

ULTRAMINE: A High-Capacity Polyethylene–Imine-Based Polymer and Its Application as a Scavenger Resin

Michael Roice,^[a, b] Søren F. Christensen,^[b] and Morten Meldal*^[a]

Abstract: The synthesis of a novel high-loading polyethylene–imine resin (ULTRAMINE) is described, and its application as a scavenger resin in various acylation reactions is demonstrated. The inverse suspension polymerization technique was used for the synthesis of well-defined spherical polymer beads. Polymer beads with different cross-linking densities were synthesized according to the degree of acryloylation of the polyethylene–imine polymer. The resin was characterized by

various spectroscopic techniques. The size, shape, and morphological features of the resin were demonstrated by microscopy. The resin showed excellent swelling properties in both polar and nonpolar solvents. The chemical stability of the resin in various reagents and solvents was investigated and moni-

Keywords: acylation • parallel synthesis • polymerization • polymers • scavenger resins

tored by IR spectroscopy. The mechanical stability of the beads was determined by a single-bead compressive experiment. The ULTRAMINE beads can be used as an excellent scavenger for excess acylating reagent, as demonstrated for a variety of reactions. ULTRAMINE-red resin was derived from ULTRAMINE through exhaustive reduction of the amide carbonyl groups to yield an all-amine resin.

Introduction

During the last decade solid-phase synthesis has experienced a renaissance, with exploitation in general organic synthesis and combinatorial chemistry. Merrifield initially reported the classical stepwise solid-phase synthesis of peptides exemplified by synthesis of a tetrapeptide on divinyl benzene cross-linked polystyrene resin.^[1] Due to the ease of compartmentalizing and handling reagents on solid support, cross-linked polymers have played an important role in the development of combinatorial and parallel synthesis.^[2] Initially solid-phase synthesis focused on the preparation of amino acids or nucleotides, including oligomers of unnatural chemical building blocks, for example, peptoids.^[3] The synthesis of non-oligomeric small-molecule libraries by quantitative chemical transformations is currently an important research area.^[4] Important for the successful synthesis of chemical li-

braries, whether on solid support or in solution, is the rapid purification, isolation, and manipulation of chemical library members during both the intermediate and final synthetic steps. Solid-phase technology offers advantages such as ease of separating the products from the reactants in the reaction medium, ease of split–mix synthesis, and monitoring of product formation on single beads by using different spectral techniques. Desirable properties in the resin for the manipulation of the solid support during organic synthesis are chemical and mechanical stability, compatibility with various reagents, and swelling in both hydrophilic and hydrophobic solvents. Merrifield resin, most often used in synthesis, has high mechanical stability; however, the swelling in and compatibility with various polar reagents and solvents are rather poor. Furthermore, functionalizations of the resin, for example, by chloromethylation, often lead to additional cross-linking of the polymer.^[5] In order to circumvent these problems, a series of more polar polystyrene-based copolymers was developed by incorporation of more flexible and polar moieties into the polymer network. The modified polystyrene supports have all been successfully employed for solid-phase synthesis^[6] and include poly(ethylene glycol)–polystyrene (PEG-PS),^[7] tentagel graft resin,^[8] poly(ethylene glycol) (meth)acrylate cross-linked polystyrene,^[9] poly(ethylene oxide)–polystyrene (PEO-PS),^[10] and JandaJel®.^[11] The favorable properties of these resins led to a second generation of more polar resins including polyamides,^[12] poly(ethylene glycol) polyacrylamide (PEGA),^[13] poly(oxyethylene)/

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Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

poly(oxypropylene) copolymer (POEPOP),^[14] superpermeable organic combinatorial chemistry resin (SPOCC),^[15] cross-linked ethoxylate acrylate resin (CLEAR),^[16] and glycerol dimethacrylate/polymethylmethacrylate copolymer (GDMA-PMMA);^[17] these resins contain no polystyrene and present excellent swelling properties both in nonpolar and in protic and aprotic polar solvents.

Chemistry on solid supports is limited by the problems of preparative scaling, the difficulty of product validation, and the inherent decrease of the macromolecular reactivity. Solution-phase synthesis has the advantage of scalability, in addition to easy manipulation and analysis of product. The major limitation of solution-phase synthesis is in the isolation and purification of the reaction products from the reaction medium, particularly when working with compound mixtures. The use of polymeric scavenging reagents can overcome this limitation to a great extent.^[18] In scavenging, the scavenger resins contain active groups that mimic the reactivity of the limiting reagent in the reaction. After completion of the reaction, the resin is added to the reaction mixture to react with excess reagents. Filtering off the resin-bound reagent provides a relatively pure product in solution.

None of the above-mentioned polymers meet the requirements for an ideal scavenger resin. Their main disadvantage is the low loading of functional groups for the volume of resin. The relatively high-capacity polymer poly(vinyl pyridine) (PVP) has been successfully used as a scavenger resin.^[19] Polyethylene-imine-based polymers offer an inherent high amino-group loading and, upon cross-linking, can be used as scavenger resins. Polyethylene-imine polymers (for example, Lupasol®) are used in industry for promoting adhesion between similar and dissimilar materials, to disperse fillers and pigments, to flocculate suspended solids, to modify surface characteristics, such as charge and hydrophilicity, and to scavenge heavy metals and unwanted materials.^[20] Polyethylene-imine/aliphatic-polyester copolymers are used for solubilization and provide a delivery system for proteins, genes, or drugs.^[21] A polyethylene-imine, cross-linked cellulose sponge and polyethylene-imine polymer bound on silica gel were used for ion exchange and for chromatographic separation of monoclonal antibodies.^[22] A polyethylene-imine resin cross-linked with bisaldehyde was recently reported for solid-phase synthesis of peptides.^[23] The polymer formed was granulated and therefore irregular in shape, which may complicate separation from the product when used in scavenging. A degradable poly(β -amino ester) was obtained by conjugate addition of primary and secondary amine monomers to diacrylate monomers for use in gene delivery.^[24]

The present paper describes the development and efficient preparation of a high-capacity, cross-linked, beaded polyimine resin. As an example of application, the resin was employed for the scavenging of excess acylating agents in solution-phase reactions. The resin was prepared by polymerization of partially acryloylated polyethylene-imine macromonomers.

Results and Discussion

Scavenger resins are increasingly important for the separation of excess reactants and byproducts from solution-phase chemical reactions. Low cost of synthesis, chemical and mechanical stability, high rate of reactant diffusion within the polymer, and a high density of reactive primary and secondary amino groups are important properties that determine the efficacy of an amine scavenger resin. Analogous with the preparation of poly(ethylene glycol)-based resins, a novel cross-linked, beaded polymer, ULTRAMINE, based on polyethylene-imine polymer was designed to provide a high density of amino groups and appropriate swelling in both polar and nonpolar solvents. It was obtained by free-radical inverse suspension polymerization of partially acryloylated polyethylene-imine macromonomers. The chemical, physical, and mechanical properties of beaded polymers can be controlled by variation of the degree of polyimine polymerization and acryloylation and can be optimized for solid-phase synthesis or scavenging. The cross-linked polymer from polymerization of a 15% acryloylated (of all amino groups) polyethylene-imine macromonomer resulted in 16.5 mmol of amino groups per gram, which is significantly higher loading than that of previously described scavenger resins. The radical polymerization of acrylamides is extremely efficient and was employed in the formation of the ULTRAMINE polymer.

Synthesis of monomers: The acylation of amino groups in polyethylene-imine polymers with different concentrations of acryloyl chloride formed a series of macromonomers with various degrees of acrylamide functionality for polymerization. The reproducibility of the monomer synthesis and, consequently, the synthesis of polymers with a variable degree of cross-linking, can be controlled by the use of a well-defined amount of acryloyl chloride in the macromonomer synthesis. The macromonomers were prepared by the dropwise addition of acryloyl chloride to the polyethylene-imine polymer in dichloromethane at 0°C (Table 1; Scheme 1,

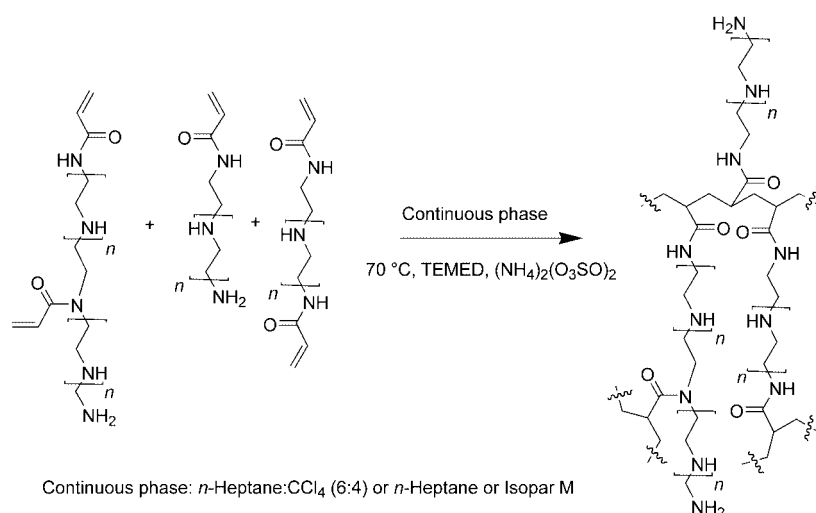
Table 1. Yield and loading of functional amines in ULTRAMINE polymers with different cross-linking density and loading after borane reduction of amides.

Amount ^[a] of acryloyl chloride [mL]	Acryloylation [%]	Yield of polymer [%]	Loading [mmol g ⁻¹]	Loading after red. [mmol g ⁻¹]
2.4	15.0	>95	16.5	18.6
2.1	13.5	91	17.3	19.5
1.9	11.5	87	17.9	20.4
1.6	10.0	80	18.6	21.0

[a] Added to 7.9 mL polyethylene-imine polymer, $M_w = 423 \text{ g mol}^{-1}$.

left). The crude reaction mixture consists of polyethylene-imine chains containing at least one acrylamide functionality for polymerization.

Polymer synthesis and characterization: To investigate the polymer synthesis, a bulk polymerization was initially performed. The bulk polymer was ground and passed through a sieve with a 1 mm mesh. The particles obtained were irregu-



Scheme 1. Synthesis of ULTRAMINE polymer by inverse suspension polymerization of partially acryloylated polyethylene-imine polymers. TEMED = *N,N,N',N'*-tetramethylethylenediamine.

lar in size and shape (Figure 1a), and the resin was fragile and shredded small particles when used for scavenging in chemical reactions.

Spherical polymer beads were then prepared by an inverse suspension polymerization method (Scheme 1). The polymer was synthesized with various cross-linking densities. The average size and shape of the beads depended on factors such as suspension medium, amount of surfactant, amount of initiator, and stirring speed. For the beading of the ULTRAMINE polymer, three different continuous phases, *n*-heptane, *n*-heptane/CCl₄ (6:4), and isopar M (a mixture of C_{10–12} hydrocarbons), were tested. The results revealed that the relative density of the suspension medium has an influence on the size and shape of the polymer bead. A low-density suspension medium, *n*-heptane, gave well-defined polymer beads with an even size distribution. The suspended macromonomer mixture has a tendency to precipitate, due to its higher density; this results in improved mixing with stirring. Sorbitan monolaurate was used as a suspension stabilizer, ammonium persulphate was the free-radical initiator, and *N,N,N',N'*-tetramethylethylenediamine (TEMED) was used to promote the reaction. The resin was suspended in 10% diisopropylethylamine (DIPEA) in EtOH in order to neutralize the HCl trapped in the resin during the acryloylation reaction of the macromonomer synthesis. Microscopy of the polymer showed that uniform spherical beads with less than 1% agglomerates were formed (Figure 1b and c).

The ULTRAMINE polymer was characterized by IR and MAS NMR spectroscopy. The IR spectrum shows a sharp band at 1622 cm^{−1} corresponding to the amide carbonyl group and broad bands at 3272 (NH stretch) and 2937 cm^{−1} (CH stretch). The gel-phase ¹H MAS NMR spectrum of the polymer contained an intense peak at δ = 3.19 ppm, which corresponds to the methylene protons of the polymer backbone. Peaks at δ = 3.41, 2.91, and 2.72 ppm correspond to the amine protons, the α -methylene protons of primary amino groups, and the CH proton at the cross-linking site, respectively (Figure S1a in the Supporting Information).

With most commercially available resins, the structure elucidation of compounds on the solid support by NMR spectroscopy is complicated by line broadening due to inhomogeneities and interference by the signals from the polymer backbone. Due to the narrow and well-defined signals of the ULTRAMINE backbone, the resin may be useful for on-resin structure elucidation by NMR spectroscopy. In order to investigate this, the resin was acylated with 9-fluorenylmethoxycarbonyl (Fmoc) amino benzoic acid; the MAS NMR spectra of

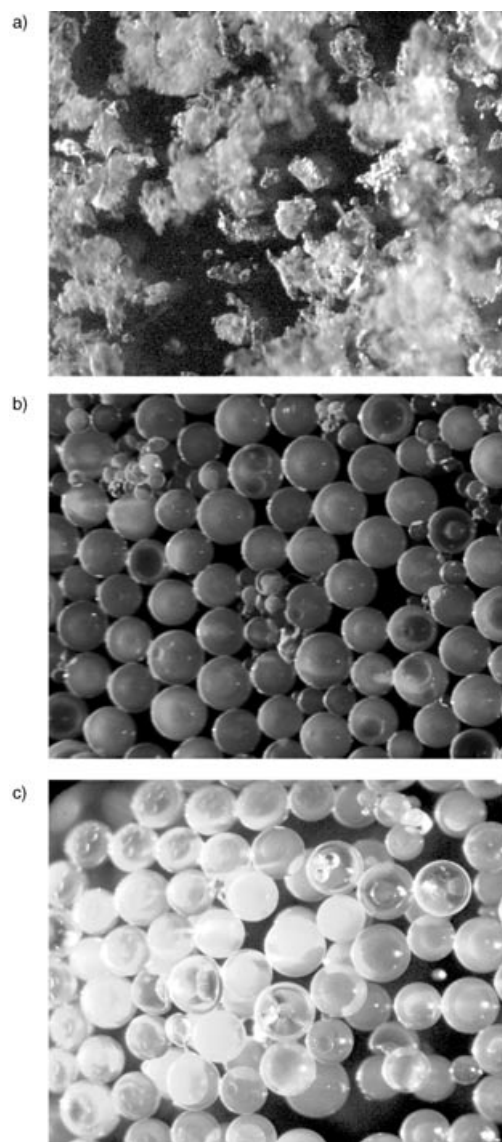


Figure 1. Microscopy of crude ULTRAMINE prepared by a) bulk polymerization, b) inverse suspension polymerization (before sieving), and c) inverse suspension polymerization (after sieving).

the product contained relatively sharp coupled signals corresponding to the Fmoc group, without interference from the polymer backbone signals (Figure S1b in the Supporting Information), while the signals of the Abz group close to the resin were significantly broader probably due to inhomogeneity of solvation caused by the high loading.

Swelling and stability studies of ULTRAMINE: The extent of swelling determines the access of reagents to active sites within the polymer network.^[25] Swelling in different solvents is important for the performance of the resins in solid-phase synthesis, in supported catalysis, as supported reagents, and as scavengers. The swelling ratio was determined from the increase in volume of the resin upon incubation with solvent (swelling ratio, mL g⁻¹) by the syringe method.^[13b] The lyophilized resin was weighed in a syringe fitted with a Teflon filter and the solvent was added to the syringe; equilibrium swelling was achieved in three hours at room temperature. The swelling ratio, measured upon removal of all excess solvent with the syringe piston, was reproducible with an experimental error of <3%. The degree of swelling (~6 mL g⁻¹) for differently cross-linked (10–15%) ULTRAMINE resin was determined (Figure S2a in the Supporting Information). As expected, the swelling of ULTRAMINE increases as the cross-linking density decreases. The resin swelled efficiently in both polar and nonpolar solvents, ranging from water to dichloromethane; swelling was more pronounced in the protic solvents than in polar nonprotic and nonpolar solvents. This is explained by the high concentration of functional amino groups. Strong cooperative hydrogen bonds induce an effect of additional cross-linking and solvents that can disrupt hydrogen bonding can therefore solvate the polymer more effectively. The rate of swelling is an important factor for the performance of a solid support. Dry ULTRAMINE polymers swell >95% in ten minutes, which indicates that the resin could be useful for solid-phase synthesis and scavenging processes.

Exposing the polymer to various reagents and conditions typical in organic synthesis demonstrated the chemical stability of ULTRAMINE. The resin was subjected to different reagents including trifluoroacetic acid (100%), piperidine (20% in *N,N*-dimethylformamide), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 100%), butyl lithium in heptane (2.7 M solution), triflic anhydride (100%), saturated NaOH, and BF₃·Et₂O (100%) for 48 hours at room temperature. No macroscopic changes such as deformation of the beads or change in particle size were observed. Neither did the treatment induce any changes in the IR spectra of these samples in comparison with those of the original resin (Figure S3 in the Supporting Information). The swelling properties of the resin after treatment with the reagents for two weeks also did not show any significant changes from the original properties (Figure S2b in the Supporting Information). The resin remained colorless and did not dissolve under any of these harsh conditions.

Mechanical stability of a polymer support is an important property in solid-phase organic synthesis and scavenging processes, particularly when they perform on a larger scale. The mechanical stability of ULTRAMINE beads was deter-

mined by a compressive stress experiment. The compressive property is a measure of the behavior of the bead when it is subjected to compressive stress. The bead (300–500 µm) was placed between a ccd camera lens and a cylindrical probe, connected to a strain gauge to measure the force applied, and an actuator; the sample was then compressed at a constant rate of 10 µm min⁻¹. The camera recorded the deformation of the bead. An apparent compressive modulus (E_A) can then be calculated as the ratio of the apparent compressive stress (σ_A , the force per area of cross section of the bead) over the apparent compressive strain (γ_A , the ratio of the diameter over the initial diameter). The apparent linear compressive modulus, E_{A0} is then given by Equation (1).

$$E_{A0} = \lim_{\gamma_A \rightarrow 0} \partial \sigma_A / \partial \gamma_A \quad (1)$$

Two examples of such stress–strain curves for single ULTRAMINE beads are given in Figure 2a and b. The average compressive modulus of an ULTRAMINE bead was found to be 0.45 MPa, which indicates that the resin is sufficiently stable to withstand various mechanical manipulations during organic synthesis. Furthermore, the compressive modulus of the resin was equal to or better than that of many commercially available polar resins (Figure 2c).

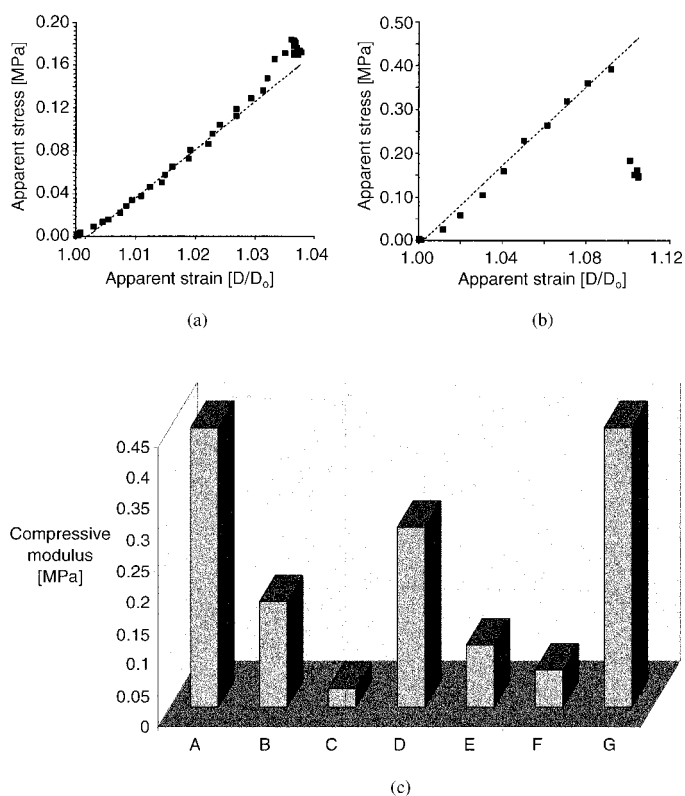


Figure 2. Mechanical stability of ULTRAMINE beads. Apparent compressive stress–apparent compressive strain plot for a) bead-size 350 µm and b) bead-size 420 µm. The dotted lines represent linear regressions used for calculation of the initial apparent modulus. D_0 is the bead diameter of the relaxed bead and D is the diameter during compression. c) Initial apparent compressive modulus of ULTRAMINE (A) and commercial resins: SPOCC 2000 (B), SPOCC 4000 (C), POEPOP 2000 (D), Sephadex G50 (E), Biogel P100 (F), and PEGA 1900 (G).

Functional capacity of ULTRAMINE: The efficiency of a resin used as scavenger depends on its functional capacity/volume. The amino-function capacity of ULTRAMINE was determined by derivatization with Fmoc-Gly-OH. The Fmoc protecting group from a weighed amount of dry resin was cleaved by 20% piperidine in MeOH, the UV absorbance of the piperidine–dibenzofulvene adduct was determined, and the adduct concentration equivalent to that of accessible amino groups was calculated (Table 1). MeOH was used because of the favorable swelling properties in MeOH compared to *N,N*-dimethylformamide. The number of accessible functional groups increases as the percentage of cross-linking decreases.

Synthesis of ULTRAMINE-Red: The available functional amino groups on ULTRAMINE can be increased considerably by the exhaustive reduction of amide groups. This exhaustive reduction was accomplished by using a mixture of borane and trimethylborate, followed by quenching of excess borane with piperidine.^[26] In the IR spectra of the resin after reduction the amide carbonyl signal had completely disappeared (Figure 3). The loading of primary and secondary amino groups in the different reduced ULTRAMINE resins is presented in Table 1.

ULTRAMINE as a scavenger resin: The amount of resin required for a scavenging process is important for the general application of scavengers in solution-phase synthesis. When the volume of the required scavenger is reduced due to increased loading, the product can be more easily washed out quantitatively from the polymer. Due to high functional loading and sufficient swelling, the ULTRAMINE polymer serves as a very efficient scavenger resin. Scheme 2 illustrates parallel solution-phase reactions of an excess of acylating agents with amines (2-aminobutane, 3-aminopentane, 4-nitroaniline, and 3-phenyl-1-propylamine). A 15% cross-linked ULTRAMINE was used for the effective removal of excess acylating agents and sequestering of byproducts, for example, HCl and hydrolyzed reagent (Scheme 3). The reaction of a 2.5-fold excess of acylating agents (acid chlorides, thiocyanates, chloroformates, and sulfonyl chlorides) with the amines yielded amides, thioureas, carbamates, and sulfonamides, respectively. The reaction mixture was then separately treated with ULTRAMINE

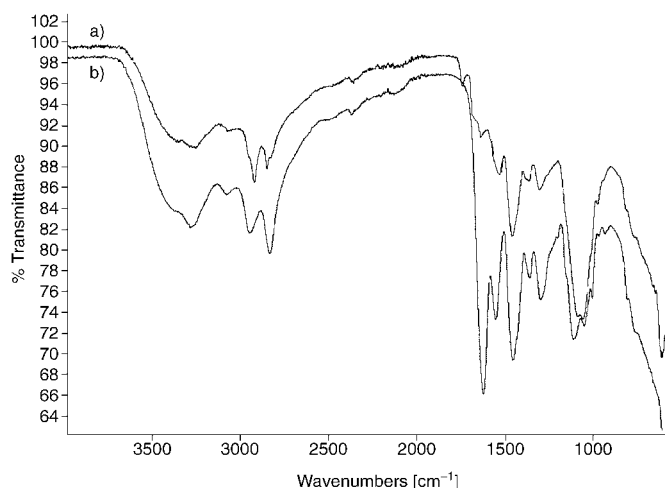
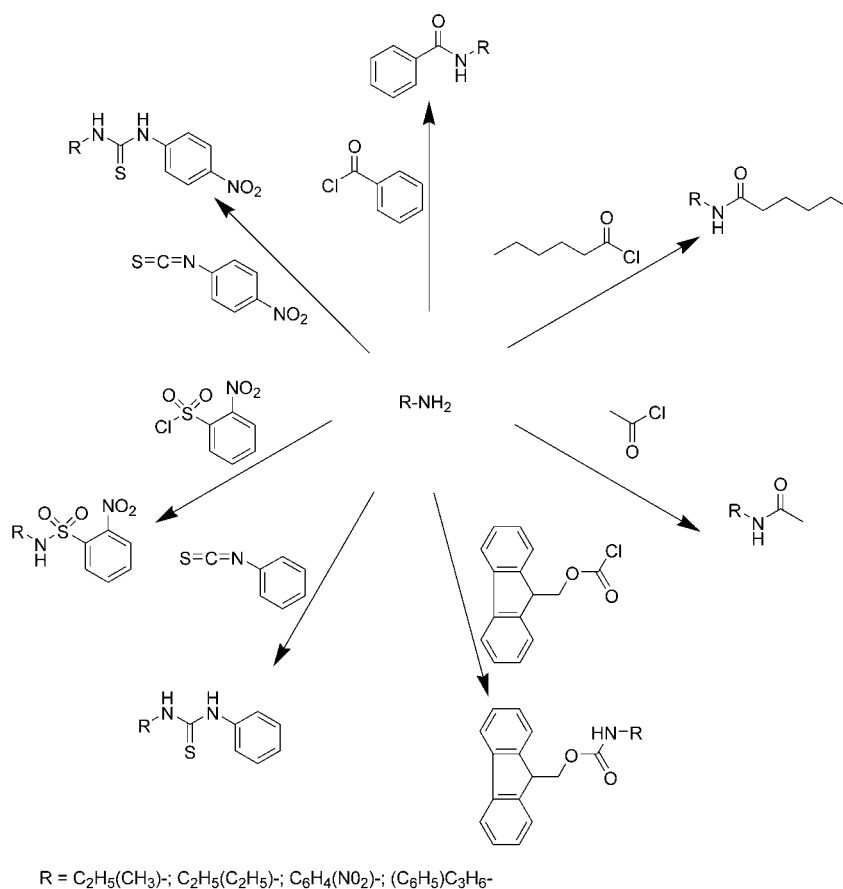


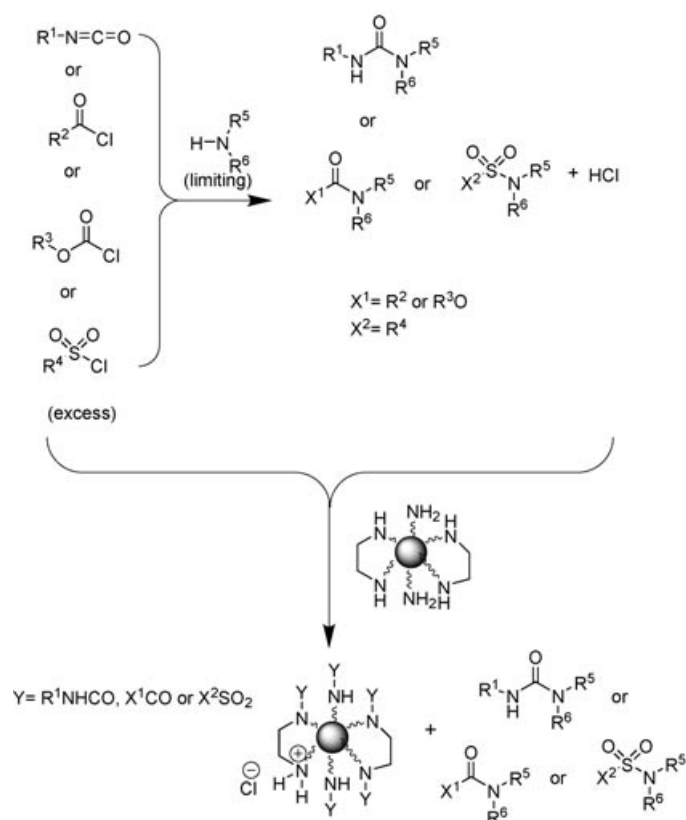
Figure 3. Comparison of the IR spectra of a) ULTRAMINE-Red and b) ULTRAMINE.

resin that had fivefold available amino groups relative to the excess acylating reagents. All the reactions and scavenging yielded products with excellent conversion and purity (Table 2). The HPLC profiles of crude products after treatment with ULTRAMINE are presented in Figure S4 in the Supporting Information.

ULTRAMINE-Red as a scavenger resin: To explore the use of ULTRAMINE-Red as a scavenger resin, we performed



Scheme 2. Parallel reactions of amines with excess acylating reagents as examples for the use of scavengers.



Scheme 3. Use of ULTRAMINE as a scavenger resin for the rapid purification of parallel amine acylation reactions.

the reaction of 3-aminopentane with a 2.5-fold excess of phenyl isothiocyanate. The excess reagent was then scavenged by using ULTRAMINE-Red. In order to demonstrate the amount of ULTRAMINE-Red required for scavenging excess isothiocyanate (0.15 mmol), different amounts of resin were used. The results revealed that only 10 mg of resin were required for the complete scavenging of the isothiocyanate (Figure 4). Approximately 22 mg of pure product were obtained.

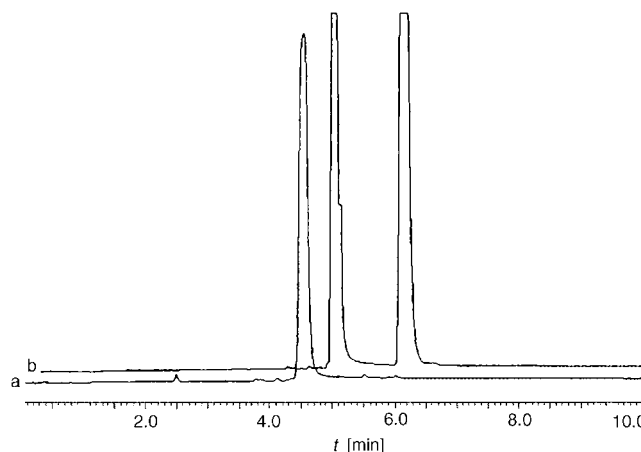


Figure 4. HPLC trace of the crude products obtained after scavenging phenyl isothiocyanate with a) 10 mg of ULTRAMINE-Red and b) 5 mg of ULTRAMINE-Red. Column: RCM C-18 (8 × 200 mm). Elution gradient: From 0–80% of buffer containing 0.1% trifluoroacetic acid in 10% aqueous acetonitrile over 10 min at a flow rate of 5 mL min⁻¹. Detection: 215 nm.

Table 2. Yields [%] and purities [%] of solution-phase amide, urea, carbamate, thiourea, and sulfonamide products **1–28** purified by ULTRAMINE scavenging of excess reagent and acidic byproducts.^[a]

	1 99.7/100	8 99.5/100	15 99.5/100	22 99.5/100
	2 99.0/98.5	9 96.3/100	16 97.2/100	23 97.4/100
	3 99.2/100	10 94.8/100	17 96.1/100	24 95.8/100
	4 96.3/96	11 92.8/95.4	18 92.4/94.9	25 94.0/95.6
	5 97.5/94.6	12 90.7/94.1	19 96.3/93.3	26 92.4/92.3
	6 96.5/95.3	13 93.8/95.6	20 97.2/94.2	27 94.1/92.7
	7 99.3/100	14 96.9/100	21 99.2/100	28 96.3/100

[a] For further details, see the Experimental Section. Chromatograms of representative products are presented in the Supporting Information.

Conclusion

ULTRAMINE, a high-capacity resin, was prepared by inverse suspension polymerization through different ratios of partial acryloylation of polyethylene-imine macromonomers. The resin performs excellently as a scavenger resin for solution-phase synthesis. It is stable to a variety of harsh reaction conditions used in conventional organic synthesis. The resin is chemically and mechanically stable and can withstand different acidic, basic, electrophilic, and nucleophilic reaction conditions.

ULTRAMINE showed a high degree of swelling in both polar and less polar solvents; it can be used as a scavenger resin in both aqueous and non-aqueous reactions. Amide groups in ULTRAMINE were quantitatively converted into

amines by borane reduction to provide an all-amine resin with up to 21 mmol of functional amino groups per gram.

Experimental Section

Synthesis of partially acryloylated polyethylene-imine polymers: Acryloyl chloride (2.403 mL, 36 mmol) in dichloromethane (DCM; 12 mL) was added dropwise to a solution of polyethylene-imine polymer (7.9 mL, 240 mmol of amino groups, $M_w = 423 \text{ g mol}^{-1}$) in DCM (18 mL) at 0°C with stirring. The reaction mixture was stirred for 1 h at 20°C. The DCM was evaporated, and drying in vacuo at 20°C yielded 15% acryloylated (of the total number of amine groups) polyethylene-imine polymer as a thick, pale yellow oil. Acryloylated polyethylene-imine macromonomers containing 13.5, 11.5, and 10% acryloylation were also prepared by using 2.1 (32), 1.9 (28), and 1.6 mL (24 mmol) of acryloyl chloride, respectively.

Synthesis of ULTRAMINE

Bulk polymerization: 15% acryloylated ((Ac)_{15%}) polyethylene-imine macromonomer (5.00 g, 9.58 mmol) in water (5 mL) and ammonium persulfate (0.25 g) in water (1 mL) were mixed in a round-bottomed flask under argon. The reaction mixture was kept in a thermostated oil bath maintained at 70°C for 30 min. The white, hard, bulky polymer obtained was washed with water (6 × 15 mL), MeOH (6 × 15 mL), EtOH (6 × 15 mL), *N,N*-dimethylformamide (DMF; 6 × 15 mL), and DCM (6 × 15 mL). The polymer was granulated through a 1 mm net and sieved. The fine particles were removed by repeated decantation. The polymer particles were characterized by microscope imaging. Yield: 4.82 g (97%); IR: $\tilde{\nu} = 3272.3$ (NH stretch), 2937.6 (CH stretch), 1622.8 (CONH) cm^{-1} .

Inverse suspension polymerization in various continuous phases: ULTRAMINE was prepared by the inverse suspension polymerization method. A mixture of *n*-heptane/carbon tetrachloride (6:4 (v/v), 140 mL) was used as the continuous phase and added to the cylindrical polymerization flask containing bafflers and a 6-blade mechanical stirrer. The flask was then heated in an oil bath at 70°C. The continuous phase was purged with argon for 10 min and stirred at a rate of 650 rpm. In a typical procedure, a solution of (Ac)_{15%} polyethylene-imine polymer (10 g, 19.16 mmol) in water (25 mL) was degassed with argon for 30 min. Solutions of sorbitan monolaurate (0.5 mL) in DMF (1 mL) and ammonium persulfate (0.5 g) in water (2 mL) were added to the monomer mixture with stirring. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 70°C. After 1 min, TEMED (1 mL) was added to the reactor. The reaction was allowed to continue for 3 h and the beads formed were filtered through a sieve. They were washed thoroughly with ethanol (10 ×), water (10 ×), and ethanol (10 ×). The resin was suspended in 10% DIPEA in ethanol for 4 h, washed with ethanol (10 ×), water (10 ×), and ethanol (10 ×), and dried under high vacuum. Yield: 9.5 g (95%); bead-size distribution: > 500 μm 2%, 300–500 μm 80%, 100–300 μm 15%, < 100 μm 3%; compressive modulus: 0.44 MPa; color: transparent, pale yellow; amino loading: 16.03 mmol g^{-1} ; swelling: water 8.2, DMF 4.2 mL g^{-1} ; IR: $\tilde{\nu} = 3272.1$ (NH stretch), 2937.4 (CH stretch), 1622.2 (CONH) cm^{-1} .

The inverse suspension polymerization was carried out with *n*-heptane (140 mL) as the continuous phase. The polymerization was performed with same reagent amounts and conditions as above. Yield: 9.7 g (97%); bead-size distribution: 300–500 μm 88%, 100–300 μm 10%, < 100 μm 2%; compressive modulus: 0.45 MPa; color: transparent, pale yellow; amino loading: 16.5 mmol g^{-1} ; swelling: water 8.4, DMF 4.6 mL g^{-1} ; IR: $\tilde{\nu} = 3272.3$ (NH stretch), 2937.4 (CH stretch), 1622.2 (CONH) cm^{-1} .

The inverse suspension polymerization was carried out with Isopar M (140 mL) as the continuous phase. The polymerization was performed with same reagent amounts and conditions as above. Yield: 9.6 g (96%); bead-size distribution: 300–500 μm 83%, 100–300 μm 15%, < 100 μm 2%; compressive modulus: 0.45 MPa; color: transparent, pale yellow; amino loading: 16.25 mmol g^{-1} ; swelling: water 8.4, DMF 4.3 mL g^{-1} ; IR: $\tilde{\nu} = 3272$ (NH stretch), 2937.6 (CH stretch), 1622.5 (CONH) cm^{-1} .

Isopar M (140 mL) was used as the continuous phase and polymerization performed at 30°C. The continuous phase was purged with argon for 10 min and stirred at a rate of 650 rpm. A solution of (Ac)_{15%} polyethylene-imine polymer (10 g, 19.16 mmol) in water (25 mL) was degassed

with argon for 30 min. Solutions of sorbitan monolaurate (0.5 mL) in DMF (1 mL) and the free-radical initiator ammonium persulfate (0.5 g) in water (2 mL) were added to the monomer mixture. The reaction mixture was then rapidly added to the suspension medium stirred at 650 rpm at 30°C. After 1 min, sodium disulfide (0.05 g) in water (1 mL) and TEMED (1 mL) were added simultaneously but separately to the reactor. The reaction was allowed to continue for 3 h at 30°C and the beads that formed were filtered through a sieve, washed thoroughly with ethanol (10 ×), water (10 ×), and ethanol (10 ×). The resin was suspended in 10% DIPEA in ethanol for 4 h, washed with ethanol (10 ×), water (10 ×), and ethanol (10 ×), and dried under high vacuum. Yield: 9.5 g (95%); bead-size distribution: 300–500 μm 86%, 100–300 μm 12%, < 100 μm 2%; compressive modulus: 0.44 MPa; color: transparent, pale yellow; amino loading: 16.35 mmol g^{-1} ; swelling: water 8.5, DMF 4.2 mL g^{-1} ; IR: $\tilde{\nu} = 3272.6$ (NH stretch), 2937.1 (CH stretch), 1622.6 (CONH) cm^{-1} .

Synthesis of ULTRAMINE with different cross-linking densities: The polymerizations were performed in *n*-heptane (140 mL). Sorbitan monolaurate (0.5 mL in DMF) was used as the suspension stabilizer and ammonium persulfate (0.5 g) in water (2 mL) was used as the free-radical initiator. A degassed solution of partially acryloylated polyethylene-imine polymer in water (25 mL) was mixed with suspension stabilizer and radical initiator and transferred to the degassed continuous phase stirred at 650 rpm and 70°C. The promoter TEMED (1 mL) was added to the reaction mixture after 1 min, and the reaction was allowed continue for 3 h. The beads were filtered and washed thoroughly with ethanol (10 ×), water (10 ×), and ethanol (10 ×). The resin was suspended in 10% DIPEA in ethanol for 4 h, washed with ethanol (10 ×), water (10 ×), and ethanol (10 ×), and dried under high vacuum.

(Ac)_{13.5%} polyethylene-imine polymer (9.8 g, 19.2 mmol) yielded 8.9 g of resin (91%); bead-size distribution: 300–500 μm 85%, 100–300 μm 12%, < 100 μm 3%; color: transparent, pale yellow; amino loading: 17.3 mmol g^{-1} ; swelling: water 8.5, DMF 4.9 mL g^{-1} ; IR: $\tilde{\nu} = 3272.2$ (NH stretch), 2937.3 (CH stretch), 1622.3 (CONH) cm^{-1} .

(Ac)_{11.5%} polyethylene-imine polymer (9.3 g, 18.6 mmol) yielded 8.1 g of resin (87%); bead-size distribution: 300–500 μm 87%, 100–300 μm 10%, < 100 μm 3%; color: transparent, pale yellow; amino loading: 17.9 mmol g^{-1} ; swelling: water 8.7, DMF 5.1 mL g^{-1} ; IR: $\tilde{\nu} = 3272.2$ (NH stretch), 2937.6 (CH stretch), 1622.2 (CONH) cm^{-1} .

(Ac)_{10%} polyethylene-imine polymer (10 g, 20.45 mmol) yielded 8 g of resin (80%); bead-size distribution: 300–500 μm 85%, 100–300 μm 10%, < 100 μm 5%; color: transparent, pale yellow; amino loading: 18.6 mmol g^{-1} ; swelling: water 9.0, DMF 5.5 mL g^{-1} ; IR: $\tilde{\nu} = 3272.2$ (NH stretch), 2937.3 (CH stretch), 1622.5 (CONH) cm^{-1} .

Characterization

Loading: The amino functional loading was determined from the Fmoc-derivatized resin. The resin (10 mg) was treated with DMF (500 μL) containing Fmoc-Gly-OH (1 M), *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyluronium tetrafluoroborate (TBTU; 0.94 M) and *N*-ethylmorpholine (1 M) overnight. It was washed with DMF (10 ×), MeOH (10 ×), and DCM (10 ×), then dried in vacuo. The resin (3–5 mg) was treated with piperidine/MeOH solution (20% (v/v), 8 mL) for 30 min. The amino capacity of the resin was calculated from the optical density value of the piperidine-dibenzofulvene solution at 290 nm. The amino functional loading of 15% cross-linked ULTRAMINE was measured to be 16.5 mmol g^{-1} .

Swelling: The swelling capabilities of the resin in different solvents were determined by the syringe method. In a typical procedure, a dry sample of the resin (100 mg) was taken up in a 2 mL syringe fitted with a Teflon filter at the bottom. The appropriate solvent was sucked into the syringe and after 3 h, excess solvent was removed by applying force on the piston. The extent of swelling of the resin in each solvent was determined from the ratio of the volume of the solvent absorbed during incubation and the weight of dry resin.

Chemical stability: The chemical stability of the resin was determined in different reagents including trifluoroacetic acid (100%), 20% piperidine in DMF, DBU (100%), butyl lithium (2.7 M solution in heptane, 100%), triflic anhydride (100%), saturated NaOH, and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (100%). The resin samples (100 mg) were separately stirred with the reagents for 48 h at room temperature. The treated resin was visually inspected for macroscopic changes. The resin was filtered, washed, and dried. IR spectra were recorded and compared with the spectra of the original resin (Fig-

ure S3 in the Supporting Information). The swelling properties of the resin after treatment with the reagents for two weeks were also compared to the original properties. The resin did not dissolve under any of these conditions and showed no changes in color or swelling, a result indicating that no significant bond cleavage had occurred.

Mechanical stability: A bead (300–500 μm) was placed between a ccd camera lens and a cylindrical probe, connected to a strain gauge, to measure the force applied, and an actuator; the sample was then compressed at a constant rate of 10 $\mu\text{m min}^{-1}$. The camera recorded the deformation of the bead. An apparent compressive modulus (E_A), can then be calculated as the ratio of the apparent compressive stress (σ_A , the force per area of cross section of the bead) over the apparent compressive strain (γ_A , the ratio of the diameter over the initial diameter).

Synthesis of ULTRAMINE-Red: The resin (500 mg, containing 1.6 mmol of carbonyl groups) and boric acid (0.6 g, 9.6 mmol, 6 equiv) were measured into a reaction vessel. Trimethylborate (1 mL, 9.6 mmol, 6 equiv) was added; this was followed by addition of 1 M borane–THF complex (32 mL, 20 equiv). After cessation of hydrogen evolution, the tubes were capped tightly and kept in an oil bath at 65 °C for 72 h. The resin was then filtered and washed with DMF (4 $\times$ 10 mL) and MeOH (4 $\times$ 10 mL). The resin was suspended in piperidine (100%, 10 mL) and heated at 65 °C for 20 h to destroy the excess borane. The piperidine–borane solution was decanted, then the resin was washed with DMF (4 $\times$ 10 mL), DCM (4 $\times$ 10 mL), and MeOH (4 $\times$ 10 mL) and dried under vacuum to provide ULTRAMINE-Red with a quantitative conversion of amides to amines, as monitored by the complete disappearance of the carbonyl bands in the IR spectrum. Loadings are presented in Table 1; compressive modulus: 0.45 MPa; color: transparent, pale yellow; IR: $\tilde{\nu}$ = 3272.3 (NH stretch), 2937.6 (CH stretch) cm^{-1} .

General procedure for acylation/scavenging: All the compounds were synthesized simultaneously in a parallel arrangement (Table 2). Acylating reagents (0.25 mmol) were added to 10 mL plastic vials, each containing amine (0.1 mmol) in dry DCM (1 mL). Each vial was closed tightly, and the mixture was agitated at room temperature with a shaker for 16 h. ULTRAMINE (50 mg) was added to each vial and the solution was diluted to a volume of 3 mL with DCM. The resulting mixture was then agitated for 6 h at room temperature and filtered. The resin was washed with DCM (4 $\times$ 4 mL). The combined filtrate and washings were concentrated and transferred to a vial, and the solvent was removed with a stream of argon. The resulting product was dried under vacuum overnight to provide the product in almost quantitative yield. The purity of each product was analyzed by HPLC (Table 2).

N-(2-Butyl)ethanamide (1): Colorless oil (11.47 mg, 99.7%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.84 (t, 3H), 1.07 (d, 3H), 1.375–1.575 (brs, 2H), 1.88 (s, 3H), 3.97 (brs, 1H), 8.32 (s, 1H) ppm; ESI MS: m/z calcd: 116.1; found: 116.1 $[M+H]^+$.

N-(2-Butyl)hexanamide (2): Colorless oil (16.94 mg, 99.0%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.84 (t, 3H), 0.88 (t, 3H), 1.12 (d, 3H), 1.23–1.37 (brs, 4H), 1.54–1.56 (brs, 4H), 2.05 (t, 2H), 3.84 (brs, 1H), 8.15 (s, 1H) ppm; ESI MS: m/z calcd: 172.16; found: 172.1 $[M+H]^+$.

N-(2-Butyl)benzamide (3): White crystalline solid (17.57 mg, 99.2%); m.p. 143–145 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.88 (t, 3H), 1.12 (d, 3H), 1.38–1.65 (brs, 2H), 4.05 (brs, 1H), 7.31–7.72 (brs, 5H), 8.25 (s, 1H) ppm; ESI MS: m/z calcd: 178.12; found 178.1 $[M+H]^+$.

N-(2-Butyl)-N'-(4-nitrophenyl)thiourea (4): Yellow crystalline solid (24.37 mg, 96.3%); m.p. 119–120 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.89 (t, 3H), 1.15 (d, 3H), 1.55 (brs, 2H), 4.29 (brs, 1H), 7.18–8.15 (brs, 4H) ppm; ESI MS: m/z calcd: 254.09; found: 254.1 $[M+H]^+$.

9-Fluorenylmethyl-2-butylcarbamate (5): Pale yellow crystalline solid (28.77 mg, 97.5%); m.p. 163–165 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.84 (t, 3H), 1.31 (d, 3H), 1.55–1.78 (brs, 2H), 4.1 (t, 1H), 4.20–4.35 (brs, 1H), 4.41 (d, 2H), 7.22–7.72 (brs, 8H), 8.23 (s, 1H) ppm; ESI MS: m/z calcd: 296.16; found: 296.1 $[M+H]^+$.

N-(2-Butyl)-2-nitrobenzenesulfonamide (6): Brown crystalline solid (24.9 mg, 96.5%); m.p. 181–183 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.78 (t, 3H), 1.05 (d, 3H), 1.35–1.45 (brs, 2H), 3.31–3.58 (brs, 1H), 5.05 (s, 1H), 7.42–7.88 (brs, 4H) ppm; ESI MS: m/z calcd: 209.1; found 209.1 $[M+H]^+$.

N-(2-Butyl)-N'-phenylthiourea (7): White crystalline solid (20.66 mg, 99.3%); m.p. 105–106 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.83 (t, 3H), 1.09 (d, 3H), 1.35–1.48 (brs, 2H), 4.22–4.35 (brs, 1H), 5.65 (s, 1H), 7.05–7.55 (brs, 5H) ppm; ESI MS: m/z calcd: 259.07; found: 259.1 $[M+H]^+$.

N-(3-Pentyl)ethanamide (8): Colorless oil (12.84 mg, 99.5%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.95 (t, 6H), 1.12–1.58 (brs, 4H), 1.68 (s, 3H), 2.91 (brs, 1H), 8.22 (s, 1H) ppm; ESI MS: m/z calcd: 130.12; found: 130.1 $[M+H]^+$.

N-(3-Pentyl)hexanamide (9): Colorless oil (17.83 mg, 96.3%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.81 (t, 3H), 1.02 (t, 6H), 1.11–1.25 (brs, 2H), 1.38–1.62 (brs, 4H), 1.66–1.88 (brs, 4H), 2.04 (t, 2H), 2.95 (brs, 1H), 8.25 (s, 1H) ppm; ESI MS: m/z calcd: 186.18; found: 186.1 $[M+H]^+$.

N-(3-Pentyl)benzamide (10): White crystalline solid (18.12 mg, 94.8%); m.p. 136–137 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 1.02 (t, 6H), 1.39–1.68 (brs, 4H), 2.93 (brs, 1H), 7.25–7.65 (brs, 5H), 8.25 (s, 1H) ppm; ESI MS: m/z calcd: 192.13; found: 192.1 $[M+H]^+$.

N-(4-Nitrophenyl)-N'-(3-pentyl)thiourea (11): Yellow crystalline solid (24.78 mg, 92.8%); m.p. 112–114 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.88 (t, 6H), 1.45–1.69 (brs, 4H), 4.25 (brs, 1H), 7.23–7.61 (brs, 4H), 8.15 (brs, 2H) ppm; ESI MS: m/z calcd: 268.1; found: 268 $[M+H]^+$.

9-Fluorenylmethyl-3-pentylcarbamate (12): White crystalline solid (28.04 mg, 90.7%); m.p. 126–128 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.84 (t, 6H), 1.24–1.58 (brs, 4H), 3.48 (brs, 1H), 4.25 (t, 1H), 4.45 (d, 2H), 7.20–7.80 (brs, 8H) ppm; ESI MS: m/z calcd: 310.17; found: 310.1 $[M+H]^+$.

2-Nitro-N-(3-pentyl)benzenesulfonamide (13): Brown crystalline solid (25.52 mg, 93.8%); m.p. 178–181 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.74 (t, 6H), 1.28–1.68 (brs, 4H), 3.25 (brs, 1H), 5.05 (s, 1H), 7.61–8.18 (brs, 4H) ppm; ESI MS: m/z calcd: 223.12; found: 223.1 $[M+H]^+$.

N-Phenyl-N'-(3-pentyl)thiourea (14): White crystalline solid (21.52 mg, 96.9%); m.p. 110–112 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.85 (t, 6H), 1.28–1.54 (brs, 4H), 4.22 (brs, 1H), 7.26–7.66 (brs, 5H) ppm; ESI MS: m/z calcd: 273.08; found: 273.1 $[M+H]^+$.

N-(4-Nitrophenyl)ethanamide (15): Pale yellow crystalline solid (17.91 mg, 99.5%); m.p. 212–213 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 2.13 (s, 3H), 7.55–7.62 (brs, 2H), 8.10–8.14 (brs, 2H) ppm; ESI MS: m/z calcd: 181.05; found: 181 $[M+H]^+$.

N-(4-Nitrophenyl)hexanamide (16): Pale yellow crystalline solid (22.95 mg, 97.2%); m.p. 271–273 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.82 (t, 3H), 1.23–1.30 (brs, 4H), 1.65 (brs, 2H), 2.30 (t, 2H), 7.38 (s, 1H), 7.60–7.66 (brs, 2H), 8.10–8.18 (brs, 2H) ppm; ESI MS: m/z calcd: 237.12; found: 237 $[M+H]^+$.

N-(4-Nitrophenyl)benzamide (17): Pale yellow crystalline solid (23.26 mg, 96.1%); m.p. 160–162 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 7.30–7.60 (brs, 4H), 7.75–8.20 (brs, 5H) ppm; ESI MS: m/z calcd: 242.9; found: 243.0 $[M+H]^+$.

N,N'-(Bis-4-nitrophenyl)thiourea (18): Yellow crystalline solid (29.38 mg, 92.4%); m.p. 186–188 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 7.15–7.32 (brs, 4H), 7.92–8.20 (brs, 4H) ppm; ESI MS: m/z calcd: 319.04; found: 319 $[M+H]^+$.

9-Fluorenylmethyl-4-nitrophenylcarbamate (19): Pale yellow crystalline solid (34.67 mg, 96.3%); m.p. 153–155 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 4.16 (d, 2H), 4.20 (brs, 1H), 7.01–7.75 (brs, 12H) ppm; ESI MS: m/z calcd: 361.11; found: 361.1 $[M+H]^+$.

2-Nitro-N-(4-nitrophenyl)benzenesulfonamide (20): Brown crystalline solid (26.53 mg, 97.2%); m.p. 252–254 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 7.45–7.88 (brs, 4H), 8.05–8.15 (brs, 4H) ppm; ESI MS: m/z calcd: 274.03; found: 274 $[M+H]^+$.

N-(4-Nitrophenyl)-N'-phenylthiourea (21): Yellow crystalline solid (32.04 mg, 99.2%); m.p. 144–145 °C; $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 7.10–7.22 (brs, 5H), 7.92–8.12 (brs, 4H) ppm; ESI MS: m/z calcd: 324.02; found: 324 $[M+H]^+$.

N-(3-Phenylpropyl)ethanamide (22): Colorless oil (17.65 mg, 99.5%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 1.72 (brs, 2H), 1.92 (s, 3H), 2.55 (brs, 2H), 3.23 (brs, 2H), 7.10–7.30 (brs, 5H), 8.05 (s, 1H) ppm; ESI MS: m/z calcd: 178.12; found: 178.1 $[M+H]^+$.

N-(3-Phenylpropyl)hexanamide (23): Colorless oil (22.71 mg, 97.4%); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ = 0.82 (t, 3H), 1.15–1.25 (brs, 2H), 1.48

(brs, 2H), 1.64–2.71 (brs, 8H), 3.24 (brs, 2H), 7.05–7.32 (brs, 5H), 8.14 (s, 1H) ppm; ESI MS: m/z calcd: 234.18; found: 234.1 $[M+H]^+$.

N-(3-Phenylpropyl)benzamide (24): White crystalline solid (22.9 mg, 95.8%); m.p. 157–159°C; ^1H NMR (250 MHz, CDCl_3): δ = 1.85 (brs, 2H), 2.58 (t, 2H), 3.38 (brs, 2H), 7.15–7.65 (brs, 10H), 8.20 (s, 1H) ppm; ESI MS: m/z calcd: 240.13; found: 240.1 $[M+H]^+$.

N-(4-Nitrophenyl)-N'-(3-phenylpropyl)thiourea (25): Yellow crystalline solid (29.61 mg, 94%); m.p. 117–118°C; ^1H NMR (250 MHz, CDCl_3): δ = 1.95 (brs, 2H), 2.60 (t, 2H), 3.60 (brs, 2H), 7.10–8.15 (brs, 9H) ppm; ESI MS: m/z calcd: 316.1; found: 316 $[M+H]^+$.

9-Fluorenylmethyl-(3-phenylpropyl)carbamate (26): White crystalline solid (33 mg, 92.4%); m.p. 98–100°C; ^1H NMR (250 MHz, CDCl_3): δ = 1.71 (brs, 2H), 2.55 (t, 2H), 3.10 (brs, 2H), 3.95 (brs, 1H), 4.28 (d, 2H), 7.10–7.75 (brs, 13H) ppm; ESI MS: m/z calcd: 358.17; found: 358.1 $[M+H]^+$.

2-Nitro-N-(3-phenylpropyl)benzenesulfonamide (27): Brown crystalline solid (25.41 mg, 94.1%); m.p. 175–178°C; ^1H NMR (250 MHz, CDCl_3): δ = 1.76 (brs, 2H), 2.50 (t, 2H), 3.05 (brs, 2H), 5.25 (s, 1H), 6.90–7.68 (brs, 9H) ppm; ESI MS: m/z calcd: 271.12; found: 271.1 $[M+H]^+$.

N-Phenyl-N'-(3-phenylpropyl)thiourea (28): White crystalline solid (30.82 mg, 96.3%); m.p. 210–212°C; ^1H NMR (250 MHz, CDCl_3): δ = 1.85 (brs, 2H), 2.56 (t, 2H), 3.55 (brs, 2H), 7.05–7.39 (brs, 10H) ppm; ESI MS: m/z calcd: 321.08; found: 321 $[M+H]^+$.

ULTRAMINE-Red as a scavenger: Phenyl isothiocyanate (30 μL , 0.25 mmol) was added to 10 mL plastic vials, each containing 3-aminopentane (11.7 μL , 0.1 mmol) in dry DCM (1 mL). Each vial was closed tightly, and the mixture was agitated at room temperature with a shaker for 16 h. ULTRAMINE-Red (50, 40, 25, 10, or 5 mg) was added to each vial and the solution was diluted to a volume of 3 mL with DCM. The resulting mixture was then agitated for 6 h at room temperature and filtered. The resin was washed with DCM (4 $\times$ 4 mL). The combined filtrate and washings were concentrated and transferred to a vial, and solvent was removed with a stream of argon to yield the product in an almost quantitative yield upon lyophilization for 16 h. The purity of products was analyzed by HPLC (Figure 4 presents the HPLC analyses for 5 and 10 mg resin), and the results indicated that 10 mg of ULTRAMINE-Red was sufficient to act as a scavenger.

Acknowledgement

This work was carried out at the Center for Solid Phase Organic Combinatorial Chemistry (SPOCC) and was supported by the Danish National Research Foundation. The authors would also like to thank Combio A/S and VersaMatrix A/S for a fellowship to M.R. The help rendered by Dr. Charlotte H. Gottfredsen in recording the MAS NMR spectra is gratefully acknowledged.

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Received: March 30, 2004
Published online: July 28, 2004