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Direct oxidative cyanation of tertiary amines promoted by *in situ* generated hypervalent iodine(III)-CN intermediate

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ABSTRACT

Article history: Received Received in revised form Accepted Available online An environmentally benign and metal-free cyanation method of tertiary amines oxidated by hypervalent iodine(III) intermediate generated *in situ* from PIFA (or DIB) and TMSCN has been developed. Variety of substituent groups on amines are tolerated to the oxidation of α -C-H bond to form C-C bond in the absence of metal catalysts with the yields of up to 74%.

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κeywords: α-Aminonitriles Cyanation *N,N*-dialkylanilines Hypervalent iodine TMSCN

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1. Introduction

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2. Results and Discussion

Since α -aminonitriles are widely used in the construction of biologically active compounds and functional materials,¹ such as α -amino acids, α -amino aldehvdes, α -amino alcohols and 1.2diamines etc., a variety of methods for the synthesis of aaminonitriles have been developed, in which Strecker reaction² involving the one pot condensation of a carbonyl compound, an amine and cyanide is a traditional method (i, Scheme 1). On the other hand, organic oxidation, especially for sp³ C-H bond oxidation to form C-C bond, is of great importance in organic synthesis owing to avoiding prefunctionalization of substrates and generally shorter synthetic procedures.³ Therefore, numerous protocols have been employed to achieve α-aminonitriles by direct C-H oxidation in recent years,⁴⁻¹³ which often go through the oxidation of tertiary amines into iminium ions catalyzed by metal-based catalysts, such as Ru,⁴ V,⁵ Au,⁶ Mo,⁷ Fe,⁸ Cu,⁹ Ir,¹⁰ Ti,¹¹ Co¹² and Re¹³ in the presence of oxidants, followed by the nucleophilic attack of the cyanide ions (ii, Scheme 1). However, expensive or moisture sensitive metal catalysts and high toxic cyanide reagents such as NaCN or HCN are inevitable in most of these protocols, and the sparse availability and expensive nature of metal catalysts limit their wide applications in organic synthesis.



Scheme 1. Methods of preparation of α -aminonitriles.



Scheme 2. Our proposal on preparation of α -aminonitriles using I(III)-CN intermediate.

In recent years, metal-free methods to prepare α -aminonitriles by direct C-H oxidation have attracted much attentions.¹⁴ In view of our research interest on hypervalent iodine reagents which have been extensively used in C-H oxidation for their low toxicity, commercial availability and environmental friendliness.¹⁵ Zhdankin's group have reported cyanation of *N*,*N*dimethylanilines to synthesize the a-aminonitriles using cyanobenziodoxole as cyanide source.14a In our previous work, we attempted to prepare β -ketonitriles through cyanation of silyl enol ethers by means of cyanobenziodoxole,16 however, our endeavours have proved to be unsuccessful. So we turned to synthesis of cyanide intermediate (I(III)-CN) in situ generated from PhIO/BF₃ OEt₂/TMSCN (trimethylsilyl cyanide), and eventually umpolong stratgy for cyanation of silyl enol ethers to furnish β -ketonitriles was achieved. Herein, we would like to report the cvanation of tertiary amines through the combination of hypervalent iodide and TMSCN where a C-H oxidation by active hypervalent iodine(III)-CN intermediate takes place to form an iminium ion and nucleophilic attack of the cyanide ions is followed to provide cyantion product (Scheme 2).

The optimization studies for C-H functionalization were initiated by using N,N-dimethylaniline as tertiary amine and TMSCN as cvanide source along with hypervalent iodine reagents as oxidants in DCE. As depicted in Table 1, the efficiencies of different additives and hypervalent iodine reagents were examined. bis(trifluoracetoxy)iodobenzene (PIFA) that was premixed with TMSCN for preactivation of 40 min before adding N,N-dimethylaniline was proved to be most effective and (diacetoxyiodo)benzene (DIB) afforded a comparable result, while using iodosobenzene (PhIO) and [Hydroxy(tosyloxy)iodo]benzene (HTIB) did not furnish the desired product (entries 1-4). With PIFA, increasing the time of preactivation and shorten the reaction time led to the same yield (entry 5 vs entry 2). In order to alleviate the side reaction resulted from high temperature under strongly oxidative conditions, the temperature was lowered, which as a result, delivered the same level of reactivity (entries 6-7). It is also observed that during the reaction, unreacted substrate was not detected by TLC due to the interaction with CF₃COOH released from PIFA. In consideration of this phenomenon, we tried to screen different bases and various inorganic salts to affect the interaction and consequently, better results were obtained except for Cs₂CO₃ (entries 8-13, for details see supporting information), in which Na₂SO₄ was found to be the best one with the yield of 52%.

Table 1: Evaluation of additives and oxidants in the cyanation of tertiary amines^a



Entry	Oxidant	<i>T</i> (°C)	<i>t</i> (h)	Additive	Yield (%) ^b
1	1a	80	8	-	30
2	1b	80	8	-	32
3	1c	80	8	-	0
4	1d	80	8	-	0
5	1b	80	1	-	32
6	1b	r.t.	1	-	32
7	1b	0	1	-	35
8	1b	0	1	Na ₂ SO ₄	52
9	1b	0	1	NaOH	37
10	1b	0	1	K_2CO_3	46
11	1b	0	1	t-BuOK	38
12	1b	0	1	CsF	48
13	1b	0	1	Cs ₂ CO ₃	0

^a Conditions: *N,N*-dimethylaniline (0.5 mmol), Oxidant (0.75 mmol), TMSCN (1.0 mmol) and additives (2.0 mmol) in DCE (3.0 mL).

^b Isolated yields. DCE = 1,2-dichloroethane.

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The effects of different amounts of PIFA, TMSCN, additives and solvents on the reaction were further studied (Table 2, for details see supporting information). The results showed that 0.5 equivalent of Na2SO4 proved to be the most suitable by comparing different amounts of Na2SO4 in the presence of 1.5 equivalents of PIFA and 2.0 equivalents of TMSCN (entries 1), while varying the amounts of TMSCN is unfavorable and further increasing the loading of PIFA to 2.0 equivalents were observed to be optimal for this reaction (entry 2). Different solvents such as DCE, CH₃CN, CHCl₃, CH₂Cl₂ and CH₃OH were screened and the highest yield was obtained in DCE (entries 3-6). The reaction was found to be sensitive to the premixed time of PIFA with TMSCN (entries 7-9). It is worthy to note that only trace of desired product was yielded without preactivation of TMSCN and PIFA. According to the procedures reported, the attempt to improve the yields through elevating reaction temperature, prolonging reaction time and adding metal catalysts such as Pd(OAc)₂, FeCl₂, and CuBr failed (entries 10-14).

Table 2: Optimization of reaction conditions^a

N.	Me Na ₂ SO ₄ (0.5	TMSCN (2 eq.) 5 eq.), solvent ►	
2			3
Entry	PIFA (x eq.)	Solvent	Yield (%) ^b
1	1.5	DCE	54
2	2	DCE	56
3	2	CH ₃ CN	36
4	2	CHCl ₃	37
5	2	CH_2Cl_2	50
6	2	CH ₃ OH	0
7	2	DCE	trace ^c
8	2	DCE	26 ^d
9	2	DCE	40 ^e
10	2	DCE	$50^{\rm f}$
11	2	DCE	52 ^g
12	2	DCE	55 ^h
13	2	DCE	40 ⁱ
14	2	DCE	20 ^j

а Conditions: Oxidant (specified), TMSCN (1 mmol), Solvent (3.0 mL), Na₂SO₄ (0.25 mmol), N,N-dimethylaniline (0.5 mmol), 0 °C, 1 h.

Preactivation for 0 min. ^d Preactivation for 10 min.

^e Preactivation for 70 min.

^f Reaction time was 2 h.

^g At r t

i 10 mmol% FeCl2 was added.

^j 10 mmol% CuBr was added.

With the optimal conditions for the oxidative cyanation of tertiary amines in hand, the scope of the reaction was investigated by using TMSCN as the cyanide source, PIFA as the oxidant and Na_2SO_4 as the additive. As described in Table 3, the reactions of substituted N,N-dimethylanilines, containing electron-donating groups such as methyl, i-Pr, t-Bu and electron-withdrawing groups such as ester, bromo, iodo, nitro effectively afforded the

corresponding α -aminonitriles **3b-i** in yields of 17 to 74%. ortho-Substituent was found to be more favorable than msubstituent (3e vs 3f) and the ability of withdrawing electron of groups have less influence on the reactions (3f vs 3g). Additionally, disubstituted derivates even having big steric hindrance like 21 provided cyanation products 3j-1 in moderate to good yields (37-60%). Furthermore, the system can also be efficiently applied to cyclic amine affording **3m** and **3n** in 20% and 25% yield, respectively.





Conditions: PIFA (1.0 mmol), TMSCN (1.0 mmol), DCE (3.0 mL), premixed at r.t. for 40 min, Na₂SO₄ (0.25 mmol) and tertiary amine (0.5 mmol) reacted at 0 °C for 1 h; isolated yields. ^b Reaction at 0 °C for 1 h.

° Reaction at 0 °C for 5 h.

^d 1.25 mmol DIB and 1.25 mmol TMSCN, reflux in seal tube for overnight.

^e Reaction at r.t. for overnight.

Interestingly, in the absence of TMSCN, N,N-dimethylaniline was oxidated by HTIB and DIB, and benzidine was generated with the yield of 14% and 9%, respectively (Scheme 3), which deliveries metal-free strategy for self-coupling of aniline as Ichikawa's work.¹⁷ With the addition of TEMPO (2,2,6,6-Tetramethylpiperidin-1-oxyl), the pathway of self-coupling was blocked, which suggested a free radical coupling process.¹⁸



Scheme 3. Synthesis of benzidine using hypervalent iodine reagents.

To gain insight into the mechanism, 2 equivalents of radical scavenger TEMPO were added to the reaction mixture under optimal conditions and resulted in the nearly same yield of 52%,

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^b Isolated yields.

^h 10 mmol% Pd(OAc)₂ was added.

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which indicated that the reaction did not proceed through a radical pathway. As mentioned above, only trace of cyanation product yielded without preactivation, which suggested that conversion of N,N-dimethylanilines into iminium ion and successively nucleophilic attack of cyanide anion was not promoted by PIFA. Kita's group¹⁹ have reported active hypervalent iodine(III)-CN intermediate were generated from PIFA and TMSCN in the presence of BF₃•Et₂O. Attempts in isolation and spectroscopic detection of the hypervalent iodine(III) intermediate that were precipitated during the period of preactivation were made but failed due to their instability. So a similar hypervalent iodine intermediate is speculated to be formed in our reaction, an oxidation of 2a is followed to give 5 and then H-absorption of trifluoroacetyl anion affords the iminium ion intermediate 6 which is attacked by cyanide ion to furnish 3a.



 $X = OCOCF_3$ or CN

Scheme 4. The proposed reaction mechanism for the cyanation of tertiary amines.

In conclusion, we have developed an oxidative cyanation to accomplish α -aminonitriles, which directly oxidates sp³ C-H bond using a hypervalent iodine reagent combined with TMSCN in the absence of metal catalysts to form C-C bond and provides a useful tool for the synthesis of various nitrogen-containing compounds. Further studies about synthetic utility of this versatile oxidative system and more mechanistic details are presently pursued in our laboratories.

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Supplementary Material

Supplementary data (detailed experimental description and condition optimization; characterization data of NMR for all compounds; details of copies of the ¹H NMR and ¹³C NMR) associated with this article can be found in the online version.

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