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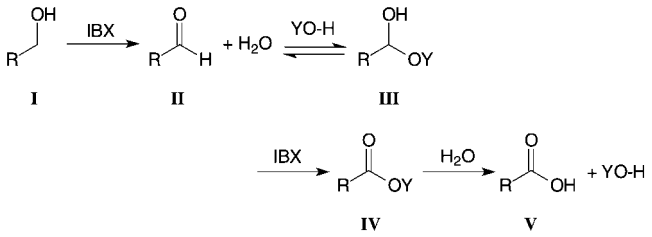
IBX-Mediated Oxidation of Primary Alcohols and Aldehydes To Form Carboxylic Acids**

Ralph Mazitschek, Marcel Mülbaier, and Athanassios Giannis*

Dedicated to Professor Peter Welzel on the occasion of his 65th birthday

During recent years the hypervalent iodine reagent 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide (IBX) was utilized for numerous novel and synthetically valuable oxidative transformations, including, among others, the cyclization of anilides,[1] the preparation of amino desoxy sugars from glycals,[2] the benzylic oxidation of aromatic compounds,[3] and the synthesis of α,β-unsaturated aldehydes and ketones from homologous, saturated precursors.[4]

IBX is safe and easily accessible, and is especially suited to the oxidation of alcohols in homogenous solution to yield the corresponding aldehydes and ketones.[5,6] Recently, analogous reactions using polymer-supported IBX have been reported.[7,8] The transformation of primary alcohols to carboxylic acids has never been observed using IBX. For the first time, we report here that primary alcohols are oxidized easily in the presence of IBX and certain O nucleophiles to give carboxylic acids at ambient temperature in high yields. Starting from the hypothesis that the aldehyde **II**, which is generated from a primary alcohol **I** and an excess of IBX, reacts with suited O nucleophiles (YO-H) to form the intermediate **III**. This intermediate can be oxidized to the corresponding active ester **IV**, which in turn is hydrolyzed to give the desired carboxylic acid **V** (Scheme 1).



Scheme 1. Mechanism of the IBX-mediated oxidation of primary alcohols to give the carboxylic acids.

In our initial attempt 2-hydroxypyridine (**1**, HYP) was used as an O nucleophile. We were pleased to find that, in the presence of 2 equivalents of IBX and 4 equivalents of 2-hydroxypyridine, 1-decanol was oxidized to form decanoic acid in 48 h in 92% yield. A series of other aliphatic alcohols (and aldehydes) was oxidized under the same reaction conditions in high yields to give the carboxylic acid analogues (Table 1). That only catalytic amounts of hydroxypyridine are

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[**] IBX = 1-hydroxy-1,2-benziodoxole-3(1*H*)-one-1-oxide.

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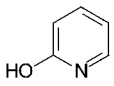
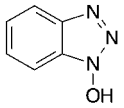
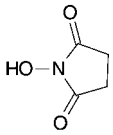


1



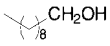
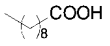
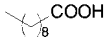
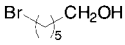
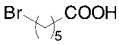
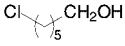
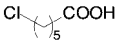
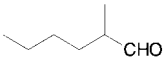
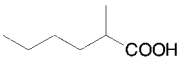
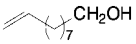
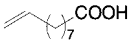
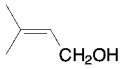
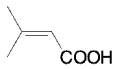
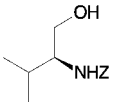
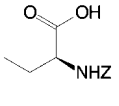
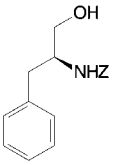
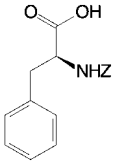
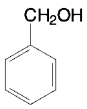
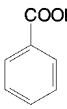
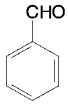
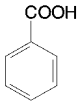
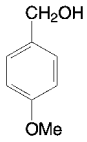
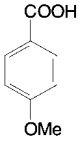
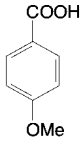
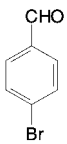
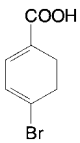
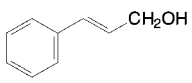
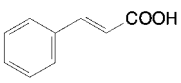
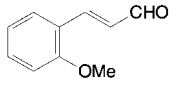
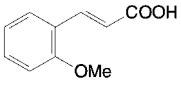
2



3

required for the transformation is consistent with the proposed mechanism, however the reaction times also increase dramatically. Benzaldehyde (and benzylic alcohol) was not oxidized under these conditions. Also the oxidation of 2-decenal (and of 2-decen-1-ol) was not observed. We suppose that 2-hydroxypyridine is insufficiently nucleophilic to form

Table 1. Oxidation of primary alcohols and aldehydes to form carboxylic acids.

Entry	Substrate	Method	Product	Ratio A:AE[a]	Yield[b] of A [%]
1		HYP		–	91
2		NHS		1:10	80
3		HYP		–	91
		NHS		1:10	40
4		HYP		–	85
5		HYP		–	74
6		NHS		1:10	67
7		NHS		0:1	64
8		HYP		–	90
		NHS		1:10	40
9		HYP		–	79[c]
10		HYP		–	85[c]
11		NHS		2:3	79
12		NHS		1:2	93
13		NHS		1:4	76
14		NHS		1:2	90
15		NHS		1:1	68
16		NHS		1:0	64
17		NHS		1:0	95

[a] A: acid, AE: active ester. [b] Yield of product isolated. [c] The enantiomeric purity was determined by chiral HPLC.[10]

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the semiacetals of type **III** with these compounds. Therefore we decided to test 1-hydroxybenzotriazole (**2**, HOBT), as its hydroxy group shows an increased nucleophilic character, caused by the α effect. Actually, using benzaldehyde, IBX, and HOBT (1:1:1) we were able to detect the formation of benzoic acid within a few minutes. However, the yield was only 20%. The reason for this is the decomposition of **2** under the reaction conditions. To circumvent this problem, we decided to substitute HOBT with *N*-hydroxysuccinimide (NHS) **3**, because this compound is stable to IBX. Indeed, we could oxidize aromatic aldehydes as well as α,β-unsaturated aldehydes to the corresponding carboxylic acids. Identical products were obtained from benzyl and allyl alcohols. Aliphatic aldehydes were also oxidized to form carboxylic acids. Interestingly, the NHS-mediated oxidation yielded the preparatively valuable active esters (*O*-succinimidyl) in most cases.[9] This observation endorses the mechanism postulated in Scheme 1. The addition of water (approximately 10 vol%) did not influence the reaction. The hydroxypyridine and the NHS-mediated methods both tolerate a wide variety of functional groups, such as isolated and conjugated double bonds, alkyl halogenides, urethanes, and electron-rich and -poor aromatic compounds. Starting from *N*-protected α-amino alcohols, the corresponding amino acids can be generated without racemization.[10]

In the past, various highly efficient methods for oxidizing alcohols to give carboxylic acids have been developed. However, all of these methods have inherent disadvantages.[11–14] For example, using the TEMPO/NaOCl/$NaOCl_2$ method, electron-rich aromatic alcohols are scarcely oxidized and the chlorination of the aryl ring is often a side reaction. Double bonds require special reaction conditions. Similar is true for the Sharpless-Katsuki-method as well as for the recently reported Pd-mediated oxidation of alcohol groups to give carboxylic acids.

Our method is mild, efficient, and avoids the use of toxic metals. It is compatible with various functional groups and the iodosobenzoic acid can be separated from the reaction mixture and easily reoxidized to form IBX.

Experimental Section

HYP method: IBX (2.6 equiv, 13 mmol; 1.6 equiv of IBX or 8 mmol, when starting from the aldehyde) were dissolved in DMSO (10 mL). The alcohol/aldehyde (5 mmol) was added in a single portion at room temperature. After oxidation of the alcohol (in most cases after 10–20 min) of HYP (5 equiv, 25 mmol) was added and the reaction mixture was stirred for an additional 72 h. It is not necessary to exclude moisture and oxygen. For the workup semisaturated $NaHCO_3$ solution (50 mL) was added and the reaction mixture extracted with diethyl ether (2 × 30mL). The iodosocarboxylic acid, which precipitated as an off-white amorphous solid, was removed by filtration. After acidification to pH 1 with 10% sulfuric acid, the aqueous phase was extracted (3 × 50 mL) with diethyl ether. The combined organic phases were washed once with a 5% $KHSO_4$ solution and dried over Na_2SO_4. The solvent was removed under reduced pressure, to leave the acid containing traces of iodobenzoic acid. Analytically pure product was obtained by column chromatography on silica gel.

NHS method: IBX (2.6 equiv, 13 mmol; 1.6 equiv of IBX or 8 mmol starting from the aldehyde) were dissolved in DMSO (15 mL). The alcohol/aldehyde (5 mmol) was added in a single portion at room temperature. After oxidation of the alcohol to the aldehyde, *N*-hydroxysuccinimide (5 equiv, 25 mmol) was added slowly so that the temperature did not exceed 30 °C. The reaction mixture was stirred over 16 h.

To isolate the active esters, semisaturated $NaHCO_3$ solution (50 mL) was added. After stirring for 5 min the reaction mixture was extracted (3 × 50 mL) with diethyl ether. The iodosocarboxylic acid, which precipitated as an off-white amorphous solid, was removed by filtration. The organic phase was washed once more with 10% $NaHCO_3$ solution (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Analytically pure product was obtained by column chromatography on silica gel.

For isolation of the carboxylic acid, 1N NaOH (50 mL) was added to the reaction mixture and stirring was continued until a clear solution was obtained. This solution was washed with diethyl ether (1 × 50 mL) and acidified with 2N hydrochloric acid to pH 1. The aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed once with 5% $KHSO_4$ solution and dried over Na_2SO_4. The solvent was removed under reduced pressure. Analytically pure product was obtained by column chromatography on silica gel.

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