Synlett Y. Fan et al. Letter

A Facile Synthesis of β-Iodonitro Alkenes via Iodonitration of Alkynes with *tert*-Butyl Nitrite and Iodine

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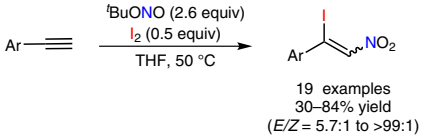


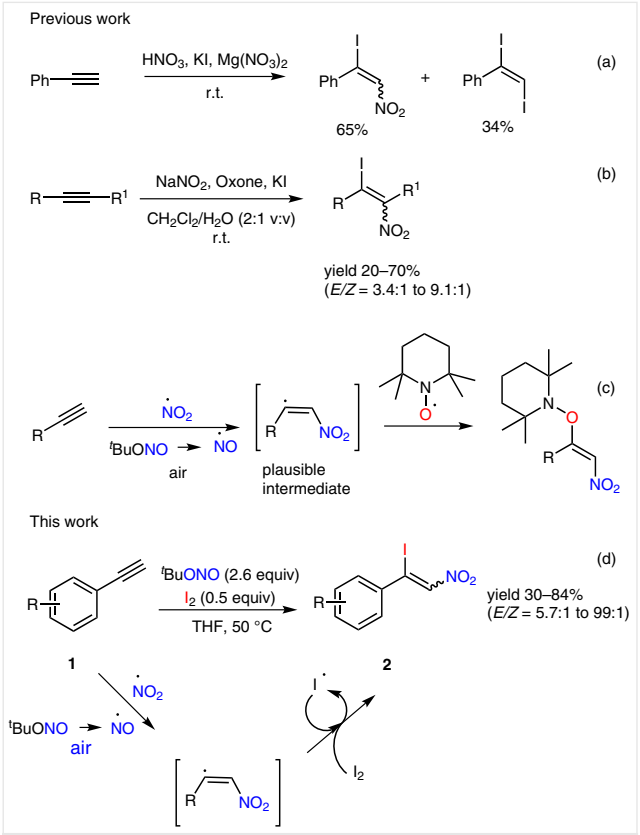
Received: 19.03.2017
Accepted after revision: 26.03.2017
Published online: 27.04.2017
DOI: 10.1055/s-0036-1588794; Art ID: st-2017-w0005-l

Abstract A convenient synthetic approach to β-iodonitro alkenes based on the iodonitration of alkynes with ^{t}BuONO and I_2 is described. No acid or oxidant is required in this reaction.

Key words β-iodonitro alkenes, iodonitration, alkynes, free radical, difunctionalization

The free-radical-mediated difunctionalization of alkynes represents one of the most powerful methodologies for the construction of polysubstituted alkenes,[1] which are widely present in natural products,[2] pharmaceuticals,[3] and functional materials.[4] In this context, the iodonitration of alkynes is a particularly useful reaction, because both the iodo and nitro group in the resulting β-iodonitro alkenes offer rich possibilities for synthetic manipulations. Despite significant advances in the free-radical-mediated difunctionalization of alkynes, convenient and selective methods for the formation of β-iodonitro alkenes via the iodonitration of alkynes have been little explored. Yusubov and co-workers developed a KI–HNO_3–$Mg(NO_3)_2$ system for the iodonitration of phenylacetylene (Scheme 1, a).[5] Kuhakarn and co-workers developed the iodonitration with $NaNO_2$ and KI using Oxone as the oxidant (Scheme 1, b).[6] However, these methods suffered from poor selectivity or the use of an acid, an additive or an oxidant.

Recently, the application of ^{t}BuONO as a green nitro radical precursor for the construction of various nitro compounds has attracted much attention, because only air is needed to initiate the formation of nitro radicals.[7] In 2015, Maiti reported the aerobic oxynitration of alkynes with ^{t}BuONO and TEMPO (Scheme 1, c).[8] In this reaction, a vinyl radical formed by the addition of a nitro radical to the alkyne was thought to be the plausible intermediate, which was trapped by TEMPO to form the nitro product. We hypothesized that the vinyl radical may also be trapped by iodine to allow the iodonitration of alkynes (Scheme 1, d). As part of the continuing efforts in our laboratory toward the

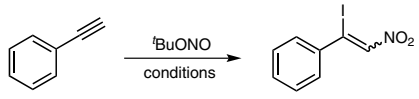


Scheme 1 Difunctionalization of alkynes with a nitro radical

development of a novel free-radical-mediated difunctionalization of alkynes,[9] herein we disclose an efficient and selective method to construct β-iodonitro alkenes by a metal-free iodonitration of alkynes with ^{t}BuONO and I_2.

We commenced our studies by investigating the iodonitration of phenylacetylene (**1a**) with ^{t}BuONO. In an initial attempt, no product **2a** was obtained by using KI or NaI as the iodine source in THF at 60 °C (Table 1, entries 1 and 2). To our delight, replacement of the iodine salts by I_2 gave the desired product **2a** in 78% yield as a mixture of *E* and *Z* isomers in a ratio of 9:1 (Table 1, entry 3). The regiochemistry and stereochemistry was confirmed by comparing the ^{1}H NMR spectrum with the reported data.[6] Inspired by this result, we first tested different solvents. We found that the iodonitration occurs in MeCN, acetone and DCE as well, to give a good yield of product **2a** with the *E*-isomer as the main product (Table 1, entries 4–6), while DMF, DMSO, MeOH and ^{i}PrOH proved to be ineffective (Table 1, entries 7–10). The reaction was also tested at different temperatures (Table 1, entries 11–14), and 50 °C was the best condition giving the product in 81% yield. Interestingly, the stereochemistry of the reaction is temperature-dependent. *Z*-Products turn out to be the main products at higher temperatures. Notably, reducing the iodine to 0.5 equivalent has no effect on the reaction outcome (Table 1, entry 15).

Table 1 Optimization of the Reaction Conditions[a]

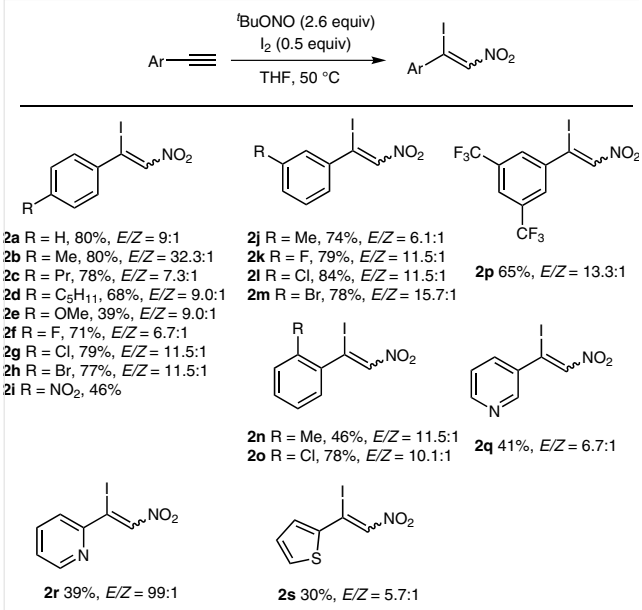


1a **2a**

Entry	Iodine source	Solvent	Temp (°C)	Yield (%)[b]	*E*/*Z* ratio[c]
1	KI (2 equiv)	THF	60	NR	
2	NaI (2 equiv)	THF	60	NR	
3	I_2	THF	60	78	9:1
4	I_2	MeCN	60	77	9:1
5	I_2	acetone	60	65	10:1
6	I_2	DCE	60	73	5:1
7	I_2	DMF	60	trace	
8	I_2	DMSO	60	trace	
9	I_2	MeOH	60	trace	
10	I_2	^{i}PrOH	60	trace	
11	I_2	THF	r.t.	65	7:1
12	I_2	THF	50	81	4:1
13	I_2	THF	70	78	1:4
14	I_2	THF	80	76	1:3
15[d]	I_2	THF	50	80	9:1

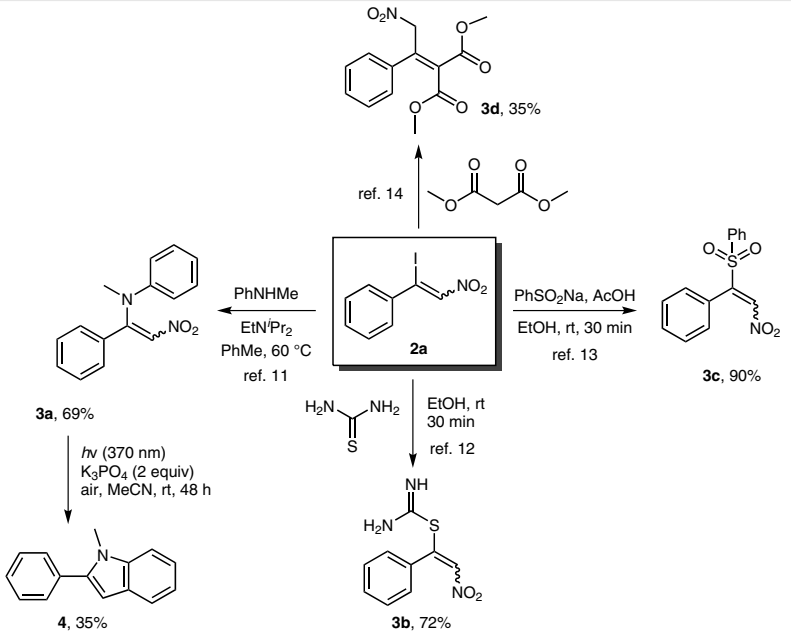
[a] Reaction conditions: **1** (0.5 mmol), I_2 (0.5 mmol), ^{t}BuONO(1.3 mmol) in solvent (2.0 mL) for 4 h.
[b] Isolated yield; NR = no reaction.
[c] The isomeric ratio was determined by ^{1}H NMR.
[d] 0.25 mmol of I_2 was used.

With the optimized reaction conditions in hand, we next investigated the alkyne scope (Scheme 2).[10] In general, the reaction tolerated a wide variety of substrates, including not only aryl acetylenes bearing an electron-donating group (products **2b–e**, **2j** and **2n**), but also one bearing a strong electron-withdrawing NO_2-substituent (product **2i**). It is worth noting that halogen-substituted substrates (F, Cl, Br) were also tolerated in this reaction (products **2c–h**, **2k–m**, **2o**), with these halogen atoms enabling further elaboration of the products into more complex molecules. The application of a polysubstituted aryl acetylene provided the desired product **2p** as well. Moreover, the iodonitration of heterocyclic acetylenes delivered the desired products **2q–s** in moderate yields. Notably, compared with the iodonitration reported by Kuhakarn[6] our method provided both better yields and higher stereoselectivities of the products.



Scheme 2 Substrate scope for the synthesis of β-hydroxy ketones. *Reagents and conditions*: alkyne (0.5 mmol), ^{t}BuONO (1.3 mmol), I_2 (0.25 mmol), THF (2 mL), 50 °C, 4 h. Regioisomeric ratios were determined by ^{1}H NMR.

As mentioned above, β-iodonitro alkenes are versatile intermediates and building blocks in organic synthesis. When **2a** was treated with *N*-methylaniline in the presence of *N*,*N*-diisopropylethylamine, **3a** was produced in 69% yield, which can further undergo a photoinduced cyclization to form 1-methyl-2-phenylindole **4**.[11] Similarly, substitution reactions with other nucleophiles, such as thiourea,[12] sodium benzenesulfinate[13] and dimethyl malonate[14] gave **3b–d**, respectively (Scheme 3).



Scheme 3 Transformations of β-iodonitro alkenes

In summary, we have demonstrated a facile and efficient radical-mediated iodonitration of alkynes using ^{t}BuONO and I_2 as the nitro and iodine sources, respectively. No acid, additive or additional oxidant is needed in this reaction. This methodology provides a simple and selective way to construct synthetically useful β-iodonitro alkenes.

Funding Information

Natural Science Foundation of China (51503181)

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588794.

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(10) **(1-Iodo-2-nitrovinyl)benzene: Typical Procedure**
To a stirred solution of phenylacetylene (0.5 mmol), and I_2 (0.25 mmol) in THF (2 mL) was added ^{t}BuONO (1.3 mmol) at room temperature. The mixture was stirred at 50 °C for 4 h and then cooled to room temperature. The excess solvent was removed under vacuum, and the residue was directly purified by silica gel column chromatography (petroleum/ethyl acetate = 250:1) to afford product **2a** (111.3 mg, 81%, *E*/*Z* = 9:1) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.41–7.35 (m, 3 H), 7.33–7.28 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.93, 138.47, 130.22, 128.55, 127.27, 113.82.

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