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Tandem oxidative radical decarboxylation-β-iodination of amino acids. Application to the synthesis of chiral 2,3-disubstituted pyrrolidines

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Abstract

A mild and efficient procedure for the tandem decarboxylation-halogenation of α-amino acids is reported. The iodine is introduced at previously unfunctionalized positions, in good yields. The methodology has been used for the diastereoselective synthesis of 2,3-disubstituted pyrrolidines. © 2000 Elsevier Science Ltd. All rights reserved.

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Enantiomerically pure pyrrolidine derivatives are interesting chiral synthons because numerous natural products possess this type of heterocyclic ring system in their structures.[1] Some of these metabolites isolated from a large variety of natural sources are important therapeutic agents in a number of pharmaceutical contexts.[2] Furthermore, substituted enantiomerically pure pyrrolidines have been used as chiral auxiliaries.[3] All these facts have stimulated efforts from natural product and synthetic chemists for the isolation and development of the stereocontrolled synthesis of this class of compounds.[4]

We have recently reported on a new method for the synthesis of *N*-acyliminium ions by oxidative decarboxylation of α-amino acids. The *N*-acyliminium intermediate can be trapped inter- or intramolecularly by different nucleophiles.[5] In further studies on this subject, we were pleased to find that under certain conditions this reaction can be transformed into a new tandem process of decarboxylation-β-iodination, which allows the synthesis of 3-iodinated pyrrolidine and piperidine derivatives (Scheme 1). Thus, when *N*-(methyloxycarbonyl)-L-proline **1a** (Table 1, entry 1) was treated with (diacetoxyiodo)benzene (DIB) and iodine in acetonitrile under the conditions shown in Table 1, 3-iodo-2-hydroxypyrrolidine **3a** was obtained in good yields after aqueous work-up, along with the non-iodinated analog **2a**.

When the reaction was quenched with dry methanol before work-up, 3-iodo-2-methoxypyrrolidine **4a** was obtained as the major product. Only the 2,3-*trans*-disubstituted product was isolated, since the bulky iodine group hinders the approach of the nucleophile from the same face. The reaction also proceeds

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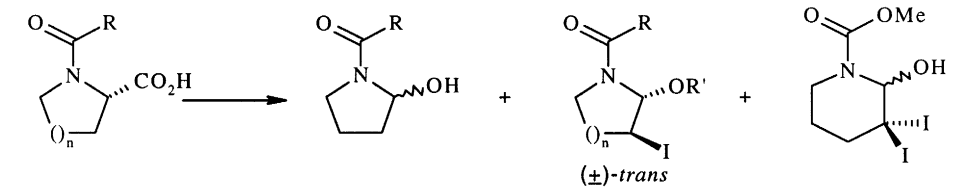


n=1 **1a** R= OMe; **1b** R= OBn; **1c** R= OPh; **1d** R= Ph

2a R= OMe; **2b** R= OBn; **2c** R= OPh; **2d** R= Ph

(±)-*trans*: **3a** R= OMe, R'= H; **4a** R= OMe, R'= Me; **3b** R= OBn, R'= H; **3c** R= OPh, R'= H

n=2 **1e** R= OMe

3e R= OMe, R'= H; **4e** R= OMe, R'= Me

5e

Scheme 1. Oxidative decarboxylation-β-iodination of α-amino acids

Table 1
One-pot decarboxylation-halogenation-nucleophilic addition[a]

entry	acid	iodine (eq)	solvent	time (h)	products (%)[b]
1	**1a**	2	MeCN	5	**2a** (12); **3a** (64)
2	**1a**	2	MeCN[c]	3	**3a** (6); **4a** (62)
3	**1b**	2	MeCN	5	**2b** (8); **3b** (54)
4	**1c**	1.5	MeCN	18	**2c** (6); **3c** (66)
5	**1e**	2	CH_2Cl_2[c]	3	**3e** (9); **4e** (62)
6	**1e**	2	MeCN	5	**3e** (9); **5e** (36)

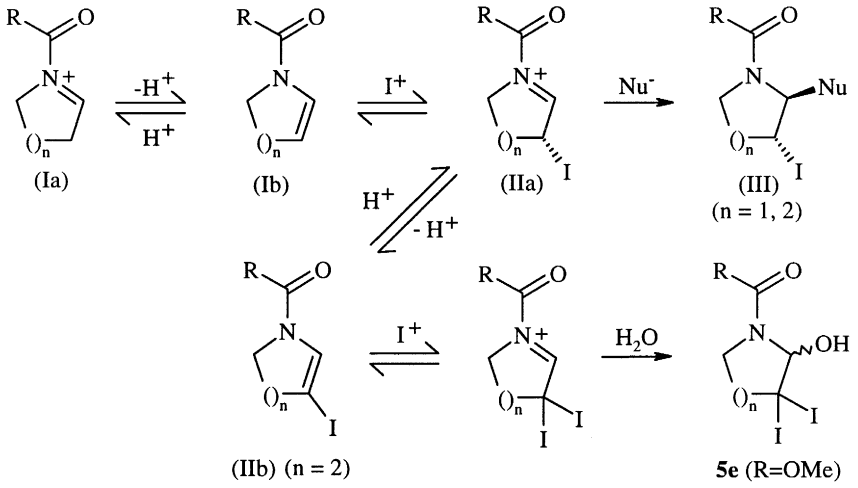
[a] The reaction was conducted at room temperature under nitrogen and sunlight irradiation. Two equivalents of DIB were used. After the time noted, the reaction was poured into aq. $Na_2S_2O_3$ and extracted with CH_2Cl_2.
[b] Yields are for products isolated after chromatography on silica gel. All products were completely characterised by ^1H NMR, ^{13}C NMR, IR, mass spectrometry and elemental analysis.
[c] The reaction was quenched with dry methanol, and stirred for 1h before work-up.

with good yields with other proline carbamates, such as compounds **1b–c** (entries 3 and 4), although the halogenation process requires longer times with the phenyl carbamate group. However, using an amide derivative, such as **1d**, only the non-iodinated product **2d** was isolated, even after extended reaction times.

To extend further the scope of the reaction, we have investigated the feasibility of applying this methodology to the synthesis of 3-iodopiperidine derivatives. The decarboxylation of L-pipecolinic acid methyl carbamate **1e** (Scheme 1) proceeded even in CH_2Cl_2 (Table 1, entry 5). After quenching with dry methanol (entry 5) *trans*-3-iodo-2-methoxypiperidine **4e** was obtained in good yield. Interestingly, a 3,3-dihalogenated compound **5e** was formed when acetonitrile was used as solvent (entry 6).

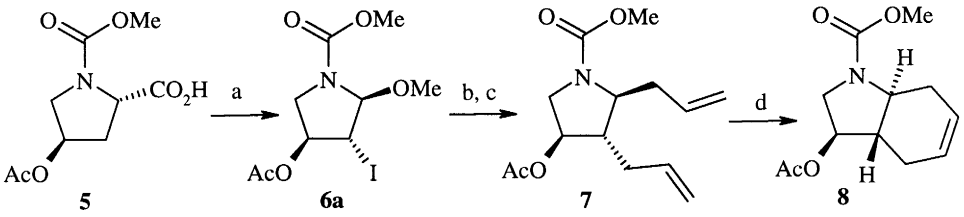
A plausible mechanism for this tandem decarboxylation-iodination is outlined in Scheme 2. Each step of the sequence must proceed in excellent yield to account for the observed overall yields. The first step involves an equilibrium between the *N*-acyliminium ion (**Ia**) formed initially and its enecarbamate (**Ib**), which is subsequently halogenated by the excess of iodine present in the medium. The iodinated *N*-acyliminium ion (**IIa**) can then be trapped by nucleophiles (e.g. methanol) to give (**III**). Alternatively, (**IIa**) may equilibrate with (**IIb**); the iodination of the latter accounts for the formation of **5e**. The acid-catalyzed equilibrium *N*-acyliminium–enamide has been observed as an important side reaction in *N*-acyliminium ion chemistry, leading in most cases to undesired dimeric products.[6] The halogenation of enamides/carbamates has also been described and proven useful in the synthesis of natural products.[7]

When we applied this methodology to the commercially available *trans*-4-hydroxy-L-proline derivative **5**, two isomeric monoiodinated compounds **6a** (2*S*,3*R*,4*S*) and **6b** (2*R*,3*S*,4*S*) were obtained in



Scheme 2. Proposed mechanism for the formation of iodinated products

moderate overall yield (Scheme 3). Compounds **6a** and **6b** are interesting chiral synthons from which 3- or 2,3-substituted pyrrolidines can be easily prepared.



Scheme 3. Synthesis of chiral 2,3 disubstituted pyrrolidines. (a) (i) DIB, I_2, MeCN, 5 h; (ii) MeOH, TsOH catalytic, 12 h; 53% **6a** (2*S*,3*R*,4*S*): **6b** (2*R*,3*S*,4*S*) 2:1. (b) allyltributyltin, AIBN cat., PhH, 80°C, 92%. (c) allyltrimethylsilane, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 99%. (d) Grubbs' catalyst, CH_2Cl_2, reflux, 95%

To illustrate the synthetic versatility of this methodology we have performed a radical allylation at C-3 and an ionic allylation at C-2 (Scheme 3), both with excellent yields and stereoselectivity, to give the diallylated pyrrolidine **7**. This compound was transformed via a metathesis reaction[8] into the hexahydroindole derivative **8**. The hexa- or octahydroindole ring is present in Amarillidaceae and Sceletium alkaloids[9a] and peptides as Aeruginosins.[9b] The application of the present strategy to the synthesis of bicyclic alkaloids is underway and will be reported in due course.

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References

1. (a) Braekman, J. C.; Daloze, D. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1990; Vol. 6, pp. 421–466. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964. (c) O'Hagan, D. *Nat. Prod. Rep*. **1997**, *14*, 637–651. (d) Elbein, A.; Molyneux, R. I. In *Alkaloids, Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley: New York, 1990; Vol. 5, pp. 1–54. (e) Attygalle, A. B.; Morgan, E. D. *Chem. Soc. Rev.* **1984**, *13*, 245–278.

2. (a) Elliott, R. L.; Kopecka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772–774. (b) Basha, F. Z.; Debernardis, J. F. *Pure Appl. Chem.* **1994**, *66*, 2201–2204. (c) Lin, N.-H.; Carrera Jr., G. M.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542–3553.
3. (a) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp. 64–75. (b) Enders, D.; Klatt, M. *Synthesis* **1996**, 1403–1418. (c) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawadi, S. *Synthesis* **1993**, 298–302. (d) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375–378. (e) Corey, E. J.; Yuen, P.-W.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784–786. (f) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415–7418. (g) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763–769.
4. For some examples, see: (a) Viso, A.; Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 9373–9374. (b) Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G. *Tetrahedron Lett.* **1997**, *38*, 5891–5894. (c) Bardou, A.; Céleriér, J. P.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 8507–8510. (d) Blot, J.; Bardou, A.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Céleriér, J. P.; Lhommet, G.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett.* **1997**, *38*, 8511–8514. (e) Sudau, A.; Nubbemeyer, U. *Angew. Chem., Int. Ed.* **1998**, *37*, 1140–1143. (f) Ungureanu, I.; Bologa, C.; Chayer, S.; Mann, A. *Tetrahedron Lett.* **1999**, *40*, 5315–5318. (g) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979–1985.
5. Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1999**, *40*, 5945–5948.
6. (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Wijnberg, J. B. P. A.; Boer, J. J. J.; Speckamp, W. N. *Rec. Trav. Chim. Pays-Bas* **1978**, *97*, 227–231. (c) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143–148.
7. (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785–3788. (b) Billon-Souquet, F.; Martens, T.; Royer, J. *Tetrahedron* **1996**, *52*, 15 127–15 136 and references cited therein. (d) Matsamura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, *49*, 8503–8512. (e) Shono, T.; Matsumara, Y.; Onomura, O.; Ogaki, M.; Kanazana, T. *J. Org. Chem.* **1987**, *52*, 536–541. (f) Torii, S.; Inokuchi, T.; Akahosi, M.; Kubota, M. *Synthesis* **1987**, 242–245.
8. For recent reviews, see: (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056. (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452.
9. (a) *Dictionary of Alkaloids*; Southon, I. W.; Buckingham, J., Eds.; Chapman and Hall: London, 1989. (b) Murakami, M.; Ishida, K.; Okino, T.; Okita, Y.; Matsuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 2785–2788 and references cited therein.