4, 24.3, 13.4; MS m/z (%) 333 (M^++1, 65), 332 (M^+, 86), 298 (100), 270 (53), 259 (56), 225 (69), 198 (52), 170 (43), 142 (34), 109 (43), 91 (78), 77 (75%); Anal. Calcd. for $C_{15}H_{16}N_4O_3S$ (332.3): C, 54.20; H, 4.85; N, 16.86; Found C, 54.2; H, 4.8; N, 16.8%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-methyl phenyl) 2-oxo-2-ethoxyethanethiohydrazonate (**8Bb**)**:** Yield 70%, Mp. 127 °C (pet. ether), ν (cm^{-1}) 3150, 1747, 1708; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t, 3H), 2.25 (s, 3H), 2.4 (s, 3H), 4.6 (q, 2H), 5.95 (s, 1H), 7.1-7.4 (m, 4H), 8.05 (s, 1H), 11.3 (s, 1H); Anal. Calcd. for $C_{16}H_{18}N_4O_3S$ (346.4): C,

55.48; H, 5.24; N, 16.17; Found C, 55.6; H, 5.5; N, 16.1%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-chloro phenyl) 2-oxo-2-ethoxyethanethiohydrazonate (**8Bc**)**:** Yield 73%, Mp. 125 °C (pet. ether), ν (cm^{-1}) 3150, 1720, 1690; ^{1}H NMR ($CDCl_3$) δ_H 1.5 (t, 3H), 2.4 (s, 3H), 4.6 (q, 2H), 6.9 (s, 1H), 7.1-7.4 (m, 4H), 8.2 (s, 1H), 11.3 (s, 1H); δ_C ($CDCl_3$) 167.0, 156.0, 154.6, 146.4, 135.3, 134.4, 132.7, 128.9, 121.2, 101.0, 63.5, 24.2, 13.4; Anal. Calcd. for $C_{15}H_{15}ClN_4O_3S$ (366.8): C, 49.11; H, 4.12; N, 15.27; Found C, 49.0; H, 4.3; N, 15.2%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-phenyl 2-oxopropane-thiohydrazonate (**8Ca**)**:** Yield 70%, Mp. 203 °C (MeOH), ν (cm^{-1}) 3160, 3120, 1650; ^{1}H NMR ($CDCl_3$) δ_H 2.35 (s, 3H), 2.5 (s, 3H), 6.0 (s, 1H), 7.0-7.7 (m, 5H), 8.2 (s,1H), 11.5 (s, 1H); MS m/z (%) 303 (M^+ +1, 5), 302 (10), 260 (23), 234 (23), 201(17), 187 (9), 160 (18), 142 (14), 109 (10), 91 (72), 77 (100); Anal. Calcd. for $C_{14}H_{14}N_4O_2S$ (302.3): C, 55.62; H, 4.67; N, 18.53; Found C, 55.7; H, 4.5; N, 18.5%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-methyl phenyl) 2-oxo-propanethiohydrazonate (**8Cb**)**:** Yield 71%, Mp. 196 °C (EtOH), ν (cm^{-1}) 3180, 3160, 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.3 (s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 6.15 (s, 1H), 7.0-7.7 (m, 4H), 8.3 (s, 1H), 11.45 (s, 1H); Anal. Calcd. for $C_{15}H_{16}N_4O_2S$ (316.3): C, 56.95; H, 5.10; N, 17.71; Found C, 56.6; H, 5.0; N, 18.0%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-(4-chloro phenyl) 2-oxo-propanethiohydrazonate (**8Cc**)**:** Yield 75%, Mp. 198 °C (EtOH), ν (cm-^{1}) 3112, 3040, 1650; ^{1}H NMR ($CDCl_3$) δ_H 2.4 (s, 3H), 2.5 (s, 3H), 5.7 (s,1H), 7.0-7.7 (m, 4H), 8.6 (s, 1H), 11.5 (s, 1H); Anal. Calcd. for $C_{14}H_{13}ClN_4O_2S$ (336.8): C, 49.93; H, 3.89; N, 16.63; Found C, 49.9; H, 3.9; N, 16.6%.

(6-Methyl-4-oxo-(3H)pyrimidin-2-yl) N-phenyl benzenecarbothio-hydrazonate (**8Da**)**:** Yield 61%, Mp. 164 °C (EtOH), ν (cm^{-1}) 3188, 1650; ^{1}H NMR ($CDCl_3$) δ_H 2.5 (s, 3H), 6.0 (s, 1H), 7.0-8.0 (m, 10H), 8.4 (s, 1H), 11.4 (s, 1H); Anal. Calcd. for $C_{18}H_{16}N_4OS$ (336.4): C, 64.27; H, 4.79; N, 16.65; Found C, 64.6; H, 4.8; N, 16.7%.

Synthesis of 3-Oxo-2-[(6-methyl-4-oxo pyrimidin-2-yl)thio]butanoic acid derivatives 11A,B and 3-[(6-methyl-4-oxopyrimidin-2-yl) thio]-2,4-pentanedione 11C

General Procedure. To a mixture of equimolar quantities of the appropriate chloromethylene compound **10** and 6-methyl-2-thiouracil **1** (10 mmoles each) in absolute ethanol (30 ml) was added triethylamine (1.4 ml, 10 mmoles). The mixture was stirred for 24 h at room temperature. During this period the reactants dissolved. The solvent was then distilled under reduced pressure in a rotatory evaporator. The oily residue left was triturated with methanol and left in a refrigerator for 2 h. The solid that produced was collected by filtration and crystallized from the proper solvent to give the respective **11**. The physical constants of the products **11A-C** are given below.

N-Phenyl 3-oxo-2-[(6-methyl-4-oxopyrimidin-2-yl) thio]butanamide (**11A**)**:** Yield 71%, Mp. 160 °C (EtOH), ν (cm^{-1}) 3425, 3249, 1678, 1654; ^{1}H NMR ($CDCl_3$) δ_H 1.85 (s, 3H), 2.3 (s, 3H), 4.45 (s, 1H), 6.05 (s, 1H), 7.9-8.2 (m, 5H), 8.4 (s, 2H) ; MS m/z (%) 317 (M^+,3), 273 (17), 232 (100), 196 (28), 189 (51), 155 (19), 127 (26), 109 (49), 93 (68), 77 (27); Anal. Calcd. for $C_{15}H_{15}N_3O_3S$ (317.3): C, 56.77; H, 4.73; N, 13.24; Found C, 56.7; H, 4.9; N, 13.2%.

Ethyl 3-oxo-2-[(6-methyl-4-oxopyrimidin-2-yl) thio] butanoate (**11B**)**:** Yield 68%, Mp. 190 °C (EtOH), ν (cm^{-1}) 3400, 3200, 1700, 1650; ^{1}H NMR ($CDCl_3$) δ_H 1.3 (t, 3H), 2.1 (s, 3H), 2.4 (s, 3H), 4.3 (q, 2H), 5.5(s, 1H), 8.5 (s, 1H), 12.5 (s, 1H); MS m/z (%) 270 (M^+, 87), 228 (98), 182 (98), 153 (100), 109 (37), 98 (19); Anal. Calcd. for $C_{11}H_{14}N_2O_4S$ (270.3): C, 48.88; H, 5.22; N, 10.36; Found C, 48.8; H, 5.2; N, 10.3%.

3-[(6-methyl-4-oxopyrimidin-2-yl)thio]-2,4-pentane dione (**11C**)**:** Yield 70%, Mp. 175 °C (EtOH) (Lit. mp. 175 °C [21]), ν (cm^{-1}) 3500, 3320, 1675, 1660; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.45 (s, 3H), 2.5 (s, 3H), 6.0 (s, 1H), 8.3 (s, 1H), 12.5 (s, 1H); MS m/z (%) 240 (M^+, 74), 207 (24), 198 (50), 183 (56), 165 (26), 155 (100), 127 (95), 109 (57), 83 (18), 69 (57).

Synthesis of 2-Arylazo-3-Oxo-2-[(6-methyl- 4-oxopyrimidin -2-yl)thio]- butanoic acid derivatives 12Aa-c and 2-arylazo-3-[(6-methyl-4-oxopyrimidin-2-yl)thio]-2,4-pentanedione 12Ca-c

General Procedure. To a solution of the appropriate **11** (10 mmoles) in ethanol (40 ml) was added sodium acetate trihydrate (3 g) and the mixture was cooled in an ice-bath to 0-5 ^{o}C while being stirred. To the resulting cold solution was added portionwise a cold solution of arenediazonium chloride, prepared as usual by diazotizing the respective aniline (10 mmoles) in hydrochloric acid (6 ml, 6 M) with sodium nitrite (0.7 g, 10 mmoles) in water (10 ml). After all diazonium salt solution was added, the reaction mixture was stirred for 30 min while cooling in ice-bath and left overnight in a refrigerator. The solid that precipitated was

filtered, washed with water, air dried and finally crystallized from the appropriate solvent to give the respective arylazo derivative **12**. The products **12Aa-c** and **12Ca-c** prepared together with their physical constants are listed below.

N-Phenyl 2-phenylazo-3-oxo-2-[(6-methyl-4-oxo pyrimidin-2-yl)thio]-butanamide (**12Aa**)**:** Yield 66%, Mp. 110 °C (MeOH), ν (cm^{-1}) 3399, 1715, 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.2 (s, 3H), 5.9 (s, 1H), 7.0-8.0 (m, 10H), 8.7 (s, 1H), 13.0 (s, 1H); MS m/z (%) 422 (M^++1, 2), 421 (M^+,10), 387 (70), 345 (100), 316 (39), 301 (82), 252 (14), 225 (36), 200 (15), 158 (10), 116 (7), 91 (10), 77 (14); Anal. Calcd. for $C_{21}H_{19}N_5O_3S$ (421.5): C, 59.84; H, 4.54; N, 16.62; Found C, 59.8; H, 4.5; N, 16.6%.

N-Phenyl 2-(4-methylphenylazo)-3-oxo-2-[(6-methyl-4-oxopyrimidin-2-yl)thio]-butanamide (**12Ab**)**:** Yield 65%, Mp. 136 °C (EtOH), ν (cm^{-1}) 3430, 1715, 1700; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.4 (s, 3H), 2.5 (s, 3H), 5.9 (s, 1H), 7.1-8.0 (m, 9H), 8.5 (s, 1H), 12.9 (s, 1H); Anal. Calcd. for $C_{22}H_{21}N_5O_3S$ (435.5): C, 60.68; H, 4.86; N, 16.08; Found C, 60.6; H, 4.8; N, 16.1%.

N-Phenyl 2-(4-chlorophenylazo)-3-oxo-2-[(6-methyl-4-oxopyrimidin-2-yl)thio]-butanamide (**12Ac**)**:** Yield 67%, Mp. 120 °C (EtOH), ν (cm^{-1}) 3120, 1700, 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.45 (s, 3H), 5.9 (s, 1H), 7.1-8.0 (m, 9H), 8.25 (s, 1H), 12.9 (s, 1H); Anal. Calcd. for $C_{21}H_{18}ClN_5O_3S$ (455.9): C, 55.32; H, 3.98; N, 15.36; Found C, 55.3; H, 4.0; N, 15.4%.

3-Phenylazo-3-[(6-methyl-4-oxopyrimidin-2-yl)thio]-2,4-pentanedione (**12Ca**)**:** Yield 69%, Mp. 110 °C (hexane), ν (cm^{-1}) 3400, 1720, 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.05 (s, 3H), 2.6 (s,3H), 2.65 (s, 3H), 5.9 (s, 1H), 7.1-8.0 (m, 5H), 12.4 (s, 1H); MS m/z (%) 345 (M^++1, 4), 344 (M^+, 11), 301 (100), 268 (98), 259 (27), 213 (17), 200 (40), 170 (9), 145 (15), 118 (11), 91 (12), 77 (18); Anal. Calcd. for $C_{16}H_{16}N_4O_3S$ (344.4): C, 55.80; H, 4.68; N, 16.27; Found C, 55.9; H, 4.7; N, 16.2%.

3-(4-Methylphenylazo)-3-[(6-methyl-4-oxopyrimidin-2-yl)thio]-2,4-pentanedione (**12Cb**)**:** Yield 68%, Mp. 121 °C (hexane), ν (cm^{-1}) 3425, 1705, 1680; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.4 (s, 3H), 2.55 (s, 3H), 2.60 (s, 3H), 5.9 (s, 1H), 7.0-8.0 (m, 4H), 13.0 (s, 1H); Anal. Calcd. for $C_{17}H_{18}N_4O_3S$ (358.4): C, 56.97; H, 5.06; N, 15.63; Found C, 56.9; H, 5.0; N, 15.6 %.

3-(4-Chlorophenylazo)-3-[(6- methyl-4-oxopyrimidin-2- yl)thio]-2,4-pentanedione (**12Cc**)**:** Yield 70%, Mp. 120 °C (EtOH), ν (cm^{-1}) 3110, 1720, 1650; ^{1}H NMR ($CDCl_3$) δ_H 2.0 (s, 3H), 2.55 (s, 3H), 2.60 (s, 3H), 5.9 (s, 1H), 7.1-8.0 (m, 4H), 12.8 (s, 1H); Anal. Calcd. for $C_{16}H_{15}ClN_4O_3S$ (378.8): C, 50.73; H, 3.99; N, 14.79; Found C, 50.7; H, 4.0; N, 14.8%.

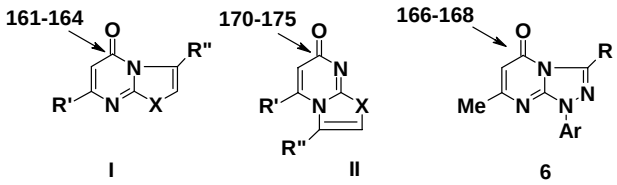

Chart 1

RESULTS AND DISCUSSION

The required 6-methyl-2-thiouracil **1** [9], 6-methyl-2-methylthiopyrimidin-4(3H)-one **2** [10] and hydrazonoyl chlorides **3A-D** [11] were prepared as previously described. Reaction of **2** with **3** in ethanol in the presence of sodium ethoxide in refluxing ethanol was found to give a single product in each case. Both spectroscopic data and elemental analyses were consistent with either [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one structure **6** or [1,2,4]triazolo[4,3-a]pyrimidin-7(1H)-one structure **7** (Scheme 1). An immediate distinction between these two structures was reached by comparison of the ^{13}C NMR and IR spectra with those of similar annelated pyrimidinones. Literature reports [12,13] have shown that the chemical shift for the carbonyl carbon in 4-pyrimidinone derivatives is markedly affected by the nature of the adjacent nitrogen (N3) (pyrrole type in our structure **6** and pyridine type as in structure **7**). For example, the ^{13}C nmr spectra of **6Aa**, **6Bb**, **6Ca** and **6Da**, taken as typical examples of the series prepared, revealed the signals of the carbonyl carbon of the pyrimidinone ring residue at δ 168, 167.5, 167.7 and 167.8, respectively. Such chemical shift values are similar to those of annelated pyrimidinones of type **I** rather than those of type **II** (Chart 1). On the basis of this similarity, the isolated products were assigned structure **6** and structure **7** was therefore discarded. Furthermore, the assignment of structure **6** to the products isolated from the studied reactions is also substantiated by the similarity of their carbonyl stretching frequencies (υ = 1690-1710 cm^{-1}) with those reported for pyrimidinones **I**. For example, pyrimidinones **I** exhibit their CO bands in the region 1680-1690 cm^{-1} whereas pyrimidinones **II** exhibit their CO bands in the region1640-1660 cm^{-1} [13].

To account for the formation of **6** from **2** with **3**, the two step reaction sequence outlined in Scheme 1 is suggested. The first step involves acylation of **2** with **3** to give N3-hydrazonoyl derivative **4** rather than N1-substituted analog **5**. This site selectivity is similar to that found for alkylation and acylation reactions of 2-methylthiopyrimidin-4(3H)-ones which were reported to occur at N3 rather than N1 [3, 14,15]. This is because the tautomeric of 2-alkylthiouracils were reported to exist in the 3H-form rather than the 1H-form [16]. The second step in the suggested mechanism (Scheme 1) involves cyclization of the amidrazone intermediate **4** with concurrent elimination of methanethiol to give **6** as end product. This latter step is comparable with the sodium hydride catalyzed cyclization of 3-[(benzylaminocarbonyl)methyl]-2-methylthiopyrimidin -4 (3H)-ones to give 1H-imidazo[1,2-a]pyrimidine-2,5-diones [15].

Finally, as the hydrazonoyl chlorides are known to be skin irritant [17] and in the light of the foregoing mechanisms, we thought of an alternative synthesis of the title compounds. The synthetic strategy, we thought of , is based on synthesis of the thiohydrazonate esters **8** *via* application of Japp-Klingemann reaction [18] to the active methine compounds of type **11**. The latter compounds **11** were prepared in this work by reaction of 6-methyl-2-thiouracil **1** with the active chloromethylene compounds **10** in ethanol in the presence of triethylamine at room temperature. The formation of **11** from **1** and **10** (Scheme 1) is analogous to S-alkylation reactions reported to be exhibited by 2-thiouracil [15]. The structures of the products **11A-C** thus prepared were evidenced by their microanalyses and spectra (MS, IR and ^{1}H NMR) (see Experimental). For example, their ^{1}H NMR spectra showed two characteristic singlet signals near δ 2.40 and 4.90 assignable to the CH_3CO and -SCH- protons, respectively. The latter signal for the methine hydrogen is lost on shaking the solution with deuterium oxide showing its ready exchangeability through enolization.

Next, coupling of **11** with diazotized anilines was investigated in ethanol in the presence of sodium acetate at low temperature (0-5 ^{o}C). On the basis of previous literature on coupling of active methine compounds with diazonium salts [18], we anticipated that reactions of **11** with diazotized anilines would give the thiohydrazonate esters **8** directly (Scheme 1). However, in our hands such reactions yielded products that were identified, on the basis of their spectra and microanalyses, as the aliphatic azo derivatives **12** (see Experimental) (Scheme 1). In an attempt to effect Japp-Klingemann cleavage of the acetyl group from **12** to get the thiohydrazonate esters **8**, the azo derivatives **12** were treated with sodium ethoxide in refluxing ethanol. Unexpectedly, such treatment was found to give products that proved to be identical in all respects with the products **6** obtained above. This finding indicates that both types of reactions namely **12** + EtONa → **6** , and **8** + EtONa → **6**, proceed *via* the same intermediates, namely the thiohydrazides **9**. Accordingly, it is not unreasonable to conclude that in the studied conversion **12** → **6**, the initially formed thiohydrazonate esters **8** undergo *in situ* tandem Smiles rearrangement [19] to give the products **9** and cyclization of the latter to yield **6** as soon as they are formed under the employed reaction conditions (Scheme 1).

REFERENCES

[1] A.S. Shawali, Chem. Rev. 93 (1993) 2731; A.S. Shawali, M.A. Abdallah, Adv. Heterocycl. Chem. 63 (1995) 277; A.S. Shawali, Heterocycles 20 (1983) 2239; A.S. Shawali, C. Parkanyi, J. Heterocycl. Chem. 17 (1980) 833.

[2] For review see E.S.H. El-Ashry, N. Rashed, Adv. Heterocycl. Chem. 72 (1999) 27.

[3] E.S.H. El-Ashry, Y. El-Kilany, N. Rashed, A. Mousaad, H. Assafir, Z. Naturforsch. 53b (1998) 1203.

[4] K. Awal. Ger Pat 3,839,711 (1989); Chem. Abstr. 112 (1990) 55902.

[5] G. Barthelemy, A. Hallot, J.N. Vallat, Fr Pat 2, 549, 834 (1985); Chem. Abstr. 103 (1985) 71335.

[6] N. Bru-Magniez, T. Guengor, J.M. Teulon, U S Pat 5,387,747 (1995); Chem. Abstr. 123 (1995) 228204.

[7] J.D. Albright, J.P. Dusza, R.A. Hardy, U S Pat 4,209,621 (1980); Chem. Abstr. 93 (1980) 168298.

[8] H. Nakamura, Y. Hosoi, J. Fukawa, Jpn Kokai Pat 0,313934 (1991); Chem. Abstr. 115 (1991) 60769.

[9] A.O. Fitton, R.K. Smalley, Practical Heterocyclic Chemistry, Academic Press, 1968.

[10] C.R. Ganellin, M.E. Parsons, D.A. Rawlings, T.F. Walker, Eur. J. Med. Chem. 23 (1988) 53.

[11] J.V. Greenhill, M.J. Ismail, G.R. Bedford, P.N. Edwards, P.J. Taylor. J. Chem. Soc. Perkin Trans II (1985) 1265; G.R.P. Bedford, J. Taylor, G.A. Webb, Magnetic Res. Chem. 33 (1995) 389.

[12] J. Reiter, L. Bongo, P. Dyortsak, Tetrahedron 43

(1987) 2497.

[13] S.M. Hussain, A.A. El-Barbary, S.A. Mansour, J. Heterocycl. Chem. 22 (1985) 169; E.S.H. El-Ashry, Y. El-Kilany, N. Rashed, A. Musaad, H. Assafir, Z. Naturforsch. 53B (1998) 1203.

[14] B. Abarca, M. Jimenez, G. Jones, C. Soriano. J. Chem. Res. (1986) (S) 395, (M) 3358.

[15] V.J. Ram, D.A.V. Berghe, A. Vlietinck, Liebigs Ann. Chem. (1987) 797.

[16] A. Rothe, Contact Dermatitis 18 (1988) 16; Chem. Abstr. 108 (1988) 162843c.

[17] R.R. Phillip, Org. Reactions 10 (1959) 143.

[18] K. Ishii, M. Hatanaka, I. Ueda., Chem. Pharm. Bull. 39 (1991) 3331; J.F. Bunnett, Quart. Rev. (London) 12 (1985) 12.

[19] A.J. Elliott, P.D. Callaghan, M.S. Gibson, S.T. Nemeth, Can. J. Chem. 53 (1975) 1484.

[20] A.M. Abdelfattah, A.M. Negm, A.M. Gaafar, Phosphorus, Sulfur & Silicon 72 (1992) 145.