ASYMMETRIC α-AMIDOALKYLATION. SYNTHESIS OF α-SUBSTITUTED PIPERIDINES OF HIGH ENANTIOMERIC PURITY

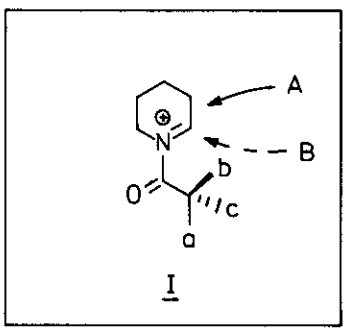
Klaus Th. Wanner* and Annerose Kärtner

Institut für Pharmazie und Lebensmittelchemie der Universität München,

Sophienstr. 10, 8000 München 2, FRG

Abstract - A stereoselective α-amidoalkylation was performed employing the chiral and cyclic enamide 1. The resulting amides 6 were employed in the synthesis of the title products.

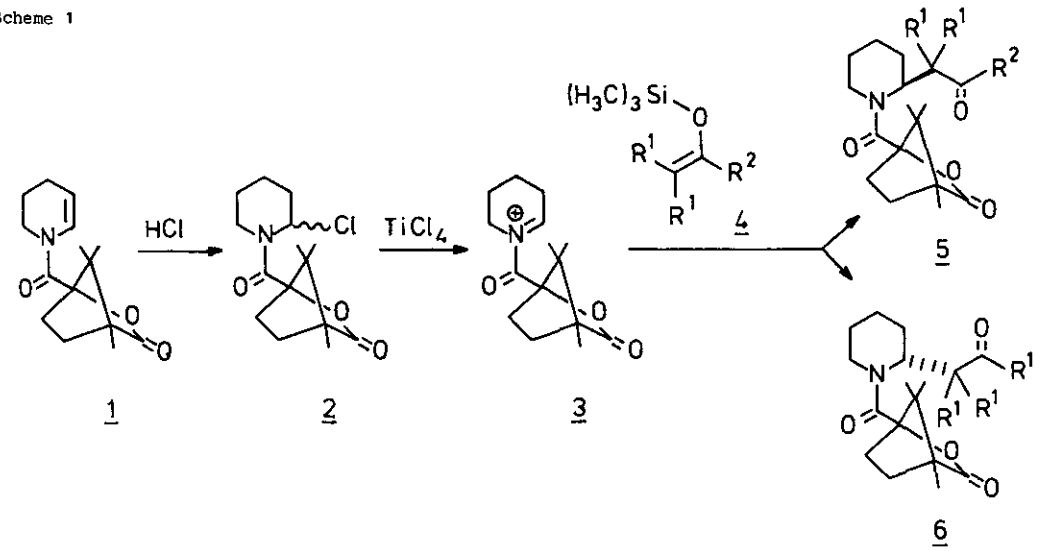
Designing highly efficient methods for asymmetric synthesis constitutes one of the most challenging and exciting problems in synthetic organic chemistry and there is an unabating search for new enantio- and diastereoselective bond forming reactions[1]. Most of the well established methods comprise the reaction of chiral nucleophiles such as enolates, wherein the chirality stems from a chiral auxiliary, with achiral electrophiles[2]. In contrast thereto reactions of electrophilic equivalents provided with a chiral auxiliary are few and have appeared in the literature only recently[3].We have designed a novel asymmetric synthesis based on the concept of α-amidoalkylation which in general is accomplished by trapping an electrophilic N-acyliminium ion (e.g.I) with a nucleophile. It occurred to us that a chiral appendix adjacent to the iminium subunit in I could favour the approach of a nucleophile along one path (either A or B) resulting in a stereoselective bond formation. Subsequent removal of the chiral auxiliary would then afford substituted piperidines in optically active form.



I

In this letter we wish to report the successful implementation of this plan. Enamides can act as α-amidoalkylation agents and therefore 1, which is readily available even in 20 g quantities by catalytic isomerization [5], seemed best suited for our purposes. Indeed 1 could be coupled with various silyl enolethers (4) to give a mixture of the diastereomeric α-substituted amides 5 and 6.

Scheme 1



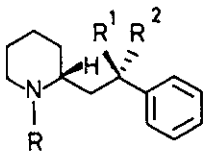
The transformation was effected by adding 1 in CH_2Cl_2 to a solution of HCl in CH_2Cl_2 at -78°C, stripping off excess HCl, treating the remaining solution with $TiCl_4$ or $SnCl_4$ (1.05 eq, 0.5 h) and subsequent addition of the respective enol ether 4 (1.25-2.0 eq, 0.5-1.0 h, -78°C). Aqueous workup then yielded a residue containing almost exclusively the desired amidoalkylation products 5[6] and 6[6] (as established by TLC) beside some ketone resulting from silyl enol ether hydrolysis. We assume that the reaction proceeds via the α-chloroamide 2 and the iminium ion 3 having the indicated structures. The stereoselectivity of the bond forming reaction was determined by HPLC and ranged from a modest 35.3:64.7 ratio (entry 1) to a quite reasonable 6.2:93.8 ratio when the sterically demanding enolether 4c was applied (entry 4).

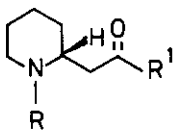
Table		Enol ether			Ratio	α-Subst. Amide 6		
entry	Lewis-Acid	4	R^1	R^2	5/6[a]	%yield[b]	$[\alpha]_{578}$[c]	conf.
1	$TiCl_4$	a	H	C_6H_5	35.3/64.7	47.0	+2.03°	R
2	$SnCl_4$	a	H	C_6H_5	30.7/69.3	d	-	
3	$TiCl_4$	b	H	$C(CH_3)_3$	21.8/78.2	57.9	+0.99°	R
4	$TiCl_4$	c	CH_3	C_6H_5	6.2/93.8	30.4	-76.60°	e

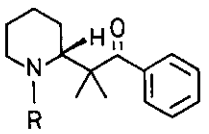
a) Determined by HPLC on a LiChrosorb Si 60 column eluted with 10-20% EtOAc in hexane. b) Yield of pure diastereomer 6, from flash or radial chromatography c) Specific rotation (c=1.0 in CH_3OH). d) Not determined. e) The absolute configuration of the newly produced asymmetric center is presently unknown. However, it is reasonably expected that the major product belongs to (R)-series (6c), by taking into account the results obtained with 4a,b.

In each case the major diastereomer could be separated from its epimer by chromatography and subsequent crystallisation. The compounds 6a-c are valuable intermediates in the synthesis of enantiomerically pure piperidine derivatives. This is best demonstrated by their transformation to sedamine 10 , a piperidine alkaloid of the sedamine family, homopipecolic acid 12 and the phenacylpiperidine 13 as outlined below. Said reactions also enabled us to assign the configuration for the newly created stereocenter at C-2 in some cases.

Scheme 2







6a R=Ca, R^1, R^2=O

7 R=Ca,R^1=OH,R^2=H

8 R=Ca,R^1=H, R^2=OH

9 R=H,R^1=OH, R^2=H

10 R=CH_3,R^1=OH,R^2=H

6b R=Ca,R^1=$C(CH_3)_3$

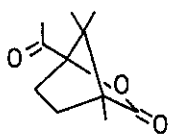
11 R=Ca,R^1=OH

12 R=H, R^1=OH

6c R=Ca

13 R=H

Ca:



Reduction of the amide 6a with $LiAlH_4$ (0.5 eq., Et_20: THF= 80:1,1.5 h, -78°C) occurred in a notably stereoselective manner, yielding the alcohol 7[6] as the major product along with the minor isomer 8[6] in a 91.5: 8.5 ratio. The epimer 7 was readily separated from 8 by chromatography (83.7% yield) and cleaved to the aminoalcohol 9[6](90.1% yield; $[\alpha]_{578}$= + 32.0°, c=2.03, CH_3OH) using 0.5 M KOH in CH_3OH and heating to reflux for 18 h. Methylation of 9 (CH_20,2.5 eq. $NaCNBH_3$) followed by chromatography afforded optically pure (+)-sedamine (10) in 93.0 % yield. The physical data of the piperidine alkaloid 10 were in good accord with those of the natural 2S,8S-(-)-sedamine, except for the sign of specific rotation [2S, 8S-(-)-sedamine[7]:$[\alpha]_D$= -82.4°, c=5.0, CH_3OH); 10:$[\alpha]_D$=+92.9°[8], c=1.0,CH_3OH] indicating that the major product (6a) from the amidoalkylation has 2R-configuration. In order to synthesize homopipecolic acid (12), 7a was subjected to a Baeyer Villiger oxidation (3 eq.CF_3CO_3H, 0-20°C, 1h) which afforded the N-protected amino acid 11[6](87.6% yield). Treatment of the amide 11 with 1.5 M H_2SO_4 (4h, 95°C) furnished after chromatography pure R-(-)-homopipecolic acid (12)in 90.6% yield. The R stereochemistry has been established by a comparison of the specific rotation of 12 ($[\alpha]_D$ = -36.9°[8], c=0.37, H_20) with reported literature values [9](R:$[\alpha]_D$ = -24°, c=0.4, H_20; S:$[\alpha]_D$= +29°, c=1.0, H_20). Finally 6c was converted to the aminoketone 13[6] in 61.6% isolated yield by the action of HCl/CH_3OH (25°C, 72h; $[\alpha]_D$= + 9.9°[8], c=1.8, CH_3OH).

In order to unequivocally verify that no racemization had occured during hydrolysis (6c- 13 and 11-12) a sample of each 13 and 12 was treated with (-)-camphanic acid chloride. 6c and 11 were formed each as a single diastereomer[10] indicating that the piperidine derivatives (12 and 13) were virtually enantiomerically pure.

In summary we have developed a method for the asymmetric amidoalkylation mediated by a chiral enamide (1) and demonstrated its utility in the synthesis of α-substituted piperidines of high enantiomeric purity. Currently we are engaged in further expand the scope of the reaction.

ACKNOWLEDGEMENT

We are greatly indebted to Prof. F. Eiden for generous support. We also thank Dr. S. Jendrzejewski for NMR measurements.

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(1) J.D. Morrison, Ed.; "Asymmetric Synthesis"; Academic Press, New York 1984, Vol. 1-5.

(2) See ref. 1, Vol. 2 p 243 and Vol. 3 pp 1-341.

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(5) See the preceding letter.

(6)Satisfactory spectroscopic data (^{1}H-NMR, JR, MS) and elemental analyses were obtained for the compounds reported in this paper.

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(8) Calculated from $[\alpha]_{546}$ and $[\alpha]_{578}$.

(9) T. Wakabayashi and K. Watanabe (Teijin Ltd.), Jpn Kokai Tokkyo Koho 78103490(1978); Chem. Abstr., 90, 87280 w (1979). See also: T. Wakabayashi, K. Watanabe, and Y. Kato, Synthet. Commun., 7, 239 (1977).

(10) Determined by HPLC (5c/6c) and 360 MHz ^{1}H-NMR(11). A control experiment had revealed that the ^{1}H-NMR signals of 11 and its epimer derived from 5b can clearly be resolved.

Received, 22nd December, 1986