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Letter

Metal-, Photocatalyst-, and Light-Free Minisci C−H Acetylation of N-Heteroarenes with Vinyl Ethers

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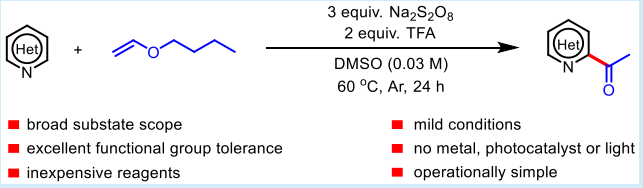
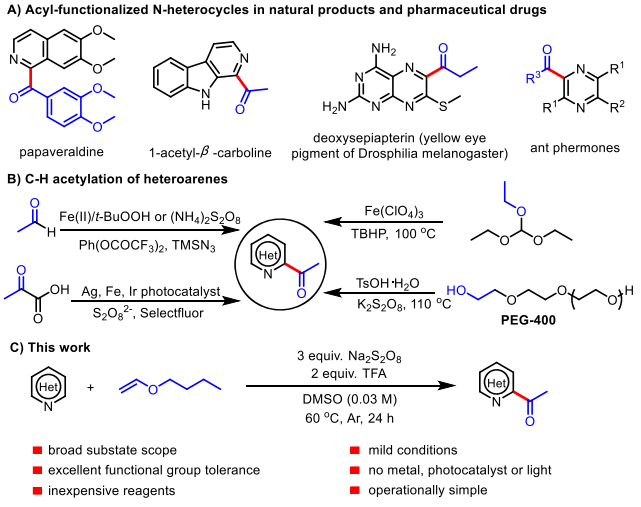
ABSTRACT: Herein, we report a mild, operationally simple method for Minisci C−H acetylation of N-heteroarenes using vinyl ethers as robust, inexpensive acetyl sources. The reactions do not require a conventional photocatalysis, electrocatalysis, metal catalysis, light activation, or high temperature. This method is thus significantly more sustainable than previously reported methods in terms of cost, reagent toxicity, and waste generation. This protocol can be expected to obtain medically relevant molecules from abundant feedstock materials.



N-Heterocycles,[1] especially N-heteroarenes,[2] are widely present in drug molecules. Therefore, it is of great significance to develop methods for the functionalization of N-heteroarenes;[3] this is particularly true for C−H acylation, owing to the many pharmaceutical drugs and natural products containing acylated N-heteroarenes (Scheme 1A).[4] Although

Scheme 1. Minisci Acetylation of N-Heteroarenes



electron-rich aromatic compounds can readily be acylated via the Friedel−Crafts reaction, very few reactions are used for acylation of N-heteroarenes. Minisci reaction provides a good method for acylation of N-heteroarenes.[5] Following this seminal work, a variety of protocols for acylation of N-heteroarenes with aldehydes,[6b] α-keto acids,[6c] benzylamines,[6d] and aryl methanes[6e] have been reported.[6] However, Minisci C−H acetylation of N-heteroarenes is challenging.[6]

Minisci acetylation reactions are typically carried out with acetaldehyde using Fe(II)/*t*-BuOOH, Fe(II)/$(NH_4)_2S_2O_8$, or phenyliodine bis(trifluoroacetate)/$TMSN_3$ oxidation systems (Scheme 1B).[7] In addition, Ag(I)/$(NH_4)_2S_2O_8$,[8] Fe(II)/$(NH_4)_2S_2O_8$,[9] photoredox catalysis,[10] and electrocatalysis have been employed to induce Minisci acylation reactions with α-keto acids.[11] Recently, Reddy et al. reported iron-catalyzed acetylation of electron-deficient N-heteroarenes using triethyl orthoformate as the acetyl source and *tert*-butyl hydroperoxide as an oxidant.[12] In parallel, Kudalea and Wang acetylated N-heteroarenes by using PEG-400 as a coupling partner in combination with potassium persulfate ($K_2S_2O_8$) at high temperature (Scheme 1B).[13] However, most of the previous methods require transition-metal catalysts, expensive photocatalysts, excess radical precursors, or high temperatures. Therefore, these methods are generally not suitable for complex natural products and drug molecules. Moreover, the harsh conditions make the reaction incompatible with certain functional groups, and various radical-addition byproducts are formed. Therefore, we want to develop a practical Minisci acetylation reaction without a metal, a photocatalyst, or high temperature.

We speculated that reaction of vinyl ethers with acid could result in the generation of acetaldehyde, which can be used as the acetyl-radical precursor. Recently, we discovered that Minisci C−H alkylation of N-heteroarenes with alkyl oxalates can be accomplished without a metal, a photocatalyst, or light in dimethyl sulfoxide (DMSO) containing persulfate ($S_2O_8^{2-}$)

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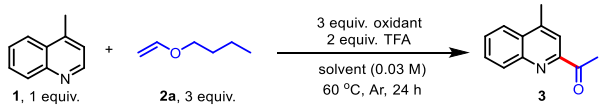
as an oxidant.[14] The DMSO allows for uncatalyzed decomposition of $S_2O_8^{2-}$ to a sulfate radical anion ($SO_4^{-\bullet}$) at low temperatures (50 °C), presumably because the decomposition rate is solvent dependent.[15] As part of our ongoing work on Minisci reactions,[16] we envisioned that $SO_4^{-\bullet}$ generated from $S_2O_8^{2-}$/DMSO could undergo a hydrogen atom transfer reaction with acetaldehyde (generated from readily available vinyl ethers) to produce an acetyl radical. Indeed, we now report the first protocol for acetylation of N-heteroarenes using vinyl ethers as acetyl radical precursors (Scheme 1C).

We began by investigating the acetylation reaction with lepidine (**1**, 1 equiv), *n*-butyl vinyl ether (**2a**, 3 equiv), $Na_2S_2O_8$ (3 equiv), and trifluoroacetic acid (TFA, 2 equiv) in 1,2-dichloroethane at 60 °C for 24 h (Table 1). Unfortunately,

Table 1. Optimization of Acetylation[a]



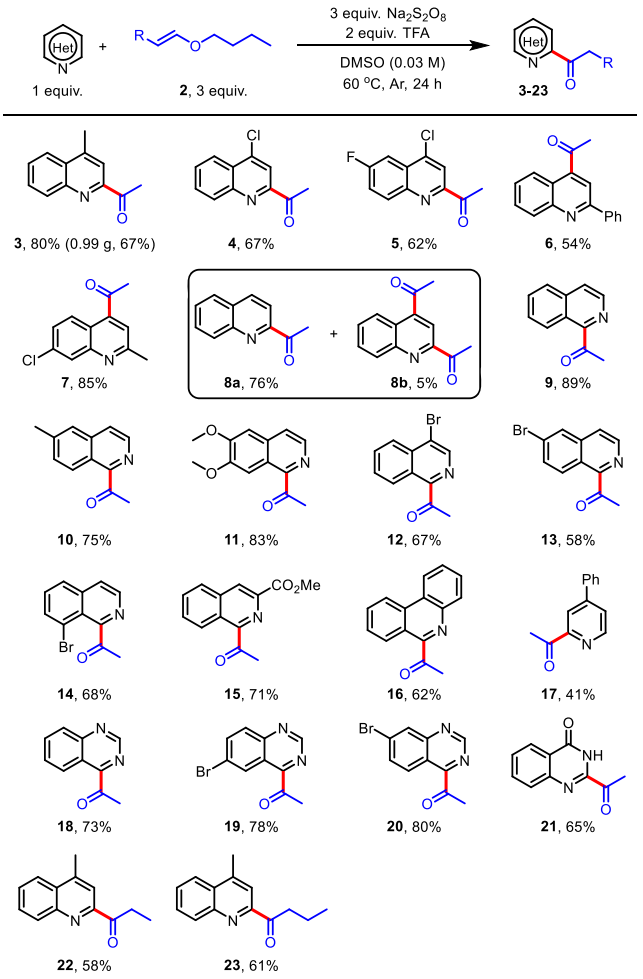
entry	oxidant	solvent	yield (%)[b]
1	$Na_2S_2O_8$	DCE	<5
2	$Na_2S_2O_8$	CH_3CN	NR
3	$Na_2S_2O_8$	toluene	NR
4	$Na_2S_2O_8$	DMSO	84 (80%[c])
5	$(NH_4)_2S_2O_8$	DMSO	58
6	$K_2S_2O_8$	DMSO	66
7	TBHP	DMSO	43
8	*t*-BPA	DMSO	<5
9	O_2	DMSO	<5
10[d]	$Na_2S_2O_8$	DMSO	58–73
11[e]	$Na_2S_2O_8$	DMSO	49
12	–	DMSO	NR
13[f]	$Na_2S_2O_8$	DMSO	21

[a]General conditions: **1** (0.2 mmol), **2** (0.6 mmol), oxidant (0.6 mmol), TFA (0.4 mmol), and DMSO (6 mL) under Ar atmosphere. DCE, 1,2-dichloroethane; TBHP, *tert*-butyl hydroperoxide; *t*-BPA, *tert*-butylperacetate. NR = no reaction. [b]Determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard. [c]Isolated yield. [d]Vinyl ethers **2b**, **2c**, and **2d** were used instead of **2a**. [e]Reaction performed at 20 °C. [f]No TFA.

we could only obtain a very low yield of desired product **3**, owing to the poor solubility of $K_2S_2O_8$ (entry 1). Then we tested other solvents (entries 2–4) and were delighted to find that **3** could be obtained in excellent yield when DMSO was used as the solvent (entry 4). When we used other persulfates, the yields of **3** were decreased (entries 5 and 6), which also resulted with use of the peroxide oxidants *tert*-butyl hydroperoxide and *tert*-butylperacetate (entries 7 and 8). The use of oxygen as the oxidant was strongly deleterious (entry 9). When other vinyl ethers were employed under the conditions shown in entry 4, the yields were only 58–73% (entry 10). When we performed the reaction at 20 °C, the yield of **3** was decreased to 49% (entry 11). Control experiments showed that $Na_2S_2O_8$ and TFA were necessary for the reaction (entries 12 and 13). Notably, the reaction proceeded only in DMSO; none of the typical Minisci solvents worked. As discussed above, $S_2O_8^{2-}$ decomposes more readily in DMSO,[14,15] and DMSO has the added benefit of being more environmentally benign than the commonly used solvent CH_3CN.

With optimized conditions established, we examined the scope of the acetylation (Table 2). Quinolines bearing various

Table 2. Scope of the Acylation Reaction[a]



[a]Reactions were performed on a 0.2 mmol scale. Isolated yields are given.

substituents (methyl, phenyl, fluorine, chlorine) gave the acetylation products at C2 or C4 in good yields (**3**–**7**, 54–85%), depending on the position of the substituent. We were pleased to find that a compound with a fluorine atom, which is often linked to the drug-like activity, was suitable for this reaction (giving **5**). Quinoline substrate gave the C2 acetylation product **8a** in 76% yield and trace of C2 and C4 difunctionalization product **8b**. Notably, isoquinolines bearing various substituents (methoxy, methyl, bromine, ester) underwent acetylation at C1, giving **9**–**15** in 58–89% yields. Phenanthridine was also suitable for this reaction, giving **16** in 62% yield, and acetylation of 4-phenylpyridine gave monoacetylated product **17** in 41% yield. This reaction was also suitable for N-heteroarenes containing two nitrogen atoms: quinazolines (**18**–**20**, 73–80%). Notably, 4-hydroxyquinazoline also participated in the reaction, giving **21** in 65% yield. Although radical-type S_NAr reactions have been reported,[17] we observed no products of substitution reactions involving the C–Cl bonds of the chloro-substituted compounds we tested (i.e., those that gave **4**, **5**, and **7**). Finally, we tested this acylation protocol with other vinyl ethers. Fortunately, ethyl propenyl ether and 1-butenyl ethyl ether afforded the

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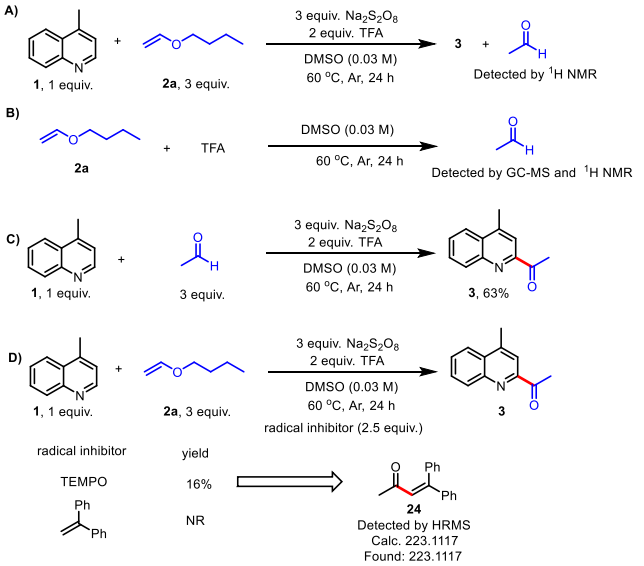
corresponding acylated heteroarenes (**22** and **23**) in 58% and 61% yields. Incomplete conversion of N-heteroarenes accounted for the moderate yields of some of the products (e.g., **6**, **17**, **21**, **22**, **23**). Notably, a gram-scale (8 mmol) reaction of **1** and **2a** afforded **3** in an isolated yield of 67%.

Then we studied the mechanism (Scheme 2). To determine the acetyl source, we used ^{1}H NMR spectroscopy. After the

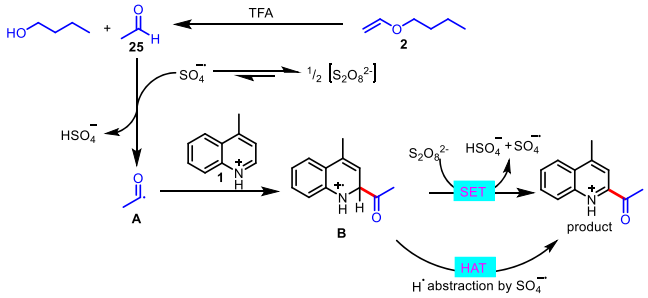
Scheme 2. Mechanistic Studies



reaction, acetaldehyde was detected by ^{1}H NMR (Scheme 2A). When *n*-butyl vinyl ether (**2a**) was allowed to react with TFA, acetaldehyde was detected by gas chromatography−mass spectrometry and ^{1}H NMR (Scheme 2B). These experiments demonstrated that reaction of **2a** and TFA generated acetaldehyde in situ and that acetaldehyde was converted to an acetyl radical in the presence of $Na_2S_2O_8$. This was confirmed by the fact that reaction of **1** and acetaldehyde afforded desired product **3** in 63% yield (Scheme 2C). Then we optimized the acetylation reaction with acetaldehyde substrate; however, we only obtained a 68% yield in the best situation. Next, we carried out experiments with radical inhibitors (Scheme 2D). When the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction, the yield of **3** decreased markedly (to 16%). When radical scavenger 1,1-diphenylethylene was added to the reaction, the reaction was completely inhibited, and radical trapping product 4,4-diphenylbut-3-en-2-one (**24**) was detected by high-resolution mass spectrometry.

Based on these experimental results, the mechanism is outlined in Scheme 3. The generation of $SO_4^{-\bullet}$ from $S_2O_8^{2-}$ typically proceeds via metal mediation or photolysis.[5] However, in our system, $S_2O_8^{2-}$ decomposes under mild conditions without catalysis, which we attribute to the solvent-dependence of the decomposition rate (as mentioned above, $S_2O_8^{2-}$ reportedly decomposes much more readily in DMSO than in other solvents[15]). At the same time, in the presence of TFA, *n*-butyl vinyl ether (**2a**) reacts to generate acetaldehyde in situ. Then $SO_4^{-\bullet}$ selectively abstracts the hydrogen atom from acetaldehyde to afford acetyl radical **A**. Nucleophilic radical **A** adds to the protonated N-heteroarene to afford radical cation **B**. Finally, product **3** can then form either via a

Scheme 3. Proposed Mechanism for Acetylation of N-Heteroarenes



single electron transfer reaction with $S_2O_8^{2-}$ or via abstraction of a hydrogen radical by $SO_4^{-\bullet}$.

In summary, a method for metal-, photocatalyst-, and light-free acetylation of N-heteroarenes using vinyl ethers as robust, inexpensive acetyl sources is reported. The application of this protocol to obtain medically relevant molecules is being studied in our group.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01310.

Experimental procedures, characterizations and copies of ^{1}H and ^{13}C NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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