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Copper-Catalyzed Synthesis of Purine-Fused Polycyclics

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ABSTRACT

A novel protocol for a Cu-catalyzed direct $C_{(sp^2)}$–H activation/intramolecular amination reaction of 6-anilinopurine nucleosides has been developed. This approach provides a new access to a variety of multiheterocyclic compounds from purine compounds via Cu-catalyzed intramolecular N–H bond tautomerism which are endowed with fluorescence.

Purine nucleoside analogues are an important class of nitrogen-containing heterocycle that exhibit great therapeutic potential,[1] possessing anti-HCV,[2] antimicrobacterial,[3] and antineoplastic[4] activities. Although investigations into the modification of purine nucleosides have attracted increasing attention,[5] intramolecular C–H bond amination reactions on purine rings remain challenging due to their inherent reduced activity in metal-catalyzed transformations as a result of nitrogen coordination deactivating the catalyst. Moreover, it is known that the glycosidic bond is fragile and is often cleaved under harsh conditions. To the best of our knowledge, there are no reports on Cu-catalyzed C–H activaton/intramolecular amination reactions as a basis for the synthesis of purine nucleosides.

Employing C–H bond activation to obtain nitrogen-containing heterocycles with good biological activities has attracted extensive interest.[6]x The construction of nitrogen-containing heterocycles *via* the formation of C–N bonds through transition-metal-catalyzed C–H activation/amination reactions employing palladium,[7] rhodium,[8] and

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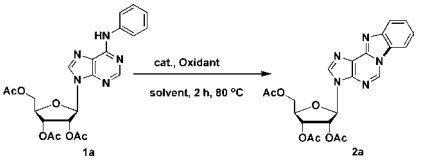
ruthenium[9] for example have shown certain advantages in some cases over more established procedures, such as Buchwald–Hartwig,[10] Ullmann, and Goldberg couplings.[11] Such direct C–H activaton/amination reactions require fewer steps and proceed under milder conditions in comparison to the more classical coupling reactions.[12] However, construction of these heterocycles *via* an intramolecular C–N bond formation strategy remains challenging. In this context, Buchwald reported on a C–H activation/intramolecular amination for carbazole synthesis catalyzed by palladium, which unveiled a new approach to the intramolecular formation of C–N bonds.[13]

Since then, Pd-catalyzed intramolecular direct amination of C–H bonds has been widely exploited and has now become well established.[7] More recently, metal-free or less expensive Cu-catalyzed direct C–N bond formation *via* C–H activation/amination utilizing various oxidants has become regarded as an effective and practical strategy, for the construction of such hetereocycles.[14]

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (5 mol %)	oxidant (1.5 equiv)	solvent	additive (1.5 equiv)	yield/ %[b]
1[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	PhMe	—	38
2[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	PhMe	K_2CO_3	48
3[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	PhMe	TFA	52
4[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	PhMe	NaOAc	55
5[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	DMF	—	30
6[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	AcOH	—	52
7	$Cu(OTf)_2$	$PhI(OAc)_2$	$AcOH/Ac_2O$	—	88
8	$Cu(OAc)_2$	$PhI(OAc)_2$	$AcOH/Ac_2O$	—	82
9	CuI	$PhI(OAc)_2$	$AcOH/Ac_2O$	—	42
10	CuBr	$PhI(OAc)_2$	$AcOH/Ac_2O$	—	44
11	$Cu(OTf)_2$	oxone	$AcOH/Ac_2O$	—	83
12	$Cu(OTf)_2$	$Fe_2(NO_3)_3 \cdot 9H_2O$	$AcOH/Ac_2O$	—	n.d.[d]
13	$Cu(OTf)_2$	BQ	$AcOH/Ac_2O$	—	82
14	$Cu(OTf)_2$	$K_2S_2O_8$	$AcOH/Ac_2O$	—	81

[a] Reaction conditions: **1a** (0.3 mmol), oxidant (0.45 mmol), AcOH (1 mL), Ac_2O (1 mL), 80 °C for 2 h. [b] Isolated yield. [c] solvent (2 mL), 120 °C for 24 h. [d] n.d. = not detected.

Herein, we report a copper-catalyzed intramolecular C–H bond amination reaction of purine and its derivatives related to our previous work.[15] By employing $PhI(OAc)_2$ as a simple oxidant, a useful and facile alternative process for the synthesis of purine-fused polycyclics is provided that might be useful in medicinal studies.

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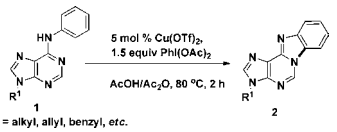
The direct C−H activation/intramolecular amination of 6-anilinopurine nucleoside **1a** using conditions optimized by Gaunt,[7k] albeit for a different reaction, led to no reaction. However the knowledge that copper could catalyze the carbazole formation reactions of Gaunt prompted us to further investigate conditions for our proposed reaction. Upon changing the copper source to $Cu(OTf)_2$ (5 mol %) along with $PhI(OAc)_2$ (1.5 equiv) as the oxidant in toluene at 120 °C for 48 h, cyclized product **2a** was formed, but only in 38% yield (unreacted **1a**, 40%) (Table 1, entry 1). Upon varying the additives and changing the solvent, improved yields were possible (Table 1, entries 2−7). Interestingly, it was found that the presence of Ac_2O significantly improved the reaction rate, and starting material **1a** was consumed within 2 h. Further investigation revealed that a 1:1 mixture of acetic acid and acetic anhydride was the optimal solvent. To our delight, under these conditions, **1a** readily cyclized to give compound **2a** in high yield (88%, Table 1, entry 7). Subsequently, several copper sources were also probed as

Table 2. Effect of N9-Substitutent[a]



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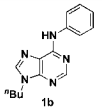
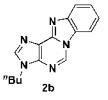
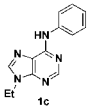
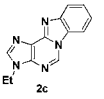
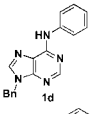
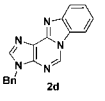
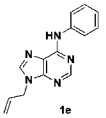
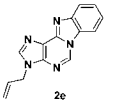
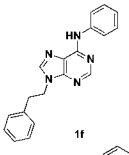
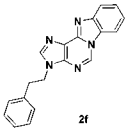
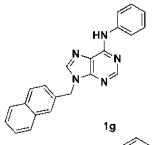
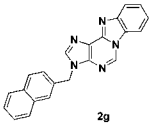
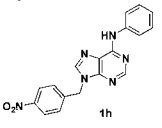
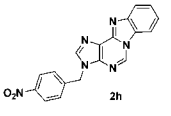
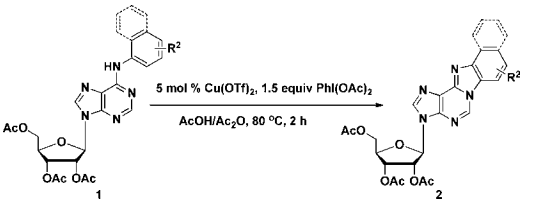
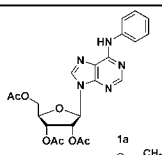
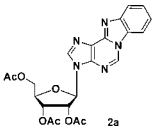
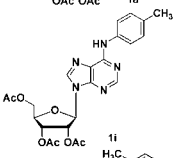
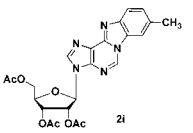
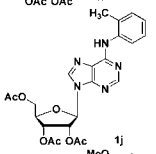
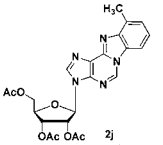
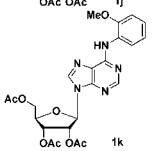
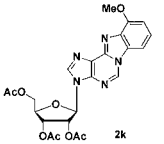
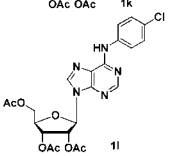
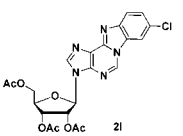
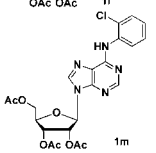
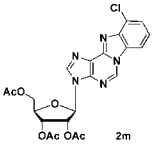
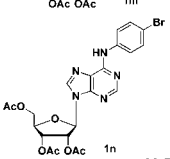
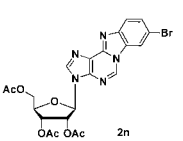
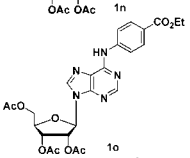
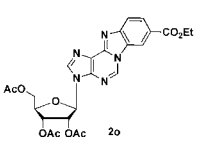
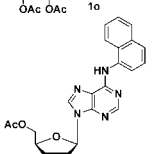
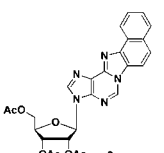
1			80
2			84
3			85
4			86
5			84
6			85
7			81

[a] The reactions were carried out with **1** (0.3 mmol), catalyst (5 mol %), oxidant (0.45 mmol), AcOH (1 mL), Ac_2O (1 mL) at 80 °C for 2 h. [b] Isolated yield.

Table 3. Electronic and Steric Effects[a]



entry	substrate	product	yield /%[b]
1			88
2			62
3			51
4			45
5			90
6			85
7			88
8			92
9[c]			40

[a] Unless otherwise stated, all reactions were carried out with **1** (0.3 mmol), catalyst (5 mol %), oxidant (0.45 mmol), AcOH (1 mL), Ac_2O (1 mL) at 80 °C for 2 h. [b] Isolated yield. [c] Reaction conditions: **1** (0.3 mmol), catalyst (5 mol %), oxidant (0.45 mmol), AcOH (1 mL), at 80 °C for 1 h, then 1 mL of Ac_2O was added and stirred for an additional 1 h.

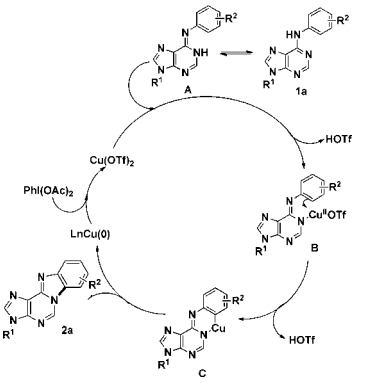
catalysts for the present reaction. Cu(II) exhibited better catalytic activity than Cu(I), and $Cu(OTf)_2$ won out as the copper source of choice (Table 1, entries 7−10). With $Cu(OTf)_2$ as the catalyst, a range of oxidants were tried (Table 1, entries 11−14). The yield observed with $PhI(OAc)_2$ as oxidant was higher than any other oxidant tried. As such the optimal conditions were determined to be 5 mol % of $Cu(OTf)_2$, 1.5 equiv of $PhI(OAc)_2$ in a mixture of AcOH and Ac_2O (1:1) as the solvent at 80 °C for 2 h.

With optimized conditions in hand, the scope of this intramolecular amination reaction was next tested. As shown in Table 2, a series of N9-substituted substrates, including alkyl, benzyl, allyl, *etc*., afforded the corresponding cyclized products in good to excellent yields (**2b**−**2h**). Thus it may be concluded that the N9-substituents have little effect on the course of the reaction. Notably, the tolerance of the reaction to the presence of double bonds offers an ideal opportunity for further synthetic manipulation (**2e**).

To explore the electronic and steric effects of substituents on the aniline ring, the reactions of **1i**−**1o** were investigated. Each reaction proceeded smoothly to afford the corresponding product **2i**−**2o** in moderate to high yield (Table 3, entries 1−8). Among these reactions substrates with electron-withdrawing groups gave higher yields than those with electron-donating groups. Steric effects may also play a role since further studies showed that the substrates with substiuents at the *ortho* position of the aniline ring were less reactive than those with a *para* substituent (entries 2−3, 5−6). Particularly noteworthy is the reaction of 6-(*o*-chloroaniline)-purine-nucleoside **1m** which gave exclusively product **2m**, demonstrating that the present catalytic system exploiting a C−H activation/amination reaction was more readily executed than traditional Ullman-type couplings (entry 6). Although optimized conditions generally worked well compound **1p** did not cyclize under these conditions. Various cyclization attempts unveiled conditions where it was possible to obtain compound **2p** by adjusting the acetic anhydride addition time, but the yield was still lower than that with other substrates (entry 9).

Based on the previous studies of intramolecular C−H activation/amination reactions[7i,14d] and our experimental results, a plausible catalytic cycle was outlined in Scheme 1. Coordination of $Cu(OTf)_2$ with substrate **A**, followed by an electrophilic substitution process, yields a Cu(II) intermediate **C**. Reductive elimination delivers Cu^0, which can be reoxidize to regenerate $Cu(OTf)_2$ to close the Cu^{II}/Cu^0 catalytic cycle.

Scheme 1. Plausible Catalytic Cycle



It was envisaged that the nucleoside derivatives prepared in this study might be useful as fluorescent tags in biological scenarios. For the investigation of fluorescence properties, see the Supporting Information.

In conclusion, we have developed an intramolecular C−H activation/amination reaction of purine nucleosides to synthesize a series of multiheterocyclic compounds, which are of great importance in medicinal chemistry. To the best of our knowledge, this is the first example that uses an intramolecular C−H activation/amination reaction for the synthesis of purine nucleosides, which offers facile alternative access to some useful multifused ring purine-heterocyclic compounds. The fluorescence of these purine nucleoside compounds will be helpful for the study of their medicinal relevance. Further studies into the mechanism and the role of acetic anhydride are currently planned.

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Supporting Information Available. Typical experimental procedures, characterization of compounds, compound spectroscopic information, and the investigation of fluorescence properties. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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