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Concise Xanthine Synthesis via a Double Amidination Reaction of a 6-Chlorouracil with Amidines using Base Metal Catalysis

Bénédicte Morel,[a] Philippe Franck,[a] Johan Bidange,[a] Sergey Sergeyev,[a] Dan Smith,[b] Jonathan Moseley,[b] Bert U. W. Maes*[a]

Abstract: A novel and concise route towards xanthines via a double amidination reaction is described; consecutive intermolecular C-Cl and intramolecular oxidative C-H amidination. *N*-uracil amidines are obtained via S_NAE on a 6-chlorouracil with amidines. Direct Cu-catalyzed oxidative C-H amidination on these *N*-uracil amidines yields polysubstituted xanthines. Sustainable oxidants, di-*tert*-butyl peroxide or oxygen, can be used in this oxidase type reaction. The protocol allows for the introduction of N1, N3, N7 and C8 substituents during the xanthine scaffold construction, thus avoiding post-functionalization steps. Both 6-chlorouracils and amidines are readily available commercially or through synthesis.

Introduction

The purine scaffold is one of the most important heterocyclic motifs and can be considered as a privileged scaffold in medicinal chemistry.[1] Purine derivatives, such as xanthines, display a wide variety of biological activities and this core can be found in natural products (e.g. caffeine, theobromine) and APIs (e.g. Linagliptin, Dasantafil, Bamifylline and Istradefylline).[2] The most common way to synthesize xanthines is known as the Traube synthesis (Scheme 1),[3] involving imidazole ring formation via condensation of a one-carbon fragment (an activated carboxylic acid[4] or an aldehyde[5]) with a 5,6-diaminouracil. The latter is made via nitrosation of a 6-aminouracil followed by reduction. A second general but less frequently applied synthetic approach to xanthines builds up the uracil ring via addition of an alkyl 4-aminoimidazole-5-carboxylate to an isocyanate, which then cyclizes under basic conditions.[6] This route is less attractive as the pre-functionalized imidazole substrate requires a multi-step synthesis. Herein we report a new and general approach towards N1, N3, N7 and C8 substituted xanthines, involving two consecutive C-N bond forming steps starting from readily available N1, N3 substituted 6-chlorouracils (**A**) (Scheme 1). S_NAE of the C6 halogen by an amidine leads to an *N*-uracil amidine (**B**), which can be further converted to the corresponding xanthine (**C**) via a direct oxidative amidination reaction.[7] The required amidine reagents can be easily prepared using a Pinner approach, starting from the corresponding nitriles and amines, and allow installation of R^7 at N7 regioselectively.[8,9] In comparison to the Traube synthesis our approach is shorter, prevents a post-functionalization step on N7 of the xanthine, and avoids a two-step pre-activation, involving nitrosation with unstable nitrous acid and subsequent reduction, at C5 of the uracil precursor.[10] These aspects make our approach attractive from a sustainable chemistry point of view.

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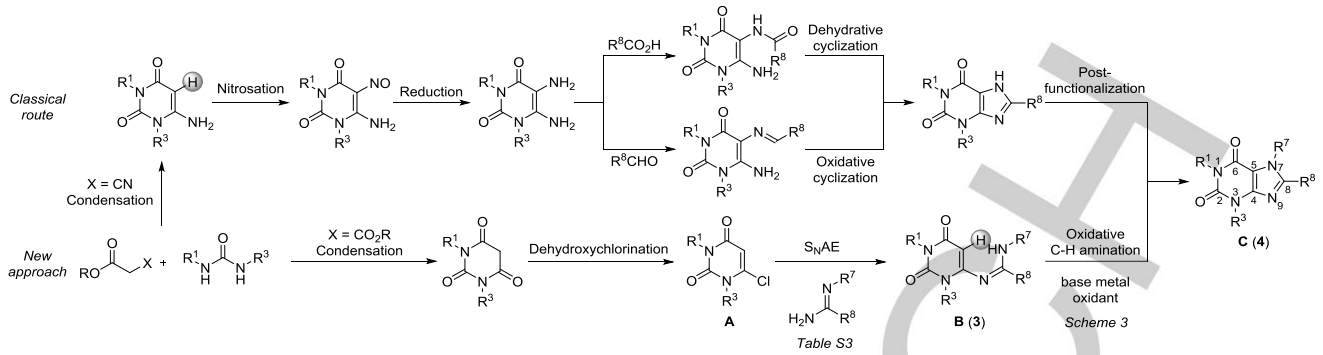
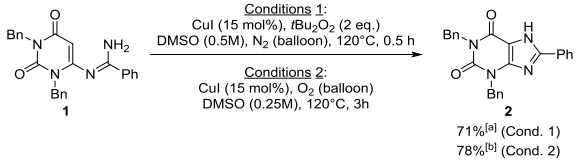
Results and Discussion

Two protocols were developed towards the synthesis of *N*-uracil amidines **3** via S_NAE on 6-chlorouracils (Table S3). The first one requires 2.3 equivalents of amidine, acting both as nucleophile and base, in 3-ethyl-3-pentanol at 100°C. The second one uses 1.5 equivalents of amidine in combination with 0.7 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *tert*-butanol at 80°C Alcohols as solvent and DBU as a base are preferred from a sustainability point of view.[11] The latter approach is especially interesting for expensive amidines. Interestingly, with *N*-substituted amidines generally only the unsubstituted nitrogen participates in the S_NAE reaction allowing to obtain one regiosiomer. The target *N*-uracil amidines could often be purified by simple precipitation, avoiding solvent-consuming chromatography on silica gel.

Then, the direct oxidative amidination was investigated. Cross dehydrogenative C-N bond formation using base metal catalysis has received considerable attention in the last 5 years.[12,13] Only one direct oxidative amination reaction on uracils is hitherto described and reported by our group.[14] In this oxidase type reaction a stoichiometric oxidant is required. From a sustainability point of view, oxygen and peroxides (H_2O_2 or RO_2R) are the most desirable candidates as the waste compounds are respectively water and alcohols.[15] Therefore, these were considered for the optimization of our cyclization reaction. In a preliminary set of experiments with *N*-(1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzimid-amide (**1**) as model substrate, aerobic conditions highlighted CuI as the catalyst of choice (Figure S1). A few other copper sources ($Cu(OAc)_2{\cdot}H_2O$, $CuBr_2$, Cu^0 nanoparticles) gave similar yields of the desired xanthine, but converted slower than CuI. Ligands and acids had no or negative effect on the reaction (Table S9, Figure S2). The choice of solvent was critical for the reaction efficiency. Apart from dimethylsulfoxide (DMSO) and tetramethylene sulfoxide, the other solvents tested afforded maximum 15% of reaction product. This solvent scores well from the point of view of health and safety and intermediate with respect to environmental aspects.[16] Using DMSO, full conversion was achieved within 3 hours using 15 mol% of CuI at 120°C under O_2 atmosphere. This afforded 1,3-dibenzyl-8-phenylxanthine (**2**) in 78% yield (Scheme 2).[17]



Scheme 1. Classical and new approach for the synthesis of polysubstituted xanthines.



Scheme 2. Direct Cu-catalyzed oxidative C-H amidination of **1** using O_2 or tBu_2O_2 as oxidant. [a] Isolated yield. [b] NMR yield (1,3,5-trimethoxybenzene as internal standard).

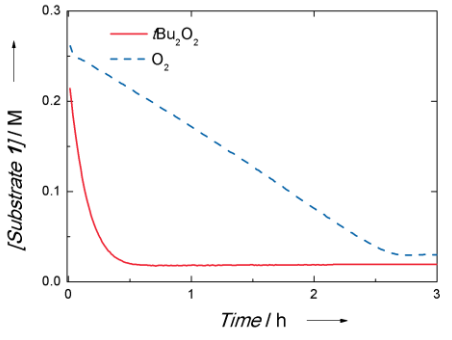


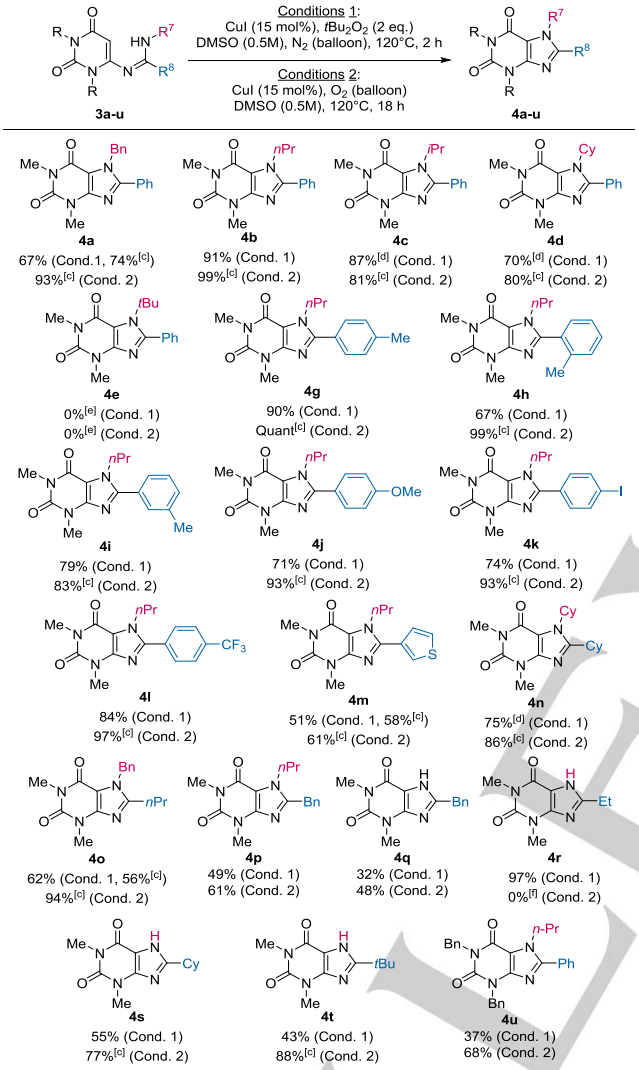
Figure 1. Comparison of reaction rates on the direct oxidative amidination of *N*-(1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)benzimidamide (**1**) using oxygen and tBu_2O_2 as oxidant. Measured initial rates of the reactions: $v_{in}(O_2) = 2.3086.10^{-5}$ M.s^{-1}; $v_{in}((tBuO)_2) = 28.051.10^{-5}$ M.s^{-1}.

Interestingly, when using tBu_2O_2 as the oxidant, **1** fully converted within 30 minutes and **2** was isolated in 71% yield (Scheme 2). Comparison of the initial rates revealed that the reaction with peroxide is more than 10 times faster than with O_2 as oxidant (Figure 1). The specific dialkyl peroxide used is one of the most stable ones, widely used in polymer industry and only produces *tert*-butanol as waste. Other peroxides gave a lower yield and sometimes a low mass balance was obtained (Table S12). Different copper sources were probed using tBu_2O_2 as the oxidant, but the Cu^I and Cu^{II} salts tested performed worse than CuI (Table S14). Other cheap and abundant base-metal catalysts (iron, cobalt and nickel) were also tried, but they did not give any reaction (Table S15). Control experiments showed that both catalyst and peroxide were essential as no reaction product was obtained when one of them was omitted (Table S13). Other solvents than DMSO were also explored such as cyclopentylmethyl ether, 2-methyl THF or propylene carbonate.[11b,11c] Although the latter showed a good mass balance, the yield was low in all cases (Table S16). Therefore DMSO was retained as the solvent of choice for the transformation.[16] Lowering the reaction temperature to 90°C gave a slower reaction and full conversion of the substrate required 3 hours (Figure S5); the use of O_2 at this temperature required 16 hours. Although the use of a lower temperature is feasible for the direct oxidative amidination reaction, we decided to stick to 120°C and tBu_2O_2 as oxidant for the scope study as this combination gave the fastest reactions. Interestingly, a gradual addition of the peroxide can also be applied, allowing the peroxide concentration to be kept low in the reaction medium (Scheme S3, Figure S3). However, from a practical point of view on a small scale (discovery), we decided not to apply this procedure during the scope study.

We then applied the optimized conditions with tBu_2O_2 (15 mol% of CuI and 2 eq. of tBu_2O_2, in DMSO at 120°C) to a set of synthesized *N*-uracil amidines **3** (Table S3). To our delight, the majority of these substrates were converted into the corresponding xanthines in good to excellent yields (Scheme 3). The *N*-uracil benzenecarboximidamide could bear both primary and secondary *N*-alkyl substituents (**3a-d**). The structure of **4b** was confirmed by X-ray crystallography (Figure S8). Only a *tert*-butyl group (**3e**) proved to be incompatible, presumably due to its steric character. The protocol tolerated a variety of substituents on the aryl ring of the *N*-uracil benzenecarboximidamide, with both electron-donating and electron-withdrawing groups (**3g-l**). Notably, the *para*-iodo substituted xanthine **4k**, which can be used for further cross-coupling reactions, was obtained in a good yield. As fluorine can have a major influence on the pharmacological properties of a drug[18], we were pleased to see that this method is also compatible with this halogen (**3l**). *N*-uracil heteroarene-carboximidamide derivatives could also be used as exemplified

by **3m**. Even *N*-uracil alkanimidamides were generally well tolerated (**3n-t**), although some of these substrates gave a lower yield.

Scheme 3. Scope of the direct Cu-catalyzed oxidative C-H amidination of *N*-uracil amidines (**3**) using O_2 or tBu_2O_2 as oxidant [a,b].



[a] Cond. 1: **3** (0.5 mmol), CuI (15 mol%), tBu_2O_2 (2 eq.), DMSO (0.5M), 120°C (oil bath), 2 h, closed vial, N_2 atmosphere (balloon). Inert atmosphere is not essential for this reaction but was applied to exclude contribution of O_2 oxidant present in air. Cond. 2: **3** (0.5 mmol), CuI (15 mol%), DMSO (0.5M), 120°C, 18 h, O_2 atmosphere (balloon). Reaction times were not minimized. [b] Isolated yield. [c] NMR yield (1,3,5-trimethoxybenzene as internal standard). [d] 6 h. [e] Only **3e** was detected in the crude reaction mixture via NMR analysis. [f] No **3r** or **4r** were isolated.

O_2 was then tested as alternative oxidant for the substrate scope. Generally, under the optimized conditions (15 mol% of CuI, with an O_2 balloon, in DMSO at 120°C) higher and in some cases similar yields were obtained under the aerobic conditions though a much longer reaction time was required (Scheme 3). Again no product could be obtained for **3e**. Remarkably, 1,3-dimethyl-8-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (**4r**) was afforded in 97% yield using peroxide as oxidant while under aerobic conditions no xanthine was formed. No **3r** was recovered in the latter case and its decomposition mechanism is unclear. It is interesting to note that **4q** is an intermediate in the synthesis of the API Bamyfilline.[19] Importantly, irrespective of the oxidant used several xanthines could be isolated by simple precipitation (**2,4a-b,g,j,k,q**).

Subsequently, we investigated whether the copper catalyst could be reused with model substrate **1**. When adding new substrate and tBu_2O_2 oxidant at the end of the first amidination reaction, full conversion to **2** could be again achieved within 20 minutes in a second reaction (Figure 2). Even a successive four times loading of substrate **1** and tBu_2O_2 resulted in a similar yield (69% versus 71%) of the desired xanthine **2**, demonstrating that the copper does not degrade at the end of the reaction (Scheme 4). A similar result was obtained when O_2 was used as the oxidant giving 65% yield (Scheme 4).

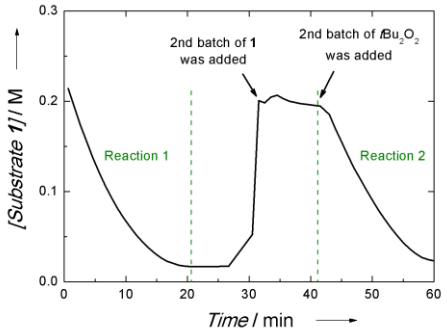
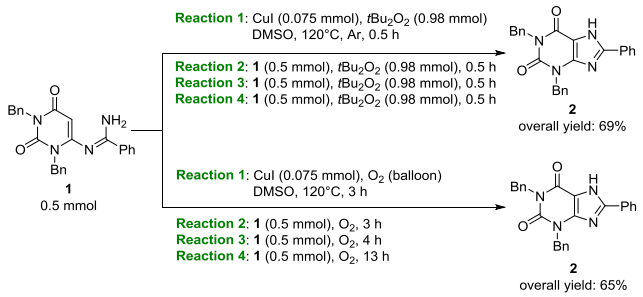


Figure 2. Graphical representation of the reuse of the copper catalyst exemplified for substrate **1** and tBu_2O_2. After the first reaction was completed, a second batch of **1** and tBu_2O_2 were added. Conversion was determined by Online IR reaction monitoring.



Scheme 4. Catalyst reuse: experiments with four successive loadings of substrate **1** and oxidant, using tBu_2O_2 or O_2.

Finally, although our method is designed to install the target substituents at N1 and N3 when building up the xanthine scaffold, it is also possible to work with *N*-protective groups. 1,3-Dibenzyl-8-phenyl-7-propylxanthine (**3u**) for instance could be

deprotected with BBr_3 in 58% yield using a literature procedure (Scheme S5).[20] This allows post-decoration of the uracil moiety, via *N*-alkylation/arylation or dehydroxychlorination and subsequent consecutive S_NAr which is especially interesting for medchem purposes.

Conclusions

In summary, we have developed a short two-step procedure for the synthesis of polyfunctionalized xanthines starting from readily available 1,3-disubstituted 6-chlorouracils and amidines. S_NAE with amidines afforded the substrates for direct oxidative amidination in moderate to good yields. Cu-catalyzed cross dehydrogenative coupling on these substrates provided N1, N3, N7 and C8 substituted xanthines in good yields. Although O_2 gives a significantly slower reaction versus tBu$_2$O$_2$ as oxidant for the cross dehydrogenative C-N bond formation, the former is generally preferred from a yield point of view. Both the use of a readily available and cheap base metal (Cu) and a sustainable oxidant (O_2 or tBu$_2$O$_2$) make this protocol valuable for application in both discovery and chemical development projects. Interestingly, in both steps of the new approach, precipitation of the target compound can often be used for purification, avoiding wasteful column chromatography. The copper catalyst was proven to be reusable hereby further contributing to the sustainability of the new approach.

Acknowledgements

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Keywords: Xanthine • oxidative C-H amination • cross dehydrogenative reaction

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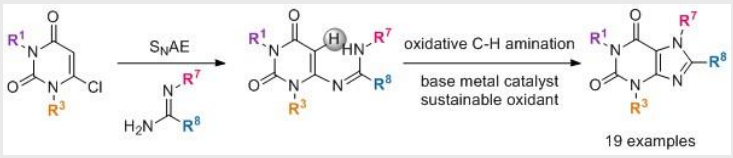

A novel two-step approach for the synthesis of polysubstituted xanthines is described. Starting from simple building blocks, 6-chlorouracil and amidines, a S_NAE amidination reaction was developed, followed by a base-metal catalyzed intramolecular direct oxidative amidination. Molecular oxygen or di-*tert*-butyl peroxide can be used as oxidant for the latter transformation.

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