JOC*Note*

# Single-Step Syntheses of 2-Amino-7-chlorothiazolo[5,4-*d*]pyrimidines: Intermediates for Bivalent Thiazolopyrimidines

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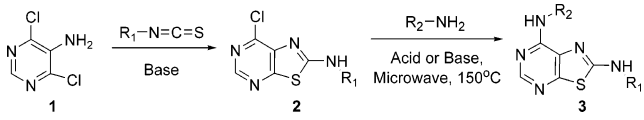
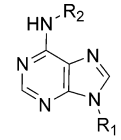


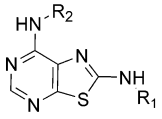

1 2 3

A single-step process for the preparation of 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines, **2**, was achieved by the reaction of the commercially available 4,6-dichloro-5-aminopyrimidine **1** with isothiocyanates. This mild reaction accommodates a variety of functionalized isothiocyanates and proceeds in good to excellent yields. The utility of such intermediates is exemplified by subsequent reaction with alkyl or arylamine nucleophiles to afford novel, differentially functionalized 2,7-diaminothiazolo[5,4-*d*]pyrimidines, **3**.

Thiazolopyrimidines have been widely recognized as biologically useful systems due to their structural similarities to purine bases. As such, thiazolopyrimidines have been found to exhibit a range of biological activities, particularly in the antiviral and immunology areas.[1] Thiazolopyrimidines have also been utilized as templates that have been additionally functionalized to achieve selective receptor or enzyme interactions.[2] In this capacity, analogues have been identified with utilities as chemokine receptor antagonists useful in treating neurodegenerative disorders,[2a] as anti-angiogenic kinase inhibitors,[2b] as inhibitors of MIF-induced T-cell proliferation,[2c] and others.[2d−f] However, among these various cases, the 2,7-substitution pattern has been only minimally explored.[2c,d]




Purine (adenine) template




Thiazolopyrimidine template

Common methods for assembling this bicyclic system involve treatment of substituted pyrimidines with reagents such as phosgene,[3a] carbon disulfide,[2e] phosphorus pentasulfide,[4] or cyanogen bromide[1a] to form the fused thiazole ring. Alternatively, the fused pyrimidine ring has been formed from functionally advanced thiazoles by treatment with reagents such as formamidine acetate,[3b] carbon disulfide,[5] formamide,[6] and phosphorus pentoxide.[7] However, both of these approaches suffer from the requirements of using toxic reagents, harsh conditions, and/or somewhat lengthy reaction sequences.[3c−n]

Herein, we report a convenient, single-step synthesis of 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines directly from commercially available 5-amino-4,6-dichloropyrimidine and isothiocyanates under mild conditions. Furthermore, the reactive 7-chloro substituent provides a handle for additional functionalization to afford bivalent 2,7-disubstituted thiazolo[5,4-*d*]pyrimidines. In this Note, we demonstrate the initial scope of this methodology by the facile syntheses of a variety of 2,7-diaminothiazolo-[5,4-*d*]pyrimidines (Figure 1).

During the course of a recent investigation with a series of thioureas, we observed that treatment of 6-chloro-$N^4$-(3,4,5-trimethoxybenzyl)pyrimidine-4,5-diamine **4** (prepared from 4,6-dichloro-5-aminopyrimidine **1** and 3,4,5-trimethoxybenzylamine) with phenylisothiocyanate **5** under mild, basic conditions did not afford the desired thiourea, but rather provided a product of further cyclization with concomitant loss of HCl. X-ray crystallographic analysis provided unambiguous confirmation

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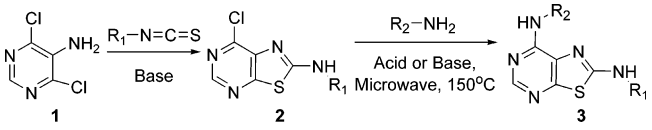


**FIGURE 1.** Process for the preparation of 2,7-diaminothiazolo[5,4-*d*]pyrimidines.

of the thiazolopyrimidine structure **6** resulting from this reaction.[8] To our surprise, a literature survey revealed a dearth of examples of thiazolo[5,4-*d*]pyrimidines with this particular pattern of substitution. Thus, we initiated a study to establish the scope and generality of this sequence and to optimize reaction conditions for this type of transformation.

As indicated in Scheme 1, the isolated yield of benzothiazole **6** was modest (20% after 48 h), with mostly unreacted diaminopyrimidine **4** remaining and no thiourea intermediate being detected. Reasoning that this low conversion might be reflective of reduced nucleophilicity of the 5-amino group due to an intramolecular hydrogen-bonding interaction between the adjacent amino groups of **4**, we reversed the reaction sequence (Scheme 2). In this case, treatment of dichloroaminopyrimidine **1** with phenylisothiocyanate under similar conditions led to thiazolopyrimidine **7** with a 50% yield in 16 h. Subsequent treatment of **7** with 3,4,5-trimethoxybenzylamine under basic conditions afforded **6** in a 90% yield.

Encouraged by these results, we turned our attention toward optimizing parameters affecting the formation of **7**, namely solvent, temperature, and base (Table 1). In screening a set of solvents, we observed a direct correlation between polarity and yield (DMSO > DMF, MeCN > acetone ≈ THF, DCM > toluene). Thus, the highest yields of thiazolopyrimidine **7** were obtained in polar aprotic solvents, whereas toluene proved to be the least effective solvent for this transformation. While DMSO provided the best yield for this reaction, we opted to proceed with MeCN for purposes of practical handling. In this solvent, a temperature increase from 25 to 50 °C afforded a modest improvement in yield (60%, entry 8); however, a further increase in temperature to 80 °C proved to be detrimental to the process, leading to a reduced yield of **7** among a more complex product mixture (28%; entry 9).

Both the amount and choice of base were found to influence the course of this reaction. Reducing the amount of DBU from 2 equiv (entry 8) to one (entry 10) resulted in a 33% decrease in thiazolopyrimidine product. Without base, the reaction was quite slow; only a 5% conversion was obtained (entry 11). This is in stark contrast to the results obtained by Altland et al.[9] with 3-amino-2-chloropyridine, wherein reaction with phenyl isothiocyanate in refluxing ethanol afforded thiazolo[5,4-b]pyridine in 67% yield without the requirement of additional base. Given that pyridine proved unsuitable for our reaction (3%, entry 12), this is suggestive of a reduced nucleophilicity of aminopyrimidine **1** compared with Altland's aminopyridine system. Diisopropylethylamine (55%, entry 13) functioned similarly to DBU, while TEA was quite unsatisfactory (10%, entry 14).

Among the inorganic bases we examined, $Cs_2CO_3$ provided the best result, affording an excellent yield of thiazolopyrimidine (entry 17). However, the precise role of $Cs_2CO_3$ in the present process is unclear. Thiourea intermediates were not detected in any of these reactions, indicating that their subsequent cyclizations are fast regardless of the base used. The advantageous effects of $Cs_2CO_3$ must be due to its influence on the initial acylation step, possibly through the formation of a cesium amide of **1**. This aspect of the so-called "cesium effect"[10] has been invoked by Salvatore et al. to provide mechanistic rationale for the selective monoalkylation of primary amines in the presence of cesium hydroxide.[11] To our knowledge, such an effect upon arylamine acylations has not been previously reported.

Having identified suitably optimized conditions for our model reaction (entry 17), we next focused our investigation on determining the generality of this process with respect to the nature of isothiocyanates that would undergo this transformation. As indicated in Table 2, the success of this reaction with arylisothiocyanates is apparently largely independent of steric effects and, to a certain extent, to electronic effects as well. Thus, even the sterically encumbered 2,6-dimethylphenyl isothiocyanate underwent a smooth conversion to the corresponding thiazolopyrimidine **18** (90%; entry 2). Electron-donating groups such as *p*-Me and *p*-MeO are well tolerated in this process (entries 3 and 4). However, electron-withdrawing groups on the aryl isothiocyanate are somewhat detrimental to this reaction, an effect that is particularly pronounced in the case of *p*-nitrophenylisothiocyanate (**12** → **22**, entry 6, 50%); less so with the *m*-$CF_3$ counterpart (**11** → **21**, entry 5, 82%). Finally, heterocyclic arylisothiocyanates are also suitable for this reaction, as exemplified by 3-pyridylisothiocyanate **13**. This electron-deficient isothiocyanate behaved similarly to *m*-$CF_3$-substituted phenylisothiocyanate **11**, affording thiazolopyrimidine **23** in a comparable yield (entry 7, 80%).

In contrast to the results obtained with aryl isothiocyanates, the course of reactions with aliphatic isothiocyanates proved to be susceptible to steric influences (Table 3). Thus, whereas the reactions with *tert*-butyl and isopropyl isothiocyanates afforded the corresponding thiazolopyrimidines **24** and **25** in good yields (75 and 67%, respectively), less sterically demanding alkyl isothiocyanates over-reacted. Thus, with primary alkyl isothiocyanates **16** and **17**, the initially formed 2-aminothiazolopyrimidine adduct underwent a further smooth acylation to form thiourea derivatives **26** and **27**, respectively (entries 3 and 4).

These latter results highlight the relative differences in nucleophilicities between aminopyrimidine **1**, primary alkylaminothiazolopyrimidines **A**, secondary and tertiary alkylaminothiazolopyrimidines **B**, and arylaminothiazolopyrimidines **C** (Scheme 3). With primary alkylami-

(8) Thermal ellipse rendering of compound **6** and corresponding crystallographic information file are provided in the Supporting Information.

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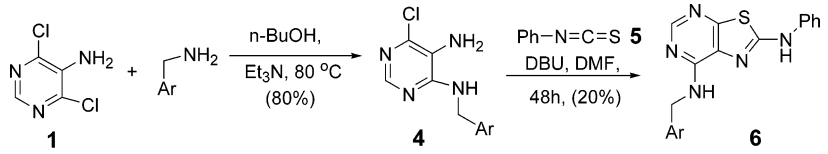
(12) All aryl and alkyl isothiocyanates were purchased from Sigma-Aldrich and used directly.

**SCHEME 1. Formation of $N^2$-Phenyl-$N^7$-(3,4,5-trimethoxybenzyl)thiazolo[5,4-*d*]pyrimidine-2,7-diamine 6**




**SCHEME 2. Alternative Route to $N^2$-Phenyl-$N^7$-(3,4,5-trimethoxybenzyl)thiazolo[5,4-*d*]pyrimidine-2,7-diamine 6**

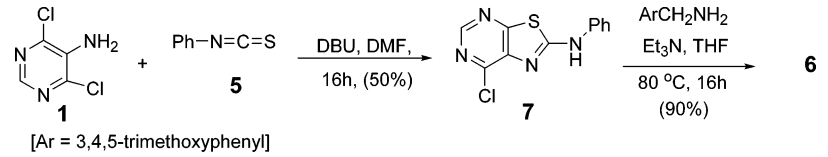
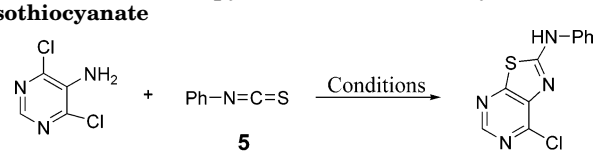
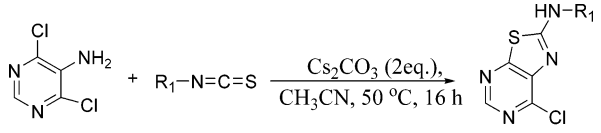



**TABLE 1. Parameter Optimization for the Reaction of 4,6-Dichloro-5-aminopyrimidine 1 with Phenyl Isothiocyanate**




| entry | solvent | temp (°C) | base | yield of **7** (%) |
|---|---|---|---|---|
| 1 | DMSO | 25 | DBU (2 equiv) | 60 |
| 2 | DMF | 25 | DBU (2 equiv) | 50 |
| 3 | MeCN | 25 | DBU (2 equiv) | 50 |
| 4 | acetone | 25 | DBU (2 equiv) | 44 |
| 5 | THF | 25 | DBU (2 equiv) | 40 |
| 6 | DCM | 25 | DBU (2 equiv) | 40 |
| 7 | toluene | 25 | DBU (2 equiv) | 10 |
| 8 | MeCN | 50 | DBU (2 equiv) | 60 |
| 9 | MeCN | 80 | DBU (2 equiv) | 28 |
| 10 | MeCN | 50 | DBU (1 equiv) | 40 |
| 11 | MeCN | 50 | none | 5 |
| 12 | MeCN | 50 | pyridine (2 equiv) | 3 |
| 13 | MeCN | 50 | DIPEA (2 equiv) | 55 |
| 14 | MeCN | 50 | TEA (2 equiv) | 10 |
| 15 | MeCN | 50 | $Na_2CO_3$ (2 equiv) | 5 |
| 16 | MeCN | 50 | $K_2CO_3$ (2 equiv) | 41 |
| 17 | MeCN | 50 | $Cs_2CO_3$ (2 equiv) | 92 |

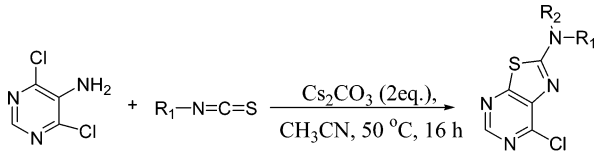
**TABLE 2. Reaction of 4,6-Dichloro-5-aminopyrimidine 1 with Aryl Isothiocyanates**




| entry | isothiocyanate[12] | $R_1$ | product (yield) |
|---|---|---|---|
| 1 | **5** | Ph− | **7** (92%) |
| 2 | **8** | 2,6-$Me_2$Ph− | **18** (90%) |
| 3 | **9** | *p*-MePh− | **19** (93%) |
| 4 | **10** | *p*-MeOPh− | **20** (95%) |
| 5 | **11** | *m*-$CF_3$Ph− | **21** (82%) |
| 6 | **12** | *p*-$NO_2$Ph− | **22** (50%) |
| 7 | **13** | 3-pyridyl− | **23** (80%) |

nothiazolopyrimidines **A**, the exocyclic amino groups are more nucleophilic than that of the aminopyrimidine starting material itself; once formed, they out-compete with **1** for the isothiocyanate electrophile that is present in the reaction mixture, barring any steric encumbrance.

**TABLE 3. Reaction of 4,6-Dichloro-5-aminopyrimidine 1 with Alkyl Isothiocyanates**




| entry | isothiocyanate[12] | $R_1$ | $R_2$ | product (yield) |
|---|---|---|---|---|
| 1 | **14** | *t*-butyl− | H | **24** (75%) |
| 2 | **15** | 2-propyl | H | **25** (67%) |
| 3 | **16** | Me− | MeHN, S | **26** (98%)[a] |
| 4 | **17** | $PhCH_2$− | $PhCH_2NH$, S | **27** (94%)[a] |

[a] Yield based on isothiocyanate.

The opposite is true with secondary and tertiary alkylaminothiazolopyrimidines **B**, and with arylaminothiazolopyrimidines **C**, whose amine nucleophilicities must be less than that of **1** since no over-acylated adducts were observed in their reactions (even in the presence of excess isothiocyanate).

Finally, to demonstrate the synthetic utilities of these intermediate 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines, we have prepared a set of differentially substituted thiazolo[5,4-*d*]pyrimidine-2,7-diamines (Table 4). Using chlorothiazolo[5,4-*d*]pyrimidine **7** as our model system, we found that amination could be effected quite readily under thermal conditions without the assistance of metal catalysis. Aliphatic amines reacted with **7** under basic conditions, whereas aromatic amines required mildly acidic conditions to undergo this transformation. Primary and secondary aliphatic amines reacted smoothly to afford the corresponding diamines in good to excellent yields (entries 1−3). Even the weakly nucleophilic *tert*-butylamine produced the corresponding product, **30**, albeit in modest yield (entry 4). The conditions employed for aliphatic amine displacement were not suitable for aromatic amines; the latter required a slight excess of glacial acetic acid and microwave heating to enable this displacement. Under such conditions, amination with primary anilines occurred readily, affording the corresponding 7-anilino products in good yields (entries 5−7). However, both electronic and steric factors influenced this

**SCHEME 3. Relative Nucleophilicities toward Isothiocyanates**

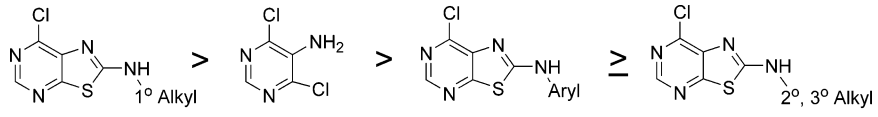
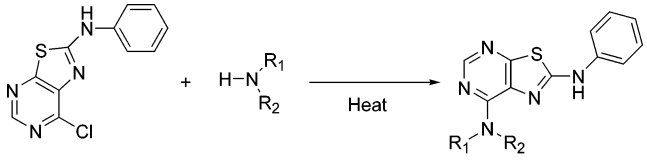



**TABLE 4. Amination of (7-Chlorothiazolo[5,4-*d*]pyrimidin-2-yl)phenylamine 7**




| entry | $R_1$ | $R_2$ | product[a,b] |
|---|---|---|---|
| 1 | 3,4,5-$(MeO)_3PhCH_2$– | H | **6** (90%) |
| 2 | –$(CH_2)_2$–NMe–$(CH_2)_2$– | | **28** (85%) |
| 3 | Me–$(CH_2)_3$– | H | **29** (90%) |
| 4 | *t*-butyl– | H | **30** (20%)[c] |
| 5 | Ph– | H | **31** (93%) |
| 6 | *p*-MeOPh– | H | **32** (86%) |
| 7 | *m*-ClPh– | H | **33** (90%) |
| 8 | *p*-$NO_2$Ph– | H | **34** (22%)[d] |
| 9 | Ph– | Me– | **35** (60%) |

[a] Reaction conditions for alkylamines: 1.0 equiv of amine; 1.0 equiv of TEA; refluxed in 5.0 mL of THF for 16 h. [b] Reaction conditions for arylamines: 1.5 equiv of amine; 1.5 equiv of acetic acid; heated in 2.5 mL of dioxane in a microwave reactor at 150 °C for 40 min. [c] Reaction time was 72 h. [d] Reaction was carried out at 200 °C for 8 h.

substitution reaction as evidenced by the moderate yields of **34** and **35**, respectively (entries 8 and 9).

In summary, we have established a convenient method for the preparation of 2-amino-7-chlorothiazolo[5,4-*d*]-pyrimidines, which are versatile synthetic intermediates for subsequent derivatization upon treatment with reactive nucleophiles. In this present work, we have prepared a set of novel, bivalent thiazolo[5,4-*d*]pyrimidine-2,7-diamines, which are being investigated for biological utilities.

## Experimental Section

**6-Chloro-*N*$^4$-(3,4,5-trimethoxybenzyl)pyrimidine-4,5-diamine (4).** To a solution of 4,6-dichloro-5-aminopyrimidine **1** (2.0 g, 12.2 mmol) in *n*-BuOH (25 mL) were added TEA (2.04 mL, 14.6 mmol) and 3,4,5-trimethoxybenzylamine (2.19 mL, 12.8 mmol). The reaction mixture was heated to 80 °C and stirred for 16 h, then cooled to room temperature and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (hexanes/ethyl acetate, 1:1) to afford **4** as an off-white solid (3.17 g, 80%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.76 (s, 1H), 7.22 (t, $J$ = 5.4 Hz, 1H), 6.67 (s, 2H), 5.11 (s, 2H), 4.54 (d, $J$ = 5.4 Hz, 2H), 3.74 (s, 6H), 3.63 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 152.8, 151.8, 145.6, 137.0, 136.5, 134.9 (2C), 123.6, 105.0 (2C), 60.0, 55.8 (2C), 44.7; HR-MS *m/z* (M + $H^+$) calcd 325.1068, obsd 325.1078.

***N*$^2$-Phenyl-*N*$^7$-(3,4,5-trimethoxybenzyl)thiazolo[5,4-*d*]pyrimidine-2,7-diamine (6).** To a solution of **4** (162 mg, 0.5 mmol) in DMF (2 mL) was added DBU (0.15 mL, 1 mmol) followed by phenyl isothiocyanate **5** (0.06 mL, 0.5 mmol), and the resultant mixture was stirred at room temperature for 48 h. After concentration under reduced pressure, the residue was purified by column chromatography (dichloromethane/MeOH, 19:1) to give **6** as a white solid (42.4 mg, 20%): mp 110−111 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.62 (s, 1H), 8.21 (s, 1H), 7.99 (t, $J$ = 5.4 Hz, 1H), 7.87 (d, $J$ = 7.8 Hz, 2H), 7.34 (dd, $J$ = 7.8, 7.5 Hz, 2H), 7.02 (t, $J$ = 7.5 Hz, 1H), 6.70 (s, 2H), 4.67 (d, $J$ = 5.4 Hz, 2H), 3.71 (s, 6H), 3.61 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.8, 152.8 (2C), 152.7, 151.8, 140.4, 136.3, 135.8, 129.0 (2C), 128.8, 122.2, 117.8 (2C), 105.5, 104.7 (2C), 60.0, 56.5 (2C), 44.4; HR-MS *m/z* (M + $H^+$) calcd 424.1444, obsd 424.1444.

**General Method for Preparation of 2-Amino-7-chlorothiazolo[5,4-*d*]pyrimidines.** To a solution of 4,6-dichloro-5-aminopyrimidine **1** (164 mg, 1 mmol) in MeCN (4 mL) was added $Cs_2CO_3$ (0.651 g, 2 mmol) followed by isothiocyanate (1 mmol). The mixture was stirred at 50 °C for 16 h, then cooled to room temperature and concentrated under reduced pressure. The resultant residue was purified by column chromatography (hexanes/ethyl acetate, 4:1) to give the desired product.

**Preparation of Thiazolo[5,4-*d*]pyrimidine-2,7-diamines: Method A. Aliphatic Amines.** A solution of (7-chlorothiazolo-[5,4-*d*]pyrimidin-2-yl)phenylamine **7** (50 mg, 0.19 mmol), aliphatic amine (0.19 mmol), and TEA (0.026 mL, 0.19 mmol) in THF (5 mL) was refluxed for 16 h. After being cooled to room temperature and concentrated under reduced pressure, the resulting residue was purified by column chromatography (dichloromethane/MeOH, 9:1) to afford the corresponding substitution product. Using this protocol, we obtained *N*$^2$-phenyl-*N*$^7$-(3,4,5-trimethoxybenzyl)thiazolo[5,4-*d*]pyrimidine-2,7-diamine (**6**) as a white solid (72 mg, 90%).

**Preparation of Thiazolo[5,4-*d*]pyrimidine-2,7-diamines: Method B. Aromatic Amines.** A solution of (7-chlorothiazolo-[5,4-*d*]pyrimidin-2-yl)phenylamine **7** (50 mg, 0.19 mmol), the aromatic amine (0.28 mmol), glacial acetic acid (0.016 mL, 0.28 mmol), and dioxane (2.5 mL) in a sealed tube was heated to 150 °C in microwave reactor (Smith Synthesizer, Personal Chemistry) for 40 min. After being cooled to room temperature and concentrated under reduced pressure, the resulting residue was purified by column chromatography (dichloromethane/MeOH, 19:1) to afford the corresponding substitution product.

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**Supporting Information Available:** Analytical data and $^1$H NMR spectra for all product compounds (Tables 2−4) and a thermal ellipse rendering and corresponding crystallographic information file for compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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