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Oxidative decarboxylation of α-amino acids to nitriles using *o*-iodoxybenzoic acid in aqueous ammonia*

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Abstract: Formation of the nitrile was the outcome of the investigation of biochemically significant oxidative decarboxylation of amino acids using *o*-iodoxybenzoic acid (IBX) in aqueous ammonia system.

Keywords: amino acids; decarboxylation; *o*-iodoxybenzoic acid; nitrile; oxidation.

INTRODUCTION

Oxidative decarboxylation of α-amino acids is an important metabolic transformation in a variety of organisms. It finds applications in biochemistry and peptide cleavages [1], such as reaction of coenzyme pyrroloquinolinequinone (PQQ) and amino acids [2], decarboxylation of certain *N*,*N*-dialkylamino acids toward selective generation of synthetically useful enamine functions in specific positions of given molecules [3], and decarboxylative functionalization of α-amino acids for construction of useful motifs [4]. It is also a reaction of significance in understanding the action of chlorine components as sanitizers in food industry [5]. Because of its importance, this transformation in the field of synthetic organic chemistry and biological chemistry has attracted the attention of chemists.

Many reagents have been investigated toward oxidative decarboxylation of α-amino acids, which give nitrile or a mixture of nitrile and aldehyde as the products depending on reaction conditions and reagents employed [6,7]. Oxidation with 1-chlorobenzotriazole (CBT) [6a] and trichloroisocyanuric acid [6b,c] nitriles were formed in the range of 90–99 %, whereas lower yields (53–83 %) were observed with copper(II) bromide-lithium *tert*-butoxide [6d] reagent. However, oxidation with other oxidizing agents such as sodium hypobromite [7a], *N*-bromosuccinimide [7b,c], *t*-BuOCl [7d], chloramine-T [7e,f], enzyme bromoperoxidase [7g], and electrolytic method using silver electrode [7h], a mixture of aldehydes and nitriles was formed in varying ratios depending on reaction conditions employed.

Hypervalent iodine(III) reagents have been investigated for the oxidative decarboxylation. Reaction with [1,1-bis(trifluoroacetoxy)iodo]benzene/pyridine [8a] reagent, a mixture of aldehyde and nitrile was formed in different ratios depending on the reaction conditions whereas with the iodosobenzene diacetate/iodine [8b] system, decarboxylative β-iodination occurred. The oxidative decarboxylation has been studied using $(PhIO)_n$ as oxidant but only with cyclic amino acids as substrates to give

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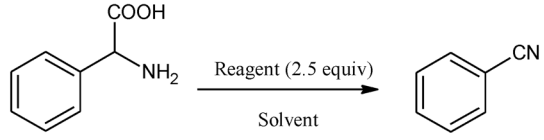
lactams as products [8c]. Similar oxidations attempted on amino acids tyrosine and tryptophan with iodosobenzene diacetate resulted in formation of 4-(methoxymethyl)phenol and 3-(methoxymethyl)-1*H*-indole, respectively [8d,e].

Hypervalent iodine(V) reagents, especially *o*-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP), are of current interest, and using them in a variety of oxidative transformations is being reported as evidenced by recent reviews [9]. Mild, selective, and wide reactivity spectrum of IBX is responsible for its popularity as oxidant in the synthesis of complex natural products and, in general, synthetic organic chemistry [10]. Our research group is actively investigating oxidative transformations using IBX and DMP [11]. IBX being acid is readily soluble in aqueous ammonia and is very stable. Recently, we have reported a facile transformation of aldehyde to nitrile in almost quantitative yield using IBX in aqueous ammonia exploiting fast oxidation of aldimines by IBX [11c,12]. Considering the importance of oxidation of α-amino acids and current interest in hypervalent iodine(V) reagents and facile conversion of aldimines to nitrile by IBX in aqueous ammonia systems, we investigated hypervalent iodine(V) reagents, particularly IBX in aqueous ammonia, for the oxidative decarboxylation. The results are presented here.

RESULT AND DISCUSSION

Preliminary experiments were carried out using α-phenylglycine **1a** as model substrate, and results are summarized in Table 1. α-Phenylglycine **1a** was treated with IBX in aqueous ammonia at rt for 12 h but reaction did not occur. The experiment was repeated at elevated temperature, and at 75 °C the reaction occurred rapidly, yielding 95 % of benzonitrile **2a** in just 30 min (Table 1, entries 1 and 2). To ascertain the role of ammonia, an experiment was conducted with only water as solvent and as expected practically there was no reaction even at 75 °C and this was attributed to insolubility of IBX in water, because when a cosolvent such as dimethylsulfoxide (DMSO) was added, the reaction occurred giving a mixture of benzonitrile and benzaldehyde (Table 1, entries 3–5).

Table 1 Optimization of reagent and reaction conditions.[a]



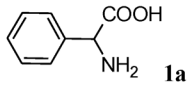
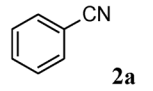
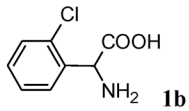
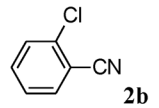
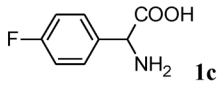
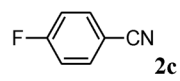
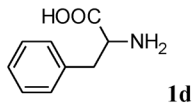
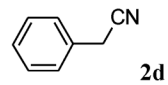
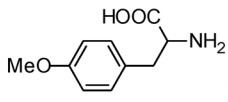
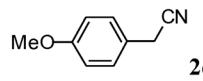
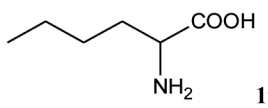
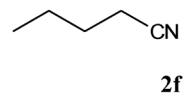
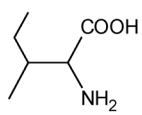
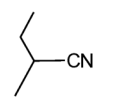
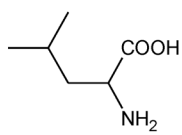
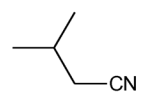
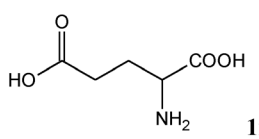
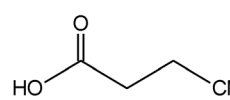
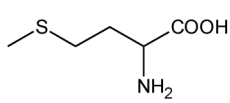
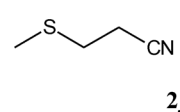
1a **2a**

Entry	Reagent/solvent	Temperature (°C)	Time (min/h)	Yield (%)[b] **2a**
1	IBX/aqueous ammonia	rt	12 h	NR[c]
2	IBX/aqueous ammonia	75	30 min	95
3	IBX/water	rt	12 h	NR[c]
4	IBX/water	75	7 h	NR[c]
5	IBX/DMSO:water	rt	1 h	80[d]
6	DMP/aqueous ammonia	75	45 min	89

[a]Reaction performed on 5 mmol of **1a**.
[b]Yields obtained after column chromatography.
[c]NR = No reaction.
[d]5 % of benzaldehyde was isolated.

Therefore, it can be concluded that the aqueous ammonia is playing the dual role of a solvent and as well as favoring equilibrium toward aldimine intermediate, leading to nitrile as the sole product

Table 2 Oxidative decarboxylation of α-amino acids to corresponding nitriles.[a]

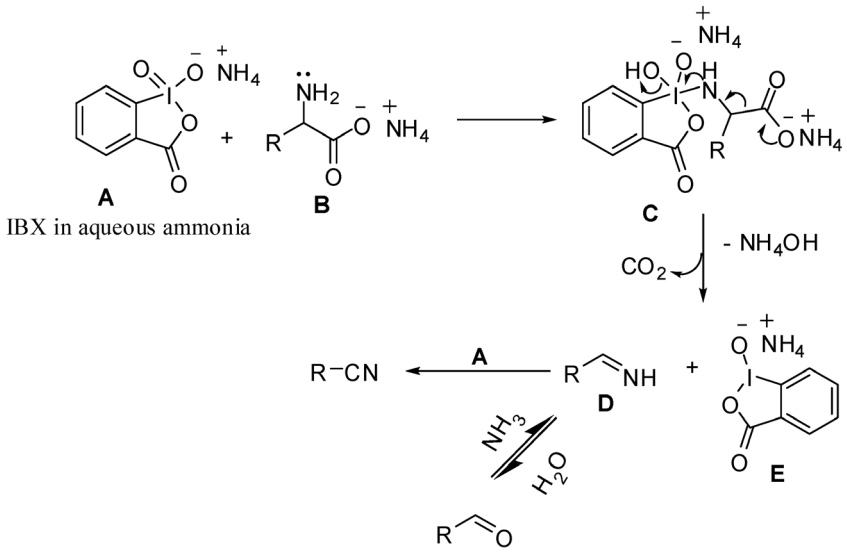
Entry	Substrate **1**	Product **2**[b]	Time (min)	Yield (%)[c]
1	 **1a**	 **2a**	35	95
2	 **1b**	 **2b**	40	86
3	 **1c**	 **2c**	40	84
4	 **1d**	 **2d**	45	85
5	 **1e**	 **2e**	50	85
6	 **1f**	 **2f**	65	87
7	 **1g**	 **2g**	60	90
8	 **1h**	 **2h**	60	90
9	 **1i**	 **2i**	60	70[d]
10	 **1j**	 **2j**	75	80

[a]Reactions were carried out on 5 mmol scale in aqueous ammonia at 75 °C with IBX (2.5 equiv).
[b]All products obtained were known compounds and were characterized by IR, ^{1}H NMR and compared with standard.
[c]Yields by column chromatography.
[d]Isolated as ethyl ester.

instead of a mixture of aldehyde and nitrile [12]. DMP was also found to be viable for the reaction, and results were similar (Table 1, entry 6).

To study generality and chemoselectivity, a variety of α-amino acids were subjected to the reaction conditions, and the results are summarized in Table 2. The results indicate that reaction was comparatively fast with arylglycines (Table 2, entries 1–3) as compared to alkylglycines (Table 2, entries 6–10). In the case of arylalkyl glycines, the reaction was equally facile and a noteworthy feature is that the benzylic position remained unaffected (Table 2, entries 4 and 5). Both glutamic acid **1i** and methionine **1j** underwent smooth transformation to give corresponding nitriles with intact carboxylic acid and thioether moieties, respectively (Table 2, entries 9 and 10), indicating chemoselectivity.

Mechanism postulated for the transformation is depicted in Scheme 1 where IBX–amino acid adduct **C** formed in the first step undergoes decarboxylation to form aldimine intermediate **D** and which on subsequent oxidation gives nitrile [12]. Because of the high concentration of ammonia, equilibrium is favored toward aldimine leading to formation of nitrile as the sole product instead of a mixture of aldehyde and nitrile as observed in the case of hypervalent iodine(III) reagent system, [1,1-bis(trifluoroacetoxy)iodo]benzene/pyridine and others.



Scheme 1 Postulated mechanism for oxidative decarboxylation of amino acids to nitriles.

CONCLUSION

In conclusion, it can be said that IBX in aqueous ammonia brings about chemoselective and rapid oxidative decarboxylation of α-amino acids to produce nitriles as sole product in very high yields. Aqueous ammonia plays a dual role as a solvent for IBX and favoring equilibrium toward aldimine so that formation of aldehyde is avoided.

SUPPLEMENTARY INFORMATION

Experimental procedure and characterization of compounds can be found in the supplementary information, which is available online (doi:10.1351/PAC-CON-10-09-15).

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