Efficient Asymmetric Synthesis of α-Amino Acids from α-Keto Acids and Ammonia with Conservation of the Chiral Reagent

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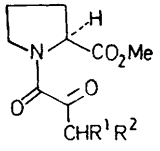
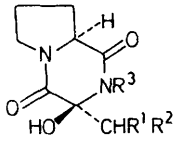
Summary A general synthesis with high optical efficiency of L-amino acids and L-*N*-methyl amino acids from α-keto acids and ammonia employing (*S*)-proline as the chiral reagent is described.

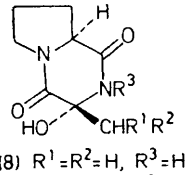
OVER the past decade considerable synthetic effort has been expended on the development of general methods for the asymmetric synthesis of α-amino acids.[1] However, few have proved operative with respect to both optical efficiency and product yield. Two notable exceptions are the chiral induction method of Corey[2] and the reduction of *N*-acyldehydroamino acids using optically active rhodium complexes.[3] As a result of our broad interest in dehydroamino acid chemistry, we now report a general synthesis from α-keto acids and ammonia employing (*S*)-proline as the recoverable chiral reagent.



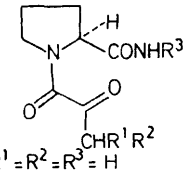
(1) $R^1 = R^2 = H$
(2) $R^1 = H, R^2 = CHMe_2$
(3) $R^1 = Me, R^2 = Et$



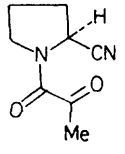
(4) $R^1 = R^2 = R^3 = H$
(5) $R^1 = H, R^2 = CHMe_2, R^3 = H$
(6) $R^1 = Me, R^2 = Et, R^3 = H$
(7) $R^1 = R^2 = H, R^3 = Me$



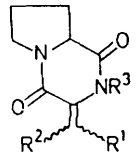
(8) $R^1 = R^2 = H, R^3 = H$
(9) $R^1 = R^2 = H, R^3 = Me$



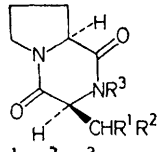
(10) $R^1 = R^2 = R^3 = H$
(11) $R^1 = R^2 = H, R^3 = Me$



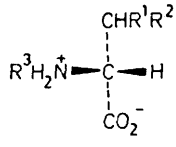
(12)



(13) $R^1 = R^2 = R^3 = H$
(14) $R^1 = H, R^2 = CHMe_2, R^3 = H$
(15) $R^1 = R^2 = H, R^3 = Me$
(16) $R^1 = Me, R^2 = Et, R^3 = H$



(17) $R^1 = R^2 = R^3 = H$
(18) $R^1 = H, R^2 = CHMe_2, R^3 = H$
(19) $R^1 = Me, R^2 = Et, R^3 = H$
(20) $R^1 = R^2 = H, R^3 = Me$



(21) $R^3 = H$
(22) $R^3 = Me$

(*S*)-Proline methyl ester coupled readily with a number of α-keto acids in CH_2Cl_2 in the presence of dicyclohexylcarbodi-imide (DCC) to give the *N*-α-ketoacyl derivatives (**1**)—(**3**) in high yield (75—80%).† When stored at room temperature in dry dimethoxyethane containing anhydrous ammonia the α-keto amides cyclised to afford specifically the 5-hydroxydioxopiperazines (**4**)—(**6**).‡ Reaction of (**1**) with anhydrous $MeNH_2$ under similar conditions gave the

† All new compounds described possess the required analytical and spectral data.

‡ This stereoselectivity accords with recent observations in similar reactions.[4]

N-methyl derivative (**7**). When the above reactions were conducted in prototropic solvents a mixture of diastereoisomers was formed, *i.e.*, (**4**) and (**8**), and (**7**) and (**9**).

Recently the amides (**10**) and (**11**) have been prepared in poor yield and shown to cyclise under neutral conditions to (**4**) and (**7**) respectively.[4] Attempts by us to prepare these compounds by acylation of the corresponding amide in the presence of DCC were unsuccessful, and with L-proline amide led exclusively to the cyano compound (**12**).

The α-hydroxy *cyclo*-dipeptides are surprisingly stable and there is no evidence of equilibration with the corresponding pyruvyl derivatives. Dehydration of (**4**), (**5**), and (**7**) to the dehydro compounds (**13**)—(**15**) respectively was readily achieved with anhydrous CF_3CO_2H at room temperature. However, (**6**) failed to react under these conditions and was subsequently dehydrated to (**16**) using $SOCl_2$ in pyridine.

The ^1H n.m.r. spectrum ($CDCl_3$) of (**14**) exhibited a single olefinic peak at τ 4·1 which is consistent with the presence of only one stereoisomer. The spectrum of (**16**) showed two C–Me signals at τ 7·58 and 8·12 of approximately equal intensity indicating an isomeric mixture.

Hydrogenation of the α,β-dehydro derivatives (**13**)—(**16**) in ethanol with Adam's catalyst at room temperature and pressure afforded the (*S,S*)-*cyclo*-dipeptides (**17**)–(**19**) in essentially quantitative yield.§ The (*S,S*)- and (*R,S*)-alanyl proline anhydride, prepared from the corresponding dipeptides display characteristic C–Me signals at τ 8·52 and 8·64 (d, J 7 Hz). The chiral induction in the hydrogenation of (**13**), as determined by the integration of the C–Me signals and g.l.c. analysis,[5] is >90%.

Considerably lower asymmetric induction is observed on the hydrogenation of dehydro-dioxopiperazines derived from (*S*)-Phe and (*S*)-Ala rather than (*S*)-Pro.[6] In addition, *N*-substitution with either alkyl, *e.g.*, (**15**) or acyl[7] groups also markedly reduces the optical efficiency of the hydrogenation step.

Acid hydrolysis of the *cyclo*-dipeptides yielded the appropriate L-amino acid (**21**) and L-proline. The product efficiency of the synthesis is illustrated for L-alanine which was obtained in *ca.* 60% yield from pyruvic acid. The method is equally applicable to the synthesis of *N*-methyl amino acids (**22**).

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§ After one crystallisation the specific rotations for (**17**) and (**18**) were $[\alpha]_D^{25}$ −119° ± 2° and −127° ± 2°; authentic samples prepared from the optically pure dipeptides $[\alpha]_D^{25}$ −116 ± 2° and −131 ± 2° respectively. Compound (**19**) is assumed to be an epimeric mixture of L,L-isoleucyl and -*allo*isoleucyl proline anhydride.

[1] See J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions', Prentice-Hall Inc., New Jersey, 1971, p. 297; J. W. Scott and D. Valentine, Jr., *Science*, 1974, **184**, 943.
[2] E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Amer. Chem. Soc.*, 1970, **92**, 2476; E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, p. 2488.
[3] T. P. Dang and H. B. Kagan, *J. Amer. Chem. Soc.*, 1972, **94**, 6429; W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *ibid.*, 1975, **97**, 2567.
[4] J. Hausler and U. Schmidt, *Chem. Ber.*, 1974, **107**, 2804.
[5] See J. W. Westley, V. A. Close, D. N. Nitecki, and B. Halpern, *Analyt. Chem.*, 1968, **40**, 1881.
[6] See S. Akabori, T. Ikenaka, and K. Matsumoto, *Proc. Japan Acad.*, 1951, **27**, 7; G. Maeda, *Nippon Kagaku Zasshi*, 1956, **77**, 1011.
[7] H. Poisel and U. Schmidt, *Chem. Ber.*, 1973, **106**, 3408.