

Selective Oxidation of Hydrazides Using *o*-Iodoxybenzoic Acid to Carboxylic Acids, Esters, and Aldehydes

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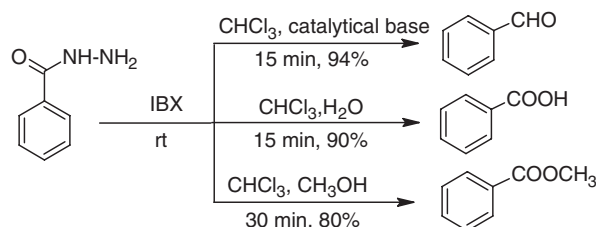
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A selective method for conversion of hydrazide to corresponding aldehydes, acids, and esters by using hypervalent iodine reagent *o*-iodoxybenzoic acid (IBX) has been developed under different reaction conditions. The developed method is mild and gives moderate to good yields for both aliphatic and aromatic substrates.

Hydrazides are important intermediates required in protection and deprotection of carboxylic acids in peptide chemistry.¹ However, potential utility and applicability as a protecting group are diminished considerably owing to high hydrolytic stability. Hence, much less work has been done for deprotection of hydrazide and thus deprotection of hydrazide to the corresponding acid using mild conditions is of great interest. Similarly there are few methods reported for the conversion of aldehydes and esters from corresponding hydrazides. Previous methods for all these conversions included use of acidic resin,² benzeneseleninic acid anhydride,³ copper(II) catalyst,⁴ enzymatic cleavage,⁵ lead tetraacetate,⁶ oxone,⁷ ceric ammonium nitrate,⁸ NaBH₄/copper chloride,⁹ and thallium(III) in acidic medium,¹⁰ however, all these methods require either toxic metals or tedious work up procedure. Hypervalent iodine reagents have found widespread applications in organic synthesis because of their selectivity and simplicity in use.¹¹ Ever since the innovative work by Dess and Martin,¹² explorations into the chemistry of pentavalent iodine compounds have become the subject of growing interest due to their mild nature. Our group has been working extensively on the development of novel methodologies under mild reaction conditions using various hypervalent iodine reagents like *o*-iodoxybenzoic acid (IBX).¹³ Recently efficient cleavage of *N,N'*-dimethylhydrazide has been reported by using PhI(OH)Ts to corresponding acids, however, no attempts have been made to prepare aldehydes and esters from corresponding *N,N'*-dimethylhydrazides.¹⁴

Herein we report for the first time a new application of IBX for oxidative conversion of hydrazides into corresponding aldehydes, acids, and esters. During our reaction study we found that hydrazides can be converted selectively into corresponding carboxylic acids, esters, and aldehydes under different reaction conditions using IBX at room temperature in short reaction time. We carried out reactions using benzohydrazide as a model substrate (Scheme 1). In the first case, benzohydrazide was converted into benzaldehyde by using different organic and inorganic bases in chloroform (Table 1). The reactions were carried out by using 0.1 equivalent base in 15 min at room temperature and it was observed that liquor ammonia is suitable base for this conversion.

In the second case, the presence of a methanol and chloroform mixture (1:1) reaction gave methyl benzoate. In



Scheme 1. Conversion of benzohydrazide into benzaldehyde, benzoic acid, and methyl benzoate using IBX at room temperature.

Table 1. Effect of different base on formation of benzaldehyde from benzohydrazide^a

Entry	Base	Yield ^b /%
1	Ammonia	94
2	Pyridine	80
3	Triethylamine	90
4	NaOH	50
5	NaOMe	35

^aReaction conditions: benzohydrazide (1 equiv), IBX (1 equiv), and base (0.1 equiv); 15 min. ^bIsolated yield by column chromatography.

the presence of neat methanol as a solvent reaction does not take place, due to the insolubility of IBX, thus combination of methanol and chloroform is required. In the third case, combination of chloroform and water (1:1) gives benzoic acid as a product. All these reactions give quantitative yield in short reaction time. We also observed that higher esters are possible when higher alcohols are used. Chloroform can be replaced by dichloromethane and acetonitrile without affecting the results.

In order to explore the reaction scope, a variety of hydrazides were prepared by standard reported procedures and were selectively converted to corresponding aldehydes, carboxylic acid, and esters in moderate to good yields.¹⁵

It was clearly indicated that hydrazides substituted with electron-donating groups like hydroxy or methoxy undergo very fast transformation giving desired aldehydes (Table 2, Entries 2 and 3), carboxylic acid (Table 3, Entries 2 and 3), and esters (Table 4, Entries 2 and 3) in a short reaction time and good yields. On the other hand electron-withdrawing groups such as nitro, comparatively lower yields and slower reaction rate were observed (Table 2, Entry 4; Table 3, Entry 4; and Table 4, Entry 4).

With the same reagent system heterocyclic hydrazides also gave good yields of the corresponding aldehydes, carboxylic acid, and esters, with lower reaction rate (Table 2, Entry 5; Table 3, Entry 5; and Table 4, Entry 5). These reaction systems are also suitable for conversion of aliphatic hydrazides to

Table 2. Aldehyde formation from hydrazides^a

$\text{R}-\text{C}(=\text{O})\text{NH-NH}_2 \xrightarrow[\text{rt, CHCl}_3]{1 \text{ equiv IBX, liquor ammonia}} \text{R}-\text{C}(=\text{O})\text{H}$			
Entry	R	Yield ^b /%	Time /min
1	Ph (1a)	94	15
2	2-HOC ₆ H ₄ (1b)	90	10
3	3,4-(OCH ₃) ₂ C ₆ H ₃ (1c)	93	10
4	4-NO ₂ C ₆ H ₄ (1d)	73	60
5	4-Pyridine (1e)	75	60
6	C ₃ H ₇ (1f)	85	60

^aReaction conditions: substrate (1 equiv), IBX (1 equiv), and liquor ammonia (0.1 equiv). ^bIsolated yield by column chromatography.

Table 3. Carboxylic acid formation from hydrazides^a

$\text{R}-\text{C}(=\text{O})\text{NH-NH}_2 \xrightarrow[\text{rt, CHCl}_3]{2 \text{ equiv IBX, H}_2\text{O}} \text{R}-\text{C}(=\text{O})\text{OH}$			
Entry	R	Yield ^b /%	Time /min
1	Ph (1a)	90	15
2	2-HOC ₆ H ₄ (1b)	92	15
3	3,4-(OCH ₃) ₂ C ₆ H ₃ (1c)	93	10
4	4-NO ₂ C ₆ H ₄ (1d)	75	60
5	4-Pyridine (1e)	75	60
6	C ₃ H ₇ (1f)	87	60

^aReaction conditions: substrate (1 equiv) and IBX (2 equiv).

^bIsolated yield by column chromatography.

Table 4. Ester formation from hydrazides^a

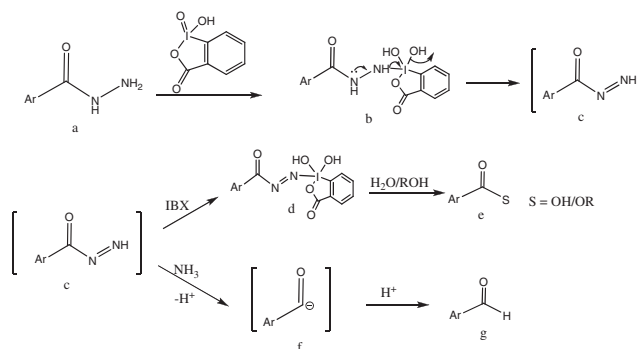
$\text{R}-\text{C}(=\text{O})\text{NH-NH}_2 \xrightarrow[\text{rt, CHCl}_3]{2 \text{ equiv IBX, CH}_3\text{OH}} \text{R}-\text{C}(=\text{O})\text{OCH}_3$			
Entry	R	Yield ^b /%	Time /min
1	Ph (1a)	87	30
2	2-HOC ₆ H ₄ (1b)	85	30
3	3,4-(OCH ₃) ₂ C ₆ H ₃ (1c)	85	25
4	4-NO ₂ C ₆ H ₄ (1d)	75	60
5	4-Pyridine (1e)	70	60
6	C ₃ H ₇ (1f)	85	60

^aReaction conditions: substrate (1 equiv) and IBX (2 equiv).

^bIsolated yield by column chromatography.

aldehydes, carboxylic acid, and esters (Table 2, Entry 6; Table 3, Entry 6; and Table 4, Entry 6).

From the reaction conditions it was observed that one equivalent of IBX is required for the formation of aldehydes, while two equivalent of IBX is needed for the transformation to acids and esters from corresponding hydrazides thus a plausible mechanism for formation of aldehydes, carboxylic acids, and esters is proposed in Scheme 2. The mechanism is on the basis of the McFadyen–Stevens procedure for conversion of aroylhydrazines, through their *N*-benzenesulfonyl derivative into aldehyde.¹⁶ Iodine in a higher oxidation state like (+V) or (+VII) is highly electrophilic, hence nucleophilic attack from hydrazide to iodine takes place easily to form complex (b) which then under-

**Scheme 2.** Plausible reaction mechanism.

goes oxidation to acyldiimide (c), once acyldiimide is formed it can further undergo reaction in two ways; it can attack a second mole of iodine reagent to give an intermediate, which finally undergoes nucleophilic substitution to give corresponding product, while in the second case as acyldiimide is less nucleophilic than hydrazide, in the presence of a catalytic amount of base elimination of a proton and nitrogen gas takes place to give ArCO[−] (f) which further accepts a proton giving an aldehyde.¹⁷

In conclusion, a new reaction system using hypervalent iodine reagent IBX for selective transformation of hydrazide to corresponding aldehydes, carboxylic acids, and esters at different reaction conditions, has been developed. The method developed is mild and gives moderate to good yields for both aliphatic and aromatic substrates.

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