Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Inexpensive Radical Methylation and Related Alkylations of Heteroarenes

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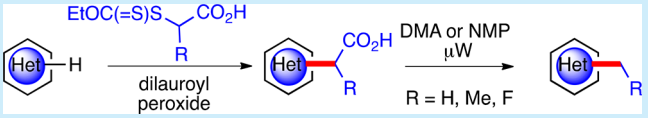
Supporting Information

ABSTRACT: A simple method for the introduction of a methyl and higher aliphatic group to various heteroarenes using very inexpensive reagents is described. It is based on the radical addition of a carboxylic xanthate followed by decarboxylation. Depending on the heteroarene structure, the decarboxylation can be spontaneous or induced by heating in *N*,*N*-dimethylacetamide or *N*-methyl pyrrolidone in a microwave oven.



The need by pharmaceutical and agrochemical laboratories for rapid optimization of the biological activity profile of promising leads through late-stage structural modification has rekindled the interest of the community in the possibilities of radicals.[1] Older chemistries, such as the various Minisci reactions,[2] have been revived,[3] and newer methods are being developed.[4] In this respect, the introduction of a methyl and possibly other alkyl groups has acquired a special prominence and urgency.[5] Nature has elaborated over the eons highly sophisticated machineries for methylating biological molecules using both radical and ionic mechanisms.[6] Methylation is thus involved in many fundamental biological phenomena such as replication, transcription, and epigenetics, and cell differentiation. One fundamental example is the methylation of uracil present in RNA leading to tymine, one of the four DNA bases.[6a] Nature has evolved receptors exquisitely capable of detecting the presence of this simplest but ubiquitous functional group. Disruptions in the recognition of methylated DNA, for instance, can cause debilitating diseases.[7] Rett Syndrome, a serious neurodevelopmental disorder, is caused by a mutation in the methyl-CpG-binding protein 2 (MECP2) gene, which modifies its ability to bind to methylcytosine bearing DNA.[8]

One vivid illustration of the influence of a methyl group on the activity profile can be seen in theophylline **1**, theobromine **2**, and caffeine **3** (Figure 1), three molecules that are present in coffee beans, tea leaves, and cocoa and ingested daily by a large fraction of the human population. Theophylline is not an excitant, but it is the strongest diuretic and bronchodilator of the three, whereas the most lipophilic, caffeine, is a CNS stimulant but a weak bronchodilator and diuretic.[6a] In the case of desogestrel, a third-generation oral contraceptive, the extra methyl on C-13 (i.e., an ethyl group instead of methyl) increases the potency by 50-fold.[9]

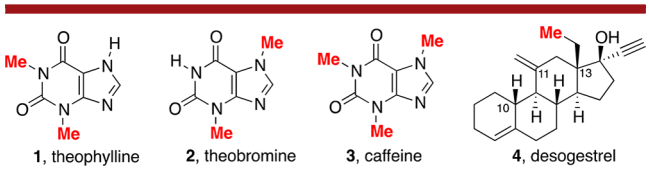


Figure 1. Examples of biologically active methylated products.

The introduction of a methyl group into various heteroaromatic molecules at a late stage to better map the structure−activity profile remains therefore an important research goal. In addition to the recently revived Minisci-type reactions, Baran and collaborators described a two-step route based on the addition of sulfonylmethyl radicals to heteroarenes followed by desulfonylation.[10] We now describe an alternative approach allowing the introduction of both acetic acid and methyl groups. It is inexpensive and, in some cases, sufficiently efficient and selective to be useful as a preparative tool. It can also be extended to higher groups.

We have reported extensively on the unique properties of the degenerate addition−exchange of xanthates.[11] However, the direct formation of reactive and unstabilized methyl radicals is problematic. The reason is inherent to the addition−fragmentation mechanism, where intermediate adduct radical **6** derived from *S*-methyl xanthate **5** does not fragment to produce xanthate **7** and the desired but high energy methyl radical (Scheme 1). An indirect route was therefore developed involving xanthate **8** which, upon addition−fragmentation initiated by dilauroyl peroxide (DLP), readily gives rise to stabilized radical **9**.[12] A normal chain reaction can now be sustained. Thus, addition of xanthate **8** to *N*-allylacetanilide gives adduct **10**, and further exposure to stoichiometric DLP induces ring closure onto the aromatic ring. Finally, reductive desulfurization of intermediate **11** with Raney nickel furnishes indoline **12** with the requisite methyl group.

While it is possible to consider xanthate **8** as a reagent for the introduction of a methyl group onto hetereoarenes, a much better solution emerged in the guise of xanthate **13**. This nicely crystalline compound is made on a large scale by mixing

Received: January 18, 2018

DOI: 10.1021/acs.orglett.8b00190
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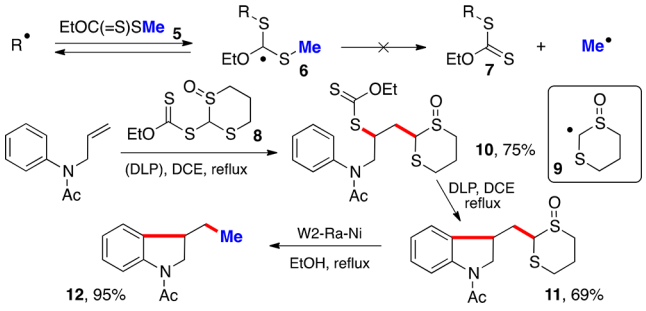
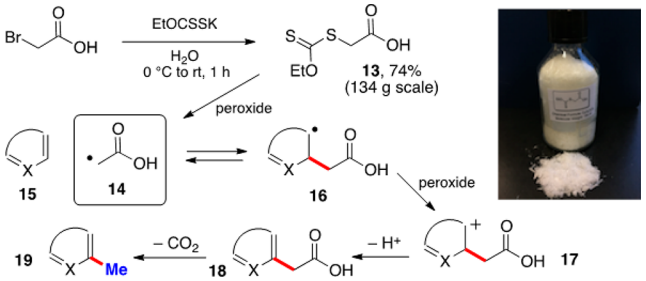
Scheme 1. Indirect Radical Methylation



bromoacetic acid and potassium *O*-ethyl xanthate in water and filtering the product (Scheme 2). Indeed, a >100 g batch could thus be completed in one afternoon. The bulk cost of goods is practically insignificant, at less than $10 (US) per kg!

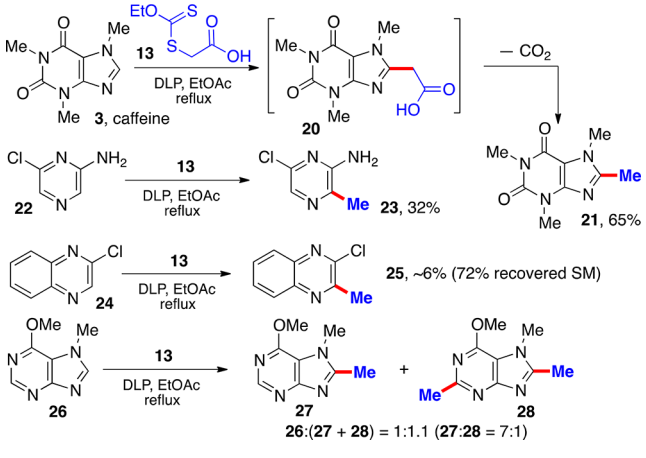
Scheme 2. Carboxymethyl Radical as a Methyl Radical Equivalent



Xanthate **13** readily acts as the precursor of the relatively stabilized carboxymethyl radical **14**.[13] Addition of the latter to a heteroarene **15** would give adduct radical **16** which, upon oxidation by electron transfer to the peroxide and aromatization of the resulting cationic species **17**, would afford addition product **18**.[14] Finally, thermal elimination of CO_2 would produce methylated heteroarene **19** (Scheme 2).

Indeed, heating a solution of caffeine, **3**, and excess xanthate **13** (3 equiv) in refluxing ethyl acetate with portionwise addition of stoichiometric DLP resulted in the smooth formation of methylcaffeine **21** (Scheme 3). In this example, the decarboxylation of the initial carboxymethyl adduct **20** occurred spontaneously under the reaction conditions. We

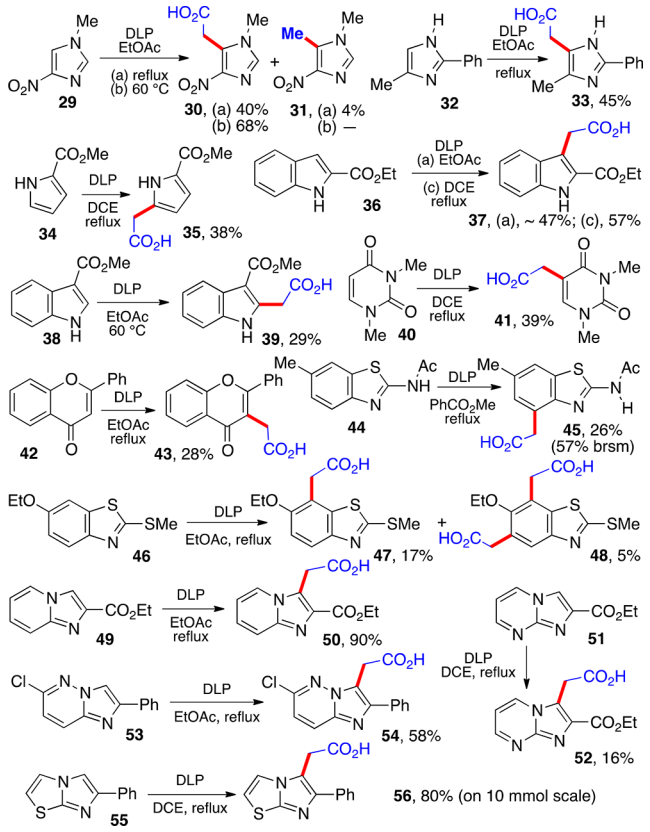
Scheme 3. Radical Methylation of Various Heteroarenes



observed such addition/decarboxylation with a few other heteroarenes, such as pyrazine **22**, quinoxaline **24**, and purine **26**. In the last case, the reaction furnished an inseparable 1:1.1 mixture of starting material **26** and mono- and dimethylated products **27** and **28**. The ratio of **27** and **28** was 7:1 (NMR). The yield of methylated pyrazine **23** was modest (32%), but only one regioisomer was observed. The reaction with 3-chloroquinoxaline **24** furnished a low yield of product **25** in poor yield (6%), with a large amount of returned starting material (72%).

With most of the other heteroarenes, incomplete or no decarboxylation was observed (Scheme 4). Thus, 1-methyl-4-

Scheme 4. Formation of Heteroareneacetic Acids



nitroimidazole **29** gave rise to 1-methyl-4-nitro-5-imidazoleacetic acid **30**, which precipitated from the reaction mixture and could be isolated by simple filtration in 40% yield. A small yield (4%) of 1,5-dimethyl-4-nitroimidazole **31** was also isolated. A higher yield (68%) of acid **30** and a product of better quality was obtained by lowering the reaction temperature to 60 °C.

No decarboxylation occurred with imidazole **32**, which gave adduct **33**, or with pyrrole **34** and indole substrates **36** and **38**. In the case of indole 2-carboxylate **36**, we noted a significant increase in the yield of adduct **37** (57%) and a cleaner reaction when ethyl acetate was replaced with 1,2-dichloroethane (DCE). The yield was comparable on a 10 mmol scale (~2 g). With indole 3-carboxylate **38**, the yield of product **39** was rather poor but could be improved somewhat by operating at 60 °C. Addition without decarboxylation took place with 1,3-dimethyluracil **40** and flavone **42** to give the corresponding carboxylic acids **41** and **43**, respectively.

Interestingly, the regiochemistry was not the same with benzothiazoles **44** and **46**. Whereas the former gave the 7-

DOI: 10.1021/acs.orglett.8b00190
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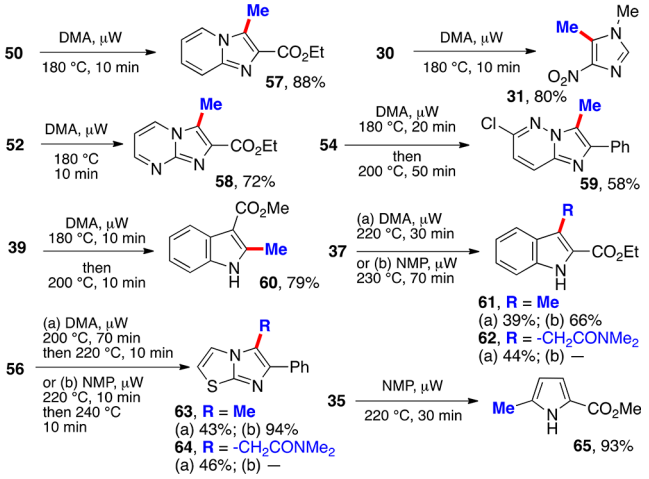
substituted product, the latter reacted at the 4-position. It appears that in the latter case the regioselectivity is dictated by the ethoxy group on C-6, and in the former case, it is the acetamido group on C-2 that directs the addition (radical **14** is electrophilic in character and will add preferentially to electron-rich positions on the heteroarene). Because of the insolubility of benzothiazole **44**, the unusual methyl benzoate had to be used as solvent.

Imidazopyridine **49**, imidazopyrimidine **51**, and imidazopyridazine **53** behaved similarly and furnished carboxylic acids **50**, **52**, and **54**. Imidazopyridine **49** proved to be the best substrate in the whole series, giving product **50** in 90% yield *after direct filtration from the reaction mixture*. The introduction of the acetic acid group increases the crystallinity and decreases the solubility of the product. In the favorable cases where the product actually precipitates during the reaction, it (the product) finds itself shielded from further attack by any radical species in the medium. Moreover, this simplifies the purification immensely and allows for practical large-scale syntheses. Indeed, compounds **37**, **50**, and **56** were readily prepared on a gram scale.

The decarboxylation proved more problematic than expected. Thermolysis of carboxylic acid **50**, neat or in an inert high boiling solvent such as *tert*-butylbenzene, gave rather modest yields (ca. 30−35%) of the methyl imidazopyridine **57**. Similar results were obtained upon heating in DMF at 170−190 °C in a sealed tube in the presence of potassium fluoride, according to the recent method of Amii.[15] A much better yield (88%) was obtained by heating in a microwave oven in *N*,*N*-dimethylacetamide (DMA), a thermally more stable solvent (Scheme 5). Methylheteroarenes **31** and **58**−**60** were cleanly prepared using similar conditions.

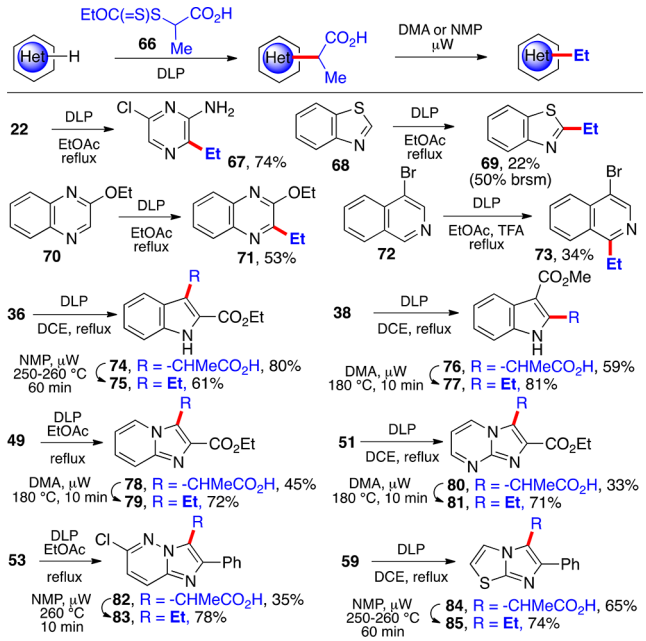
Scheme 5. Decarboxylation of Heteroareneacetic Acids



The decarboxylation of carboxylic acids **37** and **56** required even higher temperatures, which led to the unwanted concomitant formation of carboxamides **62** and **64**, obviously derived from reaction with DMA. We therefore switched to the even more robust *N*-methylpyrrolidone (NMP). In this manner, compounds **61** and **63**, as well as pyrrole carboxylate **65**, were produced in good yield without complication from amide formation. This represents a practical and apparently general method for decarboxylating heteroarylacetic acids.

The present approach for the introduction of a methyl group into heteroarenes is of much greater generality. More substituted carboxylic acid xanthates allow the introduction of various groups that cannot be installed directly. The use of propionic acid derived xanthate **66** thus leads to the attachment of an ethyl group. Some examples are collected in Scheme 6. In

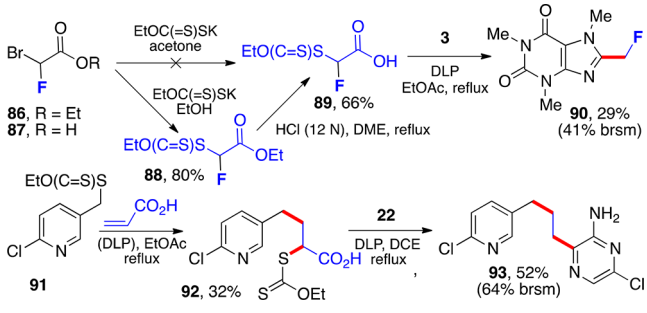
Scheme 6. Introduction of an Ethyl Group



the first four examples, decarboxylation occurred spontaneously under the reaction conditions (in the case of compound **72**, 1.2 equiv of trifluoroacetic acid was added). For the others, heating in DMA or NMP in a microwave oven proved necessary. The ability to introduce directly a propionic acid motif is not devoid of interest, since arylpropionic acids constitute an important class of nonsteroidal anti-inflammatory substances in clinical use.[16] Some members have also found application as herbicides.[17]

Another interesting extension is the introduction of the valuable fluoromethyl group, accomplished by starting with fluoroacetic acid xanthate **89**. Attempts to access this reagent by substitution of bromofluoroacetic acid **87** failed; however, ester **88** is accessible[18] and could be selectively cleaved with acid to give reagent **89** (Scheme 7). Reaction with caffeine **3** indeed gave fluoromethylcaffeine **90**, albeit in significantly lower yield (29%) than for the corresponding methylation. This is probably due, at least in part, to a polarity mismatch, but more work is needed to clarify the various factors involved.

Scheme 7. Introduction of Other Alkyl Chains



DOI: 10.1021/acs.orglett.8b00190
Org. Lett. XXXX, XXX, XXX−XXX

α-Bromocarboxylic acids can be obtained by the classical Hell−Volhard−Zelinsky reaction opening access to numerous xanthate-substituted carboxylic acids. A more direct route is by radical addition to acrylic acid, as illustrated by the synthesis of compound **92** from chloropyridylmethyl xanthate **91**.[19] The yield is modest because of the tendency of acrylic acid to polymerize. Nevertheless, the reaction with pyrazine **22** proceeded nicely with spontaneous decarboxylation to furnish addition product **93** in 52% yield.

The initial aim of this work was the development of a practical synthetic tool for late-stage functionalization of biologically active substances in order to rapidly optimize their pharmacological profile. From this perspective, the chemical yield is of less importance than quick access to the few milligrams needed for testing. We found, nevertheless, that this method has significant preparative value in many instances. We have also uncovered some limitations. A number of heteroarenes could not be functionalized in this manner, including the particularly important pyridines.[20] Further work will hopefully allow us to overcome these shortcomings and expand the scope further.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00190.

Experimental procedures, full spectroscopic data, and ^{1}H and ^{13}C NMR for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Ecole Polytechnique for a scholarship to Q.H. and Dr. Béatrice Sire (Ecole Polytechnique) for a first preparation of xanthate **89**.

■ DEDICATION

This paper is dedicated with respect to the memory of Professor Francesco Minisci (Politecnico di Milano).

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(20) See the SI for a list of heteroarenes that reacted poorly or not at all. In addition to unreacted starting material, unidentified side products, and products from direct reaction with radicals from the peroxide were observed.

DOI: 10.1021/acs.orglett.8b00190
Org. Lett. XXXX, XXX, XXX−XXX