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o-Iodoxybenzoic Acid- and Tetraethylammonium Bromide-Mediated Oxidative Transformation of Primary Carboxamides to One-Carbon Dehomologated Nitriles

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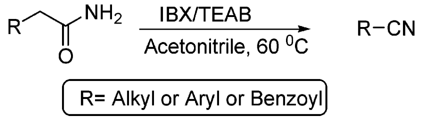

A clean and efficient method for the oxidative transformations of primary carboxamides to one-carbon dehomologated nitriles using the combination of *o*-iodoxybenzoic acid and tetraethylammonium bromide has been developed. This method exhibits a broad scope and is expected to be of great utility in organic synthesis.

The use of hypervalent iodine reagents in synthetic organic chemistry is a field of much curiosity.[1] The surging interest in iodine compounds is mainly due to the strong oxidizing properties of polyvalent organic iodine reagents combined with their benign environmental character and commercial availability. Hypervalent iodine reagents have found widespread applications in organic synthesis because of their selectivity and simplicity in use. Our group has been extensively working on the development of novel methodologies using hypervalent iodine reagents,[2] mainly, *o*-iodoxybenzoic acid (IBX) and Dess−Martin periodinane (DMP). Though IBX finds widespread application in oxidative transformations, to the best of our knowledge there are no reports on IBX-mediated oxidative transformation of primary carboxamide, $RCH_2C(O)NH_2$, to nitrile, RCN, bearing one less carbon atom.

One-carbon dehomologation is a demanding transformation in organic synthesis and with very little literature precedence.[3] Methods allowing the direct transformations of carboxylic acid derivatives to one-carbon shorter nitriles are rare.[4] Hypervalent iodine reagents normally employed for Hofmann-type one-carbon shorter transformations are $PhI(OCOCF_3)_2$,[5] PhIO−HCOOH,[6] PhI(OTs)OH,[7] and $PhI(OAc)_2$−KOH.[8] In continuation of our studies on the development of newer applications of hypervalent iodine (λ^5) compounds, herein we wish to report the application of IBX with tetraethylammonium bromide (TEAB) for oxidative transformations of primary carboxamides to one-carbon dehomologated nitriles under neutral conditions.

A variety of ligands have been reported to tune the reactivity of the iodine nucleus in hypervalent iodine compounds.[9] During the course of our investigations, it was evident that a combination of IBX and TEAB exerts a strong impact on the reactivity of IBX.[10]

To begin our study, the effect of the various reaction parameters on the oxidative transformation of 4-methoxybenzene acetamide **1** was examined as shown in Table 1. It was evident from the experiments performed that TEAB plays an important role in the formation of nitrile and in accelerating the reaction rate (entries 1−5). When the experiments were carried out in an equivalent of IBX/TEAB lower than 2.5 equiv, the reactions remained incomplete and no other byproducts were observed indicating that first step might be slow followed by rapid conversion to nitrile **1a** (entries 7−9). The reaction also proceeds at room temperature; however, it required longer reaction time (entry 10).

The reaction was also standardized with respect to solvent (entries 11−14), and the results are recorded in Table 1. On the basis of the studies performed, we obtained the best results with 2.5 equiv of IBX/TEAB in acetonitrile at 60 °C (entry 6), and all further reactions were carried out using these optimized parameters.

We also examined other hypervalent iodine compounds for this transformation, as shown in Table 2. The combination of DMP and TEAB was used and found viable for this transformation, although the yield of nitrile **1a** was comparatively low

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(7) (a) Lazbin, I. M.; Koser, G. F. *J. Org. Chem.* **1986**, *51*, 2669. (b) Vasudervan, A.; Koser, G. F. *J. Org. Chem.* **1988**, *53*, 5158.

(8) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.

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(10) (a) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *J. Org. Chem.* **2003**, *68*, 5422. (b) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *Synlett* **2005**, *9*, 1483.

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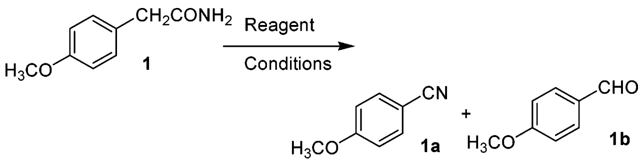
TABLE 1. Optimization of Reagent and Reaction Conditions for Amide to Dehomologated Nitrile[a]



entry	IBX/TEAB mol equiv wrt **1**	conditions	isolated yield		recovered starting material[b]
			1a (%)	**1b** (%)	**1** (%)
1	2.5/0	MeCN, 60 °C, 12 h	-	20	70
2	2.5/0.5	MeCN, 60 °C, 5 h	20	10	60
3	2.5/1	MeCN, 60 °C, 5 h	40	-	50
4	2.5/1.5	MeCN, 60 °C, 5 h	60	-	30
5	2.5/2.0	MeCN, 60 °C, 5 h	80	-	-
6	2.5/2.5	MeCN, 60 °C, 25 min	95	-	-
7	2/2	MeCN, 60 °C, 5 h	80	-	-
8	1.5/1.5	MeCN, 60 °C, 5 h	65	-	30
9	1/1	MeCN, 60 °C, 5 h	45	-	50
10	2.5/2.5	MeCN, RT, 8 h	70	-	
11	2.5/2.5	toluene, 60 °C, 15 h	30	-	60
12	2.5/2.5	THF, 60 °C, 15 h	30	-	60
13	2.5/2.5	$CHCl_3$, 60 °C, 3 h	70	-	-
14	2.5/2.5	*tert*-butanol, 60 °C, 2 h	80	-	-

[a] Reactions were carried out on 5 mmol. [b] Starting material quantity is specified only when it exceeds 30%.

TABLE 2. Evaluation of Other Hypervalent Iodine Reagents for the Transformation of Amide 1 to Nitrile 1a[a]

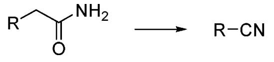
entry	reagent	reagent/TEAB mol equiv wrt **1**	conditions	isolated yield	recovered starting material
				1a (%)	**1** (%)
1	DMP	2.5/2.5	MeCN, 60 °C, 2 h	75	20
2	HIO_3	3/3	MeCN, 60 °C, 5 h	NR[b]	95
3	I_2O_5	3/3	MeCN, 60 °C, 5 h	NR[b]	98
4	IBA	5/5	MeCN, 60 °C, 1.5 h	80	-

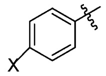
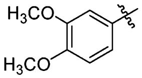
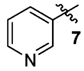
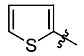
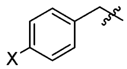
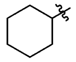
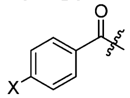
[a] Reactions were carried out on 5 mmol. [b] NR = No reaction.

(entry 1). No reaction was observed when HIO_3/TEAB and I_2O_5/TEAB combinations were used (entries 2 and 3). The hypervalent iodine (λ^3) compound IBA was also examined to assert that the observed conversion of **1** to **1a** was occurring as a result of the action of IBX and also by its byproduct IBA (entry 4).

With these results in hand, we sought to examine the scope and generality of the method. As can be seen from the results in Table 3, a wide variety of substrates were studied, including aromatic, heteroaromatic, and aliphatic carboxamides (entries 1−12), which furnished desired nitriles in excellent to moderate yields. The reaction is accelerated by incorporation of an electron-donating group. This is the same trend that is followed in the other reactions in which migration to an electron-deficient center occurs. A wide range of functional groups were tolerated by this protocol, including benzyl ether, alkene, and aromatic halide, further signifying the chemoselectivity (entries 3, 4, and 9). Interestingly, β-keto amides were also converted to the corresponding benzoyl cyanides in moderate yields (entries 13 and 14).

TABLE 3. IBX/TEAB-Mediated Oxidative Transformations of Primary Amides to Dehomologated Nitriles[a]



Entry	R	Product	Time (min)	Yield[b] (%)
				
1	**2:** X= -H	**2a**	25	95
2	**3:** X= $-NO_2$	**3a**	50	85
3	**4:** X= $-OCH_2Ph$	**4a**	15	92
4	**5:** X= $-OCH_2CH{=}CH_2$	**5a**	30	82
5	 **6**	**6a**	20	95
6	 **7**	**7a**	35	83
7	 **8**	**8a**	40	80
				
8	**9:** X= $-CH_3$	**9a**	80	82
9	**10:** X= -Cl	**10a**	100	78
10	 **11**	**11a**	150	72
11	$CH_3(CH_2)_3$– **12**	**12a**	210	60[c]
12	$CH_3(CH_2)_5$– **13**	**13a**	240	55[d]
				
13	**14:** X= -H	**14a**	110	75
14	**15:** X= $-CH_3$	**15a**	90	80

[a] Reactions were carried out on 1−10 mmol scale using 2.5 equiv of IBX and TEAB in acetonitrile at 60 °C. [b] Yield of chromatographically isolated compound. Some starting material was recovered; however, the quantity is only specified when it exceeds 20%. [c] Plus 20% recovered starting material. [d] Plus 26% recovered starting material.

With this result, we then turned our attention to secondary and tertiary amides, as shown in Table 4. When we performed the reaction with secondary amide under the established reaction condition, it led to benzylic oxidation (entry 1),[11] whereas tertiary amides remained unaffected under the reaction condition (entries 2 and 3).

If this reaction proceeds through Hofmann rearrangement, followed by dehydrogenation, the corresponding isocyanate should be an intermediate, as was the case with trivalent iodine compounds.[6] The isocyanate survives long enough to be isolated because it hydrolyzes somewhat slower than it is formed.[12] While performing the reaction with benzene acetamide in acetonitrile as well as *tert*-butanol, the formation of corresponding isocyanate or *tert*-butylurethane[13] was never observed. In an effort to probe the mechanism, authentic *N*-bromobenzene acetamide[14] and benzyl isocyanate[15] were synthesized and subjected to established reaction conditions, and benzonitrile **2a** was produced in 90 and 93% yields, respectively (Table 5, entries 1 and 2).

On the basis of these investigations, we propose a plausible reaction pathway, as shown in Scheme 1. Addition of TEAB

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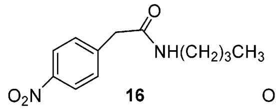
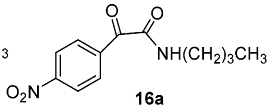
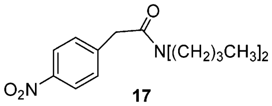
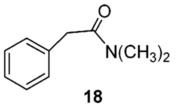
(11) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

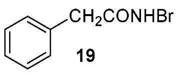
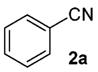
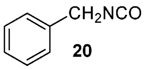
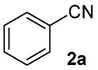
(12) Boutin, R. H.; Loudon, G. M. *J. Org. Chem.* **1984**, *49*, 4277.

TABLE 4. IBX/TEAB-Mediated Oxidation of Substituted Amides[a]

Entry	Substrate	Product	Time (min)	IsolatedYield (%)
1	 **16**	 **16a**	300	50
2	 **17**	NR[b]	300	--
3	 **18**	NR[b]	300	--

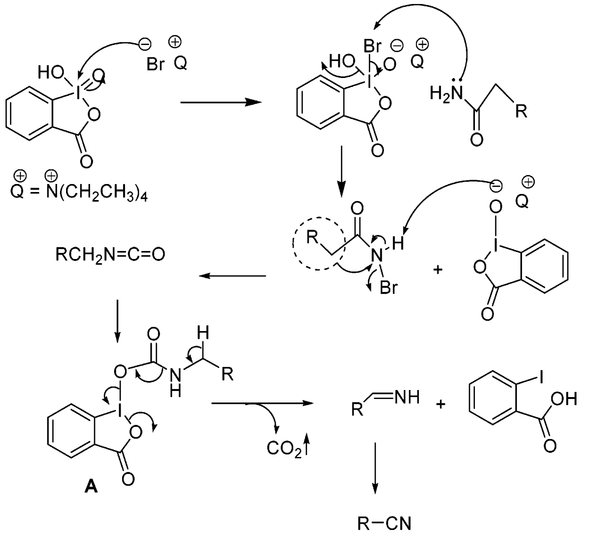
[a] Reactions were carried out on 1−5 mmol scale using 2.5 equiv of IBX and TEAB in acetonitrile at 60 °C. [b] NR = No reaction.

TABLE 5. IBX/TEAB-Mediated Reactions with Postulated Intermediates[a]

Entry	Substrate	Product	Time (min)	IsolatedYield (%)
1	 **19**	 **2a**	15	90
2	 **20**	 **2a**	05	93

[a] Reactions were carried out on 5 mmol scale using 2.5 equiv of IBX and TEAB in acetonitrile at 60 °C.

SCHEME 1. Postulated Mechanism for the IBX/TEAB-Mediated Oxidative One-Carbon Dehomologation of Primary Carboxamide to Nitrile



to IBX causes the oxidation of amide to *N*-bromoamide, which on subsequent rearrangement forms isocyanate. Nucleophilic attack by oxygen of IBA to isocyanate gives the intermediate (**A**), which subsequently decomposes to give imine, carbon dioxide, and *o*-iodobenzoic acid. Imine on further rapid oxidation gives nitrile.

In summary, we have developed an efficient and novel method for oxidative transformations of primary carboxamides to one-carbon dehomologated nitriles using the combination of IBX and TEAB. This method possesses high functional group tolerance under the reaction conditions. By using this combination, a series of amides could be dehomologated to nitriles. This method exhibits a broad scope, affords clean product in moderate to high yields, and will be of great utility in organic synthesis. Further investigations are in progress to expand the scope of reaction and gain the mechanistic understanding of the process.

Experimental Section

General Experimental Procedure for the Preparation of One-Carbon Dehomologated Nitriles. To a stirred suspension of IBX (2.5 equiv) in CH_3CN was added TEAB (2.5 equiv). A yellow suspension was observed to which amide (1−10 mmol) was added in one portion after 5 min. The reaction mixture was stirred at 60 °C until complete consumption of starting material as observed by TLC. Acetonitrile was removed under reduced pressure, and the resultant residue was extracted with EtOAc, and the organic layer was washed with 10% sodium bisulfite solution, saturated sodium carbonate, and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated to give crude nitrile. Pure nitrile was isolated after column chromatography (silica gel mesh size 60−120).

Typical Experimental Procedure for 4-Benzyloxybenzonitrile (4a). To a stirred suspension of IBX (3.50 g, 12.5 mmol) in CH_3CN (50 mL) was added TEAB (2.62 g, 12.5 mmol). A yellow suspension was observed to which 4-benzyloxybenzene acetamide

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(13) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.

(14) Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* **1984**, *12*, 2045.

(15) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430.

4 (1.20 g, 5 mmol) was added in one portion after 5 min. The reaction mixture was stirred at 60 °C until complete consumption of starting material as observed by TLC. Acetonitrile was removed under reduced pressure, and the resultant residue was extracted with EtOAc (50 mL) and the organic layer was washed with 10% sodium bisulfite solution (2 × 50 mL), saturated sodium carbonate (2 × 50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give crude nitrile **4a**. Silica gel column purification afforded pure nitrile **4a** (0.96 g, 92%) as a white solid. mp 87−89 °C. $R_f = 0.78$ (silica gel EtOAc/hexane, 5:95). IR (KBr) $\nu_{\max}$ (cm^{-1}): 2221 (CN). ^{1}H NMR (60 MHz, CDCl$_3$): δ 7.54 (d, $J = 8.5$ Hz, 2H), 7.32 (s, 5H), 6.95 (d, $J = 8.5$ Hz, 2H), 5.09 ppm (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 161.9, 125.6, 133.9, 128.7, 128.3, 127.3, 119.1, 115.5, 105.1, 70.9 ppm; elemental analysis calcd for $C_{14}H_{11}NO$: C, 80.38; H, 5.26; N, 6.69. Found C, 80.38; H, 5.27; N, 6.70.

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Supporting Information Available: General methods and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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