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NBS mediated nitriles synthesis through C=C double bond cleavage[†]

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An NBS mediated nitriles synthesis through C=C double bond cleavage has been developed. TMSN₃ was employed as the nitrogen source for this Cu(OAc)₂ promoted nitrogenation reaction. This transformation has a relatively high regio-selectivity to form aromatic nitriles.

The cyano group is a key intermediate in organic synthesis as a very useful precursor for the generation of a variety of functional groups, such as amines, amides, aldehydes,¹ as well as heterocyclic compounds.² Moreover, the cyano group itself is also an important functional group in many compounds, such as dyes, medicines, and agrochemicals.3 Considering the broad application of the cyano group, many methodologies have been reported to prepare nitriles, including the Sandmeyer reaction from aryl diazonium salts,⁴ the dehydration approach from amines, alcohols or oximes⁵ and so on. Despite the significances of these methods, some drawbacks, such as multiple steps, harsh reaction conditions, bad functional group tolerance, or expensive and hazardous reagents, are involved in these processes. In past decades, some novel approaches to nitriles through C-H or C-C bond cleavage have been developed.⁶ Our group has also developed some direct conversions from methyl and alkynes into nitriles.⁷ Very recently, we successfully achieved the transition metal free TEMPO catalyzed transformation of alkenes to nitriles through C=C bond cleavage (a, Scheme 1).^{8,9} Unfortunately, there are some limitations in the substrates scope. For styrene derivative substrates, the desired aromatic nitriles could not be afforded under the standard conditions (b, Scheme 1).

In order to realize the direct transformation from styrenes to aromatic nitriles, we proposed a tandem reaction process by



Scheme 1 The TEMPO catalyzed nitriles synthesis from alkenes and the design of this report.

employing an alkenyl azide intermediate^{7d} generated *in situ* (c, Scheme 1). According to this hypothesis, the styrene derivatives could be attacked by an electrophile to generate a threemembered ring halonium ion,¹⁰ which could be attacked by azido nucleophiles,¹¹ and then underwent the following relay of elimination and rearrangement to afford the corresponding aromatic nitriles (c, Scheme 1). Herein, we describe an NBS mediated aromatic nitriles synthesis through highly regioselective C==C double bond cleavage of styrenes.

We began our experiments by choosing the trimethylsilyl azide (TMSN₃) as the nucleophile, and 1-methoxy-4-vinylbenzene (1a) as the substrate in the presence of N-bromosuccinimide (NBS), Cu(OAc)₂ and K₂CO₃. We were excited to obtain the desired aromatic nitrile 2a under an atmosphere of O_{2} , although the yield was only 47% (Table 1, entry 1). This initial system was very complex with the formation of many unknown byproducts, which made the purification difficult. It is noteworthy that the yield of the reaction under air was almost the same as that under O_2 (Table 1, entry 2), while the system was much more simple and easy to purify. Other kinds of azides, such as diphenylphosphoryl azide (DPPA) and tosyl azide (TsN₃), showed worse results than that of TMSN₃ (Table 1, entries 3 and 4). As for the catalysts, we tried many kinds of copper salts but no better results were obtained than those using $Cu(OAc)_2$ (Table 1, entries 5–6, and also see ESI[†]). After

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Table 1 Optimization of the reaction conditions^a

	MeO 1a	[N₃]	MeO 2a	
Entry	Cat. (20%)	[N ₃] (eq.)	Base (eq.)	Yield ^b
1 ^{<i>c</i>}	$Cu(OAc)_2$	$TMSN_{3}(2.0)$	K_2CO_3 (1.0)	42%
2	Cu(OAc) ₂	$TMSN_3(2.7)$	$K_2CO_3(1.0)$	47%
3	$Cu(OAc)_2$	DPPA (2.7)	$K_2CO_3(1.0)$	Trace
4	$Cu(OAc)_2$	$T_{sN_{3}}(2.7)$	$K_2CO_3(1.0)$	Trace
5	Cul	$TMSN_3(2.7)$	$K_2CO_3(1.0)$	25%
6	$CuCl_2$	$TMSN_3(2.7)$	$K_2 CO_3 (1.0)$	<25%
7	$Cu(OAc)_2$	$TMSN_3(2.7)$	Na_2CO_3 (1.0)	22%
8	$Cu(OAc)_2$	$TMSN_3(2.7)$	<i>t</i> -BuONa (1.0)	<10%
9	$Cu(OAc)_2$	$TMSN_3(2.7)$	$K_{3}PO_{4} \cdot 7H_{2}O(1.0)$	49%
10	$Cu(OAc)_2$	$TMSN_3(2.7)$	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	61%
11	$Cu(OAc)_2$	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	77%
$12^{d,e}$	$Cu(OAc)_2$	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	64%
$13^{d,f}$	$Cu(OAc)_2$	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	65%
14^d	None	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	59%
$15^{d,g}$	$Cu(OAc)_2$	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	55%
16^{h}	$Cu(OAc)_2$	$TMSN_3$ (2.3)	$K_{3}PO_{4} \cdot 7H_{2}O(2.0)$	49%

^{*a*} The reaction was stirred in MeCN (2.5 mL) at 80 °C employing **1a** (0.4 mmol, 1.0 eq.) for 25 h. ^{*b*} Isolated yields. ^{*c*} The reaction was carried out under O₂ and in 2 mL of MeCN. ^{*d*} NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. ^{*e*} 10 mol% of Cu(OAc)₂ was used. ^{*f*} 5 mol% of Cu(OAc)₂ was used. ^{*g*} The reaction was carried out under Ar. ^{*h*} 72 mg of water (10.0 eq.) was added.

all these attempts, we thought maybe the base was not suitable for the elimination step to generate the alkenyl azide intermediate in situ. Therefore, different types of bases, including Na₂CO₃, t-BuONa, and Et₃N, were investigated (Table 1, entries 7-8, and also see ESI[†]). However, these bases did not perform well. Interestingly, when K₃PO₄·7H₂O was chosen as the base, the desired aromatic nitrile 2a was obtained in a 77% yield (Table 1, entry 11). Considering that the base was very important for this transformation, we also tried other kinds of potassium phosphates. However, they did not show higher efficiency than K₃PO₄·7H₂O (see ESI[†]). The addition of 10.0 eq. of water decreased the efficiency (entry 16). Further investigations showed that Argon atmosphere was not required for this present chemistry (Table 1, entry 15). In addition, a copper-salt is not essential for this transformation, although the presence of $Cu(\pi)$ could enhance the efficiency (Table 1, entry 14).

With the optimized condition in hand (Table 1 entry 11), we investigated the substrate scope of this transformation (Table 2). Substrates with an electron-donating or weak electron-donating group at the *para* position of vinyl in benzene rings proceeded well (Table 2). Substrates with a methoxyl- or an ethoxyl- group at the *para* position gave good results with yields up to 77% (Table 2, **1a** and **1b**). When there was a phenyl- group at the *para* position of the vinyl-, the corresponding nitrile product was obtained in a 66% yield with the formation of a trace amount of (1% yield) the diazidation byproduct (Table 2, **1c**). Unfortunately, substrates with electron-withdrawing substituent groups at the benzene ring could not afford the corresponding nitriles (Table 3). If a methoxyl-

group was at the *para* position, but with an electron-withdrawing group, the desired nitrile product **2f** was obtained in a 53% yield without the diazidation byproduct (Table 2). When *tert*-butyl(2-methoxy-5-vinyl-phenoxy) dimethylsilane (**1k**) was treated using this method, the corresponding 3-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzonitrile was not achieved. However, 51% of 3-hydroxy-4-methoxybenzonitrile with a naked hydroxyl group was obtained. Notably, 1,2-disubstituted styrene could also accomplish this transformation smoothly, leading to the corresponding aromatic nitriles in moderate yields (Table 2, **1l** and **1m**). To our delight, 1-ethynyl-4-methoxy-benzene **1n** could also be smoothly transformed into the corresponding nitrile product in a 39% yield (Table 2), which largely expanded the substrate scope of this transformation.

It is noted that when electron deficient styrenes or styrenes with weak electron-donating groups were employed as the substrates, the reactions afforded not only the desired aromatic nitriles but also the diazidation byproducts, which could not be converted into aromatic nitriles under the standard conditions even with longer reaction time (Table 3). In some cases, the diazidation of C=C became the main process, although the nitriles could also be obtained. The yields of the nitriles suffered from the strength of the electron-withdrawing of the substituent groups at the benzene ring. The stronger the groups withdraw electrons, the higher the yield of the diazidation products. The control experiment indicates that the diazidation product 3q could not be further converted into the desired nitrile under the optimal conditions with 94% recovery of 3q (eqn (1)). Fortunately, the diazidation products¹¹ of styrenes have some special applications,^{11a,12} such as an intermediate for the synthesis of certain ligands.

To probe the mechanism of this transformation, some control experiments have been investigated. When 4-methoxybenzaldehyde 4 was treated under the standard conditions, 4-methoxybenzonitrile 2a was not obtained, with 80% of the starting materials recovered (eqn (2)). In the absence of NBS, 4-methoxybenzaldehyde was completely recovered (eqn (3)). These results may rule out the pathway of going through an aldehyde intermediate, which has been widely reported.¹³ Although the preparation of the proposed (1-azido-2-bromoethyl)benzene intermediate C (Scheme 2) failed, we synthesized 1-(1-azidovinyl)-4-methoxybenzene 5, which performed well under the standard conditions in the absence of NBS and TMSN₃, affording 4-methoxybenzonitrile 2a in an 84% yield (eqn (4)).



Table 2 The substrate scope of this transformation^a



^{*a*} Reaction conditions: substrate 1 (0.4 mmol, 1.0 eq.), NBS (0.48 mmol, 1.2 eq.), TMSN₃ (1.1 mmol, 2.7 eq.), K₃PO₄·7H₂O (0.8 mmol, 2.0 eq.), Cu(OAc)₂ (0.08 mmol, 20 mol%), isolated yields. ^{*b*} 2.5 eq. of TMSN₃ were used, and NBS was 1.0 eq. ^{*c*} TMSN₃ 2.5 eq. and NBS 1.2 eq., GC yield using *n*-dodecane as an internal standard. ^{*d*} NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. ^{*e*} 1.0 eq. of NIS was used instead of NBS, 2.5 eq. of TMSN₃ were used.



 Table 3
 The reaction of substrates with electron-withdrawing groups^a



^{*a*} Reaction conditions: substrate 1 (0.4 mmol, 1.0 eq.), NBS (0.48 mmol, 1.2 eq.), TMSN₃ (1.1 mmol, 2.7 eq.), $K_3PO_4 \cdot 7H_2O$ (0.8 mmol, 2.0 eq.), $Cu(OAc)_2$ (0.08 mmol, 20 mol%), isolated yields. ^{*b*} 3.0 eq. of TMSN₃ were used. ^{*c*} 1.2 eq. of NIS were used instead of NBS.

Scheme 2 Possible mechanism.



On the basis of all the results mentioned above, a possible mechanism is illustrated (Scheme 2). Substrate 1 reacts with NBS forming a three-membered ring bromonium ion A, which could equilibrate to a benzylic cation \mathbf{B}_{14a}^{14a} which is subsequently attacked by azide ions to generate species C. The intermediate C undergoes elimination assisted by a base to form the corresponding alkenylazide intermediate **D**.^{7d,14} The following rearrangement of **D** promoted by the copper catalyst *via* intermediate \mathbf{E}^{6i} leads to the nitrile products 2 through carbon-carbon bond cleavage. For the electron deficient styrene substrates, it is difficult for intermediate A to equilibrate to a benzylic cation **B**.^{14a} An azide nucleophile could attack the three-membered ring bromonium ion A, resulting in intermediates C and/or F. Due to the effect of the electronwithdrawing group, the elimination of intermediates F and C to generate an alkenyl azide intermediate is difficult. They prefer the substitution reaction with another azide nucleophile to form diazidation products 3, which could not be further converted to nitriles 2 under the standard conditions.

Conclusions

In conclusion, we have developed a novel NBS mediated highly selective aromatic nitriles synthesis from styrenes through C=C double bond cleavage. This kind of nitrogenation transformation has a relatively high position-selectivity. Tandem substitution, elimination, and rearrangement reactions are involved in this process. Further investigations on expanding the reaction scope and the application of this transformation are ongoing in our laboratory.

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