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Oxidative Decarboxylation of α-Amino Acids: A Mild and Efficient Method for the Generation of *N*-Acyliminium Ions

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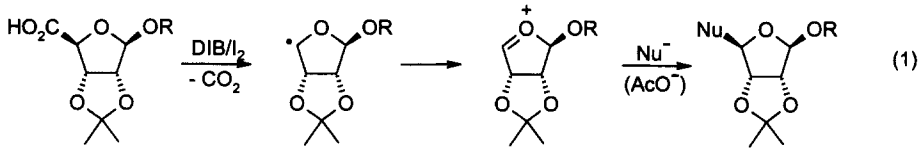
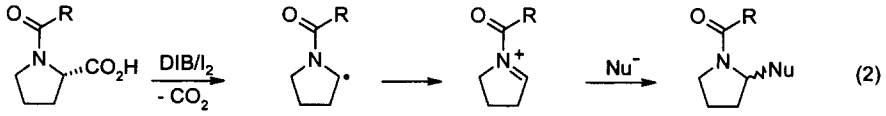
Abstract: The oxidative decarboxylation of α-amino acids using the system (diacetoxyiodo)benzene or iodosylbenzene and iodine proceeded smoothly at room temperature. The intermediacy of an *N*-acyliminium cation has been demonstrated through intermolecular and intramolecular trapping with nucleophiles.

The replacement of the carboxyl group by a halogen through a radical intermediate (Hunsdiecker reaction) is a useful and selective procedure for the synthesis of halogenated organic substrates.[1] We have introduced the use of hypervalent iodine reagents and iodine in this reaction, and have applied it to steroidal substrates.[2a] We have also studied the decarboxylation of carbohydrate uronic or ulosonic acids,[2b,c] whose mechanism involves radical and ionic stages, as shown in eq 1. Thus, the initial carboxyl radical evolves by loss of CO_2 generating an alkyl radical which is α to an oxygenated function. This radical is oxidized by excess reagent to a cation, and the resulting oxycarbenium ion intermediate can be trapped by nucleophiles (*eg* acetate).





One would expect that the decarboxylation of amino acids using this methodology would also take place by a mechanism similar to that of carbohydrates. Thus, the resulting radical α to nitrogen would evolve to an iminium ion, that could be trapped inter- or intramolecularly by nucleophiles (eq 2). In fact, iminium and *N*-acyliminium ions are highly useful intermediates in organic synthesis.[3] Their generation and trapping with nucleophiles, particularly π-systems, have been used in the preparation of natural and synthetic biologically active molecules.[4] Many of these syntheses use the acid-catalysed heterolysis of hemiaminals or *N*-(α-oxyalkyl)amides. Since our radical oxidative decarboxylation can be carried out under mild, neutral

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Table 1. Conditions for the Decarboxylation-Oxidation Reaction of Amino Acids.[a]

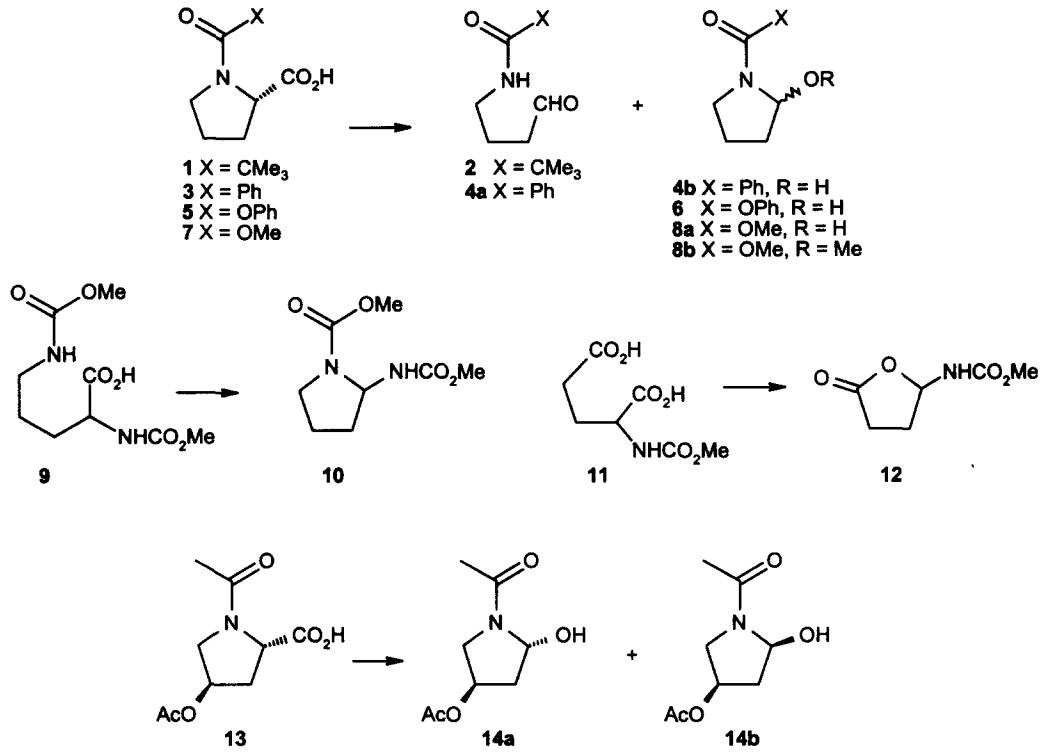
Entry	Acid	Reagent	Iodine (eq)	Solvent	t (h)	Products (%)
1	**1**	PhIO	-	CH_2Cl_2	12	**2** (21)
2	**1**	PhIO	0.5	CH_2Cl_2	3	**2** (82)
3	**1**	PhIO	1	CH_2Cl_2	3	**2** (60)
4	**1**	PhIO	0.5	CH_3CN	2	**2** (81)
5	**1**	DIB	0.5	CH_2Cl_2	2	**2** (83)
6	**1**	DIB	0.5	CH_3CN	1	**2** (84)
7	**3**	DIB	0.5	CH_2Cl_2	4	**4a,b** (66)
8	**5**	DIB	0.5	CH_2Cl_2	3	**6** (95)
9	**7**	DIB	0.5	CH_2Cl_2	2	**8a** (99)
10	**7**	DIB	0.5	CH_2Cl_2	3	**8a** (16) **8b** (80)
11	**9**	DIB	0.5	CH_2Cl_2	4	**10** (89)
12	**11**	DIB	0.5	CH_3CN	1	**12** (66)
13	**13**	DIB	0.5	CH_2Cl_2	2	**14a,b** (80)

[a]All reactions were conducted in dry solvents (15 mL) at room temperature under nitrogen containing PhIO or DIB (2 mmol) and iodine per mmol of acid. The reactions with PhIO were irradiated with a 100 W tungsten filament lamp.

conditions, we considered that it could be an interesting alternative for the generation of *N*-acyliminium ions, compatible with most functional groups.

The conditions for the generation of iminium ions and their subsequent intermolecular trapping by a nucleophile were studied with *N*-(pivaloyl)-L-proline (**1**) (Scheme 1, Table 1). In all cases, the reaction of **1** in the presence of iodosylbenzene (PhIO) or (diacetoxyiodo)benzene (DIB) and iodine (Table 1, entries 2-6) gave γ-amino aldehyde **2** in good yields. The possibility that the oxidative decarboxylation could be due to DIB or PhIO alone could not be ruled out,[5] so a reaction was carried out without iodine (entry 1). While this reaction proceeded very slowly, giving only 21% of the aldehyde **2** after 12 h, in the presence of iodine (entries 2-3) it proceeded quickly in good yields. It is noteworthy that a stoichiometric amount of iodine was not necessary (entry 3). It should also be commented that, unlike the case of oxycarbenium ions, acetonitrile (entries 4 and 6) did not react with the *N*-acyliminium intermediate in a Ritter type-reaction.[2b,6]

The generation of iminium ions and their intermolecular trapping by nucleophiles was further studied with L-proline derivatives **3**, **5** and **7** (Scheme 1). Decarboxylation of *N*-(benzoyl)-L-proline (**3**) (Table 1, entry 7) gave a mixture of the aldehyde **4a** and the corresponding hemiaminal **4b** in 66% yield. Similarly, the reaction with *N*-(phenyloxycarbonyl)-L-proline (**5**) and *N*-(methyloxycarbonyl)-L-proline (**7**) (entries 8-9) also took place with good to excellent yields to give hemiaminals **6** and **8a**, respectively. It is remarkable that ω-amino aldehydes and lactamols are useful synthons, as precursors of ω-amino acids present in pseudo-peptidic drugs.[7] The hemiaminals result from intermolecular trapping of the *N*-acyliminium intermediate with water during the aqueous work-up. However, other nucleophiles can be used instead. For instance, when the reaction of the L-proline derivative **7** was quenched with dry methanol (Table 1, entry 10), 2-methoxypyrrolidine **8b** was obtained in good yield (80%, alongside 16% of **8a**).



Scheme 1

The intramolecular trapping of the *N*-acyliminium ion was studied with L-ornithine and L-glutamic acid derivatives. Thus, decarboxylation of *N,N*-(dimethyoxycarbonyl)-ornithine (**9**) (Table 1, entry 11) afforded the interesting diazoderivative **10** as the sole product, in excellent yield, while that of *N*-(methyloxycarbonyl)-glutamic acid (**11**) (entry 12) proceeded with absolute regioselectivity to give azalactone **12**.

This methodology allows the generation of more complex chiral molecules. For example, decarboxylation of *trans*-4-hydroxy-L-proline derivatives would allow the synthesis of chiral pyrrolidines related to *azasugars*, many of which are biologically active as glycosidase inhibitors.[8] Thus, *trans*-4-hydroxy-L-proline diacetate (**13**) (Scheme 1) gave a mixture of isomeric hemiaminals **14a-b** in 80% yield, in a ratio of 1:2. Isomers **14a-b** could be separated by flash chromatography on silica gel, but interconverted upon standing in chloroform solution at room temperature. The stereochemistry of isomers **14a-b** is given on the basis of their spectroscopic data.

In summary, a mild, high-yield methodology has been developed for the decarboxylation of α-amino acids. The intermediacy of an *N*-acyliminium cation has been demonstrated through intermolecular trapping with water and methanol and intramolecular trapping with carbamate and carboxylate nucleophiles. The application of the present methodology to the synthesis of biologically active products will be reported in due course.

General procedure: A solution of *N*-(methyloxycarbonyl)-L-proline (7) (1.0 mmol) in dichloromethane (15 ml) was treated with DIB (2 mmol) and iodine (0.5 mmol) under nitrogen. After stirring at room temperature for 2 h, the reaction was poured into saturated sodium thiosulphate and extracted with dichloromethane. The organic layer was washed with brine, dried and evaporated under vacuum. The residue was immediately purified by chromatotron chromatography, yielding hemiaminal **8a** (0.99 mmol, 99%).

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