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Synthesis of Cytimidine through a One-Pot Copper-Mediated Amidation Cascade

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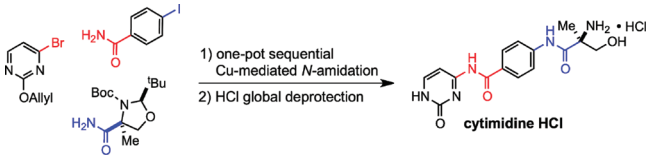
ABSTRACT



A concise synthesis of cytimidine was developed utilizing tandem Cu-mediated *N*-aryl amidations followed by global deprotection. This sequence exploits a regioselective coupling of an iodobenzamide with a halopyrimidine that allows the union of three fragments in a single synthetic manipulation and will permit the efficient and rapid diversification of the cytimidine core.

Various classes of antibiotics including aminoglycosides,[1] macrolides,[2] and tetracyclines[3] have long demonstrated the drugability of the ribosome. These families comprise clinically relevant compounds that inhibit protein synthesis by binding to rRNA.[4] One particular class of ribosomal antibiotics, the aminohexopyranose nucleosides, have remained significantly less explored (Figure 1). Members of this family include amicetin,[5] bamicetin,[5] oxamicetin,[6] plicacetin,[7] and cytosaminomysin B[8] among others. Previous studies have suggested that these natural products share a common binding site near the peptidyl transferase center (PTC) of the ribosome.[9,10]

Of particular interest to us is the antibiotic amicetin, isolated from *Streptomyces plicatus* in 1953, for its potent antibacterial activity against *Mycobacterium tuberculosis* H37Rv (IC_{100} 0.5 μg/mL) and *Staphylococcus aureus* FDA-209 (IC_{100} 0.2 μg/mL).[5] To date, the total synthesis of amicetin and its analogues, bamicetin and oxamicetin, have yet to be reported. Total synthesis of other members of the aminohexopyranose nucleoside family are quite few and far in between.[12,13] With the resurgence of drug resistant pathogens such as multidrug resistant (MDR) and extensively drug resistant (XDR) strains of *M. tuberculosis*[14] the need for more efficient therapeutics prompted us to develop a convergent approach to the synthesis of amicetin and its close analogues.

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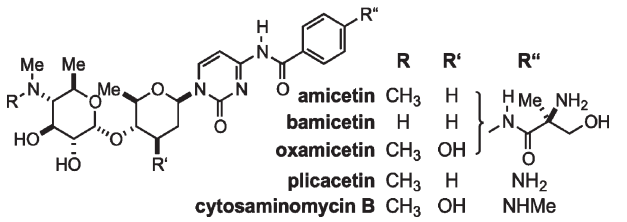


Figure 1. Aminohexopyranose nucleoside antibiotics.

Our initial synthetic efforts were guided by early biological studies with amicetin and other related natural products. Haskell and co-workers reported lower *in vitro* and *in vivo* activity against *M. tuberculosis* (H37Rv) for plicacetin, the compound lacking the α-methylserine moiety, compared to amicetin and bamicetin.[7] Degradation studies on amicetin by Flynn and co-workers reported a significant loss of activity at a measurable rate under basic conditions (pH = 8), but not under acidic conditions (pH = 1.3) (Figure 2).[5] Cytosamine, the base hydrolysis product, was reported to be devoid of antibacterial activity.[7] This suggests that cytimidine, which arises from the acid catalyzed hydrolysis, retains activity and points to the importance to the cytosine-peptidic portion of the molecule as being requisite for activity. To the best of our knowledge, there have been no structure–activity relationship (SAR) studies on cytimidine, which appears to be a more relevant analog to amicetin than cytosamine. Thus, our initial efforts toward the total synthesis of amicetin were directed at developing a highly efficient route to cytimidine. This would allow us to evaluate a truncated version of amicetin and other analogues for antimicrobial activity.

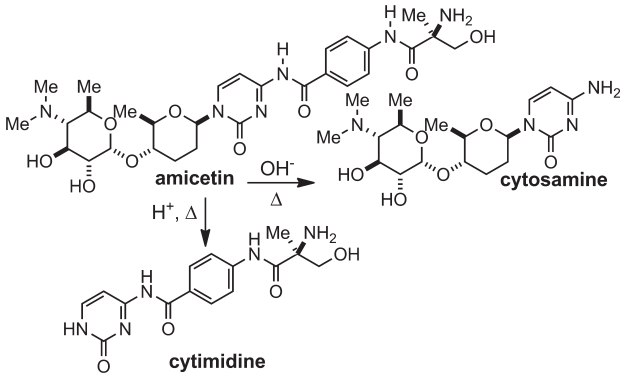
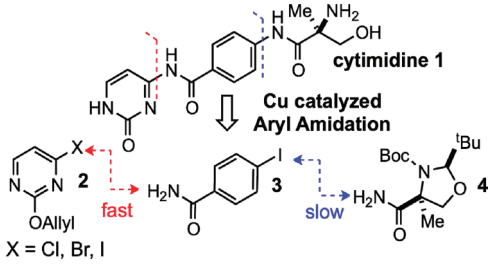


Figure 2. Base and acid hydrolysis products of amicetin.

We envisioned that cytimidine could be prepared quite efficiently if we could exploit a regioselective coupling of this halopyrimidine **2** to 4-iodobenzamide **3**, and the oxazolidine carboxamide **4**, via copper catalyzed *N*-aryl amidation reactions (Scheme 1). This strategy would avoid a series of protection–deprotection chemistries normally employed in peptide synthesis. We anticipated that the steric differentiation between **3** and **4**, which bears a quaternary α-stereocenter, would afford a significant difference in their respective rates of amidation that could be exploited. In concert with the fact that the carbon–halogen bond in the pyrimidine is weaker that that in the aryl halide we hypothesized that **2** and **3** would undergo relatively fast coupling followed by coupling to **4**. Thus we attempted a one-pot three-component tandem *N*-aryl amidation to unite these fragments. This approach proved problematic (*vide infra*), and it became apparent that the same copper-ligand set would not be applicable for both couplings. We then sought to study the coupling reactions individually to learn more about the subtleties that govern these amidations, specifically with pharmacologically important scaffolds such as 4-halopyrimidines.

Scheme 1. Retrosynthetic Analysis



We began our synthesis with the formation of 4-halopyrimidines **2a–c** (Scheme 2). These were prepared by halide exchange of the commercially available 4-chloro-2-methylthiopyrimidine **5a** with TMSBr or TMSI to give the corresponding halides **5b** and **5c**.[15] The halopyrimidines **5a–c** were then oxidized to the sulfone,[16] followed by nucleophilic aromatic substitution[17] with the potassium salt of allyl alcohol to give **2a–c**, in good to excellent yields. The allyl group was introduced to offer the flexibility to be unmasked separately from α-methylserine, for glycosylation, or to be deprotected concurrently en route to cytimidine and its analogues.

We then proceeded with the synthesis of the oxazolidine carboxamide **4** which corresponds to the α-methylserine moiety cytimidine (Scheme 3). Oxazolidine ester **7** was formed from L-serine methyl ester hydrochloride as a single diastereomer based on published procedures.[18] It was then alkylated employing Seebach's memory of chirality,[19] giving the α-methylated oxazolidine ester **8** in excellent yield and >95:5 dr. The ester was then saponified to the acid **9** and converted to the carboxamide **4** via the acid chloride.

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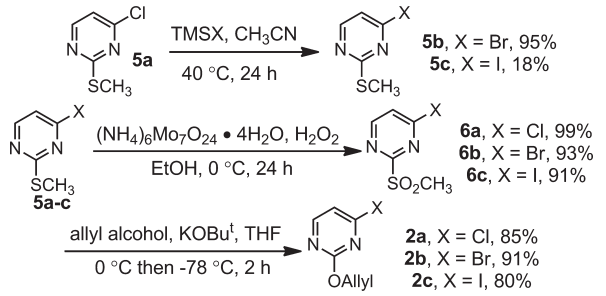
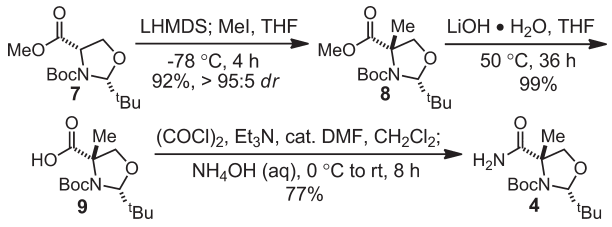
Scheme 2. Synthesis of 4-Halopyrimidines

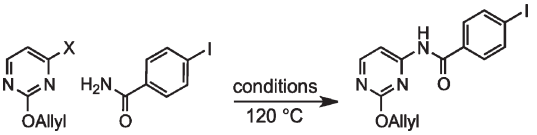


Scheme 3. Synthesis of Oxazolidine Carboxamide



Reaction conditions for the copper catalyzed *N*-aryl amidation of **2a**–**c** with 4-iodobenzamide **3** were then investigated (Table 1). Surprisingly, there was little precedence for the Cu-mediated amidation of halopyrimidines.[20,21] Buchwald has shown a single example of the *N*-amidation of cyclohexanecarboxamide with 5-bromopyrimidine, utilizing the *trans-N,N′*-dimethylcyclohexane-1,2-diamine ligand. Legraverend has reported the synthesis of purines from the one-pot amidation–condensation of 5-amino-4-iodopyrimidines with benzamides using the same ligand set. Given this precedence, we first applied these conditions to our first coupling reaction (Table 1, entries 1–4). However, instead of giving the desired pyrimidylbenzamide **10**, NMR analysis showed that these halopyrimidines had reacted with the diamine ligands to give the aminopyrimidines[22] via the copper-mediated *N*-aryl amination with the diamine ligand, as similarly described by Fukuyama with the amination of 2-iodopyridine.[23] We also tried the ligandless Goldberg protocol[24] (entries 5–7) which gave only a trace of the product as detected by LCMS. Other ligands typically used

Table 1. Optimization of the 1st *N*-Aryl Amidation[a]



entry	X	ligand	solvent	base	time	yield
1	Cl	dmeda	toluene	K_3PO_4	24 h	–
2	Br	dmeda	toluene	K_3PO_4	24 h	–
3	I	dmeda	toluene	K_3PO_4	24 h	–
4	I	diamine 2	dioxane	Cs_2CO_3	24 h	–
5	Cl	–	dioxane	K_3PO_4	24 h	–
6	Br	–	dioxane	K_3PO_4	24 h	<1%
7	I	–	dioxane	K_3PO_4	24 h	<1%
8	Cl	1,10-phen	toluene	K_3PO_4	18 h	–
9	Br	1,10-phen	toluene	K_3PO_4	18 h	69%
10	I	1,10-phen	toluene	K_3PO_4	24 h	71%
11	I	2,2′-bipy	toluene	K_3PO_4	24 h	37%
12	I	8-hq	toluene	K_3PO_4	24 h	14%
13	I	2,4,6-collidine	toluene	K_3PO_4	24 h	14%
14	I	*β*-ketoester	toluene	K_3PO_4	24 h	12%
15	I	1,10-phen	dioxane	K_3PO_4	18 h	72%

[a] Performed with 10 mol % CuI, 20 mol % ligand, 1.0 equiv of **2a**–**c**, 1.0 of equiv **3**, and 2.0 equiv of base; dmeda = *N,N′*-Dimethylethylenediamine; diamine 2 = *trans-N,N*-dimethylcyclohexyldiamine; 1, 10-phen = 1,10-phenanthroline; *β*-ketoester = Ethyl 2-cyclohexanone carboxylate; 8-hq = 8-hydroxyquinoline; 2,2′-bipy = 2,2′-bipyridine.

in copper-mediated chemistry were also screened (entries 8–14).[25–29] The most promising ligand for the reaction was found to be 1,10-phenanthroline giving pyrimidylbenzamide **10** in good yields. 4-Chloropyrimidine **2a**, however, was unreactive in any of the reaction conditions (entry 8), while 4-bromo- and 4-iodopyrimidines **2b** and **2c** exhibited similar yields (entries 9 and 10). This suggests that the coupling process does not occur via a nucleophilic aromatic substitution mechanism, wherein chlorides have been reported to react faster than bromides and iodides.[30] This rather supports the oxidative addition of the aryl halide to the copper complex as proposed earlier.[31]

We then proceeded with the coupling of pyrimidylbenzamide **10** and oxazolidine carboxamide **4**, for which 1, 10-phenanthroline was found to be a less competent ligand (Table 2, entry 1). The steric demands of the amide oxazolidine **4** in the copper complex may not be well suited for coupling when a very rigid Cu-phen complex[31] is involved, as compared to a more flexible Cu-diamine

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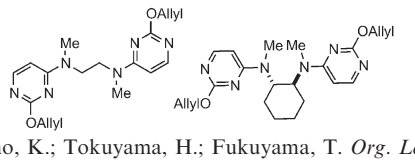

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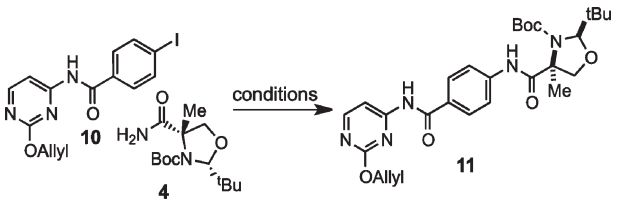
complex, which, in this case, has shown to be highly effective in mediating the amidation reaction.

Table 2. Optimization of the 2nd *N*-Aryl Amidation[a]



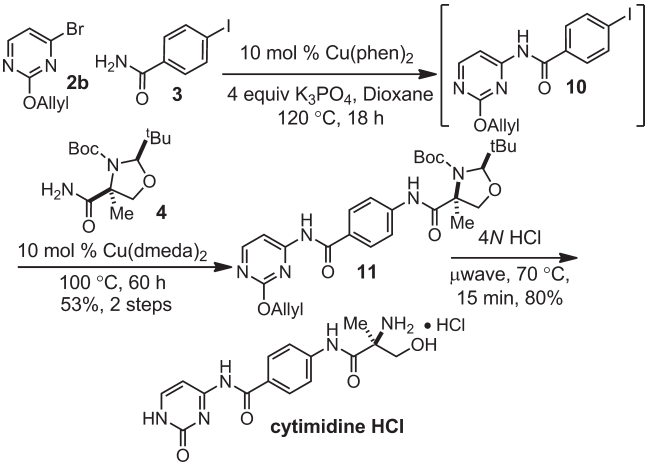
entry	ligand	solvent	base	temp	time	yield
1	1,10-phen	dioxane	K_3PO_4	120 °C	48 h	20%
2	dmeda	dioxane	K_3PO_4	100 °C	60 h	93%

[a] Performed with 10 mol % CuI, 20 mol % ligand, 1.0 equiv **10**, 1.0 equiv **4**, and 2.0 equiv base.

The differences in reactivities of the $Cu(phen)_2$ or $Cu(dmeda)_2$ ligand systems with respect to the first and second *N*-aryl amidations did not favor our initial goal of presenting a three-component tandem route toward cytimidine as described earlier (Scheme 1). The competing amination of 4-halopyrimidines **2a**–**c** with the diamine ligands in the first amidation and the incompatibility of the $Cu(phen)_2$ in the second amidation reaction essentially lead us to consider an alternative strategy.

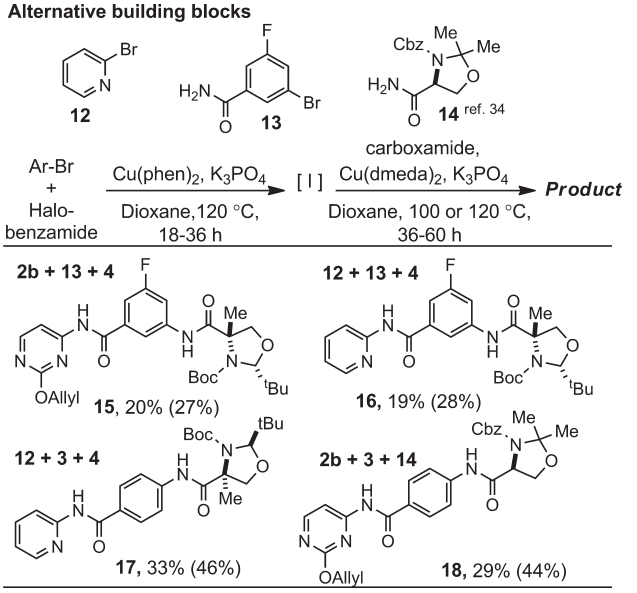
We then investigated the feasibility of a one-pot sequential amidation (Scheme 4). The sequential *N*-aryl amidation of bromopyrimidine **2b** with 4-iodobenzamide **3** and oxazolidine carboxamide **4** gave an overall 53% yield. Masked cytimidine **11** was then subjected to the final deprotection sequences[32] to give cytimidine in 34% overall yield in five steps from the commercially avaiable 4 chloro-2-methylthiopyrimidine.

Scheme 4. One-Pot Cu-Mediated *N*-Aryl Amidation and Completion of the Synthesis of Cytimidine



The method was then applied to a number of masked cytimidine analogues (Scheme 5). The yields obtained for these unoptimized couplings are slightly lower than those of our optimized coupling process for cytimidine but still represent ~60% for each step. We have observed that under these prolonged reaction times each substate's performance is dependent on competetive decomposition. In these reactions we were also unable to detect any of the homocoupled benzamide or the Ullmann[33] product by LCMS. We are currently trying to identify reaction conditions that obviate these issues. Nevertheless, this suggests that both bromo- and iodobenzamides can be chemoselectively cross-coupled with heterocyclic systems bearing a halogen adjacent to the heteroatom without competetive homocoupling.

Scheme 5. Synthesis of Cytimidine Analogues[a]



[a] Overall yields for the two-pot sequence with intermediate purification are given in parentheses.

In summary, we have developed an efficient route to cytimidine via a one-pot sequential Cu-mediated *N*-amidation cascade. This sequence exploits a uniquely regioselective coupling of a halopyrimidine and an iodobenzamide. Further investigation is underway to tailor the amidation sequences to generate medicinally relevant analogues of this natural product fragment.

Acknowledgment. We are grateful for financial support from the University of Utah Research Foundation and the Department of Chemistry, University of Utah.

Supporting Information Available. Experimental details and ^1H, ^{13}C, and ^{13}C DEPT NMR spectra for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

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