ORGANIC LETTERS

2013
Vol. 15, No. 8
1882–1885

Selective Synthesis of 1-Substituted 4-Chloropyrazolo[3,4-*d*]pyrimidines

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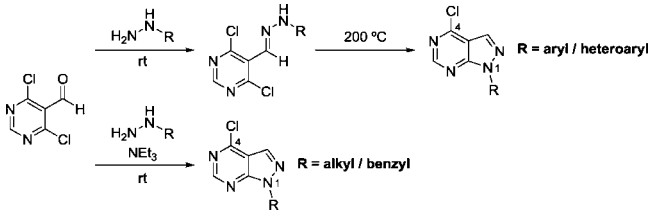
Received February 26, 2013

ABSTRACT



Strategies for carrying out the reaction of 4,6-dichloropyrimidine-5-carboxaldehyde with various hydrazines to generate 1-substituted 4-chloropyrazolo[3,4-*d*]pyrimidines in a selective and high-yielding manner are presented. For aromatic hydrazines, the reaction is performed in the absence of an external base, which promotes exclusive hydrazone formation. The hydrazones subsequently cyclize at an elevated temperature to form the desired pyrazolo[3,4-*d*]pyrimidine products. For aliphatic hydrazines, the reaction sequence proceeds as a single step in the presence of an external base.

Pyrazolo[3,4-*d*]pyrimidines are frequently employed as structural units in drug discovery programs. Compounds containing this structure have been developed for the treatment of Parkinson's disease,[1] as well as various inflammatory and autoimmune diseases.[2] Pyrazolo[3,4-*d*]pyrimidines are also present as a core structure in inhibitors of numerous oncogenic targets.[3] Both the 1- and 4-positions of these subunits have been used as points of structural diversification.

We recently became interested in synthesizing a series of 1-substituted 4-chloropyrazolo[3,4-*d*]pyrimidines. The most efficient known route to obtain these structures involves the direct condensation of commercially available 4,6-dichloropyrimidine-5-carboxaldehyde (**1**) with a substituted hydrazine (**2**) in the presence of an external base (Scheme 1).[4] This procedure can potentially be carried out in a single step. Unfortunately the reaction can generate several products, including hydrazone **3**, 1-substituted pyrazolo[3,4-*d*]pyrimidine **4**, and 2-substituted pyrazolo-[3,4-*d*]pyrimidine **5**. Product mixtures have been observed for similar reactions,[3e,4a] but achieving high selectivity remains a challenge. Herein, we report (1) observations regarding the factors that influence selectivity in the reaction of **1** with **2** and (2) optimized reaction conditions to generate 1-substituted pyrazolo[3,4-*d*]pyrimidine **4** selectively and in high yield.

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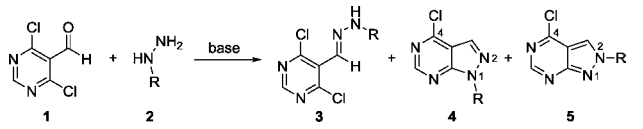
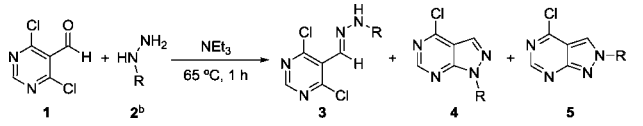
10.1021/ol4005382
Published on Web 04/10/2013

Scheme 1. Direct Condensation of **1** with **2**



Our initial efforts focused on the reaction of **1**[5] with various phenylhydrazines using the conditions reported in the literature (NEt_3, 65 °C, 1 h).[4a] The major products were pyrazolo[3,4-*d*]pyrimidines **4** and **5** (Table 1, entries 1−4). Small quantities of hydrazone **3** were also observed. Electron-rich hydrazines favored the formation of **4** (entry 1), whereas electron-poor hydrazines favored the formation of **5** (entry 4). Performing these reactions without triethylamine led to dramatically different results: hydrazone **3** was almost the sole product (entries 5−8).

Table 1. Initial Reactions of **1** with Phenylhydrazines[a]



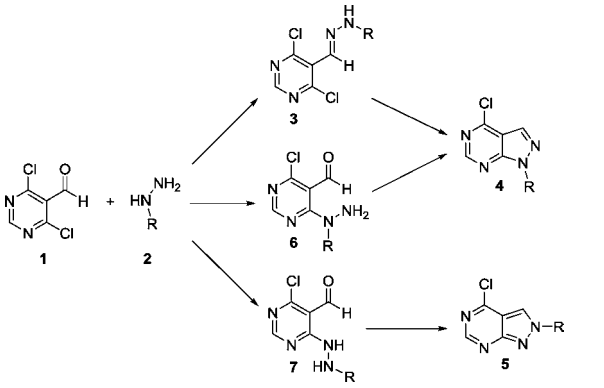
entry	R	NEt_3 (equiv)	**1** (%)[c]	**3** (%)[c]	**4** (%)[c]	**5** (%)[c]
1	4-MeO-C_6H_4 (**a**)	2.1	ND	ND	91	9
2	Ph (**b**)	2.1	ND	2	63	35
3	4-Cl-C_6H_4 (**c**)	2.1	2	7	40	51
4	4-CF_3-C_6H_4 (**d**)	2.1	9	9	8	74
5	4-MeO-C_6H_4 (**a**)	0	3	92	5	ND
6	Ph (**b**)	0	4	96	ND	ND
7	4-Cl-C_6H_4 (**c**)	0	2	98	ND	ND
8	4-CF_3-C_6H_4 (**d**)	0	21	79	ND	ND

[a] 0.2 M in THF, 1.05 equiv of **2**, 0.3−0.6 mmol scale. [b] HCl salt. [c] Determined from relative ^1H NMR ratios in the crude reaction mixture. ND = not detected.

Scheme 2 illustrates the various pathways through which the reaction of **1** with **2** can proceed. Selectivity issues arise due to the presence of two different electrophilic sites on **1** and two different nucleophilic sites on **2**. Three intermediates are possible: **3**, **6**, and **7**. Initial condensation with the aldehyde moiety of **1** can only proceed with the external nitrogen of **2**, generating **3**, which then can cyclize to form **4**. Initial displacement of the chloro substituent of **1**, on the other hand, can occur with either nitrogen of **2**, generating both **6** and **7**, which in turn form **4** and **5**, respectively. Entries 5−8 of Table 1 suggest that **3** does not readily cyclize to form **4** at 65 °C in the absence of an external base. Formation of **4** did readily occur when an external base was used (entries 1−3). To provide insight into the pathway through which **4** formed in these cases, hydrazone **3a** was resubjected to the reaction conditions (Scheme 3).[6] Cyclization to form **4a** was not observed. This result indicates that, at 65 °C in the presence of an external base, **4** arises from intermediate **6**, rather than through hydrazone **3**. Although **3** can form under these conditions (Table 1, entries 2−4), it does not cyclize.

These observations suggest that the reaction conditions have a significant impact on selectivity. Use of an external base favors the initial displacement of the chloro substituent of **1**, which inherently leads to product mixtures. In the absence of an external base, however, **2** preferentially undergoes initial condensation with the aldehyde moiety of **1**, allowing only the **1** → **3** → **4** pathway to proceed. Thus we postulated that **4** could be selectively synthesized by performing the condensation reaction in the absence of an external base, which would quantitatively form **3**. A subsequent cyclization reaction would then generate **4**.

Scheme 2. Possible Reaction Pathways

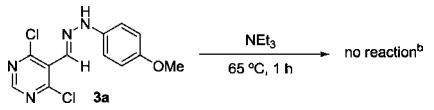


Our next task was to optimize the synthesis and isolation of hydrazone **3**. Having established reaction conditions to generate **3** selectively at 65 °C (Table 1, entries 5−8), we screened additional solvents at rt. Nucleophilic solvents such as isopropanol were not compatible with **1**, as they readily displaced its chloro substituents. The conversion of **1** into **3** did proceed cleanly in THF, dioxane, acetonitrile, acetic acid, and DMF. The reaction was the most efficient in DMF, exhibiting essentially quantitative conversion within 2 h. Either the free base or the HCl salt of **2** was a viable starting material, but for electron-poor hydrazines such as **2d**, reactions involving the HCl salt progressed more slowly. Adding cold aqueous sodium bicarbonate to the crude reaction mixture and filtering the resultant precipitate led to the isolation of **3**. Purification via column chromatography was not necessary. Table 2 shows the conversion of **1** into a variety of aromatic hydrazones (**3a**−**n**) using our optimized reaction conditions. The reaction worked efficiently for electron-rich substrates (entries 1 and 5−6), electron-poor substrates (entries 3−4 and 8−10), sterically hindered substrates (entries 5, 8, and 11), and heteroaromatic substrates (entries 12−14).

(5) **1** was unstable at rt for extended time periods. Commercially purchased **1** was initially purified and stored in the refrigerator. See the Supporting Information for further details.

(6) To fully mimic the original reaction conditions, HCl (1.05 equiv) was added, since **2a** was an HCl salt. H_2O (1 equiv) was also added, since formation of **3a** generated 1 equiv of H_2O.

Scheme 3. Resubjection of **3a** to Original Reaction Conditions[a]



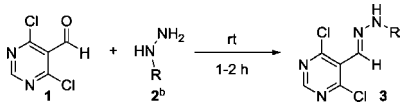
[a] 0.2 M in THF, 2.1 equiv of NEt_3, 1.05 equiv of HCl, 1 equiv of H_2O, 0.3 mmol scale. [b] Only **3a** was detected in the crude reaction mixture by ^1H NMR.

With hydrazones **3a**–**n** in hand, we needed to find reaction conditions under which they would efficiently cyclize to form **4a**–**n**. Hydrazones such as **3** tend to resist cyclization, presumably because they exist in the *E*-configuration.[4a,7] Heating at elevated temperatures can sometimes facilitate the process.[4a,8] Cyclizations that have been reported in the literature for other heterocyclic systems generally involved heating the substrates under neat reaction conditions or in polar solvents (e.g., water, alcohols).[8] Unfortunately these reaction conditions are not compatible with pyrazolo[3,4-*d*]pyrimidine **4**, due to its highly labile chloro substituent. We found, however, that heating **3a**–**n** at 200 °C, in solvents such as THF, dioxane, or acetonitrile, led to quantitative cyclization to form **4a**–**n** within 20 min (Table 3).[9] Both microwave and conventional heating (sealed tube) were evaluated, and no difference was observed between the two methods in terms of the reaction efficiency. Dioxane was utilized as the solvent for reactions involving conventional heating, due to its higher boiling point. Acetonitrile, on the other hand, was the preferred solvent for the microwave reactions because it reached 200 °C more readily in our microwave reactor compared to THF or dioxane. Pyrazolo[3,4-*d*]-pyrimidine products **4a**–**n** were isolated by adding cold aqueous sodium bicarbonate and filtering the resultant precipitate. Purification via column chromatography was again not necessary.

Finally, we investigated the reaction of **1** with aliphatic hydrazines. Unlike the aromatic hydrazines (Table 1, entries 1–4), these substrates selectively generated **4** in high yield in the presence of an external base (Table 4).[10] Essentially quantitative conversion to **4** was observed within 1 h at rt, and isomeric product **5** was not detected. The products (**4o**–**s**) were cleanly isolated after an aqueous workup without the use of column chromatography. We obtained significantly higher isolated yields than those reported in the literature for the corresponding reactions to form **4p**, **4q**, and **4s** carried out at 65 °C.[4a] We suspect that, in the case of aliphatic substrates, some decomposition of **4** occurs at elevated temperatures, which could account for the higher yields observed in our studies.[11]

The difference in product selectivity between aliphatic and aromatic hydrazines in the presence of an external base is striking. Aliphatic substrates selectively generate **4** (Table 4), whereas aromatic substrates generate mixtures of **3**, **4**, and **5** (Table 1, entries 1–4). We attribute this observation to the difference in reactivity between the nitrogen atoms of **2**. For the aliphatic hydrazines, the internal nitrogen is likely more nucleophilic than the external nitrogen. It has been previously observed that the internal nitrogen of methylhydrazine (**2p**) is more nucleophilic than the external nitrogen.[12] This increased reactivity of the internal nitrogen ensures that the **1**→**6**→**4** pathway (Scheme 2) will predominate in reactions involving aliphatic hydrazines.

Table 2. Optimized Conversion of **1** into **3**[a]



entry	R	isolated yield (%)
1	4-MeO-C_6H_4 (**a**)	87
2	Ph (**b**)	97
3	4-Cl-C_6H_4 (**c**)	93
4	4-CF_3-C_6H_4 (**d**)[c]	99
5	2-MeO-C_6H_4 (**e**)	93
6	4-Me-C_6H_4 (**f**)	92
7	4-F-C_6H_4 (**g**)	94
8	2-Cl-C_6H_4 (**h**)	92
9	3-Cl-C_6H_4 (**i**)	89
10	4-Br-C_6H_4 (**j**)	96
11	1-naphthyl (**k**)	92
12	2-pyridyl (**l**)[d]	85
13	2-quinoxalyl (**m**)[d]	88
14	2-benzo[*d*]oxazolyl (**n**)[d]	91

[a] 0.3–1 M in DMF, 1.05 equiv of **1**, 0.5–3 mmol scale. [b] HCl salt unless otherwise noted. [c] Free base of **2** was used. [d] Bis-HCl salt of **2** was generated *in situ* using 4 M HCl in dioxane (2 equiv).

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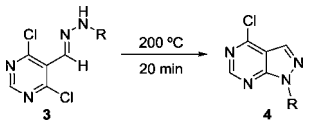
(9) We also attempted to perform the reaction sequence illustrated in Tables 2 and 3 as a one-pot procedure by heating a mixture of **1** and **2** at 200 °C for 20 min. Selective formation of **4** was observed. However, a significant amount of **4** decomposed via chloride hydrolysis, presumably due to the water that was generated *in situ*. Further optimization of this one-pot process is currently underway.

(10) We also investigated the corresponding reactions of **2p**–**s** in the absence of an external base. In cases where **2** was an HCl salt (**2r**–**s**), exclusive formation of hydrazone **3** was observed. When **2** was used in its free base form (**2p**–**q**), a mixture of **1** and **4** (ca. 1:2) was observed, as well as several unidentified minor byproducts. When 2.1 equiv of **2p**–**q** were used instead of 1.05 equiv, **4** formed quantitatively. In the latter case **2p**–**q** presumably functioned as the external base, thus leading to similar results as those obtained in Table 4.

(11) Another possible explanation is that the isolated yields reported in ref 4a were obtained after silica gel chromatography, whereas those reported in Table 4 were not. We observed that the products shown in Table 4 were partially unstable to silica gel chromatography, observing an approximately 25% loss of material when this purification method was attempted.

(12) Nigst, T. A.; Antipova, A.; Mayr, H. *J. Org. Chem*. **2012**, *77*, 8142–8155.

Table 3. Optimized Cyclization of **3** to Form **4**[a]



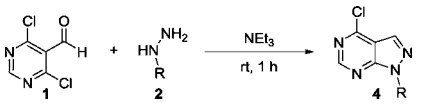
entry	R	isolated yield (%)
1	4-MeO-C_6H_4 (**a**)	97
2	Ph (**b**)	91
3	4-Cl-C_6H_4 (**c**)	97
4	4-CF_3-C_6H_4(**d**)	96
5	2-MeO-C_6H_4 (**e**)	85
6	4-Me-C_6H_4 (**f**)	98
7	4-F-C_6H_4 (**g**)	99
8	2-Cl-C_6H_4 (**h**)[b]	94
9	3-Cl-C_6H_4 (**i**)	92
10	4-Br-C_6H_4 (**j**)	86
11	1-naphthyl (**k**)	92
12	2-pyridyl (**l**)[c]	90
13	2-quinoxalyl (**m**)	92
14	2-benzo[*d*]oxazolyl (**n**)	92

[a] 0.5 M in CH_3CN using microwave heating (entries 1–4) or 0.5 M in dioxane using conventional heating in a sealed tube (entries 5–14), 0.5 mmol scale. [b] 40-min reaction time. [c] **4** was isolated as the HCl salt.

With aromatic hydrazines, on the other hand, we suggest that the two nitrogens of **2** react in a more competitive fashion, and thus product mixtures arise when an external base is present. Product selectivity becomes highly sensitive to the substrate's electronic properties. Electron-rich hydrazines such as **2a** behave more similarly to the aliphatic hydrazines, favoring initial chloride displacement by the internal nitrogen (Table 1, entry 1). With electron-poor hydrazines such as **2d**, however, the external nitrogen becomes the preferred site for initial chloride displacement, and the product distribution reverses (Table 1, entry 4). Thus for aromatic hydrazines, the most general strategy for attaining selectivity is to perform the reactions in the absence of an external base, which favors the initial condensation of **2** with the aldehyde moiety of **1** (i.e., favors the **1**→**3**→**4** pathway in Scheme 2). The above discussions provide a rationale to explain our observations, which can serve as a predictive model for other systems. However, further mechanistic studies are required in order to more fully determine the operative reaction pathways.

In summary, we have developed efficient procedures to selectively convert 4,6-dichloropyrimidine-5-carboxaldehyde (**1**) and various hydrazines (**2**) into 1-substituted 4-chloropyrazolo[3,4-*d*]pyrimidines (**4**), using either aromatic

Table 4. Reaction of **1** with Aliphatic Hydrazines[a]



entry	R	NEt_3 (equiv)	isolated yield (%)
1	H (**o**)	1	74
2	Me (**p**)[b]	1	92
3	CH_2CH_2OH (**q**)	1	81
4	cyclohexyl (**r**)[c]	2	84
5	benzyl (**s**)[d]	3	95

[a] 0.3–0.8 M in THF, 1.05 equiv of **2**, 0.5–0.8 mmol scale. [b] Diisopropylethylamine was used instead of NEt_3. [c] HCl salt of **2** was used. [d] Bis-HCl salt of **2** was used.

or aliphatic hydrazines. Each type of hydrazine has its own optimal set of conditions under which **4** will form selectively. For aromatic substrates, selectivity is achieved by utilizing a two-step procedure carried out in the absence of an external base, which preferentially promotes the initial condensation reaction of **2** with the aldehyde moiety of **1**. For aliphatic substrates, selectivity can be attained through a single-step reaction performed in the presence of an external base. Initial displacement of the chloro substituent of **1** is favored, but the greater nucleophilicity of the internal nitrogen of **2** ensures selectivity. This chemistry can thus be used to rapidly generate a structurally diverse array of 1-substituted 4-chloropyrazolo[3,4-*d*]pyrimidines (**4**) in a selective and high-yielding manner. In addition, the highly reactive 4-chloro substituent of **4** is preserved throughout all of the reactions reported herein. These 4-chloropyrazolo[3,4-*d*]pyrimidine substrates are therefore poised to readily undergo further diversification through substitution reactions at the 4-position.

Acknowledgment. The authors wish to thank Dr. Joseph M. Colacino (PTC Therapeutics, Inc.), Dr. Ramil Baiazitov (PTC Therapeutics, Inc.), and Prof. Scott E. Denmark (University of Illinois, Urbana–Champaign) for helpful discussions and Jane Yang (PTC Therapeutics, Inc.) for analytical support.

Supporting Information Available. Experimental details and characterization data for compounds **3a**–**n** and **4a**–**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.