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Transition-Metal-Free Oxidative Aliphatic C−H Azidation

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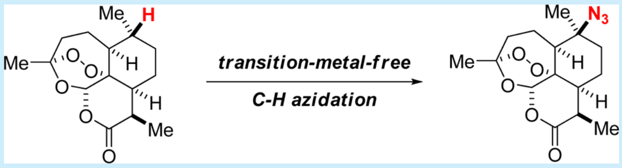
Ⓢ *Supporting Information*

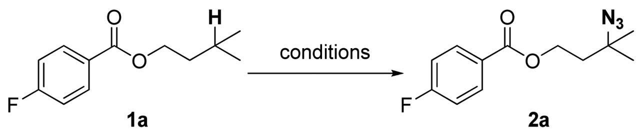
ABSTRACT: The first example of a practical and selective azidation of unactivated aliphatic C−H bonds with easily handled sulfonyl azides as azide source without the use of transition metals has been explored. This method is operationally simple, scalable, and applicable to late-stage azidation of natural products and derivatives, which make it a valuable method for the synthesis of organic azides.



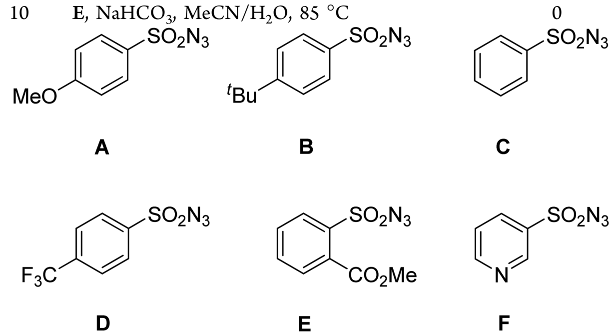
The importance of organic azides in chemical biology, medicinal chemistry, and materials science has spurred vigorous research into the development of new methods for the synthesis of organic azides.[1] Additionally, organic azides have become widely used as versatile intermediates in organic synthesis,[2] including Huisgen "click" cycloaddition[3] and Staudinger ligation.[4] Despite numerous methods for the synthesis of organic azides from a variety of functionalities, methods for the direct azidation of unactivated aliphatic C−H groups are comparatively rare.[5] Traditional methods for the synthesis of alkyl azides through C−H bond functionalization suffer from limited substrate scope and require the use of dangerous reagents such as iodine azide.[6] Enantioselective C−H azidation adjacent to a carbonyl group has been achieved.[7] In addition to the recent success of Csp^3−H azidation in allylic and benzylic positions,[8] methods for the transformation of unactivated Csp^3−H bonds to Csp^3−N_3 bonds have been developed with transition metals. Recently, Hartwig reported an iron-catalyzed late-stage azidation of tertiary and benzylic C−H bonds using azidoiodinanes as azidating reagents.[9] Groves presented a manganese-catalyzed late-stage azidation of secondary, tertiary, and benzylic C−H bonds with NaN_3.[10] Although sulfonyl azides are commonly used as azidating agents,[11,12] no examples of practical and selective azidation of unactivated aliphatic C−H bonds with sulfonyl azides have been reported.[13] Therefore, due to the favorable stability and ease of preparation of sulfonyl azides,[14] the development of general and complementary methods for the aliphatic C−H azidation with sulfonyl azides is highly desirable.

Herein, we report a practical and direct $C(sp^3)$−H azidation method using sulfonyl azide as the azide source without transition metal. The initial investigation focused on the reaction of isopentyl 4-fluorobenzoate (**1a**) with various sulfonyl azides. As briefly illustrated in Table 1 (see the Supporting Information for more details), various sulfonyl azides were evaluated (entries 1−6), and methyl 2-(azidosulfonyl)benzoate (**E**) gave the best results. In addition, peroxydisulfate salts were evaluated, and $K_2S_2O_8$ gave a highest yield (entries 5−8). During the screening of this reaction, the hydrolysis byproduct was observed in 10% yield, and we hypothesized that acid was generated under the reaction conditions which caused the product to decompose at high temperature, so we evaluated bases to neutralize the acid and

Table 1. Screening of Azidation Conditions



entry	conditions[a]	conversion[b] (%)
1	**A**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	49
2	**B**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	55
3	**C**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	60
4	**D**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	60
5	**E**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	65
6	**F**, $K_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	46
7	**E**, $Na_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	46
8	**E**, $(NH_4)_2S_2O_8$, $NaHCO_3$, $MeCN/H_2O$, 85 °C	64
9	**E**, $K_2S_2O_8$, $NaHCO_3$, MeCN, 85 °C	0
10	**E**, $NaHCO_3$, $MeCN/H_2O$, 85 °C	0



[a]1.5 equiv of sulfonyl azide was used. 3.0 equiv of oxidant and 1.0 equiv of base were used under N_2 atmosphere for 4 h. [b]Yields were determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as a standard.

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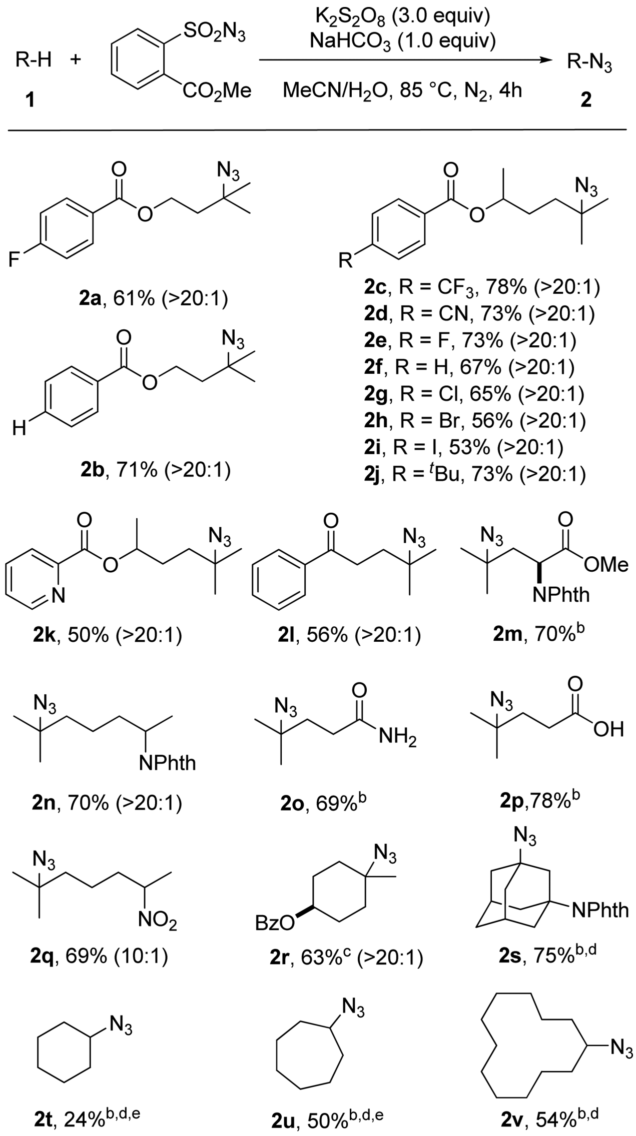
identified sodium bicarbonate ($NaHCO_3$) as being optimal. Water also proved to be essential; no product occurred in anhydrous acetonitrile (entry 9). The role of water has not yet been explored. The reaction was performed under N_2 atmosphere, and a slightly lower yield was obtained under air. The control experiment was performed in the absence of $K_2S_2O_8$ and no desired product was observed (entry 10). The reaction is sensitive to the amount of $K_2S_2O_8$. After thoroughly optimizing the reaction conditions, reactions with 3.0 equiv of $K_2S_2O_8$, 1.0 equiv of $NaHCO_3$ and 1.5 equiv of methyl 2-(azidosulfonyl)benzoate (**E**) in 3:2 (v:v) acetonitrile/H_2O at 85 °C for 4 h under N_2 atmosphere were found to produce high yields of the desired product.

With the optimized conditions in hand, we then investigated the substrate scope as displayed in Scheme 1. A variety of simple molecules which have multiple unactivated Csp^3−H bonds were smoothly transformed into the corresponding desired products with isolated yields up to 78%. Ketone, ester, amide, carboxylic acid, aromatic nitrile, chloride, bromide, even iodide functionality were all tolerated under the standard reaction conditions. The azidation occurs with high selectivity for a tertiary C−H bond over the secondary and primary C−H bonds for simple substrates. The selectivity of azidation was observed at methines which are remote from electron-withdrawing groups if substrate contains two electronically distinct methines. For example, the transformation of 5-methyl-2-hexyl benzoate (**1f**) to the corresponding product (**2f**) occurred predominantly at the methine position remote from the carboxylic ester. Additionally, the reaction worked with heteroaromatic substituted alkyl chain derivative (**1k**). Notably, amino acid derivative was also successfully employed to provide corresponding desired compound with high selectivity and good yield (**2m**). When *cis*-4-methyl-1-cyclohexanol benzoate (**1r**) was used as substrate and the two diastereomers of **2r** were formed in a 1:0.75 ratio. With cycloalkanes (**2s, 2t, 2u, 2v**), an excess of substrate (3 equiv for **2s**, 5 equiv for **2t, 2u, 2v**) was used, and azidation yields for the substrates were measured based on sulfonyl azide. With cycloalkanes (**2t, 2u, 2v**), lower yields were observed due to oxidative byproducts (such as ketone) being formed. Substrate **2b** was prepared on a gram scale under the standard reaction conditions in 73% isolated yield, proving the operational simplicity and practicality of this method.

The late-stage azidation of biologically active molecules containing multiple C−H bonds was also successful, giving the corresponding azidation products. The azidation mostly occurred at more electron-rich and least sterically hindered position with complex substrates. For example, the azidation of sclareolide (**1w**),[15] a terpenoid natural product with antifungal and cytotoxic activities, proceeded to form the azidation compound (**2w**) under standard reaction conditions in 29% isolated yield as the major isomers (around 18% recovered starting material) (Scheme 2A). The C3 azidation product was observed in 7% yield determined by ^{1}H NMR. Since other two 3 °C−H position were more sterically hindered, selective azidation was observed at the C2 methylene position, which was remote from electron-withdrawing groups and less sterically hindered. Additionally, a diterpene compound (**1x**) derived from pleuromulin, an antibacterial drug, which displays five 3 °C−H bonds, reacted smoothly to give **2x** in 24% isolated yield after 4 h (around 43% recovered starting material) (Scheme 2B). Azidation at the C11 methylene position occurred as the major product due to it being more

Scheme 1. Transition-Metal Free Oxidative Azidation of Simple Molecules[a]



[a]Reaction conditions: substrate **1** (1.0 equiv), sulfonyl azide (1.5 equiv), $K_2S_2O_8$ (3.0 equiv) and $NaHCO_3$ (1.0 equiv), 85 °C, N_2. Yields refer to isolated product unless otherwise noted. The ratio of the shown product to other regioisomers was determined by GC−MS and are given in parentheses. [b]Other regioisomers were not detected by GC−MS. [c]1:0.75 dr. [d]Excess of substrate (3 to 5 equiv) was used. [e]Yields were determined by GC or ^{1}H NMR with acetophenone as a standard due to lower boiling point of product.

electron-rich and less sterically hindered compared to the other positions. Furthermore, artemisinin (**1y**), a drug against *Plasmodium falciparum* malaria, which contains a peroxide bridge and five 3 °C−H bonds, proceeded smoothly to provide the azidation product **2y** in 33% isolated yield (around 18% recovered starting material) (Scheme 2C). The selective azidation occurred at the C6 methine position as the major product due to it being more electron-rich and less sterically hindered compared to the other 3 °C−H bonds.

Although detailed mechanistic studies have not been clear, some preliminary mechanistic studies were conducted. The cyclized product **3** was observed when the ketone **1l** was used as the substrate under the standard reaction conditions

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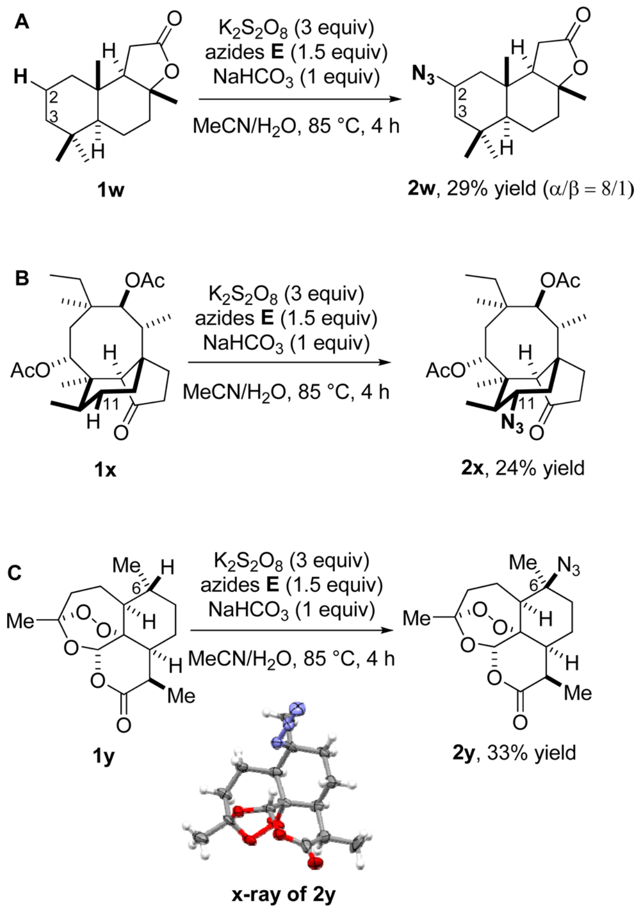
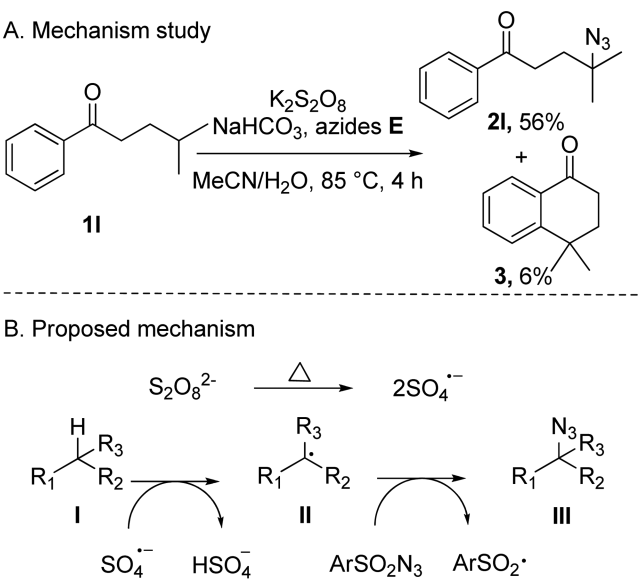
Scheme 2. Late-Stage Azidation of Complex Molecules



(Scheme 3A), which is consistent with a radical or a carbocation involved in the reaction mechanism. In addition, less than 10% azidation yield were found when $TMSN_3$ or NaN_3 was used as the azide sources, which indicates that the reaction may not proceed through a carbocationic intermediate. Furthermore, no azidation product was formed when 1.0 equiv of the radical inhibitor butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added. Finally, the deuterium kinetic isotope effect (KIE) was evaluated in separate vessels from initial reaction rates with cyclohexane and cyclohexane- d_{12} to give a small KIE of 1.45, which suggests that the C−H bond cleavage might not be the rate-limiting step.[16] Together, these observations indicated that a radical-chain mechanism or single-electron transfer (SET) may be involved in this transformation. Based on these experiments, we have proposed the mechanism depicted in Scheme 3B, where peroxydisulfate anion decomposes into sulfate radical anion,[17] which can potentially oxidize the aliphatic C−H bond into a carbon radical (**II**). Sulfonyl azide is known to azidate alkyl radicals to form C−N_3 bonds (**III**).[12]

Scheme 3. Mechanism Study and Proposal Mechansim



In conclusion, the first example of a direct and selective azidation of unactivated aliphatic C−H bonds with easily handled sulfonyl azides as the azide source without a transition metal has been developed. This azidation reaction has broad substrate scope and is applicable to late-stage azidation of natural products and derivatives. Expansions of this approach to the site selective C−H functionalization of other classes of small molecules are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03001.

Experimental procedures and characterization of all new compounds including ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)

X-ray data for (CIF)

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Notes

The authors declare no competing financial interest.

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