ASYMMETRIC PHOTOCYCLIZATION OF N-α,β-UNSATURATED ACYLANILIDES

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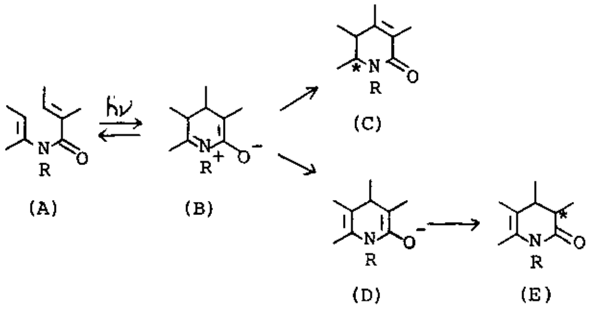
Abstract —— Photocyclization of the acylanilides (1a and b) and (3a and b) in the presence of a chiral dibasic acid yielded the optically active quinolones (2a and b), (4b), and (5a and b) with optical yields ranging from 12 to 42 %.

A cyclic intermediate (B) that has been postulated to be formed in the photocyclization of enamide (A) contains two functional moieties consisting of the iminium and enolate groups.[1] Previously,[2,3] we have reported asymmetric photocyclization of enamides that involved enantioselective reduction of the iminium moiety of the postulated intermediate (B) and gave the optically active lactam (C). As a part of the program aimed at the exploration of asymmetric synthesis of the heterocyclic compounds, we now report another new asymmetric photocyclization of acylanilides in the presence of a chiral dibasic acid possessing a C_2 axis.

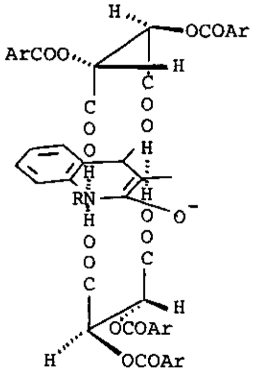
Irradiation of the N-(methacryloyl)anilide (1a) in the presence of a chiral source in a (3:1) solution of benzene-ether at 5-10°C for several hours gave the photocyclized lactam (2a) with the chemical and optical yields[4] as summarized in the table 1. The optically active lactam (2a) was obtained only when the diacyltartaric acids (di-p-toluoyl- and diacetyltartaric acids) were used as the chiral source which has also been employed as an effective chiral source in the enantioselective protonation of an enamine group as reported by Duhamel et al.[5,6] The effect of substituents on nitrogen of the methacryloylanilides was investigated by using three types of the acylanilides (1a, b, and c) as substrates and (-)-di-p-toluoyltartaric acid as a chiral source. Although the N-nor- and N-methylanilides (1a and b) gave the corresponding optically active lactams (2a and b), the N-benzylanilide (1c) yielded only racemic lactam (2c).

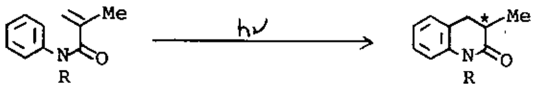
In order to establish asymmetric photocyclization of acylanilides as a useful synthetic tool for the preparation of optically active heterocyclic compounds, we then carried out photocyclization of the N-cyclohexenoylanilides (3a and b) in the presence of each of enantiomeric pair of di-p-toluoyltartaric acids as shown in the table 2. The photocyclized products were obtained as a mixture of cis- and trans-lactams (4a and b) and (5a and b) which were separated by preparative thin layer chromatography and characterized by comparisons with racemic authentic samples respectively.[7,8] In these cases studied, the cis-lactams (4a and b) were obtained in higher chemical yields but in lower optical yields[9] than the corresponding trans-lactams (5a and b). When (-)-chiral acid was used, (+)-lactams were predominantly formed and when (+)-chiral acid was used, (-)- lactams were formed predominantly. The best result was observed in the formation of trans-(6aS,10aS)-N-methyllactam (5b) with 42 % optical yield. Irradiation of the racemic lactams (2a) and (5b) in the presence of (-)-di-p-toluoyltartaric acid under the same condition as in the photocyclization of the acylanilides (1a) and (3b) recovered only the starting lactams. Therefore, it is assumed that an interaction would first occur between the chiral dibasic acid and a photocyclized intermediate to form an intermediary complex from which an optically active product is formed. In addition, the fact that all the optically active (+)-lactams (2a and b), (4b), and (5a and b),which were obtained only from the photocyclization employing (-)-di-p-toluoyltartaric acid, had the same absolute R-configuration at α-carbon to their lactam-carbonyl groups can be well explained by postulating the following stereomodels for the above complex as shown in the figure. (-)-Di-p-toluoyltartaric acid would interact with both β-carbon and nitrogen atoms of the enamine portion of an intermediate (D)[1] in the photocyclization. Therefore, top-side attack of the chiral acid would be hindered severely by steric congestion between benzene ring in an intermediate and ester group in the chiral source, thus making top-side attack unfavorable. On the other hand, attack of the acid from the less hindered bottom-side of the intermediate would be favored to afford the lactams (2a and b), (4b), and (5a and b), all of which thus have the same absolute configuration at α-carbon to the lactam-carbonyl groups.

Thus, asymmetric photocyclization of acylanilides in the presence of the chiral dibasic acid would provide a new and simple synthetic methodology of the optically active heterocyclic compounds. In addition, from the proposed mechanistic point of view, it would be possible to synthesize both of the enantiomeric pair



Figure





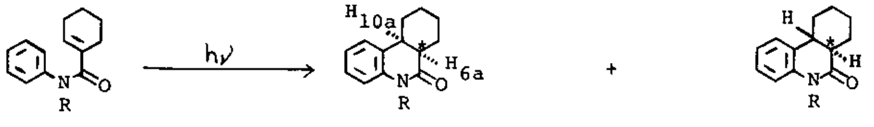
(1a,b,c) (2a,b,c)

a: R=H
b: R=Me
c: R=CH_2Ph

Table 1

Compd.	R	Chiral Source	C.Y.[1] (%)	$[\alpha]_D$(c,$CHCl_3$)	O.Y.[2] (%e.e.)	Abs. Config.[3]
1a	H	(-)-Di-p-t-L-(+)-t[4]	78	+10.2°(1.47)	12	R
1a	H	(+)-Di-p-t-D-(-)-t[4]	69	-13.3°(1.13)	16	S
1a	H	Diacetyl-L-(+)-tartaric Acid	76	+10.3°(1.16)	12	R
1a	H	L-(+)-Tartaric Acid	65	0°	--	--
1a	H	D-(-)-Mandelic Acid	45	0°	--	--
1a	H	Diethyl L-(+)-Tartrate	68	0°	--	--
1b	Me	(-)-Di-p-t-L-(+)-t[4]	63	+11.8°(1.36)	16	R
1c	CH_2Ph	(-)-Di-p-t-L-(+)-t[4]	42	0°	--	--

1) Chemical Yield, 2) Optical Yield, 3) Absolute Configuration, 4) Di-p-toluoyltartaric Acid



(3a,b) (4a,b) (5a,b)

a: R=H
b: R=Me

Table 2

Compd.	R	1)	C.Y.[2] (%)	$[\alpha]_D$(c,$CHCl_3$)	O.Y.[3] (%e.e.)	4) 6a,10a	C.Y.[2] (%)	$[\alpha]_D$(c,$CHCl_3$)	O.Y.[3] (%e.e.)	4) 6a,10a
3a	H	(-)	38	0°	--	---	25	+40.7°(0.27)	26	R , R
3a	H	(+)	40	0°	--	---	21	-20.7°(1.16)	13	S , S
3b	Me	(-)	34	+5.7°(2.30)	11	R , S	20	+63.8°(0.58)	38	R , R
3b	Me	(+)	40	-5.1°(1.17)	9	S , R	25	-71.3°(0.53)	42	S , S

1) Symbol for Optical Rotation of Di-p-toluoyltartaric Acid, 2) Chemical Yield, 3) Optical Yield, 4) Absolute Configuration

of the optically active quinolones with the desired absolute configurations by variation of enantiomeric pair of the chiral dibasic acid to be used.

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4 Optical yields were determined by nmr analysis of the NH-signal in (2a) and 3-methyl-signal in (2b) using the shift reagent ($Eu(tfc)_3$)[10] and absolute configurations were determined by the comparisons with data of the known (R)-(+)-(2a)[11] .

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cis-(6aR, 10aS)-(+)-(4a); $[\alpha]_D$ +22.9° (c=0.48, $CHCl_3$)
cis-(6aR, 10aS)-(+)-(4b); $[\alpha]_D$ +53.9° (c=0.36, $CHCl_3$)
trans-(6aS, 10aS)-(-)-(5a); $[\alpha]_D$ -158.8° (c=0.16, $CHCl_3$)
trans-(6aS, 10aS)-(-)-(5b); $[\alpha]_D$ -169.2° (c=0.50, $CHCl_3$)

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