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Synthesis of 7-Aza-5-deazapurine Analogues via Copper(I)-Catalyzed Hydroamination of Alkynes and 1-Iodoalkynes

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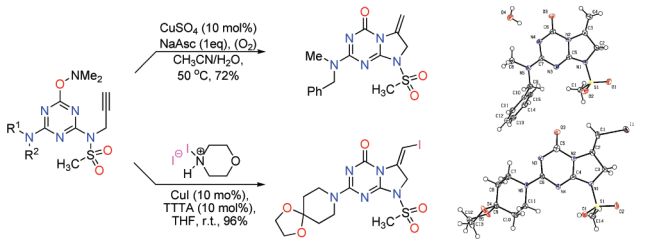
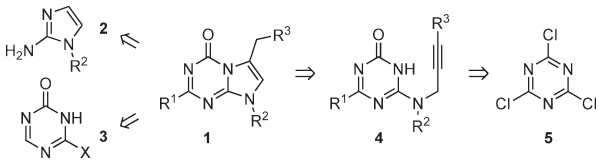


A new method for the synthesis of dihydroimidazo[1,2-*a*]-[1,3,5]triazin-4(6*H*)-ones via copper(I)-catalyzed hydroamination was developed. In addition, for the first time, iodoalkynes were shown to participate in the copper(I)-catalyzed intramolecular hydroamination reaction with exclusive formation of *E*-isomers.

The unique role that purine and pyrimidine heterocycles play in biology makes them timeless subjects of research in disciplines encompassing the fields of organic synthesis, medicinal chemistry, biotechnology, and materials science.[1] Small molecules containing the imidazo[1,2-*a*]-*s*-triazine fragment, which is an analogue of 5-aza-7-deazapurine, have shown promising activity in the treatment of type 1 diabetes, rhinovirus infections and against the *Flaviviridae* family of viruses.[2] Whether the goal is the discovery of compounds with new biological function or expansion of the genetic alphabet, a methodology that allows simple and reliable access to novel purine analogues would be a valuable addition to these fields. Herein, we report a new approach toward dihydroimidazo[1,2-*a*][1,3,5]triazinone derivatives via a copper-catalyzed hydroamination, delivering a practical, scalable, and versatile route to these rarely studied heterocycles.

The construction of imidazo[1,2-*a*]-*s*-triazine (**1**) core can commence from 2-aminoimidazole (**2**),[1c,3a,b] 5-azacytosine (**3**, X = NH_2),[3c,d] or 1,3,5-triazine heterocycles (**3**, X = Cl) (Scheme 1).[2a,b,3e,f] However, these methodologies have not proven to be practical due to the low conversions and limited substrate scope. We envisioned assembling the imidazo-[1,2-*a*]-*s*-triazine ring system via transition-metal-catalyzed hydroamination of alkynyl triazinones **4**,[4] which are easily accessible from cyanuric chloride (**5**).

SCHEME 1. Synthetic Routes to 7-Aza-5-deazapurines



First, we examined the effect of different transition metal catalysts on the intramolecular cyclization of triazine **6** as a model substrate. The results of a focused screen employing group 11 transition metals are presented in Table 1.[5] Although gold(I) and silver(I) salts promoted the reaction at ambient temperature, the yields were moderate, and long reaction times were required (entries 1 and 2). In contrast, copper(I) salts were more active catalysts for the desired intramolecular cyclization (entries 3−11).[6] The addition of water increased the yield of the reaction (cf. entries 3 and 4). The optimal results were obtained when copper(I) acetylide was generated in situ (entries 9−11).[7] The addition of tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (TBTA) ligand further improved the efficiency of the reaction (entry 11).[8]

A general method for the preparation of 1,3,5-triazine-2-ones (**4**) was then investigated. Temperature-controlled sequential displacement of chlorines in **5** provides facile access to substituted 1,3,5-triazines (Scheme 1).[9] However, conversion of less electrophilic intermediates, such as **8**, to the corresponding

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(5) An expanded screen of catalysts can be found in the Supporting Information.

(6) For a recent example of a one-pot cascade Mannich−Cu(I)-promoted hydroamination of alkynes, see: Wang, H.-F.; Yang, T.; Xu, P.-F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916–3918.

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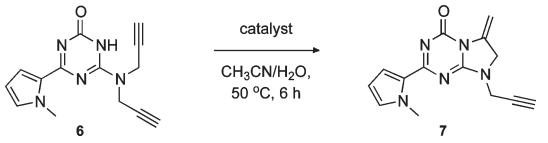
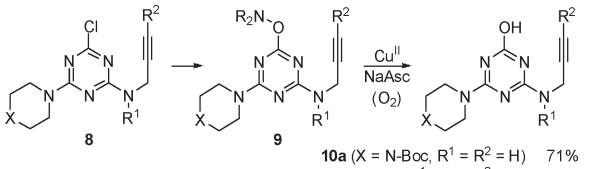
TABLE 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive	yield,[b] %
1	$Au(PPh_3)Cl$[c]	$AgBF_4$ (5 mol %)	44
2	$AgNO_3$[d]		60
3	$[Cu(CH_3CN)_4]PF_6$[e]		52
4	$[Cu(CH_3CN)_4]PF_6$		64
5	CuOTf × $^1/_2$ PhMe		42
6	CuOAc		46
7	CuI		60
8	CuTC		68
9	$CuSO_4$	NaAsc (20 mol %)	70
10	$CuSO_4$	NaAsc (1 equiv)	82
11	$CuSO_4$	NaAsc (20 mol %), TBTA (10 mol %)	99

[a]Conditions: **6** (0.5 mmol), 10 mol % of catalyst, CH_3CN/H_2O (2/1, 0.1M), 50 °C, 6 h unless noted otherwise. [b]Isolated yield of **7**. [c]5 mol %, DCE, rt, 48 h. [d]20 mol %, CH_3CN, rt, 48 h. [e]CH_3CN without water.

SCHEME 2. Cleavage of N−O Bond with Cu(II)/NaAsc/O_2

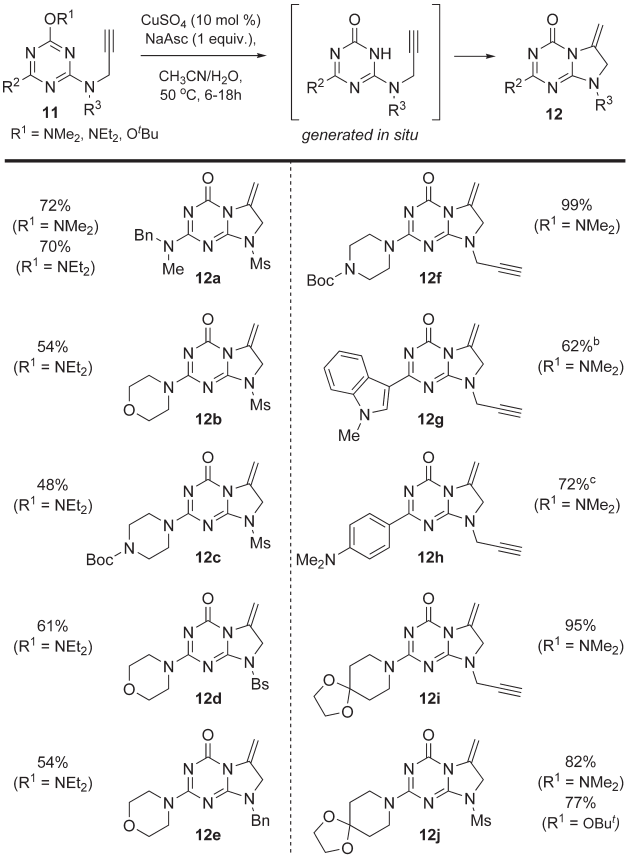


1,3,5-triazin-2-ol (**10**) via direct addition of hydroxide is problematic (Scheme 2).[5]

N,N-Dialkylhydroxylamine-substituted triazines (**9**) have been converted to the corresponding hydroxyl derivatives under acidic conditions or with prolonged heating.[10] While these conditions failed to produce the desired product, treatment of **9** with $CuSO_4$ and sodium ascorbate gave the desired 1,3,5-triazin-2-ol (**10**). In order to achieve good conversions, a stoichiometric amount of sodium ascorbate has to be employed.[11]

With the developed procedure in hand, the scope of the direct intramolecular hydroamination was examined (Figure 1). Both *N*-dimethyl- and *N*-diethylhydroxylamine derivatives were utilized and gave similar results (**12a**).[12] The regiochemistry of **12a** was confirmed by single-crystal X-ray analysis, allowing the geometry of other cyclized products to be inferred via ^1H and ^{13}C NMR. While most substrates were easily converted to the corresponding dihydroimidazo[1,2-*a*][1,3,5]triazinones using the optimized conditions within 12−18 h, cyclization to give **12g** and **12h** was markedly slow requiring the use of a ligand (TBTA or its analogue, tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl)amine, TTTA).

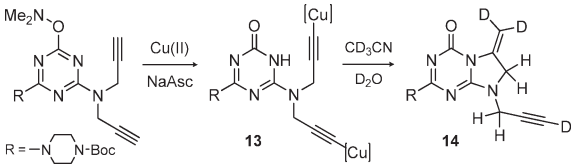
1,3,5-Triazines containing the N*H*-propargyl group (**10a**) or internal alkynes (**10b**) failed to undergo cyclization (Scheme 2). The latter result points to the activation of the alkyne via σ-copper acetylide intermediate, which was supported by the results of a deuterium-labeling experiment (Scheme 3). The reaction performed in deuterated solvent



[a] *General Reaction Conditions:* $CuSO_4$ (10 mol %), sodium ascorbate (1 equiv), CH_3CN/H_2O (2/1, 0.1M), 50 °C, unless specified otherwise; [b] in the presence of TBTA (10 mol %); [c] in the presence of TTTA (10 mol %).

FIGURE 1. Substrate scope for the Cu(I)-catalyzed hydroamination.

SCHEME 3. Deuterium-Labeling Experiment

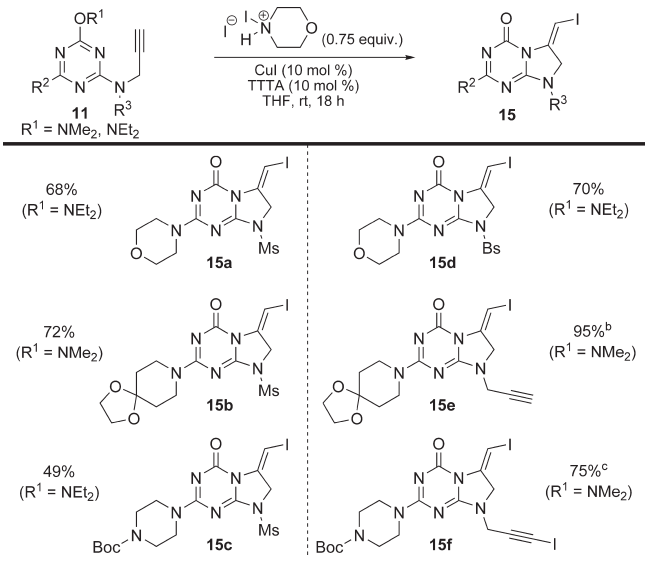


showed exchange of only acetylenic protons, excluding the intermediacy of allene species.

In principle, the acetylide intermediate can be trapped with other electrophiles in situ, for example, with electrophilic iodine reagents. Our group recently reported a copper-catalyzed iodination of terminal alkynes with *N*-iodomorpholine.[13] In addition, a CuI/TTTA catalytic system was shown to activate 1-iodoalkynes toward the cycloaddition with organic azides.[13] We envisioned that the same catalytic system could be employed in hydroamination of 1-iodoalkynes. Thus, several substrates were treated with *N*-iodomorpholine in the presence of CuI and TTTA (Figure 2) forming vinyl iodide **15** via 5-exo-dig cyclization of the transient 1-iodoalkyne. Strikingly, this process generated **15b** as a single regioisomer, as confirmed by the X-ray analysis.

The LC−MS analysis of the reaction mixture at different time points indicated that the annulation proceeds through a

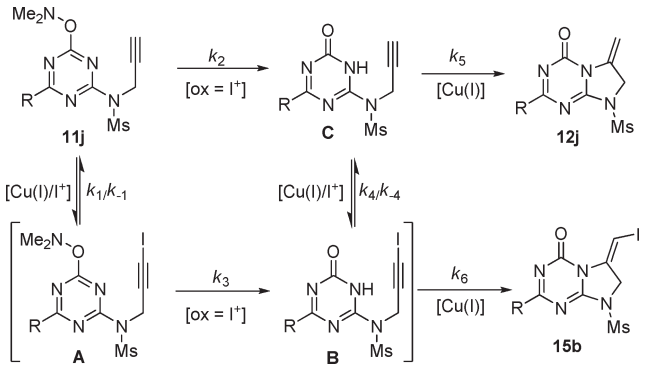
(10) Sanders, M. E.; Ames, M. M. *Tetrahedron Lett.* **1985**, *26*, 5247–5250.
(11) We are currently investigating the mechanism of this transformation; a comprehensive report will be published in due course.
(12) *tert*-Butyl peroxide derivatives can be used with equal success (cf. **12j**).
(13) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018–8021.



[a] *General Reaction Conditions:* CuI (10 mol %), TTTA (10 mol %), THF (0.1M), rt, 18 h; [b] 1.5 equiv. of *N*-iodomorpholine; [c] 2 equiv. of *N*-iodomorpholine.

FIGURE 2. Substrate scope for Cu(I)-catalyzed cyclization.

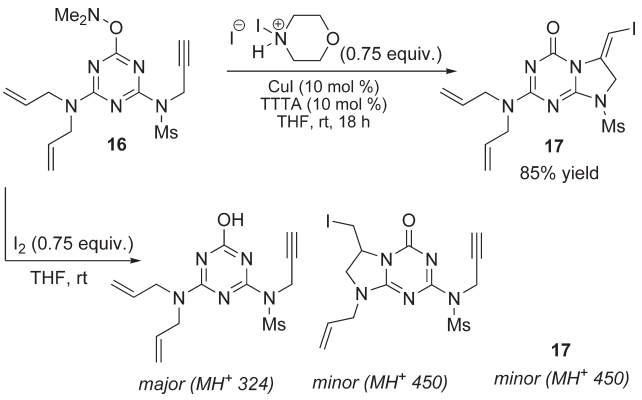
SCHEME 4. Proposed Sequence of Steps for One-Pot Generation of 1-Iodoalkynes and Following Cyclization



series of steps outlined in Scheme 4. We observed formation of intermediates **A**−**C** during the course of the reaction. Under the optimized reaction conditions, intermediates **A** and **B** predominate and led to the formation of **15b**. The presence of a proton source and suboptimal Cu(I)/*N*-iodomorpholine/substrate ratios led to the accumulation of intermediate **C** and, as a result, generation of byproduct **12j**. Since formation of the desired product may be affected by multiple equilibria, the optimal ratio of the starting material to *N*-iodomorpholine is substrate dependent and was optimized on a case by case basis. Regardless of the substrate, Cu(I) and TTTA are essential for the formation of vinyl iodide **15b**. Treatment of **11j** with *N*-iodomorpholine for 24 h at ambient temperature in the absence of a copper catalyst gave a mixture consisting mostly of starting material and a small amount of iodoallkyne **A**.

Thus, preliminary results suggest that the Cu(I)/*N*-iodomorpholine system acts as a mild oxidant, and its reactivity toward alkynes is fundamentally divergent from the iodoamination reaction, which is characterized by lower chemo- and

SCHEME 5. Comparative Study of the Reaction Promoted by CuI/*N*-Iodomorpholine vs Iodine



regioselectivity.[14] To further support this proposal, we prepared starting material **16** and subjected it to the optimized reaction conditions and, separately, to the treatment with iodine (Scheme 5). After 18 h at room temperature, the copper-catalyzed reaction produced exclusively **17** in 85% isolated yield, whereas reaction with iodine resulted in a complex mixture of at least four compounds.[15]

In summary, the new hydroamination protocol allowed generation of dihydroimidazo[1,2-*a*][1,3,5]triazinones. Further, 1-iodoalkynes were shown, for the first time, to participate in the copper(I)-catalyzed intramolecular hydroamination reaction with the exclusive formation of the *E*-vinyl iodides. The procedures are simple to perform, utilize inexpensive reagents, and easily provide access to densely decorated purine analogues containing functional groups amenable for further derivatization.

Experimental Section

Procedure for Intramolecular Hydroamination. Synthesis of 6-Methylene-8-(methylsulfonyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-7,8-dihydroimidazo-[1,2-*a*][1,3,5]triazin-4(6*H*)-one (12j). A reaction flask was charged with *N*-(4-(dimethylaminooxy)-6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-1,3,5-triazin-2-yl)-*N*-(prop-2-ynyl)methanesulfonamide (**11j**) (1.50 g, 3.64 mmol), $CuSO_4$ (365 μL, 1M, 10 mol %), and acetonitrile/water mixture (2:1, 35 mL). After addition of sodium ascorbate (0.72 g, 3.64 mmol), the reaction flask was capped and heated at 50 °C for 5 h.[16] Upon completion, the reaction mixture was cooled and quenched with NH_4OH/brine solution (10 mL, 1:1). The yellow crystalline precipitate was collected by filtration, washed with NH_4OH/brine and water, and dried in vacuo. Compound **12j** was obtained as a yellow solid (1.10 g, 82% yield): mp 206 °C dec; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.82 (s, 1H), 4.59 (s, 2H), 3.96 (s, 6H), 3.91 (s, 2H), 3.38 (s, 3H), 1.71 (s, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.1, 156.1, 152.5, 132.5, 106.9, 97.8, 64.7, 48.3, 42.9, 42.8, 41.3, 35.4, 34.9; HRMS (ESI) 370.1180 (MH^+) (exact 370.1180 for $C_{14}H_{20}N_5O_5S$).

Procedure for One-Pot Generation of Iodoalkyne and Intramolecular Cyclization. Synthesis of (*E*)-6-(Iodomethylene)-8-(methylsulfonyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-7,8-dihydroimidazo-[1,2-*a*][1,3,5]triazin-4-(6*H*)-one (15b). Compound **11j** (300 mg,

(14) Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581–6590.

(15) Retention times and molecular ion obtained by LCMS analysis were used in structure assignment. Another major intermediate of molecular ion 576 corresponds to the addition of two iodine atoms to intermediate of general structure **C** (Scheme 4).

(16) White precipitate of oxy-triazine intermediate is formed within first 30 min and gradually disappears as a reaction progresses toward **12j**.

0.73 mmol), copper iodide (14 mg, 0.073 mmol, 10 mol %), TTTA (31 mg, 0.073 mmol, 10 mol %), and *N*-iodomorpholine (186 mg, 0.55 mmol) were mixed together in dry THF (7.5 mL, 0.1 M). The reaction tube was flushed with N_2, sealed, and stirred at room temperature for 18 h. Upon completion, the reaction mixture was quenched with satd NH_4Cl (10 mL), and the product was allowed to crystallize upon slow removal of organic solvent. Beige-yellow precipitate was collected by filtration, washed with satd NH_4Cl (10 mL), washed extensively with water, and dried in vacuo to give **15b** (259 mg, 96% yield): mp 200.5 °C dec; ^{1}H NMR (600 MHz, DMSO) δ 7.11 (t, J = 2.8 Hz, 1H), 4.50 (d, J = 2.7 Hz, 2H), 3.92 (s, 4H), 3.87−3.82 (m, 2H), 3.82−3.79 (m, 2H), 3.47 (s, 3H), 1.70−1.62 (m, 4H); ^{13}C NMR (151 MHz, D_2O) δ 161.1, 156.1, 151.1, 134.8, 106.2, 63.9, 61.5, 53.4, 42.2, 42.0, 39.8, 34.6, 34.2; HRMS (ESI) 496.0140 (MH^+) (exact 496.0146 for $C_{14}H_{19}IN_5O_5S$). Crystal suitable for the X-ray crystallographic analysis was obtained upon slow crystallization from water/DMSO mixture.

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Supporting Information Available: Experimental procedures, compound characterization data, crystallographic information files (CIFs), and copies of ^{1}H, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.