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A novel synthesis of substituted 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones

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Abstract—A novel synthesis of 4*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ones is described. This approach utilizes an in situ generated imino-chloride as a key precursor for amidine formation, with subsequent base-catalyzed ring closure. This method represents a mild and efficient entry into this ring system which is amenable to diversification of the core template.
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Several reports have demonstrated the utility of 4*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ones as inhibitor templates of various biological targets.[1] Along those lines, we have become interested in the design and synthesis of such scaffolds, seeking an approach that would allow diversification of the pyrimidinone three-position in the presence of a 2-aminomethyl moiety was of particular interest. We found several literature accounts detailing the synthesis of these or related 6,5-fused heterocycles with the desired substitution pattern.[1–4] Our initial approach was envisaged to proceed through an oxazinone intermediate (**3**), generated from 5-(acetylamino)-carboxylate precursor **2** (Fig. 1).[2] Subsequent opening of the oxazinone with an amine,[3] and base induced cyclization[4] was predicted to furnish the desired pyrazolo-pyrimidinone ring system **5**.

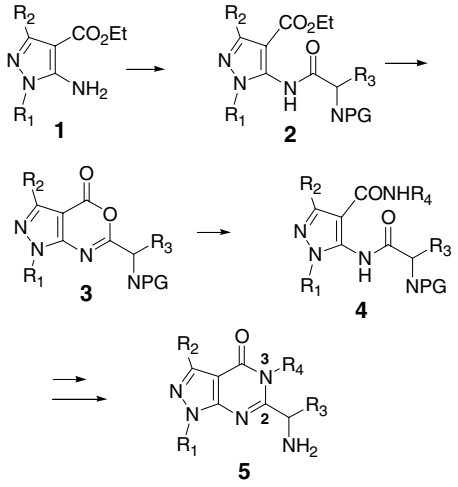

Figure 1.

Our synthetic efforts commenced with acylation of commercially available ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate (**6**) by racemic *N*-phthalyl valine acid chloride **7**[5] under thermal conditions (Scheme 1). Several solvents (CH_2Cl_2, 1,2-dichloroethane, DMF, PhH, toluene) and bases (TEA, *i*-Pr_2NEt, pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene) were employed initially, however portionwise addition of acid chloride **7** (1.0 equiv) to amine **6** (1.0 equiv) in refluxing toluene in the presence of *i*-Pr_2NEt (2.0 equiv) was found to be optimal, providing amide **8** in high yield. We surmized that these somewhat forcing acylation conditions were required due to the 5-amino group being a vinylogous amide with the potential to internally hydrogen bond to the ethyl ester. At this stage, intramolecular cyclization of ester–amide **8** to the oxazinone was investigated. Accordingly, treatment of amide **8** with hexachloroethane and triphenylphosphine in refluxing 1,2-dichloroethane in the presence of *i*-Pr_2NEt furnished crude oxazinone **9** as a white solid after concentration of the reaction mixture.[2] Opening of the oxazinone ring was then attempted in order to provide the requisite pyrimidinone precursor. Unfortunately, treatment of oxazinone **9** with benzylamine under thermal conditions

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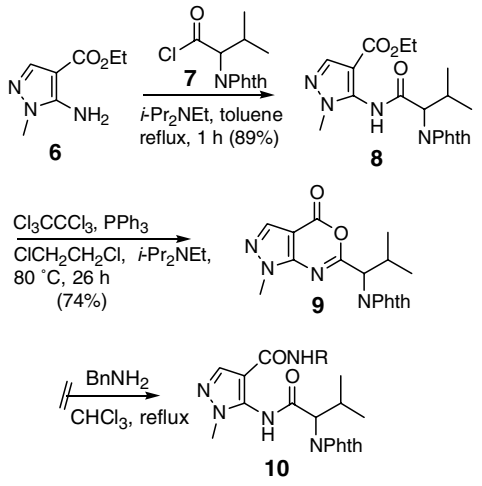
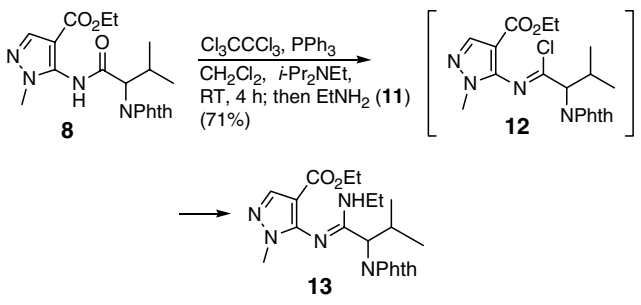


Scheme 1.

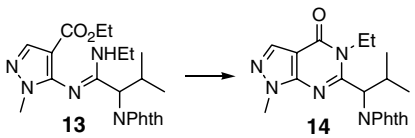
led to an intractable mixture of products, and was thought to be a result of incompatibility of the nucleophile with the phthalimide group. Use of a *tert*-butoxycarbonyl (Boc) or a benzyloxycarbonyl (Cbz) as an alternative protecting group was not pursued since *N*-(oxycarbonyl)amino acid chlorides have the propensity to undergo facile intramolecular cyclization to the corresponding Leuch anhydrides.[6] Furthermore, even if opening the oxazinone with amines proved feasible, the typical strongly basic conditions (excess NaOH, ethylene glycol, reflux) required for the dehydrative cyclization may have also proved incompatible with the phthalimide group.[4,7] For these reasons, an alternate approach was pursued.

During the course of these investigations, we observed that treatment of amide **8** with hexachloroethane and triphenylphosphine in dichloromethane at *room temperature*, instead of refluxing dichloroethane (83 °C), resulted in clean conversion to iminochloride intermediate **12**, with no detectable amounts of oxazinone **9** by LCMS and ^{1}H NMR (Scheme 2), indicating that higher temperature was required for oxazinone formation in this system. We reasoned that in situ displacement of the iminochloride with amines should provide an intermediate amidine which could undergo facile cyclization to the desired pyrimidinone ring system. In order to test this hypothesis, iminochloride **12**, generated in situ from amide **8**, was treated with ethylamine at room tempera-



Scheme 2.

Table 1.



Entry	Base[a]	Solvent (T, °C)	Time (h)	Yield (%)
1	No base	Toluene (110)	24	0
2	NaOMe	MeOH (60)	16	0
3	NaOH	Aq MeOH (65)	24	0
4	K_2CO_3	DMF (60)	1	Trace
5	K_2CO_3	DMF (100)	3	65[b]

[a] 1.2 equiv of base employed except entry 3 (0.05 equiv).
[b] Isolated yield after silica gel chromatography.

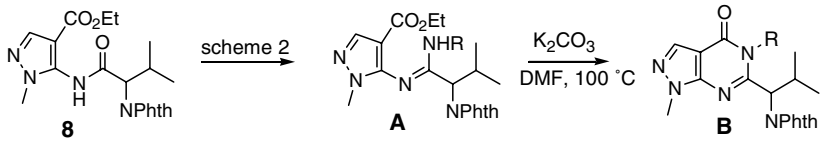
ture. Encouragingly, the chloride displacement took place at room temperature to provide amidine **13** in 71% yield after silica gel chromatography.[8]

With amidine **13** in hand, intramolecular cyclization to form the pyrimidinone ring was explored. Thermal cyclization in refluxing toluene resulted in recovered starting material, while base-mediated cyclization with sodium methoxide or aqueous sodium hydroxide in methanol resulted in the formation of the corresponding methyl ester and carboxylic acid, respectively, with no cyclized product (Table 1).[9] Although reasons for the resistance of amidine **13** to cyclize utilizing sodium methoxide or sodium hydroxide remain unclear, we ultimately found that treatment with 1.2 equiv of potassium carbonate in DMF at 100 °C resulted in clean conversion to pyrimidinone **14** in good yield.[10] It should be noted that high temperature was required for a reasonable reaction time (3 h).

To test further the scope of this sequence, as well as to investigate diversification of the pyrimidinone three-position, reaction of iminochloride **12** with other amines was examined (Table 2). Accordingly, the reaction to prepare the amidine intermediates appears to be fairly general with comparable yields across different types of amines, including aliphatic, propargylic and benzylic. Cyclization of the resultant amidines with potassium carbonate in DMF provided the desired pyrazolopyrimidinones in yields ranging from 63% to 72%.

In summary, a synthesis of 4*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ones has been developed. This novel approach to the core template utilizes an in situ generated iminochloride as a key intermediate for amidine formation, with subsequent base-catalyzed ring closure. The method provides a mild and efficient entry into these ring systems, which is amenable to diversification of the pyrimidinone three-position. Furthermore, elimination of a later stage sequence to incorporate the 2-aminomethyl functionality represents an advantage over the previously reported methods.[4] Although not described herein, this method can be applied to the preparation of related heterofused systems, such as oxazolo- and thiazolopyrimidinones, and these findings will be reported in due course.

Table 2.



Amine	Amidine[a,b] (**A**)	Yield,[c] % (**A**)	Pyrimidinone[b] (**B**)	Yield, % (**B**)
Me, H_2N **11**	CO_2Et, NHEt, NPhth **13**	71	Me, NPhth **14**	65
H_2N **15**	CO_2Et, HN, NPhth **16**	79	NPhth **17**	63
Ph, H_2N **18**	CO_2Et, NHBn, NPhth **19**	84	Ph, NPhth **20**	72

[a] Reaction conditions detailed in Scheme 2 were employed.
[b] All compounds were characterized by ^{1}H NMR, LCMS and provided satisfactory elemental analyses.
[c] Isolated yield after silica gel chromatography.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.043.

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stirred vigorously for 15 min. The precipitated product was collected by vacuum filtration and rinsed with small portions of cold water. Drying of the precipitate to constant weight under high vacuum, provided 291 mg (65%) of 2-[1-(5-ethyl-1-methyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (**14**) as a white powder. R_f 0.42 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.91–7.86 (m, 4H), 5.14 (d, $J = 10.0$ Hz, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.91 (s, 3H), 3.33 (m, 1H), 1.08 (t, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H); LCMS m/z 380.2 (M+1). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.13; H, 5.46; N, 18.43.