Tetrahedron Letters 54 (2013) 4610–4612

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Selective addition of amines to 5-trifluoromethyl-2,4-dichloropyrimidine induced by Lewis acids

Daniel T. Richter [a,*], John C. Kath [a], Michael J. Luzzio [b], Nandell Keene [b], Martin A. Berliner [b], Matthew D. Wessel [b]

[a] Pfizer Global R&D, 10614 Science Center Drive, La Jolla, CA 92121, United States
[b] Pfizer Global R&D, Eastern Point Road, Groton, CT 06340, United States

ARTICLE INFO

Article history:
Received 17 May 2013
Revised 3 June 2013
Accepted 6 June 2013
Available online 13 June 2013

Keywords:
Dichloropyrimidine
Lewis acid
Addition
Diaminopyrimidine
Selective

ABSTRACT

A variety of 2,4-diamino-pyrimidine systems can be prepared from the corresponding 2,4-dichloropyrimidine by sequential addition of two amines, the first adding selectively to the 4-position. In contrast it was found that 2,4-dichloro-5-trifluoromethyl-pyrimidine yields a 1:1 mixture of the two possible isomers. Lewis acids were employed to increase the ratio of isomers to >10:1 in favor of the 2-addition product. Optimization of the effect of Lewis acid additives on this and other dichloropyrimidine systems will be discussed.

The 2,4-diaminopyrimidine moiety (**1**) plays a critical role in a variety of molecules that display a rich diversity of pharmacological activity. Kinase inhibitors,[1] CRF antagonists,[2] 5HT antagonists,[3] and HIV reverse transcriptase inhibitors[4] are some of the many classes of drugs that contain this structural motif. The synthesis of 2,4-diaminopyrimidines (Fig. 1) commonly starts with the coupling of a pyrimidine intermediate (**2a–f**) and one equivalent of an amine (**3**) It is well documented that for the vast majority of pyrimidines (**2**) and amines (**3**), this first amine addition occurs preferentially (or exclusively) at the more reactive pyrimidine 4-position to provide amino-pyrimidine (**4**).[5] The primary factors that influence the selectivity of this addition are the stereoelectronic effects associated with substituents in both **2** and **3** and to a lesser extent the reaction solvent.[5] Subsequent heating of **4** with a second amine (**5**) provides diaminopyrimidine (**1**).

Interestingly, 5-trifluoromethyl-2-chloro-4-aminopyrimidines prepared from 5-trifluoromethyl-2,4-dichloropyrimidine (**6**), unlike the analogous 5-substituted pyrimidines **2a–f** provided a nearly equivalent mixture of two pyrimidine isomers **7**:**8** as opposed to a >10:1 mixture favoring the more polar 2-chloro-4-aminopyrimidine **8**. While it was possible to separate the mixture of **7**:**8** by reverse phase preparative HPLC, this process was difficult and tedious at best, yielding less than 50% of each regioisomer. This issue coupled with the relatively lower yields of desired isomer obtained severely limits the utility of these intermediates. As exemplified in Table 1, lack of selectivity in the 5-trifluoromethyl series is a surprising anomaly in the reactivity of these heterocyclic systems. When this substitution is desired, this unusual behavior represents a huge hurdle to preparation of compounds of this type.[6] Yields of <50% for the first step of a synthesis are not desirable, especially in a case where the chemistry is traditionally very high yielding and versatile. Therefore a regioselective route for the preparation of these molecules was desired.

Initially minor adjustments to the reaction conditions were investigated using 4-methylaniline as the amine control. A series of reactions were carried out over a temperature range of −78 °C to ambient temperature as well as screening a variety of solvents. Temperature modifications yielded only extended reaction times with no increase in selectivity. Additionally in those cases where the temperature was below 0 °C, reagents became insoluble such that no reaction occurred until the reaction was warmed to room temperature. Results from a solvent screen were equally unproductive. Using a wide range of anhydrous solvents (tetrahydrofuran, 1,2-dichloroethane, *t*-butanol, ether, methylene chloride, acetonitrile, methanol, ethanol, 2-propanol, dioxane, 1,2-dimethoxyethane, toluene, chloroform, ethyl acetate, or a mixture of 1:1 DCE/*t*-butanol) afforded no discernible changes to the reaction results.

Due to the lack of success altering reaction conditions, it became apparent that other means of influencing the selectivity would be necessary. Additives such as protic and Lewis acids

* Corresponding author. Tel.: +1 8586226008.
E-mail address: daniel.richter@pfizer.com (D.T. Richter).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.06.025

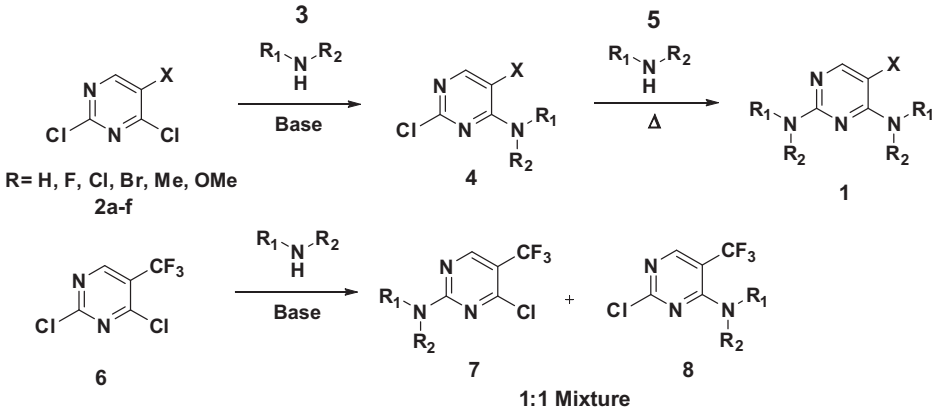


Figure 1. 2,4-Diaminopyrimidine synthesis.

(LA) appeared to be the only viable solution. Initially, protic acids (HCl or Acetic acid) were employed, both as an additive and by preparing amine salts. However, due to the diminished solubility of these salts the reactions were slow or did not occur at all. Upon the addition of base, the reaction would proceed but only give the same 1:1 mixture of isomers observed previously. This result led us to investigate Lewis acids, which also have the potential to coordinate with the nitrogens of the pyrimidine. If coordination occurs to the pyrimidine it was believed to favor substitution at the less sterically hindered C-2 position.

For this initial study, **6** was combined with 1.1 equiv of a commercially available Lewis acid prior to addition of 4-methylaniline (1.0 equiv) followed by the triethylamine base (1.1 equiv). The crude reaction mixtures from this screen were analyzed by HPLC to determine the isomeric ratio of **7** to **8**. Using the original reaction conditions (THF, RT, 1 equiv Et_3N), a screen of 18 readily available Lewis acids was employed ($ZnCl_2$, $Zn(OAc)_2$, BF_3–Et_2O, $Mg(OTf)_2$, $MgCl_2$, $MgBr_2$, CuCl, $CuCl_2$, $SnCl_2$, $SnCl_4$, LiCl, LiOAc, $AgNO_3$, AgOTf, $TiCl_4$, $EtAlCl_2$, DIP-Cl, BCl_3, 1.1 equiv). Initial results offered some small improvements, in particular zinc salts were most effective followed by $CuCl_2$ and AgOTf. $ZnCl_2$ exhibited the best improvement of selectivity with a 4:1 ratio of **7** to **8**. A more detailed investigation involving $ZnCl_2$ as an additive and some minor optimization of reaction conditions provided a 10-fold increase in selectivity from the initial 1:1 ratio seen with no Lewis Acid (Table 2). By switching to a solvent mixture of DCE/*t*-BuOH and allowing the Lewis acid to complex with the amine and pyrimidine before the addition of the base (which eliminated the need for cooling reactions to 0 °C) >10:1 selectivity could be obtained. Comparison of this data with the isomeric ratio of the substitution reaction run in the absence of an additive, provided evidence suggesting that the addition of zinc chloride enhanced the selectivity ratio of **7**:**8** in favor of the less polar isomer **7**. Additionally, these simple changes applied to a wide variety of substituted anilines, including those with electron withdrawing (EWG) and donating groups (EDG), demonstrated that the selectivity in some cases could be increased up to 17:1 (Table 2).

Table 1
Percent isomer ratios for selected pyrimidines reacted with 4-methylaniline

Pyrimidine	X	4-Isomer	2-Isomer
2a	H	95 (49)	5 (51)
2c	CH_3	95 (58)	<5 (28)
2e	Cl	100 (100)	0 (0)
6	CF_3	40 (5)	60 (95)

* Results in parenthesis are with $ZnCl_2$.

While these results were quite exciting there were a few anilines that did not show any changes in selectivity. Most notably, *p*-methoxyaniline gave an 8:1 ratio while *o*-methoxyaniline gave only a 1:1 ratio (Table 2). In this case it was believed that the *o*-methoxy aniline was involved in a chelating effect with the LA such that coordination to the pyrimidine was not occurring. Upon addition of 2 equiv of LA the selectivity increased from 1:1 to 9:1. A similar result was obtained for 4-dimethylaminoaniline which went from 1:1 to 11:1 (Table 2). As a result anilines with any substitution capable of complexing with the zinc or forming a chelate as in the *o*-methoxy case can be added selectively with additional equivalents of LA.

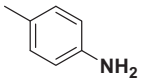
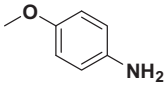
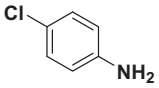
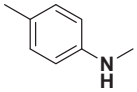
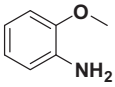
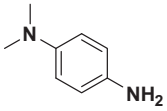
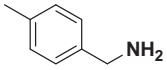
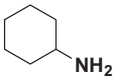
These positive results suggested that the effect could carry over to more nucleophilic alkyl amines which also did not show any increased selectivity with 1 equiv of LA. Because of the increased nucleophilicity of these amines the initial attempts with 1 equiv of $ZnCl_2$ were unsuccessful. With 2 equiv of LA, the complex formed crashes out of solution immediately. However, the reaction takes 24 h to reach completion compared to the typical 2–4 h seen with anilines while the selectivity increased to only 5:1 (Table 2). Yet, this moderate selectivity is quite useful since these analogs can be isolated via crystallization.

Initially it was believed that the Lewis acid was complexing with the pyrimidine and thus directing the chemistry to the less hindered site, however attempts at isolating a pyrimidine/LA complex were unsuccessful and no discernable effects could be seen in the Fluorine NMR when $ZnCl_2$ was present. Since precipitate formed when the two reagents were combined, it was believed that the Lewis acid was instead coordinating with the amine. Since zinc is capable of coordinating with two coordinating nitrogens it was expected that this selectivity would be seen with fewer than 1 equiv of Lewis acid, and that is indeed the case. Increased selectivity was observed with as little as 0.25 equiv of $ZnCl_2$ although optimal results were obtained when sufficient LA was present to moderate the reaction.

With the conditions optimized, it was of interest to see if $ZnCl_2$ could be used to alter the selectivity of additions to other dichloropyrimidines. The results from a small set of pyrimidines showed that 5-H and 5-Me were both shifted from approximately 9:1 to nearly 1:1, 5-Cl experienced no change (see Table 1). This represents an encouraging breakthrough in the chemistry of these systems, as the two isomers formed are easily separable by normal phase chromatography. Other LA may be able to shift the product distribution even more significantly to the typically unfavored isomers.

The addition of Lewis acids, most notably $ZnCl_2$, to amine substitution reactions on 2,4-dichloro-5-trifluoromethylpyrimidine

Table 2
Selectivity of substitution as a result of $ZnCl_2$ addition for various amines

Amine	Ratio of 7:8 (1.0 equiv $ZnCl_2$)	Ratio of 7:8 (2.0 equiv $ZnCl_2$)	Isolated yield of **7**
	15:1	—	87
	8:1	—	72
	17:1	—	95
	10:1	—	78
	1:1	9:1	28
	1:1	11:1	73
	1:1	5:1	33
	1:1	5:1	33
	1:1	5:1	30

* All reactions carried out on 500 mg scale at ambient temperature, C-2 isomer isolated by crystallization from MeOH/water. Ratios calculated from HPLC of crude reaction.

produces unprecedented results in the selectivity of the final products. Additions of anilines at the 2-position of the pyrimidine are heavily favored with 0.25–1 equiv of $ZnCl_2$ with isomerically pure products easily isolated via recrystallization. In addition, alkyl amines can also be added selectively in a 5:1 ratio with 2 equiv of $ZnCl_2$. This effect is observed to a lesser extent with 5-H and 5-Me-2,4-dichloropyrimidines. This breakthrough affords the heretofore unavailable selective preparation of 5-trifluoromethyl-2,4-diaminopyrimidines, opening the door to many exciting possibilities to the future use of this template in a variety of syntheses. Future investigations are warranted to further flesh out the utility of this chemistry with similar systems as well as the application of these intermediates to various coupling reactions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.025.

References and notes

1. (a) Chen, H.; Chan, B. K.; Drummond, J.; Estrada, A. A.; Gunzer-Toste, J.; Liu, X.; Liu, Y.; Moffat, J.; Shore, D.; Sweeney, Z. K.; Tran, T.; Wang, S.; Zhao, G.; Zhu, H.; Burdick, D. J. *J. Med. Chem.* **2012**, *55*, 5536–5545; (b) Verma, S.; Nagarathnam, D.; Shao, J.; Zhang, L.; Zhao, J.; Wang, Y.; Li, T.; Mull, E.; Enyedy, I.; Wang, C.; Zhu, Q.; Altieri, M.; Jordan, J.; Dang, T.; Reddy, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1973–1977; (c) Hardcastle, I. R.; Wang, L. Z.; Noble, M. E. M.; Newell, D. R.; Johnson, L. N.; Jewsbury, P.; Griffin, R. J.; Golding, B. T.; Gibson, A. E.; Endicott, J. A.; Davies, T. G.; Curtin, N. J.; Boyle, F. T.; Bentley, J.; Arris, C. E.; Parsons, R. J.; Mesguiche, V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 217–222.
2. (a) Nakazato, A.; Kumagai, T.; Okubo, T.; Tanaka, H.; Chaki, S.; Okuyama, S.; Tomisawa, K. *Bioorg. Med. Chem.* **2000**, *8*, 1183–1193; (b) Nakazato, A.; Kumagai, T.; Okubo, T.; Kataok-Okubo, H.; Chaki, S.; Okuyama, S. *Bioorg. Med. Chem.* **2001**, *9*, 1349–1355.
3. (a) Borowski, T.; Krol, M.; Broclawik, E.; Baranowski, T. C.; Strekowski, L.; Mokrosz, M. *J. Med. Chem.* **2000**, *43*, 1901–1909; (b) Russell, M. G. N.; Baker, R. J.; Barden, L.; Beer, M. S.; Bristow, L.; Broughton, H. B.; Knowles, M.; McAllister, G.; Patel, S.; Castro, J. L. *J. Med. Chem.* **2001**, *44*, 3881–3895.
4. Ludovici, D. W.; DeCorte, B. L.; Kukla, M. J.; Ye, H.; Ho, C. Y.; Lichtenstein, M. A.; Kavash, R. W.; Andries, K.; De Bethune, M. P.; Azijn, H.; Pauwels, R.; Lewi, P. J.; Heeres, J.; Koymans, L. M. H.; DeJonge, M. R.; Van Aken, K. J. A.; Daeyaert, F. F. D.; Das, K.; Arnold, E.; Janssen, P. A. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2235–2239.
5. Brown, Demond J. Chemistry of Heterocyclic Compounds, The Pyrimidines, Vol. 52, Wiley, New York 1994, 371.
6. (a) Estrada, A. A.; Liu, X.; Baker-Glenn, C.; Beresford, A.; Burdick, D. J.; Chambers, M.; Chan, B. K.; Chen, H.; Ding, X.; DiPasquale, A. G.; Dominguez, S. L.; Dotson, J.; Drummond, J.; Flagella, J.; Flynn, S.; Fuji, R.; Gill, A.; Gunzer-Toste, J.; Harris, S. A.; Heffron, T. P.; Kleinheinz, T.; Lee, D. W.; LePichon, C. E.; Lyssikatos, J. P.; Medhurst, A. D.; Moffat, J. G.; Mukund, S.; Nash, K.; Scearce-Levie, K.; Sheng, Z.; Shore, D. G.; Tran, T.; Trivedi, N.; Wang, S.; Zhang, S.; Zhang, X.; Zhao, G.; Zhu, H.; Sweeney, Z. K. *J. Med. Chem.* **2012**, *55*, 9416–9433; (b) Kath, J. C.; Richter, D. T.; Luzzio, M. J. WO 2005/023780 A1.