ENANTIOMERIC SYNTHESIS OF 2-ALLYL-4-HYDROXYPYRROLIDINE FRAMEWORK VIA IODINE-MEDIATED REACTION

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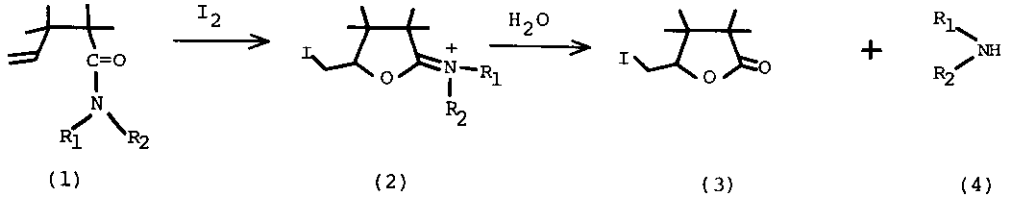
Abstract——The amide (14), prepared from the symmetric amine (12) and a chiral acid, (S)-(-)-proline, furnished a mixture of the epimeric (2S,4R/S)-(-)-2-allyl-4-hydroxypyrrolidine derivatives in good yield upon reaction with iodine in an aqueous solvent. Chiralities of the both products are established by correlating them to (2S,4R)-(-)-4-hydroxyproline (27).

A certain γ,δ-unsaturated amide (1) derived from an unsaturated acid, upon treatment with iodine, has been shown to yield a corresponding iodo-γ-lactone derivative (3) with loss of an amine component (4) via an iminium intermediate (2) under hydrolytic work-up[1-4] (Schme 1). This iodine-mediated reaction using



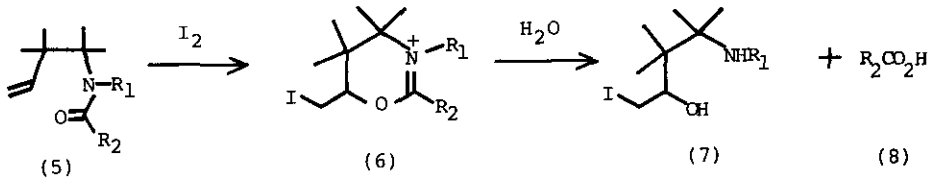
(1) (2) (3) (4)

Scheme 1

amide substrates has been successfully employed in the synthesis of thromboxane B_2 by Corey's group[1] and in the syntheses of a series of the indole alkaloids by the present authors.[2-4] The same reaction, however, has not been fully applied to an alternative amide substrate (5) derived from an unsaturated amine so far,[5-6] in which a formation of an amino-alcohol (7) may be expected with recovery of a carboxylic acid (8) via an oxazinium intermediate (6) under hydrolytic work-up (Scheme 2).

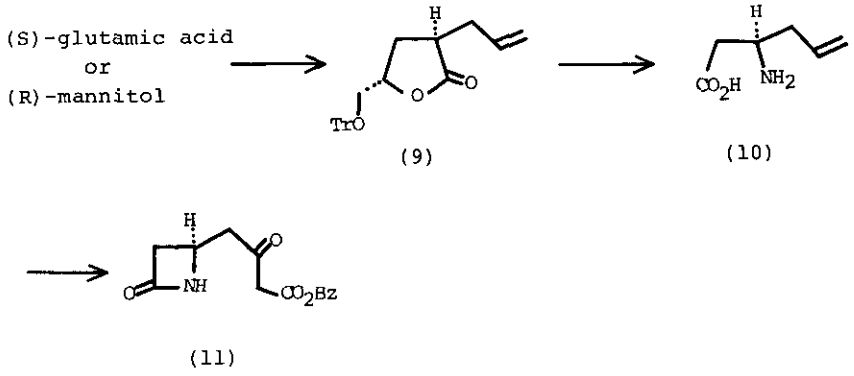
In relation to our recent synthesis of the β-lactam derivative (11)[7] starting from the chiral starting

material (9)[8] (Scheme 3), we examined the iodine-mediated reaction to apply to the unsaturated amide (14), obtained from the symmetric unsaturated amine (12) and a chiral acid, (S)-(-)-proline, with anticipating enantiomeric formation[9] of the potential intermediate (16) for the synthesis of the β-lactam derivative (11) accompanied by recovery of the chirality control element (13, X=OH) via enantiomeric intervention of the oxazine intermediate (15) (Scheme 4). In practice, the anticipated iodine-mediated reaction did occur



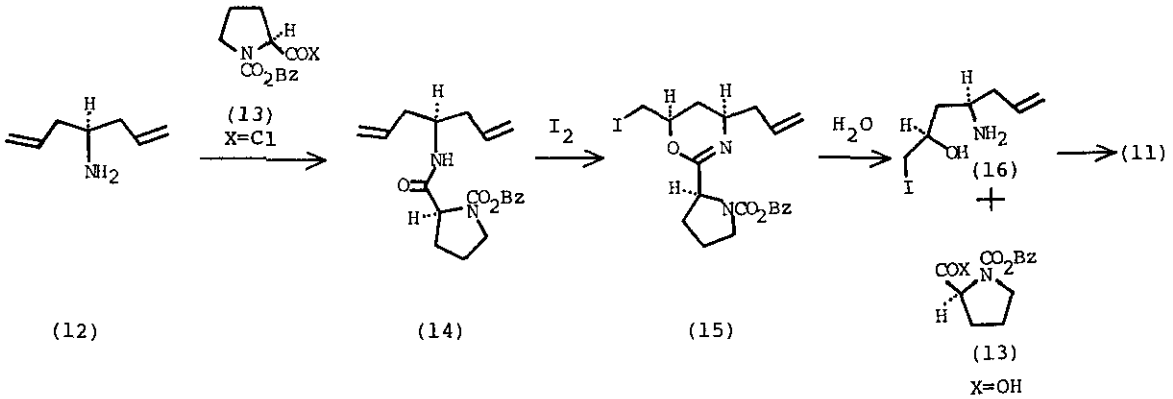
(5) (6) (7) (8)

Scheme 2



(9) (10) (11)

Scheme 3

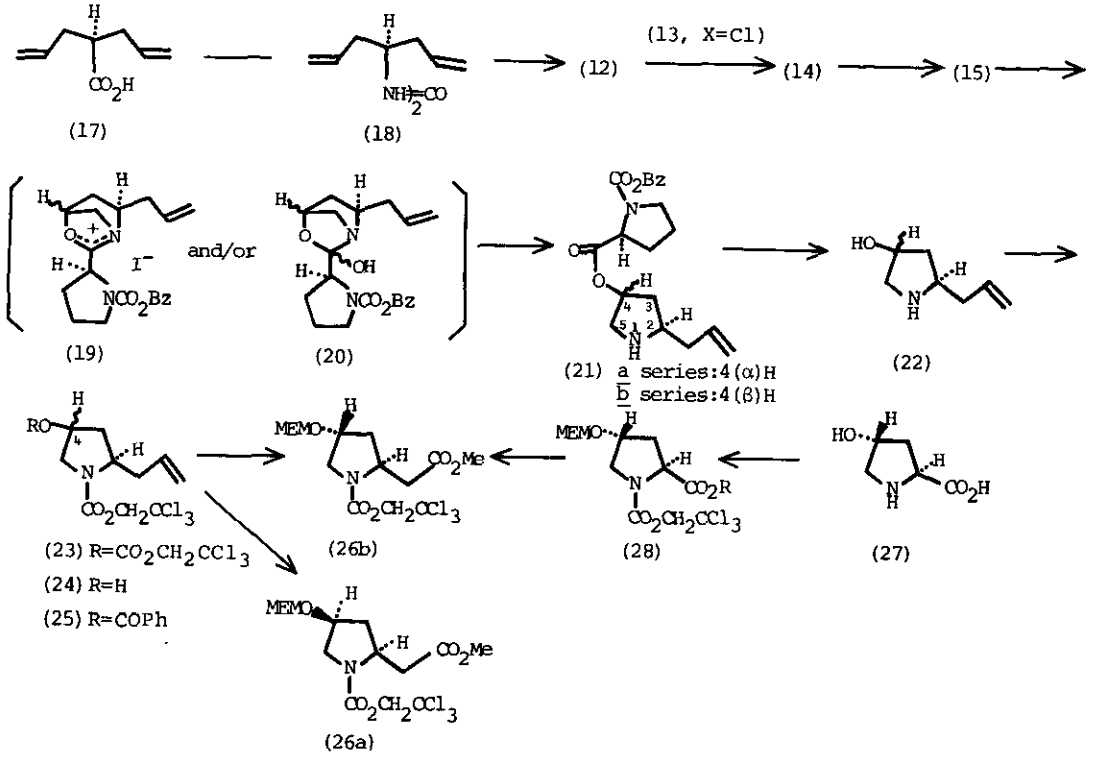


(12) (14) (15)

Scheme 4

in facile, but the reaction further proceeded to give rise to a mixture of the epimeric (2S,4R)- and (2S,4S)-(-)-2-allyl-4-hydroxypyrrolidine derivatives (21a and b) instead of giving the expected oxazine (15). Herein, we describe the novel iodine-mediated reaction leading to the 2,4-disubstituted pyrrolidine derivatives and its stereochemical outcome.

The amide substrate (14)[10] was prepared from the symmetric acid (17)[3] in good overall yield. Thus, the acid (17), on treatment with diphenylphosphoryl azide (DPPA)[11] in the presence of triethylamine, afforded the urea derivative (18)[12] which without purification was hydrolyzed with potassium hydroxide in ethyleneglycol to give the amine (12) in 80% overall yield. Acylation of the amine (12) with the acid chloride (13, X=Cl), obtained from (S)-(-)-proline via a two-step sequence ((i) BzOCOCl, pyridine (ii) $(COCl)_2$), in the presence of triethylamine yielded the amide (14), quantitatively. Treatment of the amide (14) with iodine in aqueous solvent underwent facile cyclization reaction yielding an inseparable mixture of pyrrolidine derivatives (21a and b) and the initially expected oxazine derivative (15) could not be detected (Table). Preferential formation of the 2,4-trans isomer (21b) over the 2,4-cis isomer (21a) could be deduced in the later stage after separating the mixture as the carbamates (23a and 23b). Formation of the pyrrolidine derivatives (21) may be simply interpreted by a sequential formation of the highly strained bicyclic quaternary iodide (19) or the carbinol amine (20) and hydrolysis under the conditions employed (Scheme 5).



Scheme 5

Table

entry	solvent	temperature (^{o}C)	ratio 23a/23b	total yield of 23[a] (%)	optical rotation $[\alpha]_D$(% e.e.)[b] 26a	26b
1	THF-H_2O 1:1	r.t.	2.9	76.0	-4.31^{o}	-9.26^{o}(26.0)
2	THF-H_2O 1:1	-20	5.2	83.4		-3.07^{o}(8.6)
3	CH_3CN-H_2O 1:1	r.t.	4.6	58.0		0^{o}(0)
4	CH_3CN-H_2O 1:1	5-8	10>	25.8		0^{o}(0)
5	DMF-H_2O 1:1	r.t.	4.5	71.4		-2.72^{o}(7.6)

a. Overall yield from the amide (14).

b. Calculated based on the optically pure material 26b, $[\alpha]_D^{24}$ -35.6^{o}, prepared from (2S,4R)-(-)-4-hydroxyproline (27).

A mixture of the epimers (21) was hydrolyzed with methanolic potassium hydroxide to a mixture of the epimeric amino-alcohols (22) with an excellent recovery of the chiral acid (16). The resulted epimeric mixture was then treated with 2,2,2-trichloroethyl chloroformate in pyridine solution to give a mixture of the epimeric diesters (23a and b) which could be separated using a silica gel column chromatography. Structures and stereochemistry of these products were unambiguously established by correlating them to (2S,4R)-(-)-4-hydroxyproline (27). Thus the each ester (23) was saponified (KOH, MeOH), etherified (β-methoxyethoxymethyl chloride (MEMCl), Hunig base)[13], oxidized (O_3-MeOH, then pyridinium dichromate (PDC-DMF)[14], then esterified (CH_2N_2, MeOH) to give the corresponding homoproline derivative (26), respectively. While (2S,4R)-(-)-4-hydroxyproline (27) was sequentially acylated ($ClCO_2CH_2CCl_3$, pyridine), saponified (K_2CO_3, aq. MeOH), esterified (CH_2N_2, MeOH), etherified (MEMCl, Hunig base), saponified (K_2CO_3, aq. MeOH), and homologated ((i)$(COCl)_2$ (ii)CH_2N_2 (iii)Ag_2O, MeOH) to yield the (2S,4R)-homoproline derivative (26b), $[\alpha]_D^{24}$ -35.6^{o}(c=1.6, $CHCl_3$), with 2,5-trans relationship. Of two homoprolinates obtained from the cyclization mixture (21), since the one from major component was found to be in accord with the authentic material (26b) thus obtained from (2S,4R)-(-)-4-hydroxyproline (27) though its optical rotation was somewhat lower, $[\alpha]_D^{23}$ -9.26^{o}(c=3.78, $CHCl_3$), the structures and the stereochemistry of the products relating to the major component (21b) could be deduced as shown ((2S,4R)).

Having established structure of the major component (21b), the carbamate (24b) obtained from (21b) was treated with benzoic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine[15] to give the benzoate (25a) with inversion at C-4 center((R)→(S)). The benzoate (25a) after saponification was converted via a sequential four-step reaction ((i) MEMCl-Hunig base (ii)ozonolysis (iii) PDC-DMF

(iv) CH_2N_2-MeOH) into the cis-(2S,4S)-(-)-homoproline derivative (26a), $[\alpha]_D^{23}$ -4.60°(c=3.48, $CHCl_3$), with (2S,4S)-chirality, which was completely identical to the product (26a), $[\alpha]_D^{19}$ -4.31(c=10.0, $CHCl_3$), obtained directly from the minor component (21a). This indicated that the both homoproline derivatives (26a) and (26b) possessed the same chirality at C-2 center ((S)-configuration) with a similar extent of enantiomeric purity.

At this stage, structures and stereochemistry as well as optical purities of the pyrrolidine derivatives (21a and 21b) generated from the amide substrate (14) via the iodine-mediated reaction have been clarified. Although more improvement must be required in the enantiomeric induction, the present reaction embraces a potential utility for the construction of some 2,4-disubstituted pyrrolidines based on the exhibited facile work-up, good chemical yield, excellent recovery of chirality control element, and selective chirality induction at C-2 center. Further investigation of the present reaction is currently under way.

REFERENCES AND NOTES

1. E.J. Corey, M. Shibasaki, and J. Knolle, Tetrahedron Lett., 1977, 1625.
2. S. Takano, M. Hirama, and K. Ogasawara, J. Org. Chem., 1980, 45, 3729.
3. S. Takano, C. Murakata, Y. Imamura, N. Tamura, and K. Ogasawara, Heterocycles, 1981, 16, 1291.
4. S. Takano, M. Yonaga, and K. Ogasawara, J. Chem. Soc. Chem. Comm., 1981, 1153.
5. There has been reported one example using iodonium dicollidine perchlorate: H.W. Pauls and B. Fraser-Reid, J. Am. Chem. Soc., 1980, 102, 3956.
6. Some examples undertaking on the carbamate substrates have been reported recently: a) M. Georges and B. Fraser-Reid, Tetrahedron Lett., 1981, 22, 4635. b) S. Takano and S. Hatakeyama, Heterocycles, 1982, 19, in press. c) I. Inui, Y.-F. Wang, T. Isawa, and M. Ohno, 102nd Aunual Meeting of the Japan Pharmaceutical Society, Osaka, 1982, Abstract Paper, p. 502.
7. S. Takano, C. Kasahara, and K. Ogasawara, Chemistry Lett., 1982, 631.
8. a) S. Takano, K. Chiba, M. Yonaga, and K. Ogasawra, J. Chem. Soc. Chem. Comm., 1980, 616. b) S. Takano, N. Tamura, and K. Ogasawara, ibid., 1981, 1155.
9. Enantiomeric iodolactonization of the amides type (1) (Scheme 1) has been reported: see ref. 3.
10. Satisfactory spectral and analytical data have been obtained for all new compounds isolated.
11. K. Ninomiya, T. Shioiri, and S. Yamada, Chem. Pharm. Bull., 1974, 22, 1398.
12. Cf. S. Takano, Y. Suzuki, and K. Ogasawara, Heterocycles, 1981, 16, 1479.
13. E.J. Corey, J.-L. Gras, and P. Ulrich, Tetrahedron Lett., 1976, 809.
14. E.J. Corey and G. Schmidt, ibid., 1979, 399.
15. a) O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 1972, 94, 679. b) Pertinent review: O. Mitsunobu, Synthesis, 1981, 1.

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