Synthesis of 1-alkyl-6-aryl-3-n-propyl-5-thioxo/oxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-ones

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1-Alkyl-6-aryl-3-n-propyl-5-thioxo/oxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-ones are obtained from the reactions of 4-amino-1-alkyl-3-n-propyl pyrazole-5-carboxamides with aryl isothiocyanates and phenyl isocyanate.

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Pyrazolopyrimidines such as oxyallopurin (xanthine analogue) and thiopurinol (thiohypoxanthine analogue) act as antimetabolites in purine biochemical reactions and are useful in the treatment of gout and related diseases in which diminished oxidation of purines is required.\(^1\)\(^3\) Development of physiologically highly potent purine analogues with interesting properties\(^4\)\(^7\) prompted a great current interest in the synthesis of similar systems in synthetically useful yields. In the light of these observations we have studied the reactions of 4-amino-1-alkyl-3-n-propyl pyrazole-5-carboxamides (1a/1b) with aryl isothiocyanates and phenyl isocyanate, as an approach to thioxo and oxo derivatives of pyrazolo[4,3-d]pyrimidines. The results are described in this paper.

An equimolar reaction of 4-amino-1-methyl-3-n-propyl pyrazole-5-carboxamide\(^8\) 1a and 4-methylphenyl isothiocyanate in refluxing acetic acid, followed by usual work-up and subsequent chromatographic separation on neutral alumina afforded two crystalline products, characterised as 6-(4-methylphenyl)-1-methyl-3-n-propyl-5-thioxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (2a, 67%, m.p. 240-41°C) and 1-methyl-3-n-propyl-5-thioxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (3a, 19%, m.p. 264-66°C) based on their IR, Mass and NMR spectral data (Table 1). Assigned structures of 2a and 3a were confirmed by the independent preparation of these two compounds. Reaction of 4-amino-1-methyl-3-n-propyl pyrazole-5-N(4-methyl-phenyl)carboxamide 1e with thiophosgene in THF furnished pyrazolo pyrimidinone 2a as the sole product. In a similar reaction, pyrazole carboxamide 1a afforded dearyl product 3a on treatment with thiophosgene in THF (Scheme I).

Formation of compounds 2a and 3a is envisaged to proceed through a common open chain thiourea

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>Ar</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>2a</td>
<td>CH₃</td>
<td>-</td>
<td>246°</td>
<td>67</td>
</tr>
<tr>
<td>2b</td>
<td>CH₃</td>
<td>-</td>
<td>241°</td>
<td>58</td>
</tr>
<tr>
<td>2c</td>
<td>CH₃</td>
<td>Cl</td>
<td>276°</td>
<td>63</td>
</tr>
<tr>
<td>2d</td>
<td>CH₃</td>
<td>Br</td>
<td>274°</td>
<td>70</td>
</tr>
<tr>
<td>2e</td>
<td>C₃H₅</td>
<td>-</td>
<td>238°</td>
<td>59</td>
</tr>
<tr>
<td>2f</td>
<td>C₃H₅</td>
<td>Cl</td>
<td>279°</td>
<td>61</td>
</tr>
<tr>
<td>3a</td>
<td>CH₃</td>
<td>--</td>
<td>263°</td>
<td>--</td>
</tr>
<tr>
<td>3b</td>
<td>C₃H₅</td>
<td>--</td>
<td>286°</td>
<td>--</td>
</tr>
</tbody>
</table>

a: recrystallised from methanol  
b: recrystallised from ethyl acetate

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intermediate 4. We have isolated thiourea derivative 4 by conducting the reaction of 1a with 4-methylphenyl isothiocyanate in refluxing benzene and obtained a mixture of 2a and 3a by heating 4 in acetic acid. Obviously, cyclisation of open chain intermediate 4 is proceeding through two competing pathways (Scheme II). Nucleophilic attack of relatively more reactive aniline amino group on amide carbonyl and subsequent elimination of ammonia (path A) leads to major compound 2a. On the other hand, nucleophilic attack of amide NH$_2$ on thiocarbonyl carbon and subsequent loss of aryl amine (Path B) results in minor compound 3a.

Three other aryl isothiocyanates reacted with aminopyrazole carboxamides 1a/1b in refluxing acetic acid in a similar manner and yielded the corresponding 6-aryl pyrazolo[4,3-c]pyrimidine 2 as major product along with dearyl product 3 (Table I).

However, reaction of phenyl isocyanate with 1a/1b in refluxing acetic acid yielded corresponding pyrazolo[4,3-d]pyrimidin-5,7-dione derivative 6a/6b as the sole product in excellent yield (Scheme III). Isolation of open chain urea derivative 5a by conducting this reaction of 1a in boiling benzene and its subsequent cyclisation into 6a in refluxing acetic acid proved the intermediacy of 5 in the formation of 6.

Thus, reaction exclusively proceeded through the attack of amide NH$_2$ on the urea carbonyl carbon in 5 to provide pyrazolopyrimidine dione 6.
Conclusion

Reaction of 4-aminopyrazole-5-carboxamide with aryl isothiocyanates proceeded through two competing pathways and yielded 6-aryl-5-thioxo pyrazolo[4,3-d]pyrimidin-7-one 2 as major product along with the corresponding dearylated product 3. Phenyl isocyanate merely served as a source of carbonyl group and provided pyrazolopyrimidin-5,7-dione 6 by bridging the two amino functions of 1a/1b.

Experimental Section

General procedure for the preparation of 1-alkyl-6-aryl-3-n-propyl-5-thioxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-ones 2a-f and 1-alkyl-3-n-propyl-5-thioxo-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-7-ones 3a,b. A solution of 4-amino-1-alkyl-3-n-propylpyrazole-5-carboxamide (1a/1b, 0.01 mole) and the appropriate aryl isothiocyanate (0.01 mole) in acetic acid (15 mL) was refluxed for 4 hr. The reaction mixture was cooled and poured into ice cold water (50 mL). The separated solid was filtered, dried and passed over neutral alumina column using benzene-ethyl acetate (8:2) as eluent. Compounds 2 and 3 were isolated and recrystallised from suitable solvents.

Cyclisation of 4-[substituted anilino(thioxo) methylamino]-1-alkyl-3-n-propyl-1H-pyrazole-5-carboxamide 4. A solution of 4 (0.01 mole) in acetic acid (20 mL) was refluxed for 4 hr. The reaction mixture was cooled and poured into ice cold water (75 mL). The separated solid was filtered, dried and passed over neutral alumina column using benzene-ethyl acetate (8:2) as eluent. Compounds 2a and 3a were isolated and recrystallised from suitable solvents (Table II).

Reaction of pyrazole carboxamides 1a/1c with thiophosgene. A solution of 1a/1c (0.01 mole) in THF (25 mL) was cooled to 0°C and thiophosgene
(0.012 mole) dissolved in THF (10 mL) was added dropwise while maintaining the temperature at 0-5°C. After the addition, the temperature was allowed to rise to 25°C and reaction mixture was stirred for 12 hr and poured in cold water (50 mL). Pyrazolo[4,3-d]pyrimidin-7-one derivative 2a/3a separated out as a crystalline solid. It was filtered, washed with water (10 mL), dried and recrystallised from suitable solvent.

**General procedure for the preparation of 1-alkyl-3-n-propyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-5,7-diones 6.** A mixture of 4-aminol-1-alkyl-3-n-propyl pyrazole-5-carboxamide (1a/1b, 0.01 mole) and phenyl isocyanate (0.01 mole) in acetic acid (15 mL) was refluxed for 4 hr. The reaction mixture was cooled and poured in ice cold water (50 mL). The separated solid was filtered, dried and recrystallised from suitable solvent to give 6.

4-[Anilino(oxo)methylamino]-1-alkyl-3-n-propyl-1H-pyrazole-5-carboxamide 5. A mixture of 1a (0.01 mole) and phenyl isocyanate (1.19 g, 0.01 mole) in dry benzene (25 mL) was heated on steam bath for 1 hr. On cooling, urea derivative 5 separated out as a crystalline solid. It was filtered, washed with benzene (10 mL) and recrystallised from methanol, yield 91%. UV (MeOH):254, 237, 205 nm; IR (KBr):3302, 3169, 2964, 1688, 1648, 1596, 1493, 1255 cm⁻¹; ¹H NMR (DMSO-d₆): δ 8.3 (t, 3H, CH₃), 1.7 (m, 2H, CH₂), 2.4 (s, 3H, Ar-CH₃), 2.8 (t, 2H, CH₂, J = 8.5 Hz), 4.1 (s, 3H, N-CH₂), 7.0 (d, 2H, J = 10.5 Hz, Ar-H), 7.3 (d, 2H, J = 10.5 Hz, Ar-H), 13.0 (br s, 1H, NH).

(in dry benzene (25 mL) was heated on steam bath for 1 hr. On cooling, urea derivative 5 separated out as a crystalline solid. It was filtered, washed with benzene (10 mL) and recrystallised from methanol, yield 91%).
1-Methyl-3-n-propyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione 6a. Recrystallised from aqueous DMSO, yield 81%, m.p. 297°C; UV (MeOH): 292, 245, 222 nm; IR (KBr): 3180, 3065, 2960, 1710, 1490, 1397, 1324, 1209 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.0 (t, 3H, CH₃, J = 8.3 Hz), 1.6 (m, 2H, CH₂), 2.6 (t, 2H, CH₂, J = 8.5 Hz), 4.05 (s, 3H, N-CH₃), 10.8 (br s, 1H, NH), 11.0 (br s, 1H, NH); Mass (EI, 70 eV): m/z 208 (M⁺), 193, 180 (base peak), 179, 165, 136, 122, 96, 81, 68, 53.

1-Ethyl-3-n-propyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-d]pyrimidin-5,7-dione 6b. Recrystallised from DMF, yield 83%, m.p. 277°C; UV (MeOH): 294, 246, 227 nm; IR (KBr): 3177, 3060, 2959, 2869, 1712, 1666, 1494, 1397, 1142, 1062, 991 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.0 (t, 3H, CH₃, J = 8.3 Hz), 1.4 (t, 3H, N-C-CH₃, J = 8.0 Hz), 1.7 (m, 2H, CH₂), 2.7 (t, 2H, CH₂, J = 8.5 Hz), 4.5 (q, 2H, -N-CH₂, J = 8.0 Hz), 12.0 (br s, 1H, NH), 12.6 (br s, 1H, NH); Mass (EI, 70 eV): m/z 222 (M⁺), 207, 194, 193, 179, 165, 150, 136, 122, 96, 83, 69, 65, 54, 43.

References