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Aryl Nitriles from Alkynes Using *tert*-Butyl Nitrite: Metal-Free Approach to C≡C Bond Cleavage

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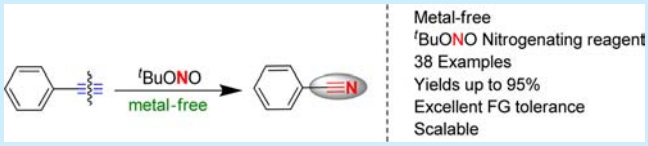
Supporting Information

ABSTRACT: Alkyne C≡C bond breaking, outside of alkyne metathesis, remains an underdeveloped area in reaction discovery. Recently, nitrogenation has been reported to allow nitrile formation from alkynes. A new protocol for the metal-free C≡C bond cleavage of terminal alkynes to produce nitriles is reported. This method provides an opportunity to synthesize a vast range of nitriles containing aryl, heteroaryl, and natural product derivatives (38 examples). In addition, the potential of ^{t}BuONO to act as a powerful nitrogenating agent for terminal aryl alkynes is demonstrated.

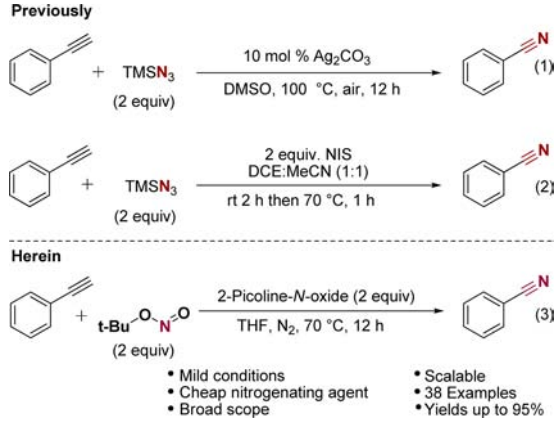


Alkyne derivatizations are widely used in organic synthesis. Some important transformations of alkynes include addition[1] and hydration reactions,[2] while alkynes have been employed in industrially useful processes such as the Pd-catalyzed Wacker oxidation to produce 1,2-diketones,[3] and the Sonogashira coupling to achieve C(sp)−C(sp^2) bond formation.[4] Academically and industrially, perhaps the most widely used reaction is the (3 + 2) cycloaddition (click chemistry).[5] In the modern era, fragmentation of alkynes has received increasing attention. For example carboxylic acids have been prepared by the cleavage of a carbon−carbon triple bond,[6] while alkyne metathesis is the most important reaction within this class.[7]

Although reactions involving C≡C bond cleavage are difficult owing to high bond energy, reaction design using this event is possible. Recently, Jiao and co-workers reported an unprecedented silver catalyzed synthesis of nitriles from alkynes using TMS-N_3 as the nitrogenating reagent (Scheme 1, eq 1).[8] The potential utility of this new entry to nitrile[9] is significant with the nitrile group prevalent in natural products,[10] drug molecules,[11] dyes,[12] and in the polymer industry.[13] Specifically, more than 30 nitrile-containing drugs have been approved for the treatment of depression, breast cancer, and Parkinson's disease, while 20 more are in clinical trials.[14] In addition nitrile groups can be used as a synthetic precursor to install acids, amides, ketones, etc. or as directing groups for remote C−H activation through weak coordination.[15] Yanada reported a related C≡C cleavage by exploiting TMS-N_3 as the nitrogenating agent; however, this reaction is designed to cleave both internal and terminal alkynes (eq 2).[16]

Following our recent success with α-trifluoromethylation[17] and oxynitration[18] of alkynes, we planned to achieve a related terminal alkyne nitrogenation using *tert*-butyl nitrite (eq 3).[19] Such a strategy would address safety and cost concerns that can plague reactions with azides, defining the first metal-free approach to aryl nitriles from terminal alkynes.

Scheme 1. Transformation of Alkynes



Initial investigations were carried out with phenyl acetylene to identify optimal conditions. Under aerobic conditions exploiting quinoline-*N*-oxide as oxidant, and at temperatures suited to the homolysis of *tert*-butyl nitrite, we were pleased to form benzonitrile in 30% yield (Table 1, entry 1). Subsequently, variation of oxidant showed that 2-picoline-*N*-oxide can produce the desired cyanobenzene in improved yield (Table 1, entry 2). Though the reaction is compatible with nonpolar aprotic solvent (Table 1, entries 1−4), THF was found to be the best. While yield has decreased under an oxygen atmosphere, it was drastically improved when the reaction was carried out under inert atmosphere (Table 1, entry

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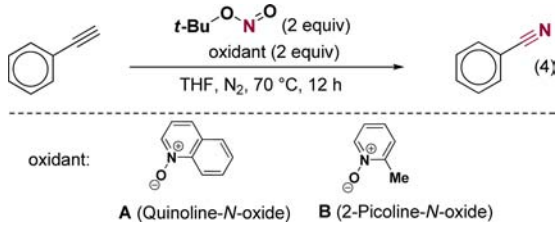
Table 1. Optimization of Reaction Conditions



entry	solvent	oxidant (equiv)	condition	yield (%)[a]
1	DCE	**A** (2)	air	30
2	DCM	**B** (2)	air	35
3	DCE	**B** (2)	air	39
4	THF	**B** (2)	air	45
5	MeOH	**B** (2)	air	<1
6	DMSO	**B** (2)	air	<1
7	THF	**B** (2)	air	25
8	THF	**B** (2)	air	32
9	THF	**B** (2)	air	45
10	THF	**B** (2)	O_2	10
11	**THF**	**B** (2)	N_2	**76 (70)**[b]

[a]Yield calculated by GC except as noted. [b]Isolated yield.

11). This may well be due to inhibition of alkyne oxidation under an inert atmosphere.

After obtaining the optimized conditions, we examined the substrate scope with differentially substituted phenylacetylenes (Scheme 2). Electron-rich 3-methyl, 4-methyl-, and 4-*tert*-butyl phenylacetylenes gave the desired product in 65%, 68%, and 71% yields, respectively (**2b**, **2c**, and **2d**). The expected nitriles were obtained from phenanthrene (**2e** and **2f**, 88% and 70%) and pyrene (**2g**, 95%) acetylenes. Various functional moieties were tolerated under the standard reaction conditions and resulted in formation of nitriles (e.g., 4-OMe, **2h**, 75%; 2-Me-4-OMe, **2i**, 77%; 4-pentoxy, **2k**, 78%; 4-Br, **2l**, 82%). Strongly electron-withdrawing cyano phenylacetylenes produced dinitriles in preparatively useful yields (**2m** and **2n**). Notably, esters (**2p**, 70%; **2q**, 62%; **2r**, 82% and **2s**, 66%), amides (**2t**, 69% and **2u**, 78%), and ketones (**2v**, 78% and **2w**, 81%) remained unaffected.

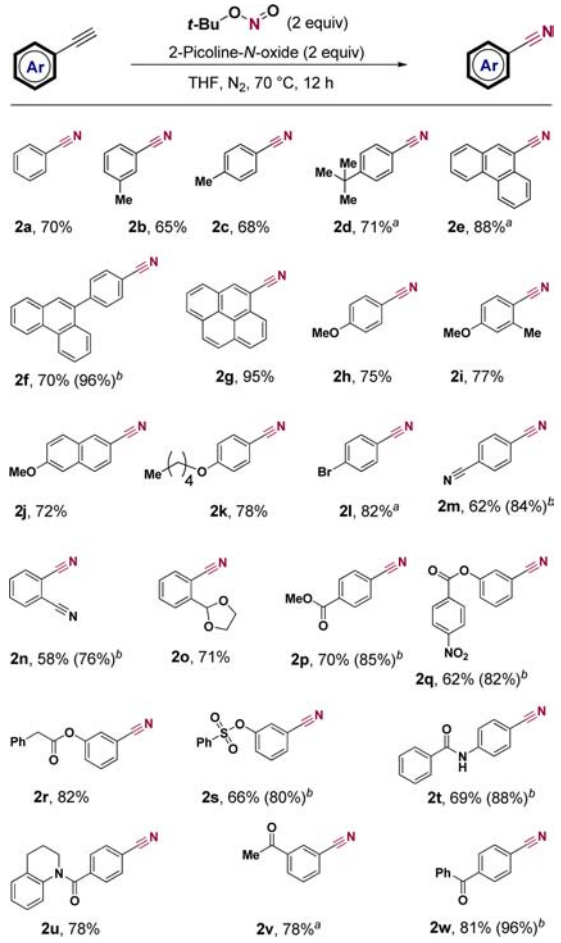
We have also tested the present reaction conditions with various heterocyclic alkynes (Scheme 3). Heterocyclic nitriles derived from quinoline and isoquinoline were formed in 67−86% yields (**3a**−**3d**). Similarly sulfur-containing benzothiophene (**3e** and **3f**) and benzofuran (**3g** and **3h**) nitriles were prepared in 63−81% isolated yields. Finally pyrazole-containing alkynes were converted to the nitriles (**3i** and **3j**).

Next, the nitrogenation of alkynes was examined in the context of natural product derivatives. Specifically we focused our attention on application to various natural product derived esters. Thus, the alkynyl ester of *vitamin*-E was converted to nitrile **4a** in 45% yield, while the estrone derivative **4b** was prepared in 39% isolated yield (Scheme 4). Finally oleic acid derivative **4c** was prepared in 68% isolated yield.

Despite our best efforts, different internal alkynes including prop-1-ynylbenzene, 1,2-diphenylethyne, ethyl-3-phenylpropiolate, trimethyl(phenylethynyl)silane and terminal alkyl alkynes such as oct-1-yne, ethynylcyclopentane, prop-2-ynylbenzene failed to deliver nitriles under standard reaction conditions.

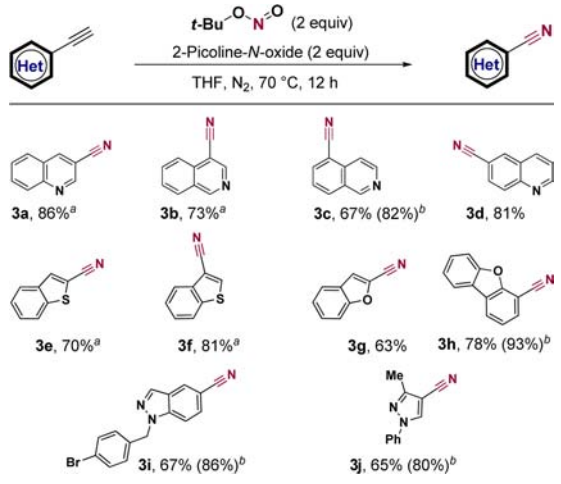
To further expand the scope of this reaction and gain mechanistic insight, the nitrogenation of 1,3-dialkynyl benzene

Scheme 2. Synthesis of Nitriles from Arylacetylenes



[a]6 h. [b]Yield based on recovered starting material.

Scheme 3. Synthesis of Heterocyclic Nitriles



[a]6 h. [b]Yield based on recovered starting material.

5 was examined. We expected that a mixture of product formation is likely due to the presence of multiple alkynes, and the ratio will potentially clarify the roles of the electronic substituent on the reaction. With 1,3-diethynylbenzene (**5**) under standard reaction conditions, the monocyanoarene **5a** was the major product (58%) suggesting that the second

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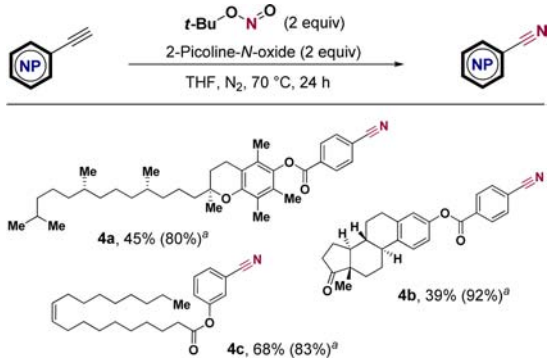
Scheme 4. Nitriles Based on Natural Products



[a]Yield based on recovered starting material.

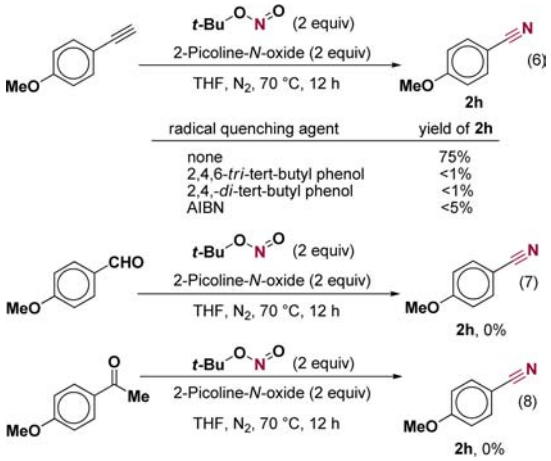
nitrogenation is impeeded by the first (Scheme 5). Addition of twice the stoichiometry of nitrogenating reagent allowed dicyanoarene **5b** to form as the major product (70%) from 1,3-diethynylbenzene **5**.

Scheme 5. Nitrile from 1,3-Diethynylbenzene, 5

conditions	5a	5b
"2 equiv" (as above)	58%	15%
"4 equiv"	7%	70%

In order to understand the mechanism of the nitrile formation, a number of control experiments were performed (Scheme 6). First to probe the formation of free radical

Scheme 6. Control Studies to Elucidate the Mechanism

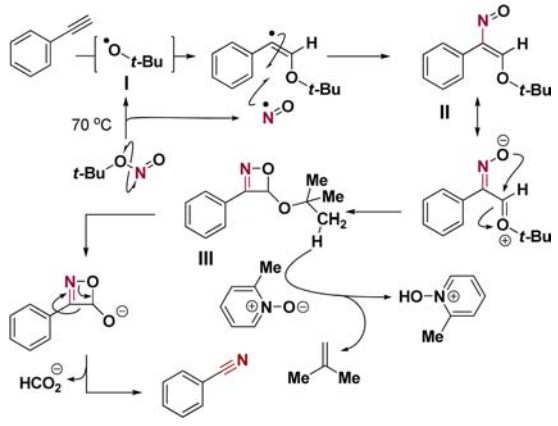


radical quenching agent	yield of **2h**
none	75%
2,4,6-*tri*-tert-butyl phenol	<1%
2,4,-*di*-tert-butyl phenol	<1%
AIBN	<5%

intermediates, the reaction was repeated in the presence of a number of radical quenchers (eq 6). Thus, 2,4,6-tri-*tert*-butyl phenol, 2,4-di-*tert*-butyl phenol, and AIBN all lead to significant retardation of the reaction suggesting that it is likely proceeding via a radical pathway. To test whether aldehyde or ketone intermediates are formed, various aryl aldehydes and ketones were examined (eqs 7 and 8). In none of these cases was the expected benzonitrile compound formed.

Based on these observations, a plausible mechanism has been outlined (Scheme 7). First *in situ* homolysis of *tert*-butyl nitrite

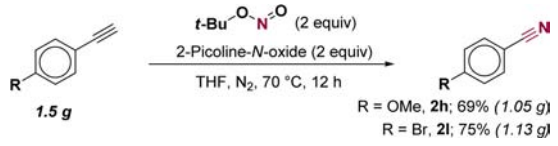
Scheme 7. Plausible Reaction Mechanism



yields the *tert*-butyl oxy radical and nitroso radical. Addition of the former to the alkyne forms a phenyl-substituted vinyl radical **I** which is trapped by the nitroso radical to yield **II**. Cyclization of **II** then provides the strained four-membered intermediate **III** with elimination of formic acid leading to the formation of benzonitrile.[20] Presumably a *tert*-butyl cation is formed in the conversion of **III** to the final product, and a proton abstraction by the 2-picoline-*N*-oxide resulted isobutylene.

Scalability of the reaction was tested successfully by preparing **2h** and **2l** in 69% and 75% yields, respectively (Scheme 8).

Scheme 8. Gram-Scale Reactions



In conclusion, we have developed the first metal-free nitrogenation of terminal alkynes to provide arylnitrile under mild conditions. This is the first example where *tert*-butyl nitrite is used as the nitrogenating reagent for alkynes. A wide range of functional groups are compatible with the reaction conditions. This metal-free nitrile synthesis avoids the use of hazardous materials, allowing potential application in industry and academia.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00147.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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