Pergamon

Tetrahedron Letters 41 (2000) 2899–2902

TETRAHEDRON LETTERS

Synthesis of alkaloids from amino acids via *N*-acyliminium ions generated by one-pot radical decarboxylation–oxidation

Alicia Boto, Rosendo Hernández * and Ernesto Suárez

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Avda. Astrofísico F. Sánchez, 3, CP: 38206 La Laguna, Tenerife, Spain

Received 6 January 2000; accepted 12 February 2000

Abstract

A one-pot methodology for the synthesis of α-substituted nitrogen heterocycles from commercial amino acids has been developed. Good stereoselectivity can be achieved with chiral substituted rings. This procedure has been applied to the synthesis of piperidine, pyrrolidine and indolizidinone alkaloids.

Keywords: radical decarboxylation; *N*-acyliminium ion; alkaloids; nitrogen heterocycles; indolizidinone.

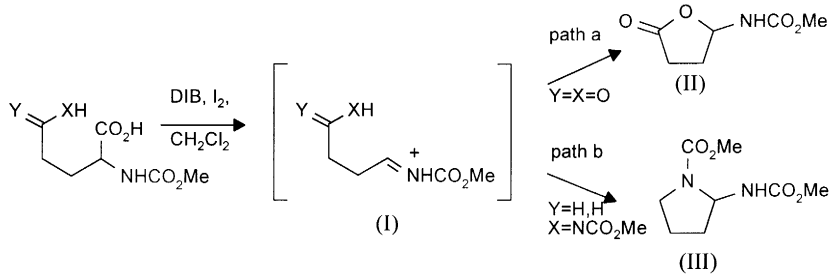
The synthetic utility of *N*-acyliminium ions is widely recognized, and their trapping by carbon nucleophiles has been used in the synthesis of many biologically active products.[1] Accordingly, several methodologies have been developed to generate these ions, such as acid treatment of *N*,*O*-acetals or aminals;[1] treatment of imines with acyl chlorides;[1,2] or electrochemical oxidation of amino or amido derivatives.[1,3] In addition to these, we have recently reported on a mild and operationally simple method based on the tandem radical decarboxylation–oxidation of commercial amino acids.[4] On treatment with (diacetoxyiodo)benzene (DIB) and iodine, an *N*-acyliminium intermediate (I) (Scheme 1) was generated, and trapped in situ with oxygen (path a) or nitrogen (path b) nucleophiles to give (II) or (III), respectively. The reaction proceeded at room temperature with high yields and was applied to the synthesis of azasugar analogues.

We assumed that the use of carbon nucleophiles would broaden the scope of this reaction. The feasibility of this approach and its application to the synthesis of alkaloids are reported herein.

We decided to explore nucleophiles which would be compatible with most common functional groups on the substrate. Allylsilanes and silyl enol ethers seemed ideal for this purpose. Initially, the proline derivative **1a** (Scheme 2) was treated with the system (diacetoxyiodo)benzene (DIB) and iodine to generate the acyliminium intermediate,[4] and after 3 h the reaction was cooled at 0°C and quenched with allyltrimethylsilane (Table 1, entry 1). Disappointingly, in this first attempt the desired allylation

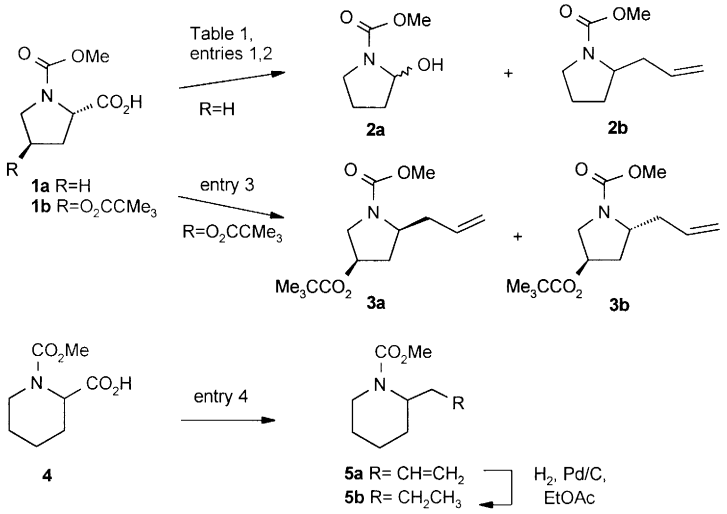
* Corresponding author. Tel: 34 922 251004; fax: 34 922 260135; e-mail: rhernandez@ipna.csic.es (R. Hernández)

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00306-3



Scheme 1. *N*-Acyliminium intermediate trapping by oxygen or nitrogen nucleophiles

product **2b** was not obtained, but rather hydroxypyrrolidine **2a**.[4] However, the problem was solved by adding boron trifluoride–etherate to the reaction mixture (entry 2), yielding the allylproline derivative **2b** in excellent yield after purification by chromatography. The role of the Lewis acid may be double: (a) to regenerate the *N*-acyliminium ion in the event of trapping by nucleophiles (e.g. acetate) in the reaction mixture[3c,5] and (b) to coordinate the carbonyl group on the substrate, increasing the electronic deficiency of the acyliminium intermediate.



Scheme 2. One-pot radical decarboxylation–oxidation addition of allyltrimethylsilane

Table 1
Decarboxylation–oxidation-*N*-acyliminium trapping with allyltrimethylsilane[a]

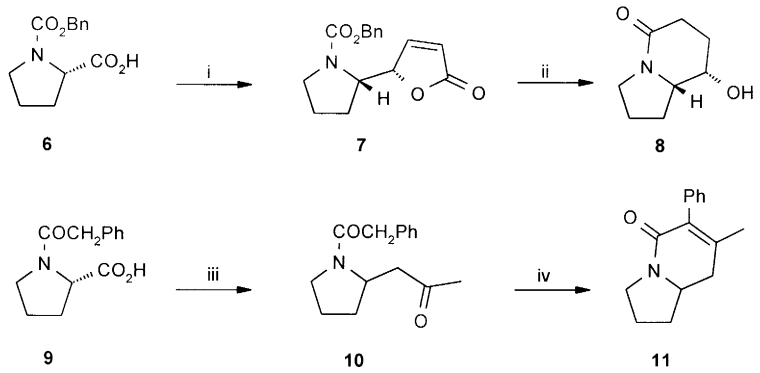
entry	acid	I_2 (equiv.)	BF_3•Et_2O (equiv.)	allyltrimethylsilane (equiv.)	time (h)	products (%)[b]
1	**1a**	0.5	0	10	12	**2a** (89)
2	**1a**	0.5	2	5	4	**2b** (91)
3	**1b**	1.0	2	10	4	**3a** (78), **3b** (13)
4	**4**	0.5	2	5	3	**5a** (67)

[a] The substrate in CH_2Cl_2 was treated with DIB (2 equiv.) and iodine and stirred at rt and under ambient light for 3 h. Then the reaction was cooled to 0°C and allyltrimethylsilane (5 equiv.) was added, followed by BF_3•Et_2O (dropwise). The reaction was allowed to reach rt and then was stirred for the time noted before being poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2.
[b] Given yields are for products purified by chromatography. The ratio of the diastereomers was determined by ^{1}H-NMR

To study the stereoselectivity of the reaction, 4-(trimethylacetyloxy)-L-proline derivative **1b** was treated under the previous conditions (entry 3), giving 78% of the (2*S*,4*R*) diastereomer **3a**, versus 13% of the 2*R* epimer **3b** (91% overall yield, d.r. 6:1). It is noteworthy that the major diastereomer has the *cis*-configuration, opposite to that present in the starting material.[6] Thus, our one-pot methodology is complementary to the elaboration of the allyl substituent from the carboxylic group of the amino acid, which would give **3b**.

The reaction also works well with six-membered rings. Thus, the decarboxylation–allylation of *N*-methyloxycarbonyl pipecolinic acid (**4**) (Scheme 2), afforded (±)-*N*-methyloxycarbonyl-2-allylpiperidine (**5a**) (Table 1, entry 4), which could be quantitatively reduced to (±)-*N*-methyloxycarbonyl coniine (**5b**). (±)-Coniine is the active principle of hemlock poison.[7]

We next applied this methodology to the synthesis of alkaloids with the indolizidine skeleton, many of which have potent biological activity, as inhibitors of glycosidases and as immunoregulatory agents.[8] The synthesis of these alkaloids and analogues is necessary for structure–activity relationship (SAR) studies. Two approaches to the indolizidinone system are shown in Scheme 3.



Scheme 3. (i) DIB (2 equiv.), I_2 (0.5 equiv.), CH_2Cl_2, 3 h, then 2-(trimethylsilyloxy)furan (5 equiv.), $BF_3 \cdot Et_2O$ (1.5 equiv.), 0°C to rt, *threo* **7**:*erythro* 6:1, 66%; (ii) $Pd(OH)_2$, H_2, MeOH, 12 h, 99%; (iii) DIB (2 equiv.), I_2 (0.5 equiv.), CH_2Cl_2, 3 h; then $BF_3 \cdot Et_2O$ (1.5 equiv.), isopropenyl acetate (5 equiv.), 0°C to rt, 4 h, 58%; (iv) ^{t}BuOK, ^{t}BuOH, reflux, 12 h, 98%

Thus, treatment of the acyliminium ion obtained from *N*-benzyloxycarbonyl-L-proline **6** with 2-(trimethylsilyloxy)furan[9] yielded the 2-pyrrolidinyl-2(5*H*)-furanone **7** and its *erythro* diastereomer in a 6:1 ratio and 66% yield.[10] The reduction of the double bond, the removal of the benzyl carbamate group and the cyclization were accomplished in one step, in quantitative yield, by hydrogenation catalyzed by palladium hydroxide in methanol, affording the hydroxyindolizidinone **8**. This constitutes an improved procedure with respect to previous syntheses.[11] The functionalization of the furanone ring prior to hydrogenolysis would broaden the range of available derivatives.

In a second and new approach, proline amide **9** (Scheme 3) was treated with DIB-I_2, followed by isopropenyl acetate and $BF_3 \cdot OEt_2$, yielding the (±)-norhygrine derivative **10** in good yield. Treatment of **10** with base afforded the 6,7-disubstituted indolizidinone **11** in excellent yield. Other substituents can be introduced in the bicyclic system by using derivatized prolines as substrates, and/or by varying the amido and ketone chains, offering a versatile route to other analogues. Further work on the synthesis of indolizidine alkaloids is underway and will be reported in due course.

Acknowledgements

This work was supported by Investigation Programme PB96-1461 of the Dirección General de Investigación Científica y Técnica.

References

1. For general reviews on *N*-acyliminium ions, see: (a) Padwa, A. *Chem. Commun.* **1998**, 1417–1424. (b) De Koning, H.; Speckamp, W. N. In *Methoden der Organischen Chemie*; (Houben-Weyl), Georg Thieme Verlag: Stuttgart, 1995; Vol. E21b, p. 1953. (c) Overman, L. E. *Acc. Chem. Res*. **1992**, *25*, 352–359. (d) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Chemistry*; Trost, B.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p. 1047. (e) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p. 1007. (f) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 32, p. 271. (g) Hart, D. J. In *The Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, p. 227. (h) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (i) Zaugg, H. E. *Synthesis* **1984**, 85–110. (j) Zaugg, H. E. *Synthesis* **1984**, 181–212. (k) Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143–148. (l) Wijnberg, J. B. P. A.; Boer, J. J. J.; Speckamp, W. N. *Rec. Trav. Chim. Pays-Bas* **1978**, *97*, 227–231. See also: (m) Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem*. **1996**, *61*, 314–323. (n) Rigo, B.; El Ghammarti, S.; Couturier, D. *Tetrahedron Lett*. **1996**, *37*, 485–486.
2. (a) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Fujita, K.-i. *Chem. Commun.* **1999**, 2213–2214. (b) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154–1156 and references cited therein.
3. Reviews on electroorganic synthesis: (a) Utley, J. *Chem. Soc. Rev.* **1997**, 157–167. (b) Shono, T. *Tetrahedron* **1984**, 811–850. For recent applications: (c) Yoshida, J.-i.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc*. **1999**, *121*, 9546–9549 and references cited therein.
4. Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett*. **1999**, *40*, 5945–5948.
5. We have noticed that an acetate from the reagent (DIB) reacts with oxycarbenium ion intermediates during the photolysis of carbohydrates: (a) Francisco, C. G.; González, C. C.; Suárez, E. *Tetrahedron Lett.* **1997**, *38*, 4141–4144. (b) de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 772–774.
6. The stereochemistry of **3a** was determined on the basis of its spectroscopic data, including irradiations and 2D-experiments. For a similar result, see: Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704–1710.
7. *Dictionary of Alkaloids*; Southon, I. W.; Buckingham, J., Eds.; Chapman and Hall: London, 1989.
8. (a) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905–917. (b) Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505–522. (c) Michael, J. P. *Nat. Prod. Rep*. **1998**, 571–594 and references cited therein.
9. For a review of trialkylsilyloxyfurans, see: Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–626.
10. Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55–57.
11. (a) Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395–1400. For interesting reviews with related strategies, see: (b) Hanessian, S. *Tetrahedron* **1997**, *53*, 12789–12854. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872.