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A one step synthesis of 1-alkylpyrazolo[5,4-*d*]pyrimidines

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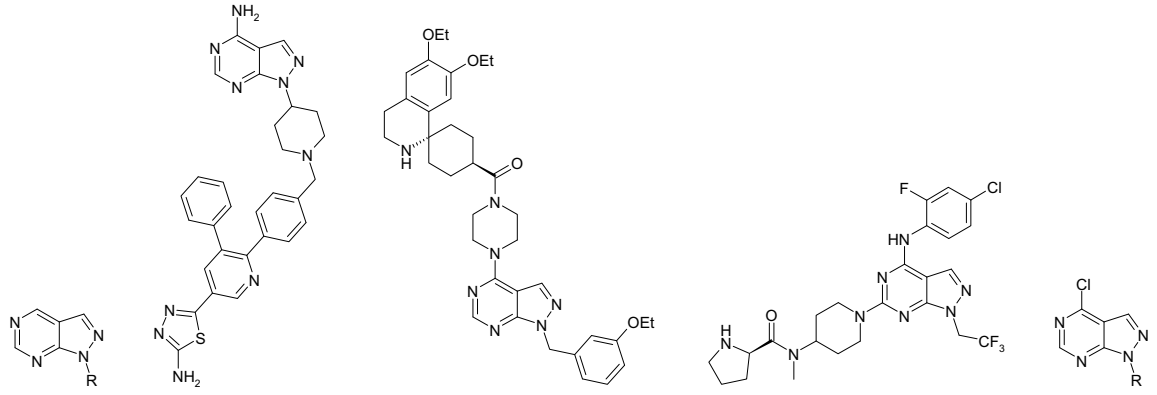
ABSTRACT

A new synthesis of 1-alkylpyrazolo[5,4-*d*]pyrimidines is described. The reaction of 4,6-dichloropyrimidine-5-carbaldehyde with various substituted hydrazines provides such compounds in a single step from commercially available starting materials. This method has advantages over methods currently described in the literature for the construction of such ring systems.

1-Alkylpyrazolo[5,4-*d*]pyrimidines **1** (Fig. 1) are an important class of compounds for the pharmaceutical industry. Such substructures are found in compounds spanning a range of biological activity from kinase inhibitors such as **2**[1] to ion channel blockers such as **3**[2] and receptor antagonists such as **4**.[3] As part of a campaign to develop libraries based on this template, we had cause to investigate the synthesis of chloro-substituted derivatives such as **5** substituted with a range of different alkyl and aryl groups at the 1-position with the 1-substituent originating from the appropriately substituted hydrazine.

Perhaps the most common method for the preparation of such systems reported in the literature is the stepwise condensation of the hydrazine with a 2-alkoxy-1,1-dicyanoalkene[4] or equivalent[5] to obtain the pyrazole derivative, onto which the fused pyrimidine is annulated and chlorinated (Scheme 1). This sequence requires multiple discrete steps, and the conditions involved are incompatible with a number of functional groups, in particular additional nitrile functionality. A more efficient method for achieving such a transformation would be to condense a substituted hydrazine with 4,6-dichloropyrimidine-5-carbaldehyde allowing formation of the desired ring system in a single step. Such a transformation is known for chloroformylpyridines,[6] and condensations of hydrazine itself with such pyrimidinylaldehydes[7] and pyrimidinylketones have been reported,[8,9] and related transformations



1 2 3 4 5

Figure 1.

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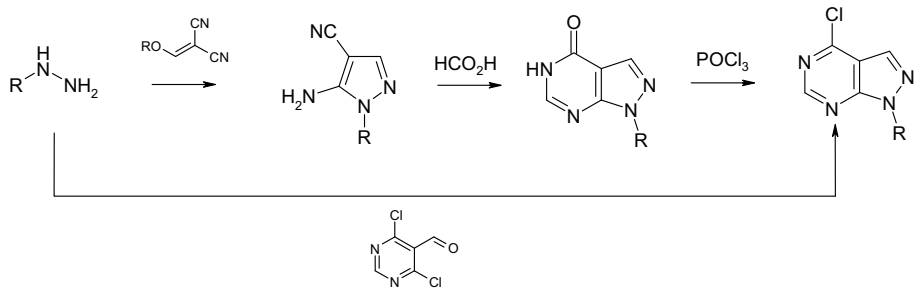


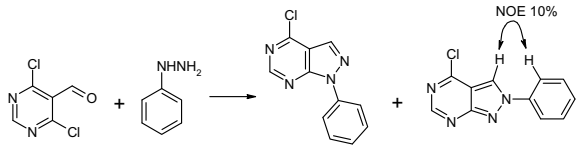
Scheme 1.

have been carried out on solid support to yield pyrimidone products.[10] Such a transformation of 4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde and phenylhydrazine proceeding with concomitant displacement of a second hydrazine molecule to form *N* -[(1,6-diphenyl-7*H*-pyrazolo[4,5-*e*]pyrimidin-4-ylidene)amino]-aniline has been reported.[11]

Hence, the condensation of 4,6-dichloropyrimidine-5-carbaldehyde **6** with phenylhydrazine in the presence or absence of triethylamine as a base was investigated. After a short reaction screening process, it was shown that such a transformation to form 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **7** is indeed possible (Scheme 2),[12] and proceeds more efficiently in the presence of base and in ethereal rather than alcoholic solvents. The regioisomer **8** has also been isolated from the reaction (2:1 ratio) but is readily separable by chromatography. Its identity was established by the observance of an NOE between the phenyl *o*-hydrogen and hydrogen of the pyrazole ring of **8** which is absent in **7**. In addition, the product 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine has been observed to react readily with methanol on dissolution to form the corresponding methyl ether (data not shown) and has been found to be sensitive to adventitious moisture. These factors could contribute to the discrepancy between the measured LC–MS conversion and the isolated yield although the corresponding 1-phenyl-5*H*-pyrazolo[4,5-*e*]pyrimidin-4-one hydrolysis product has not been isolated during chromatography.

Subsequently, it emerged that this reaction can be applied to a range of more diverse hydrazines (Scheme 3). The reaction is applicable to electron-rich aryl- (entry 2) and electron poor heteroaryl (entries 3 and 4) hydrazines as well as a range of alkyl hydrazines (entries 5 to 8) including those with a sterically encumbered nitrogen (entry 8). Additionally, the reaction is compatible with an additional nucleophilic (hydroxyl) functionality (entry 7) albeit with diminished yield. Gratifyingly, the undesired regioisomer akin to **8** was not observed in any of these subsequent transformations.

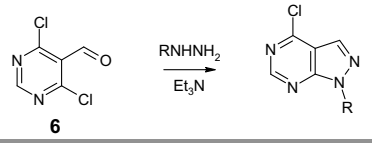
It has been observed that when carrying out this reaction on unpurified commercial 4,6-dichloropyrimidine-5-carbaldehyde,



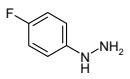
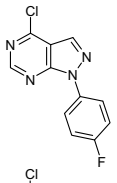
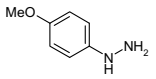
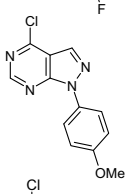
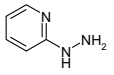
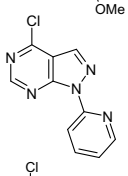
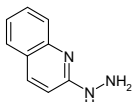
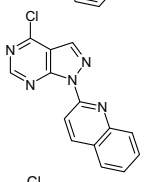
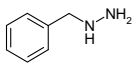
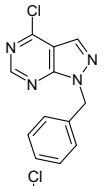
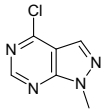
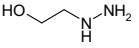
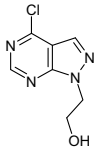
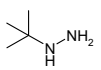
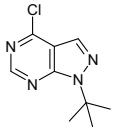
6 **7** **8**

Conditions	LCMS conversion	Isolated yield of **7**
EtOH, Et_3N, 65 °C, 40 min	30%	-
THF, 65 °C, 40 min	40%	-
THF, Et_3N, 65 °C, 40 min	80%	54%[12]

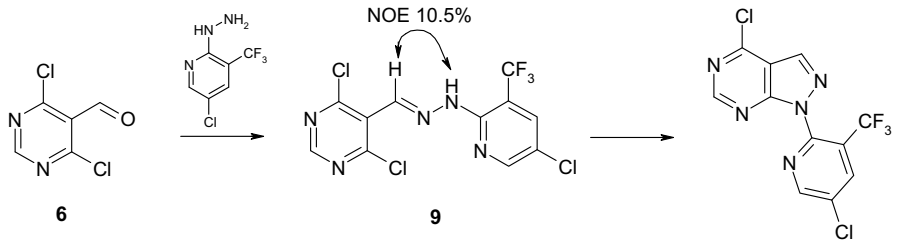
Scheme 2.



6

Entry	Hydrazine	Product	Isolated Yield
1			54%
2			69%
3			53%
4			72%
5			49%
6	$MeNHNH_2$		36%
7			31%
8			51%

Scheme 3.



Scheme 4.

the reaction appears to be sensitive to changes in conditions and, on occasions, failed to proceed to the desired products. The reaction proceeds much more reliably with freshly prepared substrate.[13] In cases where the hydrazine is very electron poor such as (5-chloro-3-methylpyridin-2-yl)hydrazine, (3-methylpyrazin-2-yl)hydrazine and (5-chloropyrimidin-4-yl)hydrazine, the reaction under the above conditions has been observed to halt at the uncyclised species such as **9** (Scheme 4) which is potentially an intermediate en route to the final products. In these cases prolonged heating at higher temperatures can effect the final cyclisation, although, in our hands, we have found this reaction to be capricious. Moreover, it is suggested by NOE studies that **9** exists predominantly in the trans-configuration and presumably this would further disfavour the subsequent cyclisation step.

Nevertheless, in the majority of cases, this methodology allows access in a single step to a diverse range of 1-alkyl-4-chloropyrazolo[3,4-*d*]pyrimidines. Such chloro derivatives are known to undergo a wide range of transformations including nucleophilic displacements[5,14] and palladium couplings,[15] and can also be reduced to the corresponding CH derivatives.[16] Hence, this work represents a new, general method for preparation of the 1-alkylpyrazolo[4,5-*d*]pyrimidine system which has advantages over existing methods.

References and notes

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12. *Representative experimental procedure*: A suspension of 4,6-dichloropyrimidine-5-carbaldehyde (5 g, 28.4 mmol) and phenylhydrazine (31.2 mmol) in anhydrous THF (150 mL) and triethylamine (3.9 mL, 28.4 mmol) was stirred for 10 min at room temperature and then heated to 65 °C for 50 min. The solvent was removed under vacuum and the crude product was purified by flash chromatography on silica to give the product (3.5 g, 54%).
4-Chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, J = 6.8 Hz, 1H), 7.60 (t, J = 6.8 Hz, 2H), 8.22 (d, J = 8.0 Hz, 2H), 8.38 (s, 1H), 8.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 115.38, 121.82, 127.69, 129.59, 133.52, 138.46, 153.10, 155.35, 155.41. IR (KBr) 3110 cm^{-1}. HRMS: m/z calcd for $C_{11}H_8N_4Cl$ (M+H$^+$): 231.0432; found: 231.0434.
4-Chloro-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, J = 8.1 Hz, 2H), 8.17 (d, J = 8.1 Hz, 2H), 8.34 (s, 1H), 8.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.30, 116.36, 116.59, 123.53, 123.61, 133.55, 134.61, 152.98, 155.44, 155.51, 161.73; IR (KBr) 3061, 3086, 3108 cm^{-1}; HRMS: m/z calcd for $C_{11}H_7N_4ClF$ (M+H$^+$): 249.0338; found: 249.0343.
4-Chloro-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.07 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 8.32 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.61, 114.52, 114.82, 123.36, 131.36, 132.86, 152.51, 155.03, 155.12, 158.89; IR (KBr) 2973, 2940, 2841 cm^{-1}; HRMS: m/z calcd for $C_{12}H_{10}ON_4Cl$ (M+H$^+$): 261.0538; found: 261.0532.
4-Chloro-1-pyridin-2-yl-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 6.9 Hz, 1H), 7.93 (t, J = 8.4 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 4.8 Hz, 1H), 8.84 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.29, 115.48, 122.40, 125.05, 139.93, 148.99, 150.87, 155.58, 156.21, 158.52; IR (KBr) 3149 cm^{-1}; HRMS: m/z calcd for $C_{10}H_7N_5Cl$ (M+H$^+$): 232.0384; found: 232.0378.
2-(4-Chloro-pyrazolo[3,4-d]pyrimidin-1-yl)-quinoline: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H) 8.06 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 8.7 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.86 (s, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.87, 112.98, 126.06, 127.47, 127.90, 128.59, 128.66, 131.52, 140.86, 146.13, 149.02, 149.39, 158.95, 160.29; IR (KBr) 3088, 3111 cm^{-1}; HRMS: m/z calcd for $C_{14}H_9N_5Cl$ (M+H$^+$): 282.0541; found: 282.0544.
1-Benzyl-4-chloro-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 2H), 7.39 (m, 5H), 8.20 (s, 1H), 8.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 51.51, 113.76, 128.16, 128.29, 128.81, 132.38, 135.54, 153.10, 154.70, 154.85; IR (KBr) 2850, 2920, 2978, 3007, 3030, 3063, 3099 cm^{-1}; HRMS: m/z calcd for $C_{12}H_{10}N_4Cl$ (M+H$^+$): 245.0594; found: 245.0589.
4-Chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 3H), 8.18 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.67, 113.61, 131.88, 153.19, 154.52, 154.80; IR (KBr) 2861, 2922, 3102, 3166 cm^{-1}; HRMS: m/z calcd for $C_6H_6N_4Cl$ (M+H$^+$): 169.0276; found: 169.0276.
2-(4-Chloro-pyrazolo[3,4-d]pyrimidin-1-yl)-ethanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (t, J = 5.2 Hz, 2H), 4.69 (t, J = 5.2 Hz, 2H), 8.21 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.76, 61.20, 113.82, 132.36, 153.34, 154.58, 155.18; IR (KBr) 3298, 3097, 2963, 2923, 2880, 2851 cm^{-1}; HRMS: m/z calcd for $C_7H_8ON_4Cl$ (M+H$^+$): 199.0381; found: 199.0383.
1-tert-Butyl-4-chloro-1H-pyrazolo[3,4-d]pyrimidine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 9H), 8.12 (s, 1H), 8.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.41, 61.72, 115.02, 130.49, 153.00, 153.32, 154.78; IR (KBr) 2875, 2935, 2983, 3046, 3108 cm^{-1}; HRMS: m/z calcd for $C_9H_{12}N_4Cl$ (M+H$^+$): 211.0745; found: 211.0743.
13. Prepared according to: Klötzer, W.; Herberz, M. *Monatsh. Chem.* **1965**, *96*, 1567–1572. Material prepared in this way is a colourless crystalline solid. Commercial material has been observed to be coloured. The commercial material can be purified by flash chromatography prior to reaction to give similar results to freshly prepared substrate.
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