Site selectivity in reaction of hydrazonoyl halides with 2-(aroylmethyl)-6-methylpyrimidin-4(3H)-ones

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Reaction of hydrazonoyl halides **1** with 2-(aroylmethyl)-6-methylpyrimidin-4(3H)-ones **3** proved to be site selective and gave 2-(3-acetyl-1,5-diarylpyrazol-4-yl)-6-methylpyrimidin-4(3H)-ones **5** *via* dehydrative cyclisation of the hydrazone intermediates **4**. The structures of both **4** and **5** were elucidated by spectral data and alternative synthesis. The mechanism of the reaction was discussed.

Keywords: site selectivity, hydrazonoyl halides, 2-(aroylmethyl)-6-methylpyrimidin-4(3H)-ones

Hydrazonoyl halides **1** are well known synthons and their reactions have been extensively investigated.[1-9] Although there have been diverse studies on reactions of such halides **1** with various enamines **2**,[7] their reactions with 2-aroylmethyl-6-methyl-pyrimidin-4(3H)-ones **3**, which were reported in 1988 and were shown to exist in the ketene aminal form **3B** (Fig. 1)[10] have not been explored hitherto. In view of this finding and in continuation of our research work on the chemistry of hydrazonoyl halides,[1-9] it was thought interesting to study reactions of hydrazonoyl halides with the latter 1,2-cyclic ketene aminals **3B** (Scheme 1). Our objective of this study is to explore the site selectivity in such reactions as they can theoretically lead to one or more of the products **4 -11** (Schemes 1 and 2).

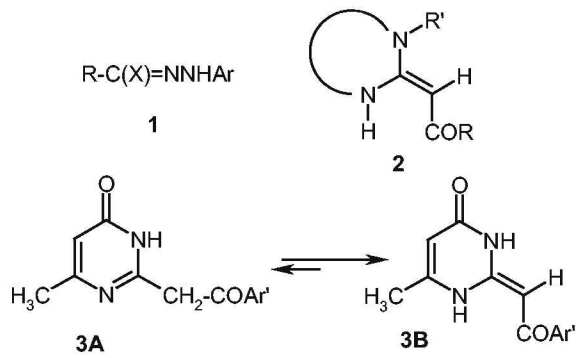
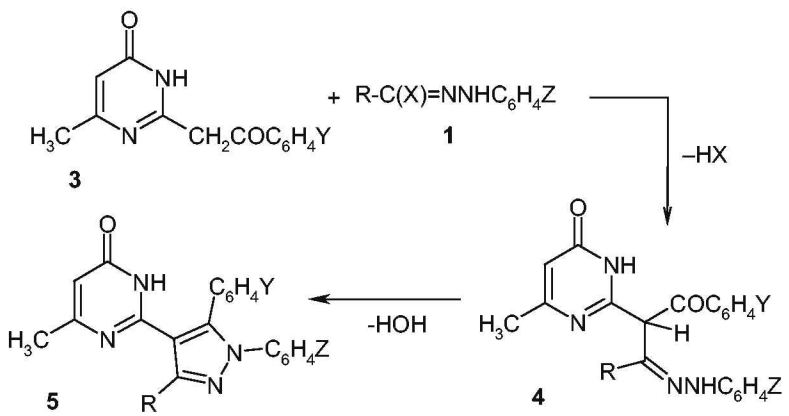


Fig. 1

Results and discussion

The starting compounds **3** were prepared from 6-methyl-2-thiouracil as previously described.[10] Reaction of **3** with each of the α-ketohydrazonoyl halides **1A–C** in ethanol in the presence of sodium ethoxide at room temperature gave, in each case, one isolable product as evidenced by TLC analysis of the crude products isolated. This finding indicates that the studied reactions are site selective. Mass spectra and elemental analysis data of the isolated products were consistent with each of the isomeric structures **5** (Scheme 1) and **8–11** (Scheme 2). However, IR, ^{1}H and ^{13}C NMR spectra were found consistent with structure **5**. For example, the mass



3	Y
a	H
b	4-CH_3
c	4-Cl

X, Cl or Br

R : **A**, CH_3CO; **B**, PhCO; **C**, 2-thienoyl; **D**, Ph; **E**, EtOCO; **F**, PhNHCO

Y / Z : **a**, H/H; b, H/4-CH_3; **c**, H/4-Cl; d,H/4-NO_2; **e**, 4-CH_3/H; **f**, 4-CH_3/4-CH_3; **g**, 4-CH_3/4-Cl; h, 4-CH_3/4-NO_2; **i**, 4-Cl/H; j, 4-Cl/4-CH_3; **k**, 4-Cl/4-Cl; l, 4-Cl/ 4-NO_2

Scheme 1

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spectra of compounds **5** were consistent with their structures. They revealed in each case the respective molecular ion peaks together ($M^+ + 1$) peak. Such peaks were not the base peaks, however. In addition, the spectra revealed characteristic peaks at *m/z* values corresponding to C_6H_5, XC_6H_4, $XC_6H_4N_2$, XC_6H_4CN and $C_5H_5N_2O$ ionic fragments. The latter fragment corresponds to 6-methyl-4(3H)-pyrimidinone ring residue. The IR spectra of the products prepared revealed in each case two carbonyl bands and one NH band in the regions 1682–1655, 1654–1624 and 3286–3080 cm^{-1}, respectively. In addition, the ^1H NMR spectra of the isolated products showed, in each case, one NH signal at δ 11.80–10.16. This chemical shift value while it is similar to that of pyrimidin-4(3H)-one derivative (δ 11.2–10.2),[11] it is different from that of hydrazone NH (16.2–16.0).[12] On the basis of these spectral findings, structures **8–11** (Scheme 2) were discarded and the isolated products from the studied reaction were thus assigned structure **5** (Scheme 1). This conclusion was further evidenced by the ^{13}C NMR spectrum of the product **5Ab** taken as a typical example of the series prepared. This spectrum revealed the carbonyl carbon signal at δ 162.10 indicating that the adjacent nitrogen is of pyrrole type *i.e.* sp^3-hybrised.[12-14]

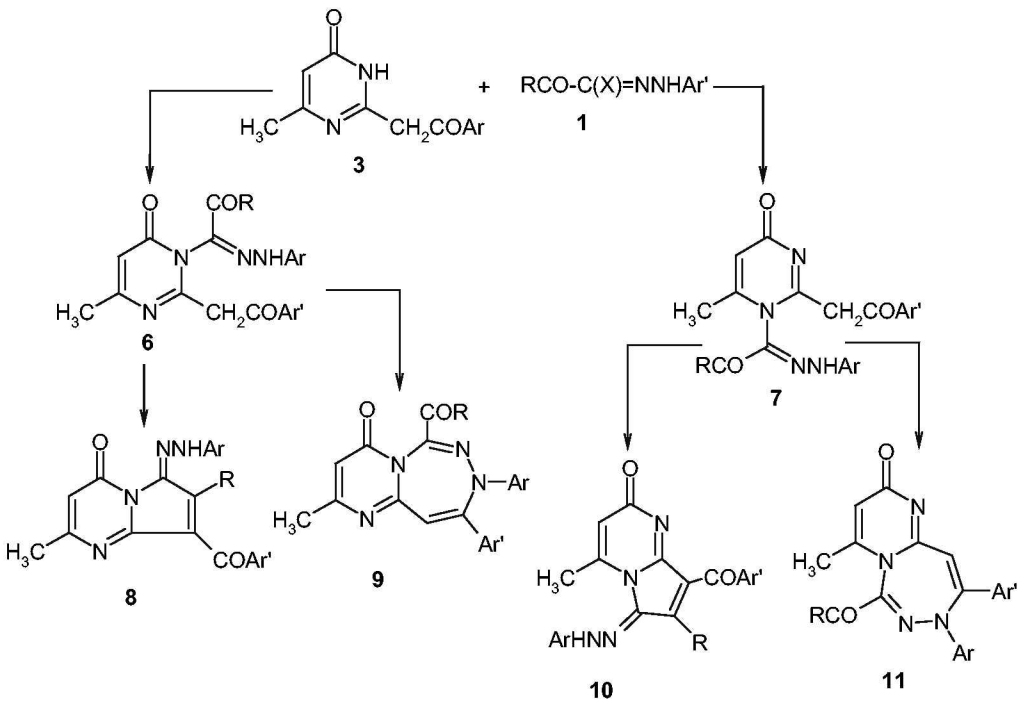
The formation of the products **5** can be rationalised as follows. As compounds **3** have been shown to exist in the ketene aminal tautomeric form **3B** (Scheme 1),[10,12,15] they will act, like other ketene aminals, as carbon rather than nitogen nucleophiles. Thus, reactions of **3** with **1** will start with the formation of the hydrazone derivatives **4** (Scheme 1), which in turn undergo *in situ* dehydrative cyclisation under the employed reaction conditions, to give **5** as end products.

The assigned structure **5** and the suggested pathway were evidenced by isolation of the intermediate hydrazone **4** and alternative synthesis of **5**. For this purpose, we investigated the reaction of N-phenyl benzenecarbohydrazonoyl chloride **1Da** with **3a** in ethanol in the presence of sodium ethoxide at room temperature. In our hands, such a reaction yielded one product that was identified as **4Da**. Its IR spectrum showed two carbonyl band at 1670 and 1632 cm^{-1} and two NH bands at 3421 and 3180 cm^{-1}. Its ^1H NMR spectrum revealed characteristic signals at δ 2.18 (s, 3H), 6.47 (s, 1H), 6.63 (s, 1H), 7.43–7.99 (m, 15H), 11.63 (s, 1H) and 14.44 (s, 1H) which are consistent with the assigned structure **4Da**.

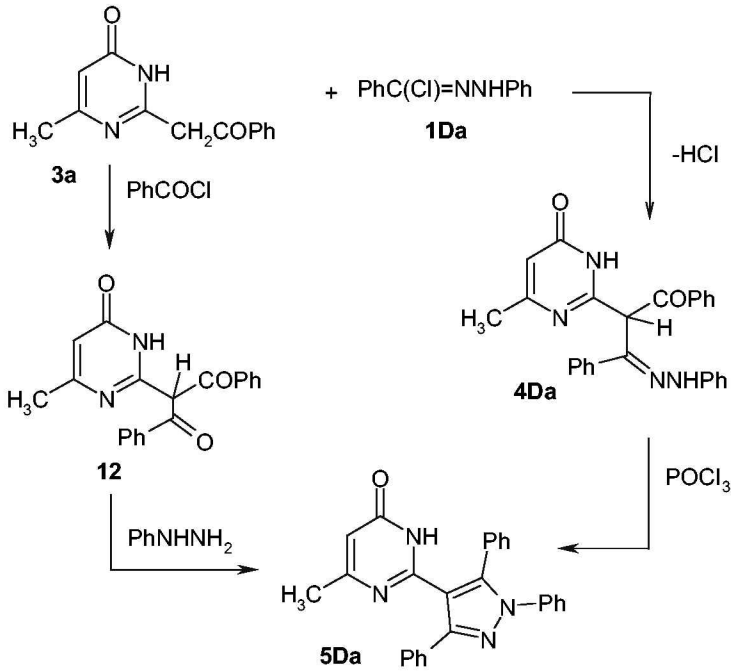
When the latter hydrazone **4Da** was heated with phosphorus oxychloride, it underwent cyclisation and afforded a product that was identified as 2-(1,3,5-triphenylpyrazol-4-yl)-6-methylpyrimidin-4(3H)-one **5Da**. The IR spectrum of the latter showed only one carbonyl band and one NH band at 1667 and 3186 cm^{-1}, respectively. Its ^1H NMR spectrum in DMSO-d_6 showed four characteristic signals at δ 2.06 (s, 3H), 6.25 (s, 1H), 7.62–7.98 (m, 15 H) and 12.83 (s, 1H) which are consistent with its assigned structure **5Da**. The assigned structure **5Da** was substantiated by its alternative synthesis. Thus, reaction of **3a** with benzoyl chloride in ethanolic sodium ethoxide yielded 2-(dibenzoylmethyl)-5-methylpyrimidin-4(3H)-one **12**. Treatment of the latter with phenylhydrazine in acetic acid at 60 °C gave a product that proved identical in all respects (m.p., mixed m.p., IR and mass spectra) with **5Da** prepared above by reaction of **4Da** with phosphorus oxychloride (Scheme 3).

Similar reactions of **3** with each of N-aryl C-ethoxycarbonyl-methanehydrazonoyl chlorides **1E** and N-aryl C-phenylaminocarbonyl-methanehydrazonoyl chlorides **1F** afforded in all cases only the respective hydrazones **4E** and **4F** as end products. Attempts to cyclise the latter hydrazones by heating them in acetic acid, xylene or in ethanol in the presence of sodium ethoxide failed, however. The structures of such products were confirmed by their spectra (MS, IR and ^1H NMR) and elemental analyses (see Experimental).

In conclusion, the studied reactions of **1** with **3** are site selective and depending on the structure of the hydrazonoyl halide used, they can yield either the hydrazone derivatives **4** or 2-(1,3,5-trisubstitutedpyrazol-4-yl)-6-methylpyrimidin-4(3H)-ones **5** as end products. The latter type of products having both pyrazole and pyrimidinone residues are expected to be of biological interest. This is because several pyrazole and pyrimidinone derivatives have been reported to display a wide range of potent biological activities.[16-30] The compounds **5** prepared herein will be screened for their biological activity and the results will published in due course.



Scheme 2



Scheme 3

Experimental

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts were related to that of the solvent DMSO-d_6. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionising voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Centre of Cairo University, Giza, Egypt. 2-Aroylmethyl-6-methylpyrimidine-4(3H)-ones **3a–c** were prepared as previously described.[10]

Reaction of of hydrazonoyl halides **(1A–C)** *with 2-aroylmethyl-6-methylpyrimidine-4(3H)-ones* **(3)**

To a solution of a given compound **3** (5 mmole) in ethanolic sodium ethoxide solution, prepared by dissolving sodium metal (0.12 g, 5 mmole) in absoute ethanol (20 ml), was added the appropraite hydrazonoyl halide **1A–C** (5 mmoles). The reaction mixture was left while being stirred overnight at room temperature. The precipitate was filtered, washed with water and finally crystallised from ethanol to give the respective products **5A–C**, respectively. When the above procedure was repeated using **1D–F** in place of **1A–C**, the products obtained were the intermediate hydrazone derivatives **4D–F**. The physical constants and the spectral data of the products **5A–C** and **4D–F** isolated are listed below.

2-[3-Acetyl-1,5-Diphenyl-pyrazol-4-yl]-6-methylpyrimidin-4(3H)-one **(5Aa)**: Orange powder (1.10 g, 62%), m.p. 220–222 °C; IR (KBr) 3097, 1659, 1624 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.15 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 5.73 (s, 1H, ArH), 7.48–7.77 (m, 10H, ArH), 11.68 (s, 1H, NH); MS *m/z* (%) 371 (M^+ + 1, 1), 370 (M^+, 2), 228 (23), 227 (10), 200 (16), 151 (24), 105 (100), 84 (31), 77 (83); Anal. Calcd for $C_{22}H_{18}N_4O_2$ (370.41): C,71.34; H,4.90; N, 15.13. Found: C, 71.22; H, 4.65; N, 15.00%.

2-[3-Acetyl-1-(4-methylphenyl)-5-phenyl-pyrazol-4-yl]-6-methyl-pyrimidin-4(3H)-one **(5Ab)**: Orange powder (1.20 g, 64%), m.p. 199–200 °C; IR (KBr) 3097, 1662, 1627 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.22 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.78 (s, 1H, ArH), 7.42–7.85 (m, 9H, ArH), 11.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6)20.27, 22.00, 24.83, 114.87, 120.59, 121.25, 126.26, 128.11, 128.34, 128.62, 129.38, 129.70, 129.93, 130.88, 133.11, 139.20, 152.97, 162.10, 194.68; MS *m/z* (%) 385 (M^+ + 1, 7), 384 (M^+, 8), 228 (29), 200 (18), 151 (29), 105 (100), 84 (25), 77 (80); Anal. Calcd for $C_{23}H_{20}N_4O_2$ (384.44): C,71.86; H,5.24; N, 14.57. Found: C, 71.59; H, 5.05; N, 14.80%.

2-[3-Acetyl-1-(4-chlorophenyl)-5-phenyl-pyrazol-4-yl]-6-methyl pyrimidin -4(3H)-one **(5Ac)**: Red crystals (1.40 g, 70%), m.p. 216–217 °C; IR (KBr) 3136, 1658, 1624 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.23 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 5.80 (s, 1H, ArH), 7.54–7.87 (m, 9H, ArH), 11.79 (s, 1H, NH); MS *m/z* (%) 405 (M^+ + 1, 2), 404 (M^+, 2), 229 (25), 228 (29), 227 (12), 201 (12), 199 (10), 151 (28), 106 (10), 105 (100), 84 (28), 77 (88); Anal. Calcd for $C_{22}H_{17}ClN_4O_2$ (404.86): C,65.27; H,4.23; N, 13.84. Found: C, 65.10; H, 4.50; N, 13.48%.

2-[3-Acetyl-1-(4-nitrophenyl)-5-phenyl-pyrazol-4-yl]-6-methyl pyrimidin-4(3H)-one **(5Ad)**: Red powder (1.20 g, 60%), m.p. 230–232 °C; IR (KBr) 3080, 1662, 1624 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.23 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 5.80 (s, 1H, ArH), 7.54–7.87 (m, 9H, ArH), 11.80 (s, 1H, NH); MS *m/z* (%) 417 (M^+ + 2, 22), 416 (M^+ + 1, 46), 415 (M^+, 40), 410 (32), 278 (43), 250 (18), 153 (27), 138 (22), 122 (20), 108 (22), 105 (100), 91 (24), 77 (99); Anal. Calcd for $C_{22}H_{17}N_5O_4$ (415.41): C,63.61; H,4.12; N, 16.86. Found: C, 63.35; H, 4.00; N, 16.51%.

2-[3-Acetyl-5-(4-methylphenyl)-1-phenyl-pyrazol-4-yl]-6-methyl-pyrimidin-4(3H)-one **(5Ae)**:Red needles (1.20 g, 60%), m.p. 200–201 °C; IR (KBr) 3286, 1674, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.20 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 6.05 (s, 1H, ArH), 7.22–7.80 (m, 9H, ArH), 10.95 (s, 1H, NH); MS *m/z* (%) 386 (M^+ + 2, 12), 385 (M^+ + 1, 56), 384 (M^+, 60), 367 (32), 293 (39), 292 (37), 266 (11), 120 (10), 119 (100), 106 (19), 91 (77), 84 (22), 77 (51); Anal. Calcd for $C_{23}H_{20}N_4O_2$ (384.44): C,71.86; H,5.24; N, 14.57. Found: C,72.00; H, 5.53; N, 14.24%.

2-[3-Acetyl-1,5-di-(4-methylphenyl)-pyrazol-4-yl]-6-methyl pyrimidin-4(3H)-one **(5Af)**: Orange needle crystals (1.20 g, 62%), m.p. 230–232 °C; IR (KBr) 3128, 1662, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.06 (s, 1H, ArH), 6.99–7.83 (m, 8H, ArH), 10.16 (s, 1H, NH); MS *m/z* (%) 399 (M^+ + 1, 3), 398 (M^+, 2), 243 (28), 242 (19), 241 (12), 214 (14), 151 (21), 119 (100), 91 (52), 84 (21), 77 (5); Anal. Calcd for $C_{24}H_{22}N_4O_2$ (398.47): C,72.34; H,5.57; N, 14.06. Found: C, 72.09; H, 5.42; N, 14.20%.

2-[3-Acetyl-5-(4-methylphenyl)-1-(4-chlorophenyl)-pyrazol-4-yl]-6-methylpyrimidin-4(3H)-one **(5Ag)**: Red powder (1.40 g, 62%), m.p. 210–212 °C; IR (KBr) 3150, 1666, 1630 cm-1; ^{1}H NMR ($CDCl_3$) 2.23 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 6.08 (s, 1H, ArH), 6.91–7.83 (m, 8H, ArH), 10.94 (s, 1H, NH); MS *m/z* (%) 420 (M^+ + 2, 2), 419 (M^+ + 1, 5), 418 (M^+, 8), 292 (35), 243 (21), 242 (20), 241 (24), 214 (15), 151 (21), 119 (100), 91 (66), 84 (23), 77 (5); Anal. Calcd for $C_{23}H_{19}ClN_4O_2$ (418.89): C,65.95; H,4.57; N, 13.38. Found: C, 65.70; H, 4.36; N, 13.09%.

2-[3-Acetyl-5-(4-methylphenyl)-1-(4-nitrophenyl)-pyrazol-4-yl]-6-methyl-pyrimidin-4(3H)-one **(5Ah)**: Red needles (1.30 g, 60%), m.p. 222–223 °C; IR (KBr) 3160, 1666, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.75 (s, 1H, ArH),

7.22–8.26 (m, 8H, ArH), 10.77 (s, 1H, NH); MS *m/z* (%) 431 (M^+ + 2, 5), 430 (M^+ + 1, 20), 429 (M^+, 9), 411 (14), 292 (10), 120 (100), 119 (62), 91 (50), 76 (9); Anal. Calcd for $C_{23}H_{19}N_5O_4$ (429.44): C,64.33; H,4.46; N, 16.31. Found: C, 64.52; H, 4.21; N, 16.30%.

2-[3-Acetyl-5-(4-chlorophenyl)-1-phenyl-pyrazol-4-yl]-6-methyl pyrimidi-4(3H)-one (**5Ai**): Orange powder (1.30 g, 66%), m.p. 286–288 °C; IR (KBr) 3132, 1655, 1624 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.19 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.72 (s, 1H, ArH), 7.07–7.80 (m, 9H, ArH), 11.19 (s, 1H, NH); MS *m/z* (%) 406 (M^+ + 2, 1), 405 (M^+ + 1, 1), 404 (M^+, 1), 264 (20), 234 (24), 151 (49), 139 (100), 113 (18), 111 (54), 84 (21), 75 (28); Anal. Calcd for $C_{22}H_{17}ClN_4O_2$ (404.86): C,65.27; H,4.23; N, 13.84. Found: C, 65.22; H, 4.51; N, 13.70%.

2-[3-Acetyl-5-(4-chlorophenyl)-1-(4-methylphenyl)-pyrazol-4-yl]-6-methyl pyrimidin-4(3H)-one (**5Aj**): Orange platelets (1.50 g, 70%), m.p. 276–278 °C; IR (KBr) 3131, 1658, 1631 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.18 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.72 (s, 1H, ArH), 7.20–7.79 (m, 8H, ArH), 11.23 (s, 1H, NH); MS *m/z* (%) 420 (M^+ + 2, 1), 419 (M^+ + 1, 1), 418 (M^+, 10), 262 (60), 234 (22), 233 (18), 151 (46), 141 (34), 139 (100), 113 (17), 111 (50), 106 (25), 91 (14), 84 (21), 77 (18); Anal. Calcd for $C_{23}H_{19}ClN_4O_2$ (418.89): C,65.95; H,4.57; N, 13.38. Found: C, 65.62; H, 4.31; N, 13.20%.

2-[3-Acetyl-1,5-di-(4-chlorophenyl)-pyrazol-4-yl]-6-methyl pyrimidin-4(3H)-one (**5Ak**): Orange powder (1.40 g, 66%), m.p. 270–272 °C; IR (KBr) 3130, 1660, 1629 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.12 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 5.74 (s, 1H, ArH), 7.42–7.78 (m, 8H, ArH), 11.74 (s, 1H, NH); MS *m/z* (%) 441 (M^+ + 2, 2), 440 (M^+ + 1, 5), 439 (M^+, 10), 438 (3), 264 (20), 263 (20), 261 (30), 234 (25), 151 (51),139 (100), 113 (19), 111 (51), 84 (45), 75 (47); Anal. Calcd for $C_{22}H_{16}Cl_2N_4O_2$ (439.30): C,60.15; H,3.67; N, 12.75. Found: C,60.00; H, 3.95; N, 12.51%.

2-[3-Acetyl-5-(4-chlorophenyl)-1-(4-nitrophenyl)-pyrazol-4-yl]-6-methyl pyrimidin-4(3H)-one (**5Al**): Red needles (1.40 g, 62%), m.p. 158–159 °C; IR (KBr) 3085, 1682, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.19 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.73 (s, 1H, ArH), 7.13–8.50 (m, 8H, ArH), 11.32 (s, 1H, NH); MS *m/z* (%) 451 (M^+ + 2, 1), 450 (M^+ + 1, 1), 449 (M^+, 2), 410 (100), 368 (14), 341 (56), 313 (50), 285 (56), 274 (34), 262 (49), 163 (33), 139 (88), 111 (27), 90 (40), 76 (32); Anal. Calcd for $C_{22}H_{16}ClN_5O_4$ (449.86): C,58.74; H,3.59; N, 15.57. Found: C, 58.59; H, 3.24; N, 15.25%.

2-[3-Benzoyl-1,5-diphenyl-pyrazol-4-yl]-6-methylpyrimidin-4(3H)-one (**5Ba**): Orange powder (1.73 g, 80%), m.p. 226–227 °C; IR (KBr) 3413, 1678, 1654 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.49 (s, 3H, CH_3), 6.05 (s, 1H, ArH), 7.48–7.81 (m, 15H, ArH), 10.76 (s, 1H, NH); MS *m/z* (%) 432 (M^+, 10), 429 (67), 363 (80), 291 (99), 203 (100), 181 (80), 154 (80), 136 (80), 112 (73), 104 (73), 75 (73); Anal. Calcd for $C_{27}H_{20}N_4O_2$ (432.49): C,74.99; H,4.66; N, 12.95. Found: C, 74.70; H, 4.38; N, 12.67%.

2-[3-thenoyl-1-(4-chlorophenyl)-5-phenyl-pyrazol-4-yl]-6-methyl-pyrimidin-4(3H)-one (**5Cc**): Orange powder (1.54 g, 65%), m.p. 197–198 °C; IR (KBr) 3078, 1681, 1654 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.39 (s, 3H, CH_3), 6.01 (s, 1H, ArH), 7.51–8.59 (m, 12H, ArH), 10.63 (s, 1H, NH); MS *m/z* (%) 474 (M^+ + 2, 1), 473 (M^+ + 1, 1), 472 (M^+, 1), 372 (2), 283 (1), 177 (3), 134 (2), 113 (6), 111 (100), 109 (1), 83 (6), 76 (3); Anal. Calcd for $C_{25}H_{17}ClN_4O_2S$ (472.5): C,63.49; H,3.60; N, 11.85. Found: C,63.21; H, 3.34; N, 11.60%.

1,3-Diphenyl-2-(6-methyl-4-oxo-3H-pyrimidin-2-yl)-propane-1,3-dione-1-phenylhydrazone (**4Da**): Pale yellow needles (1.40 g, 65%), m.p. 238–239 °C; IR (KBr) 3421, 3180, 1670, 1632 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.18 (s, 3H, CH_3), 6.05 (s, 1H, CH), 6.47 (s, 1H, ArH), 7.43–7.99 (m, 15H, ArH), 11.63 (s, 1H, NH), 14.44 (s, 1H, NH); MS *m/z* (%) 423 (M^+ + 1, 5), 422 (M^+, 11), 195 (18), 194 (100), 105 (76), 91 (91), 77 (84); Anal. Calcd for $C_{26}H_{22}N_4O_2$ (422.49): C,73.92; H,5.25; N, 13.26. Found: C,73.70; H, 5.10; N, 13.00%.

3-(4-Methylphenyl)-2-(6-methyl-4-oxo-3H-pyrimidin-2-yl)-1-phenyl propane-1,3-dione-1-phenylhydrazone (**4De**): Pale yellow powder (1.69 g, 72%), m.p. 194–195 °C; IR (KBr) 3409, 3100, 1685, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.04 (s, 3H, CH_3),2.15 (s, 3H, CH_3), 5.47 (s, 1H, CH), 5.74 (s, 1H, ArH), 6.89–7.65 (m, 14H, ArH), 9.90 (s, 1H, NH), 14.17 (s, 1H, NH); Anal. Calcd for $C_{27}H_{24}N_4O_2$ (436.52): C,74.29; H,5.54; N, 12.83. Found: C,74.00; H, 5.72; N, 12.51%.

Ethyl 2,4-dioxo-3-(6-methyl-4-oxo-3H-pyrimidin-2-yl)-4-phenyl-butanoate-2-phenylhydrazone (**4Ea**): Pale yellow powder (1.25 g, 60%), m.p. 220–222 °C; IR (KBr) 3464, 3171, 1701, 1659, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.38 (t, J = 7 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 4.36 (q, J = 7 Hz, 2H, CH_2), 5.46 (s, 1H, CH), 5.66 (s, 1H, ArH), 7.02-7.60 (m, 10H, ArH), 11.05 (s, 1H, NH), 14.21 (s, 1H, NH). MS *m/z* (%) 420 (M^+ + 2, 1), 419 (M^+ + 1, 4), 418 (M^+, 6), 374 (14), 298 (10), 118 (3), 105 (100), 91 (41), 77 (79); Anal. Calcd for $C_{23}H_{22}N_4O_4$ (418.46): C, 66.02; H, 5.30; N, 13.39. Found: C, 66.20; H, 5.40; N, 13.61%.

Ethyl 2,4-dioxo-3-(6-methyl-4-oxo-3H-pyrimidin-2-yl)-4-(methyl-phenyl)-butanoate-2-phenylhydrazone (**4Ee**): Pale yellow needles (1.3 g, 60%), m.p. 205–206 °C; IR (KBr) 3402, 3190, 1735, 1670, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.26 (t, J = 7 Hz, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.29 (q, J = 7 Hz, 2H, CH_2), 5.28 (s, 1H, CH), 5.93 (s, 1H, ArH), 7.05–7.55 (m, 9H, ArH), 11.33 (s, 1H, NH), 14.06 (s, 1H, NH). MS *m/z* (%) 433 (M^+ + 1, 4), 432 (M^+, 3), 388 (12), 299 (22), 186 (5), 134 (11), 119 (100), 91 (75), 77 (32); Anal. Calcd for $C_{24}H_{24}N_4O_4$ (432.48): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.60; H, 5.32; N, 13.00%.

3-(6-Methyl-4-oxo-3H-pyrimidin-2-yl)-4-oxo-4-phenyl-2-(phenyl-hydrazono)butanilide (**4Fa**): Pale yellow powder (1.60 g, 70%), m.p. 218–220 °C; IR (KBr) 3395, 3236, 1690, 1681, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.45 (s, 3H, CH_3), 5.53 (s, 1H, CH), 5.95 (s, 1H, ArH), 7.05–7.86 (m, 15H, ArH), 10.21 (s, 1H, NH), 10.86 (s, 1H, NH), 14.82 (s, 1H, NH); MS *m/z* (%) 467 (M^+ + 1, 1), 466 (M^+, 2), 346 (14), 345 (15), 229 (9), 118 (5), 105 (100), 91 (33), 77 (96); Anal. Calcd for $C_{27}H_{23}N_5O_3$ (465.52): C,69.66; H,4.98; N, 15.04. Found: C, 69.60; H, 5.30; N, 15.10%.

3-(6-Methyl-4-oxo-3H-pyrimidin-2-yl)-4-oxo-4-(4-methylphenyl)-2-(phenylhydrazono)butanilide (**4Fe**): Pale yellow needles (1.60 g, 65%), m.p. 209–210 °C; IR (KBr) 3394, 3232, 3028, 1712, 1678, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 5.40 (s, 1H, CH), 5.81 (s, 1H, ArH), 6.95–8.13 (m, 14H, ArH), 10.07 (s, 1H, NH), 10.71 (s, 1H, NH), 14.75 (s, 1H, NH); MS *m/z* (%) 479 (M^+, 2), 397 (11), 345 (9), 301 (6), 226 (7), 134 (6), 119 (100), 91 (61), 77 (36); Anal. Calcd for $C_{28}H_{25}N_5O_3$ (479.54): C,70.13; H,5.25; N, 14.60. Found: C, 70.00; H, 5.30; N, 14.30%.

Cyclisation of **4Da** *into* **5Da**

A mixture of **4Da** (0.0025 mole) and phosphourus oxychloride (10 ml) was refluxed for 10 h, then the reaction mixture was cooled and neutralised with sodium carbonate. The solid, that precipitated, was filtered off and crystallised from ethanol to give **5Da**.

Dark yellow needles (0.50 g, 50%), m.p.180–181 °C; IR (KBr) 3186, 1667 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.06 (s, 3H, CH_3), 6.25 (s, 1H, ArH), 7.62–7.96 (m, 15H, ArH), 12.83 (s, 1H, NH); MS *m/z* (%) 404 (M^+, 1), 402 (32), 401 (78), 400 (56), 399 (71), 198 (22), 150 (16), 141 (32), 139 (70), 136 (100), 113 (33), 111 (95), 91 (12), 75 (64); Anal. Calcd for $C_{26}H_{20}N_4O$ (404.48): C,77.21; H,4.98; N, 13.85. Found: C, 77.57; H, 4.80; N, 13.62%.

Alternate synthesis of **5Da**

To a solution of compound **3a** (1.14 g, 5 mmole) in ethanolic sodium ethoxide solution prepared by dissolving sodium metal (0.12 g, 5 mmoles) in absolute ethanol (20 ml), was added benzoyl chloride (0.70 g, 5 mmoles). The reaction mixture was left whilst being stirred for 3 days at room temperature. The precipitate was filtered, washed with water and finally crystallised from ethanol to give compound **12** as pale yellow powder, (0.58 g, 35%), m.p. 204–206 °C; IR (KBr) 3421, 1678, 1658 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.15 (s, 3H, CH_3), 5.59 (s, 1H, CH), 5.75 (s, 1H, ArH), 7.51–7.80 (m, 10H, ArH), 11.76 (s, 1H, NH); MS *m/z* (%) 333 (M^+ + 1, 10), 332 (M^+, 21), 227 (18), 223 (31), 122 (25), 118 (14), 109 (72), 105 (90), 77 (100); Anal. Calcd for $C_{20}H_{16}N_2O_3$ (332.36): C,72.28; H,4.85; N, 8.43. Found: C, 72.05; H, 4.60; N, 8.05%.

To a solution of compound **12** (1.66 g, 5 mmole) in acetic acid (20 ml), was added phenyl hydrazine (0.54 g, 5 mmole). The reaction mixture was left while being stirred for 2 days at 60 °C in water bath. The precipitate was filtered, washed with water and finally crystallised from ethanol to give compound **5Da** which found identical in all respects with that produced from method A

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