A Facile One-pot Synthesis of 1-Arylpyrazolo[3,4-d]Pyrimidin-4-ones

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Received: 19 March 2010; in revised form: 9 April 2010 / Accepted: 21 April 2010 /
Published: 27 April 2010

Abstract: One pot synthesis of 1-arylpyrazolo[3,4-d]pyrimidin-4-ones by the reaction of
5-amino-N-substituted-1H-pyrazole-4-carbonitrile with different lower aliphatic acids in
the presence of POCl3 has been developed. The structures of all the title compounds have
been confirmed by IR, 1H-NMR, 13C-NMR, and elemental analyses. Moreover, the
structures of one of these compounds, 2c, was confirmed by single-crystal X-ray
diffraction.

Keywords: POCl3; one-pot; RCOOH; pyrazolo[3,4-d]pyrimidine

1. Introduction

Pyrazolopyrimidinone derivatives have attracted the attention of numerous researchers over many
years due to their important biological activities [1–4]. Structural analogs of pyrazolo[3,4-d]-
pyrimidines have displayed good activities as inhibitors of cyclin-dependent kinase 2 [5] and PI3
kinase-A [6], anticancer and radioprotective activity [7], antimicrobial [8] and other biology activity
[9]. The importance of pyrazolo[3, 4-d]pyrimidines had resulted in the development of several
synthetic methods for their construction [10,11]. The traditional transformation utilizes two steps to
assemble aminopyrazolo[3, 4-d] pyrimidin-4-ones, as illustrated in Schemes 1 and 2. However, the
transformation of compounds 2 requires two steps and suffers from several disadvantages such as
vigorous conditions, long reaction times and low yields [12,13]. The development of one-step and efficient syntheses of aminopyrazolo[3,4-\(d\)]pyrimidin-4-ones under mild conditions remained a work in progress.

**Scheme 1.** Synthesis of pyrazolo [3, 4-\(d\)] pyrimidin-4-ones by the reaction of esters.

Scheme 2. Synthesis of pyrazolo [3, 4-\(d\)] pyrimidin-4-ones by the reaction of acyl chlorides.

Here, we report a simple and efficient method for the synthesis of usefully functionalized pyrazolo[3,4-\(d\)] pyrimidins-4-ones 2 by heteroannulation under mild conditions using POCl\(_3\).

2. Result and Discussion

The 5-amino-N-substituted-IH-pyrazole-4-carbonitrile starting materials 1, synthesized by a one–pot synthesis literature procedure [14], was then reacted with lower aliphatic acids in the presence of POCl\(_3\) to give the target N-substituted pyrazolo[3,4-\(d\)]pyrimidin-4-ones 2 (Scheme 3).

**Scheme 3.** Synthesis of pyrazolo[3, 4-\(d\)]pyrimidin-4-ones by the reaction of carboxylic acid in the presence of POCl\(_3\).

A number of works about POCl\(_3\)-catalyzed reactions, especially intramolecular condensations [15] have been reported. In our reaction system POCl\(_3\) acted not only as a chlorinating reagent, but also an oxidant. Thus, we concluded that the 5-amino-N-substituted-IH-pyrazole-4-carbonitrile were first oxidized to give the corresponding N-substituted-5-amino-pyrazole-4-carboxamide, which immediately reacted with the acyl chloride which might be generated *in situ* from the reaction of the carboxylic acid with POCl\(_3\). Followed by cyclization and condensation of the intermediate, the target
products were formed. The reaction went smoothly by controlling the amount of POCl₃, and the products were obtained in good yields. The results were presented in Table 1.

Table 1. N-substituted prazolo[3, 4-d]pyrimidin-4-one 2a-j via Scheme 3.

| Entry | R² | R¹ | Yield a | Time(h) |
|-------|----|----|---------|---------|
| 2 a   | H  | 2,6-Cl₂-4-CF₃-C₆H₂⁻ | 90      | 1.5     |
| 2 b   | CH₃| 2,6-Cl₂-4-CF₃-C₆H₂⁻ | 87      | 2       |
| 2 c   | CH₂CH₃ | 2,6-Cl₂-4-CF₃-C₆H₂⁻ | 90      | 2.5     |
| 2 d   | CCl₃| 2,6-Cl₂-4-CF₃-C₆H₂⁻ | 89      | 2       |
| 2 e   | CH₃| 4-OCH₃-C₆H₄⁻         | 83      | 1       |
| 2 f   | CH₃| 2,4-(NO₂)₂-C₆H₄⁻     | 90      | 1.5     |
| 2 g   | CH₃| 2,4,6-Cl₃-C₆H₂⁻      | 97      | 1.5     |
| 2 h   | CH₃| 2-Cl-C₆H₄⁻          | 82      | 2       |
| 2 i   | CH₃| H                   | 75      | 2.5     |
| 2 j   | CH₃| n-Bu                | 70      | 2.5     |

a isolated yields based on compound 2

The structures of compounds 2a-j were deduced from their elemental analyses and their IR, ¹H-NMR, ¹³C-NMR and mass spectra and all elemental and spectral data of compounds 2a-j were in accord with the suggested structures. The ¹H-NMR spectrum of 2c, as an example, consisted of a singlet at δ 11.06 from the NH function, a singlet at δ 8.27 is from the H-3 proton, a singlet at δ 8.11 due to the phenyl ring (two protons), a multiplet at δ 2.74 (two protons) from the CH₂ and a triplet at δ 1.23 due to the methyl group (three protons). Moreover the structure of 2c was confirmed via X-ray crystallographic analysis (Figure 1).

Figure 1. Single crystal X-ray crystal structure of 2c.

3. Experimental

3.1. General

All the melting points were uncorrected. ¹H-, ¹³C-, and ¹⁹F-NMR spectra were recorded on a FT-Bruker AT-300 instrument using CDCl₃ or CD₃COCD₃ as a solvent with tetramethylsilane (TMS) as the internal standard. J-values are given in Hz. Compounds were properly characterized by
3.2. General procedure for the preparation of the pyrazolo[3,4-d]pyrimidines 2a-2j: preparation of 2c

5-Amino-1-[2,6-dichloro-4-(trifloromethyl)phenyl]-1H-pyrazole-4-carbonitrile (0.321 g, 1 mmol) was dissolved in propanoic acid (3 mL). Then POCl₃ (0.2 mL) was added quickly. The mixture was refluxed for 2 h (the reaction system was carefully observed by TLC). After the mixture was cooled, added ice water (50 mL). A mass of white precipitate was produced. K₂CO₃ was added to neutralize the acid till no bubble occurs. The reaction mixture was filtered, and washed with a small amount of ethanol, dried. A 90% yield of the compound was obtained. Crystals of 2c suitable for X-ray diffraction were obtained by slow evaporation of ethanol-acetone mixture solution. The other compounds were also synthesized according to this method.

6-Methyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2b): White solid; mp 259-260 °C, IR (KBr, cm⁻¹): 3772, 3105, 2896, 1598, 1392, 1317, 1131; ¹H-NMR (DMSO-d₆, 300 MHz): δ 12.42 (s, 1H), 8.40 (s, 1H), 8.27 (s, 2H), 2.31 (s, 3H); ¹³C-NMR (DMSO-d₆, 75 MHz): δ 21.2 (1C), 104.3 (1C), 122.2 (q, J = 272 Hz, 1C), 126.4 (1C), 132.6 (q, J = 33.70 Hz, 1C), 135.6 (2C), 136.3 (1C), 137.6 (2C), 149.8 (1C), 153.8 (1C), 157.0 (1C); MS: m/z (%) = 361 (100, [M⁺ - 1]); Anal. Calcd for C₁₃H₇Cl₂F₃N₄O: C, 43.00; H, 1.94; N, 15.43. Found: C, 42.91; H, 1.90, N, 15.38.

6-Ethyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2c): White solid; mp 232-233 °C, IR (KBr, cm⁻¹): 3094, 2989, 1615, 1598, 1319, 1173, 1124; ¹H-NMR (CD₂COCD₃, 300 MHz): δ 11.16 (s, 1H), 8.27 (s, 1H), 8.11 (s, 2H), 2.74 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H); ¹³C-NMR (DMSO-d₆, 75 MHz): δ 11.8 (1C), 104.3 (1C), 122.2 (q, J = 272 Hz, 1C), 126.5 (1C), 132.7 (q, J = 33.75 Hz, 1C), 135.7 (2C), 136.5 (1C), 149.8 (1C), 153.8 (1C), 157.0 (1C); MS: m/z (%) = 375 (100, [M⁺ - 1]); Anal. Calcd for C₁₄H₉Cl₂F₃N₄O: C, 44.59; H, 2.41; N, 14.86. Found: C, 44.51; H, 2.36, N, 14.83.

6-Trichloromethyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2d): White solid; mp 238-239 °C, IR (KBr, cm⁻¹): 3013, 2920, 1683, 1589, 1333, 1317, 1124, 663; ¹H-NMR (DMSO-d₆, 300 MHz): δ 12.50 (s, 1H), 8.45 (s, 1H), 8.24 (s, 2H); ¹³C-NMR (DMSO-d₆, 75 MHz): 79.0 (1C), 105.6 (1C), 122.6 (q, J = 273 Hz, 1C), 126.8 (1C), 132.9 (q, J = 33.75 Hz, 1C),
136.0 (2C), 137.0 (1C), 138.1 (2C), 155.3 (1C), 159.0 (1C), 164.7 (1C); MS: \( m/z \) (%) = 463 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_{13}\)H\(_4\)Cl\(_5\)F\(_3\)N\(_4\)O: C, 33.47; H, 0.86; N, 12.01. Found: C, 33.451; H, 0.85, N, 12.05.

6-Methyl-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2e): White solid, mp 258-260 °C; IR (KBr, cm\(^{-1}\)): 3850, 3745, 3618, 2926, 1690 (s), 1518, 1463, 675; \(^1\)H-NMR (DMSO-d\(_6\), 300 MHz): \( \delta \) 12.23 (s, 1H), 8.19 (s, 1H), 7.86 (d, \( J = 7.5 \) Hz, 2H), 7.08 (d, \( J = 7.5 \) Hz, 2H), 3.80 (s, 3H), 2.37 (s, 3H); \(^{13}\)C-NMR (DMSO-d\(_6\), 75 MHz): \( \delta \) 21.5 (1C), 55.5 (1C), 105.2 (1C), 114.3 (2C), 123.5 (2C), 131.5 (1C), 135.3 (1C), 152.1 (1C), 157.9 (1C), 158.1 (1C), 158.3 (1C); MS: \( m/z \) (%) = 255 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_{13}\)H\(_{12}\)N\(_4\)O\(_2\): C, 60.93; H, 4.72; N, 21.86. Found: C, 60.88; H, 4.68, N, 21.76.

6-Methyl-1-(2,4-dinitrophenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2f): Yellow solid, mp 229-230ºC; IR (KBr, cm \(-1\)): 3749, 2921, 1695 (s), 1605, 1533, 1348; \(^1\)H-NMR (DMSO-d\(_6\), 300 MHz): \( \delta \) 12.52 (s, 1H), 8.85 (s, 1H), 8.70 (d, \( J = 9 \) Hz, 1H), 8.37 (s, 1H), 8.19 (d, \( J = 9 \) Hz, 1H), 2.44 (s, 3H); \(^{13}\)C-NMR (DMSO-d\(_6\), 75 MHz): \( \delta \) 21.5 (1C), 105.6 (1C), 121.3 (1C), 128.5 (1C), 128.8 (1C), 134.1 (1C), 138.4 (1C), 143.3 (1C), 146.1 (1C), 153.9 (1C), 157.5 (1C), 160.1 (1C); MS: \( m/z \) (%) = 315 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_{12}\)H\(_8\)N\(_6\)O\(_5\): C, 45.58; H, 2.55; N, 26.58. Found: C, 45.45; H, 2.50, N, 26.46.

6-Methyl-1-(2,4,6-trichlorophenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2g): White solid, mp 236-237 ºC; IR (KBr, cm \(-1\)): 3432, 1685, 1599, 1536, 1386, 667; \(^1\)H-NMR (DMSO-d\(_6\), 300 MHz): \( \delta \) 12.4 (s, 1H), 8.3 (s, 1H), 8.0 (s, 2H), 2.3 (s, 3H); \(^{13}\)C-NMR (DMSO-d\(_6\), 75 MHz): \( \delta \) 21.4 (1C), 104.4 (1C), 129.2 (2C), 132.2 (1C), 135.4 (2C), 136.4 (1C), 137.4 (1C), 154.6 (1C), 1587.9 (1C), 159.7 (1C); MS: \( m/z \) (%) = 327 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_{12}\)H\(_7\)Cl\(_3\)N\(_4\)O: C, 43.73; H, 2.14; N, 17.00. Found: C, 43.67; H, 2.10, N, 16.88.

6-Methyl-1-(2-chlorophenyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2h): White solid, mp 217-219 ºC; IR (KBr, cm \(-1\)): 3842, 2925, 2272, 1741, 1645, 1461, 1391, 1121, 669; \(^1\)H-NMR (DMSO-d\(_6\), 300 MHz): \( \delta \) 12.03 (s, 1H), 10.36 (s,1H), 8.33 (s, 1H), 7.6 (m, 4H), 2.3 (s, 3H); \(^{13}\)C-NMR (DMSO-d\(_6\), 75 MHz): \( \delta \) 21.2 (1C), 104.2 (1C), 128.1 (1C), 130.2 (2C), 131.2 (1C), 131.4 (1C), 134.9 (1C), 136.0 (1C), 153.9 (1C), 157.9 (1C), 158.8 (1C); MS: \( m/z \) (%) = 259 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_{12}\)H\(_9\)ClN\(_4\)O: C, 55.29; H, 3.84; N, 21.49. Found: C, 55.12; H, 3.80, N, 21.36.

6-Methyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2i): White solid, mp 264-265 ºC; IR (KBr, cm \(-1\)): 3842, 2925, 2272, 1741, 1645, 1461, 1391, 1121, 669; \(^1\)H-NMR (DMSO-d6, 300 MHz): \( \delta \) 12.03 (s, 1H), 10.36 (s,1H), 8.33 (s, 1H), 7.6 (m, 4H), 2.3 (s, 3H); \(^{13}\)C-NMR (DMSO-d\(_6\), 75 MHz): \( \delta \) 13.7; 105.00 (1C), 135.17 (1C), 153.70 (1C), 158.78 (1C), 159.20 (1C); MS: \( m/z \) (%) = 149 (100, [M\(^+\) - 1]); Anal. Calcd for C\(_6\)H\(_6\)N\(_4\)O: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.95; H, 4.00, N, 37.28.

6-Methyl-1-n-butyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (2j), White solid, mp 144-145 ºC; IR (KBr, cm \(-1\)): 2925, 2855, 1387, 1120, 676; \(^1\)H-NMR (CD\(_3\)COCD\(_3\)): \( \delta \) 11.60 (s, 1H), 8.44 (s, 1H), 4.20 (t, \( J = 6.8 \) Hz, 2H), 2.26 (s, 3H), 1.78 (m, \( J = 10.6 \) Hz, 2H), 1.20 (m, \( J = 7.41 \)Hz, 2H), 0.86 (t, \( J = 6.8 \) Hz).
7.4 Hz, 3H); $^{13}$C-NMR (CD$_3$COCD$_3$): 13.36 (1C), 19.09 (1C), 21.43 (1C), 31.50 (1C), 52.1 (1C), 104.73 (1C), 128.46 (1C), 155.52 (1C), 159.24 (1C), 159.32 (1C); MS: m/z (%) = 205 (100, [M$^+$ - 1]); Anal. Calcd for C$_{10}$H$_{14}$N$_4$O: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.20; H, 6.80; N, 27.10.

3.3. X-ray crystallography

Compound 2c was subjected to single crystal X-ray crystallography and intensity data were collected at 298(2)K on an Siemens P4 diffractometer and use graphite Monochromated MoK$_\alpha$ radiation ($\lambda$ = 0.71073Å). The structure was solved by a direct method using the SHELXL-97 program [16] and refined with the SHELXL-97 program. All H atoms bonded to the C atoms were placed geometrically at the distances of 0.93–0.96Å and included in the refinement riding motion approximation with U$_{iso}$ (H) = 1.2 or 1.5U$_{eq}$ of the carrier atom. The thermal ellipsoids were plotted with the SHELXL-97 program at 50% probability. The molecular structure is shown in Figure 1. Selected crystal data and structure refinement details are presented in Table 2. Selected bond distances and angles are listed in Table 3.

CCDC 774536 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk.

Table 2. Crystal data and structure refinement for C$_{14}$H$_9$Cl$_2$F$_3$N$_4$O.

| Property                        | Value                                      |
|---------------------------------|--------------------------------------------|
| Empirical formula               | C$_{14}$H$_9$Cl$_2$F$_3$N$_4$O              |
| Formula weight                  | 377.15                                     |
| Temperature                     | 298(2) K                                   |
| Wavelength                      | 0.71073 Å                                  |
| Crystal system                  | Monoclinic                                 |
| space group                     | P 2/n                                      |
| Unit cell dimensions            | a = 13.468(4) Å, alpha = 90 deg.           |
|                                | b = 8.234(3) Å, beta = 112.056(6) deg.     |
|                                | c = 15.047(5) Å, gamma = 90 deg            |
| Volume                          | 1546.4(9) Å$^3$                            |
| Z                               | 4                                          |
| Absorption coefficient          | 0.463 mm$^{-1}$                            |
| F(000)                          | 760                                        |
| Theta range for data collection | 2.47° to 25.02°                            |
| Limiting indices                | -16<=h<=15, -9<=k<=9, -17<=l<=14            |
| Reflections collected / unique  | 7730 / 2740 [R(int) = 0.0213]              |
| Completeness to theta = 25.02   | 99.6%                                      |
| Absorption correction           | Semi-empirical from equivalents            |
| Max. and min. transmission      | 0.9214 and 0.8154                          |
| Refinement method               | Full-matrix least-squares on F$^2$         |
| Data / restraints / parameters  | 2740 / 0 / 218                             |
| Goodness-of-fit on F$^2$         | 1.142                                      |
| Final R indices [I>2sigma(I)]   | R1 = 0.0866, wR2 = 0.2087                   |
| R indices (all data)            | R1 = 0.0945, wR2 = 0.2142                  |
| Largest diff. peak and hole     | 0.660 and -0.897 e.Å$^3$                   |
Table 3. Selected bond distances (Å) and angles (°) for compound 2c.

| Bond Distance/Angle | Value |
|---------------------|-------|
| F(1)-C(1)           | 1.341(6) |
| O(1)-C(10)          | 1.236(5) |
| N(1)-C(11)          | 1.369(6) |
| N(2)-C(12)          | 1.355(6) |
| C(1)-C(2)           | 1.504(7) |
| C(6)-C(7)           | 1.377(7) |
| C(11)-N(1)-C(10)    | 125.1(4) |
| C(8)-N(3)-C(9)      | 110.2(4) |
| C(12)-N(4)-C(5)     | 127.9(4) |
| C(7)-C(2)-C(3)      | 120.3(4) |
| C(4)-C(3)-C(2)      | 119.8(4) |
| C(12)-C(9)-C(10)    | 117.6(4) |
| N(3)-N(1)-C(11)     | 123.9(4) |

4. Conclusions

In summary, we have successfully developed a simple and efficient method for the synthesis of variously functionalized pyrazolo[3,4-d]pyrimidin-4-ones by heteroannulation under mild conditions using POCl₃. This works has been patented [17]. Further heteroannulation studies are underway in our laboratory.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant No. 20972114), the Natural Science Foundation of Zhejiang Province (grant No. Y407079 and Y4080027), and the Foundation of Science and Technology Department of Zhejiang Province (No. 2007C21116).

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Sample Availability: Samples of the compounds 2a-j are available from the authors.