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Cu-Catalyzed C–H Activation Reaction: One-Pot Direct Synthesis of Xanthine and Uric Acid Derivatives from 5-Bromouracil

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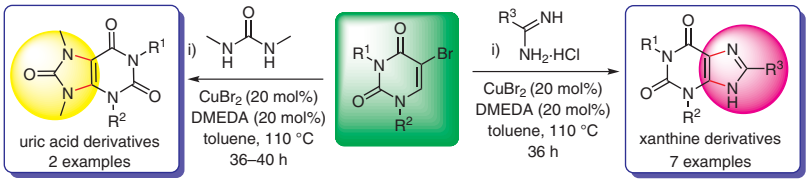

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Abstract A one-pot direct synthesis of xanthine and uric acid derivates is reported. This simple yet efficient methodology illustrates concurrent formation of two C–N bonds using $CuBr_2$ as catalyst and one of those C–N bonds is formed by uracil C6–H bond activation.

Key words C–H activation, C–N bond formation, xanthine, uric acids, copper, one-pot cyclization

Metal-catalyzed C–N bond formation is a topic of extreme importance to the synthetic chemists[1] and much attention has been given in developing newer methods. The bulk share of focus was deployed for the development of Ullmann N-arylations[2] and the palladium-catalyzed amination of aryl halides, pioneered by the laboratories of Buchwald and Hartwig.[3] Very recently a surge of interest has been poured in developing methods for constructing C–N bonds by direct aromatic C–H functionalization. Most of these reactions utilize Pd(II) as catalysts.[4] In this context we have also developed a Pd/Cu co-catalytic system for indole C2–H bond functionalization.[5] In 2008, Buchwald and coworkers reported a novel method in their effort to synthesize benzimidazoles from amidines by Cu(II)-catalyzed intramolecular C–H activation reaction.[6]

Substituted xanthine derivatives are well-known for their pharmacological activities,[7] as adenosine receptor antagonists, inducers of histone deacetylase, phosphodiesterase inhibitors, etc. For example, denbufylline and pentoxifylline are potent phosphodiesterase inhibitors (Figure 1).[8–10] Whereas theophylline and 1,3-dimethylxanthine, which naturally occur, are extensively utilized as an antiasthmatic drug,[11,12] lisofylline, another xanthine derivative, is an experimental anti-inflammatory drug.[13] The plant alkaloid caffeine, 1,3,7-trimethylxanthine, on the other hand, is the most frequently used psycho stimulant drug worldwide.[14] Caffeine is central nervous system and metabolic stimulant[7] and it has huge positive[15] effects on human body. It decreases the risk of cardiovascular disease and type 2 diabetes.[15c] Crude caffeine has potent hydrophilic antioxidant activity (145 µmol Trolox equivalent TE/g) and lipophilic antioxidant activity (66 µmol TE/g). It also inhibits cyclooxygenase-2 with a higher potency (IC50, 20 lg/mL) in comparison to aspirin (IC50, 190 lg/mL). It also increases glucose uptake 1.45-fold in cultured human skeletal muscle cells and 2.20-fold in adipocytes.[16] So far as the side effect is concerned, the excess use of it may increase the chance of bladder cancer.[17] Previously, xanthine derivatives were prepared from uracil in mainly three ways. The first method involves multiple steps, from 5,6-disubstituted uracil and amidines,[18a] in the second method 5,6-diaminouracil was microwave irradiated with triethyl orthoformate (not shown here),[18b] and the third way involves treating sodium azide with 5-halo-6-substituted uracil (Scheme 1).[19]

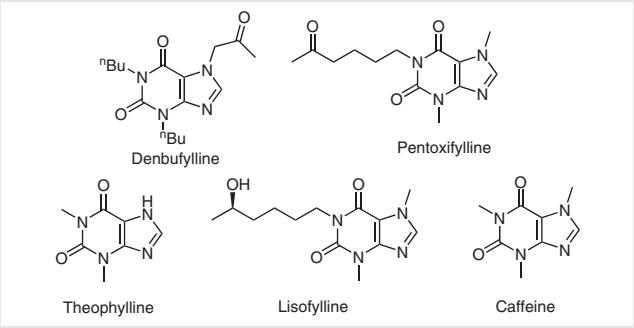

Figure 1 Xanthine drugs

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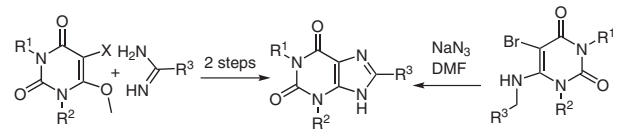
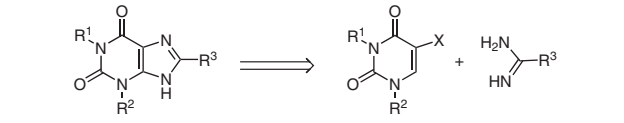


Scheme 1 Previous synthesis of xanthine derivative

We envisioned that if we would manage to activate the uracil C6–H bond[20] to form a C–N bond, a possible disconnection could be hypothesized which would bring high degree of variability into the core structure of xanthine derivatives. Our goal was to carry out an amidination reaction on 5-halouracil with amidine and then to explore the amidinated product for a C–H activation study (Scheme 2).

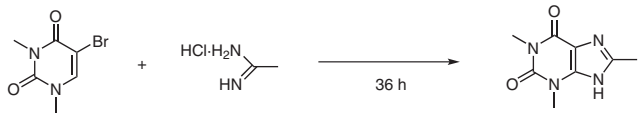


Scheme 2 Our disconnection strategy at the ring fusion

At the outset, we treated 5-bromouracil with acetamidine under various metal-free conditions (explorations were done with the amount of amidine, temperature, solvent, and introduction of base, not shown in Table 1), but failed to obtain the amidinated product.

As there are a number of methods available for similar amination or amidination reactions where copper[21,22] or palladium[23] were used as catalysts, so we first attempted the amidination reaction of 5-bromouracil with $Pd_2(dba)_3$ catalysts. We noticed that it resulted in complete debromination when polar solvents like DMAc or dioxane were used (Table 1, entries 2, 4) and in nonpolar solvent (*o*-xylene) 5-bromouracil (**2a**) remained intact. Changing the base also did not alter the course of the reaction (Table 1, entries 1, 3). We then started exploring the amidination reaction with copper salts. Interestingly, when CuI (10 mol%) was used in the presence of K_2CO_3 and DMEDA (10 mol%, ligand) in toluene at 110 °C, it gave the xanthine derivative **3a** along with some debrominated product and not the amidinated product. This exciting result prompted us to explore further

Table 1 Optimization of Amidination and C–H Activation Reaction[a]



2a **1** **3a**

Entry	Cat (mol%)	Additive/base	Temp (°C)	Solvent	Yield (%)[b]	Conv. (%)
1	$Pd_2(dba)_3$	Cs_2CO_3, Xanthphos	110	*o*-xylene	N.R.	0
2	$Pd_2(dba)_3$	Cs_2CO_3, Xanthphos	100	dioxane	debromination	100
3	$Pd_2(dba)_3$	Nat-BuO	110	*o*-xylene	N.R.	0
4	$Pd_2(dba)_3$	Nat-BuO	110	DMAc	debromination	100
5	CuI	K_2CO_3, DMEDA	110	toluene	40	80
6	CuBr	K_2CO_3, DMEDA	110	toluene	10	50
7	$CuCl_2$	K_2CO_3, DMEDA	110	toluene	20	60
8	$CuBr_2$	K_2CO_3, DMEDA	110	toluene	66	65
9	$CuBr_2$	Cs_2CO_3, DMEDA	110	toluene	debromination	100
10	$CuBr_2$	Cs_2CO_3, DMEDA	110	toluene	82[c]	72
11	$CuBr_2$	KOAc, DMEDA	110	toluene	20	65
12	$CuBr_2$	K_3PO_4, DMEDA	110	toluene	14	60
13	$CuBr_2$	Cs_2CO_3, DMEDA	110	DMF	–	15
14	$CuBr_2$	Cs_2CO_3, DMEDA	100	dioxane	–	21
15	$CuBr_2$	Cs_2CO_3, DMEDA	110–130	*o*-xylene	10	80
16	$CuBr_2$	Cs_2CO_3, L-proline	110	toluene	25	70
17	$CuBr_2$	Cs_2CO_3, 1,10-phen	110	toluene	22	62
18	$CuBr_2$	Cs_2CO_3, DMEDA	140	toluene	36	90

[a] Reaction conditions: 5-bromouracil (1 equiv), acetamidine hydrochloride (2 equiv), Cs_2CO_3 (3 equiv), $CuBr_2$ (20 mol%), DMEDA (20 mol%).
[b] Yields were calculated after flash chromatography.
[c] Reaction performed in sealed tube; N.R. = no reaction.

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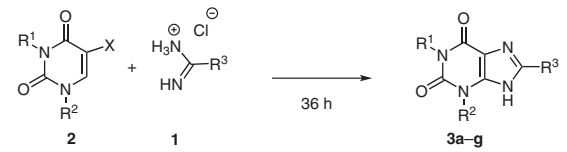
for the preparation of xanthine derivatives in one pot. We noticed that the reaction under inert atmosphere (after degassing the reaction mixture) produced greater amount of the desired product and suppressed the formation of debrominated product to a large extent. However, the reaction was sluggish in nature. An increase in catalyst and ligand loading to 20 mol% resulted in a better yield of the product **3a** (40%, 36 h, Table 1, entry 5). CuBr did not respond very well in the desired transformation as it gave mostly the debrominated uracil along with the product (10%, Table 1, entry 6). Then we tried other Cu(II) salts for the transformation. The use of $Cu(OAc)_2$ was not fruitful as it resulted in the debromination of the substrate (Table 1, entry 9). $CuCl_2$ yielded the product (20%) along with some debrominated product (Table 1, entry 7), but $CuBr_2$ was found to be more effective as the yield increased to 66% (conversion 65%) and very small amount of debrominated product was formed (Table 1, entry 8). Then we explored further with $CuBr_2$ salts under different conditions. The roles of other bases were screened. Eventually a better yield (82%) was observed (Table 1, entry 10) with Cs_2CO_3 (conversion 72%), but the formation of debrominated product could not be avoided entirely. Other bases like KOAc and K_3PO_4 were found to be less useful (Table 1, entries 11, 12). We then changed the solvent system and the polar solvents behaved very poorly in this reaction. In DMF and dioxane, neither the debrominated product nor the xanthine product was formed. Most of the starting materials remained intact while some of it got decomposed (Table 1, entries 13, 14). In *o*-xylene, the reaction was carried out in 110 °C at first for 24 h and then the temperature was increased to 130 °C. The yield was disappointing (10%) resulting mainly in the debrominated product. The optimization of ligands ensured that DMEDA is by far the most effective compared to L-proline or 1,10-phenanthroline (Table 1, entries 16, 17). We then carried out the reaction in sealed tube at 140 °C, but the yield was moderate and the amount of debrominated product was also greater, if compared to entry 10 (Table 1, entry 18).

With the optimized reaction conditions[24] in hand, we explored the substrate scope of the reaction. The yield of the reaction was moderately good with various uracil substrates (66–82%) depicted in Table 2. One major setback was the debrominated product, as we could not stop its formation entirely, and another was the moderate conversion of the substrate in spite of carrying out the reaction for longer periods of time (36 h). However, when we ran the reaction with a mixture of **2e** and **2e′** (1:1), where the *n*-Bu and Et groups were exchanged on uracil N-atoms, we isolated the corresponding products in a 3:2 ratio (in favor of **2e′**), as a mixture in a combined yield of 66%.

Therefore, we assume a steric effect operates and produces the **3e′** as the major product (Table 2, 3e/**3e′**). We also found that the benzamidine took part in this reaction efficiently (Table 2, 3f and **3g**). The 5-iodouracil is believed to be a good substrate for this reaction, but under the set of our reaction conditions only the deiodination product was obtained. 5-Fluorouracil was also employed as a substrate for the reaction, but it failed to deliver the corresponding product owing to its poor leaving-group capacity.

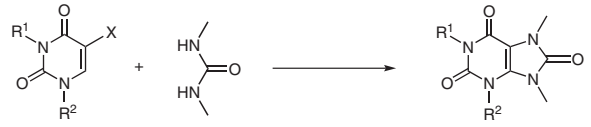
We then wanted to explore the same methodology for the formation of uric acid derivatives, and we successfully synthesized two uric acid derivatives **4** with *N*,*N*-dimethylurea. The reaction was found to be a little bit sluggish compared to acetamidine analogues. The amount of debrominated product was slightly greater (conversion around 70%). The yields of the products were 65% and 56%, respectively (Table 3).

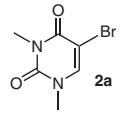
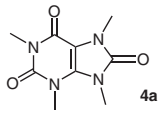
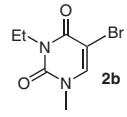
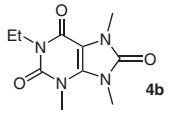
Table 2 Synthesis of Xanthine Derivatives



Product **3**	R^1	R^2	R^3	Yield (%)
3a	Me	Me	Me	82
3b	Et	Me	Me	81
3c	Et	Et	Me	77
3d	Et	*n*-Pr	Me	68
3e/**3e′**	*n*-Bu/Et		Me	66
3f	Me	Me	Ph	75
3g	Et	Et	Ph	82

Table 3 Synthesis of Uric Acid Derivatives[a]



Entry	Starting material **2**	Product **4**	Time (h)	Yield (%)[b]
1	 **2a**	 **4a**	36	65
2	 **2b**	 **4b**	40	56

[a] Reaction conditions: 5-bromouracil (1 equiv), *N*,*N*-dimethylurea (2 equiv), Cs_2CO_3 (3 equiv), $CuBr_2$ (20 mol%), DMEDA (20 mol%) refluxed in toluene at 110 °C.
[b] Yields were calculated after flash chromatography.

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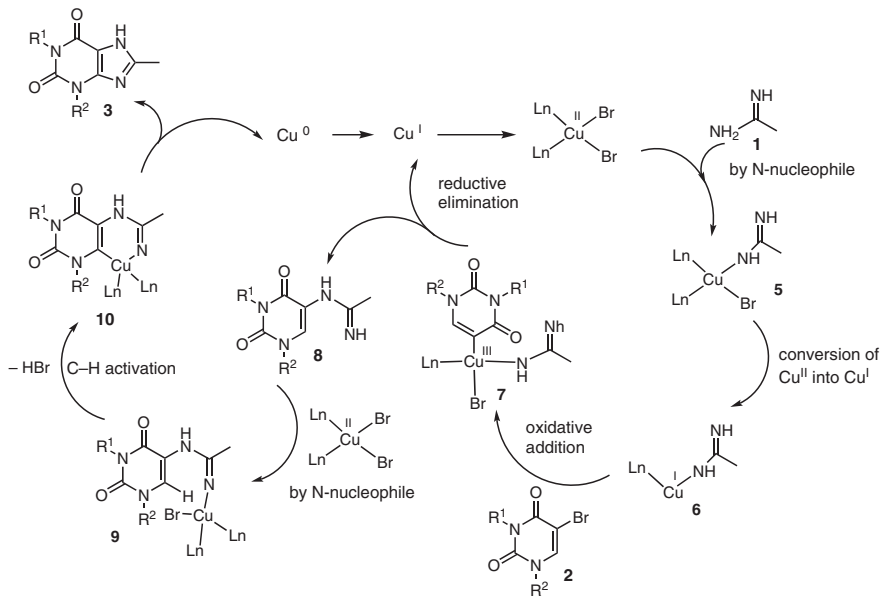

Scheme 3 Proposed mechanism of the reaction

Under metal-free conditions 5-bromouracil did not react at all, and in the presence of Pd salts debromination was observed. The mechanistic pathway of copper-mediated coupling reaction has been extensively studied by Yu Lan and his group.[25] In a recent study, they have shown that the Cu^{II} species can be generated from Cu^{I} by radical-type reaction or single-electron transfer (SET) oxidation and it can also be oxidized to Cu^{III} species by SET or using a nucleophilic radical.[25] Based on the literature precedents[21,22,25,26] a hypothesized mechanism of this reaction is depicted in Scheme 3.

The acetamidine **1** reacts with Cu^{II} to form the adduct **5** which subsequently produces the intermediate **6**. The oxidative addition of **6** to the uracil **2** provides intermediate **7**. The reductive elimination of **7** generates compound **8** and Cu^{I} species. The Cu^{I} on further oxidation produces Cu^{II} species in the cycle. In compound **8** where nitrogen acts as a nucleophile reacted with Cu^{II} and produces intermediate **9** in which a suitable C–H bond is present for activation. The C6–H bond of uracil gets activated and a new Cu–C bond is formed as shown in the intermediate **10**. Further, the reductive elimination of **10** produces the desired compound **3**.

In conclusion, we have developed a very important method for the synthesis of xanthine and uric acid derivatives by Cu-catalyzed C–H activation reaction. Though the reaction is sluggish in nature, the one-pot convergence of two components uracil and amidine or *N*,*N*-dimethylurea, makes it a very unique and interesting reaction. It leads to the simultaneous formation of two C–N bonds without preactivating uracil C6–H bond. Considering the one-pot nature of the reaction, the yield of the reaction is undoubtedly very good.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1542-9683.

References

(1) (a) Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011**, 1. (b) Bellina, F.; Rossi, R. *Adv. Synth. Catal.* **2010**, *352*, 1223. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (e) Wu, X.-F.; Neumann, H. *Adv. Synth. Catal.* **2012**, *354*, 3141. (f) Ranu, B. C.; Dey, R.; Chatterjee, T.; Ahammed, S. *ChemSusChem* **2012**, *5*, 22.

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(2) (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; Angew. Chem. 2003, 115, 5558. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054; and references therein.
(3) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (d) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (e) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (f) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (g) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (h) Sperotto, E.; van Klink, G. P. M.; van Kotenand, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338. (i) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
(4) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Xiao, Q.; Wang, W. -H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem. Eur. J.* **2009**, *15*, 7292.
(5) Hazra, S.; Mondal, B.; Rahaman, H.; Roy, B. *Eur. J. Org. Chem.* **2014**, 2806.
(6) Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1932.
(7) (a) Kalla, R. V.; Elzein, E.; Perry, T.; Li, X.; Palle, V.; Varkhedkar, V.; Gimbel, A.; Maa, T.; Zeng, D.; Zablocki, J. *J. Med. Chem.* **2006**, *49*, 3682. (b) Lin, R.-Y.; Wu, B.-N.; Lo, Y.-C.; An, L.-M.; Dai, Z.-K.; Lin, Y.-T.; Tang, C.-S.; Chen, I.-J. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 709. (c) Ito, K.; Lim, S.; Caramori, G.; Cosio, B.; Chung, K. F.; Adcock, I. M.; Barnes, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 8921.
(8) Nicholson, C. D.; Jackman, S. A.; Wilke, R. *Br. J. Pharmacol.* **1989**, *97*, 889.
(9) Thiel, M.; Bardenheuer, H.; Poech, G.; Madel, C.; Peter, K. *Biochem. Res. Commun.* **1991**, *180*, 53.
(10) Palacios, J. M.; Beleta, J.; Segarra, V. *Farmaco* **1995**, *50*, 819.
(11) Daly, J. W. *Analogs of caffeine and theophylline: Activity as antagonists at adenosine receptors. In 'Role of Adenosine and Adenine Nucleotides in the Biological System'*. Imai, S.; Nakazawa, M. Eds.; Elsevier Science Publishers: Amsterdam, **1991**, 119–129.
(12) Stefanovich, V. *Drug News Perspect.* **1989**, *2*, 82.
(13) Bright, J. J.; Du, C.; Coon, M.; Sriram, S.; Klaus, S. J. *J. Immunol.* **1998**, *161*, 7051.
(14) Daly, J. W.; Fredholm, B. B. *Drug Alcohol Depend.* **1998**, *51*, 199.
(15) (a) Ding, M.; Bhupathiraju, S. N.; Satija, A.; van Dam, R. M.; Hu, F. B. *Circulation* **2014**, *129*, 643. (b) Ker, K.; Edwards, P. J.; Felix, L. M.; Blackhall, K.; Roberts, I. *Cochrane Database Syst. Rev.* **2010**, *CD008508*, DOI: 10.1002/14651858.CD008508. (c) van Dam, R. M. *Appl. Physiol. Nutr. Metab.* **2008**, *33*, 1269. (d) Muriel, P.; Arauz, J. *Fitoterapia* **2010**, *81*, 297.
(16) Chu, Y.-F.; Chen, Y.; Brown, P. H.; Lyle, B. J.; Black, R. M.; Cheng, I. H.; Ouc, B. X.; Prior, R. L. *Food Chem.* **2012**, *131*, 564.
(17) Arab, L. *Nutr. Cancer* **2010**, *62*, 271.
(18) (a) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833. (b) Burbiel, J. C.; Hockemeyer, J.; Müller, C. E. *ARKIVOC* **2006**, *(ii)*, 77.
(19) Hirota, K.; Sako, M.; Sajiki, H. *Heterocycles* **1997**, *46*, 547.
(20) Roy, B.; Hazra, S.; Mondal, B.; Majumdar, K. C. *Eur. J. Org. Chem.* **2013**, 4570.
(21) (a) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2598. (b) Carril, M.; SanMartin, R.; Domínguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639.
(22) Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463.
(23) (a) Anbazhagan, M.; Stephens, C. E.; Boykin, D. W. *Tetrahedron Lett.* **2002**, *43*, 4221. (b) Fulp, A. B.; Johnson, M. S.; Markworth, C. J.; Marron, B. E.; Seconi, D. C.; Wang, X.; West, C. W.; Zhou, S. WO 2009012242, **2009** (c) Yin, J. J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481. (d) Zhang, H. Q.; Xia, Z. R.; Vasudevan, A.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4881.
(24) **General Procedure for the Preparation of Xanthine Derivatives**
To an oven-dried 25 mL round-bottom flask was added 5-bromouracil (1 mmol), acetamidine or benzamidine hydrochloride (1.4 mmol), $CuBr_2$ (0.2 mmol), and Cs_2CO_3 (3 equiv) under nitrogen. Dry toluene (2 mL) was added with a syringe, and the mixture was degassed for 30 min. Then DMEDA (20 mol%) was added via a syringe under nitrogen. After the resulting reaction mixture was stirred for 36 h, the product was extracted with ethyl acetate and washed with water three times. The organic layer was dried over anhydrous Na_2SO_4 and filtered. Following concentration under reduced pressure, the residue was purified by silica gel chromatography to elute the product.
1,3,8-Trimethyl-1*H*-purine-2,6(3*H*,9*H*)-dione (3a)
Yield 82%; mp >225 °C. IR (neat): 1644, 1709, 2965, 3049, 3105, 3158 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.59 (s, 3 H, CCH_3), 3.47 (s, 3 H, NCH_3), 3.62 (s, 3 H, NCH_3), 12.16 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.7, 28.3, 30.2, 106.6, 149.6, 151.5, 152.0, 155.8. HRMS (TOF, MS, ES^+): *m/z* calcd for $C_8H_{10}N_4O_2H$ $[M^+ + H]$: 195.0882; found: 195.0874.
(25) Li, S.-J.; Lan, Y. *Chem. Commun.* **2020**, *56*, 6609.
(26) (a) Zhang, C.; Jiao, N. *J. Am. Chem Soc.* **2010**, *132*, 28. (b) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *8*, 1475.

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