Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 20, pp. 2461-2464, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00359-9

SYNTHESIS OF *cis*-δ-PHENYLMETHYL-D-PROLINE USING A NITROGEN-CENTERED RADICAL DERIVED FROM A CHIRAL OXAZIRIDINE

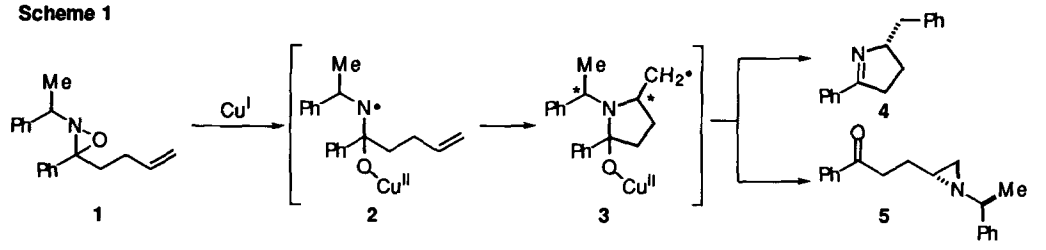
Jeffrey Aubé,* Belgin Gülgeze, and Xin Peng

Department of Medicinal Chemistry
University of Kansas
Lawrence, Kansas 66045-2506

Abstract: Oxaziridines react with Cu(I) salts to afford products resulting from the initial formation of a nitrogen-centered radical/oxygen-centered anion pair. For an α-aryl radical, a chiral pyrrolidine was obtained with high enantioselectivity and was transformed into *cis*-δ-phenylmethyl-D-proline. 3-Carbomethoxy- or 3-(2'-furyl)-substitution gave products resulting from β-cleavage or C→N migration, respectively.

Nitrogen-centered radicals, as generated by various processes, are increasingly useful intermediates in organic synthesis.[1] Oxaziridines react with low-valent metal salts, such as $FeSO_4$, to generate reactive species that are functionally equivalent to nitrogen radical/oxygen anion pairs, as discovered by Emmons[2] and elucidated principally by Minisci.[3] Work from this laboratory[4] recently showed that the treatment of 3-(3'-butenyl)oxaziridines **1** resulted in the formation of species such as **2**, that cyclize to give the carbon-centered radical **3** (Scheme 1). Depending on the relative stereochemistry between the α-methylbenzyl group and the emerging methylene radical substituent, pyrrolidines such as **4** or aziridines **5** were obtained as the ultimate products of these reactions. In either case, the products were obtained with high stereoselectivities (≥95% ee or de for **4** or **5**, respectively) and good yields.

Scheme 1

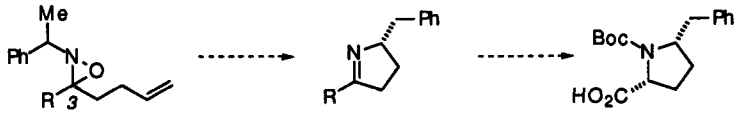


1 2 3

We wished to improve upon the synthetic utility of this reaction by examining oxaziridines with substituents other than phenyl at C-3 (Scheme 2). In particular, we are interested in the synthesis of unnatural amino acids for use in the design of peptides with unusual conformational and biological properties.[5] We chose proline derivative **6** for synthesis because the benzyl group placed at C-5 of the pyrrolidine ring provides an additional hydrophobic binding site. The choice of proline is especially apt because this amino acid residue frequently occupies the *i* + *1* position of a β-turn, a kind of secondary peptide structure often involved in peptide-macromolecule interactions.[6]

In addition, we have discovered that *oxaziridines containing non-aryl substituents at C-3 give products resulting from two additional reaction pathways different from those summarized in Scheme 1.* As was the case with the stereochemically controlled bifurcation to **4** or **5**, each reaction cleanly provides only one or two of the four possible products in good yields and each may have synthetic utility in its own right.

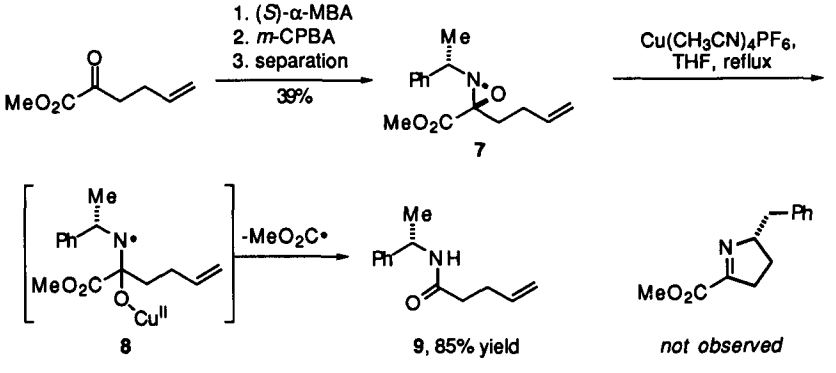
Scheme 2



R = MeO_2C, aryl, heteroaryl 6

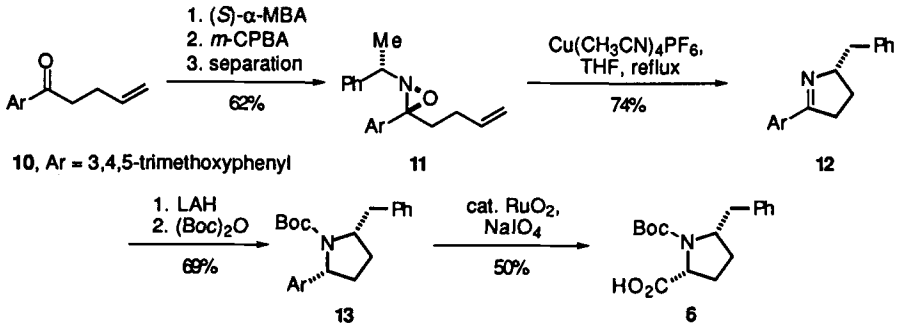
The simplest route to a δ-phenylmethyl-containing proline derivative using this chemistry would be to include a carboxylic acid derivative in the starting oxaziridine . Should the desired pyrrolidine be obtained, reduction and protecting group modification would directly afford the target amino acid. Accordingly, methyl 2-oxo-hex-5-enoate[7] was transformed into the oxaziridine **7**[8] in the usual[4] way: imine formation with (*S*)-α-methylbenzylamine ((*S*)-α-MBA) in refluxing toluene was followed by cooling the reaction mixture to -78 °C and oxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) (Scheme 3). Oxaziridine **7** was isolated from the mixture of stereoisomeric oxaziridines thus obtained in 39% unoptimized yield; the stereochemical structure shown is presumed based on our earlier experience with this type of oxaziridination.[4,9] Treatment of **7** with 1-5 mol % of either $[Cu(PPh_3)Cl]_4$[10] or $Cu(CH_3CN)_4PF_6$[11] gave none of the desired pyrrolidine; instead, amide **9** was obtained in high yield. In this reaction, the radical anion **8** generated by single electron transfer from the Cu(I) salt to the oxaziridine was labile to β-scission.[2,3] The utilization of this mechanistic pathway by intermediate **8** is presumably related to the greater stability of the carbomethoxy radical ($DH°_{298}$ = 86 kcal/mol)[12] versus the phenyl radical ($DH°_{298}$ = 112 kcal/mol).[13] The mechanistic details of this reaction, as yet undefined, are under investigation.

Scheme 3



With the intervention of the β-scission pathway preventing the direct synthesis of the desired 2-carbomethoxypyrroline, we decided to synthesize proline analogue **6** using an aromatic surrogate for the carboxylic acid. It was anticipated that an electron-rich aryl group could be oxidatively cleaved in the presence of another phenyl substituent; we chose a 3,4,5-trimethoxyphenyl group for this purpose (Scheme 4).[14] Ketone **10** was prepared from the dimethylhydrazone of 3,4,5-trimethoxyacetophenone and subjected to oxaziridination as described above. In this case, **11** was isolated in 62% purified yield along with two stereoisomers in 12% and 7% yields, respectively. As expected for isomer **11**,[4] treatment with 1 mol % of $Cu(CH_3CN)_4PF_6$ gave a 74% yield of **12**. The enantiomeric purity of **12** ($[\alpha]_D$ = -91.3 (c = 1.2)) was established to be ≥95% ee by ^1H NMR using 2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent.[15]

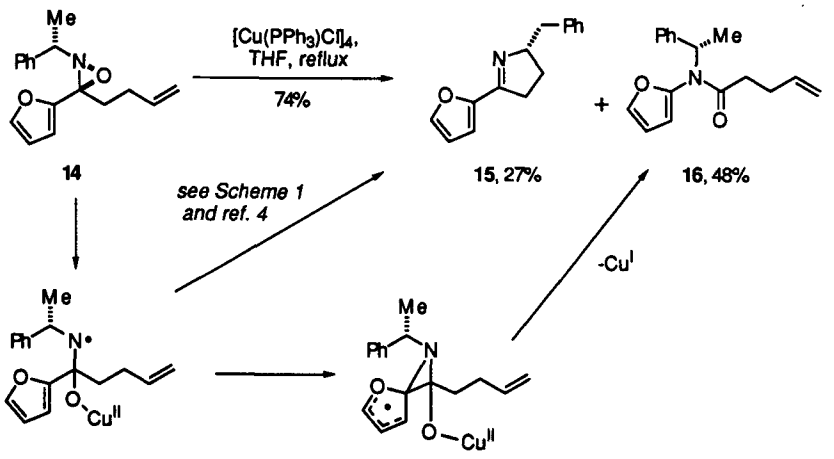
Scheme 4



Having obtained pyrroline **12**, reduction with LAH (78% yield) followed by protection (88%) afforded the *cis*-pyrrolidine **13**. The cis stereochemistry of **13** was anticipated based on the analogous reduction of 3,4-dihydro-2-phenyl-5-phenylmethyl-(5*H*)-pyrrole, established as affording cis product by X-ray crystallography;[4] this result has also been confirmed by an NOE study on **13**. Finally, oxidative demolition of the trimethoxyphenyl group was accomplished using catalytic ruthenium dioxide hydrate and sodium metaperiodate[16] to give **6**.[17] Although we prepared the isomer of **6** corresponding to D-proline, access to the L-series would result from the use of (*R*)-α-MBA in the oxaziridine-forming reaction.

Finally, we also wished to determine whether another carbomethoxy surrogate, such as a 2-furyl group,[18] could be used in place of phenyl for a sequence similar to **11**→**6** (Scheme 5). In this case, treatment of oxaziridine **14**[19] with 5 mol % of $[Cu(PPh_3)Cl]_4$ gave the expected pyrroline **15** in 27% yield. However, the major product was the surprising result of formal C→N migration of the furyl group, amide **16** (48%).

Scheme 5



Such migration reactions are the normal result of oxaziridine photolysis[20] but are much rarer under the "radical" conditions employed herein. In addition, this pathway has been conspicuously absent during our own investigations of oxaziridine-copper(I) chemistry. As a control, oxaziridine **14** was submitted to standard photolysis conditions; many products were obtained in addition to small amounts of **16** that were detected by TLC only. It is possible that **16** arises from the mechanism shown, namely, that the initially formed nitrogen

radical attacks the furyl group to give a resonance-stabilized radical. Carbon-carbon bond cleavage then forms **16** with concomitant ejection of the catalytic copper salt.

In summary, we have shown that 3-aryl-3-(3'-butenyl)oxaziridines are efficient precursors to enantiomerically enriched pyrrolines. The utility of this chemistry has been demonstrated by the synthesis of a derivative of D-proline containing a hydrophobic phenylmethyl substituent at the δ position. In addition, the mechanistic palette of nitrogen radical species obtained by single-electron transfer reactions of oxaziridines has been shown to include fragmentation (β-scission) and migration reactions.

Acknowledgments. This work was supported by the Donors of the Petroleum Research Fund, as administered by the American Chemical Society. JA also gratefully acknowledges the receipt of an Alfred P. Sloan Fellowship. Thanks go to David Vander Velde and Martha Morton for assistance with NMR.

References and Notes

1. (a) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55-64. (b) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337-422. (c) Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1993; Vol. 58; pp 1-45.
2. Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5739-5754.
3. (a) Minisci, F.; Galli, R.; Cecere, M.; Malatesta, V.; Caronna, T. *Tetrahedron Lett.* **1968**, 5609-5612. (b) Minisci, F.; Cecere, M.; Galli, R. *Gazz. Chim. Ital.* **1968**, *98*, 358-366. (c) Minisci, F.; Galli, R.; Malatesta, V.; Caronna, T. *Tetrahedron* **1970**, *26*, 4083-4091.
4. Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466-5467.
5. Aubé, J.; Wolfe, M. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 925-928.
6. Rose, G. D.; Gierasch, L. M.; Smith, J. A. In *Advances in Protein Chemistry*; Anfinsen, C. B., Edsall, J. T. and Richards, F. M., Ed.; Academic: Orlando, 1985; Vol. 37; pp 1-109.
7. Berryhill, S. R.; Price, T.; Rosenblum, M. *J. Org. Chem.* **1983**, *48*, 158-162.
8. All new compounds have been characterized by ^{1}H and ^{13}C NMR, IR, MS, elemental analysis or HRMS, and specific rotation (where appropriate).
9. Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879-4891.
10. Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J. *Inorg. Chem.* **1972**, *11*, 1818-1825.
11. Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90-92.
12. Devore, J. A.; O'Neal, H. E. *J. Phys. Chem.* **1969**, *73*, 2644-2648.
13. Rodgers, A. S.; Golden, D. M.; Benson, S. W. *J. Am. Chem. Soc.* **1967**, *89*, 4578-4583.
14. Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647-6652.
15. Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 4475.
16. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
17. Compound **6**: mp 116-120 °C; R_f 0.45 (10% $MeOH/CH_2Cl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.22 (br, 2H), 2.57 (dd, J = 9.8, 13.0 Hz, 1H), 3.13 (br, 1H), 4.13 (br, 1H), 4.36 (br, 1H), 7.26 (m, 5H), 9.70 (br, 1H). The NMR exhibited substantial broadening at room temperature due to slow rotation of the *N*-Boc carbamate linkage but sharpened upon warming to 50 °C. ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 26.6, 28.3, 28.4, 28.7, 29.0, 29.3, 31.6, 40.8, 60.1, 60.5, 80.5, 81.6, 126.3, 128.5, 129.3, 138.6, 139.0, 153.6, 156.3, 175.4, 179.1. IR ($CHCl_3$) 3000, 2970, 1715, 1690, 1390, 1365, 1170, 740, 700. HRMS *m/e* calcd for $C_{17}H_{23}NO_4$ + 1 306.1700; found 306.1705. MS (CI) 306 (M^+ + 1), 250, 206, 160, 114 (100), 91, 84, 68, 57. $[\alpha]_D$ = +36.5 (c = 0.75, MeOH).
18. Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-H. *J. Am. Chem. Soc.* **1988**, *110*, 3929-3940.
19. 2-(1'-Oxo-4-pentenyl)furan was prepared in 48% yield from furfuraldehyde by addition of 3-butenylmagnesium bromide followed by MnO_2 oxidation. The ketone was converted to oxaziridine **14** exactly as described above. Compound **14** was isolated as a mixture of stereoisomers in 41% unoptimized yield; only the dominant stereoisomer is shown.
20. (a) Fischer, M. *Tetrahedron Lett.* **1969**, 2281-2284. (b) Oliveros-Desherces, E.; Rivière, M.; Parello, J.; Lattes A.*Tetrahedron Lett.* **1975**, 851-854. (c) Oliveros, E.; Rivière, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 739-753. (d) Suda, K.; Umehara, T.; Hino, F. *Chem. Pharm. Bull.* **1990**, *38*, 839-841. (e)Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* **1994**, 949-950.

(*Received in USA* 22 *July* 1994; *accepted* 19 *September* 1994)