

An
International
Journal
for
Reviews
and
Communications
in
Heterocyclic
Chemistry

HETEROCYCLES

Volume 26
Number 4

HETEROCYCLES

An International Journal for Reviews and Communications
in Heterocyclic Chemistry

CONTENTS

COMMUNICATIONS

- GHEORGHE SURPATEANU, ALAIN LABLACHE-COMBIER, PIERRE GRANDCLAUDON, and BERNARD MOUCHEL. Cycloaddition Reaction of 1,2,4-Triazolium Phenacylides with Cinnamic Esters..... 863
- ISTVÁN BITTER, GÁBOR TÓTH, ISTVÁN HERMECZ, and ZOLTÁN MÉSZÁROS. Nitrogen Bridgehead Compounds Part 59. Nucleophilic Substitution Reactions of 9-Bromo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones..... 869
- YASUOKI MURAKAMI, YUUSAKU YOKOYAMA, CHIYOKO AOKI, CHIEMI MIYAGI, TOSHIKO WATANABE, and TAICHI OHMOTO. A New Route to 4-Oxygenated β -Carbolines: The Total Synthesis of Crenatine..... 875
- HANH DUFAT-TRINH VAN, ELISABETH SEGUIN, FRANÇOIS TILLEQUIN, and MICHEL KOCH. Total Synthesis of 7-Hydroxy-''9-oxa''-anthracyclinone and Glycoside Derivatives 879
- SHIZUAKI MURATA, TAKASHI SUGIMOTO, and SADAO MATSUURA. A Novel Ring Formation of 1,2-Dihydroquinoxalines 883
- HANS LUDESCHER, CHING-PONG MAK, GERHARD SCHULZ, and HANS FLIRI. Chemistry of Penicillin Diazoketones. Part II: From Beta-lactam to Beta-lactone 885
- MASANORI SOMEI, FUMIO YAMADA, and YOSHIHIKO MAKITA. Total Syntheses of (\pm)-Agroclavine-I, (\pm)-6-Nor-chanoclavine-II, and (\pm)-Chanoclavine-II..... 895
- MONA HASSAN MOHAMED, NADIA SOBHY IBRAHIM, and MOHAMED HILMY ELNAGDI. Nitriles in Heterocyclic Synthesis: Synthesis of Some New Pyridine, Pyridazine and Pyrimidine Derivatives..... 899
- EBTISAM ABDEL AZIZ HAFEZ, MOHAMED HILMY ELNAGDI, ABDEL GHANI ALI ELAGAMEY, and FATHY MOHAMED ABDEL AZIZ EL-TAWEEL. Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[*c*]coumarin and of Benzo[*c*]pyrano[3,2-*c*]quinoline Derivatives..... 903
- JUZO NAKAYAMA, MASAHIRO SHIBUYA, and MASAMATSU HOSHINO.

Preparation of 2,5-Diacylselenophenes by Condensation of α, α' -Diketo Selenides with Glyoxal	909
MASAKATSU MATSUMOTO and NOBUKO WATANABE. A Facile Synthesis of 4-Mercaptoindoles	913
KLAUS TH. WANNER and ANNEROSE KÄRTNER. Isomerization of <i>N</i> -Acyl-1,2,5,6-tetrahydropyridines to <i>N</i> -Acyl-enamines by Palladium on Carbon	917
KLAUS TH. WANNER and ANNEROSE KÄRTNER. Asymmetric α -Amidoalkylation. Synthesis of α -Substituted Piperidines of High Enantiomeric Purity	921
JUNKO KOYAMA, TERUYO OKATANI, KIYOSHI TAGAHARA, YUKIO SUZUTA, and HIROSHI IRIE. Synthesis of Guaipyridine, Epiguaipyridine, and Related Compounds	925
MAKOTO WADA, HIDEKI AIURA, and KIN-YA AKIBA. Synthesis of Pyrrolidine Derivatives by Improved Aminoselenation <i>via</i> Addition of Boron Trifluoride Complex of Dihomoallylcuprate to Aldimines Containing α -Hydrogen	929
YOSHITERU OSHIMA, MAKI OKAMOTO, and HIROSHI HIKINO. Epimedins A, B and C, Flavonoid Glycosides of <i>Epimedium koreanum</i> Herbs	935
JUZO NAKAYAMA, YOICHI NAKAMURA, SHIGERU MURABAYASHI, and MASAMATSU HOSHINO. Preparation of α -Quinque- and α -Septithiophenes and Their Positional Isomers	939
YANG-CHANG WU, TIAN-SHUNG WU, MASATAKE NIWA, SHENG-TEH LU, and YOSHIMASA HIRATA. Thalicsessine, a New C ₂₀ -Diterpenoid Alkaloid from <i>Thalictrum sessile</i> Hayata	943

HETEROCYCLIC PAPERS

LAJOS KOVÁCS, PÁL HERCZEGH, GYULA BATTÁ, and ISTVÁN FARKAS. Two Acyclic Analogues of 2- β -D-Ribofuranosylthiazole-4-carboxamide (Tiazofurin)	947
GURY ZVILICHOVSKY and MORDECHAI DAVID. Molecular Structure and Stability of Isoxazolium Enolates	961
SHARON MARINUZZI-BROSEMER, BHALCHANDRA H. PATWARDHAN, KENNETH A. GREENBERG, and DONALD C. DITTMER. Interaction of Thietes with Electron-deficient Molecules	969
JOSÉ M. ALONSO, M. ROSARIO MARTÍN, JAVIER DE MENDOZA, TOMÁS TORRES, and JOSÉ ELGUERO. Proton-ionizable Macrocycles Containing 1,2,4-Triazole and 4-Amino-1,2,4-triazole Subunits	989
CHING-PONG MAK, GERHARD SCHULZ, and HANS FLIRI. Chemistry of Penicillin Diazoketones. Part III: Transformation of Tricyclic Beta-lactams	1001

ETSUKO KAWASHIMA, YUKO ANDO, KATSUMI TABEL, and HIROSHI MIYAMAE. Cyclization of <i>C</i> - and <i>O</i> -Acyl Derivatives of <i>p</i> -Toluamide <i>O</i> -Acetoacetyloxime	1015
PAUL D. WOODGATE, JOHN M. HERBERT, and WILLIAM A. DENNY. The Preparation of Pyrido[4,3,2- <i>de</i>]quinazoline and Pyrido[3,4,5- <i>de</i>]quinazoline	1029
JOHN M. HERBERT, PAUL D. WOODGATE, and WILLIAM A. DENNY. Formation of <i>peri</i> -Fused Heterocycles by Intramolecular Displacement of Halide	1037
JOHN M. HERBERT, PAUL D. WOODGATE, and WILLIAM A. DENNY. Behaviour of Some Perimidines towards Oxidants	1043

REVIEWS

AHMED KAMAL and PRALHAD B. SATTUR. Chlorosulfonyl Isocyanate: A Novel Reagent for the Synthesis of Heterocycles	1051
ARYA K. MUKERJEE. Azlactones: Retrospect and Prospect	1077

NEW HETEROCYCLIC NATURAL PRODUCTS

Polyacetates	1099
Aromatics	1102
Terpenes	1111
Steroids	1129
Alkaloids	1130
Antibiotics	1139
Miscellaneous	1144

TOTAL SYNTHESIS OF HETEROCYCLIC NATURAL PRODUCTS

Polyacetates	1145
Aromatics	1148
Terpenes	1150
Alkaloids	1151
Antibiotics	1158
Miscellaneous	1159

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

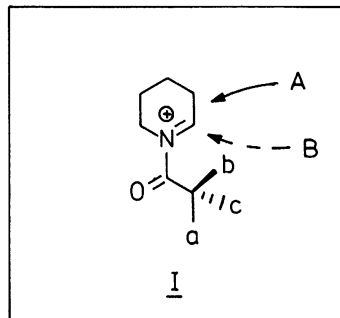
Klaus Th. Wanner* and Annerose Kärtner

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.

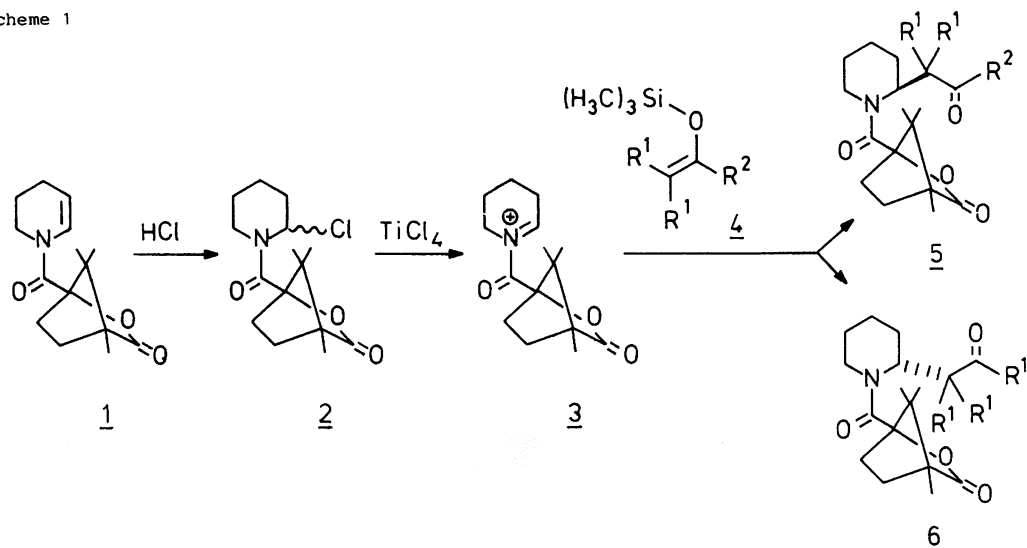
Designing highly efficient methods for asymmetric synthesis constitutes one of the most challenging and exciting problems in synthetic organic chemistry and there is an unabating search for new enantio- and diastereoselective bond forming reactions¹. Most of the well established methods comprise the reaction of chiral nucleophiles such as enolates, wherein the chirality stems from a chiral auxiliary, with achiral electrophiles². In contrast thereto reactions of electrophilic equivalents provided with a chiral auxiliary are few and have appeared in the literature only recently³. 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.

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 isomerization⁵, seemed best suited for our purposes. Indeed 1 could be coupled with various silyl enoethers (4) to give a mixture of the diastereomeric α -substituted amides 5 and 6.

Scheme 1



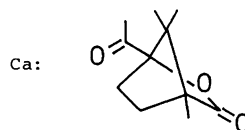
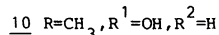
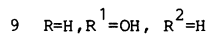
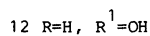
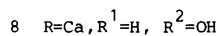
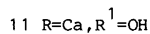
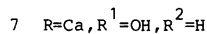
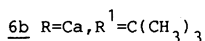
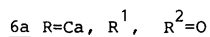
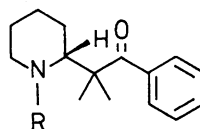
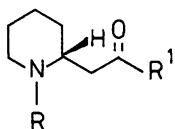
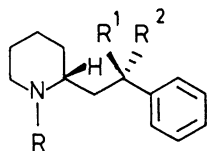
The transformation was effected by adding 1 in CH_2Cl_2 to a solution of HCl in CH_2Cl_2 at -78°C , stripping off excess HCl, treating the remaining solution with TiCl_4 or SnCl_4 (1.05 eq, 0.5 h) and subsequent addition of the respective enol ether 4 (1.25-2.0 eq, 0.5-1.0 h, -78°C). Aqueous workup then yielded a residue containing almost exclusively the desired amidoalkylation products 5⁶ and 6⁶ (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).

entry	Lewis-Acid	Enol ether		Ratio <u>5/6</u> ^a	α -Subst. Amide <u>6</u>		
		<u>4</u>	R ¹ R ²		%yield ^b	$[\alpha]_{578}^c$	conf.
1	TiCl_4	a	H C ₆ H ₅	35.3/64.7	47.0	+2.03°	R
2	SnCl_4	a	H C ₆ H 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 ₆ H 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



Reduction of the amide 6a with LiAlH₄ (0.5 eq., Et₂O: THF= 80:1, 1.5 h, -78°C) occurred in a notably stereoselective manner, yielding the alcohol 7⁶ as the major product along with the minor isomer 8⁶ 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 9⁶ (90.1% yield; [α]₅₇₈⁶ = + 32.0°, c=2.03, CH₃OH) using 0.5 M KOH in CH₃OH and heating to reflux for 18 h. Methylation of 9 (CH₂O, 2.5 eq. NaCNBH₃) 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-(-)-sedamine⁷: [α]_D⁷ = -82.4°, c=5.0, CH₃OH]; 10: [α]_D⁸ = +92.9°⁸, c=1.0, CH₃OH] 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. CF₃CO₃H, 0-20°C, 1h) which afforded the N-protected amino acid 11⁶ (87.6% yield). Treatment of the amide 11 with 1.5 M H₂SO₄ (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 ([α]_D⁸ = -36.9°⁸, c=0.37, H₂O) with reported literature values⁹ (R: [α]_D⁹ = -24°, c=0.4, H₂O; S: [α]_D⁹ = +29°, c=1.0, H₂O). Finally 6c was converted to the aminoketone 13⁶ in 61.6% isolated yield by the action of HCl/CH₃OH (25°C, 72h; [α]_D⁸ = + 9.9°⁸, c=1.8, CH₃OH).

In order to unequivocally verify that no racemization had occurred 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 diastereomer¹⁰ 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. Jendrzewski for NMR measurements.

REFERENCES AND FOOTNOTES

- (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.
- (3) For asymmetric synthesis using chiral acetals, see: J.M. McNamara and Y. Kishi, J. Am. Chem. Soc., 104, 7371(1982); W.S. Johnson, C. Edington, J.D. Elliott, and R. Silvermann, ibid., 106, 7588 (1984) and references therein. See also: A. Mori, K. Ishikara, and H. Yamamoto, Tetrahedron Lett., 27, 987 (1986); A. Alexakis, P. Mangeney, and J. F. Normant, ibid., 26, 4197 (1985) and references therein. Chiral 1,3-dioxolan-4-ones: S.H. Mashraqui and R. M. Kellogg, J. Org. Chem., 49, 2513 (1984). Chiral cyanooxazolopiperidine: M. Bonin, J. Royer, D.S. Grierson, and H.P. Husson, Tetrahedron Lett., 27, 1569 (1986) and references therein. Chiral glycinates: P.J. Sinclair, D. Zhai, J. Reibenspies, and R.M. Williams, J. Am. Chem. Soc., 108, 1103 (1986).
- (4) For Reviews, see: H.E. Zaugg, Synthesis, 1984, 85; H.E. Zaugg, ibid., 1984, 181. For a review on intramolecular amidoalkylations, see: W. N. Speckamp and H. Hiemstra, Tetrahedron, 41, 4367(1985).
- (5) See the preceding letter.
- (6) Satisfactory spectroscopic data (¹H-NMR, IR, MS) and elemental analyses were obtained for the compounds reported in this paper.
- (7) C. Schöpf, G. Dummer, and W. Wüst, Liebigs Ann. Chem., 626, 134 (1959).
- (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 ¹H-NMR(11). A control experiment had revealed that the ¹H-NMR signals of 11 and its epimer derived from 5b can clearly be resolved.

Received, 22nd December, 1986