Silver-Catalyzed Decarboxylative Radical Azidation of Aliphatic Carboxylic Acids in Aqueous Solution

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Supporting Information Placeholder

ABSTRACT: We report herein an efficient and general method for the decarboxylative azidation of aliphatic carboxylic acids. Thus with $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant, the reactions of various aliphatic carboxylic acids with tosyl azide or pyridine-3-sulfonyl azide in aqueous CH_3CN solution afforded the corresponding alkyl azides under mild conditions. A broad substrate scope and wide functional group compatibility were observed. A radical mechanism is proposed for this site-specific azidation.

Organic azides perform irreplaceable roles in chemical biology and drug discovery owing to the broad application of azide–alkyne Huisgen cycloaddition and Staudinger ligation in "click" chemistry.[1] They are also versatile intermediates in organic chemistry and materials science.[2] The access to this important class of compounds has attracted a considerable attention, and a number of new methods such as C–H azidation[3] and carboazidation[4] of alkenes, have recently been developed. Nevertheless, the discovery of general, efficient and site-specific methods under mild conditions remains a formidable challenge. Herein we report the silver-catalyzed decarboxylative azidation of aliphatic carboxylic acids in aqueous solution, providing a convenient and site-specific entry to organic azides with high efficiency and broad substrate scope.

The ready availability, high stability, and low cost of aliphatic carboxylic acids make them extremely promising raw materials for chemical synthesis.[5] In particular, the decarboxylative reactions involving the cleavage of C(sp^3)–COOH bonds allow the site-specific introduction of functional groups.[6–8] The conversion of a carboxylic acid into an azide is unique and very attractive due to the versatility of the azide function. This transformation was realized[9] by converting carboxylic acids to thiohydroxamate esters such as PTOC (pyridine-2-thione-*N*-oxycarbonyl) or MMDOC (*N*,*S*-dimethyldithiocarbamoyl-*N*-oxy-carbonyl) esters, followed by reaction with a sulfonyl azide[10] under radical initiation conditions (hv or AIBN) (Figure 1).[11] However, this two-step method is of relatively low overall efficiency and also suffers from the low stability of thiohydroxamate esters. The efficient, operationally simple, one-step and direct decarboxylative azidation, especially in a catalytic manner, is thus highly desirable. Driven by our interest in silver-catalyzed decarboxylation reactions,[7] we set out to explore this possibility.

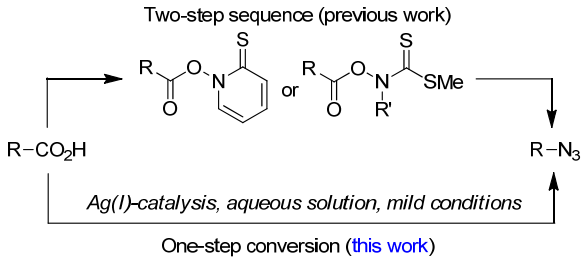
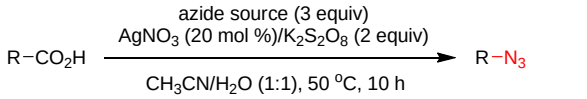


Figure 1. Decarboxylative azidation of aliphatic carboxylic acids.

Thus, 2-ethyltetradecanoic acid (**A-1**) was initially used as the model substrate for the optimization of reaction conditions (see Table S1 in the Supporting Information for details). We were pleased to find that, with $AgNO_3$ (20 mol %) as the catalyst and $K_2S_2O_8$ (2 equiv) as the oxidant, the reaction of **A-1** with pyridine-3-sulfonyl azide (3 equiv) proceeded smoothly in CH_3CN/H_2O (1:1) at 50 °C leading to the expected decarboxylative azidation product **1** in essentially quantitative yield. Among various azide reagents screened, pyridine-3-sulfonyl azide was proved to be the best, as shown in Scheme 1. Tosyl azide also afforded alkyl azide **1** in an excellent yield. Benzenesulfonyl azide, ethanesulfonyl azide and pyridine-2-sulfonyl azide were less effective, and variable amounts of acid **A-1** were recovered at the end of reactions. On the other hand, no product could be observed with the use of azidobenziodoxolones presumably because of their instability in aqueous solution. To check the consistency of the above reactivity trend, two more substrates were then tested, adamantane-1-caroboxylic acid (**A-2**) and 2,2-di(acetoxymethyl)propionic acid (**A-3**). The azidodecarboxylation of **A-2** with 3-$PySO_2N_3$ gave azide **2** in 17% yield only, while di- and tri-azidation side-products could be detected by GC-MS analysis presumably via C–H azidation. As a comparison, the use of TsN_3 afforded product **2** cleanly in 84% yield. However in the case of **A-3**, alkyl azide **3** was obtained in a good yield (68%) with 3-$PySO_2N_3$ but in a poor yield (30%) with TsN_3. In the latter case over 40% yield of **A-3** was recovered. The above results indicate that 3-

$PySO_2N_3$ is generally more reactive and also more prone to side reactions than TsN_3. Although the reasons for the difference between the two reagents remain unclear, we suspect that the basicity might play a role, as 3-$PySO_2N_3$ is more basic. Indeed, when the reaction of **A-3** with TsN_3 was carried out in the presence of pyridine (3 equiv) under otherwise identical conditions, the yield of **3** increased from 30% to 50%.[12]

Scheme 1. Effects of Different Azides in Azidodecarboxylation

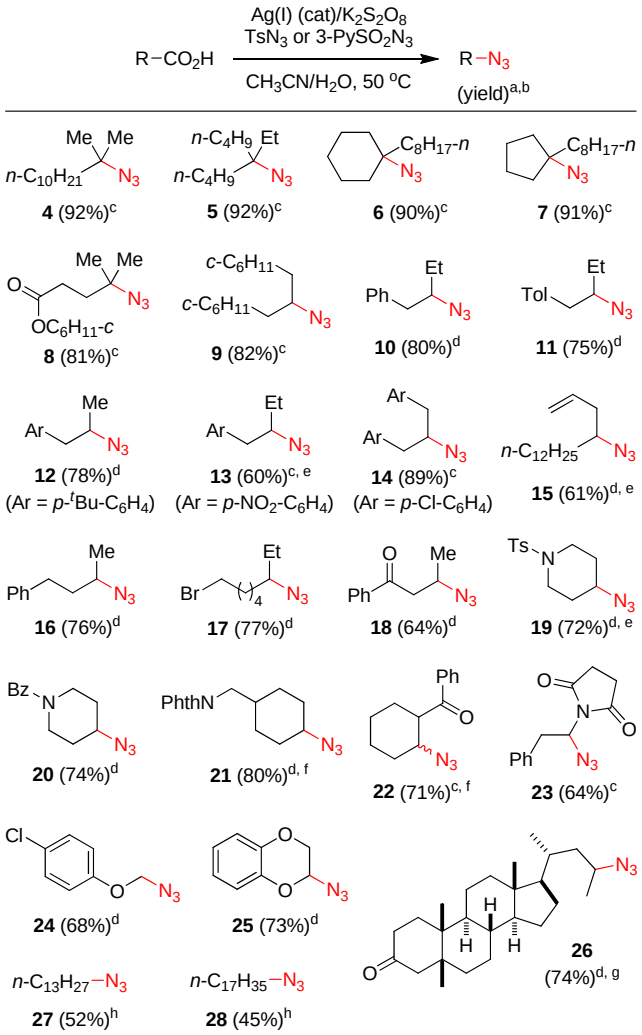


azide source	1	2	3
3-$PySO_2N_3$	**98**	17	**68**
TsN_3	91	**84**	30
$PhSO_2N_3$	74	82	20
$EtSO_2N_3$	70	68	24
2-$PySO_2N_3$	50	30	14
(X, X = O)	0	0	0
(X = Me)	0	0	0

We then moved on to examine the scope and limitation of this new decarboxylative azidation method with either 3-$PySO_2N_3$ or TsN_3 as the azide reagent, and the results are summarized in Scheme 2. Tertiary alkyl carboxylic acids underwent efficient decarboxylative azidation to afford the corresponding products **4–8** in excellent yields. The reactions of secondary alkyl carboxylic acids also proceeded smoothly, furnishing the alkyl azides **9–22** in high yields. The azidodecarboxylation was also applicable to α-oxy acids or α-amino acids, as exemplified by the synthesis of azides **23–25**. A variety of functional groups including ether, ester, ketone, amide, tosylate, sulfonamide, alkene, nitro, and aryl or alkyl halides, were well tolerated. This excellent functional group compatibility allowed the late-stage azidation of complex molecules. For example, the decarboxylative azidation of dehydrolithocholic acid led to the corresponding product **26** in 74% yield.

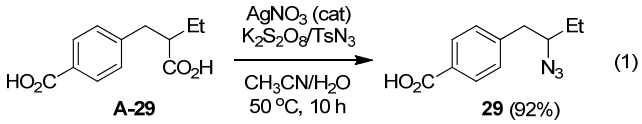
Compared to secondary and tertiary alkyl acids, primary alkyl carboxylic acids such as tetradecanoic acid and stearic acid underwent decarboxylation sluggishly under the above conditions. Nevertheless, when we increased the reaction temperature to 80 °C, the desired products **27** and **28** could be achieved in moderate yields. On the other hand, aromatic acids such as 4-chlorobenzoic acid and 4-methoxybenzoic acid failed to give any desired azidodecarboxylation products under the above experimental conditions, while all of the starting acids were recovered.

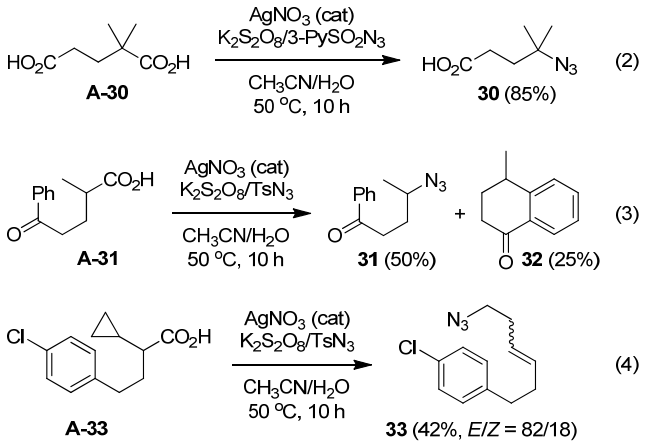
Scheme 2. Silver-Catalyzed Decarboxylative Azidation



[a] Reaction conditions: carboxylic acid (0.2 mmol), 3-$PySO_2N_3$ or TsN_3 (0.6 mmol), $AgNO_3$ (0.04 mmol), $K_2S_2O_8$ (0.4 mmol), CH_3CN (1 mL), H_2O (1 mL), 50 °C, 10 h. [b] Isolated yield based on carboxylic acid. [c] 3-$PySO_2N_3$ was used. [d] TsN_3 was used. [e] Four equivalents of azide reagent were used. [f] *trans*/*cis* = 74:26. [g] d.r. = 50:50. [h] $AgNO_3$ (0.06 mmol), 3-$PySO_2N_3$ (0.8 mmol) and $K_2S_2O_8$ (0.6 mmol), reflux, 12 h.

It can be concluded from Scheme 2 that the reactivity of carboxylic acids decreased in the order tertiary > secondary > primary >> aromatic. This reactivity pattern thus allows the implementation of chemoselective azidodecarboxylation. For example, the alkylic carboxyl group in diacid **A-29** was selectively removed while the benzoic carboxyl group remained intact, providing alkyl azide **29** in 92% yield (Eq 1). Similarly, 2,2-dimethylpentanedioic acid (**A-30**) underwent chemoselective decarboxylation to give exclusively the tertiary alkyl azide **30** (Eq 2).





The above relative reactivities of carboxylic acids also suggest that the reaction proceeds by an oxidative radical decarboxylation mechanism. A more direct evidence was the reaction of acid **A-31** in with the azidation product **31** (50%) was accompanied by the cyclization product **32** (25%), as shown in Eq 3. To provide solid evidence on the radical mechanism, cyclopropylacetic acid **A-33** was designed as the radical probe. The reaction of **A-33** with TsN_3 under the above optimized conditions gave the ring-opening product **33** in 42% yield as a 82:18 mixture of two stereoisomers determined by ^1H NMR (Eq 4). These two experiments strongly support the involvement of free radical mechanism in the azidodecarboxylation.

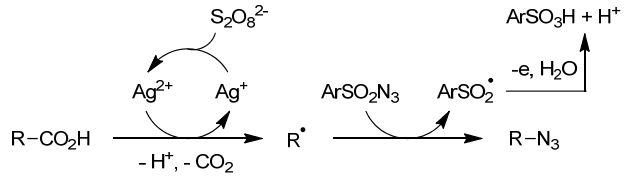
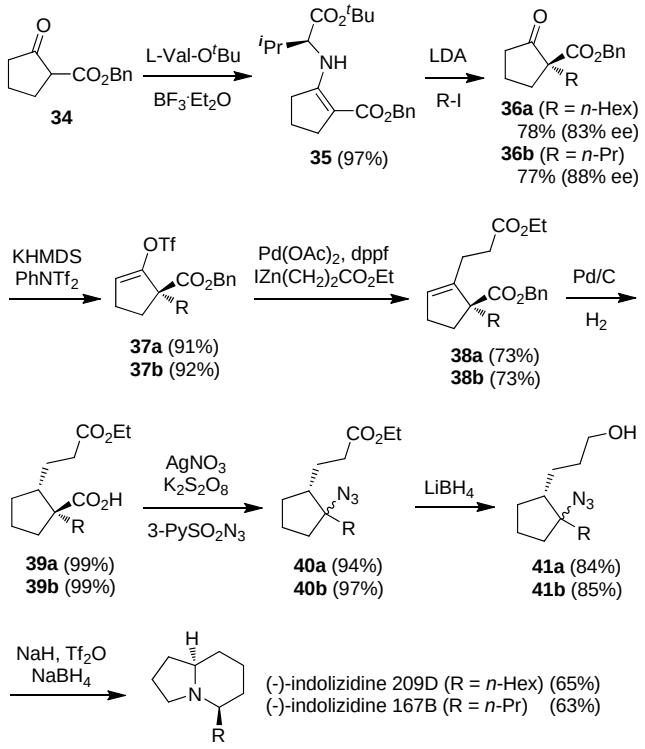


Figure 2. Proposed mechanism of decarboxylative azidation.

A plausible mechanism was thus proposed as shown in Figure 2. The oxidation of Ag(I) by persulfate generates the Ag(II) intermediate,[13] which undergoes single electron transfer with a carboxylate to produce the carboxyl radical. Fast decarboxylation of the carboxyl radical gives the corresponding alkyl radical. The subsequent attack of the alkyl radical at a sulfonyl azide affords the alkyl azide along with the generation of a sulfonyl radical. Further oxidation of the sulfonyl radical leads to the formation of arenesulfonic acid.

The above results provide a unique and efficient entry to organic azides directly from aliphatic carboxylic acids. To further demonstrate the synthetic utility of this new method, we carried out the asymmetric synthesis of (-)-indolizidine 209D and 167B with azidodecarboxylation as the key step. These two natural molecules are representatives of the rich indolizidine alkaloid family[14] and their syntheses[15] have attracted much interest from the synthetic community, both to prepare them in greater quantities and as a tool to validate new methodologies. Our synthesis started from the simple and commercially available β-keto ester **34** (Scheme 3). The asymmetric alkylation[16] of **34** (via enamine **35**) with hexyl iodide produced product **36a** with 83% ee. The treatment of ketone **36a** with KHMDS/$PhNTf_2$ gave vinyl triflate **37a**, which underwent Pd-catalyzed coupling reaction with an organozinc reagent to provide ester **38a**. The subsequent olefin hydrogenation with simultaneous debenzylation afforded acid **39a** in a stereospecific manner owing to the directing effect of the adjacent carboxyl group. Acid **39a** then underwent $AgNO_3$-catalyzed azidodecarboxylation with 3-$PySO_2N_3$ to generate azide **40a** as a 1:1 mixture of two diastereoisomers. The reduction of **40a** by $LiBH_4$ yielded alcohol **41a**. Finally, the intramolecular Schmidt reaction[17] of azidoalcohol **41a** according to Renaud's procedure[15c] led to the stereoselective synthesis of (-)-indolizidine 209D with 83% ee.[18] In a similar fashion, (-)-indolizidine 167B was also synthesized from **34** in 26% overall yield with 86% ee. Thus, the azidodecarboxylation enables the general and straightforward design towards these indolizidines.

Scheme 3. Total Synthesis of (-)-Indolizidine 209D and 167B



In conclusion, we have successfully developed the first silver-catalyzed decarboxylative azidation of aliphatic carboxylic acids in aqueous solution. This method is easily operational, mild, efficient, and chemoselective. In view of its generality and excellent functional group compatibility, this catalytic transformation should find more applications in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterizations of new compounds, copies of ^1H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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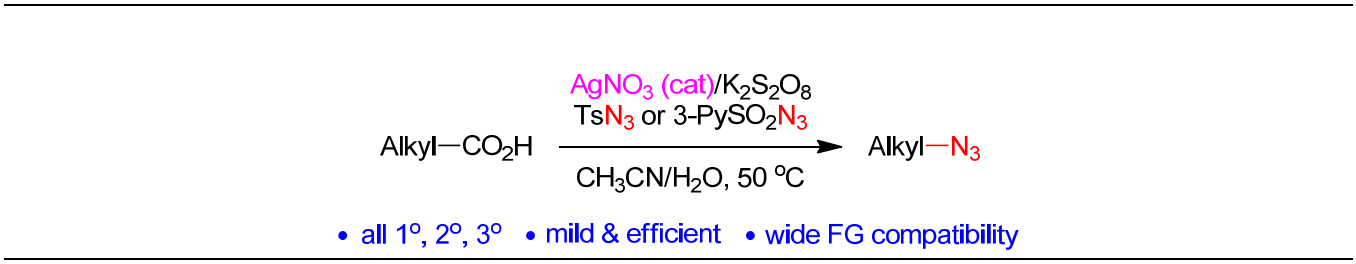
(18) The optically pure acid **39a** could be easily obtained by recrystallization of its salt with (*S*)-2-amino-2-phenylethanol, which should lead to the synthesis of optically pure (-)-indolizidine 209D. See SI for details.


AgNO3 (cat)/K2S2O8
TsN3 or 3-PySO2N3
Alkyl—CO2H
CH3CN/H2O, 50 °C
Alkyl—N3
• all 1°, 2°, 3° • mild & efficient • wide FG compatibility