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ScienceDirect
Tetrahedron Letters 49 (2008) 102–105
Tetrahedron Letters

A chemoselective aniline–chloropyrimidine coupling in a competing electrophilic environment

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Received 21 September 2007; revised 30 October 2007; accepted 1 November 2007
Available online 6 November 2007

Abstract—A highly chemoselective substitution on 4-amino-6-chloropyrimidine ring system having a competing aldehyde functionality has been realized with anilines which produces 4, 6-diaminopyrimidine-5-carbaldehyde in high yield. The reaction may involve the intermediacy of imines. A variety of aromatic amines participate in this reaction successfully to generate diaminopyrimidine aldehydes in moderate to high yield.

The chemistry of pyrimidines is one of the most widely studied subjects because of the occurrence of such heterocycles in biologically relevant systems such as nucleic acids, cofactors, various toxins, and other products.[1,2] Substituted pyrimidines, particularly with 2,4-diamino or 2,4,6-triamino substitution are known pharmacophores in several structure-based drug design approaches in medicinal chemistry.[3] Their inherent shape and hydrogen bonding capability makes this heterocyclic motif suitable for interaction with many biological targets. Therefore, extensive work has been done in this area to gain control over the sequential introduction of amino functionalities on the pyrimidine templates by using the readily available corresponding halopyrimidines as electrophiles.[4] It has been well established that for both catalytic (palladium mediated) and non-catalytic methods, the order of nucleophilic attack on the pyrimidine template occurs in the following order: C4/C6 > C2 ≫ C5.[1,2] However, to our knowledge, there is no systematic study regarding such nucleophilic displacements in the presence of other appended electrophilic centers, such as an aldehyde group (Fig. 1).

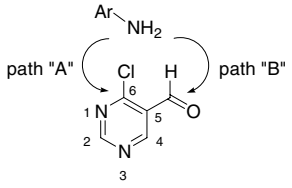
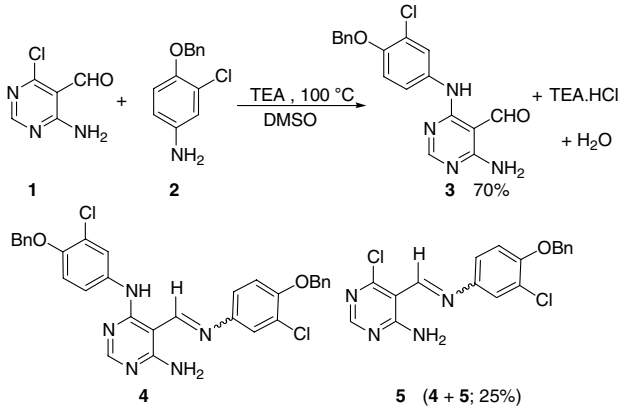


Figure 1. Pyrimidine with competing electrophilic sites.

We were very much interested in preparing 4-amino-6-(4-benzyloxy-3-chloro-phenylamino)-pyrimidine-5-carbaldehyde (**3**) via a chemoselective coupling involving 3-chloro-4-benzyloxyaniline (**2**) and 4-amino-6-chloropyrimidine-5-carbaldehyde (**1**). Early work within our laboratories called for reacting the chloropyrimidine (**1**) with benzyloxyaniline (**2**) in DMSO at 100 °C in the presence of triethylamine (TEA) (Scheme 1).[5]



Scheme 1.

Keywords: Chloropyrimidine; Acid catalyzed coupling; Diaminopyrimidines.
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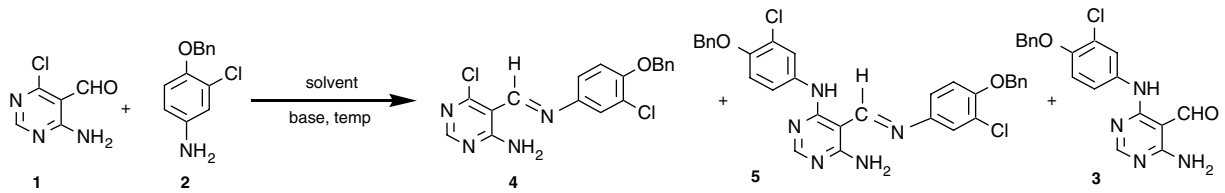
doi:10.1016/j.tetlet.2007.11.009

Table 1. A study toward chemoselective chloropyrimidine aldehyde–aniline coupling[a]



1 2 4 5 3

Entry	Solvent	TEA (equiv)	1	2	4	5	3
1	THF	2	54.0	31.3	1.3	2.9	10.5
2	2-Me-THF	2	56.3	31.9	1.4	1.3	9.1
3	ACN	2	46.3	26.7	0.6	7.6	18.7
4	Acetone	2	51.8	29.2	0.8	5.6	12.6
5	DMF	2	30.0	16.0	1.8	4.7	47.0
6[b]	NMP	2	11.2	34.4	1.6	2.9	49.8
7	MeOH	2	—[c]	10.2	0.9	1.0	70.4
8	1-Propanol	2	6.7	5.0	2.3	4.1	81.9
9	IPA	2	9.5	4.6	0.6	1.7	83.5
10	IPA	—	37.4	14.4	5.4	26.1	16.6
	IPA/H_2O	—	0.7	3.0	nd	11.0	85.3
	IPA/H_2O/HCl	—	nd	1.0	nd	0.7	98.2
11	2-Methoxyethanol/H_2O/HCl	—	0.4	1.6	0.3	nd	94.0[d]
12	ACN/H_2O/HCl	—	1.17	0.63	0.5	nd	98.0

[a] Reactions were carried out using 1 mmol of **1** and 1 mmol of **2**. For the base mediated reactions the reaction mixture was analyzed after 2.5 h at ~65 °C by HPLC and the area% to determine the composition of the mixture at 230 nm. The geometry of the imines has not been determined; the HPLC area% represents the mixture of imines (**4** and **5**).

[b] The reviewer wanted to know if resubmission of product mixture from entry 6 to conditions in entry 12 leads to an improved product distribution? Accordingly the reaction was performed in NMP for the indicated time, the solvent was removed in high vacuum (1 mm/Hg), then the resulting mixture was subjected to conditions of entry 12 as per the suggestion of the reviewer. The product distribution of entry 6 changed to 5.9, 0.5, 59.6, 0.3 and 33.6 (**1**, **2**, **4**, **5**, **3**). Further addition of 0.1 mL of H_2O and 0.1 mL of 6 N HCl resulted in substantial hydrolysis of chloropyrimidine (10.2%), 3.5% and 86.0% (**4** and **3**).

[c] **1** gets converted to methoxy amino pyrimidine (17.4%).

[d] 3.5% of the hydroxy pyrimidine resulted from the hydrolysis of the chloropyrimidinealdehyde.

The rationale for using TEA was to neutralize the HCl generated during the displacement and thus prevent any possible acid catalyzed imine formation producing imines **4** and **5**.[6] Despite this, significant amounts of these imine by-products were formed and were difficult to remove. The isolated pyrimidine carbaldehyde **3** was contaminated with up to 25% of undesired imines. We considered addressing this poor chemoselectivity using a conventional protection/deprotection sequence, but instead believed that careful choice and control of the reaction conditions could lead to a selective preparation of **3**.

Thus we briefly screened the coupling reaction of 4-amino-6-chloropyrimidine-5-carbaldehyde (**1**) with 3-chloro-4-benzyloxyaniline (**2**) with and without TEA in a variety of solvents. The results of the study are summarized in Table 1.

The reactions run in THF, 2-methyltetrahydrofuran (2-Me-THF), acetonitrile, and acetone (entries 1–4) in the presence of 2 equiv of TEA returned largely starting materials. Both DMF and NMP (entries 5 and 6) offered a very poor reaction profile with several unidentified small impurities. In general, the alcohols were found to be superior compared to other solvents in the screen leading to moderate to high conversions to product **3**. Reaction in MeOH (entry 7) was found to contain about 17% of methoxy pyrimidine aldehyde, a by-product arising from methanolysis of chloropyrimidine aldehyde. On the other hand, 1-propanol and IPA (entries 8 and 9) resulted in increased conversion to coupled product **3** while producing undetectable levels of alcoholysis by-products. Scaling-up the TEA mediated reaction in IPA resulted in an incomplete reaction. Prolonged heating or addition of more base did not improve the conversion above ~83%. The product was isolated in only 76% yield and was contaminated with imine impurities **4** and **5**. Although IPA in the presence of TEA resulted in an 83% conversion to product, we found that without TEA the coupling led to a complicated reaction mixture consisting of only 16% of desired product **3** and 5% and 26% of imines **4** and **5**, respectively, (entry 10).

We viewed these imine impurities as Schiffs bases arising from the reaction of the substituted aniline with the starting aldehyde **1** or the product aldehyde **3**.[8,9] We rationalized that the nucleophilic displacement of chloropyrimidine with aniline generates HCl and the Schiffs base formation liberates H_2O (Scheme 1). The imines could exist in equilibrium with the starting aldehyde and aniline or with the product and this equilibrium could be affected by the amount of HCl and water in the reaction. We hypothesized that *careful control of this equilibrium could then lead to the exclusive formation of the desired aniline–pyrimidine aldehyde* (Fig. 2).

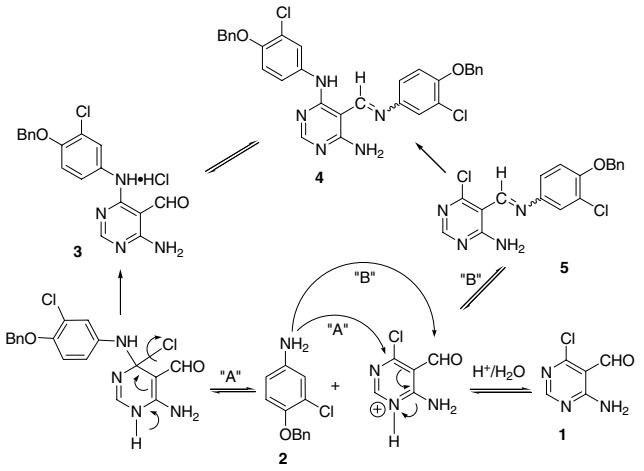


Figure 2. Possible mechanism for the H_2O/H^+ catalyzed aniline–chloropyrimidine coupling.

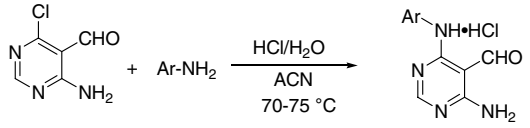
To test this idea we added a small amount of H_2O to this complex mixture (entry 10/IPA–H_2O) and heated to ~75 °C. This operation increased the product to 85% and lowered the imine by-product to 11%. The resulting mixture was heated for several hours but the composition of the reaction mixture did not change. We then added a small amount of aqueous 6 N HCl to the reaction mixture and heated the reaction to 75 °C. We were pleased to find that this addition led to 98% conversion to product.

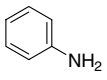
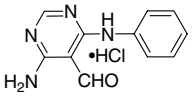
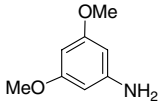
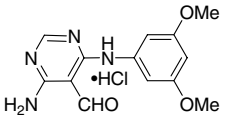
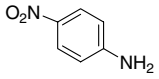
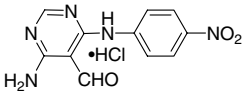
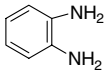
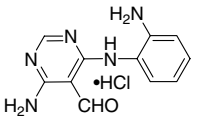
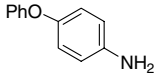
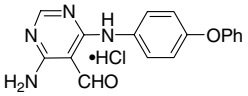
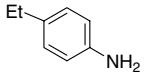
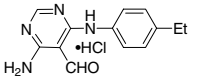
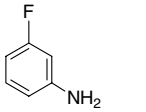
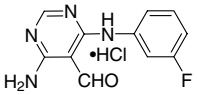
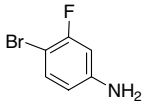
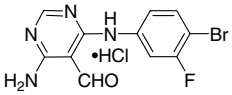
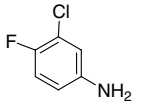
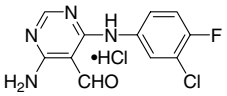
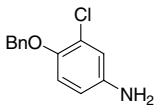
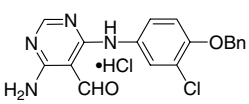
Encouraged by this result we scaled the IPA/H_2O/HCl reaction to 200 g, but the mixture became viscous and stirring was extremely difficult. We tried several variations of the solvent composition but encountered the same problem. We then tested 2-methoxyethanol and acetonitrile (Table 1, entries 11 and 12) under these aqueous acid conditions and found a similar result (~94–98%). It is remarkable that the TEA mediated coupling reaction in acetonitrile (entry 3) largely returned the starting material while the aqueous acid mediated reaction (entry 12) offered exclusively product **3**.

Intrigued by these results, we evaluated the scope of this reaction using a variety of anilines in acetonitrile, the results of which are summarized in Table 2. Several anilines, both electron poor and electron rich, successfully underwent coupling under the described acid catalyzed conditions to offer coupling products in moderate to high yields. The reaction is easily performed by heating the mixture of chloropyrimidine aldehyde **1** and an aniline in acetonitrile with a catalytic amount of aqueous acid for 4–6 h at 70–75 °C. Upon cooling the reaction mixture, the product precipitated and was simply isolated by filtration.[10]

The mechanism of chloropyrimidine displacement has been studied.[7] The leading hypothesis calls for the activation of the chloropyrimidine ring via protonation followed by the addition of a non-protonated amine, which is presumably in equilibrium with its major protonated form. At this point we can only hypothesize what is the reaction pathway of this chemoselective coupling. The product formation is believed to be an intricate interplay of a series of complex equilibria involving reaction pathways 'A and/or B' as shown in Figure 2.

Table 2. Acid catalyzed chemoselective aniline–pyrimidine coupling



Ar-NH_2	Product	Isolated yield[a] (%)
		93
		87
		88
		52
		85
		74
		88
		85
		88
		96

[a] All compounds were characterized by ^1H NMR and mass spectral analysis.

In summary, we have successfully accomplished a chemoselective nucleophilic substitution on a chloropyrimidine aldehyde template to generate diaminopyrimidines while keeping the aldehyde functional group intact and available for further functionalization. A variety of aromatic amines, electron poor and rich, participate in this reaction with almost exclusive chemoselectivity producing coupled products in moderate to high yields. The operational procedure is extremely simple and could be applied to prepare multi-kilo quantities of material.[11]

Acknowledgements

We thank Keith Sampino and Dawei Xu for analytical support. We thank Dr. Terry Hughes (Ref. 6), Dr. Xun Li, Scott Youells and Drs. Ronald Russell and Peter Connolly for helpful discussions.

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6. Personal communication from drug discovery chemists. Reaction of **1** and **2** in DMSO at 100 °C (without using TEA) resulted in 6 min: 12% **3**, 39% **4** and 2% **5**. In 60 min: 10% **3**, 46% **4**, 20% **5** were generated.
7. Successful nucleophilic substitution on pyrimidine ring has been done in alcohols as the solvents (a) Hartung, C. G.; Backes, A. C.; Felber, B.; Missio, A.; Philipp, A. *Tetrahedron* **2006**, *62*, 10055–10064; (b) Maggiolo, A.; Phillips, A. P.; Hitchings, G. H. *J. Am. Chem. Soc.* **1951**, *73*, 106–107.
8. 2,4,6-Trimethoxy-methyl-pyrimidine-5-carbaldehyde reacts with $PhNH_2$ under refluxing ethanol condition to generate the anil (a) Delia, T. J.; Wilcox, T. M.; Otteman, R. R. *J. Heterocycl. Chem* **1979**, *16*, 1647; (b) Benzyliminomethyl 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione is formed from the corresponding pyrimidine aldehyde using $PhNH_2$, EtOH H_2O, TEA, 65 °C, 5 min, 84% yield: Hoffmann-La Roche, Br. Pat. 953,876, 1964; *Chem. Abstr.* **1942**, *61*, 29110 a.
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10. *General experimental*: To a mixture of aniline (1 mmol) and chloropyrimidine aldehyde (**1**, 1 mmol) in acetonitrile (1.4 mL) are added 6 N HCl (15 μL) and H_2O (0.1 mL). The mixture is heated to 70–75 °C and is held at that temperature for ~4–6 h. After cooling naturally to ambient temperature, the product is filtered. The reaction flask is rinsed with 0.5 mL of acetonitrile twice and the rinse is used to wash the filter cake. The filter cake is washed with 0.5 mL of fresh acetonitrile. It is sucked dry under vacuum with nitrogen for 15 min. The product is dried under lab vacuum (25 mm/Hg) at ~50 °C to a constant weight.
11. This result will be communicated separately.