Diastereoselective Synthesis of 4-Substituted L-Prolines by Intramolecular Radical Cyclization of *N*-Aryl sulphonyl-*N*-allyl 3-bromoalanines: Interesting Dependence of Selectivity on the Nature of Sulphonamido Groups

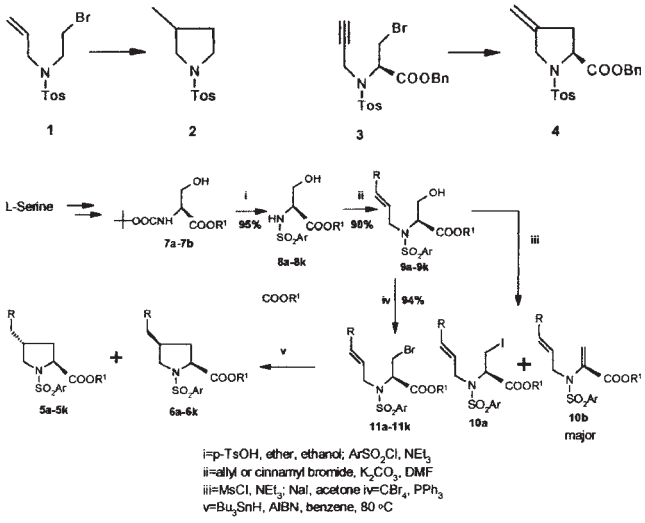
Amit Basak,* Subhendu Sekhar Bag, Kakali Rani Rudra, Jharna Barman, and Sumana Dutta
Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

(Received July 3, 2002; CL-020222)

Enantiopure 4-substituted L-proline derivatives have been prepared via intramolecular radical cyclization of *N*-aryl sulphonyl-*N*-allyl-3-bromo-L-alanines in high yields. Surprisingly, the extent of selectivity was found to be primarily dependent on the nature of sulphonamido aryl group and could be as high as 33 : 1 using naphthyl sulphonamide.

Peptide structures containing proline derivatives have received considerable interest in the area of protein folding[1] and drug design.[2] Special structural motifs like the β-turn as well as the various enzyme inhibitors very often involve proline. Proline-containing natural products[3] with interesting biological properties is also well known. Thus methods leading to the synthesis of proline derivatives especially in enantio pure forms are always important. Out of the several possibilities, stereoselective C3–C4 bond formation leading to the heterocyclic ring of proline from an acyclic intermediate is the one that drew our attention. Literature survey revealed the excellent contribution by Padwa et al.[4] in the mid eighties on the synthesis of pyrrolidines via intramolecular radical cyclization. In a closely related study, Adlington et al.[5] synthesized exomethylene proline derivatives via the cyclization of *N*-propargyl sulphones. In both the cases the reaction preferentially followed the kinetically favourable 5-exo route. However the question of any steric induction during radical cyclization did not arise in these examples. Parsons et al.[6] have also developed a radical cyclization route to various pyrrolidinones. Pandey et al.[7] synthesized pyrrolidines by a PET promoted cyclization. However the diastereoselectivity in both methods was not satisfactory. To our knowledge, intramolecular cyclization of *N*-allyl-*N*-aryl sulphonyl alanines[8] that would lead to homochiral 4-substituted L-prolines have not been tried. In this paper we provide a number of such examples. We also reveal a novel approach of increasing the diastereoselectivity to an extraordinarily high level.

Our initial attempt to prepare the iodo alanine derivative **10a** that would have been a better radical precursor under mild condition was not successful because of its extreme sensitivity towards β-elimination. This has compelled us to prepare the bromo alanines **11a–11k** from the corresponding serine derivatives **9a–9k** via reaction with PPh_3 and carbon tetrabromide (Scheme 1).[9] The bromo derivatives were stable and can be stored in the refrigerator without any elimination. On being subjected to tin hydride mediated radical generating conditions[10] (Bu_3SnH, AIBN, benzene, reflux) **11a–11k** underwent smooth intramolecular cyclization to generate the proline derivatives **5a–5k** and **6a–6k** in yields of over 80%. The results shown in **Table 1** revealed exclusive 5-exo addition[11] with predominant formation of the *trans* isomer.[12] The diastereoselectivity which varied from excellent to moderate seems not to depend upon the steric bulk of the ester as revealed in the constancy of product ratio when benzyl is replaced by diphenyl methyl (example **11a** and **11e**) both of which having the N-tosyl group. Replacement of the allyl group with cinnamyl group predictably lowered the diastereoselectivity mainly because of the generation of a stabilized radical that inhibited the equilibriation process for the generation of thermodynamically more stable product. The most interesting aspect of this cyclization was the unexpected dependence of diastereoselectivity on the nature of the sulphonamido aryl group. In case of the naphthyl sulphonamido having a benzyl ester **11d**, the selectivity went upto around 8 : 1 as compared to 3 : 1 in case of tosyl. Increasing the steric bulk of the ester in **11k** led to even higher extent of selectivity (33 : 1). Changing the electron withdrawing character of the sulphonamido aryl also improved the extent of selectivity, though to a lesser extent. Similar trend was reflected in case of the cinnamyl system. With naphthyl sulphonamide, the diastereoselectivity also improved, although much less dramatically, because of the generation of stable benzyl radical which hinders the equilibriation between the radicals. The selectivity did not change by carrying out the reaction at a higher temperature in refluxing toluene.

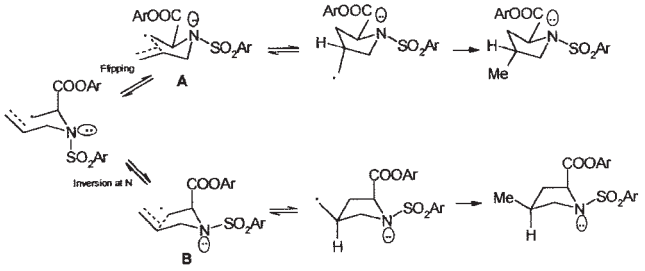


Scheme 1.

The predominant formation of the *trans* isomer could be explained on the basis of a chair-like conformation[13] for the transition states leading to the diastereomers (Scheme 2). The TS **"A"** leading to the *trans* isomer has both the ester and the sulphonamido in the pseudo equatorial configuration. Formation of the *cis* isomer involves a TS **"B"** in which the ester is in the pseudo axial orientation. The energy difference between the two

Table 1. Cyclization of Various Bromides **11a–11k**

Entry	Substituents	Substrate	Products and their ratio	Total percent yield
1	R=H, R^1=Bn Ar=p-Tolyl	**11a**	**5a** & **6a** 3 : 1	80
2	R=H, R^1=Bn Ar=p-Nitrophenyl	**11b**	**5b** & **6b** 4 : 1	83
3	R=H, R^1=Bn Ar=p-Chlorophenyl	**11c**	**5c** & **6c** 4 : 1	85
4	R=H, R^1=Bn Ar=2-Naphthyl	**11d**	**5d** & **6d** 8 : 1	85
5	R=H, R^1=$CHPh_2$ Ar=p-Tolyl	**11e**	**5e** & **6e** 3 : 1	82
6	R=Ph, R^1=Bn, Ar=p-Tolyl	**11f**	**5f** & **6f** 1.7 : 1	85
7	R=Ph, R^1=$CHPh_2$ Ar=p-Tolyl	**11g**	**5g** & **6g** 2 : 1	90
8	R=Ph, R^1=Bn Ar=2-Naphthyl	**11h**	**5h** & **6h** 2.5 : 1	87
9	R=Ph, R^1=$CHPh_2$ Ar=2-Naphthyl	**11i**	**5i** & **6i** 3.5 : 1	88
10	R=Ph, R^1=$CHPh_2$ Ar=p-Nitrophenyl	**11j**	**5j** & **6j** 2.5 : 1	90
11	R=H, R^1=$CHPh_2$ Ar=2-Naphthyl	**11k**	**5k** & **6k** 33 : 1	96



Scheme 2.

TS is dependent upon the steric bulk or electronic nature of the sulphonamides.

Thus we have demonstrated for the first time the remote effect of a sulphonamido group in controlling the selectivity of radical cyclization leading to the formation of proline derivatives. By fine-tuning the nature of sulphonyl aryl, the selectivity could be increased to a very high level. This should offer a new general strategy towards synthesis of enantiomerically pure 4-substituted proline derivatives.

SSB and KR thank Council of Scientific and Industrial Research for Research Fellowships. SD thanks Jawaharlal Nehru Centre for Advanced Research, Bangalore, India for a summer fellowship.

References and Notes

1 a) D. L. Minor and P. S. Kim, *Nature*, **367**, 660 (1994). b) K. Y. Tsang, H. Diaz, N. Graciani, and J. W. Kelly, *J. Am. Chem. Soc.*, **116**, 3988 (1994). c) T. E. Creighton, ''Proteins: Structure and Molecular Properties,'' 2nd ed., W. H. Freeman and Co, New York (1993), p 187. d) M. Kahn, *Synlett*, **1993**, 821. e) D. S. Kemp and Z. Q. Li, *Tetrahedron Lett.*, **36**, 4179 (1995).

2 R. B. Silverman, ''Organic Chemistry of Drug Design and Drug Action,'' Academic Press, New York (1992).

3 a) A. Shimazu, *Experientia*, **37**, 365 (1981). b) N. Otame, K. Furihata, and H. Yonehera, *J. Antibiot.*, **1974**, 484. c) J. Mulzer, A. Meier, J. Buscmann, and P. Luger, *J. Org. Chem.*, **61**, 566 (1996).

4 A. Padwa, H. Nimmesgern, and G. S. K. Wong, *J. Org. Chem.*, **50**, 5620 (1985).

5 R. M. Adlington and S. J. Mantell, *Tetrahedron*, **48**, 6529 (1992).

6 J. S. Bryans, J. M. Large, and A. F. Parsons, *J. Chem. Soc. Parkin Trans 1*, **1999**, 2897. b) B. C. Gilbert, W. Kalz, C. I. Lindsay, P. T. McGrail, A. F. Parsons, and D. T. E. Whittaker, *J. Chem. Soc. Perkin Trans 1*, **2000**, 1187.

7 G. Pandey, G. D. Reddy, and G. Kumaraswamy, *Tetrahedron*, **50**, 8185 (1994).

8 Use of 3-iodo L-alanine in radical reaction: a) R. M. Adlington, J. E. Baldwin, A. Basak, and R. P. Kozyrod, *J. Chem. Soc., Chem. Commun.*, **1983**, 944. b) J. E. Baldwin, R. M. Adlington, and A. Basak, *J. Chem. Soc., Chem. Commun.*, **1984**, 1284.

9 M. Falorni and L. Lardicci, *J. Org. Chem.*, **51**, 529 (1986).

10 a) D. P. Curran, *Synthesis*, **1988**, 417, 489. b) B. Giese, ''Radicals in Organic Synthesis,'' Pergamon Press, Oxford (1986).

11 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

12 The configurations were determined from NOE and coupling constants.

13 A. L. J. Beckwith, T. Lawrence, and K. S. Serelis, *J. Chem. Soc., Chem. Commun.*, **1980**, 484.