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A new strategy for synthesis of polymeric supports with triazene linkers

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Abstract—A new strategy based on the use of diethylamine triazenes for stabilization and generation of polymer supported diazonium ions was described. New economical syntheses of four new polymeric supports with 3- and 6-carbon atom spacers and triazene linkers derived from *meta*- and *para*-aminophenol were described and compared to the traditional methods. The possible application of the polymer bound triazene masked diazonium salts as supports for immobilization of secondary amines (nortropine and 4-piperidinole and their esterification and oxidation), and as amine scavengers was shown. The new supports with *meta*-C_3-T2 and *para*-C_3-T2 linkers showed higher loadings and typically gave products with good yields and purities.

1. Introduction

Triazenes are a group of organic compound with a long history.[1] Some of the triazenes showed biological activity and found use in cancer therapy.[2] In recent years triazenes have gained importance as useful tools in organic synthesis[3] such as protecting groups,[4] alkylating agents,[5] ligands for organometallic catalysts,[6] linkers in solid-phase organic synthesis (SPOS).[7] The triazene based linkers are one of the recent and fast growing additions to methodology of supported synthesis, which is one of the workhorses in drug development process based on combinatorial chemistry.[8] The so-called T2 linker originally introduced for anchoring secondary amines[7a] has been used for synthesis of a number of different classes of compounds (amides, thioureas, ureas, hydrazines, alcohols, esters, guanidines, sulfoximines and alkyl halides).[7d] The amine substrates used in solid-phase synthesis were anchored to a support through the T2 type linker by the reaction with a polymer bound diazonium salt (typically tetrafluoroborate) prepared from a polymer bound aromatic amine. In the described preparations of polymer supported diazonium salts and corresponding triazenes *m*-aminophenol[7b] or *p*-nitrophenol[5] served as the precursors of the anchored aromatic amines on Merrifield polymer. In a recent report triazenes were also prepared on polymer from an aromatic amine synthesized directly on polymeric support.[9] In our preliminary communication we have reported on synthesis of spacer-modified triazene linkers and their application in solid-phase reactions of nortropinone with LDA and Grignard reagent.[10]

Herein, we report in detail the strategy for the generation of supported diazonium ions directly from polymer bound triazenes, and a new improved, more economical and less laborious syntheses of four supports with triazene linkers (triazene masked diazonium ions) modified with 3- and 6-carbon atom spacers. The supports could be used for immobilization and derivatization of two important to medicinal chemistry scaffolds: 8-azabicyclo[3.2.1]octan-3-ol (3-nortropine)[11] and 4-hydroxypiperidine (4-piperidinol).[12]

2. Results and discussion

2.1. Preparation of polymers

The typical preparation of triazenes on polymeric support involved anchoring of an aromatic hydroxy amine (specifically *m*-aminophenol) to the Merrifield polymer followed by diazotisation to form the diazonium salt and attachment of amines.[7a] Along this scheme, we prepared *m*-aminophenol-derived precursors of the spacer-modified triazenes **1** by alkylation of *m*-aminophenol with 3-chloropropan-1-ol or 6-chlorohexan-1-ol (Scheme 1). The most suitable solvent for the alkylation of the aminophenol was found to be DMF. The results obtained with three different bases; sodium hydride, solid KOH, and potassium carbonate, did not differ significantly. The major technical problem with this procedure was purification of the products, i.e. removal of DMF and by-products (products of *N*-alkylation and *N*,*O*-bisalkylation) best achieved by distillation. The subsequent

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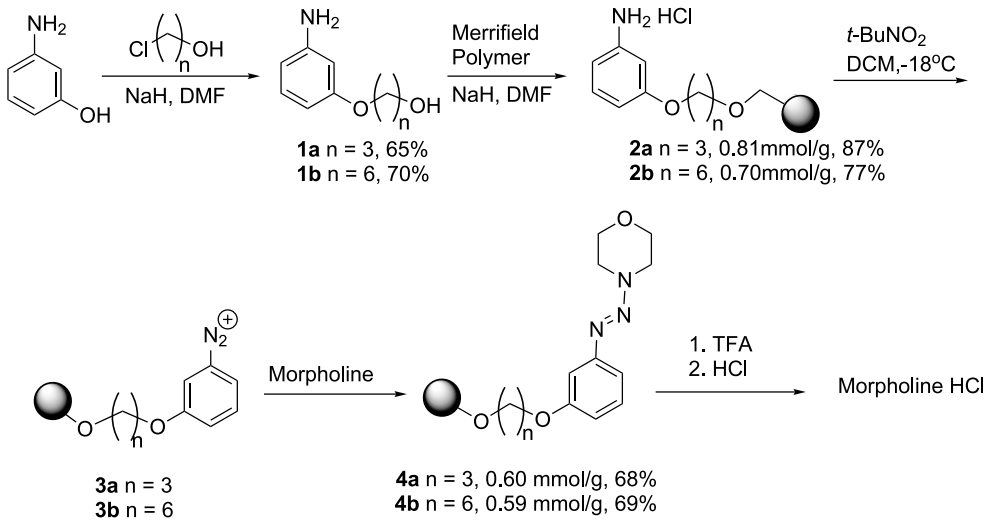
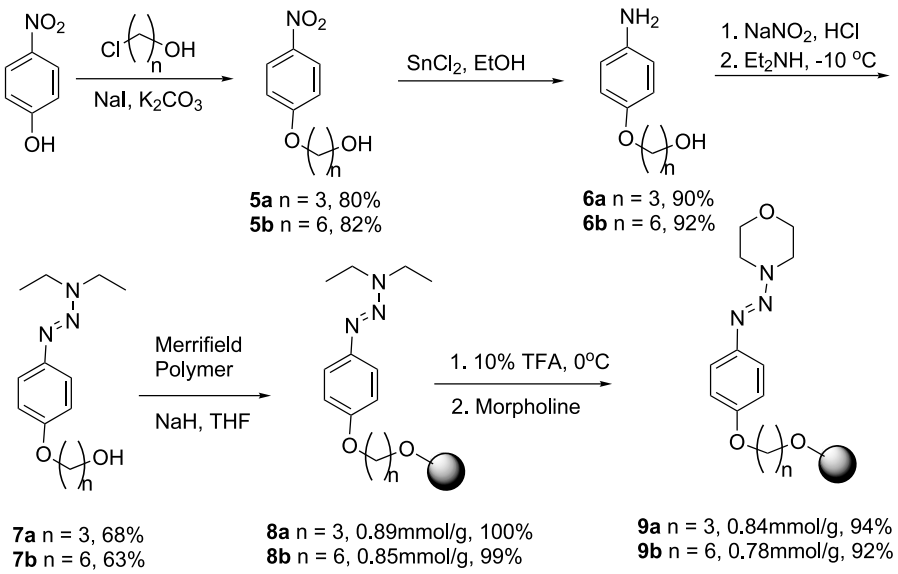


Scheme 1.

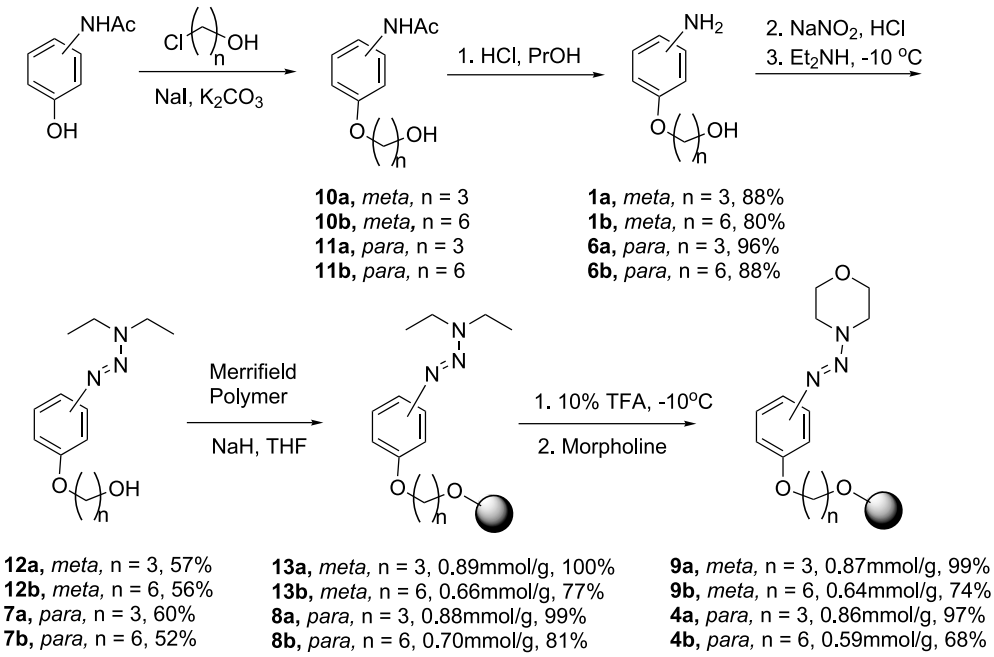
anchoring of the resulting amino alcohols **1** to Merrifield polymer by the Williamson etherification reaction followed by nitrosation of the polymer bound aromatic amines **2** (isolated in the form of hydrochlorides) with *t*-BuONO at −18 °C in dichloromethane provided the polymer bound diazonium salts, which were used for immobilization of amines. Typical test amines were 4-methylpiperidine and morpholine. Morpholine served as an especially useful cheap model of nortropanes because, in our experience, the results obtained for the 'bind and release' process of this amine were very close to those for nortopine and nortropinone. The described traditional approach (Scheme 1) suffered from hard to control chemoselectivity of anchoring of amino alcohols through alkylation with chloromethylpolystyrene as shown by simple model experiments with benzyl chloride in solution. Attempts to optimise the reaction temperature did not improve the loadings and the reaction remained capricious. As a result, the loadings of amines on so prepared supports were usually lower then the loading calculated from the percentage of nitrogen shown by elemental analysis of the triazene loaded polymers. Therefore, a more representative procedure based on direct gravimetric analysis of the obtained amine hydrochloride was used for comparing results.

The sensitivity of ethers of *p*-aminophenol to light and oxygen made the preparation of the *para* analogues more difficult and inefficient. Alkylation of *p*-aminophenol under analogous conditions to those described in Scheme 1 resulted in very low yields of *O*-alkylated products. Therefore, for the preparation of spacer-modified *p*-aminophenol-derived supports we chose to use a different strategy based on use of nitrophenol as synthetic equivalent of aminophenol and protection of amine in the form of triazene. We expected that the polymer bound triazene can serve as a latent diazonium ion. Acidolytic cleavage of the triazenes would regenerate protonated secondary amine and the diazonium ion, which under favourable conditions could be isolated and used for capturing of another amine. Such favourable conditions would be provided by low temperature and solid-phase immobilization. Thus, *p*-nitrophenol was alkylated with iodides (prepared in situ by the Finkelstein reaction) to give the nitro alcohols **5** (Scheme 2). This simple reaction suffered, however, from relatively low nucleophilicity of the nitrophenolate ion and required control of reaction progress (NMR or GC) and rather long reaction times in order to provide satisfactory yields of products. The fairly trivial reduction of nitro group of **5** was achieved with different reductants under variety of conditions ($SnCl_2$/DMF, $SnCl_2$/methanol, $SnCl_2$/ethanol, sodium dithionite/ethanol, $NaBH_4$/Pd/C/methanol) from which the optimal were tin(II) chloride in boiling ethanol. This method gave the best purities and almost quantitative yields in shortest time. In addition, the sensitive amine products **6** were protected by the acidic environment of the reaction medium eliminating the need for protective gas atmosphere. The major drawback of this method was the cumbersome extractive workup of the reaction mixture requiring large excess of potassium hydroxide for dissolving the tin hydroxides precipitate. The amines prepared by reduction of nitro alcohols **5** were promptly protected in the form of triazenes **7** (Scheme 2). Overall yields of the preparation of the key intermediates were 49% for **7a** and 47% for **7b**. These hydroxy triazenes were very effectively attached to a Merrifield polymer under typical conditions i.e. sodium hydride in THF, 60–65 °C. The new approach was proven more successful as indicated by the high loading of diethylamine (Table 1) on polymers **8**, good %N values in elemental analyses and practically quantitative substitution of chlorine by the triazenes (below the detection limit of elemental analysis).[13]

In order to apply the new strategy to the preparation of four polymeric gels (*meta* and *para* C_3 and C_6) on a larger scale we decided to develop an economical, amenable to scaling up and general synthesis of the key triazenes **7** and **12** (Scheme 3). To circumvent the mostly technical problems of preparations (long reaction times, removal of DMF, by-products, tin residues) and to minimize the purification procedures, especially the chromatography, we set up the synthetic plan shown in Scheme 3. The alkylation of the *meta* and *para* hydroxy acetanilides was reasonably fast and efficient. The crude products **10** and **11** were pure enough to be subjected to acidic hydrolysis in boiling ethanol or propanol. Propanol provided for higher reaction temperature and shorter hydrolysis time. The resulting hydroxy



Scheme 2.



Scheme 3.

Table 1. Comparison of loadings of the polymeric supports prepared with two strategies

Support (prepared from)	Theoretical loading of amine (mmol/g)	Experimental loading of amine (mmol/g) (% of theoretical value)	Experimental loading of morpholine (mmol/g)[a] (% of theoretical value)
meta-C_0 (aminophenol)	0.98	0.82 (84)[b]	0.63 (64)
para-C_0 (aminophenol)	0.98	0.79 (81)[b]	0.87 (69)
meta-C_3 (hydroxyamine) **2a**	0.93	0.81 (87)[b]	0.60 (68)
meta-C_6 (hydroxyamine) **2b**	0.89	0.70 (77)[b]	0.59 (69)
para-C_3 (nitrophenol) **8a**	0.89	0.89 (100)[c]	0.84 (94)
para-C_6 (nitrophenol) **8b**	0.86	0.85 (99)[c]	0.78 (92)
meta-C_3 (hydroxyacetanilide) **13a**	0.89	0.89 (100)[c]	0.87 (99)
meta-C_6 (hydroxyacetanilide) **13b**	0.86	0.66 (77)[c]	0.64 (74)
para-C_3 (hydroxyacetanilide) **8a**	0.89	0.88 (100)[c]	0.86 (97)
para-C_6 (hydroxyacetanilide) **8b**	0.86	0.70 (81)[c]	0.59 (68)

[a] Based on mass of morpholine HCl obtained from a weighed sample of polymer after 'bind and release' process.
[b] Loading determined from mass of triethylamine HCl obtained after washing of the gel with triethylamine.
[c] Loading determined from mass of diethylamine HCl obtained after acid cleavage.

anilines were diazotised (sodium nitrite, HCl) and gave corresponding diethylamine triazenes **7** and **12** in fairly good yields (52–60% after chromatographic purification). On larger scale the triazenes could be purified by filtration through pad of silica. The attachment of the hydroxy triazenes to Merrifield gel was accomplished via routine procedure. The overall yields of preparation of the key hydroxy triazenes **12a**, **12b**, **7a** and **7b** via the new method were 50, 45, 58, 46%, respectively. The yields were similar or slightly better then the overall yields of the method based on nitrophenol. However, the new procedure was shorter in time and less laborious. The loadings of polymers with the classical T2 linkers[7] and the new supports prepared through the on polymer diazotisation of amines (Scheme 1) and through the new strategy (Schemes 2 and 3) are shown in Table 1. The comparison suggests that the substitution of reactive sides of chloromethylpolystyrene with amine (diethylamine or morpholine) on polymers prepared by the new method was higher, especially on both of the supports with linkers with 3-carbon atom spacer.

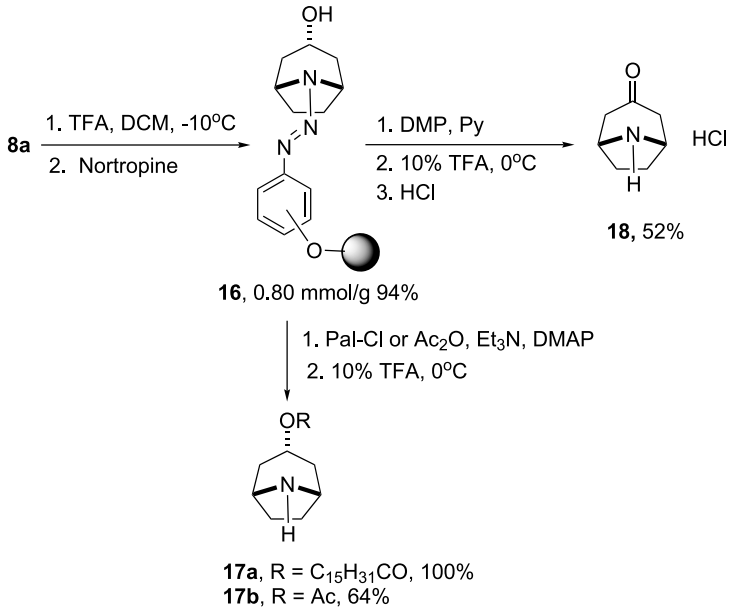
2.2. Polymer supported reactions

As envisaged, simple washing of the triazene gel **8** with a cold 10% solution of trifluoroacetic acid (TFA) in dichloromethane regenerated the supported diazonium salt. The salt could readily anchor another amine as long as the reaction medium remained cold. Such exchange of amines was accomplished with barely noticeable lowering of loadings (Table 1). The loadings of the test amine (morpholine) immobilized on the new polymers **8a** and **13a** through the exchange procedure (97 and 99% of the theoretical value) were significantly better then the loadings of the supports prepared via diazotisation of amines on polymer, i.e. the traditional approach. The data shows however, that both C_6-spacer modified supports **8b**, **13b** had lower loadings than the C_3 supports **8a**, **13a**. In addition to that performance of the *meta*-C_3-T2, *para*-C_3-T2 linkers in Grignard and aldol reactions of supported nortropinone (8-azabicyclo[3.2.1]octan-3-one) was slightly better than the *meta*-C_6-T2 and *para*-C_6-T2 analogues.[10] Encouraged by this results we have further used and tested the polymers with the C_3 linkers.

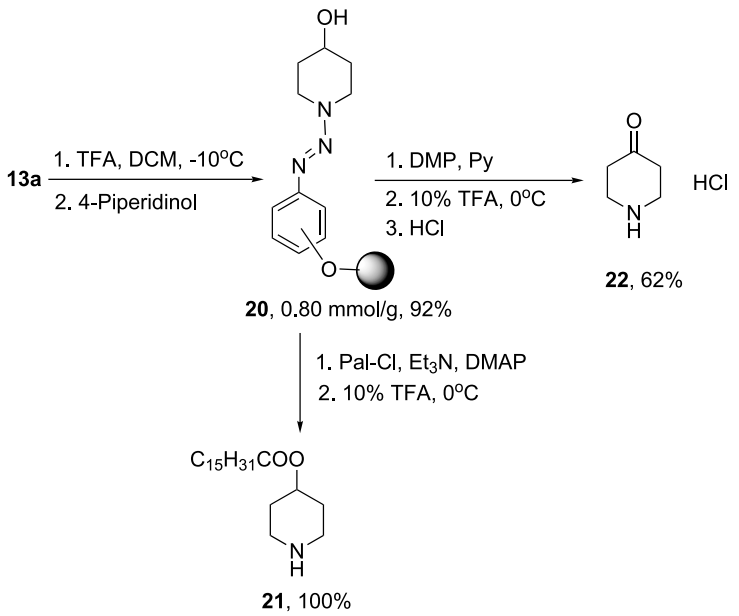
The new polymeric gels were used for immobilization of 3-nortropine and 4-piperidinol with excellent efficiency, (94 and 92% of the theoretical loadings, respectively) and for a few representative reactions of these supported amines (Schemes 4 and 5). The esterification reaction with palmitoyl chloride gave a virtually quantitative yield of esters **17a** and **21**. The simple acetylation was less effective (64 and 62%). Oxidation with Dess–Martin periodinane (DMP) provided ketones with fairly good yields and purities. The gel required thorough washing with basic thiosulfate solutions in order to remove periodinane related by-products. Other oxidants (Py–SO_3 complex) gave incomplete conversion to ketone or even harder to remove impurities (Cr(VI) based oxidants like PDC).

2.3. Stability of triazene linkers and cleavage with TFA

In order to evaluate the stability of the new linkers under reaction conditions model triazenes; *meta* and *para* propyloxy substituted triazenes were treated with the following reagents: Grignard reagent at 0 °C, LDA at −78 °C; potassium *tert*-butoxide, Dess–Martin oxidant, permanganate, hypochloride, peroxides, ethyl iodide and acyl chlorides at room temperature. Analyses of the mixtures showed no significant decomposition of the triazenes by TLC or NMR as long as the solutions remained basic, although the mixtures often discoloured. The observed stability towards strong bases was especially significant in light of recent reports on base induced fragmentation of triazenes.[14] Loadings of the polymers stored in refrigerator remained unchanged for a few months. Thus the stability of the diazonium ions masked in the form of triazenes is high. The *meta*-C_3 triazene linker was proven slightly more stable to acids than the *para* isomer, which was cleaved partially with acetic acid. All of the triazene linkers, as expected, have cleaved under action of acids



Scheme 4.



Scheme 5.

(HCl/THF, HBF_4/THF/, TFA/THF) but the least contaminated amine products were invariably provided by cleavage with TFA in DCM both below 0 °C or at room temperature.

2.4. New polymers as scavengers for amines

We observed that the triazene-loaded polymers could also act as amine scavengers after activation with cold acid solution. When the polymers **8a** or **13a** (twofold molar excess) were pre-treated with cold TFA in DCM, washed free of acid with DCM and added with an equimolar amount of polymer supported tertiary amine (piperidine) to a solution of secondary amine (piperazine or 4-methylpiperidine) the secondary amine was practically removed from the solutions in less than an hour. This observation suggests that the triazene protected polymer supported diazonium salts could also serve as amine scavengers as does the stable polymer supported diazonium tetrafluoroborate.[7e]

3. Conclusions

A new, efficient approach for preparation of resins with bound diazonium ions that are latent and thus stabilized in the form of triazenes has been developed. The masked polymer supported diazonium ions, have good shelf life, and thus can be alternatives to the specially designed thermally stable polymer bound 4-chlorobenzenediazonium tetrafluoroborate (the so-called T2* linker polymer).[7e] Use of the new approach and the three carbon atom spacer modified linkers provided useful polymeric supports with excellent loadings and good purities. The polymers, prepared by pre-loading of triazenes synthesized in solution, could be used, via the amine exchange procedure, for immobilization of secondary amines (as demonstrated on nortropane and piperidine derivatives) and solid-phase synthesis of any class of compounds already prepared with help of the traditional T2 linker.[7] The new polymers can also be used after pre-treatment with cold TFA as amine scavengers in solution.

4. Experimental

4.1. General

All air sensitive reactions were carried out under argon. Tetrahydrofuran was distilled under argon from sodium/benzophenone. Dry dimethylformamide (DMF) was distilled and stored over molecular sieves 4 Å. Chromatographic purifications were achieved by dry-column flash chromatography (DFC).[15] Thin-layer chromatography (TLC) was performed on pre-coated plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Mass spectra were recorded with an AMD-604 spectrometer and are reported as *m/z* ratio (relative intensity). Electron impact (EI) ionisation was accomplished at 70 eV. Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 FTIR Series II Spectrometer as $CHCl_3$ solutions or, in case of polymers, as pressed disks with KBr. Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker 200 spectrometer in $CDCl_3$ unless otherwise stated. The gel phase ^{13}C NMR spectra of polymers were recorded after at least 1 h swelling in $CDCl_3$. Chemical shifts are reported in ppm downfield of tetramethylsilane.

4.1.1. 3-(3-Aminophenoxy)propan-1-ol (1a). To a solution of 3-aminophenol (3.27 g, 30 mmol) in dry DMF (12 mL), under argon atmosphere, was added sodium hydride (1.21 g, 30 mmol, 60% dispersion in oil) and the mixture was stirred for 10 min. Then the mixture was cooled to 0 °C before addition of 3-chloropropan-1-ol (1.90 g, 20 mmol) and slow warming to room temperature. After stirring for 24 h, the solvent was removed in vacuo and the residue was dissolved in 2 M aqueous hydrochloric acid (60 mL). The solution was extracted with DCM (4×20 mL), alkalised with 2 M potassium hydroxide (80 mL) and extracted with DCM (6×20 mL). The combined alkaline extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The

residue was distilled in Kugelrohr apparatus to remove remaining DMF (ot 120 °C/15 Torr) and to give the product (ot 190–210 °C/0.15 Torr) as a white solid (3.245 g, 65%). Mp 65–67 °C; R_f (5% MeOH/DCM) 0.30; δ_H (200 MHz, $CDCl_3$) 7.05 (t, 8 Hz, 1H), 6.38–6.22 (m, 3H), 4.08 (t, 6 Hz, 2H), 3.85 (t, 7.5 Hz, 2H), 3.67 (br s, 2H), 2.10–1.97 (m, 2H), 1.78 (br s, 1H); δ_C (50.3 MHz, $CDCl_3$) 159.8, 147.6, 130.0, 108.0, 104.5, 101.6, 65.2, 60.0, 31.8; ν_{max}($CHCl_3$) 3624 (OH), 3456, 3340 (NH_2) cm^{-1}; *m/z* (EI) 167 (M^+, 34), 110 (17), 109 (100), 92 (6), 81 (20), 80 (25), 65 (9), 31 (12); HRMS (EI); M^+, found: 167.0939. $C_9H_{13}NO_2$ requires 167.0946.

4.1.2. 6-(3-Aminophenoxy)hexan-1-ol (1b). An analogous procedure to that described for **1a** gave the title compound **1b** (ot 140–250 °C/0.025 Torr) as a yellowish oil (2.845 g, 70%). R_f (10% MeOH/DCM) 0.6; δ_H (200 MHz, $CDCl_3$) 7.05 (t, 8 Hz, 1H), 6.37–6.21 (m, 3H), 3.92 (t, 6.5 Hz, 2H), 3.75–3.58 (m, 4H), 1.98–1.29 (m, 9H); δ_C (50.3 MHz, $CDCl_3$) 159.9, 147.6, 129.7, 107.6, 104.3, 101.5, 67.4, 62.2, 32.3, 28.9, 25.6, 25.2; ν_{max}($CHCl_3$) 3624 (OH), 3455, 3400 (NH_2) cm^{-1}; *m/z* (EI) 209 (M^+, 6), 110 (11), 109 (100), 81 (9), 80 (10), 65 (7), 55 (8), 31 (9); HRMS (EI); M^+, found: 209.1420. $C_{12}H_{19}NO_2$ requires 209.1416.

4.1.3. 3-(3-Aminophenoxy)propyloxymethylpolystyrene hydrochloride (2a). To a solution of 3-(3-aminophenoxy) propan-1-ol (**1a**, 2.896 g, 17.3 mmol, 5.3 equiv.) in dry DMF (20 mL) was added sodium hydride (0.692 g, 60% dispersion in oil, 17.3 mmol) and the mixture was stirred at room temperature for 20 min. After hydrogen evolution have stopped Merrifield gel (3 g, Novabiochem, 1% PS-DVB, 200–400 mesh, 1.1 mmol/g) was added in portions and the mixture was heated to 40 °C for 18 h with intermittent stirring. Then the gel was washed with methanol (1×8 mL, argon), a cold mixture of conc. hydrochloric acid and THF (1:1, 1×8 mL), methanol (2×8 mL), DMF (2×8 mL), methanol (4×8 mL), DCM (4×8 mL) and methanol (2×8 mL). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give yellow, free flowing powder (3.271 g, 96%, 0.81 mmol HCl/g). ν_{max}(KBr) 3442 (NH_3^+) cm^{-1}. Anal. found: C, 75.01; H, 6.35; N, 1.11. $C_{76}H_{81}NO_2Cl$ requires C, 74.58; H, 6.25; N, 1.32.

4.1.4. 6-(3-Aminophenoxy)hexyloxymethylpolystyrene hydrochloride (2b). An analogous procedure to that described for **2a** gave the title polymer **2b** as a light yellow powder (3.192 g, 89%, 0.70 mmol HCl/g). ν_{max}(KBr) 3447 (NH_3^+) cm^{-1}. Anal. found: C, 84.99; H, 7.78; N, 1.04. $C_{79}H_{87}NO_2Cl$ requires C, 84.78; H, 7.75; N, 1.27.

4.1.5. Procedure for anchoring of the test amine morpholine through the *meta*-C_3 linker. Polymer 4a. To a pre-swollen in DCM (8 mL) and cooled to −18 °C suspension of amine hydrochloride polymer **2a** (1 g, 0.81 mmol/g) was added cooled (−18 °C) *tert*-butyl nitrite (1.13 g, 1.3 mL, 11 mmol) and the mixture was agitated for 18 h in a freezer. Then the gel was washed in cold with DCM (6×8 mL) and treated with cold (−18 °C) solution of morpholine (0.233 g, 0.24 mL, 2.37 mmol, 10 equiv.) in DCM (1 mL). The mixture was agitated in a freezer for 3 h and then was allowed to warm up to room temperature. After 16 h the gel was washed successively with DCM and methanol (6×3 mL of each solvent). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give bright, free flowing powder (0.272 g, 0.60 mmol/g, 68% of the theoretical loading of morpholine). ν_{max}(KBr) 1600 (N=N), 1103 (C–N), 1255 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 113.3, 106.2, 66.3, 64.9, 48.0, 29.8. Anal. found: C, 84.75; H, 7.76; N, 2.80. $C_{80}H_{86}N_3O_3$ requires C, 84.46; H, 7.62; N, 3.69.

4.1.6. 3-(4-Nitrophenoxy)propan-1-ol (5a).[16] To a solution of 3-chloropropan-1-ol (7.56 g, 80 mmol) in dry acetone (40 mL), was added sodium iodide (13.2 g, 88 mmol) and the mixture was heated under reflux for 24 h. Then the precipitate was filtered off. To the filtrate was added 4-nitrophenol (13.344 g, 88 mmol) and anhydrous potassium carbonate (16.56 g, 120 mmol) and the mixture was stirred and heated to reflux for 72 h. Then most of the solvent was evaporated and the residue was dissolved in water (100 mL) and alkalised with 2 M solution of potassium hydroxide (pH=14). The alkaline mixture was extracted with DCM (3×70 mL). The combined extracts were washed with 2 M solution of potassium hydroxide (3×40 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was distilled in Kugelrohr apparatus (ot 180–220 °C/0.2 Torr) to give yellowish solid (12.750 g, 80%). R_f (50% AcOEt/Hex) 0.4. Mp 43–45 °C, lit.[16] Mp 48–49 °C; δ_H (200 MHz, $CDCl_3$) 8.24–8.08 (m, 2H), 7.02–6.90 (m, 2H), 4.20 (t, 6 Hz, 2H), 3.92–3.80 (m, 2H), 2.18–1.93 (m, 3H); δ_C (50.3 MHz, $CDCl_3$) 163.9, 140.9, 125.6, 114.2, 65.6, 50.7, 31.5.

4.1.7. 6-(4-Nitrophenoxy)hexan-1-ol (5b). An analogous procedure to that described for **5a** (Kugelrohr distillation ot 200–230/0.05 Torr) gave the title compound **5b** as a light yellow solid (3.927 g, 82%). Mp 80–82 °C (methanol); R_f (50% AcOEt/Hex) 0.35; δ_H (200 MHz, $CDCl_3$) 8.24–8.14 (m, 2H), 7.00–6.90 (m, 2H), 4.06 (t, 6.5 Hz, 2H), 3.79–3.61 (m, 2H), 1.98–1.76 (m, 2H), 1.76–1.37 (m, 7H); δ_C (50.3 MHz, $CDCl_3$) 164.1, 141.0, 125.7, 114.2, 68.6, 62.4, 32.4, 28.7, 25.5, 25.3; ν_{max}($CHCl_3$) 3622, 3442 (OH), 1514 (NO_2) cm^{-1}; *m/z* (EI) 239 (M^+, 12), 139 (16), 123 (24), 109 (21), 101 (29), 83 (65), 55 (100), 41 (32); HRMS (EI): M^+, found: 239.1149. $C_{12}H_{17}O_4N$ requires 239.1158.

4.1.8. 3-(4-Aminophenoxy)propan-1-ol (6a).[17] To a solution of 3-(4-nitrophenoxy)propan-1-ol (**5a**, 4.78 g, 20 mmol) in ethanol (40 mL) was added tin (II) chloride dihydrate (18 g, 80 mmol) and the mixture was stirred and heated under reflux for 20 h. After cooling to room temperature the mixture was diluted with water (150 mL) and basified with an excess of solid potassium hydroxide (35 g). The mixture was extracted with DCM (3×70 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a beige solid (3.006 g, 90%). Mp 88–90 °C ($CHCl_3$), lit.[17b] Mp 90–92 °C; R_f (50% AcOEt/Hex) 0.2; δ_H (200 MHz, $CDCl_3$) 6.83–6.71 (m, 2H), 6.71–6.59 (m, 2H), 4.06 (t, 6 Hz, 2H), 3.86 (t, 6 Hz, 2H), 2.82 (br s, 3H), 2.12–1.96 (m, 2H).

4.1.9. 6-(4-Aminophenoxy)hexan-1-ol (6b).[18] An analogous procedure to that described for **6a** gave the title

compound **6b** as a light red, sensitive to light and oxygen solid (3.846 g, 92%). R_f (10% MeOH/DCM) 0.4; δ_H (200 MHz, $CDCl_3$) 6.83–6.60 (m, 4H), 3.89 (t, 6.5 Hz, 2H), 3.65 (t, 5.5 Hz, 2H), 3.41 (br s, 2H), 1.90–1.70 (m, 2H), 1.70–1.40 (m, 7H); δ_C (50.3 MHz, $CDCl_3$) 152.1, 139.6, 116.4, 115.5, 68.4, 62.4, 32.4, 29.2, 25.7, 25.4; ν_{max}($CHCl_3$) 3624 (OH), 3440, 3366 (N–H), 1238 (C–O–C) cm^{-1}.

4.1.10. 3-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]propan-1-ol (7a). To a cooled (−10 °C) solution of 3-(4-aminophenoxy)propan-1-ol (**6a**, 4.9 g, 29 mmol) and conc. hydrochloric acid (5.3 mL, 63.8 mmol) in ethanol (50 mL) was added portionwise over 20 min. a cold solution of sodium nitrite (2.001 g, 29 mmol) in water (5 mL). After 15 min. the resulting cold solution of the diazonium salt was added to a cold, stirred mixture of diethylamine (8.4 g, 12 mL, 116 mmol, 4 equiv.) water (10 mL) and crushed ice (ca. 20 g). After 15 min the resulting mixture was allowed to warm up to room temperature, strongly basified with potassium hydroxide and extracted with DCM (3×70 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a crude product. Purification through dry-column flash chromatography (5–50% AcOEt/Hex) gave the triazene product as an orange oil (4.950 g, 68%). R_f (50% AcOEt/Hex) 0.8; δ_H (200 MHz, $CDCl_3$) 7.41–7.33 (m, 2H), 6.91–6.84 (m, 2H), 4.13 (t, 6 Hz, 2H), 3.92–3.80 (m, 2H), 3.73 (q, 7 Hz, 4H), 2.11–1.98 (m, 2H), 1.98–1.91 (m, 1H), 1.26 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 156.4, 144.9, 121.0, 114.4, 65.3, 59.5, br 44.4, 31.8, 12.7; ν_{max}($CHCl_3$) 3430 (OH) cm^{-1}; *m/z* (EI) 251 (M^+, 32), 179 (57), 152 (12), 151 (100), 94 (13), 93 (70), 65 (40), 41 (11). HRMS (EI): M^+, found: 251.1640. $C_{13}H_{21}O_2N_3$ requires 251.1634.

4.1.11. 6-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]hexan-1-ol (7b). An analogous procedure to that described for **7a** gave the title compound **7b** as a light orange oil (5.353 g, 63%). R_f (50% AcOEt/Hex) 0.7; δ_H (200 MHz, $CDCl_3$) 7.39–7.32 (m, 2H), 6.92–6.81 (m, 2H), 3.96 (t, 6.5 Hz, 2H), 3.79–3.60 (m, 6H), 1.90–1.40 (m, 9H), 1.25 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 156.7, 144.8, 121.1, 114.5, 67.9, 62.3, br 44.3, 32.4, 29.1, 25.7, 25.4, 12.7; ν_{max}($CHCl_3$) 3623, 3451 (OH) cm^{-1}; *m/z* (EI) 293 (M^+, 25), 221 (21), 123 (34), 95 (14), 94 (70), 83 (18), 55 (100), 41 (13). HRMS (EI): found: 293.2108 (M^+). $C_{16}H_{27}N_3O_2$ requires 293.2103.

4.1.12. 3-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]propyloxymethylpolystyrene (8a). To a solution of 3-[4-(3,3-diethyltriaz-1-enyl)phenoxy]propan-1-ol (**7a**, 5.522 g, 22 mmol, 5 equiv.) in dry THF (30 mL) was added sodium hydride (0.88 g, 60% dispersion in oil, 22 mmol) and the mixture was heated under argon to 60 °C for 20 min. After the resulting solution was cooled to room temperature Merrifield gel (4 g, Novabiochem, 1% PS-DVB, 200–400 mesh, 1.1 mmol/g) was added and the suspension was heated to 60 °C with intermittent stirring for 72 h. Then the polymer was washed successively with a mixture of water and methanol (1:2, 3×15 mL), methanol (2×15 mL), DCM (2×15 mL), a mixture of water and DMF (1:2, 3×15 mL), DMF (3×15 mL), DCM (3×15 mL) and methanol (3×15 mL). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give bright yellow, powder (4.676 g, 95%, 0.89 mmol of diethylamine/g, theoretical loading: 0.89 mmol/g). ν_{max}(KBr) 1227 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 156.9, 143.6, 121.3, 114.8, 66.9, 65.3, 46.0, 29.8, 13.0. Anal. found: C, 84.36; H, 7.82; N, 3.73. $C_{80}H_{88}N_3O_2$ requires C, 85.52; H, 7.89; N, 3.74.

4.1.13. 6-[4-(3,3-Diethyltriaz-1-enylo)phenoxy]hexyloxymethylpolystyrene (8b). An analogous procedure to that described for **8a** gave the title polymer **8b** as a light yellow powder (4.958 g, 97%, 0.85 mmol of diethylamine/g, theoretical loading: 0.86 mmol/g). ν_{max}(KBr) 1236 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 156.9, 145.0, 121.3, 114.7, 70.3, 68.1, 46.2, 29.7, 29.3, 26.0, 25.9, 12.9. Anal. found: C, 84.76; H, 8.12; N, 3.44. $C_{83}H_{94}N_3O_2$ requires C, 85.52; H, 8.13; N, 3.60.

4.1.14. *meta*-(3-Hydroxy)propyloxyacetanilide (10a). To a solution of 3-chloropropan-1-ol (2.836 g, 30 mmol) in dry acetone (10 mL), was added sodium iodide (4.946 g, 33 mmol) and the mixture was heated under reflux for 24 h. Then *meta*-hydroxyacetanilide (**9**, 4.989 g, 33 mmol) and anhydrous potassium carbonate (6.22 g, 45 mmol) followed by acetone (10 mL) were added and the mixture was stirred and heated under reflux. After 20 h the solids were filtered off and the filtrate was evaporated in vacuo to give the crude product as a white solid, which was used in the next step. Mp 92–94 °C; R_f (10% MeOH/DCM) 0.50; δ_H (200 MHz, CD_3OD) 7.30–7.22 (m, 1H), 7.21–7.13 (m, 1H), 7.07–6.99 (m, 1H), 6.73–6.62 (m, 1H), 4.05 (t, 6 Hz, 2H), 3.73 (t, 6.5 Hz, 2H), 2.10 (s, 3H), 2.05–1.90 (m, 2H). δ_C (50.3 MHz, $CDCl_3$) 170.0, 159.2, 139.3, 128.9, 111.7, 109.5, 106.0, 64.1, 58.0, 31.7, 22.4. ν_{max}(KBr) 3282 (OH), 1668 (C═O) cm^{-1}; *m/z* (EI) 209 (M^+, 14), 150 (7), 149 (6), 110 (15), 109 (100), 81 (14), 80 (12), 43 (30); HRMS (EI); M^+, found: 209.1060. $C_{11}H_{15}NO_3$ requires 209.1052.

4.1.15. *meta*-(6-Hydroxy)hexyloxyacetanilide (10b). An analogous procedure to that described for **10a** gave the crude title compound **10b** as a white solid, which was used in the next step. Mp 88–90 °C; R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 7.38–7.12 (m, 3H), 7.00–6.85 (m, 1H), 6.74–6.60 (m, 1H), 3.96 (t, 6.5 Hz, 2H), 3.67 (t, 6.5 Hz, 2H), 3.20 (t, 7 Hz, 1H), 2.17 (s, 3H), 1.96–1.24 (m, 8H); δ_C (50.3 MHz, $CDCl_3$) 168.5, 159.6, 139.1, 129.6, 111.8, 110.7, 106.3, 67.9, 62.8, 32.6, 29.1, 25.8. 25.4, 24.5; ν_{max}(KBr) 3307 (OH), 1667 (C═O) cm^{-1}; *m/z* (EI) 251 (M^+, 8), 151 (21), 110 (11), 109 (100), 81 (8), 55 (15), 43 (20), 41 (11); HRMS (EI); M^+, found: 251.1515. $C_{14}H_{21}NO_3$ requires 251.1521.

4.1.16. *para*-(3-Hydroxy)propyloxyacetanilide (11a).[19] An analogous procedure to that described for **10a** gave the crude title compound **11a** as a white solid, which was used in the next step. Mp 93–95 °C; R_f (10% MeOH/DCM) 0.50; δ_H (200 MHz, CD_3OD) 7.44–7.34 (m, 2H), 6.92–6.80 (m, 2H), 4.04 (t, 6 Hz, 2H), 3.73 (t, 6.5 Hz, 2H), 2.08 (s, 3H), 2.02–1.89 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) 170.8, 156.5, 132.2, 122.5, 115.0, 65.3, 59.1, 32.8, 23.2; ν_{max}($CHCl_3$) 3242 (OH), 1655 (C═O) cm^{-1}; *m/z* (EI) 209 (M^+, 25), 167 (12), 110 (9), 109 (100), 108 (33), 80 (12), 53 (8), 43 (26).

4.1.17. *para*-(6-Hydroxy)hexyloxyacetanilide (11b).[20] An analogous procedure to that described for **10a** gave the

crude title compound **11b** as a white solid, which was used in the next step. Mp 92–95 °C; R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 7.40–7.27 (m, 2H), 7.09 (br s, 1H), 6.95–6.78 (m, 2H), 3.94 (t, 6.5 Hz, 2H), 3.67 (t, 6.5 Hz, 2H), 3.26–3.13 (m, 1H), 2.16 (s, 3 h), 1.87–1.34 (m, 8H); δ_C (50.3 MHz, $CDCl_3$) 168.1, 155.9, 130.8, 121.8, 114.7, 68.0, 62.8, 32.6, 30.2, 25.8, 24.6, 24.3; ν_{max}(KBr) 3235 (OH), 1662 (C=O) cm^{-1}; *m/z* (EI) 251 (M^+, 9), 151 (27), 109 (100), 108 (13), 87 (13), 43 (16), 41 (9).

4.2. A general procedure for hydrolysis of acetanilides 10 and 11 (Scheme 3)

A solution of the crude acetanilide **10** or **11** (30 mmol) in a mixture of propanol (10 mL) and conc. hydrochloric acid (7.5 mL, 90 mmol) was heated under reflux for 4 h. Then the solvents were removed in vacuo and the residue was dissolved in water (100 mL), basified with potassium hydroxide to pH=14, and extracted with DCM (3×50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give the hydroxy amines: **1a**: as a light brown solid (4.428 g, 88% after two steps); **1b**: as a light brown solid (5.0066 g, 80% after two steps); **6a**: as a brown solid (4.906 g, 96% after two steps); **6b**: as a brown solid (5.522 g, 88% after two steps).

4.2.1. 3-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]propan-1-ol (12a). An analogous procedure to that described for **7a** gave after dry-column flash chromatography (40–50% AcOEt/Hex) the title compound **12a** as an orange oil (3.737 g, 57%); R_f (50% AcOEt/Hex) 0.50; δ_H (200 MHz, $CDCl_3$) 7.29–7.17 (m, 1H), 7.06–6.99 (m, 2H), 6.75–6.66 (m, 1H), 4.17 (t, 6 Hz, 2H), 3.88 (t, 6 Hz, 2H), 3.77 (q, 7 Hz, 4H), 2.10–1.98 (m, 3 Hz, 2H), 1.27 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 159.9, 152.4, 129.0, 113.4, 111.4, 105.7, 65.4, 60.0, br 45.0, 31.9, br 13.0; ν_{max}($CHCl_3$) 3430 (OH) cm^{-1}; *m/z* (EI) 251 (M^+, 18), 151 (100), 94 (22), 93 (72), 72 (18), 65 (65), 58 (19), 41 (18); HRMS (EI): M^+, found: 251.1641. $C_{13}H_{21}O_2N_3$ requires 251.1634.

4.2.2. 6-[3-(3,3-Diethyltriaz-1-enylo)phenoxy]hexan-1-ol (12b). An analogous procedure to that described for **7a** gave after dry-column flash chromatography (45–50% AcOEt/Hex) the title compound **12b** as an orange oil (3.995 g, 56%). R_f (50% AcOEt/Hex) 0.50; δ_H (200 MHz, $CDCl_3$) 7.29–7.19 (m, 1H), 7.07–6.96 (m, 2H), 6.75–6.65 (m, 1H), 4.00 (t, 6.5 Hz, 2H), 3.84–3.59 (m, 6H), 1.95–1.21 (m, 15H); δ_C (50.3 MHz, $CDCl_3$) 156.5, 152.4, 129.2, 113.1, 111.5, 105.8, 67.6, 62.4, br 44.0, 32.4, 29.1, 25.7, 25.3, br 16.3; ν_{max}($CHCl_3$) 3623, 3451 (–OH) cm^{-1}; *m/z* (EI) 293 (M^+, 5), 123 (22), 111 (25), 94 (24), 83 (7), 58 (18), 55 (100), 41 (25). HRMS (EI): M^+, found: 293.2111. $C_{16}H_{27}N_3O_2$ requires 293.2103.

4.2.3. 3-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]propyloxymethylpolystyrene (13a). An analogous procedure to that described for **8a** gave the title polymer **13a** as a light yellow powder (4.688 g, 96%, 0.89 mmol of diethylamine/g, theoretical loading: 0.89 mmol/g). ν_{max}(KBr) 1227 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 160.6, 152.6, 129.4, 113.8, 111.8, 106.0, 66.8, 65.0, 43.9, 29.9, 12.9. Anal. found: C, 84.19; H, 7.79; N, 3.82. $C_{80}H_{88}N_3O_2$ requires C, 85.52; H, 7.89; N, 3.74.

4.2.4. 6-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]hexyloxymethylpolystyrene (13b). An analogous procedure to that described for **8a** gave the title polymer **13b** as a light yellow powder (4.959 g, 98%, 0.66 mmol of diethylamine/g, theoretical loading: 0.86 mmol/g). ν_{max}(KBr) 1236 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 129.4, 113.4, 111.6, 106.0, 70.5, 68.0, 45.3, 29.7, 29.4, 26.1, 25.6, 13.1. Anal. found: C, 84.97; H, 7.93; N, 3.00. $C_{83}H_{94}N_3O_2$ requires C, 85.52; H, 8.13; N, 3.60.

4.2.5. A typical procedure for analysis of loading of a polymeric support: immobilization of a test amine morpholine on the polymer with *meta*-C_3 triazene linker 13a. Polymer 9a. To a swollen in DCM (3 mL) and cooled to −10 °C gel **13a** (0.30 g), was added a cold solution of trifluoroacetic acid in DCM (3 mL, 10% TFA/DCM). After 10 min the gel was washed with cold DCM (2×4 mL), solution of trifluoroacetic acid in DCM (1×3 mL, 10% TFA/DCM) and DCM (3×4 mL). To the collected solutions of diethylamine trifluoroacetate was added conc. hydrochloric acid (0.4 mL, 20 equiv.) and the volatiles were evaporated in vacuo to give pure diethylamine hydrochloride (0.030 g, 0.89 mmol/g, 100% of the theoretical loading). The gel suspension was treated with a solution of morpholine (0.29 mL, 3.3 mmol, 10 equiv.) in DCM (1 mL) and was agitated at −10 °C for 30 min., slowly warmed up to room temperature and left for 12 h. The polymer was washed successively with DCM (6×3 mL), methanol (6×3 mL) and was dried under high vacuum to give yellowish powder (**9a**). Cleavage of morpholine in the same manner as diethylamine gave morpholine hydrochloride (0.034 g, 0.88 mmol/g, 99% of the theoretical loading). ν_{max}(KBr) 1600 (N=N), 1103 (C–N), 1255 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 113.3, 106.2, 66.3, 64.9, 48.0, 29.8. Anal. found: C, 84.99; H, 7.50; N, 3.72. $C_{80}H_{86}N_3O_3$ requires C, 84.46; H, 7.62; N, 3.69.

Loadings of anchored amines were calculated from the formula:

$$\text{loading[mmol/g]} = \frac{m_{\text{amine·HCl}}[\text{g}]}{M_{\text{amine·HCl}}[\text{g/mol}]\, m_{\text{gel}}[\text{g}]} \times 10^3$$

4.2.6. Immobilization of nortropine on polymer with *para*-C_3 linker (8a). 3-[4-(3-α-Hydroxynortropanylazo)-phenoxy]propyloxymethylpolystyrene (16). The polymer **8a** (0.70 g, 0.88 mmol/g) was swollen in DCM (5 mL), cooled to −10 °C and washed with a cold solution of TFA (2×3 mL, 10 min. 10% TFA/DCM) followed by DCM (3×3 mL). Then a solution of nortropine (0.78 g, 6.16 mmol, 10 equiv.) in a mixture of DCM/methanol (4:1, 6 mL) was added and the suspension was agitated for 30 min. at −10 °C, warmed up slowly to room temperature, and agitated for 12 h. The polymer was washed with methanol (2×5 mL), DCM (2×5 mL), DMF (2×5 mL), THF (2×5 mL), methanol (2×5 mL), DCM (2×5 mL), methanol (2×5 mL) and dried under high vacuum to a constant mass to give a dark red powder (0.80 mmol/g, 94% of the theoretical loading). ν_{max}(KBr) 338 (OH) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 119.7, 114.8, 66.9, 65.1, 55.1, 37.7, 29.8, 26.7. Anal. found: C, 85.19; H, 7.83; N, 3.31. $C_{83}H_{90}N_3O_3$ requires C, 84.65; H, 7.70; N, 3.57.

4.2.7. 3-Palmitoylnortropine (17a). To the swollen in DCM (3 mL), gel **16** (0.35 g,) was added triethylamine (0.32 mL, 2.31 mmol, 6 equiv.), palmitoyl chloride (0.59 mL, 1.9 mmol, 5 equiv.) and a catalytic amount of DMAP (ok. 0.01 g). The mixture was shaken at room temperature for 12 h. Then the gel was washed successively with methanol (2×3 mL), mixture of methanol and diethylamine (1:1, 2×3 mL), methanol (2×3 mL), water (2×3 mL), methanol (2×3 mL), DCM (2×3 mL), methanol (2×3 mL), DCM (2×3 mL) and methanol (2×3 mL). The gel was dried under high vacuum to give a beige powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.105 g, 100% of the theoretical loading) as a white solid. For analyses the free base was obtained by treatment with ammonia solution. Mp 50–53 °C; R_f (10% MeOH/DCM sat. with aq NH_3) 0.45; δ_H (200 MHz, $CDCl_3$) 5.05 (t, 5 Hz, 1H), 3.55–3.47 (m, 2H), 2.29 (t, 7.5 Hz, 2H), 2.10–1.95 (m, 4H), 1.85–1.56 (m, 7H), 1.2–1.10 (m, 24H), 0.88 (t, 6 Hz, 3H); δ_C (50.3 MHz, $CDCl_3$) 173.0, 67.7, 53.3, 37.4, 34.9, 31.9, 29.65, 29.61, 29.55, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 14.1; ν_{max}(CCl_4) 3443 (NH_2), 1731 (C═O), 1169 (C–O), 1076 (C–N) cm^{-1}; *m/z* (EI) 365 (M^+, 0.1), 111 (16), 110 (100), 82 (13), 80 (18), 68 (18), 43 (18), 41 (14). Anal. (hydrochloride) found: C, 68.67; H, 10.77; N, 3.33. $C_{23}H_{44}NO_2Cl$ requires C, 68.71; H, 11.03; N, 3.48.

4.2.8. 3-α-Acetyloxynortropane (nortropine acetate, 17b).[21] An analogous procedure to that described for **17a** (using acetic anhydride instead of palmitoyl chloride) gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound as a white solid (0.095 g, 64% of the theoretical yield). For analysis the free base was obtained by treatment with ammonia solution. R_f (10% MeOH/DCM sat. with aq NH_3) 0.30; δ_H (200 MHz, DMSO-d_6) 4.86 (t, 5 Hz, 1H), 3.38 (br s, 2H), 2.08–1.92 (m, 7H), 1.65–1.42 (m, 5H).

4.2.9. Oxidation of nortropine to nortropinone (18) on polymer with *para*-C_3 triazene linker. Nortropinone hydrochloride.[22] To a suspension of gel **17a** (0.5 g, 0.811 mmol/g) in dry DCM (4 mL) was added finely ground Dess–Martin periodinane (0.86 g, 2.03 mmol, 5 equiv.) and pyridine (0.321 g, 0.33 mL, 4.06 mmol). The mixture was shaken at room temperature for 72 h. Then the gel was washed with methanol (2×4 mL), mixture of 2 M KOH with DMF (1:4, 2×4 mL), mixture of 2 M KOH in methanol (1:4, 2×4 mL), 2 M KOH (2×3 mL), mixture of alkaline aqueous sodium thiosulphate (2 mL) with DMF (2 mL), solution of sodium thiosulphate in aqueous methanol (2 mL), methanol (2×4 mL), THF (2×4 mL), methanol (2×4 mL), DCM (2×4 mL) and methanol (2×4 mL). The gel was dried under high vacuum to give a dark red powder (0.54 g, 88%). Cleavage of the product and conversion to hydrochloride under typical conditions gave the title compound (0.034 g, 52% yield of the oxidation). δ_H (200 MHz, $CDCl_3$) 10.60 (s, br, 1H), 10.25 (s, br, 1H), 4.40 (s, 2H), 3.25 (dd, *J*=4.0, 16.5 Hz, 2H), 2.65–2.38 (m, 4H), 2.10–1.85 (m, 2H).

4.2.10. Immobilization of 4-piperidinol on polymer with *meta*-C_3 linker 13a. 3-[3-(4-Hydroxypiperidinylazo)phenoxy]propyloxymethylpolystyrene (20). The polymer **13a** (0.65 g, 0.89 mmol/g) was swollen in DCM (5 mL), cooled to −10 °C and washed with a cold solution of TFA (2×3 mL, 10 min. 10% TFA/DCM) followed by DCM (3×3 mL). Then was added a solution of anhydrous 4-hydroxypiperydyne (0.72 g, 7.15 mmol, 10 equiv.) in a mixture of DCM/THF/isopropanol (1:2:1) and the suspension was agitated for 30 min. at −10 °C, warmed up to room temperature, and agitated for 12 h. The polymer was washed with methanol (2×5 mL), DCM (2×5 mL), DMF (2×5 mL), THF (2×5 mL), methanol (2×5 mL), DCM (2×5 mL), methanol (2×5 mL) and dried under high vacuum to constant mass to give an orange powder (0.80 mmol/g, 92% of the theoretical loading). ν_{max}(KBr) 3533 (OH), 1232 (C–O) cm^{-1}. Anal. found: C, 85.75; H, 7.60; N, 3.31. $C_{81}H_{88}N_3O_3$ requires C, 84.48; H, 7.70; N, 3.65.

4.2.11. 4-Palmitoyloxypiperidine (21). An analogous procedure to that described for **17a** gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.105 g, 100% of the theoretical yield). The free base for the analyses was obtained by treatment with ammonia. Mp 104–105 °C (hydrochloride); R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 5.06 (br s, 1H), 3.22–3.12 (m, 4H), 2.40–2.30 (m, 2H), 2.30–2.12 (m, 1H), 2.12–1.91 (m, 2H), 1.73–1.50 (m, 2H), 1.26 (s, 26H),1.98–1.81 (m, 3H); δ_C (50.3 MHz, $CDCl_3$) 173.2, 43.9, 43.8, 34.6, 32.0, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 29.1, 25.0, 22.6, 14.1, 1.0; ν_{max}($CHCl_3$): 1724 (C═O) cm^{-1}; *m/z* (EI) 339 (M^+, 3), 143 (23), 84 (90), 83 (100), 82 (41), 68 (26), 55 (23), 43 (25). Anal. (hydrochloride) found: C, 66.88; H, 11.54; N, 3.66. $C_{21}H_{42}NO_2Cl$ requires C, 67.08; H, 11.26; N, 3.73

4.2.12. 4-Piperidone hydrochloride (22).[23] An analogous procedure to that described for oxidation of **17a** gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.034 g, 62% of the theoretical yield). δ_H (200 MHz, CD_3OD) 3.25–3.18 (m, 4H), 2.05–1.95 (m, 4H).

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