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Solid-phase synthesis of cyclic polyamines

Pascal Bisegger, Nikolay Manov, Stefan Bienz *

Institute of Organic Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

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ABSTRACT

A method for the synthesis of cyclic polyamines based on solid-phase chemistry is shown. Linear polyamines are stepwise synthesized on solid support from the center by repetitive alkylations at benzylic N-atoms. Cyclizations at the resins were effected conventionally by direct intramolecular S_N2 reactions between sulfonyl-protected terminal amino groups and primary alkyl bromides or by intramolecular Mitsunobu reactions between sulphonamides and primary alcohols. Particularly the latter transformation proved to be powerful for the construction of medium- as well as large-sized rings.

1. Introduction

The construction of cyclic polyamines is an important task in organic synthesis because such polyamines are widely used as radiopharmaceuticals[1] and MRI contrast agents[2] and also have diagnostic applications.[3] Furthermore, macrocyclic polyamines continue to be important components in coordination chemistry.[4] Azacrowns have been utilized as additives to regulate enzyme reactivity: some cyclic polyamines significantly enhance both enantioselectivity and efficiency of enzymatic reactions, even for substrates that are otherwise not favored by the enzyme.[5] Interesting is also the fact that phenylenebis(methylene)-linked dimers of cyclic polyamines were described as a new class of antiviral agents that exhibit potent inhibitory effects on several strains of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) replication with high selectivity.[6] A high-yielding synthesis to link the two polyamine rings together was described by Le Baccon et al.[7]

The classical synthesis of macrocyclic polyamines has two major drawbacks: (i) polyamines are compounds of rather high polarity, which often enough impedes their purification and (ii) macrocyclizations to close their rings usually require high-dilution techniques to avoid dimerization and polymerization processes and are thus uneconomical. These disadvantages can be overcome by using solid-phase strategies, as shown in this paper.

2. Results and discussion

The basis of our study is the previously described solid-phase synthesis of linear polyamines and polyamine derivatives, constructing the polyamine framework in a convergent manner from the center.[8–10] Based on this strategy we planned to form cyclic polyazacompounds of different sizes on solid support by ring closing reactions with appropriately α,ω-functionalized precursors. Due to the limited loading capacity of resins and the statistical distribution of the active sites, a natural dilution effect is realized for solid-phase reactions. Limitations for the cyclizations were only expected for the formation of medium-sized or very large rings. For the closure of such rings, reaction rates might be too low, allowing competing decompositions, and, for the formation of 'very large' rings, 'cross-alkylation' of neighboring polyamine moieties on the solid support could additionally be problematic. In a first instance, we concentrated on the synthesis of 8-, 12-, and 16-membered cyclic polyamines.

The cascades of repetitive alkylations for the preparations of the targeted cyclization precursors **3**, **6**, **7**, **8**, **9**, and **10** started with the coupling of *N*-(3-aminopropyl)-2-nitrobenzenesulfonamide (**1**)[11] to the *Merrifield* polymer (200–400 mesh, loading capacity 0.73 mmol g^{-1} or 0.32 mmol g^{-1}), performed in the presence of diisopropylethylamine (DIEA), leading to resin **2** (Scheme 1). Alkylation of this resin with 1,3-dibromopropane in presence of DIEA delivered the first cyclization precursor, resin **3**. The Ns-protected amine does not react under these conditions.[12] Substitution of the Br-atom of resin **3** by reaction with either benzylamine or *N*,*N*′-dibenzylpropane-1,3-diamine in presence of DIEA, followed by alkylation of the resultant resins **4** and **5** with 1,3-dibromopropane as above, afforded the second and third cyclization precursor, resins **6** and **7**.

The hydroxy analogs **8**, **9**, and **10** were prepared from **2**, **4**, and **5**, respectively, by their alkylation with 3-bromopropanol.

Cyclization of the solid-bound α-NHNs-ω-bromoazaalkanes was performed by treatment of the resins **3**, **6**, and **7** with K_2CO_3 or Cs_2CO_3 in DMF at 50 °C to form **11**, **13**, and **14** (Scheme 2). The progress of the reactions was checked at several times by concurrent liberation of the mono-Ns-protected cyclic polyamines **12**, **15**,

* Corresponding author. Tel.: +41 44 635 4245; fax: +41 44 635 6812.
E-mail address: sbienz@oci.uzh.ch (S. Bienz).

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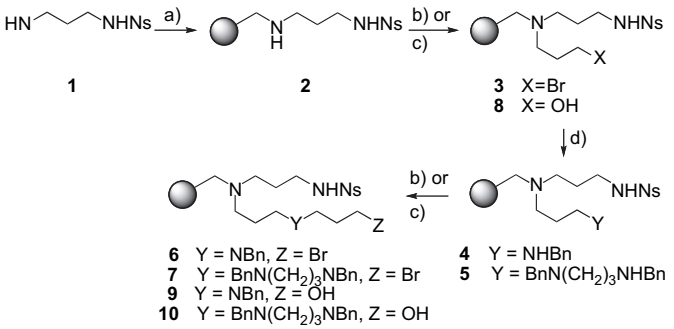
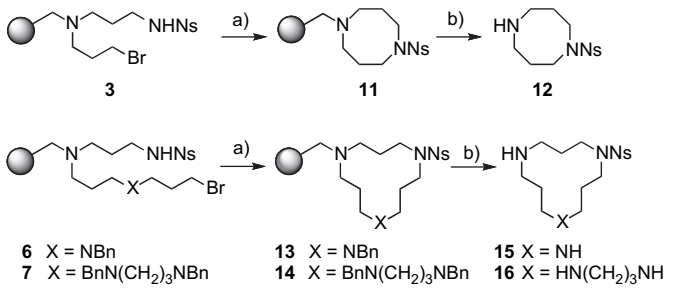


Scheme 1. (a) *Merrifield* resin, DIEA, 50 °C. (b) 1,3-Dibromopropane, DIEA, 50 °C. (c) 3-Bromopropanol, DIEA, 50 °C. (d) Benzylamine or *N*,*N*′-dibenzylpropane-1,3-diamine, DIEA, 50 °C.

and **16** from their solid support and from their benzyl protective groups using a known procedure.[13] Since the alkylation and substitution reactions with the resins usually proceed with almost quantitative yields, except for the first alkylation at the benzylic N-atom attached to the resin, the overall yields of the products **12**, **15**, and **16** can be taken as a measure for the efficiency of the cyclization reaction.

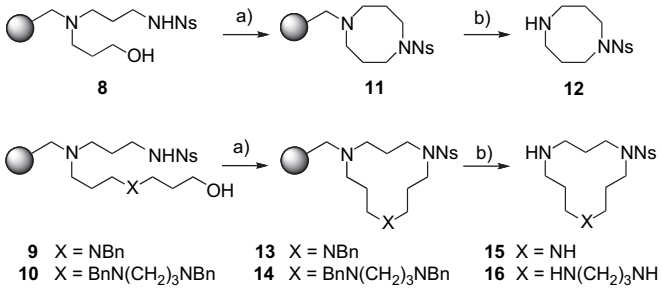


Scheme 2. (a) Cs_2CO_3, DMF, 50 °C. (b) (i) ACE-Cl, DIEA, DCE; (ii) MeOH, reflux.

The optimal reaction time for the cyclizations was found to be approximately 135 h. Performing the cyclization reaction for this period of time, resin **3** delivered finally the eight-membered cyclic diaza compound **12** in 33% overall yield. After five reaction steps 12- and 16-membered cyclic polyazacompounds **15** and **16** were obtained in overall yields of 30%. When the resins were reacted for a markedly shorter period of time, the conversions were incomplete, and prolonged treatment of the resins with the bases resulted in lower yields of the subsequently liberated products. It is interesting to mention at this point that the nature of the cation present during cyclization (K^+ or Cs^+) had no effect on the outcome of the reactions. For both bases used, K_2CO_3 or Cs_2CO_3, almost the same yields of the final products were obtained when the reactions were performed under otherwise the same conditions. Thus, it can be concluded that no template effect through chelation of the cations is necessary or even supportive for the cyclization.

In the initial phase of the investigation we have experienced that the yields of the liberated polyamines were constantly low at approximately 6–8%, when the classical cleavage procedure was applied (treatment with ACE-Cl followed by methanolysis).[13] The IR spectra of the resins recovered after the cleavage procedure revealed that still significant amounts of material bearing a sulfonamide group remained on the polymer, thus, that the product was not quantitatively liberated from the solid support. The problem of incomplete cleavage was assumed to be caused by quarternization of the resin-bound N-atom, either due to alkylation or protonation. By the addition of some DIEA to the reagent mixture, the cleavage of the polyamines from the solid support resulted in markedly improved yields. Thus, it was shown that protonation of the resin-bound N-atom represented the problem in the cleavage process.

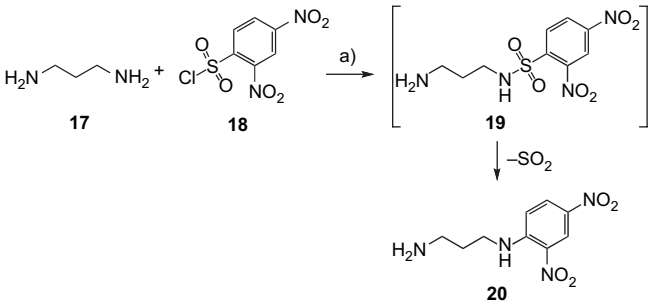
The products **12**, **15**, and **16** were also expected to be obtained by *Mitsunobu* reaction of the precursors **8**, **9**, and **10**, followed by cleavage of the cyclized products **11**, **13**, and **14** (Scheme 3), and we were confident that the *Mitsunobu* reaction would be more efficient than the direct substitution reaction of the α-Ns-ω-bromo compounds. Intramolecular *Mitsunobu* reactions on solid phase were already shown by Kung and Swayze.[14] Treatment of **8** with DEAD and PPh_3 in THF, followed by the usual cleavage procedure, afforded in fact the desired product **12** in 35.5% yield. The yield was just slightly higher than that obtained with the previous procedure, but the optimal reaction time of approximately 20 h for the cyclization was found to be much more convenient. Similarly, the ring closures of **9** and **10** under *Mitsunobu* conditions proceeded efficiently, delivering after cleavage compounds **15** and **16** in yields of 34.0 and 25.4%, respectively.



Scheme 3. (a) PPh_3, DEAD, THF, 23 °C. (b) (i) ACE-Cl, DIEA, DCE; (ii) MeOH, reflux.

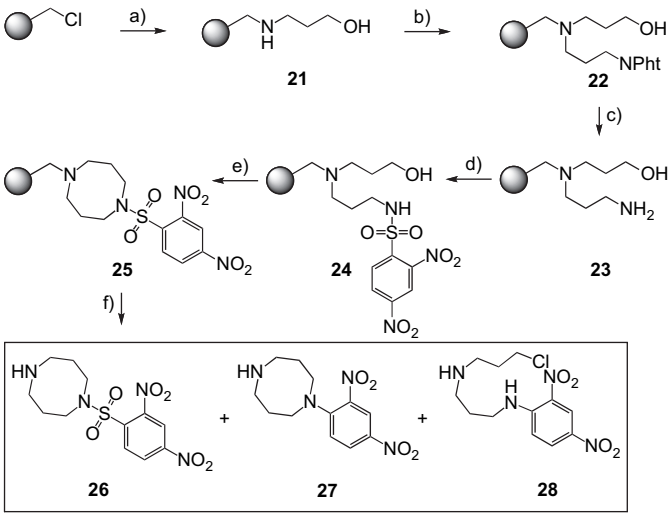
During all these cyclizations—performed with resins up to a loading level of 0.73 mmol g^{-1}—'cross-alkylation' of neighboring polyamine moieties on the solid support was not observed.

To further improve the reaction sequence, we attempted to perform the cyclizations with the aid of an even more activating sulfonyl group. It is known that the 2,4-dinitrobenzenesulfonyl group can be used as an alternative for the 2-nitrobenzenesulfonyl group in the *Mitsunobu* reaction, leading to higher reaction rates.[15] Unfortunately, the use of this sulfonyl group proved cumbersome because it was not possible to follow an analogous reaction sequence as before due to facile *Smiles* rearrangements. Already the synthesis of *N*-(3-aminopropyl)-2,4-dinitrobenzenesulfonamide was not possible to realize analogous to that of **1**. When diamine **17** was treated with sulfonylchloride **18** in presence of NEt_3 not the desired product **19**, but rather the aniline derivative **20** was obtained. It is assumed that compound **19** was in fact formed initially, but that this product, in the form of the free amine, subsequently underwent a rapid *Smiles* rearrangement, similarly as that described by Kan et al.[16] (Scheme 4). The hydro trifluoroacetic salt of compound **19** was prepared[17,18] and shown to undergo immediate rearrangement to **20** upon treatment with base.



Scheme 4. (a) Et_3N, CH_2Cl_2, 0 °C, evaporation of CH_2Cl_2 at 23 °C.

Thus, we had to find another pathway to explore the potential of 2,4-dinitrobenenesulfonamide to be used as protecting and activating group for the *Mitsunobu* cyclization (Scheme 5). For this reason we alkylated the *Merrifield* polymer under the usual conditions with 3-aminopropanol to obtain resin **21**. The possibility of insertion of aminoalcohols on the solid support as a building block for polyamines was described by Renault et al.[19] The benzylic amine of this substrate was alkylated with *N*-(3-bromopropyl)phthalimide and the sulfonyl group was finally introduced by removal of the phthalimide protecting group of **22** by treatment with H_2NNH_2 to form resin **23**, which then was reacted with **18** to form resin **24**. Cleavage of the polyamine derivative from the resin at this step showed that up to this moment no *Smiles* rearrangement had occurred.



Scheme 5. (a) 3-Aminopropanol, DIEA, 50 °C. (b) *N*-(3-Bromopropyl)phthalimide, DIEA, 50 °C. (c) $N_2H_4 \cdot H_2O$, 80 °C. (d) 2,4-Dinitrobenzenesulfonylchloride, 2,6-lutidine, DCM, 23 °C. (e) PPh_3, DEAD, THF, 23 °C. (f) (i) ACE-Cl, DCE; (ii) MeOH, reflux.

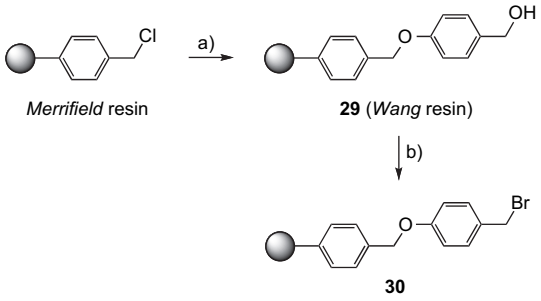
With resin **24** at hand, cyclization under *Mitsunobu* conditions was attempted under the usual conditions, and the resultant resin **25** was cleaved by treatment with ACE-Cl in DCE—without the addition of base to minimize the formation of the *Smiles* product **27**—followed by methanolysis. The reaction finally delivered compounds **26**, **27**, and **28**, however, with the desired compound **26** as a minor component only. The low overall yield of 5.8% for compound **26** can be explained on the one hand by the fact that we did not use a base during the cleavage process, but also by the production of the undesired compound **27** (6.2%) and the non-cyclized product **28** (6.0%).

To avoid *Smiles* rearrangement that still might occur during the cleavage process of the final product from the resin, standard methods to remove the 2,4-dinitrobenenesulfonyl group from the N-atom—treatment of resin **25** with mercaptoacetic acid and DIEA or with thiophenol and K_2CO_3—were applied. Unfortunately both procedures resulted in the formation of **27** as the major product showing that the *Smiles* rearrangement most probably already occurred during the *Mitsunobu* reaction.

2.1. 'Thorpe–Ingold effect'

We were rather astonished that the yields of the products **12**, **15**, and **16** were virtually the same, independent of the ring sizes formed upon cyclization. Particularly the overall yield of the eight-membered diamine derivative **12** (33–36%) is surprisingly high, considering the strain, that is, introduced into the system upon closure of the medium-sized ring.[20] The high efficiency of the cyclization to the eight-membered ring might be explained with a '*Thorpe–Ingold* effect' or the 'gem dialkyl effect'[21–26] provided by the proximate resin. Due to repulsive interactions of the functionalized alkyl chains with the polymeric resin framework, the mobility of the chains and hence the entropy of the system might be reduced.

To test whether such a '*Thorpe–Ingold* effect' is operative, we introduced a spacer in-between the resin and the attached polyamine portion. As this spacer unit, we have chosen 4-hydroxybenzyl alcohol to form *Wang* resin **29**, which was then converted to resin **30** (Scheme 6).[27]



Scheme 6. (a) 4-Hydroxybenzyl alcohol, $NaOCH_3$. (b) PPh_3Br_2.

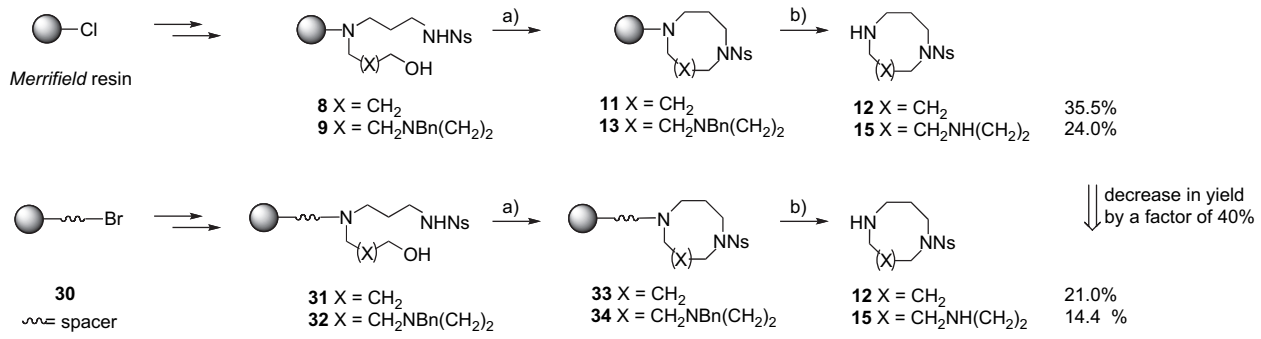
By *Volhard* titration[28] of the original *Merrifield* resin, *Wang* resin **29**, and the bromo resin **30**, it was found that the involved substitutions proceeded quantitatively. To secure that the following reactions are fully comparable, they were all performed in parallel procedures. Resins **8** and **9** were prepared anew from the *Merrifield* resin, and in parallel, resin **30** was converted to resins **31** and **32**. These four materials were exposed to the *Mitsunobu* condition.[†] Treatment of the resultant cyclized products **11** and **33** or **13** and **34**, respectively, with the cleavage reagents under the usual conditions gave finally the free cyclized products **12** and **15** as shown in Scheme 7.

The yields of the final products **12** and **15** obtained this way (21.0 and 14.4%, respectively) were markedly lower than those obtained with the *Merrifield* resin (35.5 and 24.0%, respectively). The introduction of the linker resulted for both products in a decrease of the yields by a factor of 40%. Thus, it seems that a '*Thorpe-Ingold* effect' is in fact operative for cyclizations performed with substrates directly connected to the *Merrifield* resin. Possibly due to smaller cyclization rates, substrates connected to the *Wang* resin had the opportunity to undergo side reactions to a greater extent, which finally resulted in the lower yields.

3. Conclusion

We have demonstrated that cyclic polyamines can be constructed by solid-phase synthesis on the *Merrifield* resin as an efficient alternative to 'in-solution' methodologies. The cyclizations under *Mitsunobu* conditions showed to be considerably faster and more convenient than the corresponding cyclizations by intramolecular substitution reactions of bromides. The efficiency of the cyclizations appears to be enhanced through a *Thorpe–Ingold* effect provided by the sterically demanding resin. Since the *Thorpe–Ingold* effect usually needs irreversibly bound alkyl substituents, the reversibly resin-bound alternative provides a possibility for the efficient construction of non-substituted small- and medium-sized rings. With the flexible route to the precursors for cyclic

[†] The time of 20 h showed to be optimal. Shorter reaction times resulted in incomplete cyclizations, longer reaction times of up to 80 h did not improve the overall yield for the cyclization with and without the linker.



Scheme 7. (a) PPh_3, DEAD, THF, 23 °C. (b) (i) ACE-Cl, DIEA, DCE; (ii) MeOH, reflux.

compounds with varying ring sizes, numbers of N-atoms, and numbers of methylene units in-between the amino functions, the described method represents a versatile tool for the preparation of cyclic polyamine derivatives. Due to non-desired *Smiles* rearrangement, *Mitsunobu* reactions with 2,4-dinitrobenzenesulfonamide proved not to be applicable for the construction of cyclic polyamines.

4. Experimental part

4.1. General

Unless otherwise stated, starting materials were obtained from commercial suppliers and were used without further purification. For the solid-phase reactions, an *Advanced ChemTech PLS 6 Organic Synthesizer* was used. IR spectra were recorded on a *Perkin–Elmer 1600 Series FT-IR* spectrometer or on a *Perkin–Elmer IR 'Spectrum One'*; ν in cm^{-1}. Solid supports: *Merrifield* peptide resin 200–400 mesh, 1% divinylbenzene, loading 0.73 mmol g^{-1} or 0.32 mmol g^{-1} (*Advanced ChemTech*). Chromatography: *Merck* silica gel 60 (40–63 μm) or by preparative HPLC; chromatograms were recorded with a *Dynamax* solvent delivering system model SD-300 coupled with a *Dynamax* absorbance detector model UV-1. Column used: *Kromasil* KR100-10C18. ^1H NMR spectra: in $CDCl_3$ or MeOH-d_4; *Bruker* AC-300 (300 MHz); δ in parts per million rel to $CHCl_3$ (δ 7.26) or MeOH (δ 4.87), J in hertz. ^{13}C NMR spectra in $CDCl_3$ or MeOH-d_4; *Bruker* ARX-300 (75.5 MHz); δ in parts per million rel to $CDCl_3$ (δ 77.23) or MeOH-d_4 (δ 49.15); multiplicities from DEPT-135 and DEPT-90 experiments. CI-MS: *Finnigan* MAT95 (San Jose, CA, USA); ionization energies of 70 eV for EI and 150 eV for CI (with NH_3 as reactant gas); quasi-molecular ions and characteristic fragments in m/z (rel %). Proof of structure and purity of the final polyamine derivatives is provided by their ^1H and ^{13}C NMR spectra. Compounds loaded on the resin are characterized by IR (only characteristic signals or signals, which undergo a change in intensity are given). Elemental analyses are not appropriate for polyamine derivatives since the compounds arose, as waxy or glassy solids only, from which the last solvent molecules can hardly be removed. The hydrochloric salts are rather hygroscopic, and the uptake of water falsifies the elemental analyses. Although the resins were dried after every step in a desiccator (silica gel with indicator) overnight, the mass of crude products from solid-phase syntheses is generally unsuitable for estimating the real yields, because these products are often contaminated with significant amounts of salts and solvents.

4.2. Construction of the polyamine backbones on the solid support and building blocks for the solid-phase synthesis

4.2.1. *N-(2,4-Dinitrophenyl)-1,3-diaminopropane (**20**)*

A solution of 2,4-dinitrobenzenesulfonylchloride (10.00 g, 37.5 mmol) in CH_2Cl_2 (150 ml) was added dropwise over 2 h to a stirred soln of 1,3-diaminopropane (9.4 ml, 0.113 mol) and Et_3N (5.2 ml, 37.5 mmol) in CH_2Cl_2 (100 ml) at 0 °C. After stirring at 23 °C for 2 h, the mixture was washed with satd aq NaCl soln and the organic phase was dried with Na_2SO_4. The solvent was evaporated in vacuo, and the residue purified by chromatography (CH_2Cl_2/MeOH/NH_3 (25% in H_2O) 9:0.5:0.05) to give **20** as a dark yellow oil (6.10 g, 20.0 mmol, 53%). IR: 3620w, 3363s, 3109m, 2940m, 2871m, 1623s, 1587s, 1524s, 1498s, 1470m, 1424s, 1366s, 1335s, 1310s, 1279s, 1181w, 1143s, 1135s, 1102m, 1087m, 1059m, 922m, 832m, 822m, 764w, 744s, 712m, 650w. ^1H NMR ($CDCl_3$): 9.12 (d, ^4J=2.7, 1 arom. H), 9.02 (br s, NH), 8.26 (dd, $^{3,4}J$=9.5, 2.7, 1 arom. H), 6.96 (d, ^3J=9.5, 1 arom. H), 3.54 (dt, ^3J=6.7, 5.2, 2H), 2.95 (t, ^3J=6.4, 2H), 1.91 (quint., ^3J=6.6, 2H), 1.28 (s, NH_2). ^{13}C NMR ($CDCl_3$): 148.4 (s, 2C), 135.9 (s, 1C), 130.3, 124.4, 113.9 (3d, 3 arom. C), 42.1, 39.8, 31.5 (3t, 3C). CI-MS: 241 (100, $[M+H]^+$).

4.2.2. *Derivatization of Merrifield resin with N-(3-aminopropyl)-2-nitrobenzenesulfonamide (resin **2**)*

Merrifield resin (24.00 g, 7.68 mmol, 0.32 mmol g^{-1}) was swelled in *N*-methyl-2-pyrrolidone (NMP, 180 ml) for 15 min. After addition of *N*-(3-aminopropyl)-2-nitrobenzensulfonamide[11] (18.67 g, 72.00 mmol) and ethyldiisopropylamine (DIEA, 20.5 ml, 0.120 mol), the mixture was stirred for 24 h at 50 °C. The resin was filtered off, washed successively with NMP, CH_2Cl_2, and MeOH, and dried in vacuo to give 26.48 g of resin **2**. Its loading, 0.29 mmol g^{-1} (100%), was measured by *Volhard* titration.[8,28] IR: 1690, 1542 (NO_2), 1347 (SO_2), 1167 (SO_2).

4.2.3. *Alkylation of resin **2** with 1,3-dibromopropane (resin **3**)*

Resin **2** (1.16 mmol) was swelled in NMP (30 ml) for 15 min. 1,3-Dibromopropane (1.2 ml, 11.60 mmol) and DIEA (2.0 ml, 11.60 mmol) were added, and the mixture was agitated for 20 h at 50 °C. Resin **3** was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo. IR: 1542 (NO_2), 1347 (SO_2), 1167 (SO_2).

4.2.4. *Elongation of resin **3** (resin **4**)*

Resin **3** (1.16 mmol) was swelled in NMP (30 ml), and benzylamine (1.3 ml, 11.60 mmol) and DIEA (2.0 ml, 11.60 mmol) were added. After agitation for 20 h at 50 °C, resin **4** was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo. IR: 1686, 1542 (NO_2), 1363 (SO_2), 1297, 1155 (SO_2).

4.2.5. *Elongation of resin **3** (resin **5**)*

Analogous to Section 4.2.4, resin **3** (0.51 mmol) was treated with *N*,*N*′-dibenzylpropane-1,3-diamine (0.78 g, 3.08 mmol) and DIEA (0.88 ml, 5.14 mmol) for 20 h at 50 °C delivering resin **5**. IR: 1686, 1542 (NO_2), 1362 (SO_2), 1166 (SO_2).

4.2.6. *Elongation of resin **4** (resin **6**)*

Analogous to Section 4.2.3, resin **4** (1.16 mmol) was treated with 1,3-dibromopropane (1.2 ml, 11.60 mmol) to give resin **6**.

*4.2.7. Elongation of resin **5** (resin **7**)*

Analogous to Section 4.2.3, resin **5** (1.16 mmol) was alkylated further with 1,3-dibromopropane (1.2 ml, 11.60 mmol) to give resin **7**.

*4.2.8. Alkylation of resin **2** with 3-bromopropanol (resin **8**)*

Resin **2** (0.51 mmol) was swelled in NMP (15 ml). 3-Bromopropanol (0.28 ml, 3.08 mmol) and DIEA (0.88 ml, 5.14 mmol) were added, and the mixture was agitated for 20 h at 50 °C. The resin was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo. IR: 1542 (NO_2), 1362 (SO_2), 1167 (SO_2).

*4.2.9. Elongation of resin **4** (resin **9**)*

Analogous to Section 4.2.3, resin **4** (0.51 mmol) was treated with 3-bromopropanol (0.28 ml, 3.08 mmol) and DIEA (0.88 ml, 5.14 mmol) for 20 h at 50 °C delivering resin **9**. IR: 3418 (OH), 1683, 1542 (NO_2), 1401, 1371 (SO_2), 1168 (SO_2), 1112, 984.

*4.2.10. Elongation of resin **5** (resin **10**)*

Analogous to Section 4.2.3, resin **5** (0.51 mmol) was treated with 3-bromopropanol (0.28 ml, 3.08 mmol) to give resin **10**. IR: 1686, 1542 (NO_2), 1401, 1363 (SO_2), 1167 (SO_2).

*4.2.11. Derivatization of Merrifield resin with 3-aminopropanol (resin **21**)*

Merrifield resin (20.00 g, 15.60 mmol, 0.78 mmol g^{-1}) was swelled in NMP (140 ml). After addition of 3-aminopropanol (18.67 g, 72.00 mmol) and DIEA (20.5 ml, 0.120 mol), the mixture was stirred for 24 h at 50 °C. The resin was filtered off, washed successively with NMP, CH_2Cl_2, and MeOH, and dried in vacuo. *Volhard* titration[8,28] revealed 100% loading. IR: 3520–3100 (OH), 1069.

*4.2.12. Alkylation of resin **21** with N-(3-bromopropyl)phthalimide (resin **22**)*

Resin **21** (1.17 mmol) was suspended in NMP (10 ml). *N*-(3-Bromopropyl)phthalimide (1.88 g, 7.02 mmol) and DIEA (2.0 ml, 12.00 mmol) were added, and the mixture was agitated for 20 h at 50 °C. Resin **22** was filtered off, washed with NMP, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 1712 (CO), 1394, 1364.

*4.2.13. Removing of the phthalimide protective group from resin **22** (resin **23**)*

Resin **22** (0.59 mmol) was swelled in NMP (5 ml), and $N_2H_4 \cdot H_2O$ (2.8 ml, 58.50 mmol) was added. The mixture was agitated for 3 h at 80 °C, the resin was filtered off, washed with NMP, dioxane, dioxane/H_2O (1:1), dioxane, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3520–3100 (OH, NH).

*4.2.14. Alkylation of resin **23** with 2,4-dinitrobenzenesulfonylchloride (resin **24**)*

Resin **23** (0.59 mmol) was swelled in CH_2Cl_2 (10 ml). 2,4-Dinitrobenzenesulfonylchloride (156 mg, 0.59 mmol) was added. After 5 min, 2,6-lutidine (67 µl, 0.59 mmol) was added, and the mixture was agitated for 5 h at 23 °C. The resin was filtered off, washed with CH_2Cl_2, DMF, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 1550 (NO_2), 1537 (NO_2), 1348 (SO_2), 1252, 1210, 1168 (SO_2).

*4.2.15. Derivatization of Merrifield resin with 4-hydroxybenzyl alcohol (resin **29**)*

Merrifield resin (10.00 g, 2.80 mmol, 0.28 mmol g^{-1}) was swelled in *N*,*N*-dimethylacetamide (60 ml). After addition of 4-hydroxybenzyl alcohol (0.45 g, 3.64 mmol) and NaOMe (200 mg, 3.73 mmol), the mixture was stirred for 24 h at 80 °C. The resin was filtered off, washed successively with DMF, dioxane, CH_2Cl_2, and MeOH, and dried in vacuo. *Volhard* titration[8,28] showed complete loading.

*4.2.16. Modification of resin **29** with Ph_3PBr_2 (resin **30**)*

Resin **29** (1.40 mmol) was swelled in CH_2Cl_2 (30 ml). After the slow addition of Ph_3PBr_2 (1.76 g, 4.20 mmol) suspended in CH_2Cl_2 (15 ml), the mixture was agitated for 3 h at 23 °C under Ar. The resin was filtered off, washed successively with CH_2Cl_2 and MeOH, and dried in vacuo. *Volhard* titration[8,28] showed complete conversion.

4.3. Cyclization of the polyamines on the resins

*4.3.1. Cyclization of resin **3** (resin **11**)*

Resin **3** (0.58 mmol) was swelled in dry DMF (15 ml) and Cs_2CO_3 (2.84 g, 8.70 mmol) was added to the reaction mixture. The suspension was heated to 50 °C and agitated for 135 h, the resin was filtered off, washed successively with NMP, NMP/H_2O (1:1), NMP, and CH_2Cl_2, and dried in vacuo at 50 °C. IR: 1685, 1542 (NO_2), 1374 (SO_2), 1166 (SO_2).

*4.3.2. Cyclization of resin **6** (resin **13**)*

Resin **6** (0.58 mmol) was cyclized according to Section 4.3.1 to give **13**. IR: 1686, 1542 (NO_2), 1371 (SO_2), 1166 (SO_2).

*4.3.3. Cyclization of resin **7** (resin **14**)*

Resin **7** (0.87 mmol) was cyclized analogous to Section 4.3.1 delivering **14**. IR: 1686, 1542 (NO_2), 1371 (SO_2), 1165 (SO_2).

*4.3.4. Cyclization of resin **8** (resin **11**)*

The well-dried resin **8** (0.51 mmol) was swelled in 18 ml NMP for 15 min. After addition of PPh_3 (674 mg, 2.57 mmol) and DEAD (448 mg, 2.57 mmol) the mixture was agitated for 20 h at 23 °C. The resin was filtered off, washed with CH_2Cl_2, NMP, and CH_2Cl_2, and dried in vacuo to give resin **11**.

*4.3.5. Cyclization of resin **9** (resin **13**)*

Resin **9** (0.51 mmol) was cyclized analogous to Section 4.3.4 delivering **13**.

*4.3.6. Cyclization of resin **10** (resin **14**)*

Resin **10** (0.51 mmol) was cyclized analogous to Section 4.3.4 delivering **14**.

*4.3.7. Cyclization of resin **24** (resin **25**)*

Resin **24** (0.59 mmol) was cyclized analogous to Section 4.3.4 delivering **25**.

4.4. Cleavage of the cyclic polyamine derivatives from the resins

*4.4.1. 1-[(2-Nitrobenzene)sulfonyl]-1,5-diazacyclo-octane (**12**)*

Resin **11** (0.58 mmol) was swelled in 1,2-dichloroethane (15 ml) and 1-chloroethyl chloroformate (ACE-Cl; 1.3 ml, 11.60 mmol) was added, followed by DIEA (0.5 ml, 2.90 mmol). After agitation for 3 h at 23 °C, the resin was filtered off and washed with CH_2Cl_2. The organic solutions were combined and evaporated to dryness. The residue was dissolved in MeOH, and the resulting solution was refluxed for 3 h. The solvent was removed, and the residue was purified by chromatography (CH_2Cl_2/MeOH/NH_3 (25% in H_2O) 9:2:0.05) to give **12** as the free base (58 mg, 0.19 mmol; overall yield 33% with respect to **2**). IR: 3380w, 3100w, 2940s, 1595m, 1550s, 1470m, 1380s, 1345s, 1170s, 1065m, 1000m, 860m, 785m, 750m. ^{1}H NMR ($CDCl_3$): 7.99–7.90 (m, 1 arom. H), 7.74–7.56 (m, 3 arom. H), 3.47–3.39 (m, 4H), 3.00–2.94 (m, 4H), 2.65 (s, NH), 1.91–1.81 (m, 4H). ^{13}C NMR ($CDCl_3$): 148.5 (s, CNO_2), 133.6 (d, 1 arom. C), 132.5 (s, CSO_2), 131.6, 130.7, 124.2 (3d, 3 arom. C), 47.8, 46.4, 30.2 (3t, 6C). CI-MS: 300 (100, $[M+H]^+$).

The analogous cleavage of resin **11** (0.51 mmol) obtained by the *Mitsunobu* cyclization delivered compound **12** (54 mg, 0.18 mmol) with an overall yield of 35.5%.

*4.4.2. 1-[(2-Nitrobenzene)sulfonyl]-1,5,9-triazacyclodo-decane (**15**)*

Analogous to Section 4.4.1, resin **13** (0.58 mmol) delivered after purification by chromatography (CH_2Cl_2/MeOH/NH_3 (25% in H_2O) 9:1.5:0.2) **15** as the free base (62 mg, 0.17 mmol; overall yield 30% with respect to **2**). IR: 3350w, 2980m, 2880m, 1565s, 1500w, 1400s, 1370s, 1190s, 1160m, 945w, 885w. ^{1}H NMR ($CDCl_3$): 8.04–7.97 (m, 1 arom. H), 7.74–7.56 (m, 3 arom. H), 3.49 (t, ^3J=7.0, 4H), 2.83–2.75 (m, 4H), 2.73–2.64 (m, 4H), 2.16 (br s, 2NH), 1.78–1.65 (m, 4H), 1.55 (quint., ^3J=5.4, 2H). ^{13}C NMR ($CDCl_3$): 148.4 (s, CNO_2), 133.6 (s, CSO_2), 133.5, 131.7, 130.8, 124.2 (4d, 4 arom. C), 45.8 (t, 2C), 45.4 (*t*, 2C), 44.2 (t, 2C), 28.8 (t), 26.1 (t, 2C). CI-MS: 357 (100, $[M+H]^+$).

The analogous cleavage of resin **13** (0.51 mmol) obtained by the *Mitsunobu* cyclization delivered compound **15** (62 mg, 0.17 mmol) with an overall yield of 34.0%.

*4.4.3. 1-[(2-Nitrobenzene)sulfonyl]-1,5,9,13-tetraazacyclo-hexadecane (**16**)*

Analogous to Section 4.4.1, resin **14** (0.87 mmol) delivered compound **16** as the free base (109 mg, 0.26 mmol; overall yield 30% with respect to **2**) after rinsing the crude mixture with CH_2Cl_2 and purifying the rest by chromatography (CH_2Cl_2/MeOH/NH_3 (25% in H_2O), with the following gradient 10:2:0.1 → 4:1:0.1 → 7:3:1). IR: 3290m, 2940s, 1550s, 1470m, 1375s, 1345s, 1165s, 1130m, 1020w, 855w. ^{1}H NMR (MeOH-d_4): 8.14–8.06 (m, 1 arom. H), 7.94–7.80 (m, 3 arom. H), 3.48 (t, ^3J=7.4, 4H), 2.84–2.69 (m, 12H), 1.94–1.70 (m, 8H). ^{13}C NMR (MeOH-d_4): 149.9 (s, CNO_2), 135.3 (d, 1 arom. C), 133.9 (s, CSO_2), 133.2, 131.4, 125.5 (3d, 3 arom. C), 49.4 (t, 2C), 48.9 (t, 2C), 47.9 (t, 2C), 47.0 (t, 2C), 29.4 (t, 2C), 29.3 (t, 2C). CI-MS: 414 (100, $[M+H]^+$), 396 (29), 384 (92), 350 (22).

The analogous cleavage of resin **14** (0.51 mmol) obtained by the *Mitsunobu* cyclization delivered compound **16** (54 mg, 0.13 mmol) with an overall yield of 25.4%.

*4.4.4. 1-[(2,4-Dinitrobenzene)sulfonyl]-1,5-diazacyclo-octane (**26**), 1-(2,4-dinitrobenzene)-1,5-diazacyclo-octane (**27**), and N-(3-chloropropyl)-N′-(2,4-dinitrophenyl)-propane-1,3-diamine (**28**)*

Resin **25** (0.59 mmol) was swelled in 1,2-dichloroethane (10 ml) and 1-chloroethyl chloroformate (0.65 ml, 5.85 mmol) was added. After agitation for 3 h at 23 °C under Ar, the product resin was filtered off and washed with CH_2Cl_2. The organic solutions were combined and evaporated to dryness. The residue was dissolved in MeOH, and the resulting solution was refluxed for 3 h. The solvent was removed, and the residue was purified by HPLC (RP C-18; solvent (MeCN/H_2O/TFA 25:74.95:0.05)) to give pure **26** as the TFA salt (15.6 mg, 0.034 mmol; overall yield 5.8% with respect to **21**), the *Smiles* product **27** (14.6 mg, 0.037 mmol; overall yield 6.2% with respect to **21**), and the non-cyclic compound **28** (15.1 mg, 0.035 mmol; overall yield 6.0% with respect to **21**).

*4.4.4.1. Data of **26**.* IR (KBr): 3434m, 3102m, 3034m, 2990m, 2972m, 2926m, 2875m, 2820m, 2762m, 2565m, 2474w, 1676s, 1621s, 1606m, 1563s, 1540s, 1472m, 1464m, 1430m, 1371s, 1356s, 1197s, 1176s, 1162s, 1144m, 1020s, 1051w, 1034m, 1007m, 970w, 904m, 851w, 835m, 824w, 798m, 751s, 721m, 696m, 658w. ^{1}H NMR (MeOH-d_4): 8.75 (s, 1 arom. H), 8.61 (d, ^3J=8.8, 1 arom. H), 8.29 (d, ^3J=8.6, 1 arom. H), 3.58–3.54 (m, 4H), 3.39–3.36 (m, 4H), 2.18–2.16 (m, 4H). ^{13}C NMR (MeOH-d_4): 151.8, 150.0 (2s, $2CNO_2$), 137.2 (s, CSO_2), 133.4, 127.7, 121.3 (3d, 3 arom. C), 48.6 (t, 2C), 44.9 (t, 2C), 26.3 (t, 2C). CI-MS: 345 (95, $[M+H]^+$), 315 (78), 281 (100, $[M+H-SO_2]^+$).

*4.4.4.2. Data of **27**.* IR: 2974m, 2359m, 1683s, 1604m, 1507m, 1333s, 1201m, 1138m, 1053w, 1033w, 910w, 832w, 720w. ^{1}H NMR (MeOH-d_4): 8.57 (d, ^4J=2.8, 1 arom. H), 8.29 (dd, $^{3,4}J$=9.5, 2.8, 1 arom. H), 7.42 (d, ^3J=9.5, 1 arom. H), 3.58 (t, ^3J=6.1, 4H), 3.36–3.30 (m, 4H), 2.24–2.16 (m, 4H). ^{13}C NMR (MeOH-d_4): 149.6 (s, 1C), 139.7, 139.4 (2s, $2CNO_2$), 128.9, 124.3, 119.9 (3d, 3 arom. C), 51.8 (t, 2C), 44.8 (t, 2C), 24.6 (t, 2C). CI-MS: 281 (100, $[M+H]^+$), 251 (12).

*4.4.4.3. Data of **28**.* Mp: 131.1–133.6 °C (yellow solid after lyophylization). IR (KBr): 3329m, 3097m, 3045m, 2842m, 1662s, 1624s, 1586s, 1526s, 1474m, 1422s, 1352s, 1318m, 1281s, 1270s, 1196s, 1171s, 1040s, 1104m, 1055w, 1022w, 921w, 833m, 826m, 803m, 780w, 768w, 745m, 721s, 689w, 660w. ^{1}H NMR (MeOH-d_4): 9.05 (d, ^4J=2.7, 1 arom. H), 8.32 (dd, $^{3,4}J$=9.6, 2.7, 1 arom. H), 7.21 (d, ^3J=9.6, 1 arom. H), 3.71–3.61 (m, 4H), 3.32–3.14 (m, 4H), 2.19–2.08 (m, 4H). ^{13}C NMR (MeOH-d_4): 149.5 (s, CSO_2), 137.4 (s, CNO_2), 132.2 (s, CNO_2), 131.2, 124.8, 115.6 (3d, 3 arom. C), 46.6 (t, 2C), 42.1 (t, 2C), 41.0 (t, 2C), 30.2 (t, 2C), 26.6 (t, 2C). CI-MS: 317 (25, $[M+H]^+$), 281 (25, $[M+H-HCl]^+$), 251 (18).

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