N-ACYLIMINIUM CYCLIZATIONS: FORMATION OF THE FURO[3,4-a]PYRROLIZINE RING SYSTEM[1]

Hugo Ent, Henk de Koning, and W. Nico Speckamp*

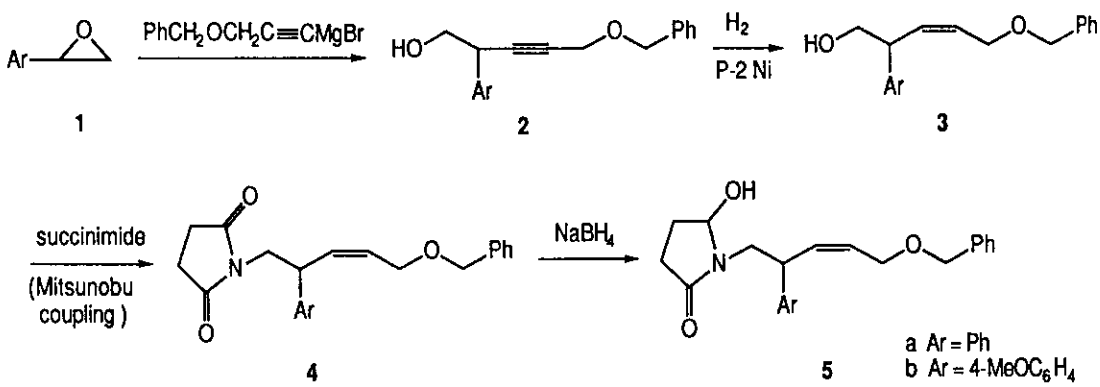
Laboratory of Organic Chemistry, University of Amsterdam,

Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract - The hydroxylactams **5a,b** could be converted into the furo[3,4-a]pyrrolizine derivatives **10a,b** *via* the 2-aza-Cope rearrangement cyclization reaction of N- acyliminium ions.

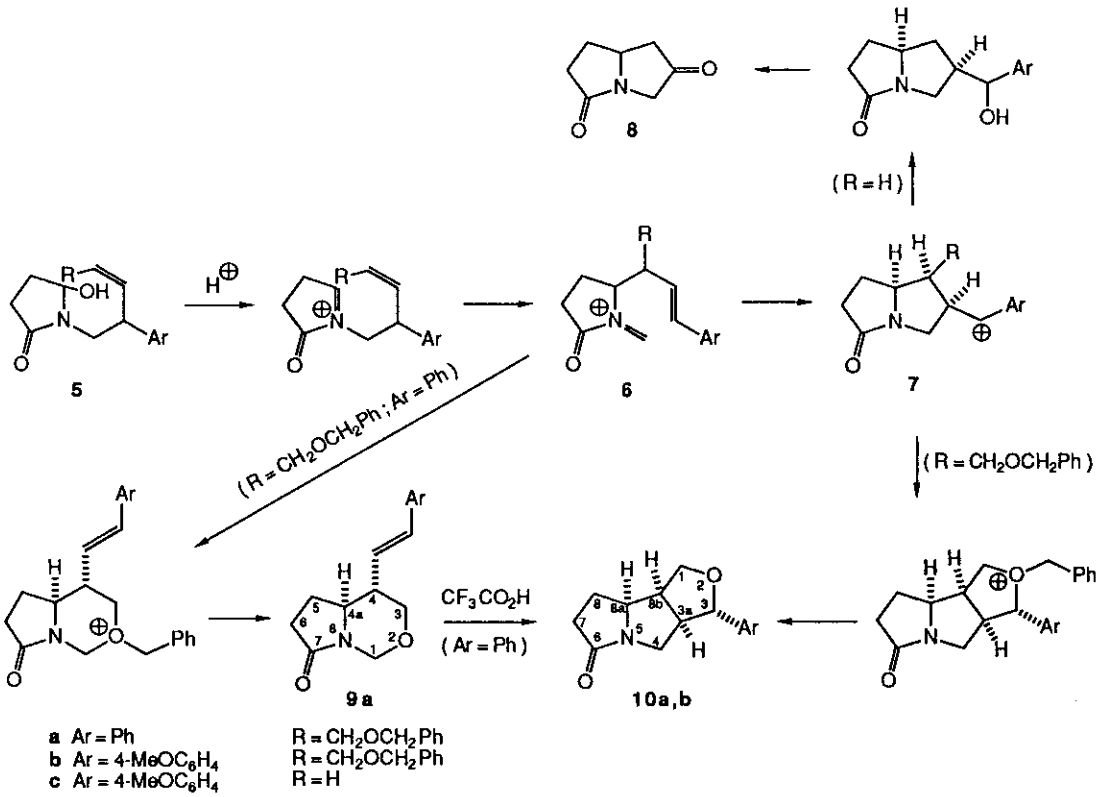
Previously we reported the synthesis of the pyrrolizidine derivative **8**, starting from N-(2-aryl-3-butenyl)hydroxylactam **5c**, using the tandem 2-aza-Cope rearrangement cyclization reaction of N-acyliminium ions as a key step (Scheme 2).[2] Searching for a new synthetic path to necine bases like macronecine[3] and petasinecine[4] *via* a similar series of reactions as mentioned above, we discovered a synthesis for the hitherto unknown furo[3,4-a]pyrrolizine ring system **10**, which is the subject of this paper.

The required starting hydroxylactams **5a,b** were prepared according to Scheme 1



Scheme 1

Upon treatment of the phenyl substituted hydroxylactam **5a**, having a *Z*-benzyloxymethyl substituent attached to the butene moiety, with formic acid or trifluoroacetic acid for 18 h at room temperature the bicyclic ether **9a** and the tricyclic ether **10a** were isolated in an approximately 1:1 ratio. More forcing reaction conditions, trifluoroacetic acid for 18 h at 60 °C, led to sole formation of the tricyclic ether **10a** (64% isolated yield). The bicyclic alkoxylactam **9a** proved to be remarkably unreactive, but upon reflux for 20 h in trifluoroacetic acid ^{1}H-nmr analysis revealed that it had been converted for the greater part into the tricyclic ether **10a**, the remainder being unchanged starting material.

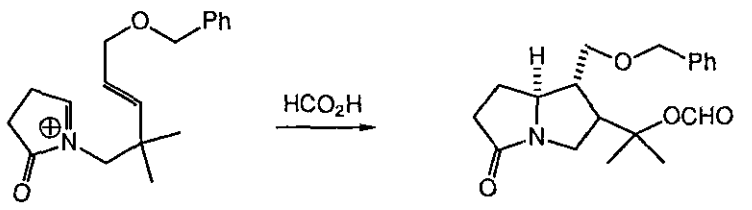


Scheme 2

Upon stirring the p-methoxyphenyl substituted hydroxylactam **5b** in formic acid for 70 h at room temperature the tricyclic ether **10b** could be isolated in 67% yield. Lower yields (30% and 23%, respectively) were obtained after reaction for 18 h in formic acid or trifluoroacetic acid. The stable tricyclic ethers **10a,b** could not be cleaved to pyrrolizidine derivatives with boron trifluoride etherate/tetra(*n*-butyl)ammonium iodide[5] and remained unchanged even upon treatment with sulfuric acid/acetic acid (1:4) at 87 °C for 1 min.

In contrast to our earlier results[2] with **5c**, the hydroxylactams **5a,b** could not be cyclized in the weaker acidic medium, formic acid/acetic acid (2:3).

The bicyclic ether **9a** and the tricyclic ethers **10a,b** would originate from the reaction of the nucleophilic benzylic oxygen atom with the intermediary carbocations[6] **6** and **7**, respectively. The bicyclic ether **9b** is not formed in case of **5b**, presumably because of the relatively fast cyclization to **7b**, in which the carbocation is stabilized by the p-methoxyphenyl substituent. In this connection it should be mentioned that Hart[7] obtained the 6,7-*trans* substituted pyrrolizidine derivative **12** upon reaction of the *E*-substituted alkenylhydroxylactam **11** in formic acid for 25 h at room temperature (Scheme 3). Apparently in this case reaction of the benzylic oxygen with the carbocation is precluded by their vicinal trans relationship. Since the bicyclic ether **9b** is not formed in case of **5b**, it is unlikely that the starting alkene geometry is a determining factor in the pathway of **6** → **9**. The type of cationic intermediate **7** therefore is of decisive influence in the rearrangement result.



11 **12**

Scheme 3

EXPERIMENTAL

5-Benzyloxy-2-phenyl-3-pentynol (2a). A solution of benzyl propargyl ether[8] (7.90 g; 54 mmol) in dry ether (60 ml) was added under N_2 to a solution of ethylmagnesium bromide, prepared from magnesium (1.46 g; 60 mmol) and ethyl bromide (5.56 g; 51 mmol) in dry ether (60 ml). The mixture was stirred under reflux for 1 h, cooled, and diluted with dry ether (60 ml). Then a solution of freshly distilled phenyloxirane (5.77 g; 48 mmol) in ether (50 ml) was added dropwise to the mixture under gentle reflux. After refluxing for another 0.5 h the mixture was cooled and treated with dilute aqueous NH_4Cl, followed by dilute HCl. The aqueous layer was extracted with ether. The combined extracts were washed with satd sodium bicarbonate solution and with brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography[9] on silica gel (acetone/CH_2Cl_2 1 : 200 → 1 : 20) gave **2a** (7.77 g; 61%) as an oil: ir 3410 cm^{-1}; nmr δ 2.61-3.06 (m, 1H, OH), 3.73-3.91 (m, 3H, $ArCHCH_2O$), 4.24 (d, *J*=2, 2H, $OCH_2C{\equiv}$), 4.60 (s, 2H, CH_2Ph), 7.23-7.40 (m, 10H, ArH); ms [*m/z* (%)] 266 (0.4), 235 (1.3), 205 (15), 144 (17), 128 (100), 91 (98). Exact mass calcd for $C_{18}H_{18}O_2$ 266.1307: Found 266.1300.

5-Benzyloxy-2-(4-methoxyphenyl)-3-pentynol (2b). Freshly prepared 4-methoxyphenyloxirane (crude product, obtained from 35 mmol of 4-methoxybenzaldehyde according to Coburn's procedure[10]) was converted to the alcohol **2b** following the procedure described above. Flash chromatography furnished **2b** (6.44 g; 62%) as a light yellow oil: ir 3572, 3440, 1608, 1507, 828 cm^{-1}; nmr δ 2.18 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 3.69-3.90 (m, 3H, $ArCHCH_2O$), 4.29 (d, *J*=2, 2H, $OCH_2C{\equiv}$), 4.65 (s, 2H, CH_2Ph), 6.82-6.98 (m, 2H, ArH), 7.28-7.42 (m, 7H, ArH); ms [*m/z* (%)] 296 (0.9), 235 (13), 158 (100), 121 (24), 91 (37). Exact mass calcd for $C_{19}H_{20}O_3$ 296.1412: Found 296.1403.

Imide 4a. To a stirred solution of $Ni(OAc)_2.4H_2O$ (0.496 g; 2 mmol) in 95% EtOH (20 ml) under H_2 was added 2 ml of a 1*M* solution of $NaBH_4$ in 95% EtOH.[11] Then 1,2-diaminoethane (0.264 ml; 4 mmol) was added, followed by a solution of alkynol **2a** (3.62 g; 13.6 mmol) in 95% EtOH (20 ml). The black mixture was stirred for 3.5 h at room temperature, after which a small amount of active charcoal was added. The mixture was filtered through hyflo super cel, and the filtrate was taken up in ether and washed with satd brine (2x). The combined aqueous solutions were extracted with ether, and the combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. To a stirred solution of the crude alkenol **3a**, triphenylphosphine (4.45 g; 17 mmol) and succinimide (1.68 g; 17 mmol) in THF (15 ml) under N_2, cooled in an ice-water bath, was slowly added a solution of dimethyl azodicarboxylate (2.48 g; 17 mmol) in THF (15 ml). The mixture was stirred overnight at room temperature, concentrated in vacuo, and then partitioned between $CHCl_3$ (150 ml) and aqueous 5% KOH (150 ml). The aqueous phase was extracted twice with $CHCl_3$ (150 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography on

silica gel (acetone/CH_2Cl_2 1: 200 → 1: 50) afforded imide **4a** (3.98 g; 84%) as a colourless oil, which solidified upon standing: mp 57-58 °C [(i-Pr)$_2$O]; ir 1773, 1700 cm^{-1}; nmr δ 2.52 (s, 4H, $COCH_2CH_2CO$), 3.66-4.26 (m, 5H, NCH_2CH and $=CCH_2$), 4.46 (s, 2H, CH_2Ph), 5.69-5.84 (m, 2H, HC=CH), 7.21-7.40 (m, 10H, ArH); ms (field desorption) M^+ = 349.

Imide 4b. The alkynol **2b** (4.03 g; 13.6 mmol) was reduced (6 h) to the alkenol **3b** and coupled with succinimide as described above to give imide **4b** (3.94 g; 76%) as a colourless oil: ir 1772, 1700 cm^{-1}; nmr δ 2.52 (s, 4H, $COCH_2CH_2CO$), 3.65-4.15 (m, 8H, NCH_2CH, OCH_3, and $=CCH_2$), 4.46 (s, 2H, CH_2Ph), 5.70-5.77 (m, 2H, HC=CH), 6.82-6.87 (m, 2H, ArH), 7.15-7.32 (m, 7H, ArH); ms (field desorption) M^+ = 379.

Hydroxylactam 5a. To a stirred solution of imide **4a** (0.528 g; 1.51 mmol) in EtOH (80 ml) under N_2, cooled in an ice-water bath, was added $NaBH_4$ (1.0 g). The mixture was stirred at -5 ~ 0 °C for 4 1/4 h while adding 2-3 drops of 4*M* ethanolic HCl every 1/4 h. The mixture was then poured into brine (400 ml) and extracted with five 60 ml portions of CH_2Cl_2. The combined extracts were washed with brine and concentrated in vacuo. Flash chromatography on silica gel (acetone/CH_2Cl_2 1:10 → 1:1) provided the hydroxylactam **5a** (0.521 g; 98%; 1:1 mixture of isomers) as a colourless oil: ir 3350 (br), 1680 cm^{-1}; nmr δ 2.03-2.52 (m, 3H, $NCOCH_aCH_2$), 3.34-3.48 (m, 1.5 H, $NCOCH_b$ and 0.5 OH), 3.65-4.34 (m, 5.5 H, $=CCH_2O$, NCH_2CH, and 0.5 OH), 4.47 and 4.52 (each s, each 1H, CH_2Ph), 4.69-4.78 and 5.02-5.11 (each m,each 0.5 H, NCHO), 5.69-5.99 (m, 2H, HC=CH), 7.15-7.35 (m, 10H, ArH); ms (field desorption) M^+ = 351.

Hydroxylactam 5b. Imide **4b** (1.138 g; 3 mmol) was reduced as described above. Flash chromatography (acetone/CH_2Cl_2 1:8 → 1:3) gave the hydroxylactam **5b** (0.934 g; 82%; 1:1 mixture of isomers) as a colourless oil, which solidified upon standing: ir 3360, 1677 cm^{-1}; nmr δ 2.06-2.43 (m, 3H), 3.13 (d, *J*=9, 0.5 H, OH), 3.29-3.39 (m, 1H, $NCOCH_a$), 3.57-4.27 (m, 8.5 H), 4.45 and 4.50 (each s, each 1H, CH_2Ph), 4.68-4.77 and 4.99-5.11 (each m, each 0.5 H, NCHO), 5.72-5.90 (m, 2H, HC=CH), 6.78-6.85 (m, 2H, ArH), 7.09-7.17 (m, 2H, ArH), 7.23-7.32 (m, 5H, ArH); ms (field desorption) 381 (32), 363 (100).

Bicyclic ether 9a and tricyclic ether 10a. A solution of the hydroxylactam **5a** (132 mg; 0.375 mmol) in 98-100% formic acid (7 ml) was stirred for 18 h at room temperature. The reaction mixture was poured into 60 ml of satd brine and the aqueous layer was extracted with three 100 ml portions of CH_2Cl_2. The combined extracts were washed with 40 ml of a satd sodium bicarbonate solution and with 40 ml of satd brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography on silica gel (acetone/CH_2Cl_2 1: 9 → 1:2) gave **9a** (43 mg; 47%) and **10a** (40 mg; 44%), in this order. Bicyclic ether **9a**: colourless oil; ir 1676 cm^{-1}; nmr δ 1.75-1.92 (m, 1H, H_5), 2.14-2.82 (m, 4H, H_5, H_6, H_6, and H_4), 3.46 (t, *J*=11.5, 1H, $H_{3\alpha}$), 3.52-3.61 (m, 1H, H_{4a}), 4.05 (dd, *J*=4.4, 11.5, 1H, $H_{3\beta}$), 4.24 (d, *J*=10.0, 1H, $H_{1\alpha}$), 5.52 (d, *J*=10.0, 1H, $H_{1\beta}$), 5.83 (dd, *J*=8.6, 16.0, 1H , =C*H*CH), 6.54 (d, *J*=16.0, 1H, =CHAr), 7.18-7.35 (m, 5H, ArH); ms [*m/z* (%)] 243 (15), 130 (100). Exact mass calcd for $C_{15}H_{17}NO_2$ 243.1259: Found 243.1248. Tricyclic ether **10a**: mp 95-98 °C [(i-Pr)$_2$O/EtOAc]; ir 1676 cm^{-1}; nmr δ 1.77-1.93 (m, 1H, $H_{8\beta}$), 2.11-2.25 (m, 1H, $H_{8\alpha}$), 2.52 (ddd, *J*=3.7, 10.1, 17.0, 1H, $H_{7\beta}$), 2.69 (dddd, *J*=1.1, 8.8, 10.1, 17.0, 1H, $H_{7\alpha}$), 2.87-3.00 (m, 2H, H_{3a} and H_{8b}), 3.12 (ddd, *J*=1.1, 7.1, 12.4, 1H, $H_{1\alpha}$), 3.59 (dd, *J*=7.4, 9.1, 1H, $H_{4\alpha}$), 3.83 (dd, *J*=1.4, 12.4, 1H, $H_{1\beta}$), 4.09 (q, *J*=7, 1H, H_{8a}), 4.20 (dd, *J*=7.5, 9.1, 1H, $H_{4\beta}$), 4.41 (d, *J*=5.5, 1H, H_3), 7.22-7.36 (m, 5H, ArH); ms [*m/z* (%)] 243 (54), 138 (100). Exact mass calcd for $C_{15}H_{17}NO_2$ 243.1259: Found 243.1263.

Tricyclic ether 10b. Hydroxylactam **5b** (302 mg; 0.79 mmol) in formic acid (20 ml) was stirred for 70 h at room

temperature. After work-up and flash chromatography on silica gel (acetone/CH_2Cl_2 1 : 10 → 1 : 2) the tricyclic ether **10b** (145 mg; 67%) was obtained as a colourless oil: ir 1675 cm^{-1}; nmr δ 1.77-1.93 (m, 1H, $H_{8\beta}$), 2.11-2.26 (m, 1H, $H_{8\alpha}$), 2.52 (ddd, *J*=3.7, 10.2, 17.1, 1H, $H_{7\beta}$), 2.72 (ddd, *J*=8.5, 8.7, 17.1, 1H, $H_{7\alpha}$), 2.86-3.02 (m, 2H, H_{3a} and H_{8b}), 3.09 (ddd, *J*=1.2, 7.4, 12.3, 1H, $H_{1\alpha}$), 3.56 (dd, *J*=7.5, 9.2, 1H, $H_{4\alpha}$), 3.78 (s, 3H, OCH_3), 3.80 (dd, *J*=1.8, 12, 1H, $H_{1\beta}$), 4.10 (q, *J*=7, 1H, H_{8a}), 4.19 (dd, *J*=7.5, 9.2, 1H, $H_{4\beta}$), 4.34 (d, *J*=6.0, 1H, H_3), 6.83-6.90 (m, 2H, ArH), 7.13-7.29 (m, 2H, ArH); ms [*m/z* (%)] 273 (39), 138 (100), 135 (58). Exact mass calcd for $C_{16}H_{19}NO_3$ 273.1365: Found 273.1389.

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