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Lithium and proton templated ω-polyazamacrolactamization, new general routes to macrocyclic polyamines

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Abstract—A general, lithium templated/catalyzed ω-polyazamacrolactamization method for the synthesis of macrocyclic polyamines including spermidine and spermine alkaloids is presented. The formation of 12-, 13-, 16-, 17-, and 19-membered N_3, N_4, N_5, and N_6 containing rings is described. A proton templated/catalyzed macrolactamization of some ω-polyazaaminoesters is also observed. © 2002 Elsevier Science Ltd. All rights reserved.

The macrocyclic polyamines (azacrowns) are of great importance for the supramolecular, bioorganic, and medicinal chemistry. Depending on the ring size and the number of N-atoms their polyaza cavities possess remarkable receptor selectivity for protons, metal cations, and anions.[1a] The spermidine and spermine polyazamacrolactam alkaloids (**13**–**16**, **18**–**21**, and their derivatives) are naturally occurring azacrowns. The receptor/ligand properties of these compounds significantly contribute to their diverse biological activity.[1b]

Several methods for synthesis of macrocyclic polyamines have been described. The Richman–Atkins alkylative ring closure of linear *N*,*N*′-bistosylamides[2] and the 'Zip-reaction' (lactam *N*-aminoalkylation, followed by acid- or base-catalyzed intramolecular transamidative ring expansion)[3] have been frequently used for this purpose.

A number of polyazamacrolactams have been prepared by statistical one-pot Michael addition–ω-macrolactamization by several weeks reflux of polyamines with α,β-unsaturated Me-esters in MeOH.[4] Usually this method leads to low yields of the macrocycle and complex mixture of by-products.[1a,4] Remarkable results have been reached using size adapted metal templated ω-macrolactamizaton methods, a boron templated for the syntheses of the spermidine (N_3) alkaloids celacinnine (**14**)[5a,e] and dihydroperiphylline (**16**),[5b,d] and antimony templated for the spermine (N_4) alkaloids protoverbine (**18**) and buchnerine (**20**).[5c,d,6]

In order to find a convenient procedure, suitable for the preparation of differently sized polyazamacrolactams, we recognized lithium halides as potential template agents and catalysts for ω-polyazamacrolactamization. This expectation appeared from the facts that: (a) LiBr catalyzes the ester aminolysis[7] and (b) in aprotic solvents lithium halides form stabile chelate complexes with polyamines.[8] Thus, we could expect that in proper dilution in aprotic solvents α,ω-polyaminoesters of the type **5**–**10** (Scheme 1) would form with lithium halides transition chelates kept by a central polycoordinated Li^+ atom, which approximates the reacting α,ω-functionalities of the molecule and additionally coordinating/activating the ester C=O group could promote a ring closure by intramolecular aminolysis to the corresponding macrolactams (as shown for the N_3-α,ω-aminoester **9b**, Scheme 1).

In accordance with the expected template role of Li^+ for the arrangement of the intermediate chelate, the presence of the interchain N-atoms, their number, and presumably the distance between them should be crucial for the formation of the macrocycles. In this order, by aza-Michael addition of several polyamines (**4a**–**g**), including spermidine (**4c**,**d**) and spermine (**4e**), to the sterically hindered α,β-unsaturated acid esters **1**–**3**, were prepared[9] the differently sized N_3, N_4, N_5, and N_6 aminoesters **5e**, **6a**–**g**, and **7e**, which were transformed by transesterification[10] to their Me-homologues **8e**, **9a**–**g**, and **10e**. Compounds **8e**, **9a**–**g**, and **10e** were used in the next macrolactamization step. The results of this reaction, summarized in Table 1, are in excellent agreement with our preliminary expectations.

Keywords: spermidine; spermine; polyazamacrolactam alkaloids; lithium template; proton template.

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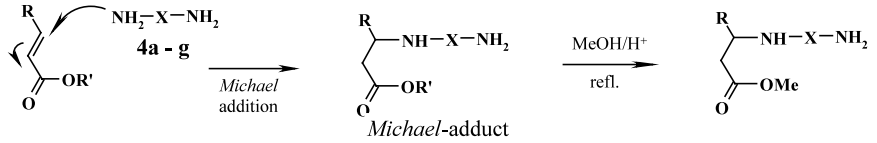


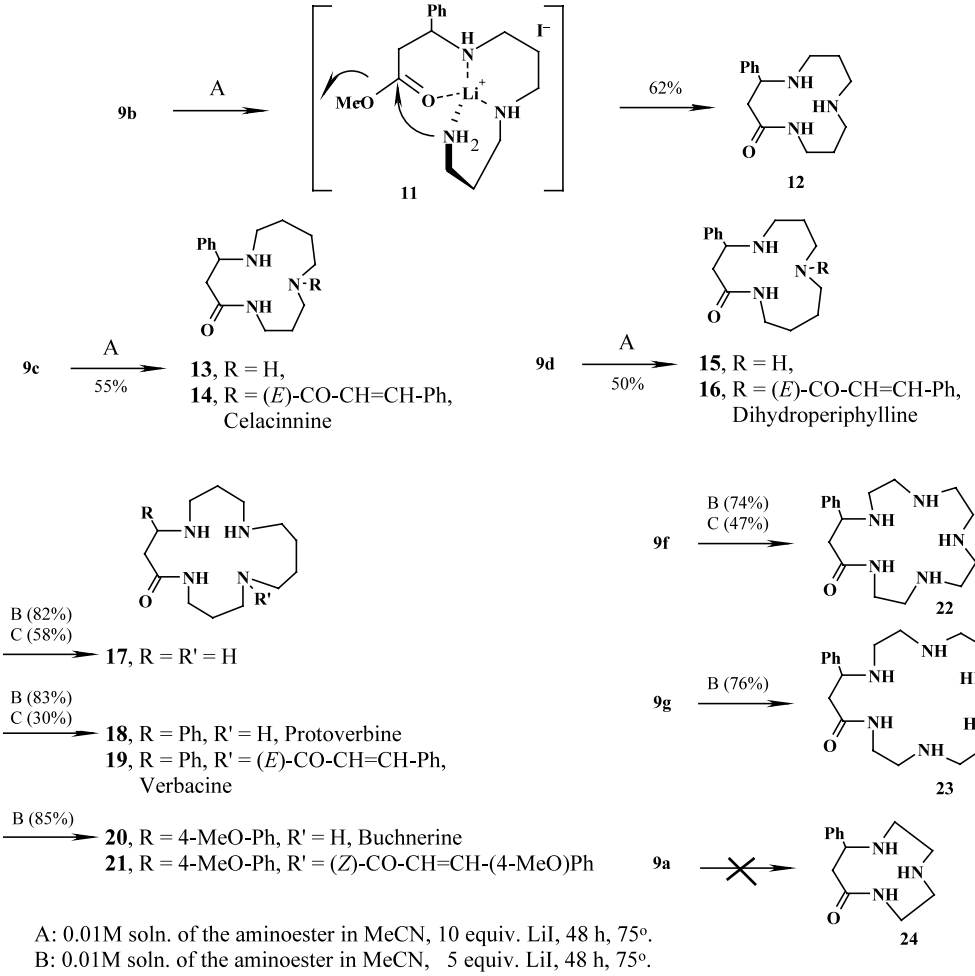
1, R = H; R' = *t*-Bu
2, R = Ph; R' = *i*-Pr
3, R = 4-MeO-Ph; R' = *i*-Pr

5e, X = e; R = H; R' = *t*-Bu
6a - g, X = a - g; R = Ph; R' = *i*-Pr
7e, X = e; R = 4-MeO-Ph; R' = *i*-Pr

8e, X = e; R = H
9a - g, X = a - g; R = Ph
10e, X = e; R = 4-MeO-Ph

	X		X
a	$-(CH_2)_2NH(CH_2)_2-$	**e**	$-(CH_2)_3NH(CH_2)_4NH(CH_2)_3-$ (spermine)
b	$-(CH_2)_3NH(CH_2)_3-$	**f**	$-(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2-$
c[a]	$-(CH_2)_4NH(CH_2)_3-$ (spermidine[a])	**g**	$-(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2-$
d[a]	$-(CH_2)_3NH(CH_2)_4-$ (spermidine[a])		

[a] Due to the unsymmetrical structure of spermidine, two constitutionally isomeric *Michael* adducts are possible.



A: 0.01M soln. of the aminoester in MeCN, 10 equiv. LiI, 48 h, 75°.
B: 0.01M soln. of the aminoester in MeCN, 5 equiv. LiI, 48 h, 75°.
C: 0.01M soln. of the aminoester in MeCN, 1 equiv. $TsOH \cdot H_2O$, 48 h, 75°.

Scheme 1.

Thus, in the presence of LiI[11a] (10 equiv.)[11b] for 48 h at 75°C, the N_3 compound **9b** (0.01 M solution in MeCN) was converted to the 12-membered N_3-macrolactam **12** in 62% yield.[11c] Similarly, the spermidine (N_3) Me-aminoesters **9c** and **9d** were macrolactamized to the corresponding isomeric 13-membered N_3-macrocycles **13** and **15** in 55 and 50% yield.[11] Using the same procedure the larger N_4 (**8e**, **9e**, and **10e**), N_5 (**9f**), and N_6 (**9g**) Me-aminoesters were smoothly converted to the corresponding N_4 17-membered (**17**, **18**, and **20**), N_5 16-membered (**22**), and N_6 19-membered (**23**) polyaza-macrolactams, respectively,[11a] whereas the shortest tested diethylenetriamine (N_3) derived Me-aminoester **9a** did not undergo macrolactamization to **24**. Obvi-

Table 1.

Michael-adduct			→	Me-ester		→	Polyazamacrolactam		
	Yield (%)	R_f		Yield (%)	R_f		Yield (%)		R_f
							(Li^+ method)	(H^+ method)	
5e	45	0.35[b]	**8e**	95	0.20[b]	**17**	82	58	0.29[b]
6a	67	0.72[c]	**9a**	93	0.63[c]	**24**	No reaction	–	–
6b	65	0.29[c]	**9b**	92	0.22[c]	**12**	6212c	–	0.53[b]
6c[a]	24[a]	0.31[c]	**9c**	94	0.25[c]	**13**	55	–	0.65[b]
6d[a]	22[a]	0.25[c]	**9d**	96	0.18[c]	**15**	50	–	0.88[b]
6e	56	0.55[b]	**9e**	99	0.45[b]	**18**	83	30	0.71[b]
6f	61	0.67[b]	**9f**	92	0.57[b]	**22**	74	47	0.80[b]
6g	53	0.49[b]	**9g**	88	0.43[b]	**23**	76	–	0.67[b]
7e	63	0.58[b]	**10e**	93	0.48[b]	**20**	85	–	0.70[b]

[a] Due to the unsymmetrical structure of spermidine, two isomeric Michael adducts (**6c**, 24%, and **6d**, 22%) are formed, which corresponds to 46% overall yield.
[b] Silica gel, $CHCl_3$:MeOH:25% aq. NH_3 7:3:1.
[c] Silica gel, $CHCl_3$:MeOH:25% aq. NH_3 8:2:0.2.

ously, the longer polyazahydrocarbon chains of **8e**, **9e–g**, and **10e** form less strained, i.e. more populated, transition α,ω-approximated chelates which results on higher yields of macrolactams (Table 1).[11f]

Significantly different reactivity was observed for differently hindered aminoesters. Et-esters (not shown) react much slower than the Me-esters, whereas *t*-Bu- and *i*-Pr-esters **5e**, **6a–g**, and **7e** are nearly inert.[11e]

MeCN seems to be the best solvent for this reaction. In protic solvents (MeOH) without catalyst (as published[4]) and with LiI the reaction leads to low yields of macrocycle and a number of by-products. LiBr catalyzes this reaction similarly as LiI, whereas LiCl and NaI are ineffective.

Surprisingly, with 1 equiv. acid ($TsOH{\cdot}H_2O$) instead of LiI in MeCN for 48 h at 75°C the N_4 Me-aminoesters **8e**, **9e**, and the N_5 **9f** (0.01 M solution) also undergo macrolactamization.[11d] Presumably, in this case the intermediate α,ω-approximated transition conformation of the open chain aminoester is kept by a polycoordinated central proton, shared between all N-atoms, similarly to **11** (Scheme 1), which is an example of proton template effect.[12] Unfortunately, due to the specific structures, containing β-aminoester fragment, the H^+-templated/catalyzed macrolactamization of the tested aminoesters, is accompanied with significant rate of retro-Michael reaction which results on lower yields of the corresponding macrolactams (**17**, **18**, **22**) (Table 1). This is more pronounced in the members with additional β-phenyl substitution (**18** and **22**). We could expect that in case of α,ω-polyaminoesters with a polyamine chain attached at α- or γ-position with respect to the ester functionality the proton templated ω-polyazamacrolactamization would lead to better results. Under the same (H^+-templated) reaction conditions the N_3 Me-aminoesters **9b–d** react poorly.

In conclusion, the here-described lithium templated ω-polyazamacrolactamization appears as a convenient, simple, and versatile method for the synthesis of differently functionalized polyazamacrolactams.[13] Their further reduction (B_2H_6/THF as published in Ref. 4a) allows the practical preparation of the corresponding macrocyclic alkylpolyamines. The proton templated ω-polyazamacrolactamization should also be taken on mind as an alternative choice for the preparation of certain macrolactams.

Acknowledgements

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9. (a) *Michael addition—a general procedure*: The sterically hindered *i*-Pr-(*t*-Bu)-esters were used in order to reduce the aminolysis of the ester group. Thus, compounds **6a**–**g** and **7d** were prepared by heating 3 equiv. of polyamine (**4a**–**g**)[9b] and 1 equiv. of **2** (or **3**) at 65°C for 48 h without solvent. The reaction mixtures were diluted with $CHCl_3$ and separated directly by CC on silica gel by consecutive elution with $CHCl_3$:MeOH:25% aq. NH_3 8:2:0.2 then 7:3:1. The isomeric aminoesters **6c** (less retained) and **6d** were separated by CC on silica gel with $CHCl_3$:MeOH:25% aq. NH_3 8:3:0.5. Compound **5e** was prepared from spermine (**4e**, 5 mmol) and commercially available *t*-Bu acrylate (**1**, 5 mmol) in 20 ml MeCN for 15 h at rt. The crude material was purified by CC on silica gel as above; (b) the commercially available (Fluka) technical tetraethylenepentamine (**4f**) and pentaethylenehexamine (**4g**) were purified by recrystalization of their perhydrochlorides from 60% aq. EtOH. TLC (silica gel, 2% NaCl in 25% aq. NH_3): **4f** R_f 0.5; **4g** R_f 0.6, detection by potassium iodoplatinate (Schlittler's reagent, Schlittler, E.; Hohl, J. *Helv. Chim. Acta* **1952**, *35*, 29). The free bases **4f** and **4g** were obtained from **4f**·5HCl and **4g**·6HCl and MeO^-Na^+ in MeOH.
10. *Preparation of the Me-aminoesters **8e**, **9a**–**g**, and **10e***: The perhydrochlorides of the Me-esters **8e**, **9a**–**e**, and **10e** were prepared by 15 h reflux of the perhydrochlorides of **5e**, **6a**–**e** and **7e** in MeOH/HCl and the pertosylates of **9f** and **9g** by 15 h reflux of the perhydrochlorides of **6f** and **6g** in mixtures of MeOH/5 equiv. $TsOH·H_2O$ and MeOH/6 equiv. $TsOH·H_2O$, respectively. For liberation of the free bases, the MeOH solutions of the corresponding Me-aminoesters perhydrochlorides **8e**, **9a**–**e**, and **10e**, and pertosylates of **9f** and **9g** were stirred for 0.5 h with an amount of Amberlite®IRA 400 in OH^--form (strong anionite, Fluka), corresponding to 10-fold excess of exchange capacity, then filtered and evaporated.
11. (a) *Lithium templated macrolactamization*: To a 0.01 M solution of the corresponding Me-aminoester in MeCN were added 5 or 10 equiv.[11b] of anhydrous LiI, then the mixture was stirred at 75°C for 48 h. After evaporation of the solvent, the residue was splashed with an aq. soln of K_2CO_3, the mixture was heated at 70°C for 1 h, then acidified, washed with $CHCl_3$, alkalinized with K_2CO_3, extracted five times with $CHCl_3$/*i*-PrOH 8:2 mixture. The extract was evaporated and the residue purified by CC on silica gel, eluted consecutively with MeOH to remove the LiI and then $CHCl_3$/MeOH/25% aq. NH_3 8:2:0.2, 7:3:1; (b) 1 equiv. of LiI is not an effective catalyst, 5 equiv. are optimal for the N_4, N_5, and N_6 aminoesters, and 10 equiv. for the N_3 aminoesters; (c) the macrocyclization of compound **9b** gives together with the macrolactam **12** also about 15% of cyclodimer (R_f 0.85); (d) *proton templated macrolactamization*: A 0.01 M solution of the corresponding Me-aminoester in MeCN, containing 1 equiv. of $TsOH·H_2O$ was stirred at 75°C for 48 h. The isolation of the macrocycles was carried out as mentioned above; (e) without catalyst under the same reaction conditions the Me-aminoesters are stable; (f) the spectral data of compounds **12**,[3c] **13**,[3b,5a] **15**,[2d,3c,5b,5d] **17**,[5c,5d] **18**,[2c,5c,5d] and **20**[2c,5c,5d,6] have been described in the literature earlier.

Compound **22**: colorless solid; ^1H NMR ($CDCl_3$): 8.13 (br. *t*, NHC=O); 7.4–7.2 (*m*, 5 arom. H); 4.04, 4.03 (2*d*, $J=9.6$ Hz, PhCHN); 3.6–3.45 (*m*, 1H, NCH); 3.45–3.25 (*m*, 1H, NCH); 2.95–2.25 (*m*, 20H, NCH+NH). ^{13}C NMR ($CDCl_3$): 171.62 (C=O); 142.59 (arom. quat. C); 128.53, 127.17, 126.40 (arom. CH); 59.58 (PhCHN); 48.59, 48.26, 48.16, 47.94, 47.19, 46.33, 44.28, 39.12 (CH_2). ESI-MS: 320 ($[M+H]^+$).

Compound **23**: colorless solid; ^1H NMR ($CDCl_3$): 8.22 (br. *t*, NHC=O); 7.4–7.2 (*m*, 5 arom. H); 4.01, 4.00 (2*d*, $J=10$ Hz, PhCHN); 3.5–3.3 (*m*, 2H, NCH); 2.9–2.4 (*m*, 25H, NCH+NH). ^{13}C NMR ($CDCl_3$): 171.88 (C=O); 142.78 (arom. quat. C); 128.50, 127.15, 126.48 (arom. CH); 59.62 (PhCHN); 48.87, 48.70, 48.61, 48.42, 48.25, 48.03, 46.26, 44.03, 39.09 (CH_2). ESI-MS: 363 ($[M+H]^+$).
12. The proton templated synthesis of macrocyclic Schiff bases was reported recently: Tian, Y.; Tong, J.; Frezen, G.; Sun, J.-Y. *J. Org. Chem.* **1999**, *64*, 1442.
13. The present method was successfully used in our laboratory also for the preparation of a group of compounds similar to the polyazamacrolactams shown here (Yurdakul, A. et al. in preparation).