ASYMMETRIC SYNTHESIS OF DIBENZO[a,g]QUINOLIZINES RELATED TO PROTOBERBERINE ALKALOIDS

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Abstract-------Reductive photocyclization of enamides in the presence of a chiral metal hydride complex was systematically investigated in order to establish as a general asymmetric route for the synthesis of berbines and 13-methylberbines.

Previously[1], we have reported an asymmetric synthesis of (-)-xylopinine by applying reductive photocyclization of enamide in the presence of a chiral metal hydride complex. In connection with our studies[1,2] on the asymmetric synthesis of the biologically active heterocyclic compounds, the present investigation was undertaken to investigate the applicability of asymmetric photocyclization of enamides to the synthesis of the optically active dibenzo[a,g]quinolizines related to the protoberberine alkaloids.

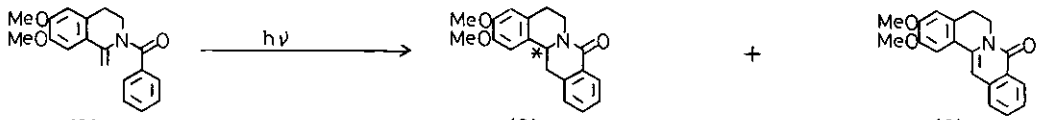
Though a number of synthetic methods for the well-known isoquinoline alkaloids have been established up to present[3], they are limited to the synthesis of racemates of alkaloids except a few examples of asymmetric synthesis of the benzylisoquinoline alkaloids[4] and two asymmetric syntheses of (-)-xylopinine[1,5]. Photocyclization of several enamides, prepared from the 1-methyl- or 1-ethylisoquinolines, in the presence of some representative chiral metal hydride complexes was systematically investigated in order to establish the condition of choice for the asymmetric synthesis with respect to both chemical and optical yields. Each chiral metal hydride complex was prepared according to the known methods[6] developed in the cases of asymmetric reductions of simple ketones and the resulting solution was cooled to 4-5°C and then diluted with a benzene solution containing an appropriate amount of the most simple enamide (1) which was prepared from 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline and benzoyl chloride.

Irradiation of the above solution with a high pressure mercury lamp (Pyrex filter) at 4-5°C under nitrogen bubbling afforded the optically active saturated lactam (2) along with a small amount of the dehydrolactam (3). Their chemical and optical yields[7] are summarized in the Table 1.

As shown in the Table 1, among six chiral sources studied, the use of chirald[8] gave the best chemical yield while quinine the best optical yield respectively. Though aging in the preparation of the chiral metal hydride complex from chirald and lithium aluminum hydride has been known to reverse optical rotation of chiral products in the asymmetric reduction of some ketones[6c], such phenomenon however was not observed in this case. The fact that no optical activity of the photo-product was observed when (-)-1-phenylethanol was used as a chiral source suggested a structural requirement of an amino-alcohol moiety as a chiral source in the photocyclization of enamides.

Further, in the use of quinine which was found to be the best chiral source as shown in the Table 1, we examined the ratio of reagents employed, enamide, lithium aluminum hydride, and quinine, as shown in the Table 2, and found that the best ratio of the enamide to metal hydride reagent was 1 : 10 and metal hydride to quinine was 1 : 1 respectively. Analogously, in the presence of each of four chiral metal hydride complexes which were prepared from quinine, quinidine, (-)-N-methylephedrine, and chirald respectively, the p-methoxy-(4) and dimethoxy-substituted enamides (5) were also irradiated to give the optically active lactams (6) and (7a) as summarized in the Table 3. A similar photocyclization of the dimethoxy-substituted enamide (5) in the presence of a chiral metal deuteride complex prepared from lithium aluminum deuteride and quinine afforded the optically active lactam (7b) ($[\alpha]_D$ -96°(c=0.77, $CHCl_3$)) in 13 % yield, which was found to contain deuterium quantitatively at the 13a-position on the basis of mass and n.m.r. spectral analyses. This result supports the proposed mechanism of reductive photocyclization of enamides as described previously[1,9].

The asymmetric synthesis of berbin-8-ones has a wide applicability as exemplified by the synthesis of optically active 13-methylberbines. 6,7-Dimethoxy-1-ethyl-3,4-dihydroisoquinoline was acylated with aroyl chlorides to give the corresponding enamides (8) and (9), which were irradiated in the presence of each of four chiral metal hydride complexes. The photocyclized products (10) and (11) were the lactams with a 13/13a-trans-stereochemistry and optical acti-



(1) (2) (3)

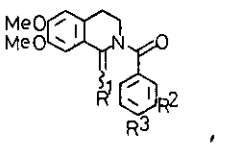
Table 1

Chiral Source	$[\alpha]_D$(c in $CHCl_3$)	Yield(%) 1 (*) 2
quinine	+73°(0.40)	19(R)14
quinidine	+50°(0.10)	13(R)28
(-)-N-methyl-ephedrine	-50°(1.00)	13(S)25
chirald	+67°(0.36)	18(R)64
(S)-2-(2,6-xylidinomethyl)pyrrolidine	+10°(0.39)	3(R)13
(-)-1-phenylethanol	0°(1.49)	0---20

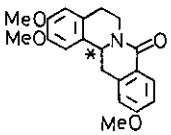
Table 2

Enamide	$LiAlH_4$	quinine	Yield(%) 1 (*) 2
1	2	2	1(R) 4
1	4	4	-----
1	10	10	19(R)14
1	10	20	12(R)37
1	10	30	-----

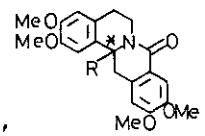
1: Optical Yield, 2: Chemical Yield, (*): Absolute Configuration



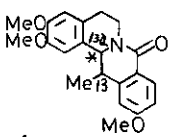
	R^1	R^2	R^3
(4)	H	H	OMe
(5)	H	OMe	OMe
(8)	Me	H	OMe
(9)	Me	OMe	OMe



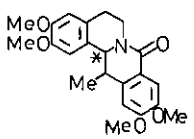
(6)



(7a: R=H)
(7b: R=D)



(10)



(11)

Table 3

Chiral Source	(6) Yield(%) 1 (*) 2	(7a) Yield(%) 1 (*) 2	(10) Yield(%) 1 (*) 2	(11)# $[\alpha]_D$(c in $CHCl_3$)	Yield(%) (*) 2
quinine	21(S)20	43(S)11	10(S) 9	-27°(0.63)	(S) 5
quinidine	23(R)15	21(R)19	14(R)31	+21°(1.18)	(R) 8
(-)-N-methyl-ephedrine	3(S)47	11(S)34	21(S)49	-16°(1.36)	(S)43
chirald	12(R)50	6(R)11	1(S)55	0°(0.88)	---65

1: Optical Yield, 2: Chemical Yield, (*): Absolute Configuration.

Optical yield could not be calculated by two methods.[7]

vity as summarized in the Table 3.

Absolute configuration of respective products was estimated from the comparisons of optical rotation and C.D. spectra of respective photo-products and also the corresponding amines. In the protoberberine alkaloids, the 13a-R or 13a-S configuration can now be simply determined[10] from the positive or negative optical rotation respectively.

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7 Optical yields were calculated either from comparisons of the optical rotation values of the optically pure compounds which were obtained by several recrystallizations or by the use of chiral lanthanide n.m.r. shift reagents[11].

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