Synthesis of Optically Active Condensed Tetrahydropyridin-3-ones as Precursors of Alkaloid Analogues

Heike Faltz, Alexander Radspieler and Jürgen Liebscher*

Institut für Chemie, Humboldt-Universität Berlin, Hessische Str. 1-2, D-10115 Berlin, Germany

Fax: 49-30-2093 7343, e-mail: liebscher@chemie.hu-berlin.de

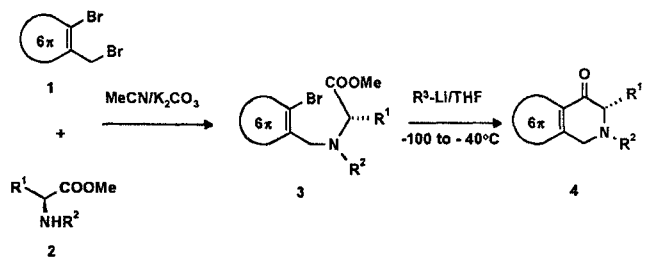
Dedicated to Prof. Ekkehard Winterfeldt on the occasion of his 65th birthday

Received 25 February 1997

Abstract: Reaction of α-aminoester **2** with *o*-bromobenzylbromide or 3-bromo-2-bromomethylindole **1** gives N-alkylation products **3**, which further undergo intramolecular acylation upon Br/Li-exchange. This sequence represents the first access to optically active condensed tetrahydropyridin-3-ones **4**.

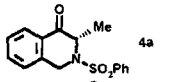
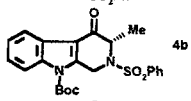
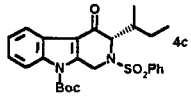
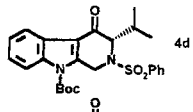
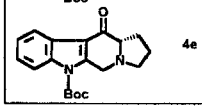
Condensed tetrahydropyridin-3-ones such as tetrahydroisoquinolin-4-ones[1], pyrrolo[1,2-b]isoquinolinones[2] or thienoindolizinones[3] are of practical interest as pharmaceutically active products, as intermediates for cholinomimetic compounds as well as in the synthesis of benzophenanthridine alkaloid analogues of potential antileukemic or anti-HIV activity. Known syntheses of condensed tetrahydropyridin-3-ones are based on intramolecular Friedel-Crafts-acylation of α-benzylamino acids[1-9] or α-heteroarylmethylamino acids[10,11] or corresponding esters and nitriles[12], intramolecular Dieckmann condensation[12] of *o*-ethoxycarbonylbenzylaminoesters, and Grignard reaction[12] of 4-hydroxyisoquinolinium salts. All these methods have not been applied to the synthesis of optically active products.

We became interested in making use of chiral naturally occurring amino acids to get access to optically active condensed tetrahydropyridin-3-ones **4** as promising starting material for the asymmetric synthesis of alkaloid-related structures in the ß-carboline and isoquinoline series. Extensive studies[13] of the known route by intramolecular Friedel-Crafts acylation of benzylamino or heteroarylmethylamino acids gave racemic materials in all cases. We therefore seeked to develop a novel synthesis of condensed tetrahydropyridin-3-ones **4** omitting high temperatures and strongly acidic conditions. Since the known intermolecular acylation of lithiated aromatics with optically active amino acids occurs without racemization[14] and intramolecular acylation of γ-(*o*-bromophenyl) or γ-(*o*-bromoheteroaryl)butyrates in the presence of BuLi afforded the corresponding condensed cyclohexanones[15,16] we decided to synthesize condensed tetrahydropyridin-3-ones **4** starting from *o*-bromobenzyl bromide or *o*-bromoheteroarylmethyl bromide **1** and esters of biogenic α-amino acids **2** (Scheme 1). Primary *N*-alkylation of the α-aminoesters **2** gave high yields of *o*-bromobenzylamino or *o*-bromoindolylmethylaminoester **3**. Br/Li-exchange with *n*-BuLi at low temperature caused the anticipated intramolecular acylation affording condensed tetrahydropyridin-3-ones **4** in optically active form.[17] In the case of **4a** also *tert*-BuLi and another temperature program was used[18] in order to increase the yield. The product however was 4-*tert*-butyl-4-hydroxy-3-methyl-2-phenylsulphonyl-1,2,3,4-tetrahydroisoquinoline



Scheme 1

Table 1. Condensed (*S*)-Tetrahydropyridine-3-ones **4**

product **4**	$[\alpha]_D^{24}$	R^3-Li	yield of 4(%)	yield of 3(%)
 **4a**	+52.1(c=1, MeOH)	*n*-BuLi or *tert*-BuLi [18]	10 58 [18]	75
 **4b**	-15.8(c=1, MeCN)	*n*-BuLi	81 [19]	81
 **4c**	-97.3(c=1, MeOH)	*n*-BuLi	41	60
 **4d**	-35.1 (c=1, MeOH)	*n*-BuLi	51	68
 **4e**	+45.7(c=1, MeOH)	*n*-BuLi	54 [20]	86

formed by addition of *tert*-BuLi to the carbonyl group of the expected tetrahydroisoquinolinone **4a** (see Table 1, note 18). As side reactions in the synthesis of condensed tetrahydropyridinones **4** addition of *n*-BuLi to the ester functional group of **3**, Br/H exchange at **3** due to incomplete cyclization or cleavage of the pyridine-ring of **4** by ß-elimination and formation of substituted 3-acryloylindole-2-methylamines were observed. Structure elucidation of products **3** and **4** is based on spectroscopic methods [18-20] and X-ray crystal analysis of the ß-carboline **4b**. No indication of racemization was found. E. g. the investigation of products **4b** by chiral HPLC using a corresponding racemate as reference did not show any trace of the (*R*)-enantiomer.

The reaction sequence **2** → **3** → **4** represents the first synthesis of optically active condensed tetrahydropyridin-3-ones. Their employment in further asymmetric synthesis is currently under investigation. First results revealed stereospecific *anti* additions to the

CO double bond affording enantiomerically pure tetrahydropyridin-3-ols (for an analogous *in situ* alkylation see note[18]).

Acknowledgement: We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie.

References and Notes

(1) González-Cameno, A. M.; Badía, D.; Domínguez, E.; Urtiaga, M. K.; Arriortua, M. I.; Solans, X. *Tetrahedron* **1994**, *50*, 10971.

(2) Martin, L. L.; Scott, S. J.; Setescak, L. L.; Van Engen, D. *J. Heterocycl. Chem.***1987**, *24*, 1541.

(3) Short, J. H.; Ours, C. W. *J. Heterocycl. Chem.* **1975**, *12*, 869.

(4) Kametani, T.; Fukumoto, K. *J. Chem. Soc.* **1963**, 4289.

(5) Rigo, B.; Kolcouris, N. *J. Heterocycl. Chem.* **1983**, *20*, 893.

(6) Grethe, G.; Lee, H. L.; Uskokovic, M.; Brossi, A. *J. Org. Chem.* **1968**, *33*, 491.

(7) Martin, L. L.; Scott, S. J.; Agnew, M. N.; Setescak, L. L. *J. Org. Chem.* **1986**, *51*, 3697.

(8) Umezawa, B.; Hoshino, O.; Terayama, Y. *Chem. Pharm. Bull.* **1968**, *16*, 180.

(9) Umezawa, B.; Hoshino, O.; Yamanashi, Y. *Tetrahedron Lett.* **1969**, 933.

(10) Marchalin, S.; Decroix, B; Morel, J. *Acta Chem. Scand.* **1993**, *47*, 287.

(11) Lebosquain, D.; Decroix, B. *Heterocycles* **1993**, *36*, 2303.

(12) for a review see: Bobbitt, J. M. in *Adv. Heterocycl. Chem.* Katritzky, A. R., Ed.; Academic Press: New York, 1973; Vol. 15; p. 99.

(13) Woydowski, K.; Faltz, H.; Liebscher, J. *unpublished results.*

(14) a) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Amer. Chem. Soc.* **1984**, *106*, 1095. b) Buckley, T. F.; Rapoport, H. *J. Amer. Chem. Soc.* **1981**, *103*, 6157.

(15) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

(16) Quallich, G. J.; Fox, D. E.; Friedmann, R. C.; Murtiashaw, C. W. *J. Org. Chem.* **1992**, *57*, 761.

(17) **General Procedure 3 → 4:** A mixture of **3** (1.8 mmol) and dry THF (30 mL) was put under nitrogen atmosphere and cooled to -100°C. 1.6M *n*-BuLi solution (1.25 mL; 2 mmol) was rapidly added while the temperature must not exceed -90°C. After stirring at -100°C for about 2 h (or in case of *tert*-BuLi for 30 min followed by stirring at -40°C for 5h) the mixture was quenched by pouring it into a saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated. The remaining oils were purified by column chromatography (silica gel, hexane / AcOEt or CH_2Cl_2 / acetone).

(18) With *n*-BuLi at -100°C 10% **(*S*)- 3-Methyl-2-phenylsulphonyl-1,2,3,4-tetrahydroisoquinoline-4-one (4a)** was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (d, 3H, CH_3, J = 7.2); 4.05 (q, 1H, CH-N, J = 7.2); 4.60 (d, 1H, CH_2-N, J =17.9); 4.93 (d, 1H, CH_2-N, J = 17.9); 7.15 (m, 4H, CH_{ar}); 7.36 (m, 2H, CH_{ar}); 7.54 (m, 2H, CH_{ar}); 7.64 (m, 1H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.4 CH_3; 43.0 CH_2-N; 58.3 CH-N; 126.1 CH_{ar}; 127.4 CH_{ar};127.8 CH_{ar}; 128.2 CH_{ar}; 129.0 $C_{q/ar}$; 129.4 CH_{ar}; 133.1 CH_{ar}, 134.6 CH_{ar}, 138.1 $C_{q/ar}$; 139.4 $C_{q/ar}$; 194.4 CO; the use of *tert*-BuLi at -100°C for 30 min and -40°C for 5h caused additional 1,2-addition of *tert*-BuLi to C=O affording 58% of the corresponding **(3*S*, 4*S*) 4-*tert*-Butyl-4-hydroxy-3-methyl-2-phenylsulphonyl-1,2,3,4-tetrahydroisoquinoline**: $[\alpha]_D^{24}$ = -6.6 (c = 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.54 (d, 3H, CH_3, J = 6.6 Hz); 1.02 (s, 9H, $(CH_3)_3C$); 3.94 (d, 1H, CH_2-N, J = 15.6 Hz); 4.64 (q, 1H, CH-N, J = 6.6 Hz); 4.66 (d, 1H, CH_2-N, J = 15.6 Hz); 6.99 (m, 1H, CH_{ar}); 7.17 (m, 2H, CH_{ar}); 7.51 (m, 4H, CH_{ar}); 7.86 (m, 2H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.2 CH_3; 25.1 $(\underline{C}H_3)_3C$; 38.6 $(CH_3)_3\underline{C}$; 42.00 CH_2-N; 50.7 CH-N; 76.7 C_q-OH; 123.8 CH_{ar}; 124.8 CH_{ar}; 125.8 CH_{ar}; 126.2 CH_{ar}; 126.4 CH_{ar}; 127.8 CH_{ar}; 130.4 $C_{q/ar}$; 131.4 CH_{ar}; 134.9 $C_{q/ar}$; 137.8 $C_{q/ar}$.

(19) **(*S*)-2-Phenylsulphonyl-9-*tert*-butyloxycarbonyl-3-methyl-1,2,3,9-tetrahydrocarbolin-4-one (4b)**: ee > 99% determined by chiral HPLC; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (d, 3H, CH_3, J = 7.3 Hz); 1.68 (s, 9H, $(CH_3)_3C$); 4.60 (q, 1H, CH-N, J = 7.3 Hz); 4.66 (d, 1H, CH_2-N, J = 19.8 Hz); 5.56 (d, 1H, CH_2-N, J = 19.8 Hz); 7.24 (m, 4H, CH_{ar}); 7.63 (m, 2H, CH_{ar}); 7.96 (m, 2H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.0 CH_3; 28.6 $(\underline{C}H_3)_3C$; 41.1 CH_2-N; 58.1 CH-N; 87.2 $(CH_3)_3\underline{C}$; 114.3 $C_{q/ar}$; 115.5 CH_{ar}; 121.8 CH_{ar}; 125.2 $C_{q/ar}$; 125.3 CH_{ar}; 126.1 CH_{ar}; 127.1 CH_{ar}; 129.5 CH_{ar}; 133.3 CH_{ar}; 135.9 $C_{q/ar}$; 139.4 $C_{q/ar}$; 145.5 $C_{q/ar}$; 149.5 CO-N; 192.2 CO.

(20) **(*S*)-6-*tert*-Butyloxycarbonyl-1,2,3,5,6,11a-hexahydro-indolizino[6.7-b]indol-11-one (4e)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.64 (s, 9H, $(CH_3)_3C$); 1.83 (m, 2H, CH_2); 2.34 (m, 2H, CH_2); 2.68 (1H, dd, CH-N, J_1 = 16.3 Hz, J_2 = 8.1 Hz); 3.09 (m, 1H, CH_2-N); 3.28 (m, 1H, CH_2-N); 4.02 (d, 1H, CH_2-N, J = 18.3 Hz); 4.69 (d, 1H, CH_2-N, J = 18.3Hz); 7.26 (m, 2H, CH_{ar}); 7.99 (m, 1H, CH_{ar}); 8.16 (m, 1H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 22.2 CH_2; 25.0 CH_2; 28.5 $(\underline{C}H_3)_3C$; 50.7 CH_2-N; 53.5 CH_2-N; 68.0 CH-N; 86.2 $(CH_3)_3\underline{C}$; 115.6 CH_{ar}; 116.3 $C_{q/ar}$; 121.8 CH_{ar}; 124.9 CH_{ar}; 125.8 CH_{ar}; 149.8 $C_{q/ar}$; 150.0 CO-N; 194.7 CO.