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Xanthate-Mediated Incorporation of Quaternary Centers into Heteroarenes

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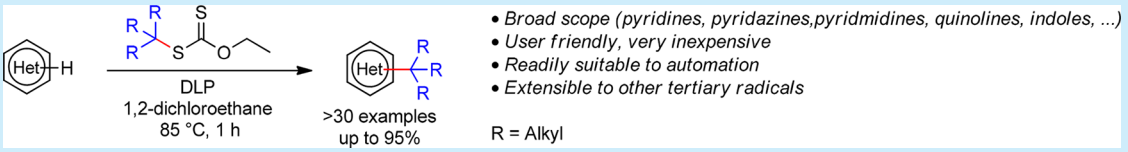
Supporting Information



ABSTRACT: The xanthate-mediated addition of tertiary alkyl radicals to heteroarenes enabled the easy functionalization of heteroaromatic rings as well as more decorated structures, such as marketed drugs or agrochemicals. This work provides a synthetic tool for efficiently exploring the chemical space by allowing late-stage diversification with a high tolerance toward functional groups.

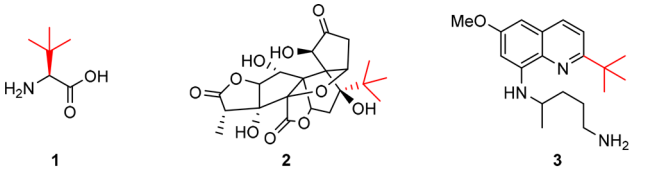
Fine-tuning the biological activity profile of a pharmaceutical lead is a challenging topic. To circumvent the need for de novo syntheses for each analogue of a promising drug candidate, the principle of late-stage diversification has often been employed. The introduction of pharmacologically relevant groups at the last step before evaluating the biological properties of potent targets enables a faster and more efficient exploration of their chemical space.[1] Heteroaromatic rings, in particular, are key scaffolds in medicinal and agrochemical research,[2] and careful attention has been paid to their late-stage modification. Radical chemistry has emerged as particularly suitable for this purpose, thanks to its high functional group compatibility and the possibility of applying various combinations.[1b,3]

In this respect, the *tert*-butyl group is of some importance, for it is well represented in biologically active compounds and in natural products.

A result of post-translational modification, *tert*-leucine (**1**) is responsible for a higher stability of peptides toward hydrolysis by shielding the amide bond but also influences the peptide's secondary structure.[4] Ginkgolide B (**2**) is an example of a *tert*-butylated natural product where the *tert*-butyl group proved to be mandatory for its biological activity.[5] Moreover, the *tert*-butyl group can be found in several drugs and agrochemicals, as exemplified by compound **3**, where the introduction of the *tert*-butyl group improved the efficiency of primaquine by blocking the main supposed metabolic degradation pathway (Scheme 1).[6] Direct *tert*-butylation of heteroarenes and, more generally, the possibility of incorporating quaternary centers to potential pharmaceutical leads thus constitutes a worthwhile endeavor.

Several methods have been proposed for the radical introduction of *tert*-butyl groups onto heteroaromatics. In 1971, Minisci and co-workers initially reported the generation of the *tert*-butyl radical via an Ag(I)-catalyzed decarboxylation of pivalic acid and its subsequent trapping by a protonated heteroaromatic ring providing the desired alkylated product.[7] Following Minisci's pioneering work, alkyl radical additions to heteroaromatic compounds were studied in terms of selectivity and reactivity.[3b,8]

Scheme 1. Examples of *tert*-Butyl-Bearing Bioactive Substances



1 ***tert*-Leucine (Tle)**
2 **Ginkgolide B** *(Ginko biloba)* *Human platelet activator*
3 **Primaquine analogue** *Antimalaria*

In this context, other *tert*-butylations were also examined. Expanding on the original Minisci concept, two methods based on Ag(I) catalysis were developed using either amino acids, carboxylic acids, or boronic acids as radical precursors.[9a,b] Photocatalytic methods were also recently reported starting with *tert*-butyl halides[9c,d] or *N*-(acyloxy)phthalimides as radical sources.[9e] A further variation was proposed involving *tert*-butyl trifluoroborate in the presence of a stoichiometric amount of $Mn(OAc)_3$.[9f] Metal-free strategies were additionally employed. Starting from the corresponding alkane, exposure to [bis-(trifluoroacetoxy)iodo]benzene (PIFA) can afford the desired radical to perform the heteroaromatic alkylation.[9g] The *tert*-butyl radical is also available by oxidation of pivalaldehyde.[9h,i] Finally, redox-neutral strategies have been considered using either Barton's ester[9j] or a *tert*-butyl sulfone derivative.[9k] These

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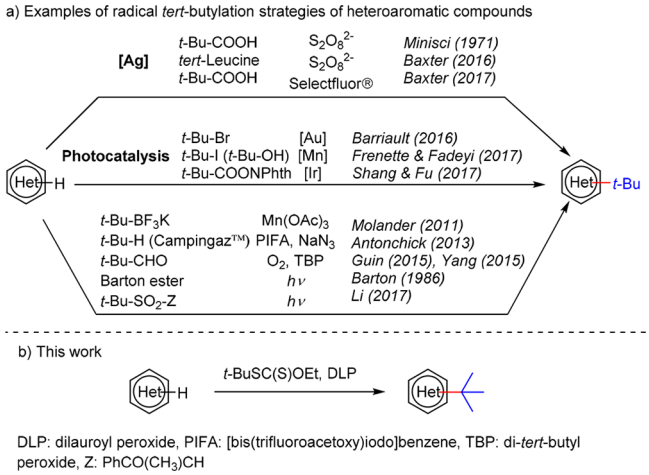
Org. Lett. XXXX, XXX, XXX−XXX

radical additions to a heteroaromatic ring are often referred to as Minisci reactions (Scheme 2a).

Scheme 2. Approaches for the Radical *tert*-Butylation of Heteroarenes



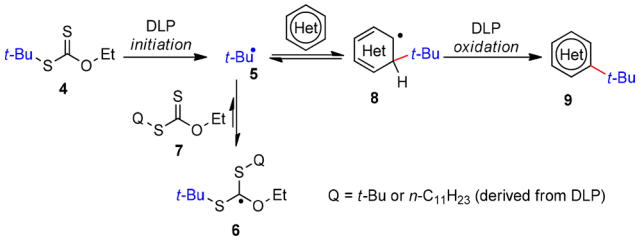
DLP: dilauroyl peroxide, PIFA: [bis(trifluoroacetoxy)iodo]benzene, TBP: di-*tert*-butyl peroxide, Z: $PhCO(CH_3)CH$

Most of these approaches, however, suffer from some drawbacks, such as the use of expensive metal catalysts, harsh conditions, elaborate starting materials, and/or limited substrate scope. With these limitations in mind, we designed a complementary strategy for the radical *tert*-butylation, starting with the cheap *S*-*tert*-butyl *O*-ethyl xanthate (**4**) (Scheme 2b). This method can be extended to the introduction of various other tertiary groups.

The first examples of xanthate-based radical alkylations were carried out by Minisci et al. in 1992, exploiting the Barton–McCombie-type C–O bond fragmentation for the cyclohexylation of heteroaromatic compounds.[10a] Intermolecular functionalization of heteroaromatic rings exploiting the C–S bond fragmentation in xanthates was first reported by Miranda and co-workers for the alkylation of electron-rich substrates such as pyrroles and indoles. All of the examples involved stabilized radicals, in particular, α-carbonyl radicals.[10c] We were interested in further expanding the limits of the xanthate methodology by studying the behavior of a less stabilized radical, namely, the *tert*-butyl radical, which is stabilized only by hyperconjugation. It is worth noting that *tert*-butylation through cleavage of a C–O bond in an *O*-*tert*-butyl xanthate would be very difficult to implement because of the high sensitivity of the tertiary xanthate to decomposition through the Chugaev elimination.[11] Fortunately, this elimination only occurs at much higher temperatures with the isomeric *S*-tertiary alkyl xanthate.[12]

Following its formation, initiated by the thermal decomposition of dilauroyl peroxide (DLP), the *tert*-butyl radical **5** is reversibly stored as its relatively nonreactive adduct **6** by addition to the thiocarbonyl of another xanthate **7**. This ability to reversibly store active radicals in a nonactive form allows the regulation of their absolute and relative concentration and represents a key and unique feature of this chemistry. The *tert*-butyl radical is continuously regenerated, thus acquiring an extended effective lifetime, enabling it to add to a suitable heteroaromatic ring. This addition, leading to radical **8**, is reversible and, when followed by the irreversible electron transfer to DLP, furnishes the desired *tert*-butylated species **9** (Scheme 3).

Scheme 3. Proposed Mechanism for the Xanthate-Based Heteroaromatic Alkylation



Our study started with the preparation of *S*-*tert*-butyl *O*-ethyl xanthate from pivaloyl chloride, according to the conditions described by Barton et al. in 1962.[13] We obtained the desired xanthate **4** in a very good 83% yield on a 20 g scale (Scheme 4a). This xanthate chemistry is compatible with heteroaromatic bases only when the latter's nucleophilicity is neutralized with acid to avoid ionic destruction of the xanthate.[10d] Fortunately, as demonstrated by Minisci et al., this protonation enhances the addition of nucleophilic radicals, such as the *tert*-butyl radical, to the heteroaromatic nucleus.[8b,10b] In our case, camphorsulfonic acid, previously employed by Barton and co-workers, was used.[9j] It has the advantage of being available in anhydrous form and giving salts that are soluble in various organic solvents.

We were pleased to find that the radical *tert*-butylation was not only feasible but also had a broad scope (Scheme 4b). Indeed, this xanthate-mediated alkylation proved to be quite general, with yields ranging from 13 to 95%. The transformation was effective on various heteroaromatic rings, bearing a wide range of functionalities, such as pyridines **10**, **12**, **14**, and **16**, pyrazines **21**, **23**, and **25**, pyrimidines **27**, **29**, and **32**, pyridazines **36**, **38**, and **40**, quinolines **42**, **46**, and **49**, isoquinoline **51**, quinoxaline **55**, indoles **59** and **61**, pyrrole **63**, and richly decorated structures **71**, **73**, **75**, **79**, **82**, and **84**.

Nicotine derivative **11** was obtained in an excellent 83% yield, in the same range as previously reported with the pivalaldehyde oxidation system,[9h] but in a far better yield than with Minisci-type procedures.[14a] C-4 *tert*-butyl-substituted pyridine **13** was obtained from the pyridine precursor **12**. The alkylation is effective on 4-cyanopyridine, furnishing a mixture of mono- and dialkylated adducts **17** and **18** in a ratio of 4:3 as determined by ^{1}H NMR spectroscopy on the crude mixture. Only mono-*tert*-butylated product **17** was then isolated in 46% yield. Remarkably, if DLP is added portionwise to the reaction mixture, monoadduct **17** is obtained in a good 60% yield in a more selective alkylation reaction. Blocking both positions C-5 and C-2 resulted in no addition, as shown by the unreacted trifluoromethylpyridine **19**. Pyrazinamide (**21**), an antituberculosis agent, underwent the reaction unexpectedly poorly to give adduct **22** in 18% yield, as compared to the previously reported results.[14b] Pyrazine **23** proved to be an interesting case. Instead of an attack on the most electron-poor site, as would have been expected, the *tert*-butyl radical surprisingly preferred to add to the C-3 position, ortho to the methoxy group. This might be the consequence of the reversibility of the attack of that *tert*-butyl radical under the present conditions, as pictured in Scheme 3. The oxidation step could be responsible for the regioselectivity since it will proceed on the predominant and most easily oxidized radical adduct in the medium, usually the most stabilized radical. Thus, although the addition of *tert*-butyl radical can occur on every free

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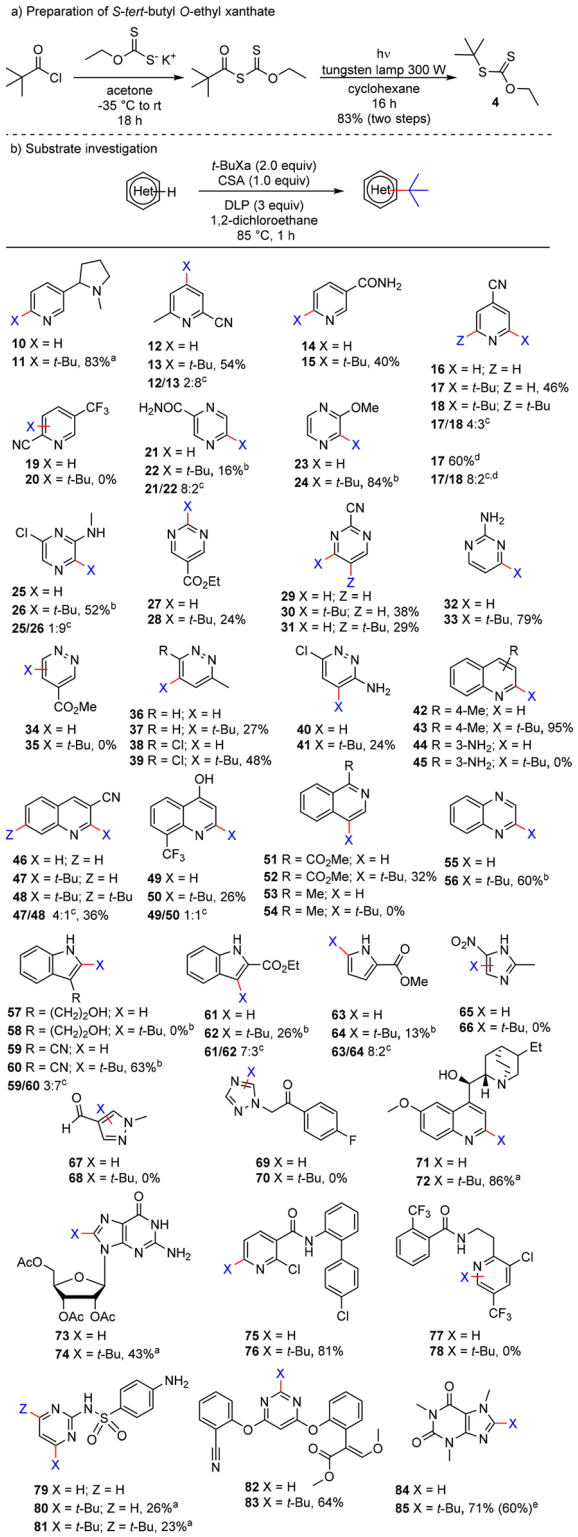
Scheme 4. Preparation of Xanthate 4 and Its Reactions with Heteroarenes



[a]2 equiv of CSA was used. [b]No CSA was used. [c]Ratio calculated by ^{1}H NMR analysis of the crude mixture. [d]DLP is added portionwise (20 mol % per hour) until depletion of the starting material. [e]Gram scale experiment.

position of the heteroaromatic ring, only the position leading to the most stabilized and oxidizable radical adduct will give rise to the observed product **24**. However, other factors may also influence the complex overall process, and predicting the regiochemistry becomes an uncertain task. This trend is further highlighted in example **26** in the pyrazine series and examples **37** and **39** in the pyridazine series. The difference between no stabilizing group (**36**) and one chlorine atom (**38**) is reflected by a 2-fold increase in yield, despite the increase in steric hindrance.

A change in regioselectivity was also observed with **41** where the methyl group is replaced by an amine, and this was accompanied by a drop in the yield to 24%.[14c] Alkylation of 4-methyquinoline (**42**) furnished compound **43** in an outstanding 95% yield. This substrate has been extensively studied in the past, and *tert*-butylation was previously accomplished in 40−85% yields.[9c−f]

Indoles exhibited an interesting reactivity trend. In the absence of electron-withdrawing groups, no reaction on the C-2 position was observed. In contrast, compound **60**, bearing a nitrile, was obtained in 63% yield. The drop in the yield for indole **62** could be ascribed to a polarity mismatch between the electron-rich *tert*-butyl radical and the C-3 position, which is more electron-rich than the adjacent C-2.

As for 2-methyl-5-nitroimidazole (**65**), however, a degradation of the substrate was observed, and no *tert*-butylimidazole **66** could be detected. Pyrazoles and triazoles seemed to be unreactive under these conditions and did not furnish any of the desired product (e.g., **68** and **70**).

This is to be contrasted with the excellent yield obtained with quinine derivative **71** in a C-2-selective reaction. Moreover, the sensitive guanosine derivative **73** and the marketed drugs and agrochemicals **75**, **79**, and **82** led to the corresponding adducts **74**, **76**, **80**, **81**, and **83**, whereas caffeine (**84**) was converted cleanly into compound **85** in 71% yield.[9h] Furthermore, performing this addition on a gram scale furnished *t*-butylcaffeine **85** in 60% yield without any further optimization. Thus, this method has an advantageous preparative value, as compared with most of the previous approaches.

We extended this methodology to the introduction of an adamantyl group using xanthate **86**, prepared in the same manner as reagent **4**. The enthusiasm for this particular group was triggered by the remarkable structural, physical, and chemical properties of its caged structure. The influence of an adamantyl group on a molecule's ADME[15] properties has also attracted attention.[16] Using our best conditions for the *tert*-butylation, we performed the addition on three examples (Scheme 5). The addition to lepidine (**42**) furnished compound **87** in 79% yield, with similar efficacy, as compared to other methods.[9d,e,j,17]

Application to boscalid (**75**) and caffeine (**84**) afforded compounds **88** and **89**, respectively in modest yields, but conversions were incomplete. No degradation was observed, however. Surprisingly, and disappointedly, no reaction was observed with indole **59**, in contrast to the *tert*-butylation which was successful, or with imidazole **91**.

The reasons underlying this difference in reactivity are still not clear, but it might be related to the lower stability of the radical, which cannot adopt the usual planar conformation observed with simple tertiary alkyl radicals.

The introduction of a *tert*-butyl or an adamantyl moiety increases significantly the lipophilicity. On some substrates, this could be detrimental to the ADME properties of the drug candidate. The same xanthate chemistry allows introduction of more polar tertiary motifs bearing hydroxyl groups, thus enhancing the water solubility of the modified substance. In this

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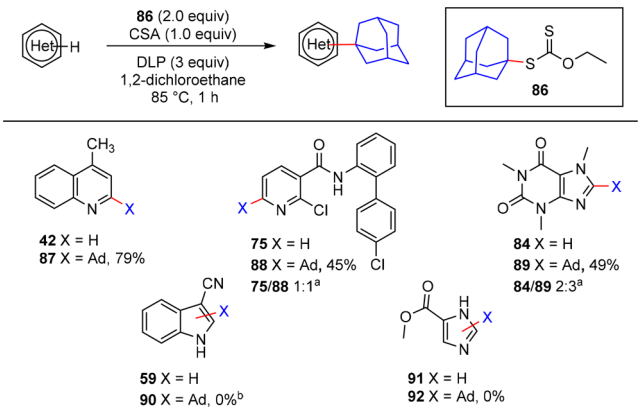
Scheme 5. Adamantylation of Heteroaromatic Compounds

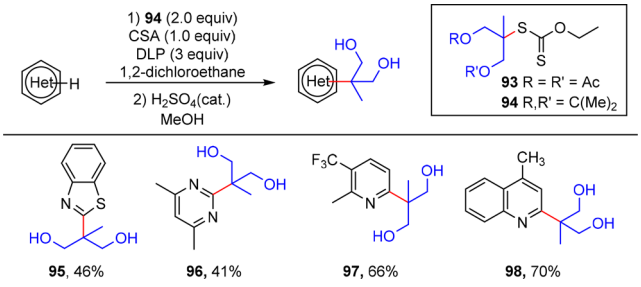


[a]Calculated by ^{1}H NMR analysis of the crude mixture. [b]No CSA was used.

respect, we first examined the tertiary acetate-protected 1,3-diol xanthate **93** recently described by Alexanian and co-workers.[18] Unfortunately, this xanthate exhibited an unsatisfactory reactivity toward a selection of heteroarenes.

Fortunately, the acetonide-protected, less polar analogue **94** proved to be more promising. Its addition to various heteroarenes, in situ hydrolysis of the acetonide furnished diols **95**–**98** in 41–70% yields (Scheme 6).

Scheme 6. Introduction of a 1,3-Diol Moiety to Heteroarenes



In addition to the use of a xanthate such as **94** to increase water solubility, the possibility of incorporating a *tert*-butyl motif bearing polar hydroxyl groups enables the direct introduction of potential *tert*-butyl metabolites of drug candidates, thus facilitating the study of their metabolic pathways.

To conclude, we report a practical, inexpensive, and versatile method for the introduction of three different, but representative, tertiary motifs into a reasonably broad range of heteroaromatic structures. The process should be applicable to many other tertiary xanthates. The simple experimental procedure should also be amenable to automation, enabling a rapid exploration of the chemical space around pharmaceutical leads.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01299.

Experimental data and procedures (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated with respect and affection to the memory of our friend, Professor Theodore (Ted) Cohen (University of Pittsburgh).

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