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Influence of Solvent and Oxidant in Copper-Catalyzed Synthesis of Xanthine Skeletons

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An interesting approach for the synthesis of xanthine skeletons by a copper-catalyzed reaction between *N*,*N*′-dialkylated 5-bromouracil derivatives and amidines are being reported. The coupling reaction was promoted by catalytic amount of $Cu(OAc)_2$ in the presence of molecular O_2. The 1,4-dioxane was found to be a better solvent for the reaction and the reaction was believed to go through a *N*-arylation and subsequent C-H activation/C-N bond formation process.

Keywords: Copper, Coupling reaction, Xanthine, C-H activation, Molecular oxygen, C-N Bond formation.

INTRODUCTION

Transition-metal catalyzed C-N bond coupling has been established as a useful tool in modern organic synthesis [1]. Copper catalysts are known to be as a promising alternative in metal-catalyzed oxidative coupling reactions to replace costly metal catalysts such as palladium and rhodium [2-10]. The organocopper(III) intermediate in the catalytic cycle of copper species enabled numerous important organic transformations such as arylation, alkenylation and alkynylation reactions [11-17].

Copper catalyzed transformation is predominating in a field of synthetic chemistry may be due to its low-cost and readily accessibility [18-26]. It is important to note that more mole-culer diversity and complexity would be introduced since there was either transitional metal catalysis pathway or radical path-way for copper catalysis. Substituted xanthine derivatives are well known for their pharmacological activities [27-29], as adeno-sine receptor antagonists, inducers of histone deacetylase and phosphodiesterase inhibitors, *etc*. In this field of research, Jacobson *et al*. [30,31] reported some xanthine derivatives endowed with good affinity but limited significant selectivity for the human A_{2B} adenosine receptor subtype. An evolution of this study led to the synthesis of 8-phenylxanthine-carboxylic acid congeners, which proved to be potent and selective A_{2B} antagonists. In particular, the derivative I, proved to be the most potent and selective A_{2B} adenosine receptor antagonist ever reported [32]. The plant alkaloid caffeine, 1,3,7-trimethylxanthine II, on the other hand, is the most frequently used psycho stimulant drug worldwide [33]. Caffeine is central nervous system and metabolic stimulant [30] and it has huge positive [34-37] effects on human body. It decreases the risk of cardiovascular disease and type 2 diabetes (Fig. 1) [36].

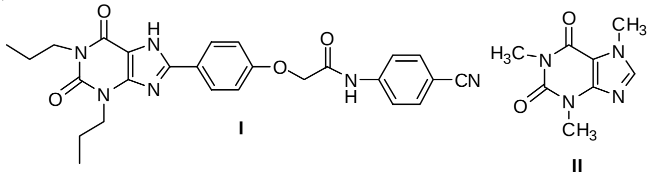


Fig. 1 Structure of caffeine and its derivatives

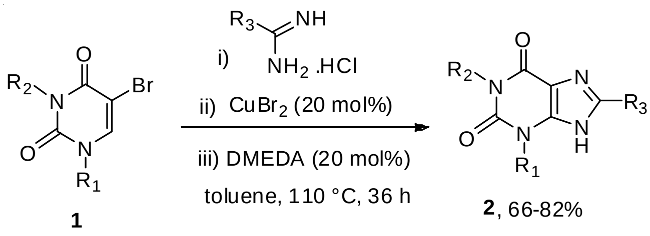
Based on these observations, we envisaged that a proper combination of copper species and oxidants would promote an intramolecular oxidative C-N bond formation for the synthesis of xanthine skeleton which is an important structural motif having a diverse range of applications, hence, a new practical synthetic method for the preparation of xanthine is highly desired.

EXPERIMENTAL

Synthesis of xanthine derivatives: To an oven-dried sealed tube was added 5-bromouracil (1 mmol), acatamidine or benzamidine hydrochloride (1.3 mmol), $Cu(OAc)_2$ (20 mol%), in 1,4-dioxane under oxygen medium. The resulting reaction mixture was heated in at 100 ºC for 16 h and the crude residue was purified by silica gel chromatography to elute the product. The NMR and other spectroscopic data can be accessed from our published paper [38].

RESULTS AND DISCUSSION

Recently, we have reported Cu-catalyzed one pot direct synthesis of xanthine and uric acid derivatives from 5-bromo uracil. The $CuBr_2$ was found to be the effective catalyst for the amidation reaction (**Scheme-I**) [38]. However, major setback of the reaction was the debrominated product as we could not stop its formation entirely and the moderate conversion of the substrate in spite of carrying out the reaction for longer periods of time. It is noticed that the reaction under inert atmosphere produced greater amount of desired product but the reaction was sluggish in nature.



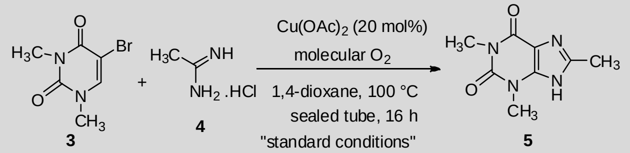
Scheme-I

The systematically choice of catalyst, solvent and oxidant is explored to overcome our reported problems. Oxidation reactions are extremely challenging because their selectivity is hard to control and/or they form significant quantities of unwanted waste derived from the stoichiometric oxidants. Undoubtedly, the utilization of green oxidants such as molecular oxygen (O_2) provides tunable oxidation abilities and produces no environmentally hazardous byproducts. We had attempted the amidination reaction of 5-bromo uracil (**3**) with $Cu(OAc)_2$ catalyst. Interestingly, when $Cu(OAc)_2$ (20 mol %) was used in the presence of molecular oxygen (O_2) in 1,4-dioxane at 100 ºC for 16 h, it gave exclusively the xanthine derivative **5** in 94% yield. It is noticed that the reaction resulted in complete conversion of the starting material when solvent dioxane was used (Table-1, entry 1) and in other polar or non-polar solvent 5-bromo uracil (**3**) did not yielded the desired coupling products (Table-1, entries 2-6). Changing of the catalyst loading and alteration of oxidant led to little desired products (Table-1, entries 7 and 8).

A variety of Cu(I) and Cu(II) sources led to significantly less efficient coupling products (Table-1, entries 9-14). Upon surveying an array of reaction parameters, a procedure is identified that achieves the desired coupling (Table-1, entry 1; 94% yield). Control experiments establish the importance of $Cu(OAc)_2$, molecular O_2 and dioxane (entries 1); notably, in our standard set of reaction conditions [38], no debrominated product was formed.

Further, the substrate scope of the reaction was also explored. The yield of the reaction was excellent with various uracil substrates depicted in Table-2. The xanthine derivatives (**5-10**) were isolated in 91-94% yields.

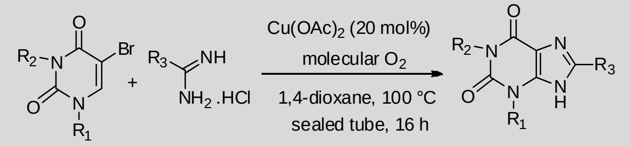
TABLE-1
CU-CATALYZED COUPLING REACTION:
EFFECT OF REACTION PARAMETERS

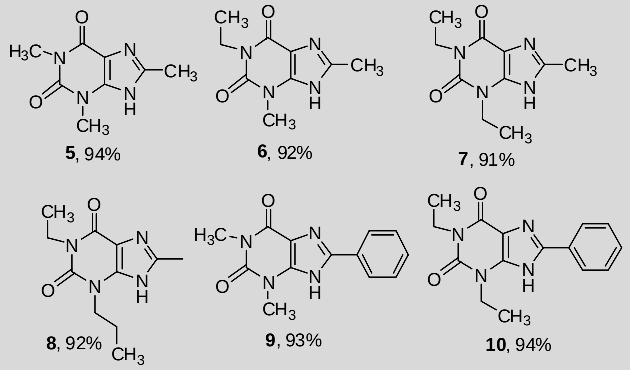


Entry	Changed form the "standard conditions"	Yield (%)[a]
1	None	94
2	THF instead of dioxane	No reaction
3	Toluene instead of dioxane	No reaction
4	*o*-Xylene instead of dioxane	No reaction
5	DMF instead of dioxane	No reaction
6	CH_3CN instead of dioxane	No reaction
7	$Cu(OAc)_2$ (10 mol%)	52
8	$K_2S_2O_8$ instead of molecular O_2	15
9	CuI instead of $Cu(OAC)_2$	< 1
10	CuCl instead of $Cu(OAC)_2$	< 1
11	CuBr instead of $Cu(OAC)_2$	< 1
12	$CuBr_2$ instead of $Cu(OAC)_2$	< 1
13	CuCN instead of $Cu(OAC)_2$	< 1
14	$CuCl_2$ instead of $Cu(OAC)_2$	< 1

[a] Yields were determined after isolation and purification of the products.

TABLE-2
CU-CATALYZED COUPLING REACTION:
EFFECT OF SUBSTITUTION





The mechanistic pathway of copper-mediated coupling reaction has been extensively studied by several researchers [39-44]. Recently, a mechanism for xanthine formation is explored [38] and it is believed that this reaction proceeds in the pathways as follows: (i) Cu^I adduct formation, (ii) oxidative addition to form the Cu^{III} species, (iii) reductive elimination, (iv) C-H activation and subsequent copper-carbon bond formation, (v) reductive elimination followed by product formation. The molecular oxygen plays an important role to convert Cu^0 to Cu^I to Cu^{II}. In short, the reaction was believed to go through a *N*-arylation and subsequent C-H activation/C-N bond formation process.

Conclusion

In conclusion, an interesting green oxidant approach for the synthesis of xanthine skeletons by a copper-catalyzed reaction between *N*,*N*′-dialkylated 5-bromouracil derivatives and acetamidine or benzamidine is developed. The Cu-catalyzed coupling reaction in the presence of molecular oxygen took shorter time and the yields of the reactions were better than earlier reported. Screening of the solvents revealed that 1,4-dioxane was influential and no debrominated product was formed by this approach. It is believed that copper-catalyzed green oxidation transformations can be made even more eco-friendly and economical in the synthesis of valuable compounds.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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