ASYMMETRIC ELECTROPHILIC α-AMIDOALKYLATION 5[1]: IMPROVED STEREOSELECTIVITIES THROUGH NEW CHIRAL AUXILIARIES[2]

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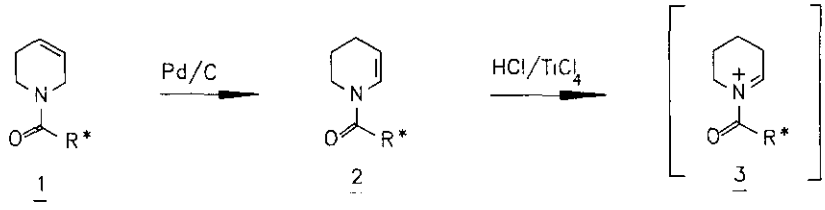
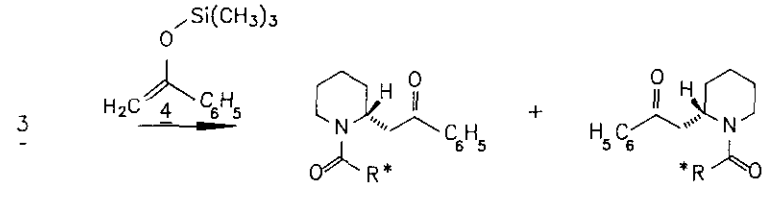
Abstract - Enamides of type 2 were employed in asymmetric α-amidoalkylation reactions with silyl enol ether 4 as nucleophile. Depending on the chiral auxiliary used, (R)-5/(S)-5 stereoselectivities up to 95/5 could be reached. Based on the obtained results a model for the transient acyliminium ion is proposed.

Acyliminium ions (e.g. 3) are common electrophilic intermediates in organic synthesis. Generally they react with nucleophiles under addition, which gives rise to the formation of α-substituted amides[3]. If such a reaction involves the generation of a stereogenic center stereoselective bond formation can be accomplished by employing N-acyliminium ions with chiral N-acyl substituents (asymmetric electrophilic α-amidoalkylation, e.g. from 3 to (R)-5 or (S)-5). Upon subsequent removal of the chiral auxiliary from the diastereomeric products of amidoalkylation ((R)-5 or (S)-5) optically pure α-substituted amines may eventually be isolated.

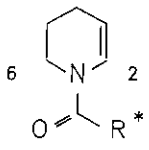




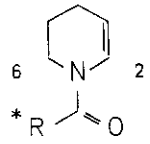
Recently we have shown[4] that stereoselectivities in asymmetric electrophilic α-amidoalkylation reactions with enamide 2b are strongly dependent (65/35 to 94/6[5]) on the nature of the nucleophile (i.e. the silyl enol ether). The lowest asymmetric induction had been obtained with silyl enol ether 4 ((R)-5b/(S)-5b = 65/35).

In this Letter we wish to report our attempts at improving said low selectivity observed with 4 as nucleophile by varying the chiral auxiliary -COR*.
To this end we have prepared the enamides[6] 2a and 2c-2e (cf. Table 1), using the isomerization of allylic amides (e.g. 1) with palladium on carbon[7] as a key step. The yields are listed in Table 1.

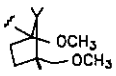
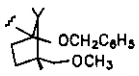
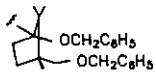
Table 1. Yields, ^{1}H[a] and ^{13}C[b] Nmr Chemical Shift Data and s-trans/s-cis-Population[c] of Enamides 2.



s-trans



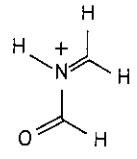
s-cis

			δ [ppm]				δ[ppm]		
2	R*	Yield [%]	H-2	C-2	C-6	s-trans/s-cis	H-2	C-2	C-6
a		79.7	6.49	124.6	41.0	66/34	7.25	124.3	43.6
b		90.7[f]	7.16	125.6	41.0	72/28	7.10	124.3	44.2
c		71.2	7.52	127.5	41.6	86/14	7.20	126.3	44.2
d		63.4	7.55	127.4[d]	41.7	86/14	7.20	126.2[d]	44.4
e		72.6	7.53	127.3[d]	41.7	85/15	7.15-7.35[e]	126.2[d]	44.3

[a] At 250 MHz (2b), 360 MHz (2a, 2c, 2e) and 400 MHz (2d) in $CDCl_3$, TMS as internal reference. [b] At 20 MHz (2b), 90 MHz (2e) and 100 MHz (2a, 2c, 2d) in $CDCl_3$, solvent as internal reference. [c] Determined from the integrals of the ^{1}H nmr spectra. [d] Assignment not verified. [e] Signal obscured.

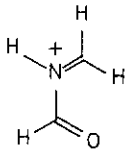
From the ^{1}H and ^{13}C nmr spectra of 2a-2e restricted rotation around the N-CO bond can be concluded. The signals to be assigned to the s-cis and s-trans rotamers differ in chemical shift and intensity (see Table 1). The conformer ratio corresponds to the intensity ratio (in ^{1}H nmr spectra) which increases significantly when going from 2a to 2b to 2c-2e. The preferred conformation of the amide group in 2a-2e can be determined by examination of the ^{13}C nmr spectra[8]. Earlier workers have shown that in amides and enamides (e.g. 2, $R^{4}=CH_3$ or C_6H_5, H in position 4 replaced by D) a carbon (attached to N) syn to the carbonyl oxygen is shielded relative to the corresponding carbon in the anti orientation. In the case of 2a-2e, the C-6 of the major isomer resonates at higher field than the C-6 of the minor isomer and in accordance therewith the opposite applies to the C-2 signals (see Table 1). Therefore one has to conclude that in enamides 2a-2e the s-trans conformation is predominant[9]. Steric interactions between the substituent on the amide carbonyl group and the substituents on nitrogen have been suggested as the major factor influencing such populations. The steric repulsion between the α-methylene group and the carbonyl substituent in such compounds has been considered to be more severe than the repulsion between the olefinic group and the carbonyl substituent.

Although in the acyliminium ion the olefinic bond of the enamide is replaced by an iminium subunit (e.g. 2->3), acyliminium ions and the corresponding enamides have in common that the steric demand of the two α-substituents at the nitrogen remains the same in principle. Both enamides 2 and acyliminium ions 3 have a methylene group and a methine unit attached to the nitrogen atom. If the conformational preference of the acyliminium ions 3 is determined by steric interactions similiar to those in enamides (2) one should expect that the s-trans conformation also predominates in acyliminium ions (3).



s-trans

6



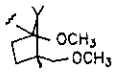
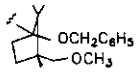
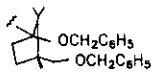
s-cis

In recent theoretical studies the acyliminium ion 6 has been included[11]. In the case of 6 the s-cis conformer has been predicted to be more stable than the s-trans conformer[11] by about 2.97 kcal/mole. One has to take into account, however,

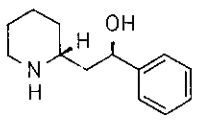
that the acyliminium ions 6 and 3 are quite different in structure.

During the course of this study we have obtained clear evidence that at least in some of the acyliminium ions (3c-3e) the s-trans conformation is preferred (see below).

Table 2. (R)-5/(S)-5-Diastereoselectivity[a] of Enol Ether Addition to 2

		Yield [%]		Selectivity
2	R*	(R)-5	(S)-5	(R)-5/(S)-5
a		38.9	11.2	69/31
b[4]		47.0	11.5	65/35
c		30.1	7.3	84/16
d		58.8	3.3	94/ 6
e		60.9	5.0	95/ 5

a) Determined by HPLC on silica gel with n-hexane/ethyl acetate = 9/1-8/2 (5b-5e) and n-hexane/Et_2O = 8/2 (5a) as eluent.



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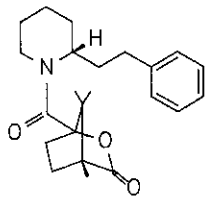

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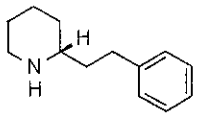
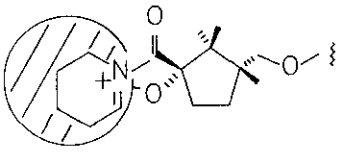


9

The transformations of enamides 2 to the α-amidoalkylation products 5 were all carried out under identical reaction conditions at -78° C. The reaction of 2a to 5a proceeded with only modest (R)-5a/(S)-5a stereoselectivity (69/31) close to the

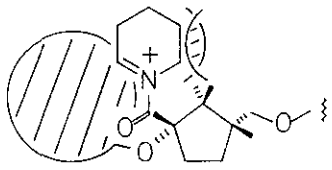
one observed earlier with 2b[4] (see Table 2). When enamide 2c was employed the stereoselectivity increased significantly to 84/16. Finally, enamides 2d and 2e underwent bond formation with pronounced stereoselectivity (94/6 and 95/5, see Table 2).

In each case the diastereomers could be separated by flash chromatography and were isolated as pure compounds in acceptable yields[12] (see Table 2). All of the major products belong to the (R)-series, as determined by chemical correlation involving compounds 7, 8 and 9[13].



s-trans

I



s-cis

II

From the obtained results a model for the transient N-acyliminium ions 3c-3e[14] can be deduced: According to said model the alkoxy group α to carbonyl (OCH_3 and $OCH_2C_6H_5$ respectively) shields the back face of the reactive intermediate and the approach of the nucleophile takes place at the front side (see I and II). Since the major diastereomers of compounds 5 belong to the R-series, it must be concluded that the product arises from addition to the si face of the intermediate. Conformations I and II having coplanar CO and N=C subunits fulfill this criterion, but the latter (II) involves severe steric interactions between the piperidine ring and the geminal methyl group attached to the cyclopentane ring. Thus it is reasonable to assume that the preferred geometry of the acyliminium ions 3c-3e that leads to the predominant isomer is represented by structure I. It is noteworthy that by regarding steric interactions as the major factor influencing the conformational equilibria (see above) one would also have predicted the s-trans geometry of the CO and N=C subunits (in I).

Further studies on asymmetric electrophilic α-amidoalkylation reactions involving enamides 2d and 2e are in progress.

GENERAL PROCEDURE

At -78°C HCl gas was passed into CH_2Cl_2 (5 ml) and after 15 min a solution of an appropriate enamide 2 (1.00 mmol) in CH_2Cl_2 (3 ml) was added dropwise under

vigorous stirring. HCl introduction was not interrupted during the addition and continued for 15 min after the addition of 2 was complete. Excess HCl was stripped off in vacuo at -78°C (15-30 min) and then a solution of $TiCl_4$ (199.2 mg, 1.05 mmol) in CH_2Cl_2 (0.2 ml) was added (frozen $TiCl_4$ was dissolved by shortly warming the reaction mixture), after 10 min followed by dropwise addition of a solution of silyl enol ether 4 (288.5 mg, 1.50 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was stirred for 30 min at -78°C and then quenched with H_2O (~10 ml). The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated. Pure diastereomers were obtained by flash chromatography[15] on silica gel using n-hexane/ethyl acetate = 8/2-9/1 or n-hexane/Et_2O = 6/4-8/2 as solvent.

ACKNOWLEDGEMENT

We are greatly indebted to Prof. F. Eiden for his generous support. Financial support of this work by Deutsche Forschungsgemeinschaft is gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. Part 4: K.Th. Wanner and G. Höfner, Arch. Pharm. (Weinheim), submitted for publication.

2. Presented in part at the meeting of the German Pharmaceutical Society, 1987 in Münster, FRG; K.Th. Wanner and G. Höfner, Arch. Pharm. (Weinheim), 320, 893 (1987).

3. For a review see: H. E. Zaugg, Synthesis, 1984, 85 (part I); H. E. Zaugg, ibid., 1984, 181 (part II).

4. K.Th. Wanner and A. Kärtner, Heterocycles, 26, 921 (1987); K.Th. Wanner and A. Kärtner, Arch. Pharm. (Weinheim), 320, 1253 (1987).

5. In a related but single case of asymmetric α-amidoalkylation a 96/4-stereoselectivity has been reported. Among others the authors refer to one of our papers[4] as describing acyclic systems of much lower stereoselectivity: K.E. Harding and C.S. Davis, Tetrahedron Lett., 29, 1891 (1988).

6. The compounds were prepared as follows: 1a: carbonyl diimidazole mediated coupling of (S)-α-methoxy- α-(trifluormethyl)phenylacetic acid and 1,2,3,6-tetrahydropyridine; 1c, 1d: alkylation of the diol obtained by reduction of 1b[7]; 2a, 2c, 2d: isomerization of 1a, 1c and 1d with Pd/C[7] at temperatures up to 150°C; 2e: double O-benzylation of the corresponding diol[7].

7. K.Th. Wanner and A. Kärtner, Heterocycles, 26, 917 (1987); K.Th. Wanner and A. Kärtner, Arch. Pharm. (Weinheim), 320, 1050 (1987).

8. B.M. Pinto, W.A. Szarek, and T.B. Grindley, Org. Magn. Res., 22, 676 (1984).

9. Others[10] have based their assignment on ^{1}H nmr data (H-2 in the s-cis conformation deshielded compared to H-2 in the s-trans conformer). According to said concept 2a would exist predominantly as s-trans conformer whereas in 2b-2e the s-cis conformation should be the prevailing one. This seems unreasonable, taking into account the considerations concerning steric interactions between the substituent on the carbonyl group and the substituents attached to nitrogen (vide supra).

10. J.K. Stille and Y. Becker, J. Org. Chem., 45, 2139 (1980).

11. We thank Prof. Würthwein for bringing his paper to our attention: R. Kupfer, E.U. Würthwein, M. Nagel, and R. Allmann, Chem. Ber., 118, 643 (1985).

12. All major isomers were fully characterised by ir and nmr spectra and combustion analysis. From some of the minor isomers only high field ^{1}H nmr spectra were recorded.

13. (R)-5a was transformed into (+)-norsedamine 7 similiar to (R)-5b[4]. Starting from (R)-5b there was also prepared compound 8 (H_2, Pd/C, HOAc, CF_3COOH; yield 66.6%) which in turn was transformed to compound 9 (LAH, THF; yield 56.6%; $[\alpha]_{578}$ = +7°, c=0.19, CH_3OH). (R)-5c - (R)-5e were converted to 9 in a similiar way. The configuration was deduced from the optical rotation or from the ^{1}H nmr spectrum of 8 obtained by treatment of 9 with (-)-camphanic acid chloride.

14. With 3a and 3b the model can be applied only with some uncertainty. In formula I, in the case of 3a the shield on the back face is represented by OCH_3, CH_2 (cyclopentane) and $-C(CH_3)_2-$ being replaced by CF_3 and phenyl respectively. In the case of 3b a -O-CO- bridge replaces the ether functional groups. Here the shielding of the back face (in 3b) might be due to Lewis acid forming a complex with this bridge.

15. W.C. Stille, M. Kahn, and A. Mitra, J. Org.Chem., 43, 2923 (1978).

Received, 8th July, 1988