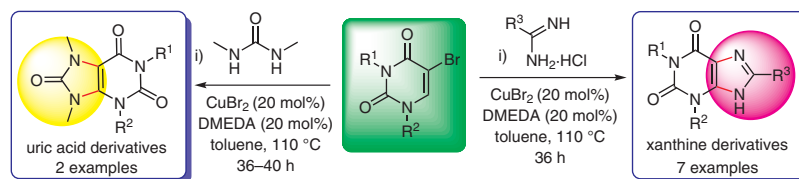


Cu-Catalyzed C–H Activation Reaction: One-Pot Direct Synthesis of Xanthine and Uric Acid Derivatives from 5-Bromouracil

Somjit Hazra^a
 Biplab Mondal^a
 Brindaban Roy^{*a}
 Habibur Rahman^{*b}

^a Department of Chemistry, University of Kalyani, Kalyani, Nadia, West Bengal, India
 broybsku@gmail.com
 broybs@rediffmail.com

^b Department of Chemistry, Ranaghat College, Ranaghat, Nadia, West Bengal, 741201, India
 hr1977@gmail.com



Received: 25.05.2021

Accepted after revision: 02.07.2021

Published online: 02.07.2021

DOI: 10.1055/a-1542-9683; Art ID: st-2021-b0203-l



Abstract A one-pot direct synthesis of xanthine and uric acid derivatives is reported. This simple yet efficient methodology illustrates concurrent formation of two C–N bonds using CuBr₂ 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 chemists¹ and much attention has been given in developing newer methods. The bulk share of focus was deployed for the development of Ullmann N-arylations² 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 co-workers 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 stimulant⁷ and it has huge positive¹⁵ 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

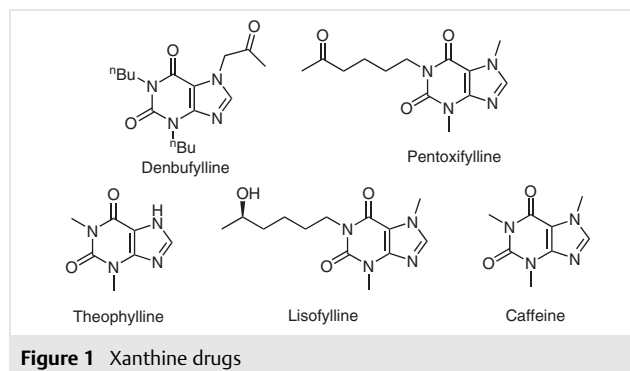
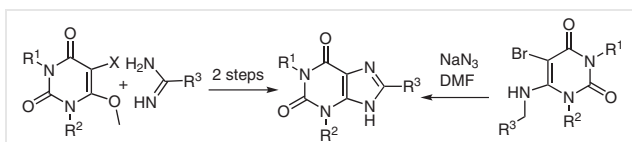
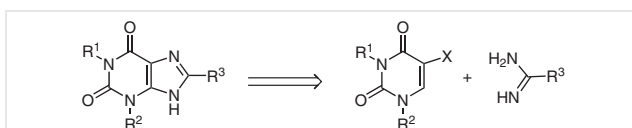


Figure 1 Xanthine drugs



Scheme 1 Previous synthesis of xanthine derivative

We envisioned that if we would manage to activate the uracil C6–H bond²⁰ 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).

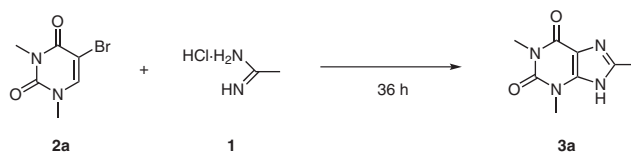


Scheme 2 Our disconnection strategy at the ring fusion

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 palladium²³ were used as catalysts, so we first attempted the amidination reaction of 5-bromouracil with Pd₂(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 K₂CO₃ 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



Entry	Cat (mol%)	Additive/base	Temp (°C)	Solvent	Yield (%) ^b	Conv. (%)
1	Pd ₂ (dba) ₃	Cs ₂ CO ₃ , Xanthphos	110	<i>o</i> -xylene	N.R.	0
2	Pd ₂ (dba) ₃	Cs ₂ CO ₃ , Xanthphos	100	dioxane	debromination	100
3	Pd ₂ (dba) ₃	Nat-BuO	110	<i>o</i> -xylene	N.R.	0
4	Pd ₂ (dba) ₃	Nat-BuO	110	DMAc	debromination	100
5	CuI	K ₂ CO ₃ , DMEDA	110	toluene	40	80
6	CuBr	K ₂ CO ₃ , DMEDA	110	toluene	10	50
7	CuCl ₂	K ₂ CO ₃ , DMEDA	110	toluene	20	60
8	CuBr ₂	K ₂ CO ₃ , DMEDA	110	toluene	66	65
9	CuBr ₂	Cs ₂ CO ₃ , DMEDA	110	toluene	debromination	100
10	CuBr ₂	Cs ₂ CO ₃ , DMEDA	110	toluene	82 ^c	72
11	CuBr ₂	KOAc, DMEDA	110	toluene	20	65
12	CuBr ₂	K ₃ PO ₄ , DMEDA	110	toluene	14	60
13	CuBr ₂	Cs ₂ CO ₃ , DMEDA	110	DMF	–	15
14	CuBr ₂	Cs ₂ CO ₃ , DMEDA	100	dioxane	–	21
15	CuBr ₂	Cs ₂ CO ₃ , DMEDA	110–130	<i>o</i> -xylene	10	80
16	CuBr ₂	Cs ₂ CO ₃ , L-proline	110	toluene	25	70
17	CuBr ₂	Cs ₂ CO ₃ , 1,10-phen	110	toluene	22	62
18	CuBr ₂	Cs ₂ CO ₃ , DMEDA	140	toluene	36	90

^a Reaction conditions: 5-bromouracil (1 equiv), acetamidine hydrochloride (2 equiv), Cs₂CO₃ (3 equiv), CuBr₂ (20 mol%), DMEDA (20 mol%).

^b Yields were calculated after flash chromatography.

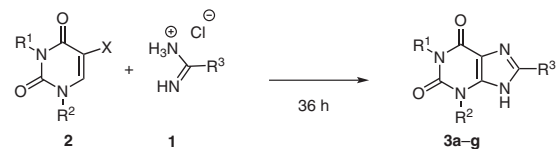
^c Reaction performed in sealed tube; N.R. = no reaction.

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 product 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). CuCl₂ yielded the product (20%) along with some debrominated product (Table 1, entry 7), but CuBr₂ 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 CuBr₂ salts under different conditions. The roles of other bases were screened. Eventually a better yield (82%) was observed (Table 1, entry 10) with Cs₂CO₃ (conversion 72%), but the formation of debrominated product could not be avoided entirely. Other bases like KOAc and K₃PO₄ 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 conditions²⁴ 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

Table 2 Synthesis of Xanthine Derivatives

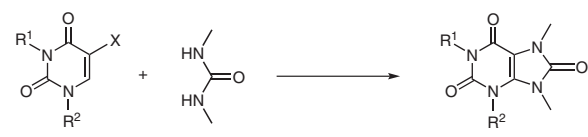


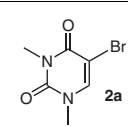
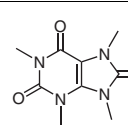
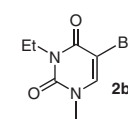
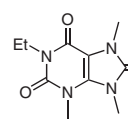
Product 3	R ¹	R ²	R ³	Yield (%)
3a	Me	Me	Me	82
3b	Et	Me	Me	81
3c	Et	Et	Me	77
3d	Et	<i>n</i> -Pr	Me	68
3e/3e'		<i>n</i> -Bu/Et	Me	66
3f	Me	Me	Ph	75
3g	Et	Et	Ph	82

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 acetamide analogues. The amount of debrominated product was slightly greater (conversion around 70%). The yields of the products were 65% and 56%, respectively (Table 3).

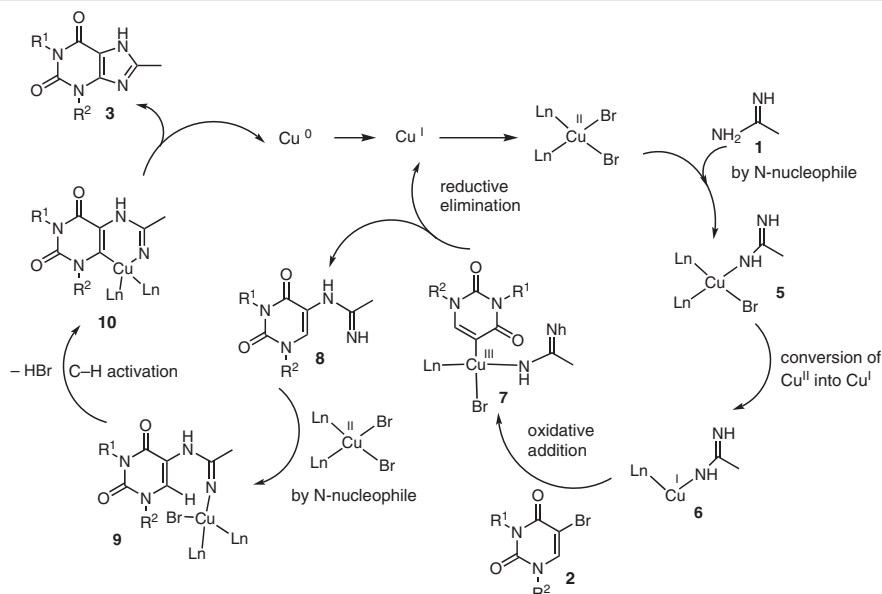
Table 3 Synthesis of Uric Acid Derivatives^a



Entry	Starting material 2	Product 4	Time (h)	Yield (%) ^b
1			36	65
2			40	56

^a Reaction conditions: 5-bromouracil (1 equiv), *N,N*-dimethylurea (2 equiv), Cs₂CO₃ (3 equiv), CuBr₂ (20 mol%), DMEDA (20 mol%) refluxed in toluene at 110 °C.

^b Yields were calculated after flash chromatography.



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 pre-activating 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.

Funding Information

We thank the Department of Science and Technology, Ministry of Science and Technology, India (DST, New Delhi) for financial assistance through DST PURSE program and DST fast track scheme. Two of us (SH & BM) are thankful to CSIR (New Delhi) and University of Kalyani, respectively, for research fellowships.

Acknowledgment

We thank the DST (New Delhi) for providing FT-IR, NMR spectrometer (400 MHz) and CHN analyzer.

Supporting Information

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

References

- (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.

- (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.; Zabolcki, 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), CuBr₂ (0.2 mmol), and Cs₂CO₃ (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 Na₂SO₄ and filtered. Following concentration under reduced pressure, the residue was purified by silica gel chromatography to elute the product.
1,3,8-Trimethyl-1H-purine-2,6(3H,9H)-dione (3a)
Yield 82%; mp >225 °C. IR (neat): 1644, 1709, 2965, 3049, 3105, 3158 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 2.59 (s, 3 H, CCH₃), 3.47 (s, 3 H, NCH₃), 3.62 (s, 3 H, NCH₃), 12.16 (s, 1 H, NH). ¹³C NMR (CDCl₃, 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 C₈H₁₀N₄O₂H [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.