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One-Step Synthesis of 2-Chloropyrimidin-4-ol Derivatives: An Unusual Reactivity of Thiophosgene

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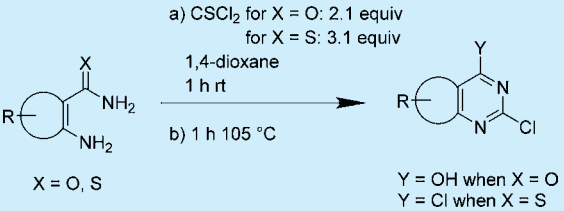
Supporting Information

ABSTRACT: A novel, high-yielding, one-step synthesis of 2-chloroquinazolin-4-ols and analogous bicycles from 2-aminoamides using thiophosgene is described. The scope of the reaction includes aminothioamides, amino acids, and fused heterocycle derivatives, furnishing quinazolines, oxazinones, and substituted fused pyrimidine bicycles, respectively. On the basis of observed results with substituted analogues, a mechanism for this transformation is thought to occur via an isothiocyanate intermediate followed by an unexpected chemoselective reaction of thiophosgene on the thiol intermediate.

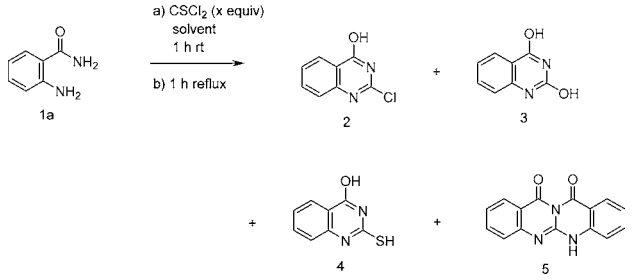


With the discovery of the biological potency of pyrimidine-containing compounds over the last 50 years, there have been a number of different methods used in their syntheses.[1−3] In this Letter we report a novel, facile one-step synthesis of pyrimidine-containing compounds from aromatic aminoamides and their analogues, using thiophosgene. Syntheses of 2-chloropyrimidin-4-ols are often carried out in three steps by treating 2-aminoamides with phosgene, followed by phosphorus oxychloride to obtain the dichloroquinazoline.[4] Careful addition of sodium hydroxide selectively hydrolyzes the chlorine at the 4-position. The work described here represents a simple, fast, one-step transformation of readily accessible starting materials to biologically relevant 2-chloropyrimidin-4-ol intermediates, which can be regioselectively diversified in one pot.

The initial reaction conditions were optimized based on the procedure used by Gochman and Wei starting from anthranilamide and thiophosgene.[5] The authors described the formation of 2-thiopyrimidin-4-ol **4** and a tetracyclic byproduct **5**, exclusively. Interestingly, in our hands these reaction conditions led to the major compound 2-chloropyrimidin-4-ol **2**, which was not described by Gochman and Wei. To the best of our knowledge, this represents a novel transformation which prompted our further investigations. The effects of solvent and stoichiometric equivalents of thiophosgene upon this reaction were investigated (Table 1).

When performing the reaction, the major side products obtained identified by LCMS only are thought to be quinazolin-2,4-diol **3**, thiol derivative **4**, and the tetracyclic species **5**. Addition of excess thiophosgene (Table 1, entry 1) in 1,4-dioxane gave excellent 95% conversion to **2** (65% isolated yield), which was improved to 100% conversion (86% isolated yield) with addition of only 2.1 equiv of thiophosgene (entry 3), with no observed side products. When thiophosgene was added in two separate portions (entry 2), very similar results were obtained, but the presence of compound **4** was clearly seen by LCMS after addition of the first portion. Using THF as solvent also led to the formation of side products (entries 4 and 5), as did acetonitrile (entry 6) which showed significant presence of unidentifiable side products, as well as **3**, **4**, and **5**, and therefore, no material was isolated for this reaction. Use of

Table 1. Optimization of Reaction Conditions



			conversion[a]				
	solvent	$CSCl_2$ (equiv)	**2** (%)	**3** (%)	**4** (%)	**5** (%)	yield[b] (%)
1	1,4-dioxane	2.5	95	0	2	3	65
2	1,4-dioxane	1.1 + 1.1[c]	97	3	0	0	57
3	1,4-dioxane	2.1	100	0	0	0	86
4	THF	2.5	93	2	4	0	70
5	THF	2.1	89	4	6	0	84
6	MeCN	2.5	51	6	4	3	nm[d]
7	toluene	2.5	63	1	2	28	43
8	CH_2Cl_2	2.5	33	0	44	9	nm[d]
9	cyclohexane	2.5	33	4	11	15	nm[d]

[a]Crude conversion by UV was measured using liquid chromatography−mass spectrometry (LCMS) after heating at reflux for 1 h. [b]Isolated yield of **2**. [c]Second portion of 1.1 equiv $CSCl_2$ was added after 30 min stirring at room temperature. [d]nm (not measured): the purity of **2** was low, and therefore, the material was not isolated.

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toluene or cyclohexane (entries 7 and 9) gave significant amounts of undesired side products, notably the tetracycle **5** (most likely formed by the reaction of **2** and additional starting material), which appears to be favored in less polar solvents. The formation of **4** appears to be favored when using CH_2Cl_2 (entry 8). The optimal conditions were therefore found to be 2.1 equiv of thiophosgene in 1,4-dioxane, stirring at room temperature for 1 h and subsequently heating at 105 °C for 1 h. At that point, the 2-chloro-4-hydroxyquinazoline **2** can easily be isolated as its hydrochloride salt by addition of Et_2O on the cold reaction mixture and collection by filtration (see Supporting Information).

To examine the scope of the reaction, various aminoamides were treated with thiophosgene using the optimized conditions (Figure 1). We found that the 2-chloro position of several of

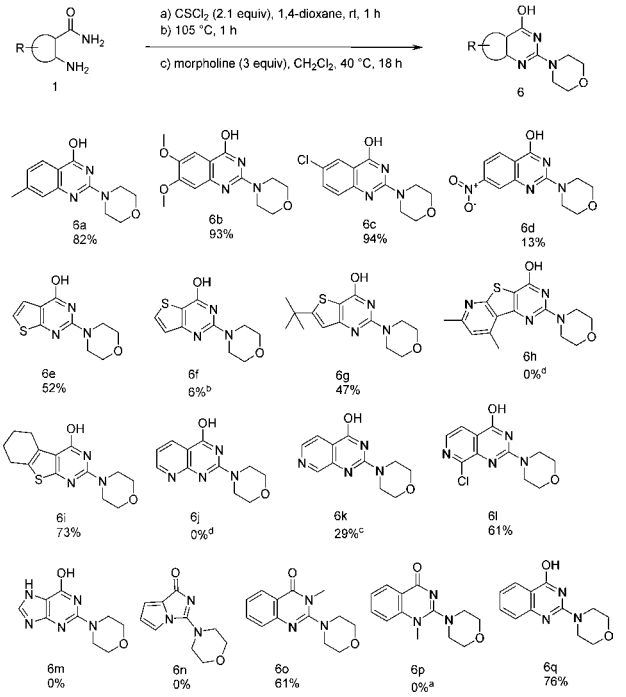


Figure 1. Scope of the reaction. Conditions: (a) No reaction despite heating at 105 °C for 24 h and addition of a further 1 equiv of thiophosgene; (b) additional heating at 105 °C for 18 h; (c) purity 85%, mixture with dihydroxylated byproduct; (d) Morpholino product not isolated but the corresponding 2-chloro derivative was clearly seen by LCMS.

these analogues was prone to hydrolysis, meaning that it was difficult to assess accurately the conversion to the desired product. Therefore, for ease of isolation, the crude reaction mixtures were concentrated under reduced pressure and the crude products obtained were subsequently reacted with an excess of morpholine in CH_2Cl_2 in order to obtain an accurate measure of conversion.

The morpholine addition was assumed to be quantitative relative to the conversion of the starting aminoamide to the 2-chloropyrimidin-4-ol species in the first step, and therefore, isolated yields of the 2-morpholine derivatives were expected to reflect conversion to the 2-chloropyrimidine derivatives.

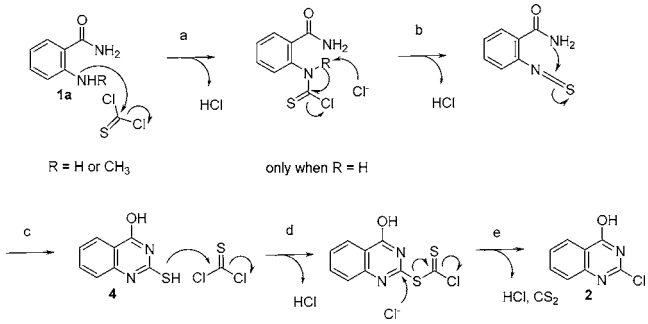
Compounds **6a**, **6b**, and **6c** (Figure 1) suggest that electron-withdrawing and electron-donating substituents are tolerated in this reaction, with excellent isolated yields of 82−94%. However, the yield was significantly lower when a nitro group was present (compound **6d**), most likely due to the poor solubility, which made purification challenging.

The solubility of the products obtained with heterocyclic aminoamides (Figure 1, compounds **6e**−**l**) was in general very poor, which made purification difficult and contributed to the lower yields.

Thiophenes (compounds **6e**−**g** and **6i**) were tolerated in this reaction with good yields obtained. However, no conversion to the 2-chloro-4-yl-3*H*-thieno[3,2-*d*]yrimidin-4-ol was seen despite an additional 18 h of heating at 105 °C (compound **6h**).

No conversion to the desired bicycle from the corresponding 2-pyridyl amino amide was observed (compound **6j**). However, for the 3-pyridyl isomers (compounds **6k** and **6l**), the desired azaquinazoline was isolated in reasonable yields of 29% and 61%. An NH on the heterocyclic ring of the substrate (compounds **6m** and **6n**) was also not tolerated; in the case of compound **6n**, this may be because the proposed reactive isothiocyanate intermediate cannot form (see mechanism in Scheme 1).

Scheme 1. Postulated Mechanism for First Step of Thiophosgene Addition



Interestingly, thiophosgene addition to the methyl-substituted amide gave the desired bicycle **6o** in good yield; however, the secondary amine (compound **6p**) did not react at all, despite additional heating at 105 °C for 24 h and addition of a further equivalent of thiophosgene.

From the experimental results, we postulate a mechanism (Scheme 1). In the initial optimization reaction (Table 1, entry 2), the addition of the first portion of 1.1 equiv of thiophosgene gave principally thiol intermediate **4**, with full conversion to the desired 2-chloropyrimidin-4-ol **2** only upon addition of the second portion. The thiol intermediate **4** was also observed in all the other optimization reactions after stirring at room temperature for 30 min, suggesting that the reaction proceeds via this intermediate.

The first step (step a) consists of the attack of the amine on one molecule of thiophosgene followed by the rearrangement to the corresponding isothiocyanate in step b. The existence of the intermediate isothiocyanate is postulated because when the amine is methyl-substituted, no reaction is observed (Figure 1, compound **6p**). In this case, it is not possible to form the isothiocyanate intermediate (Scheme 1, step b, R = CH_3).

However, methylated amides can still perform the intramolecular ring-closure (Figure 1, compound **6o**). In the next step (step c), intramolecular ring closure gives the 2-thioquinazolinol **4**. The thiol function is proposed to attack a second equivalent of thiophosgene (step d), forming a leaving group which can be readily displaced by the released chlorine anion, giving the observed 2-chloropyrimidin-4-ol **2**. It is

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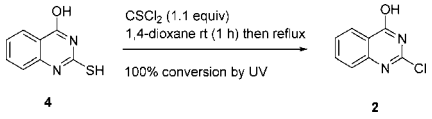
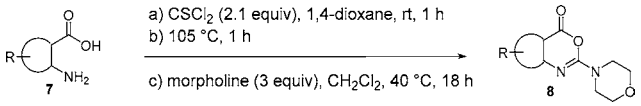
interesting to note that, during the reaction, only the thiol moiety will attack the second equivalent of thiophosgene, not the hydroxyl group. Moreover, the desired 2-chloropyrimidin-4-ol **2** can also be formed by addition of one equivalent of thiophosgene to the commercial 2-thiopyrimidine-4-ol **4**, with observed UV (LCMS) conversion of 100% (Scheme 2).

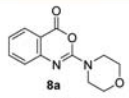
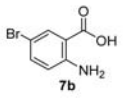
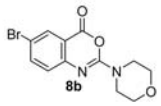
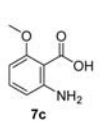
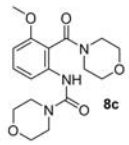
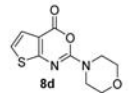
Scheme 2. Conversion of 2-Thio-4-hydroxyquinazoline 4 to 2-Chloro-4-hydroxyquinazoline 2



Amino acid substrates are also tolerated in this reaction (Table 2). The unsubstituted benzo[*d*]oxazinone **8a** (entry 1)

Table 2. Reaction with Amino Acids



entry	substrate	product	yield
1			93%
2			59%
3			71%[a]
4			0%

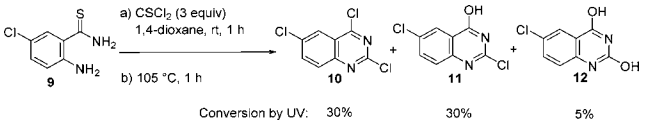
[a]Desired product not observed.

was obtained in excellent yield and the bromo-substitution **8b** (entry 2) also allowed good conversion of 59%. Two molecules of morpholine are added in compound **8c** when there is an electron-donating methoxy group present (entry 3); this was not observed for entries 1 and 2. Although the desired product 5-methoxybenzo[*d*][1,3]oxazin-2,4-dione was observed by LCMS, the stability of this ring system was poor after the addition of morpholine, and addition of a second molecule of morpholine was observed.

The thiopheno-amino acid substrate (**7d**, entry 4) did not show any conversion to the chloro intermediate **8d** after the addition of thiophosgene. An interesting point to note is that upon addition of thiophosgene to these amino acid derivatives, formation of the 2-chloro intermediate was limited. Under LCMS conditions, the major products seen were the 2-hydroxy-substituted products in each case (Table 2, entries 1−3).

The reaction of 2-amino-4-chlorothiobenzamide was also successful, furnishing the 2,4-dichloroquinazoline species **10** directly (Scheme 3). Although the desired trichloro product **10** was present (30% conversion by UV), there were also

Scheme 3. Reaction with Thioamide



significant amounts of the 2-chloropyrimidin-4-ol **11** (30% conversion by UV) and dihydroxy **12** (5% conversion by UV) byproducts after heating at 105 °C for 1 h. We believe that during the reaction, the major product formed is the 3-chloro derivative **10**. But due to its instability and under LCMS condition, **10** is readily hydrolyzed to the corresponding mono and bis-hydroxy analogues **11** and **12** in 30% and 5% yield, respectively. Further hydrolysis at the 2-position was observed during an attempt to purify the compound using flash column chromatography. Hydrolysis at the 2- and 4-chloro positions was facile, and therefore, any derivatization at these positions would require careful optimization of conditions to avoid this rapid hydrolysis.

We have reported a one-pot thiophosgene-promoted cyclization of readily available 2-aminoamides to furnish 2-chloro-4-hydroxypyrimidine derivatives. These highly versatile building blocks contain key pharmacologically active motifs and can be readily and regioselectively functionalized at both the 2- and 4-positions. We have demonstrated the highly selective reactivity of thiophosgene toward 2-thiopyrimidines in the presence of hydroxyl functionality. This allows us to consider the thiol group as a masking group for a chlorine moiety, which can then be readily displaced as shown above or cross-coupled (data not shown). Further investigation is underway to expand the scope of this new transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02375.

Experimental procedures and characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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