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LITHIUM DIPHENYLCUPRATE REACTIONS WITH 4-TOSYLOXY-L-PROLINES; AN INTERESTING STEREOCHEMICAL OUTCOME.

A SYNTHESIS OF *TRANS*-4-PHENYL-L-PROLINE.

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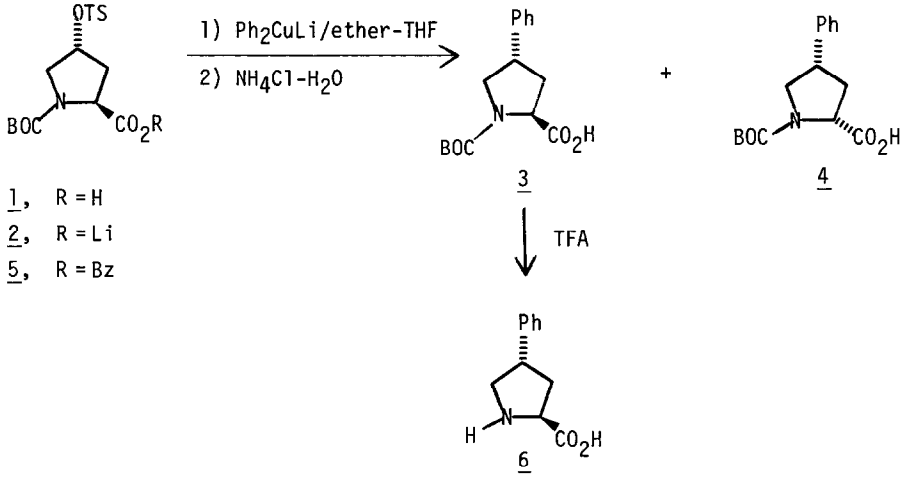
Abstract: The reaction of lithium diphenylcuprate with *trans*-4- and *cis*-4-tosyloxy-L-prolines gives excellent yields of 4-phenyl substituted L-prolines and the reaction proceeds with net retention of configuration at the carbon center bearing the tosyloxy group.

In connection with our ongoing ACE program,[1] we needed large amounts of *trans*-4-phenyl-L-proline. In this letter, we describe a very simple and efficient method for the conversion of 4-tosyloxy-L-prolines to 4-phenyl-L-prolines, which proceeds through net retention of configuration at the carbon center bearing the tosyloxy group.

When tosylate[2] 1 is reacted with two equivalents of lithium diphenyl cuprate (prepared from phenyllithium and cuprous bromide dimethyl sulfide complex[3]) in a mixture of ether and tetrahydrofuran solvent at around 0°C, the substitution products 3 and 4 are obtained in 90% yield. Contrary to literature precedent[4] substitution of the 4-tosyloxy group by the phenyl moiety has taken place not only rapidly and at low temperature, but with net retention of configuration in both products. The major product 3 is obtained in analytically pure form in 75% yield after one crystallization of the mixture from chloroform .

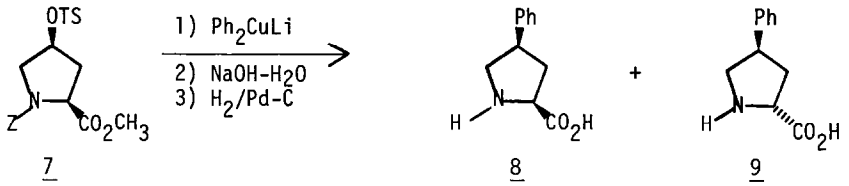


The stereochemistry of product 3 was confirmed by converting it to the free amino acid 6 by treatment with TFA followed by comparison to an authentic sample[5]. The ratio of the two products 3 and 4 depends on reaction conditions. The following factors shifted the ratio of products in favor of the desired product 3:

a. quenching the reaction with ammonium chloride immediately after the tlc endpoint is detected,
b. the use of larger percentages of diethyl ether as the solvent for the reaction,
c. maintainance of the reaction temperature at~ 0^{o}c and,
d. using little or no excess of the lithium diphenylcuprate reagent.

Utilizing these guidelines, ratios of from 11 : 1 to no spectroscopically detectable amounts of 3 were obtained reproducibly. Identical results were obtained when the lithium salt 2 was treated with one equivalent of lithium diphenylcuprate. Reaction of benzyl ester 5 under identical reaction conditions followed by hydrogenolysis of the benzyl group also gave 3 and 4 but in a poor ratio (~2:1).

In contrast, treatment of the *cis*-tosylate 7 under the above conditions, followed by ester hydrolysis and hydrogenolysis of the benzyloxycarbonyl protecting group, gave a mixture of products 8 and 9 in 82% overall yield but in a ratio of 2:3. From the above results, it is clear that the reaction of 4-tosyloxy-L-prolines with lithium diphenylcuprate proceeds through net retention of configuration.

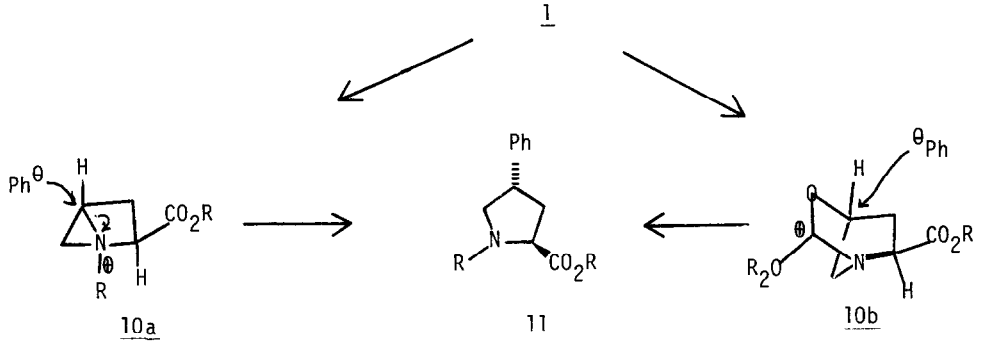


7 8 9

Z = COO-CH_2Ph **(2 : 3)**

Even though the mechanism(s?) of these transformations is not clear at this time, a few points are worth mentioning. The D-Series prolines 4 and 9 may well be produced by a secondary process. Treatment of pure 3 with lithium diphenylcuprate under the reaction conditions gave a mixture of 3 and 4 in 2:1 ratio. The same ratio of 3 and 4 is obtained by LDA-mediated epimerization of pure 3. Dehydroprolines derived via the elimination of tosyloxy group, (a common side reaction in the organocuprate displacement of tosylates[4]) are not observed either in the cases of *trans*-tosylates (1, 2, and 5) or the *cis*-tosylate 7.

From these observations we assume these reactions take place by two successive inversion processes in which the first step is the formation of an activated bicyclic intermediate (10a, 10b or their equivalent) by an inversion process which is ring-opened by the reagent in a second inversion process. A similar intermediate and mechanism has been invoked for the rearrangement of azetidine-2--carboxylic acid chlorides to chloro-gamma-lactones[6].



This facile, synthetically useful and mechanistically intriguing process for the synthesis of 4-phenyl substituted prolines has been used sucessfully for preparation of 3 on a kilogram scale. This method takes on more significance when the importance and wide occurrence of other alkyl substituted prolines[7] are considered[8-10].

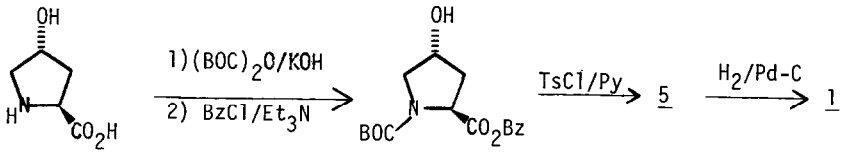
Acknowledgements:

We thank Dr. R.H. Mueller, Dr.D. E. Ryono, Dr. D. M. Floyd and Dr. C. M. Cimarusti for discussions during the course of this work, Ms. C. Przybyla for preparing some of the early intermediates, and Dr. M. A. Porubcan and Ms. M. Young, for analytical assistance during the course of this work.

References and Notes

1. a. E. W. Petrillo, Jr. and M. A. Ondetti, Med. Res. Rev., 2, 1 (1982).
   b. E. W. Petrillo, Jr., Eur. Pat. EP 063896 (1982).
   c. E. W. Petrillo, Jr., Eur. Pat. EP 053902 (1982).

2. Prepared as shown below:



3. a. P. G. M. Wuts. Synthetic Comm., 11, 139 (1981).
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4. a. C. R. Johnson and G. Dutra, J. Am. Chem. Soc., 95. 7773 and 7783 (1973).
   b. G. H. Posner, Org. React., 22, 253 (1975).

5. Dr. E. W. Petrillo, Jr., of the Squibb Institute for Medical Research, has proven the structure and stereochemistry of compound 6 obtained by an independent method by single crystal X-ray analysis an we thank Dr. Petrillo for this information.

6. a. H. H. Wasserman, W. T. Han, J. M. Schaus and J. W. Faller, Tetrahedron Lett., 25, 3111 (1984).

b. We thank Professor Wasserman for bringing this article to our attention and for the cordial discussion we had on this topic.

7. a. M. Nakajima, A. Torikata, H. Tamaoki, T. Haneishi, M. Arai, T. Kinoshita and H. Kuwano, J. Antibiotics, 36, 967 (1983).

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c. R. D. Birkenmeyer and F. Kagan, J. Med. Chem., 13, 616 (1970).

8. Detailed studies of these reactions including mechanistic aspects, reaction with other substrates, reactions using other dialkylorganocuprates and other organoheterocuprates[9] and the various analytical methods used to determine the absolute configuration of each of the four 4-phenyl proline isomers will be published elsewhere.

9. Dr. D. M. Floyd,The Squibb Institute for Medical Research, Unpublished results.

10. Satisfactory IR, NMR (^{1}H, ^{13}C), and/or elemental analysis were obtained for all new compounds.

Typical Experimental Procedure

Conversion of 1 to 3.

To a clear solution of lithium diphenylcuprate, prepared from cuprous bromide dimethylsulfide complex (270.0 g, 1.313 moles) and phenyl lithium (1200 ml, 2.64 moles) in ether (6 liters) at -15°C was added a solution of 1 (245.0 g, 0.636 moles) in THF (3 liters) over five minutes times bringing the internal temperature to 0°C. TLC indicated the absence of starting material after stirring for one hour at 4°C. The reaction mixture was cooled to -20°C and treated with saturated NH_4Cl (2 liters) over five minutes time and stirred at 0°C for two hours. Sodium hydroxide (20%) was added to bring the pH to 10 and diluted with water (2 liters) and the organic phase was separated and the aqueous phase washed with ether (3 x 2 liters). Usual extractive workup of the aqueous phase after acidification with concentrated HCl acid to pH 2.8 followed by crystallization from chloroform produced analytically pure 3 (125.0 g, 67%) devoid of 4[10]; m.p. 157-160°C, $[\alpha]_D^{22} = -66.6^{\circ}$ (c=1, $CHCl_3$).

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