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Carbonyl-Directed Addition of *N*-Alkylhydroxylamines to Unactivated Alkynes: Regio- and Stereoselective Synthesis of Ketonitrones

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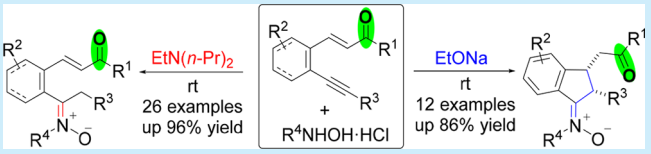
Supporting Information

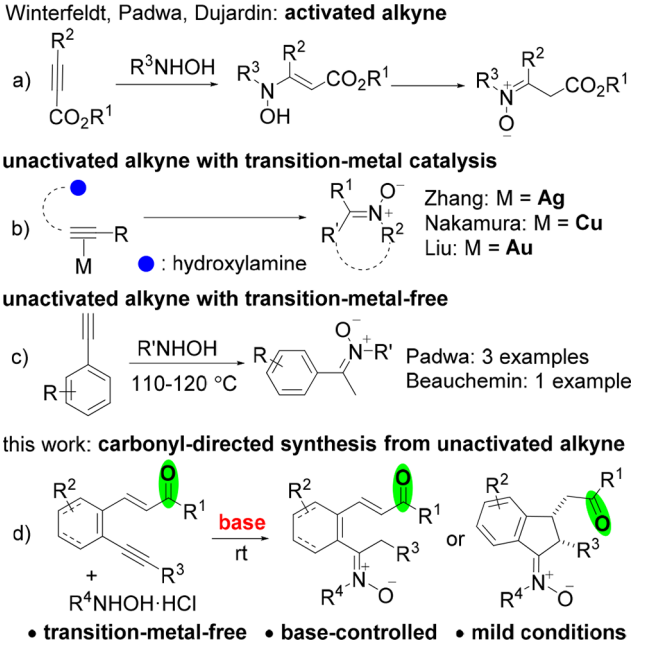
ABSTRACT: A variety of ketonitrones were synthesized in moderate to excellent yields with high chemo-, regio-, and stereoselectivity by using carbonyl-directed addition of *N*-alkylhydroxylamines to unactivated alkynes under mild conditions. The product diversity could be controlled by the use of different bases, and EtN(*n*-Pr)$_2$ could promote the formation of ketonitrones while using EtONa as base led to indanone-derived nitrones. Control experiments indicated that the carbonyl group of the substrate acted as an H-bond acceptor except for an electron-withdrawing group, and conjugated enone skeleton accounted for the high selectivity.



Nitrones, as 1,3-dipolars, have received much attention in synthetic organic chemistry, not only because they are versatile building blocks to access N,O-containing heterocycles and natural products through the stereoselective [3 + 2]-cycloadditions with various dipolarophiles[1] but also because many other novel transformations involving nitrones have been developed in recent years.[2] A large number of protocols have been intensively investigated, such as oxidation of a secondary hydroxylamine[3]/amine,[4] condensation of a carbonyl compound with a hydroxylamine,[5] and *N*-alkylation of an oxime ether[6] or oxime;[7] these are the most common strategies for the synthesis of nitrones. Despite the efficiencies of these methods, most of the methodologies have been limited to aldonitrones, and reports on ketonitrone chemistry remain scarce, owing to general kinetic instability of ketonitrones[5c] unless an electron-withdrawing group is present.[8]

An alternative approach to access ketonitrone is direct nucleophilic addition of hydroxylamine to alkyne.[9] However, this strategy still remains underdeveloped.[8a,b,e] Winterfeldt first described the synthesis of aspartate nitrone through nucleophilic addition of *N*-alkylhydroxylamines to dialkyl acetylenedicarboxylate (Scheme 1a),[8a] and then the extensive studies of their synthesis and cycloaddition with alkenes were reported by Padwa[9f] and Dujardin.[8b,e] With respect to unactivated alkyne, coordination of the triple bond to a metal is a strategy usually used to enhance the electrophilicity of the alkyne. In 2014, both Zhang[10] and Nakamura[11] demonstrated an elegant synthesis of ketonitrones via intramolecular additions of hydroxylamine to alkyne activated by Ag and Cu catalysts, respectively (Scheme 1b). Recently, Liu and co-workers developed a gold-catalyzed *N*-attack of *N*-hydroxyanilines at the alkynes to give unstable ketonitrones that reacted instantaneously with their tethered alkenes,[12a] allenes,[12b] and alkynes[12c] to afford bicyclic compounds,

Scheme 1. Overview of Synthesis of Ketonitrones from Alkyne and Hydroxylamine



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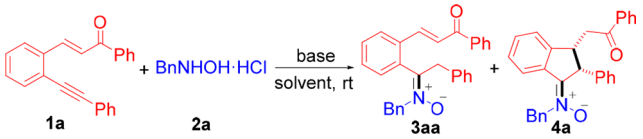
benzoazepin-4-ones, and pyrrole derivatives, respectively (Scheme 1b). Although metal-free synthesis of ketonitrone from simple alkyne and hydroxylamine has been successfully achieved by Padwa[9f] and Beauchemin,[9b] respectively (Scheme 1c), these methods suffered from several drawbacks such as high temperature, moderate yields, and limited substrate scope (only for terminal arylacetylene). Therefore, developing a metal-free, general, and efficient route to access ketonitrones from alkyne and hydroxylamine remains challenging and desirable. Herein, we report the first carbonyl-controlled addition of *N*-alkylhydroxylamines to unactivated alkynes to give ketonitrones and indanone-derived nitrones, respectively (Scheme 1d).

As shown in Table 1, the reaction between α,β-unsaturated ketone **1a** and *N*-benzylhydroxylamine hydrochloride **2a** was

Table 1. Optimization of the Reaction Conditions[a]

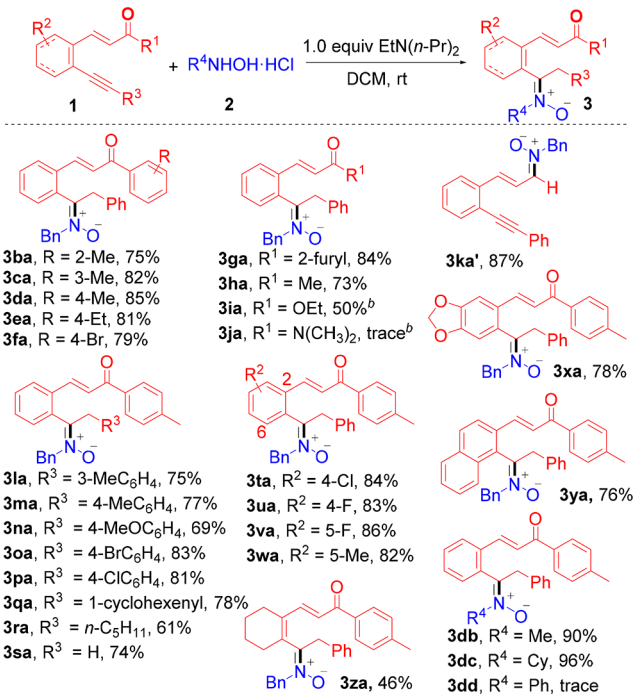


entry	base (equiv)	solvent	time (h)	yield (**3aa**/**4a**)[b] (%)
1	Et_3N (1.5)	THF	12	24/0
2	Et_3N (1.5)	dioxane	23	31/0
3	Et_3N (1.5)	MeCN	12	40/0
4	Et_3N (1.5)	toluene	12	34/0
5	Et_3N (1.5)	DCM	17	49/0
6	KOAc (1.5)	DCM	13	51/0
7	DABCO (1.5)	DCM	13	56/0
8	$EtN(CH_3)_2$ (1.5)	DCM	13	60/0
9	$EtN(n\text{-}Pr)_2$ (1.5)	DCM	12	83/0
10	$EtN(n\text{-}Pr)_2$ (1.0)	DCM	12	84/0
11[c]		DCM	12	73/0
12	DBU (1.5)	DCM	12	8/66
13	EtOK (1.5)	DCM	12	4/77
14	EtONa (1.5)	DCM	12	4/81
15	*t*-BuONa (1.5)	DCM	13	trace/24
16	MeONa (1.5)	DCM	12	5/67
17	EtONa (1.3)	DCM	12	3/83

[a]All reactions were carried out with **1a** (0.30 mmol), **2a** (0.30 mmol), base, and solvent (3.0 mL) unless otherwise stated. [b]Isolated yield based on **1a**. [c]BnNHOH instead of **2a** was used.

investigated to optimize the reaction conditions. When a mixture of **1a** and **2a** in THF was treated with 1.5 equiv of Et_3N at room temperature, a ketonitrone **3aa** was obtained in 24% yield (Table 1, entry 1). The structure of **3aa** was determined by NMR spectroscopy and further confirmed by the X-ray diffraction analysis of analogue **3ya** in Scheme 2,which indicates the C=N bond of ketonitrone **3** is an *E*-configuration and the C−N double bond is perpendicular to the benzene ring attached to nitrone. A screen of various solvents revealed that DCM was the best choice for this transformation (Table 1, entries 1−5). The base had a large effect on the yield and chemoselectivity of the reaction. When inorganic base KOAc was used, the reaction went smoothly to give the desired product **3aa** in 51% yield; a slightly higher yield was observed when Et_3N was replaced by other organic bases DABCO and $EtN(CH_3)_2$ (Table 1, entries 7 and 8), and $EtN(n\text{-}Pr)_2$ furnished the ketonitrone **3aa** in the highest yield of 83%. The reaction of **1a** and *N*-benzylhydroxylamine with

Scheme 2. Scope of Preparing Ketonitrone 3[a]



[a]All reactions were carried out with **1** (0.30 mmol), **2** (0.30 mmol), $EtN(n\text{-}Pr)_2$ (1.0 equiv), and DCM (3.0 mL), 12−24 h unless otherwise stated; isolated yield based on **1**. [b]Reaction time was 39 h.

no base also proceeded smoothly to give the **3aa** in 73% yield (Table 1, entry 11). With 1.0 equiv of $EtN(n\text{-}Pr)_2$, the reaction yield was still very good (Table 1, entry 10); however, an increase in the amount of **2a** and $EtN(n\text{-}Pr)_2$ or increasing the reaction temperature to 50 °C all led to a decrease in yield. To our surprise, a novel indanone-derived nitrone **4a** was isolated in modest yield as a major product accompanied by a lower amount of nitrone **3aa** when DBU was used (Table 1, entry 12). Compounds **3aa** and **4a** were easily separated by flash chromatography. The structure was again determined by its analogue **4k** X-ray diffraction analysis, which reveals the *cis* relationship between the 2-oxo-2-phenylethyl and phenyl groups on the five-membered ring. Encouraged by the observed switch in selectivity from ketonitrone **3aa** to **4a**, we decided to further examine other stronger bases to promote this transformation. As shown in Table 1, EtOK increased the yield of ketonitrone **4a** to 77%, while the yield was only delivered in 24% with *t*-BuONa as base (Table 1, entries 13 and 15). MeONa gave the same yield as that of DBU (Table 1, entry 16). EtONa was the choice of base for the reaction, affording ketonitrone **4a** in yield of 81% (Table 1, entry 14). The amount of EtONa could be decreased to 1.3 equiv, and the same yield was obtained (Table 1, entry 17). Of note is that no indanone-derived nitrone **4a** was observed when weaker bases were used (Table 1, entries 1−10), and all of the reactions gave single *E*-isomers of nitrone exclusively and that only *cis* isomer of **4a** was observed.

With the optimal reaction conditions in hand (Table 1, entry 10), the scope of this reaction was examined (Scheme 2). The substituents on the aryl ring of ketones had little influence on the reaction outcome (**3ba**−**fa**). Ketone **1g** containing a 2-furyl group was well tolerated for this transformation to afford the corresponding product in 84% yield (**3ga**), and the reaction of

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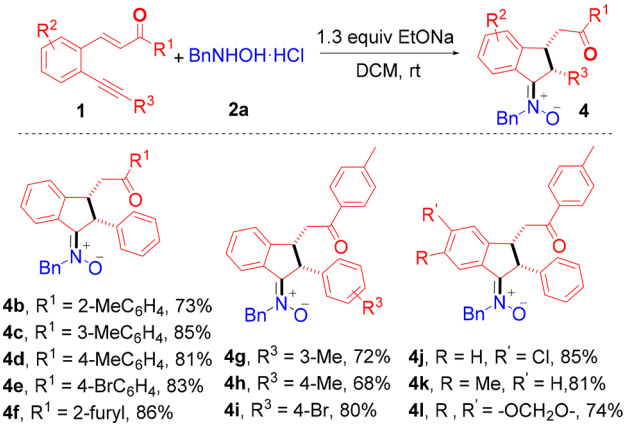
methyl ketone **1h** led to the ketonitrone in satisfactory yield (**3ha**). Modest yield was obtained using unsaturated ester **1i** as substrate; in contrast, a trace amount of ketonitrone **3ja** was observed when acrylamide **1j** was subjected to the optimal conditions. Cinnamaldehyde **1k** failed to yield the desired ketonitrone but gave the aldonitrone **3ka′** in a yield of 87%,[13] perhaps due to the higher electrophilicity of aldehyde compared to the C−C triple bond in the structure of **1k**. An array of substituents (R^3) were also examined, and all of the reactions proceeded smoothly to furnish the corresponding ketonitrones in 61−83% yields (**3la**−**sa**); it is noteworthy that ketones bearing electron-withdrawing substituents gave slightly higher yields than ketones with electron-donating substituents (**3la**−**na** vs **3oa** and **3pa**). To our pleasure, cyclohexenyl-substituted ketone **1q**, alkyl-substituted **1r**, and simple terminal alkyne **1s** were also effective substrates for this reaction to furnish the desired products **3qa**−**sa** in synthetically useful yields. For ketones having various substituents R^2, their reactions successfully furnished desired products in good yields (**3ta**−**ya**); for example, naphthalenyl nitrone **3ya** was afforded in 76% yield under optimal reaction conditions. When nonaromatic enynone **1z** was used, the reaction also went smoothly to give the desired product **3za** in moderate yield. We also examined the reactions of ketone **1d** with other hydroxylamines, *N*-hydroxyaniline **2d** failed to give the corresponding product **3dd**, while *N*-alkylhydroxylamine **2b** and **2c** afforded compounds **3db** and **3dc** in 90% and 96% yields under the standard conditions, respectively. Therefore, product yields in Scheme 2 can be significantly improved if a more basic hydroxylamine like **2b** or **2c** is used. Generally, most of the ketonitrones could be purified through flash chromatography, with some nitrones being a little labile.

Indanone-derived nitrones are valuable intermediates for constructing spiro compounds by cycloaddition reactions with a variety of dipolarophiles. However, the method for their synthesis has been rarely exploited. There is one example reported by Beauchemin that uses condensation of indanone and *N*-cyclohexylhydroxylamine simply upon heating in *t*-BuOH at 110 °C to afford indanone-derived nitrone in 47% yield.[5c] Thus, the development of new straightforward access to these nitrone is highly desirable. We decided to expand the scope of the reactions with **2a** under the optimal conditions identified in Table 1, entry 17. The results are summarized in Scheme 3, and all of the reactions proceeded efficiently to give the desired products **4b**−**l** in 68−86% yields. In all cases, the ketonitrone **3** was obtained with less than 5% yield, and only the *cis* isomer of **4** was observed.

With the two novel types of ketonitrones **3** and **4** in hand, subsequently, transformations of nitrone were investigated, and ketonitrones **3ua** and **4k** were subjected to [3 + 2] cycloaddition reactions with diethyl acetylenedicarboxylate (DEAD), giving highly functionalized 2-isoxazoline **5** and spiro-isoxazoline **6** in 85% and 90% yields, respectively (Scheme 4). The molecular structures of compounds **5** and **6** were confirmed by X-ray diffraction.

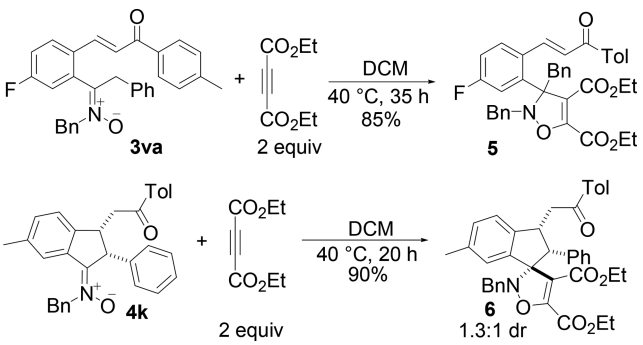
To gain insight into the effect of the ketone structure on nitrone formation, we performed the control experiments. When enyne **7** reacted with **2a**, no desired product **8** was observed (Scheme 5 (1)). Furthermore, no reaction occurred when allyl alcohol **9a**, ether **9b**, or allyl alcohol acetate **9c** was utilized under the standard conditions (Scheme 5 (2)), suggesting that the carbonyl of ketone **1** is essential for the reaction, and a possible hydrogen-bonding between carbonyl

Scheme 3. Scope of Preparing Indanone-Derived Nitrones 4[a]

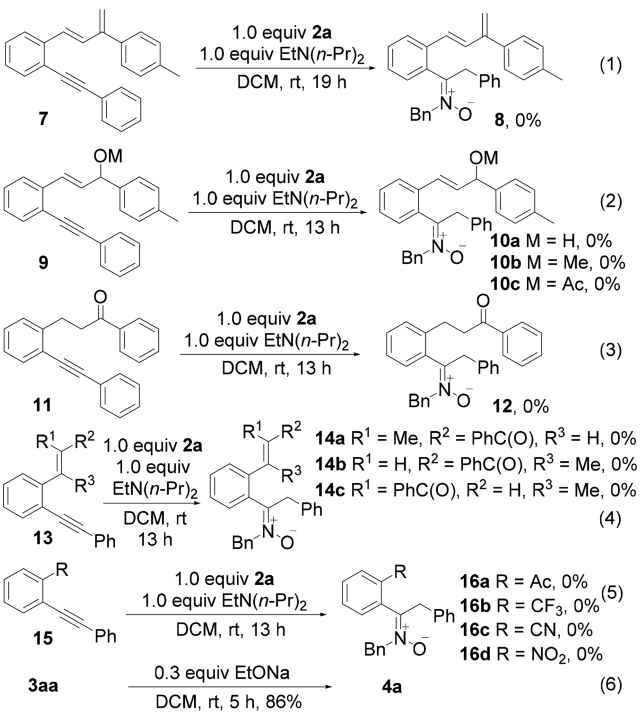


[a]All reactions were carried out with **1** (0.30 mmol), **2a** (0.30 mmol), EtONa (1.3 equiv), and DCM (3.0 mL), 12−22 h unless otherwise stated; isolated yield based on **1**.

Scheme 4. Transformations of Ketonitrones with DEAD



Scheme 5. Control Experiments



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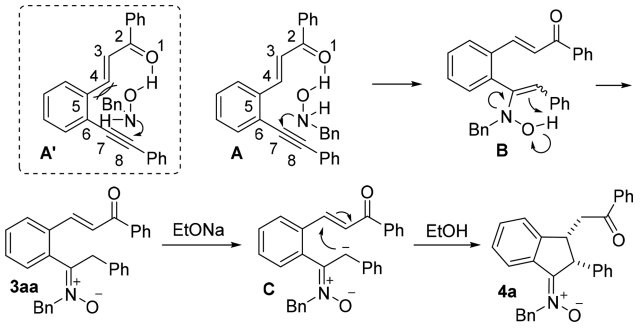
and hydroxylamine promoted the reaction.[14] The presence and configuration of C−C double bond in substrate were also important for the reaction, as no reaction occurred when **11** or **13** was used (Scheme 5 (3), (4)), which may be attributed to the fact that these compounds cannot meet the requirement of the rigid spatial relationship necessary for the reaction with *N*-alkylhydroxylamine to proceed. We found that alkynes **15** bearing an *ortho* electron-withdrawing group did not yield any product, ruling out that the carbonyl of substrate **1** only acted as an electron-withdrawing group to promote nitrone formation (Scheme 5 (5)). Compound **3aa** could be converted to **4a** in a yield of 86% under conditions similar to those in Scheme 3 (Scheme 5 (6)).

On the basis of the experimental results and existing literature,[8a,b,e,f,15] a proposed mechanism for the reaction is illustrated in Scheme 6. Initially, the intermediate *N*-

Scheme 6. Proposed Reaction Mechanism



hydroxylenamine **B** is furnished by regioselective attack of BnNHOH on the 7-position of the ketone promoted by hydrogen-bonding between carbonyl and hydroxylamine, and then **B** undergoes a rapid tautomerization in a concerted manner to afford ketonitrone **3aa**. When EtONa is used as base, deprotonation of nitrone **3aa** followed by intramolecular Michael addition produces the indanone-derived nitrone **4a**.[16] Although the 8-position is more positive than the 7-position, no corresponding nitrone through attack of BnNHOH on 8-position of the ketone was observed; perhaps **A′** was not formed due to unfavorable steric interaction between *N*-benzyl and ketone.

In summary, we have developed metal-free carbonyl-controlled synthesis of ketonitrone from *N*-alkylhydroxylamines and unactivated alkynes, and the reaction proceeds through addition of hydroxylamine to alkyne promoted by hydrogen bonding under mild conditions. The reaction provides a novel protocol for the synthesis of synthetically challenging ketonitrones in good yields with high regio- and stereoselectivity. Moreover, the highly functionalized 2-isoxazoline and spiro-isoxazoline could be afforded through cycloaddition in high yields. Further scope and application of these promising ketonitrones are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03522.

Descriptions of experimental procedures for compounds and analytical characterization (PDF)

Accession Codes

CCDC 1859249−1859250 and 1859389−1859390 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(16) See the Supporting Information for rationalization for the stereoselective formations of ketonitrones **3** and **4**.

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