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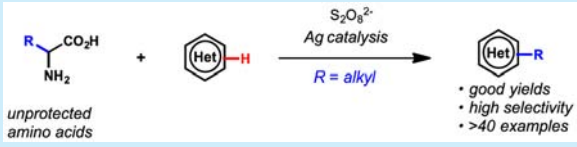
Unprotected Amino Acids as Stable Radical Precursors for Heterocycle C−H Functionalization

Duy N. Mai and Ryan D. Baxter*

Department of Chemistry and Chemical Biology, University of California, 5200 North Lake Road, Merced, California 95343, United States

Supporting Information

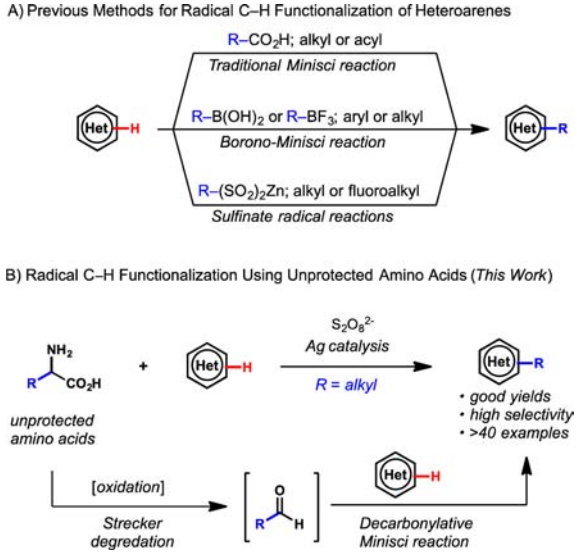
ABSTRACT: An efficient and general method for the C−H alkylation of heteroarenes using unprotected amino acids as stable alkyl radical precursors is reported. This one-pot procedure is performed open to air under aqueous conditions and is effective for several natural and unnatural amino acids. Heterocycles of varying structure are suitably functionalized, and reactivity trends reflect the nucleophilic character of the radical species generated.



Substituted aromatic heterocycles are critically important to the field of medicinal chemistry, with many small-molecule therapeutics containing one or more substituted heteroaromatics as essential structural motifs.[1] Because of this, researchers have devoted significant effort toward developing robust chemical methods for heteroaromatic substitution, traditionally via transition-metal-mediated cross-coupling reactions.[2] Recently, there has been a surge of interest in direct C−H substitution reactions that avoid prefunctionalized materials,[3] and radical-mediated processes have shown particular promise for early- and late-stage functionalization of pharmaceutically relevant molecules.[4] Pioneering work by Minisci demonstrated a direct method for C−H alkylation of heteroarenes via silver-catalyzed radical decarboxylation of carboxylic acids,[5] and recent advancements have greatly expanded the scope and efficiency of radical C−H functionalizations of heteroarenes using alternative radical precursors such as boronic acids and metal sulfinates (Scheme 1A).[6] Despite these achievements, limitations remain. The traditional Minisci reaction often produces mixtures of mono- and bis-alkylated products and requires heating at low pH (aq H_2SO_4), which is not suitable for acid-sensitive functional groups. The milder borono-Minisci reaction is restricted to the C−H arylation of heterocycles using boronic acids.[6a] Alkyl trifluoroborates may be employed for heterocycle alkylation, but require superstoichiometric metal oxidants.[6b] More recently, alkyl and fluoroalkyl sulfinates have been shown to be excellent radical precursors for C−H alkylation of heteroarenes.[6c−e] However, these costly reagents often require specifically optimized reaction conditions depending on the sulfinate and heterocycle used. With these limitations in mind, we sought to develop a strategy that utilizes unprotected amino acids as inexpensive alkyl radical precursors for the C−H alkylation of aromatic heterocycles (Scheme 1B).[7]

Amino acids are readily available, easily handled, and renewable carbon feedstock, making them ideal source material for substitution reactions. Although the incorporation of amino acids into target molecules via peptide coupling has been extensively developed,[8] the use of amino acids in C−C bond-forming reactions is less common. Few reports have described the use of *N*-protected amino acids in radical[9] or photocatalyzed functionalization of heterocycles,[10] but to the best of our knowledge, unprotected amino acids have not been used as a source of alkyl radicals for C−C bond-forming reactions. Herein we describe the design and development of a silver-catalyzed C−H alkylation reaction for the functionalization of heterocycles using unprotected amino acids as stable radical precursors (Scheme 1B). This reaction is believed to proceed via in situ aldehyde formation followed by a Minisci-type decarbonylation/alkylation radical process to yield substituted heteroarenes. The multistep oxidative degradation of amino acids to liberate alkyl radicals mimics a slow-release strategy of reactive intermediates[11]

Scheme 1. Radical C−H Functionalization Reactions



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and offers better selectivity and desired reactivity compared to C−H alkylative Minisci reactions using carboxylic acids, aldehydes, and zinc sulfinates as radical precursors (vide infra).

The development of a mild radical C−H alkylation reaction from unprotected amino acids requires a catalyst system capable of promoting both oxidative Strecker degradation and radical decarbonylation via formyl hydrogen abstraction. In addition to seminal contributions by Minisci, several recent reports have shown that radical decarboxylation under oxidative conditions is a direct and efficient method for generating alkyl radicals.[12] Although several methods for the oxidative degradation of unprotected amino acids are known,[13] Minisci-type radical alkylations via aldehyde decarbonylation are rare.[14] Nevertheless, employing conditions similar to those used in the traditional Minisci and borono-Minisci reactions (silver catalyst and persulfate oxidant) showed that in the presence of 10 mol % $AgNO_3$, 2.0 equiv of valine, 5.0 equiv of ammonium persulfate, 1.0 equiv of trifluoroacetic acid, and a 1:1 mixture of DCE/H_2O (0.1M) at 80 °C, 4-ethylisonicotinate was monoalkylated in 62% yield (**1a**, Table 1, entry 1).

Table 1. Comparison of Radical Sources for Minisci-Type Reactions[a]

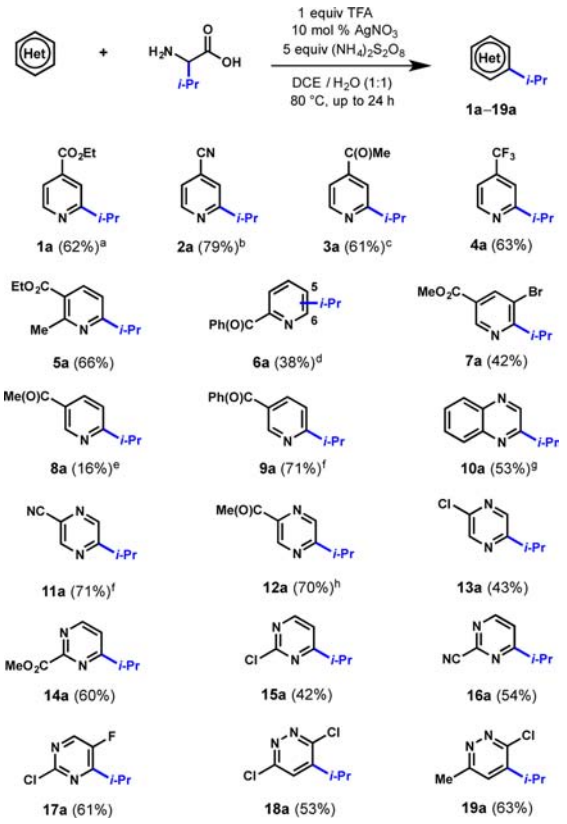
entry	radical source	yield of **1a** (%)	ratio (**1a**:**1a**′)[b]
1	valine	62	4:1
2	isobutyraldehyde	26	1:1
3	isobutyric acid	8	1:1.7
4[c]	$Zn(SO_2i\text{-}Pr)_2$	27	1.4:1

[a]Standard reaction conditions: heterocycle (0.2 mmol), radical source (0.4 mmol), TFA (0.2 mmol), $(NH_4)_2S_2O_8$ (1 mmol) in 2 mL of DCE/H_2O (1:1) at 80 °C for 24 h. [b]Ratios of **1a**/**1a**′ determined by crude ^1H NMR for entries 1−3 (see the Supporting Information). [c]Yield and ratio from ref 6e. Reported reaction conditions: heterocycle (0.25 mmol), $Zn(SO_2i\text{-}Pr)_2$ (2.00 mmol), *t*-BuOOH (5.00 mmol), 1.4 mL DCE/H_2O (2.5:1) at 50 °C for 48h. For reaction condition optimization, see the Supporting Information for details.

The use of isobutyraldehyde (entry 2) and isobutyric acid (entry 3) as radical precursors under our reaction conditions provided mixtures of mono- and bis-alkylated products in low yields. In addition, zinc isopropylsulfinate (entry 4) has previously been reported to provide a mixture of products with **1a** present in low yield. Control experiments revealed that silver catalyst and persulfate are required and reaction efficiency was reduced significantly without trifluoroacetic acid. Other metal sources known to promote the Minisci reaction, such as iron(II) salts, provided trace product.[5b] Traditional Minsci reaction conditions (heating under aqueous H_2SO_4) led to degradation of the starting material regardless of radical precursor used.[5a] With the conditions outlined in Table 1, we explored the scope of heterocycles capable of accepting an isopropyl radical from valine. Although formation of the isopropyl radical from valine is proficient at ambient temperature under purely aqueous conditions, many heterocycles required an organic cosolvent and elevated temperatures for suitable conversion. In all cases, reactions were prepared open to air at ambient temperature using solvents and reagents without prior purification.

As shown in Scheme 2, Ag(I)-catalyzed degradation of valine in the presence of ammonium persulfate promoted the addition

Scheme 2. C−H Alkylation of Heteroarenes with Valine[i]



[a]21% yield of bis-alkylated **1a**′ also isolated. [b]19% yield of bis-alkylation product **2a**′ also isolated. [c]9% yield of acyl product **3b** also isolated. [d]C6:C5 (3.7:1). [e]22% yield of acyl product **8b** also isolated. [f]20 mol % of $AgNO_3$ used. [g]18% yield of acyl product **10b** was also isolated. [h]22% yield of acyl product **12b** was also isolated. See the Supporting Information for more details on minor acyl products. [i]General reaction conditions: heterocycle (0.2 mmol), amino acid (0.4 mmol), TFA (0.2 mmol), $(NH_4)_2S_2O_8$ (1 mmol) in 2 mL of DCE/H_2O (1:1, 0.1M) at 80 °C for 24 h.

of an isopropyl group to a variety of nitrogen-containing heterocycles. Pyridines (**1a**−**9a**), pyrazines (**10a**−**13a**), pyrimidines (**14a**−**17a**), and pyridazines (**18a**−**19a**) are all suitably monoalkylated, and good functional group tolerance was observed. Most notably, potentially labile functional groups such as esters (**1a**, **5a**, **7a**, **14a**), nitriles (**2a**, **11a**, **16a**),[10a] and halides (**7a**, **13a**, **17a**−**19a**) were tolerant of our reaction conditions. Interestingly, entries **3**, **8**, **10**, and **12** also yielded minor amounts of acyl-substituted products, suggesting a competition between acyl-radical trapping and decarbonylation to the isopropyl radical. Attempts to minimize the formation of acyl-substituted products by purging the reaction system of carbon monoxide had a negligible effect on product distribution.

In addition to valine, several unprotected amino acids bearing alkyl side chains were explored with a series of aromatic heterocycles. As shown in Scheme 3, natural (leucine and isoleucine) and unnatural (norvaline and *tert*-leucine) amino acids are suitable radical precursors for a variety of electronically deficient heterocycles. Amino acids bearing primary carbon substituents (norvaline and leucine) often led to mixtures of alkyl and acyl products. Conversely, amino acids bearing secondary or

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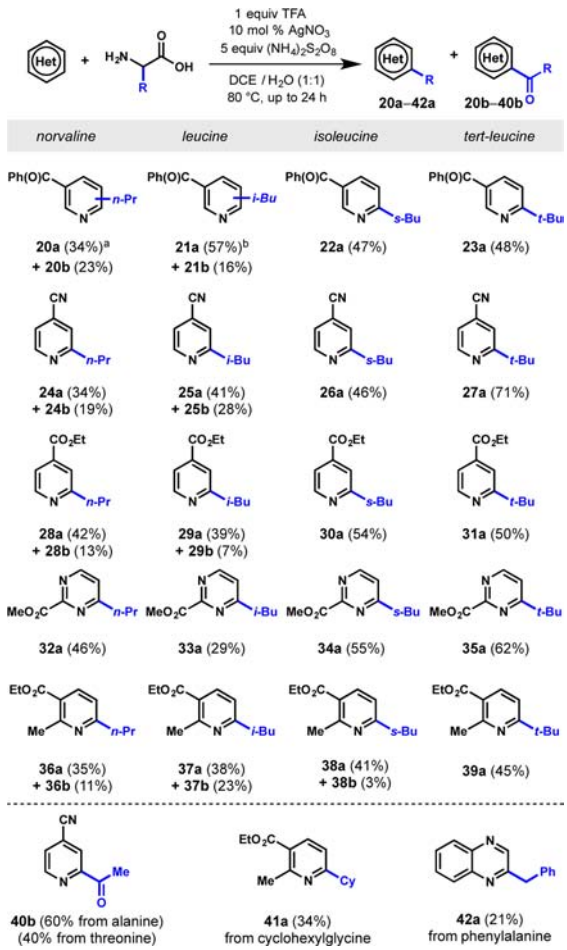
Scheme 3. Scope of Amino Acids for C−H Heteroarene Alkylation[d]



[a]C6:C5 (2:1). [b]C4:C5:C6 (1:1:1). [c]13% of a mixed acyl- and alkylated product was also observed, presumably via sequential radical additions; see the Supporting Information for details. [d]General reaction conditions: heterocycle (0.2 mmol), amino acid (0.4 mmol), TFA (0.2 mmol), $(NH_4)_2S_2O_8$ (1 mmol) in 2 mL of DCE/H_2O (1:1) at 80 °C for 24 h.

tertiary substituents (isoleucine, *tert*-leucine) yielded predominately monoalkylated heteroarenes. These results may be rationalized by considering the rate of radical decarbonylation as being mediated by the stability of the alkyl radical species generated upon decarbonylation.[14g] Although alkyl substitution is typically the major product observed, decarbonylation to produce primary alkyl radicals appears to be less favorable compared to more substituted side chains, and direct acyl trapping of the heteroarene becomes kinetically competent. This effect is also modulated by the reactivity of the heteroarene substrate, as entries **32a** and **33a** were formed exclusively as the monoalkylated products.

Other amino acids such as alanine, threonine, and cyclohexylglycine can also be employed as radical precursors, albeit in moderate yields. The reaction of 4-cyanopyridine with alanine produces **40b** as the major product, consistent with acyl trapping being preferred over decarbonylation to the unstable methyl radical. The formation of **40b** via alanine degradation is especially attractive when compared to Minisci-type chemistry using acetaldehyde as a radical precursor. Whereas alanine is indefinitely bench stable and easily handled under ambient conditions, acetaldehyde requires cold storage and special handling as a flammable liquid with an extremely high vapor pressure. Significantly, under our optimized reaction conditions, acetaldehyde produced only trace amounts of the expected products. Acyl product **40b** is also observed from the reaction of 4-cyanopyridine with threonine and represents the oxidized form of the expected alkylated product; it is unclear whether this product arises from α-oxidation of the expected alkylated product or via an acylation pathway. Although addition of benzyl radicals to heteroarenes is known,[15] low yield of **42a** was observed for the reaction of quinoxaline with phenylalanine under our general conditions, with oxidation of the intermediate tolyl radical yielding benzaldehyde as an unwanted byproduct. Reaction of cyclohexylglycine with ethyl 2-methylnicotinate produced **41a** in moderate yield, with unreacted Strecker aldehyde (cyclohexanecarboxaldehyde) accounting for the remaining mass balance of reaction material. Currently, the described method is limited to simple alkyl-bearing amino acids, as charged or polar side chains were unreactive under our general reaction conditions with no desired product or unreacted Strecker aldehydes being observed.

To support the mechanistic hypothesis of in situ aldehyde formation as a critical step of our reaction, NMR studies were undertaken for the reaction of ethyl isonicotinate with valine. As shown in Table 1, entry 1, a 4:1 mixture of monoalkylated and bis-alkylated products is produced, and unreacted isobutyraldehyde is clearly visible via NMR after 24 h. In the absence of a heterocyclic substrate, we observed full consumption of valine with concomitant formation of isobutyraldehyde over the course of 24 h.[16] These studies suggest that C−H functionalized products are likely the result of in situ aldehyde formation followed by a Minisci-type radical substitution reaction as hypothesized. Due to the in situ generation of the aldehyde as an intermediate prior to alkyl-radical formation, this method likely provides a different rate of alkyl-radical formation compared to employing either an aldehyde or carboxylic acid directly as radical precursors. A similar feature has also been observed for Suzuki reactions using trifluoroborate salts; slow generation of the active coupling species via hydrolysis prevents unwanted homocoupling and increases overall reaction efficiency.[17]

On the basis of our preliminary studies and literature precedent, a proposed mechanism is shown above in Figure 1.

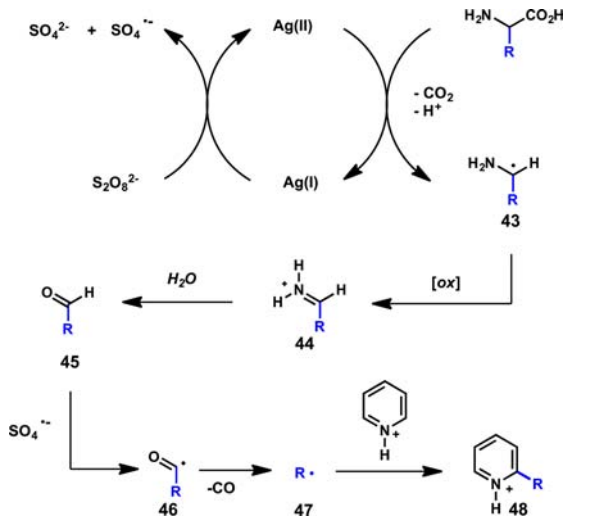


Figure 1. Proposed mechanism.

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The Ag(I)/$S_2O_8^{2-}$-promoted decarboxylation of an unprotected amino acid is expected to form 1-aminoalkyl radical species **43**.[9,13b] Under the strongly oxidizing reaction conditions,[18] we believe that **43** is rapidly converted to the corresponding iminium species **44** and hydrolyzed to aldehyde **45**.[13b] Formyl hydrogen−atom abstraction via persulfate radical anion generates acyl radical **46** which undergoes radical decarbonylation to liberate the α-amino acid side-chain as nucleophilic alkyl radical **47**. In the case of 1° substituted amino acids, **46** may be trapped directly by a heterocyclic substrate to form the observed acyl products. Addition of **47** into a protonated heterocycle followed by hydrogen atom abstraction and rearomatization provides the expected alkylated product **48**.[19]

In summary, we have developed a method that utilizes unprotected amino acids as bench-stable sources of alkyl radicals for the C−H functionalization of heterocycles. A variety of electron-deficient heterocycles are functionalized in good yield and high levels of selectivity. Preliminary mechanistic studies suggest the in situ formation of an aldehyde intermediate which undergoes a Minisci-type radical substitution reaction via a decarbonylative process. This multistep generation of reactive intermediates displays reactivity differing from using either an aldehyde or carboxylic acid directly as an alkyl-radical precursor. A comprehensive mechanistic study is ongoing and will provide insight into extending the chemistry to other amino acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01754.

Experimental procedures and spectroscopic data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rbaxter@ucmerced.edu.

Notes

The authors declare no competing financial interest.

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(19) Our current studies cannot rule out radical decyanation from an iminium intermediate to provide alkyl radicals.

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