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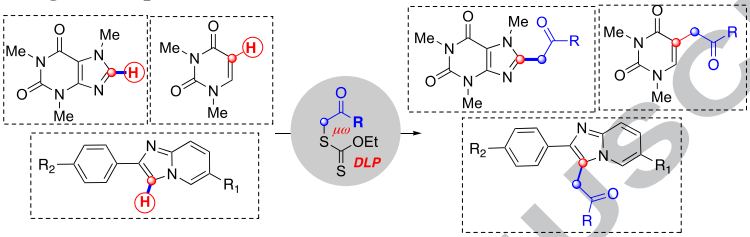

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Xanthate-based microwave-assisted C-H radical functionalization of caffeine, 1,3-dimethyluracil, and imidazo[1,2-a]pyridines.

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ABSTRACT

Xanthate-based radical chemistry was used for the regioselective direct alkylation of caffeine, uracil, and imidazo[1,2-a]pyridine systems, using dilauroyl peroxide as initiator and oxidant, under microwave irradiation. Under these conditions, several electrophilic radicals (located alpha to a carbonyl function such as esters, amides, ketones, malonates and cyano groups) were added to the title heterocyclic systems. The methodology allows the intermolecular regioselective construction of a sp^2-sp^3 C-C bond via a C-H functionalization in an aromatic substitution, from readily available starting materials.

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Direct intermolecular alkylation of heteroaromatic systems is a process of great significance (Figure 1).[1] In principle, through a C-H bond functionalization, the process allows the regioselective installation of an alkyl group onto an heteroaromatic system. The process may be used for preparation of synthetically useful intermediates or for attractive late stage functionalization in a long synthetic sequence. Although Friedel-Crafts reactions might be thought to be the method of choice to carry out this procedure, this methodology generally suffers from the well-known 1,2-hydride and/or alkyl rearrangement of the cationic intermediate (Wagner–Meerwein rearrangement), along with the requirement for electron-rich aromatic systems.[2] Indeed, due to these drawbacks, the intermolecular version of the Friedel-Crafts process has found limited synthetic applications. In contrast, its neutral nature and the lack of 1,2 shifts of free radicals have encouraged the use of this intermediates for the intermolecular creation of a sp^2-sp^3 C-C bond by a C-H functionalization in an aromatic substitution (Minisci reaction).[3] Indeed, the last decade has witnessed tremendous efforts to develop practical methods to accomplish such processes and several conditions have been established, most of them under metal-catalyzed conditions.[4] In this context, the xanthate-based radical chemistry embraces special importance because not only permits the efficient generation of alkyl radicals, but it also frequently uses lauroyl peroxide in the initiation step, which, in principle, facilitates the oxidative process for the rearomatization pathway under matal-free conditions.[5] Furthermore, the degenerated radical addition-fragmentation pathway involved in the mechanism allows the intermediate free radical to persist longer in the reaction medium, enabling it to be trapped by poor radical acceptors, such as aromatic systems.[5,6] Accordingly, in 2003 we first reported an oxidative direct intermolecular alkylation of several heteroaromatic systems (indoles, pyrroles, furans, and thiophenes) with several electrophilic radicals (located alpha to a carbonyl function), using xanthate chemistry.[7] Later, we further demonstrated that the process could be applicable to the alkylation of flavones[6d] and coumarines.[6e] In addition, Zard and coworkers observed that electrophilic radicals were also useful partners to the C-2 alkylation of indoles.[7] With the objective to extend the scope of this tool, we then became interested in the alkylation of caffeine, 1,3-dimethyluracil, and imidazo[1,2-a]pyridines using the same xanthate-based radical chemistry. Our preliminary observations within this endeavor are summarized herein.

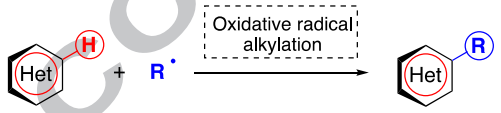


Figure 1. Oxidative radical substitution.

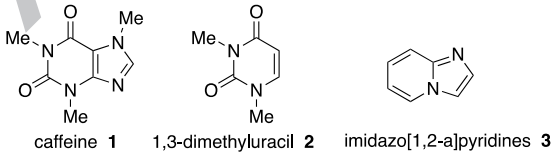
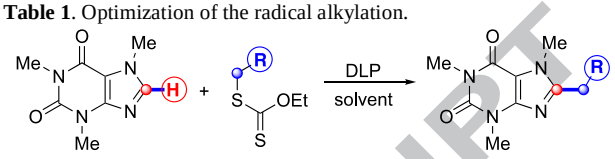


Figure 2. Caffeine, 1,3-dimethyluracil and imidazo[1,2-a]pyridines.

Caffeine is a methylxanthine alkaloid and one of the most consumed psychoactive substances in the world with several important pharmaceutical activities.[8] It has been reported that caffeine and its derivatives affect the neural and cardiovascular systems and display remarkable effects on apoptosis and DNA repair, along with cell cycle function and regulation, among other important biological activities.[9] The conjugated system of caffeine has also been reported to undergo oxidative substitution at C-8 under the presence of $^{\bullet}CF_3$[4a,e] and methyl sulfonyl radicals.[4b] Thus, to investigate if the caffeine system could be alkylated under xanthate-based conditions, a brief optimization screening was conducted. Toward this goal, caffeine (**1**) and the xanthate of ethyl acetate (**4**) were utilized as the model substrates (Table 1).

Table 1. Optimization of the radical alkylation.

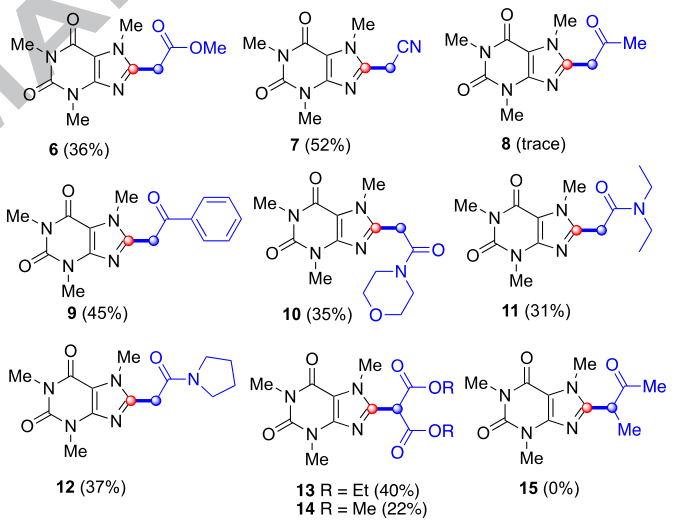


1 **4** R = COOEt **5** R = COOEt

experiment[a]	solvent	temp. (°C)	yield [%]
1[b]	$ClCH_2CH_2Cl$	85	34
2[b]	AcOEt	77	24
3[b]	Toluene	100	----
4[c]	$ClCH_2CH_2Cl$	85	39
5[c]	AcOEt	77	29
6[c]	Toluene	100	18

[a] Reaction at [0,1M]: caffeine (1 equiv), xanthate (2 equiv) and lauroyl peroxide (DLP) (2 equiv), [b] under convectional heating, [c] under microwave heating.

Table 2. Radical alkylation of caffeine

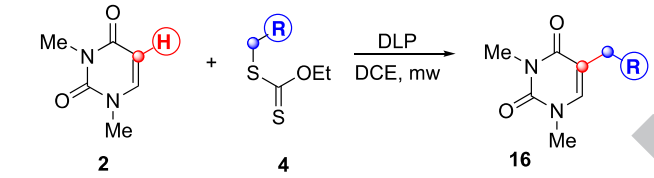


Thus, portionwise additions of lauroyl peroxide (DLP) (2 equiv.; 0.28 equiv. every 1 h) to a 0.1 M solution of **1** (1 equiv.) and xanthate **4** (2 equiv.) in 1,2-dichloroethane at 85 °C under conventional heating afforded the desired C-8 alkylated caffeine **5** in 34% yield, after 8 h of reaction (entry 1, Table 1).[6] When the solvent was changed to ethyl acetate at lower temperature (entry 2), the yield was reduced. Similarly, the use of toluene at 100 ºC lead only to decomposition of the xanthate (entry 3). In contrast, when the reaction was carried out using microwave irradiation in dichloroethane (DCE), adding 2 equiv. of lauroyl peroxide (DLP) (0.28 equiv/15 min) not only reduced the time considerably (2 h), but also slightly increased the yield (entry 4). Similar increments in the yields were observed using AcOEt and toluene under microwave irradiation (entries 5 end 6), although the best yield was observed with DCE. Consequently, conditions used in entry 4 were further utilized to explore the scope of the process. To this end, various xanthates **4a-k** (Table 2) were prepared by substitution of the corresponding halo derivative with commercially available potassium ethyl xanthogenate.[6,10]

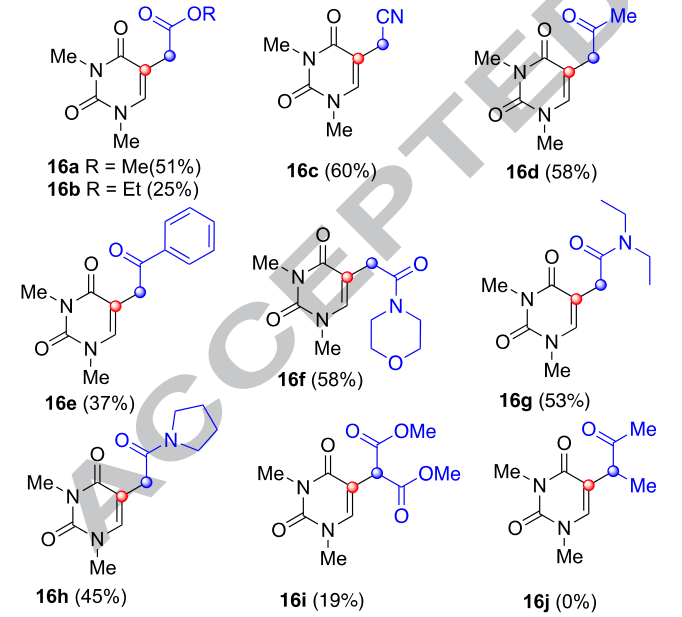
As observed in Table 2, radicals from xanthates derived not only from esters, but also from acetonitrile gave good yields in the alkylation process. Xanthates derived from amides of morpholine (**10**), diethylamine (**11**), and pyrrolidine (**12**) afforded moderate yields in the process. With the same reaction, it was also possible to introduce both the ethyl and methyl malonate moieties (**13** and **14**) in moderate yields. The acetone-derived product **8**, was only detected in trace amount in an inseparable mixture and the secondary butanone-derived radical (**15**) failed to add to the caffeine system. Along the same lines, the caffeine-demethylated congeners theobromine and theophylline were tested in the same reaction system. However, we were unable to carry out these experiments owing to the insolubility of these substances in most of the organic solvents.

After the study of the behavior of the caffeine aromatic system, we then focused our attention on the application the same methodology to directly install the same alkyl groups onto the 1,3-dimethyluracil system **2**. Uracil, one of the four nucleobases in RNA, is a pyrimidine with remarkable pharmacological activities.[11] As expected, under the optimized conditions 1,3-dimethyluracil **2** was selectively alkylated at C-5[4b,e,f] with the corresponding xanthates. Results of the radical alkylation of this conjugated system are summarized in Table 3.

Table 3. Oxidative radical alkylation of 1,3-dimethyluracil.

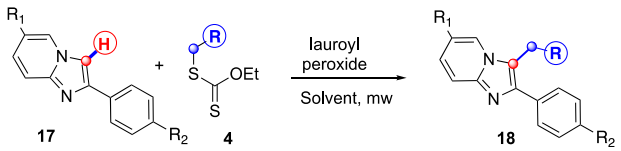


2 **4** **16**

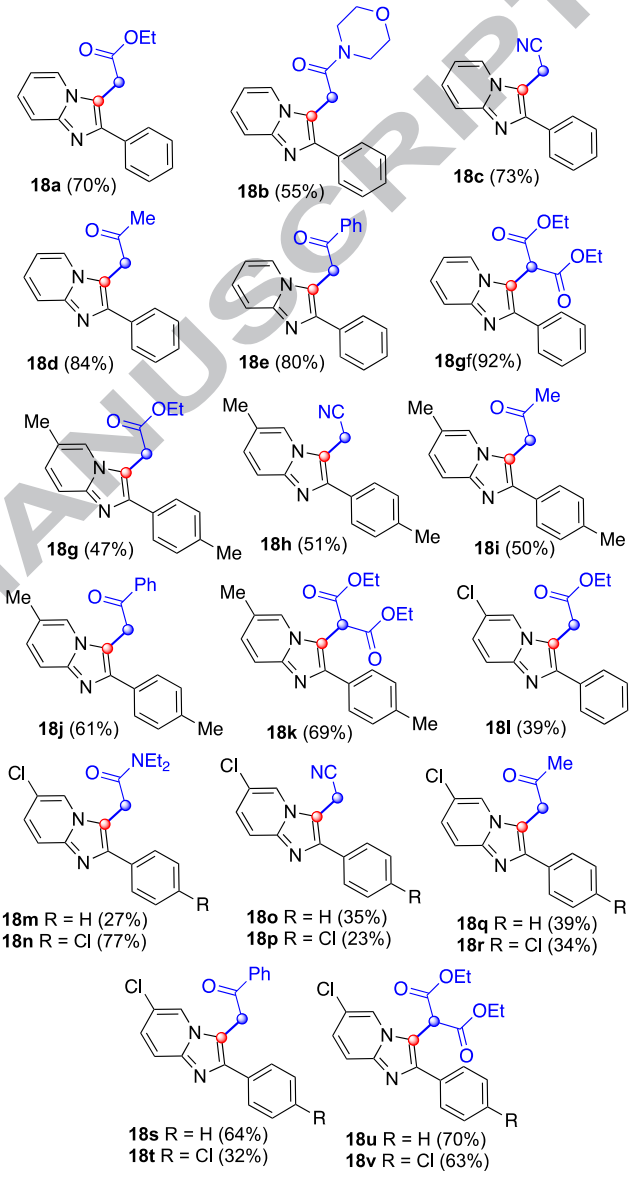


The yields of the alkylation of uracil were considerably higher than those observed in the caffeine system. Indeed, the reaction provided the efficient direct installation of ethyl (**16a**) and methyl (**16b**) acetates, acetonitrile (**16c**), and even acetone and acetophenone moieties (**16d-e**). Amides (**16g-i**) were also installed onto the uracil system in good yields. Again, secondary 2-butanoyl moiety was unable to be added under the same conditions. Methyl malonate was also added, but in low yields (**16j**).

Table 4. Oxidative radical alkylation of imidazo[1,2-a]pyridines..



17 **4** **18**

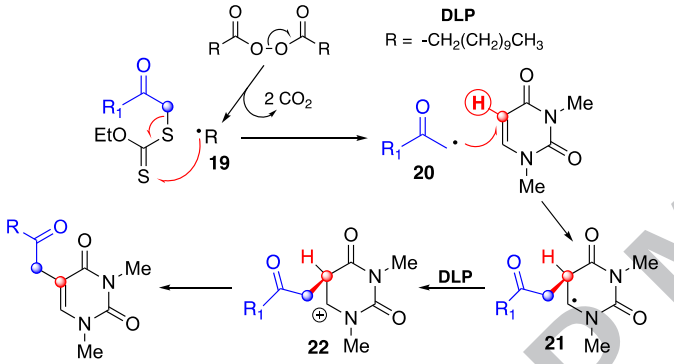


Thus far, we had demonstrated for the first time that the xanthate-based radical chemistry could be utilized for the intermolecular alkylation of caffeine and uracil with several electrophilic radicals. Similarly, imidazo[1,2-a]pyridines (IPs) had been reported to exhibit remarkable biological activities.[12] In fact, some commercial drugs contain IPs e.g., zolimidine (treatment of peptic ulcers), alpidem and saripidem (treatment of anxiety disorders), zolpidem (insomnia treatment).[13] Accordingly, at the outset, this heterocyclic system was selected to extend the scope of the xanthate chemistry. While we were working on this study, a similar paper regarding the alkylation of the IPs using the same xanthate-based radical chemistry was published.[14] Since we were using microwave irradiation in

shorter reactions times compared with the reported conditions, we decided to disclose our own results. Thus, as depicted in Table 4, the yields obtained in our study using microwave irradiation, were similar to those obtained under reported conventional heating with xanthates derived from esters (**18a,g,l**) amides (**18b,m,n**), nitriles (**18c,h,o,p**), and ketones (**18d,e,i,j,q,r,s,t**). Novel examples (different from those reported previously) using amides derived from morpholine (**18b**) and malonates (**18g,k,u,v**) also worked well in the alkylation process.

The proposed mechanism for the radical alkylation is based on the reported similar processes[6] and is illustrated in Scheme 1 with the caffeine system. First, the radical **20** is generated from the corresponding xanthate upon the action of the radical **19** which comes from the thermal fragmentation/decarboxylation process of the DLP. Then, this radical is added to the heterocyclic system producing a new radical **21** which, is promptly oxidized to the cation **22**,[6] in the presence of a stoichiometric amount of the peroxide, facilitating the regeneration of the original conjugated system.

Scheme 1. Proposed mechanism.



In closing, we have demonstrated that the xanthate-based radical chemistry is a practical methodology to regioselectively directly install several electrophilic radicals (positioned alpha to a carbonyl function, such as esters, amides, ketones, malonates and cyano groups) onto caffeine, uracil, and imidazo[1,2-a]pyridine systems, using dilauroyl peroxide as both initiator end oxidant, under microwave irradiation. This study not only streamlines the scope of the xanthate radical chemistry but also contributes to synthetizing novel derivatives of title heterocyclics towards drug candidates. The methodology allows the intermolecular regioselective construction of a sp^2-sp^3 C-C bond via a C-H functionalization in an aromatic substitution, from readily available starting materials and without substrate preactivation. We believe that this protocol might provide rapid access to more complex scaffolds by using also more complex xanthates derivatives.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Caffeine and uracil was regioselectively alkylated using xanthate radical chemistry

The study contributes to give access to novel derivatives of title heterocyclics

In the process a sp^2-sp^3 C-C bond is formed via a C-H functionalization.

The protocol may be used to attach caffeine and uracil with complex structures.