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A New and Versatile Access to Azamacroheterocycles via Ring Closing Carbonylative Hydroaminomethylation

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Abstract

The Rh(I)-catalysed hydroformylation / reductive amination of dienes in the presence of α,ω-diamines is applied to macroheterocyclic ring synthesis. Starting from (hetero)-diallylic systems 12- to 36-membered polyheterocycles are easily accessible. © 1999 Elsevier Science Ltd. All rights reserved.

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Medium or large sized oxa- or azaheterocyclic systems are of interest for various applications arising from their unique and selective binding properties towards cations[1], anions[2] and neutral molecules.[1] Thus they can be used as selectively coordinating ligands for metals,[3] as transport vehicles for contrast agents in magnetic resonance imaging,[4] as renal calculi dissolving agents,[5] or as linkers for monoclonal antibodies and radiometals in cancer treatment.[6] In addition they are valuable building blocks of natural products with potential pharmaceutical virtues.[7]

The synthesis of medium sized or large heterocyclic systems has been subject of many investigations in recent years.[1,8] A common access to these heterocycles is the Richman-Atkins approach:[9] a nucleophilic substitution of α,ω-dihalides, -tosylates or -mesylates with α,ω-ditosylamides or α,ω-diols in the presence of a base. However, the starting materials sometimes are difficult to obtain and in addition every nitrogen atom of the resulting macrocycle is generally protected with the same group.

We here now report a new, effective and versatile methodology for the synthesis of azamacroheterocyclic systems of type 3 starting from easily available diolefins of type 1 and diamines 2 by reacting these under hydroformylation conditions in an overall hydroaminomethylation[10] of each double bond[11] (hydroformylation/reductive amination of the dialdehyde intermediates).[12] The examples described include formation of ring sizes with up to 36 atoms and 9 heteroatoms in a one-pot procedure following a metal catalysed successive four molecules combining and a four bonds forming protocol.

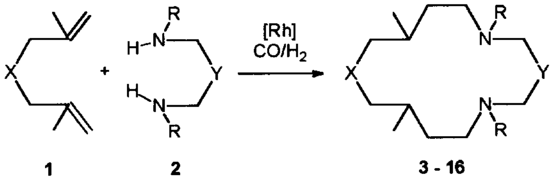

Fig. 1: Synthesis of macroheterocycles via ring closing bishydroaminomethylation

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If diolefinic systems of type **1** are converted under hydroformylation conditions, three regioisomeric dialdehydes (*n/n, n/iso, iso/iso*) and products derived therefrom have to be expected, depending on the reaction conditions, the catalyst system, and the substitution pattern within the diolefin.[11] The bis-methallylic aza-system of type **1a** (X = NAc) exclusively gives the products of the *n*-hydroformylation.[13]

As summarised in Table 1, macroheterocycles **3-16** with 13-36 ring members and up to 9 heteroatoms are obtained from diolefins **1** and diamines **2**.[14] Thus the ring size as well as the number and the position of the heteroatoms can with a high flexibility be predetermined by variation of the chain between the two olefin units within the diene **1** and the chain between the two amine units within the diamine **2**. The surprisingly good yields are presumably due to a template effect of the rhodium during the different catalytic steps especially in the final ring closure.

Table 1 Synthesis of macroheterocycles **3 – 16** from diolefins **1** and diamines **2**

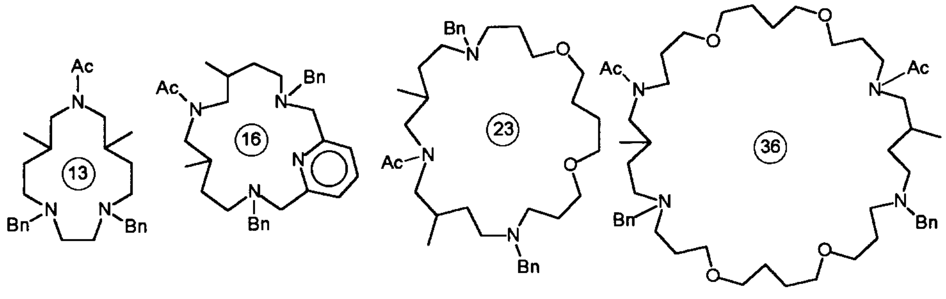
Ent.	**1**	X	**2**	Y	R	Cond.	Prod.	ring size	yield [%]
1	**1a**	NAc	**2a**	-	Bn	A	**3**	13	47
2	**1a**	NAc	**2b**	(CH_2)	Me	A	**4a**	14	39
3	**1a**	NAc	**2c**	(CH_2)	Bn	A	**4b**	14	31
4	**1a**	NAc	**2d**	$(CH_2)_2$	Et	A	**5a**	15	19
5	**1a**	NAc	**2e**	$(CH_2)_2$	Bn	A	**5b**	15	34
6	**1a**	NAc	**2f**	2,6-Dipyridyl	Bn	A	**6**	16	56
7	**1a**	NAc	**2g**	$(CH_2)_2O(CH_2)_4O(CH_2)_2$	Bn	A	**7**	23	32
8	**1b**	O	**2b**	(CH_2)	Me	B	**8**	14	26
9	**1c**	$O(CH_2)_2O$	**2b**	(CH_2)	Me	B	**9**	17	28
10	**1c**	$O(CH_2)_2O$	**2f**	2,6-Dipyridyl	Bn	B	**10**	19	12
11	**1d**	$[O(CH_2)_2]_4O$	**2b**	(CH_2)	Me	B	**11**	26	20
12	**1d**	$[O(CH_2)_2]_4O$	**2g**	$(CH_2)_2O(CH_2)_4O(CH_2)_2$	Bn	B	**12**	35	24
13	**1e**	$AcN(CH_2)_3O(CH_2)_4O(CH_2)_3NAc$	**2b**	(CH_2)	Me	C	**13**	27	44
14	**1e**	$AcN(CH_2)_3O(CH_2)_4O(CH_2)_3NAc$	**2f**	2,6-Dipyridyl	Bn	C	**14**	29	51
15	**1e**	$AcN(CH_2)_3O(CH_2)_4O(CH_2)_3NAc$	**2g**	$(CH_2)_2O(CH_2)_4O(CH_2)_2$	Bn	C	**15**	36	44
16	**1f**	-	**2f**	2,6-Dipyridyl	Bn	A	**16**	15	46

A. 0.9 mmol **1**, 0.9 mmol **2**, 1 mol % $[Rh(cod)Cl]_2$, 100 ml dioxane, 120°C, 100 bar CO/H_2 (1:1), 70h

B. 1.0 mmol **1**, 1.0 mmol **2**, 1 mol % $[Rh(acac)(CO)]_2$, 100 ml dioxane, 75°C, 100 bar CO/H_2 (1:1), 90 h

C. 0.6 mmol **1**, 0.6 mmol **2**, 1 mol % $[Rh(cod)Cl]_2$, 100 ml dioxane, 120°C, 100 bar CO/H_2 (1:1), 70 h

The cyclic compounds **3 – 16** contain several heteroatoms and thus could serve as multidentate ligands for cationic or Lewis acid species. In Fig. 2 some representative examples of the newly synthesised macroheterocycles are given of which **7** was chosen as ligand for the complexation of alkali metal cations Li^+, K^+, Rb^+, Cs^+.



3 **6** **7** **15**

Fig. 2: Representative examples of the described macroheterocycles

After mixing equimolar amounts of **7** and the corresponding metal salts in CD_3CN/D_2O (3:1) ^{13}C-NMR signals were compared to those of the free ligand. While the ^{13}C signals show only minor influences after addition of LiBr, KI or CsI with shifts the addition of RbI causes a much higher shift towards low fields (0.12 to 0.37 ppm).[15] Due to a deshielding effect of the cation, especially the signals of C-atom attached to a heteroatom show strong effects. Similar effects are observed in the ^7Li, ^{39}K, ^{87}Rb and ^{133}Cs NMR spectra of the corresponding metal salt mixtures with ligand. Only with RbI a significant $\Delta\delta_{metal}$-shift of 3.60 ppm is observed.[16] Furthermore exclusively with RbI a half width line broadening from 264 Hz to 326 Hz is measured. Similar observations in ^{87}Rh investigations of azacoronands are described.[15]

Thus **7** as a representative example shows a significant selectivity towards Rb^+ if compared with Li^+, K^+ and Cs^+. More detailed investigations of the complex structures and the binding selectivities towards other hosts are in progress as well as similar investigations of the other systems described here.

In conclusion, this new method of macroheterocyclic ring synthesis allows broad variations in ring size, heteroatom and substitution patterns. Furthermore, the synthesis of cryptoands should be verified if starting from N-benzyl substituted systems after hydrogenolysis of the benzyl group and successive hydroaminomethylation with a second diolefin of type **1**.

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14. As representative example the synthesis of 1-(5,15-dibenzyl-8,12-dimethyl-1,19-dioxa-5,10,15-triaza-cyclotricos-10-yl)-ethanone 7 is described: **1a** (0.9 mmol, 150 mg), **2g** (0.9 mmol, 346 mg), [Rh(cod)Cl]$_2$ (0.5 mol-%, 2.2 mg) and dry dioxane (100 ml) were placed in an autoclave. After flushing with argon the reactor was pressurised with 50 bar hydrogen and 50 bar carbon monoxide and heated to 120 °C for 70 h. After removing the solvent by rotary evaporation the catalyst was removed by column filtration. 7 was separated and purified by column chromatography on neutral alumina (act. III) with methyl ^{tert}butyl ether as eluent as a 1:1 mixture of two diastereoisomers (166 mg, 32 % d. Th.). 7: ^{1}H-NMR (400 MHz, CDCl$_3$, TMS, 20 °C): δ [ppm] = 0.70 (2xd, ^{3}J = 6.3 Hz, 6H), 1.14 (m, 2H), 1.53 (m, 2H), 1.63 (s br, 4H), 1.71 (qui, ^{3}J = 5.9 Hz, 4H), 1.87 (m, 2H), 2.04 (2xs, 3H), 2.39 (t, ^{3}J = 5.5 Hz, 4H), 2.48 (m, 2H), 2.58 (m, 2H), 2.93-3.22 (m) and 3.32 (dd, ^{2}J = 13.3 Hz, ^{3}J = 8.0 Hz) [4H], 3.43 (m, 10H), 3.59 (m, 2H), 7.10 (m, 2H), 7.28 (m, 8H). ^{13}C-NMR (100 MHz, [D$_6$]DMSO, 85 °C): δ [ppm] = 17.2, 17.5 (CH$_3$), 21.9, 21.9 (CH$_3$), 26.6, 26.6 (CH$_2$), 27.5 (CH$_2$), 29.2, 29.9 (CH), 32.2 (CH$_2$), 50.6 (CH$_2$), 51.7 (CH$_2$), 58.8, 58.8 (CH$_2$), 68.2 (CH$_2$), 70.2 (CH$_2$), 126.9 (CH), 128.3 (CH), 128.9 (CH), 140.3 (C$_q$), 170.0, 170.2 (C$_q$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2928 vs, 2855 vs, 1651 vs, 1645 vs. MS (EI, 70 eV): m/z (%) = 579 (M$^+$; 16), 488 (82), 210 (30), 149 (45), 134 (28), 100 (22), 91 (100), 71 (29), 57 (47), 43 (33). Anal. Calcd. for C$_{36}$H$_{57}$N$_3$O$_3$: C, 74.6; H, 9.9; N, 7.2. Found: C, 74.6; H, 9.6; N, 7.0.
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16. The chemical shifts of the alkali metal salt in CD$_3$CN/D$_2$O solutions were calibrated to 0.0 ppm before equimolar amounts of 7 were added and the differences (Δδ) determined.