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Acetic Acid Promoted Direct Iodination of Terminal Alkynes with *N*-Iodosuccinimide: Efficient Preparation of 1-Iodoalkynes

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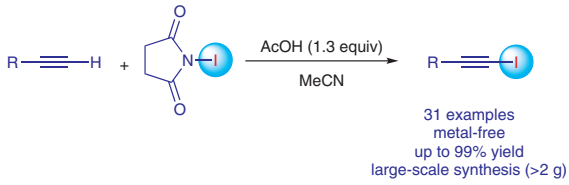

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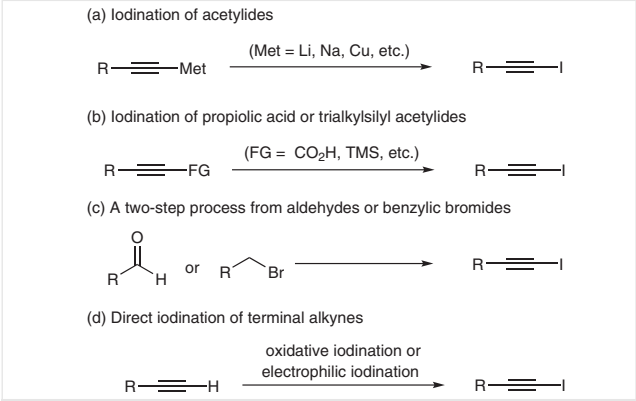
Abstract An efficient and highly chemoselective approach for the direct iodination of terminal alkynes using acetic acid as *N*-iodosuccinimide activated reagent under metal-free conditions has been developed. This facile process tolerates a variety of terminal alkynes and provides the desired products in good to excellent yields (up to 99%).

Key words terminal alkynes, halogenation, 1-iodoalkynes, carboxylic acids, *N*-iodosuccinimide

1-Haloalkynes, in particular 1-iodoalkynes, have attracted increasing attention in organic chemistry. The controllable electrophilic and nucleophilic properties make them as dual functionalized molecules, bringing about numerous applications in chemical transformations.[1,2] Significant progress has been made in the development of synthetic approaches for the construction of 1-iodoalkynes, including iodination of metal acetylides (Scheme 1, path a),[3] iodination of propiolic acid/trialkylsilylacetylides (path b),[4,5] a two-step homologation/iodination or elimination sequence from aldehydes or benzylic bromides (path c)[6,7] and direct iodination of terminal alkynes (path d).[8] Among these methods, the direct iodination of terminal alkynes is the most appealing strategy. For this reason, intensive research has been dedicated to the development of more efficient direct iodination of alkynes.[8] However, some of these protocols developed to date rely on the use of transition metals, hypervalent iodine compounds, or strong oxidizing agents, which may result in low functional-group tolerance and low chemo- or regioselectivity. Therefore, the development of mild and selective iodination methods for the synthesis of 1-iodoalkynes is still highly desirable.

N-Iodosuccinimide (NIS) is a well-known iodinating agent that has found many applications in organic synthesis. Iodination of aromatic compounds with NIS often needs various acidic catalysts.[9] It is conceivable that the acidic conditions improve chemoselectivity, regioselectivity and reaction rate in the iodination of various aromatic compounds.[10] It has been reported that the direct iodination of terminal alkynes with NIS to generate 1-iodoalkynes requires the use of silver salts as catalysts.[8f,p,w] Encouraged by the suggested role of acidic catalysts in the iodination of aromatic compounds and our interest in the halogenation of alkynes,[8a,9,10] we considered the use of NIS as iodinating reagent in combination with acid for the synthesis of 1-iodoalkynes. Herein, we describe an effective protocol for the formation of 1-iodoalkynes by direct iodination of terminal alkynes using NIS and acetic acid.



Scheme 1 Previous approaches to the synthesis of 1-iodoalkynes

Our initial attempt to generate 1-(iodoethynyl)benzene (**2aa**) involved using phenyl acetylene (**1aa**; 2.0 mmol), NIS (2.6 mmol) and 4 Å MS in the presence of AcOH (0.2 mmol) in MeCN at 70 °C (see Table S1 in the Supporting Information). To our delight, the desired product **2aa** was obtained in 83% yield (Table 1, entry 1). Subsequently, we examined

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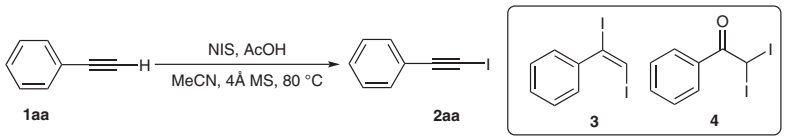
different solvents including toluene, 1,4-dioxane, ethyl acetate, 1,2-dichloroethane, DMSO and DMF, but these solvents resulted in poor yields of the desired product **2aa** (entries 5–8) or mixtures of 1-iodoalkynes **2aa**, 1,2-diiodovinylbenzene (**3**), or 2,2-diiodo-1-phenylethanone (**4**) (entries 2–4). Notably, THF could also facilitate this reaction, affording the product **2aa** in 84% yield; however, the reaction required 5 h for the raw material to be fully converted (entry 9). Efforts to decrease the reaction temperature to 25 °C or 45 °C only led to low yields and required longer reaction time (entries 10 and 11). Fortunately, the yield of the target product **2aa** increased to 88% when the reaction was conducted at 80 °C (entry 12). In addition, the investigation on the optimal amount of NIS indicated that 1.1 equivalents NIS was an appropriate amount (entries 13 and 14). Finally, the impact of AcOH loading on the reaction was also surveyed, and 1.3 equivalents of AcOH were identified as the optimal loading, which furnished **2aa** in the highest yield (entry 17). We could only obtain 8% yield of the desired product without the activation of AcOH (entry 15) and a mixture of **2aa**, 1,2-diiodovinylbenzene **3** and 2,2-diiodo-1-phenylethanone **4** in the absence of AcOH and 4 Å MS.[8a] A mixture of 1-iodoalkyne (**2aa**) and 2,2-diiodo-1-phenylethanone (**4**) could be observed by using the AcOH as solvent (entry 19). These results indicated that there was a significant improvement in the yield and the rate of the iodination reaction when the reaction was performed in the presence of acetic acid as the NIS-activated reagent (entry 15–19). Therefore, the optimized conditions to obtain **2aa** were treatment of **1aa** with NIS (1.1 equiv), AcOH (1.3 equiv) and 4 Å MS in MeCN at 80 °C for 1.5 h.

Table 1 Optimization of the Reaction Conditions[a]



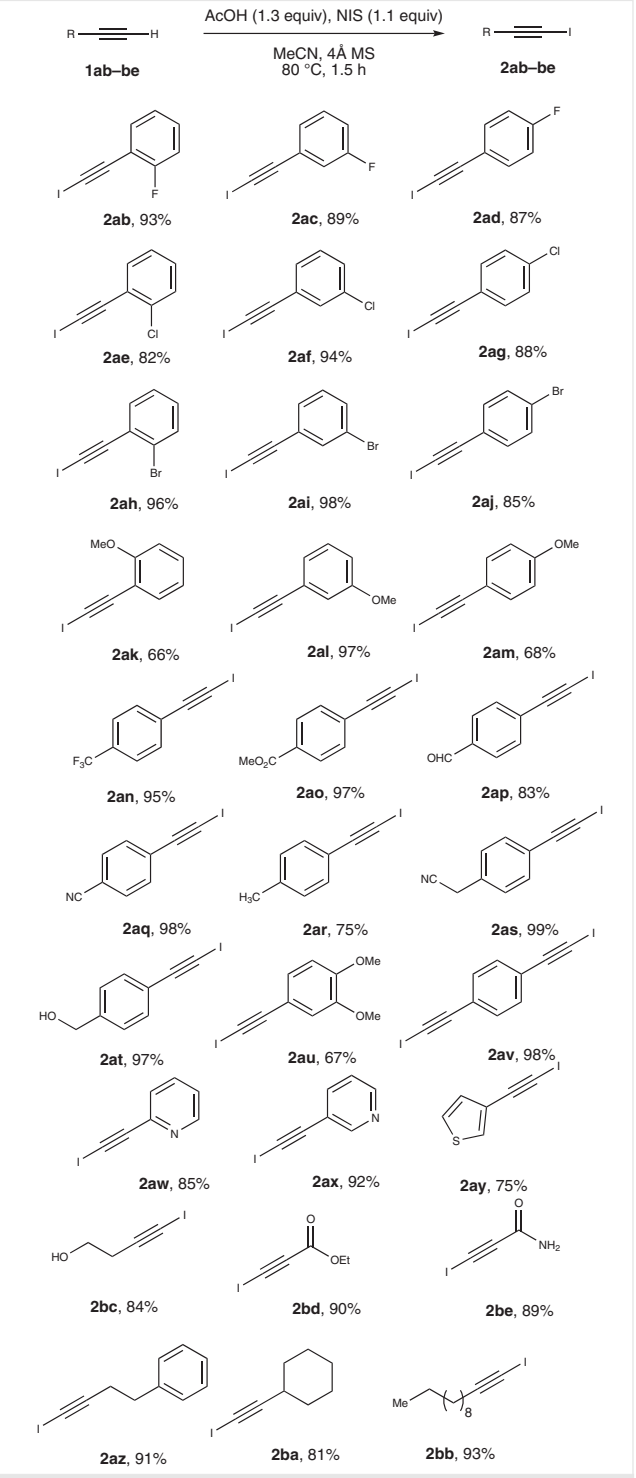
Entry	NIS (equiv)	AcOH (equiv)	Solvent	*T* (°C)	Yield (%)[b]
1	1.3	0.1	MeCN	70	83
2	1.3	0.1	toluene	70	–[c]
3	1.3	0.1	MeOH	70	–[d]
4	1.3	0.1	1,4-dioxane	70	–[d]
5	1.3	0.1	DMSO	70	55
6	1.3	0.1	DCE	70	55
7	1.3	0.1	EtOAc	70	63
8	1.3	0.1	DMF	70	82
9	1.3	0.1	THF	70	84[e]
10	1.3	0.1	MeCN	25	56[f]
11	1.3	0.1	MeCN	45	59[g]
12	1.3	0.1	MeCN	80	88
13	1.1	0.1	MeCN	80	87
14	1.0	0.1	MeCN	80	78
15	1.1	0	MeCN	80	8[h]
16	1.1	0.5	MeCN	80	86
17	1.1	1.3	MeCN	80	91
18	1.1	2.0	MeCN	80	91
19	1.1	–	AcOH	80	–[c]

[a] Reaction conditions: phenylacetylene **1aa** (2 mmol), NIS, AcOH, 200 mg 4 Å MS in solvent (10 mL) at the corresponding temperature for 1.5 h.
[b] Isolated yield.
[c] Mixture of 1-iodoalkyne **2aa** and 2,2-diiodo-1-phenylethanone (**4**).
[d] Mixture of 1-iodoalkyne **2aa** and (1,2-diiodovinyl)benzene (**3**).
[e] The reaction was stirred at 70 °C for 5 h.
[f] The reaction was stirred at 70 °C for 12 h.
[g] The reaction was stirred at 70 °C for 4 h.
[h] Mixture of **1aa**, **2aa**, **3** and **4** in the absence of 4 Å MS and AcOH.

Having identified the optimized reaction conditions, we turned our attention to the scope and limitations of this transformation, as shown in Scheme 2. A wide array of terminal aromatic alkynes bearing either electron-donating groups (e.g. methoxy, methyl, hydroxymethyl and cyanomethyl substituents) or electron-withdrawing groups (e.g. halogen, trifluoromethyl, cyano, ester and formyl moieties) on the phenyl rings reacted smoothly to afford the corresponding products **2ab–au** in good to excellent yields. The electronic nature and position of a substituent on the benzene ring had considerable impact on the efficiency of this reaction. Under the standard conditions, the stronger the electric enrichment of substituents on aromatic rings, the lower the yield of the reaction (**1am** vs. **1aq** vs. **1as**). The aryl alkynes bearing moderate electron-withdrawing or -donating groups gave better yields. For example, unidentified complex products were observed by using 1-ethynyl-4-nitrobenzene as the starting material and the iodination of **1au** only resulted in 67% yield. Moreover, the high yields observed with *meta*-substituted substrate as compared to *ortho* and *para*, such as **1al**, maybe due to the reduced influence of *meta*-substituents. In addition, the 1,4-diethynylbenzene (**1av**) was applied to this reaction and the anticipated product **2av** was formed in 98% yield. Subsequently, the selective iodination of terminal alkynes containing a heteroaromatic ring such as **1aw** and **1ay** proceeded smoothly to provide **2aw** and **2ay** in 85% and 75% yield, respectively. Notably, 3-ethynylpyridine (**1ax**) worked well under the direct electrophilic iodination to generate the useful synthon (**2ax**) in 92% yield. Encouraged by these satisfactory results, we further probed the unactivated acetylenes such as aliphatic and alicyclic alkynes. The twelve-carbon-chain containing alkyne **1bb** could be converted into the desired iodinated product **2bb** in 93% yield. Afterward, acetylenes comprising other aliphatic and alicyclic moieties such as **1az**, **1ba**, and **1bc** were iodinated successfully by using the AcOH as the activated reagent to afford the corresponding products in good yields (81–91%). Moreover, the iodination of more reactive alkynes such as propiolamide **1bd** and ethyl propionate **1be** were then evaluated and they performed well under present conditions to furnish the synthetically useful **2bd** and **2be** in 90% and 89% yield, respectively.

To further evaluate the scalability of this protocol, gram-scale reactions were conducted (Figure 1). Under standard conditions, the iodination of **1aa** (10 mmol) and **1ba** (10 mmol) afforded the product **2aa** (2.1663 g) in 95% yield and **2ba** (2.0131 g) in 86% yield, which were slightly higher than the yields obtained on the 2.0 mmol scale reaction. In addition, the large-scale reaction of **1an**, **1az** and **1bd** could also separately provide the corresponding products with good yields.

Based on the previous reports,[8e,9,11] a plausible pathway for this acetic acid mediated iodination was proposed. As shown in Scheme 3, it is assumed that the active intermediate **A** (acetyl hypoiodite, [AcO^-I^+]) for iodination generated from the protonation of NIS in the presence of acetic acid would trap alkynes to form π-coordinated species **B**. This



Scheme 2 Iodination of alkynes **1ab–be** to give 1-iodoalkynes **2ab–be**

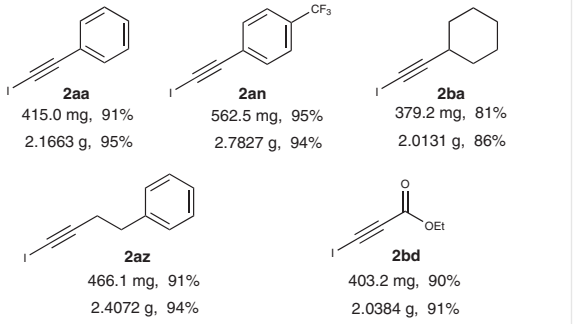
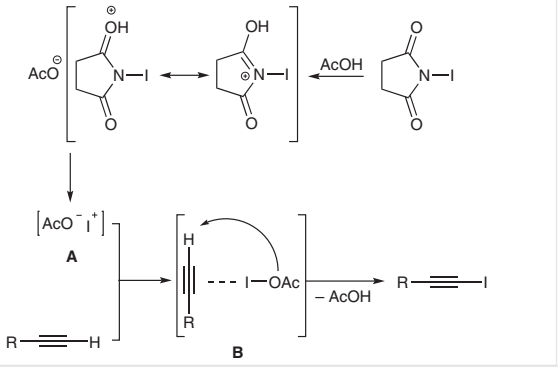


Figure 1 A scale-up synthesis of 1-iodoalkynes

species could be easily converted into 1-iodoalkynes via the deprotonation of alkynes facilitated by AcO^- along with the release of acetic acid.



Scheme 3 A plausible mechanism for AcOH-mediated iodination of alkynes

In summary, an acetic acid promoted, efficient, and chemoselective iodination protocol for the synthesis of 1-iodoalkynes with readily available NIS was developed.[12] In this method, the acetic acid plays a pivotal role in activating NIS and increasing reaction rate and the yield of the desired product. A variety of terminal alkynes could be converted into 1-iodoalkynes in good to excellent yields. This is a productive and straightforward synthetic process for the iodination of terminal alkynes.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1708002.

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(12) **Iodination of Terminal Alkynes; General Procedure:** To a mixture of terminal alkynes (2.0 mmol), acetic acid (2.6 mmol) and 4 Å MS (200 mg) in MeCN (10 mL) was added *N*-iodosuccinimide (2.2 mmol) and the resulting mixture was heated at 80 °C for 1.5 h. After completion of the reaction, the reaction was quenched with saturated aqueous sodium thiosulfate and the mixture was extracted with ethyl acetate (10 × 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel.
(Iodoethynyl)benzene (2aa): Prepared according to the general procedure. Purification by column chromatography (petroleum ether) gave **2aa** in 91% yield as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47–7.44 (m, 2 H), 7.34–7.32 (m, 3 H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 132.38, 128.88, 128.32, 123.38, 94.23, 6.74. The overall spectroscopic data are in agreement with assigned structures and consistent with reported data.[8c]