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One-Pot Three-Component Synthesis of α-Iminonitriles by IBX/TBAB-Mediated Oxidative Strecker Reaction

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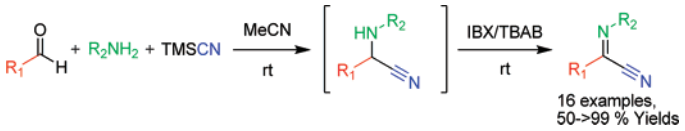
ABSTRACT



The reaction of aldehydes, amines, and TMSCN in the presence of 2-iodoxybenzoic acid (IBX) and tetrabutylammonium bromide (TBAB) afforded α-iminonitriles in good to excellent yields under mild conditions. The presence of TBAB is essential for this transformation. The methodology was applied to a two-step synthesis of indolizidine via a microwave-assisted intramolecular cycloaddition of α-iminonitrile.

The α-iminonitriles, also known as imidoyl cyanides, are an important class of densely functionalized compounds that could serve as precursors for α-ketoacids, amides, N-alkylketene-imines, cyanoenamides, amidines, etc.[1] Furthermore, they function as reactive components in cycloadditions, providing a rapid access to nitrogen-containing heterocycles.[2−4] Many synthetic methodologies have been developed.[1a,5−11] However, most of them are multistep processes and have limited application scope. Surprisingly, the direct oxidation of α-aminonitriles has rarely been employed and only aromatic α-iminonitriles were accessible by this method using either manganese dioxide[12] or air as oxidants.[13] One of the most general methods involves the chlorination of an aminonitrile, followed by the base-promoted dehydrochlorination of the resulting *N*-chloroaminonitrile.[1a,7] The inconvenience associated with this two-step sequence is the instability of some *N*-chloroaminonitriles. It has been reported that they decomposed violently and often explosively even at 0 °C.[1a] As a continuation of our interest in the development of oxidative multicomponent reactions

(1) (a) De Corte, B.; Denis, J. -M.; De Kimpe, N. *J. Org. Chem.* **1987**, *52*, 1147. (b) Roychowdhury, A.; Kumar, V. V.; Bhaduri, A. P. *Synth. Commun.* **2006**, *36*, 715.

(2) For a recent comprehensive review on imino Diels−Alder reaction, see Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React.* **2005**, *65*, 141.

(3) Iminonitrile as part of diene: (a) Sisti, N. J.; Motorina, I. A.; Tran Huu Dau, M.-E.; Riche, C.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715. (b) Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093. (c) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098. (d) Tarver, J. E.; Terranova, K. M.; Joullié, M. *Tetrahedron* **2004**, *60*, 10277.

(4) Iminonitrile as dienophile: (a) Middleton, W. J.; Krespan, C. G. *J. Org. Chem.* **1968**, *33*, 3625. (b) Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem.* Soc. **2003**, *125*, 4970. (c) Maloney, K. M.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3115.

(5) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(6) Takahashi, K.; Rimura, S.; Ogawa, Y.; Yamada, K.; Iida, H. *Synthesis* **1978**, 892. Takahashi, K.; Rimura, S.; Ogawa, Y.; Yamada, K.; Iida, H. *Synthesis* **1978**, 892.

(7) (a) Boyer, J. H.; Dabek, H. *J. Chem. Soc. D* **1970**, *18*, 1204. (b) Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099. (c) De Kimpe, N.; Verhé, R.; De Buyck, L.; Chys, J.; Schamp, N. *Synthesis* **1978**, 895. (d) Ksander, G.; Bold, G.; Lattmann, R.; Lehmann, C.; Früh, T.; Xiang, Y.-B.; Inomata, K.; Buser, H.-P.; Schreiber, J.; Zass, E.; Eschenmoser, A. *Helv. Chim. Acta* **1987**, *70*, 1115. (e) Drenkard, S.; Ferris, J.; Eschenmoser, A. *Helv. Chim. Acta* **1990**, *73*, 1373.

(8) Smith, J. G.; Irwin, D. C. *Synthesis* **1978**, 894.

(9) (a) Ducta, D. K.; Prajapati, D.; Sandhu, J. S.; Baruah, J. N. *Synth. Commun.* **1985**, *15*, 335. (b) Konwar, D.; Goswami, B. N.; Borthakur, N. *J. Chem. Res. Synop.* **1999**, 242.

(10) Pochat, F. *Tetrahedron Lett.* **1981**, *22*, 955.

(11) (a) Saegusa, T.; Taka-Ishi, N.; Ito, Y. *J. Org. Chem.* **1969**, *34*, 4040. (b) Pellissier, H.; Gil, G. *Tetrahedron Lett.* **1989**, *30*, 171. (c) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Ospita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431.

(12) Sandhu, J. S.; Mohan, S.; Kapoor, A. L. *Chem. Ind. (London)* **1971**, *5*, 152.

(13) Jursic, B. S.; Douelle, F.; Bowdy, K.; Stevens, E. D. *Tetrahedron Lett.* **2002**, *43*, 5361.

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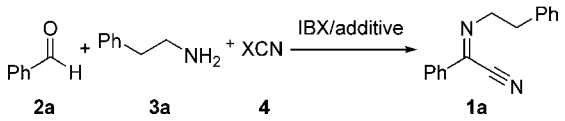
(MCRs),[14,15] we describe herein a one-pot synthesis of α-iminonitriles by reaction of aldehydes, primary amines and TMSCN using 2-iodoxybenzoic acid (IBX) as oxidant in conjunction with a catalytic amount of tetrabutylammonium bromide (TBAB). We also document a rapid construction of indolizidine skeleton by applying this new synthetic methodology.

To achieve the projected transformation, the oxidant has to satisfy the following criteria: (a) to be compatible with the conditions of the Strecker reaction or, in an ideal case, to be capable of promoting the Strecker reaction; (b) to be able to selectively oxidize the aminonitrile in the presence of two oxidizable starting materials. On the basis of this consideration, we selected 2-iodoxybenzoic acid (IBX)[16] as an oxidant for its intrinsic acidity ($pK_a^{H2O} = 2.4$, $pK_a^{DMSO} = 6.65$)[17] that would be beneficial to the Strecker reaction[18] and for its ability to oxidize amines to imines.[19,20] The condensation of benzaldehyde (**2a**), phenethylamine (**3a**), and cyanide (**4**) in the presence of IBX was examined as a test reaction, and the results are summarized in Table 1. The α-iminonitrile was indeed produced using KCN or TMSCN as a cyanide source, in either THF or acetonitrile as a solvent; however, the yield was low even after prolonged reaction periods (entries 1−3). Heating the reaction mixture to 40 °C reduced the reaction time but had adverse effect on the product yield (entries 4 vs 3). A control experiment indicated that the Strecker reaction of **2a**, **3a**, and TMSCN in acetonitrile under Ramón-Yus's catalyst-free conditions[21] was almost instantaneous, leading to aminonitrile in nearly quantitative yield. The low efficiency observed in the production of iminonitrile is thus due to the slow oxidation step. Much to our delight, adding tetrabutylammonium bromide (TBAB, 1 equiv) to the reaction mixture accelerated significantly the reaction, leading to the desired α-iminonitrile in 90% isolated yield (entry 5, Table 1).[22] A very similar result was obtained when the reaction was performed in the presence of a catalytic amount of TBAB (0.05 equiv, entry 6). We have also briefly examined the halide effect. Whereas tetrabutylammonium chloride (TBAC) is as efficient as TBAB, tetrabutylammonium iodide (TBAI) was found to be far less effective in mediating the present transformation.

Table 1. Three-Component Synthesis of α-Iminonitriles, Optimization of Reaction Parameters[a]



2a **3a** **4** **1a**

entry	X	conditions	IBX (equiv)	additive (equiv)	yield (%)
1	K	THF/rt/72 h	2	–	40[b]
2	K	MeCN/rt/24 h	2	–	18[b]
3	TMS	MeCN/rt/24 h	2	–	35[b]
4	TMS	MeCN/40 °C/4 h	2	–	28[c]
5	TMS	MeCN/rt/1 h	1	TBAB (1)	90[c]
6	TMS	MeCN/rt/1 h	1	TBAB (0.05)	90[c]
7	TMS	MeCN/rt/4 h	1	TBAI (0.05)	37[c]
8	TMS	MeCN/rt/1 h	1	TBAC (0.05)	87[c]

[a] General conditions: molar ratio **2a**/**3a**/**4** = 1:1:1.1. [b] Determined based on the ^{1}H NMR spectrum of the crude material. [c] Isolated yields after column chromatography on the silanized silica gel.

The scope of this novel synthesis of α-iminonitriles was next examined by varying the structures of aldehydes and amines. As shown in Table 2, electron-neutral, -rich, and -poor aromatic aldehydes, as well as α,β-unsaturated aldehydes (cinnamaldehyde, entry 3) were all compatible with these oxidative conditions, leading to the respective adducts in good to excellent yields. A heteroaromatic aldehyde, such as pyridinecarboxaldehyde (entry 4), was converted into the corresponding α-iminonitrile (**1e**) in 79% yield. The (*S*)-1-phenylethanamine participated in the reaction to afford **1f** in almost quantitative yield without racemization as evidenced by chiral HPLC analyis of **1f** and (±)-**1f′** (entry 5, Table 2). When bulky amines (*t*-butyl, entry 6) or aromatic amines (entries 7 and 8) were subjected to the same conditions, the reaction was slowed down significantly. However, by adding a catalytic amount of iodine, which is known to catalyze the Strecker reaction,[23] the desired iminonitrile was isolated in excellent yields (entries 6−8, Table 2). The three-component reaction is also applicable

(14) (a) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5775. (b) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3495.

(15) For a recent overview, see: Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.

(16) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6529 and references therein. (c) Moorthy, J. N.; Singhal, N.; Senapati, K. *Org. Biomol. Chem.* **2007**, *5*, 767. (d) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2008**, *49*, 80.

(17) Gallen, J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2929.

(18) (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795. (c) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (d) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.

(19) (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.

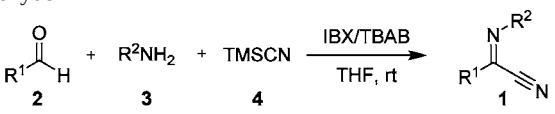
(20) For highlights, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812. (b) Wirth, T.; *Angew. Chem., Int. Ed.* **2006**, *45*, 4402.

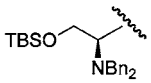
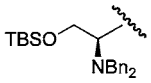
(21) (a) Martinez, R.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8472. (b) Zhu, J.; Bouillon, J.-P.; Singh, G. P.; Chastanet, J.; Beugelmans, R. *Tetrahedron Lett.* **1995**, *36*, 7081. (c) Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* **1995**, *60*, 6389.

(22) Quaternary ammonium salt were known to be beneficial in some IBX-mediated transformations, see: (a) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519. (b) Tohma, H.; Takizawa, S.; Morioka, H.; Maegawa, T.; Kita, Y. *Chem. Pharm. Bull.* **2000**, *48*, 445. (c) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *J. Org. Chem.* **2003**, *68*, 5422. (d) Zhu, J.; Germani, A. G.; Porco, Jr. J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239. (e) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *Synlett* **2005**, 1483. (f) Kuhakarn, C.; Kittigowittana, K.; Pohmakotr, M.; Reutrakul, V. *Tetrahedron* **2005**, *61*, 8995. (g) Kuhakarn, C.; Kittigowittana, K.; Ghabkham, P.; Pohmakotr, M.; Reutrakul, V. *Tetrahedron* **2005**, *61*, 8995. (h) Ozanne-Beaudenon, A.; Quideau, S. *Tetrahedron Lett.* **2006**, *47*, 5869. (i) Bhalerao, D. S.; Mahajan, U. S.; Chaudhari, K. H.; Akamanchi, K. G. *J. Org. Chem.* **2007**, *72*, 662. (j) Potassium iodide as additive: Pan, Z.-L.; Liu, X.-Y.; Liang, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 4101.

(23) (a) Royer, L.; De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 4595. (b) Masdeu, C.; Gómez, E.; Williams, N. A. O.; Lavilla, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3043.

Table 2. α-Iminonitriles from Aromatic and Aliphatic Aldehyde[a]



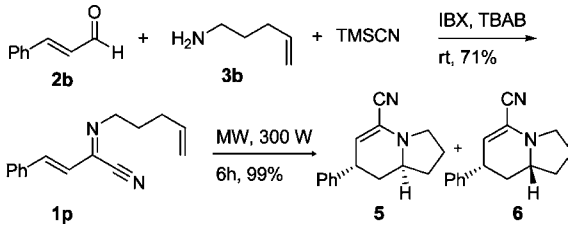
entry	R^1	R^2	product	yield (%)[b]
1	4-$MeOC_6H_4$	$Ph(CH_2)_2$	**1b**	59
2	2,6-$Cl_2C_6H_3$	$Ph(CH_2)_2$	**1c**	60
3	PhCH=CH	$Ph(CH_2)_2$	**1d**	97
4	3-Pyridine	$Ph(CH_2)_2$	**1e**	79
5	C_6H_5		**1f**	99
6	C_6H_5	*t*-Bu	**1g**	50[c]
7	C_6H_5	C_6H_5	**1h**	99[c]
8	C_6H_5	4-$MeOC_6H_4$	**1i**	95[c]
9	$Ph(CH_2)_2$	$Ph(CH_2)_2$	**1j**	68 (59)[d]
10	$(CH_3)_2CH$	$Ph(CH_2)_2$	**1k**	60
11	$CH_3(CH_2)_5$	$Ph(CH_2)_2$	**1l**	59
12	CH_2=$CH(CH_2)_2$	$Ph(CH_2)_2$	**1m**	74
13		$Ph(CH_2)_2$	**1n**	80
14			**1o**	80[e]

[a] All reactions were run in acetonitrile at room temperature in the presence of the TMSCN, IBX, and TBAB. For the alphatic aldehydes, IBX was added after the completion of the Strecker reaction. [b] Yields refer to the mass isolated after silanized silica gel chromatography. [c] General condition using iodine to catalyze Strecker reaction: molar ratio **2**/**3**/**4**/I_2/IBX/TBAB = 1:1:1.1:0.1:1.1:1.1. [d] All reagents were mixed at once. [e] Isolated as a mixture of two diastereomers in a 4:1 ratio.

to the synthesis of α-iminonitriles derived from aliphatic aldehydes, far less accessible than their aromatic counterparts (Table 2). Aliphatic aldehydes whether linear or α-branched, participate effectively in oxidative condensation process in the presence of a stoichiometric amount of TBAB. In addition, chiral nonracemic *N*,*N*-dibenzyl-*O*-TBS-serinal[24] was successfully transformed into the corresponding α-iminonitrile in excellent yield (entry 13, Table 2). However, partial epimerization occurred as the union of a chiral aldehyde and a chiral amine (entry 14, Table 2) provided **1o** as a mixture of diastereomers (dr = 4:1).[25] The formation of α-cyanoenamines resulting from the tautomerization of corresponding iminonitriles was not observed in these cases.[26] Higher yields were generally obtained, especially in the case of aliphatic aldehydes, when IBX was introduced to the reaction mixture after the completion of the Strecker reaction (entry 9, Table 2). Except for **1h**, only one stereomer was produced and was assigned as the *Z* isomer according to NMR studies. This assignment was corroborated in the case of **1i** by X-ray analysis (cf. Supporting Information).[27]

Grierson et al.[3] have demonstrated the utility of 2-cyano-1-aza dienes in the synthesis of indolizidines.[28] The literature methods for the access to these dienes are nevertheless long and low yielding. On the other hand, by applying the present methodology, a two-step synthesis of indolizidine was developed. The reaction of penten-1-amine (**3b**) with cinnamaldehyde (**2b**) and TMSCN in CH_3CN at room temperature, followed by addition of IBX/TBAB, gave rise to 2-cyano-1-aza-1,3-butadiene (**1p**) in 71% yield (Scheme 1). The thermal intramolecular hetero-Diels−Alder reaction of

Scheme 1. Two-Step Synthesis of Indolizidines Involving a Key Three-Component Synthesis of α-Iminonitriles.



1p failed to produce the desired cycloadduct. Gratefully, the cycloaddition of **1p** took place smoothly under microwave irradiation conditions (300 W for 6 h, toluene) to afford the indolizidine in 99% yield as a mixture of two diastereomers **5** and **6** (**5**/**6** = 1:1) (Scheme 1).

On the basis of the literature precedents, it is reasonable to hypothesize that the role of TBAB is to activate the IBX via the formation of a pentacoordinated 12-I-5 species **7**, which was then more susceptible to nucleophilic attack by amine, leading to **8**. The syn elimination of a molecular of water via transition state **9b**, which was less sterically congested than **9a**, would lead to the formation of the observed *Z*-iminonitrile and IBA (Scheme 2). Conceivably, a single electron transfer (SET) mechanism leading to **10** followed by dehydration could also be operating, as demonstrated by Nicolaou and co-workers.[29]

To verify this possibility, a three-component condensation of benzaldehyde (**2a**), cyclopropylamine (**3c**), and TMSCN was carried out under our standard conditions. As shown in Scheme 3, the expected α-iminonitrile (**1q**) was isolated in 91% yield. Since cyclopropylamine cation radicals are known

(24) (a) Andrés, J. M.; Barrio, R;, Martinez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem.* **1996**, *1*, 4210. (b) Laïb, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1771. (c) Andres, J. M.; Pedrosa, R. *Tetrahedron* **1998**, *54*, 5607. (d) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709.

(25) The formation of the minor product results from partial epimerization of *N*,*N*-dibenzyl serinal. The chiral amine is configurationally stable as shown in the formation of **1f**.

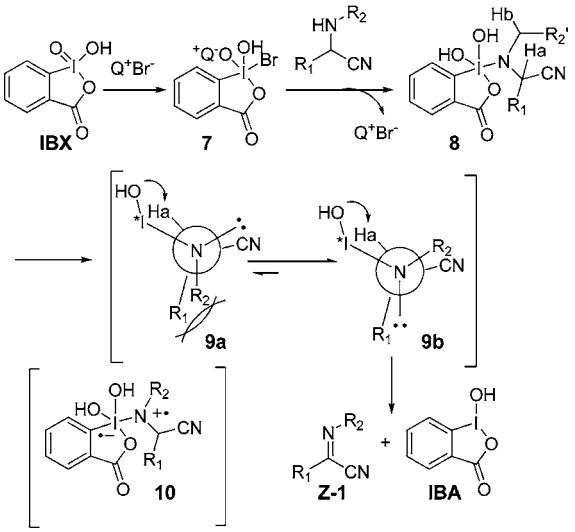
(26) De Kimpe, N.; Verhé, R.; de Buyck, L.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 3063.

(27) CDC-668053 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc-.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Center, 12 Union Road, CambridgeCB21EZ, UK; Fax: (+44)1223-336033; or deposit@ccdc.cam.ac.uk.

(28) For leading references on the biological activity of indolizidine alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 3001. (b) Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press, Inc.: San Diego, 1993; Vol. 44, Chapter 3.

(29) (a) Nicolaou, K. C.; Zhong, Y-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625. (b) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202.

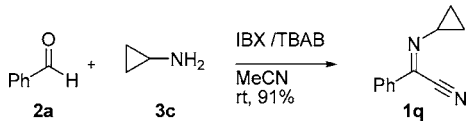
Scheme 2. Postulated Mechanism for IBX-Mediated Oxidation of Aminonitrile.



to undergo fragmentation leading to ring-opened products,[30] this observation might suggest the ionic mechanism on the way to iminonitriles. Furthermore, the clean formation of **1m** (entry 12, Table 2) and **1p** (Scheme 1) without concurrent generation of pyrrolidine derivatives is also supportive of the ionic mechanism.[31] Finally, it has also to be noted that the oxidation is highly regioselective, presumably due to the high acidity of H_a vs H_b (cf. intermediate **8**).

It is also reasonable to hypothesize that the IBX−TBAB system could influence the Strecker reaction since TMSCN is known to react with polyvalent iodines to afford the corresponding cyanoiodinanes.[32] However, preliminary experiments indicated that the reaction rate of the Strecker reaction was not affected by the presence of IBX−TBAB.

Scheme 3. Synthesis of *N*-Cyclopropyliminonitrile.



In summary, we have described a novel IBX−TBAB-promoted three-component synthesis of α-iminonitrile from readily accessible starting materials. Operational simplicity and good-to-excellent chemical yields are key features of the present protocol. To the best of our knowledge, this represented the first one-pot procedure that is applicable to a wide range of aldehydes, amines including aromatic and aliphatic ones. The ready accessibility of the α-iminonitrile should pave the way for the development of novel transformations based on this highly functionalized molecule. This potential was illustrated by developing a two-step synthesis of indolizidine via a microwave-assisted intramolecular cycloaddition of α-iminonitrile.

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Supporting Information Available: Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) (a) Lee, J.; U, J. S.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 10241. (b) Itoh, T.; Kaneda, K.; Teranishi, S. *Tetrahedron Lett.* **1975**, 2801.

(31) 5-Exo-cyclization of δ,ω-unsaturated aminium cation radical, see: Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163.

(32) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975.