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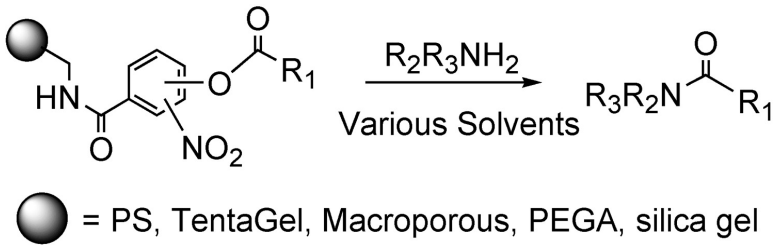

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Nitrophenol Resins for Facile Amide and Sulfonamide Library Synthesis

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Novel nitrophenol solid supports based on various resin materials (polystyrene, TentaGel, macroporous, PEGA, and silica gel) are reported for facile amide and sulfonamide library synthesis. The broad choice of resin materials available will allow the reaction to occur successfully in solvents ranging from nonpolar organic solvents to aqueous media.

Introduction

Since Merrifield published the first solid-phase reaction in his seminal 1963 paper describing the synthesis of a peptide via attachment of amino acids to a polymer backbone, the concept has become the basis of automated peptide synthesis.[1,2] With the advent of combinatorial chemistry almost a decade ago, solid-phase chemistry has elicited a staggering amount of attention, and its scope has been expanded to include the fields of small molecules,[3−9] carbohydrates,[10,11] and catalysis.[12,13] In addition to conventional solid-phase chemistry, in which the compound to be modified is loaded onto the solid support and the product is cleaved from the support at the last step, the solid-phase reagent approach is an attractive alternative method.[14] In this approach, the core structure of the library molecule resides in solution, and solid-phase reagents are added to the mixture to facilitate the reaction. The solid-phase reagents are then removed from the heterogeneous reaction mixture by filtration.

In particular, polymeric active ester reagents are widely known as useful tools in amide/sulfonamide library synthesis[15−21] and as labeling reagents.[22−25] Most of the reported functionalities, such as 4-hydroxy-3-nitrophenyl,[26] NHS,[22−24] HOBt,[27,28] TFP,[17] and Kaiser oxime,[29,30] have been attached to a polystyrene resin solid support by a Friedel−Crafts reaction[26,29] or to a thiol resin by a maleimide linker.[22−24] Consequently, the nature of the reaction limits the selection of resin compositions to mainly polystyrene, while also limiting the reaction conditions to hydrophobic organic solvents. To overcome this limitation, we previously studied the amide bond formation of tetrafluorohydroxybenzoic acid[17] to various compositions of aminomethyl resins and successfully compared their relative kinetic behaviors.[31]

A similar strategy was applied in the preparation of TentaGel-based HOBt, NHS, and TFP, and an amide forming reaction in aqueous media was demonstrated.[32] In aqueous media, the rate of the major side reaction, hydrolysis versus the desired aminolysis, was dependent on the reactivity of the active ester functionality, as well as on other reaction conditions. Although TFP favored aminolysis with minimum hydrolysis more than the HOBt or NHS resins, this broad selection of resins with a variety of activated esters will be a useful toolbox for case-by-case application. Herein, we report various nitrophenol resins loaded on a series of support materials as new species of activated esters useful for broad applications.

Results and Discussion

Novel nitrophenol resins (**2**) were synthesized by standard amide-bond-forming reactions of various aminoalkyl resins [polystyrene, TentaGel, macroporous, PEGA, and silica gel] with various hydroxynitrobenzoic acids (**1**). Although PS-, TG-, MP-, and PEGA-based aminomethyl resins are commercially available, aminopropyl SG was prepared by a slightly modified literature procedure.[33,34] The nitrophenol resins (**2**) were then coupled to various carboxyl and sulfonyl groups, resulting in the activated ester resins (**3** and **4**). Upon reaction with amine nucleophiles in various solvents, amide and sulfonamide products (**5** and **6**) were formed and released to the reaction media and collected by simple filtration, followed by rinsing and evaporation (Scheme 1). The purity and identity of the products were characterized by LC/MS equipped with a diode array detector and an ESI mass spectrometer. Various active esters (**3**, **4**) and amines were tested (Table 1, Table 2 and Table 3), and most of the products were pure and did not require further purification (90−99% pure).

We have previously studied the effect of resin composition on the aminolysis reaction rate in various solvents using in situ fluorescence measurement.[31] Using this same technique, the relative reaction rates of different nitrophenol activated benzoquinoline esters were compared (Figure 1, Table 4). Although resins **8a** and **8c** showed similar reaction rates (k = 1.08 and 1.21 M^{-1} sec^{-1}), **8b** (k = 0.51 M^{-1} sec^{-1}) was about half that of the others. This may be due to the different position of the electron-withdrawing group on the resins; although the nitro groups are all ortho or para to the ester groups, the amide groups are in the ortho or para

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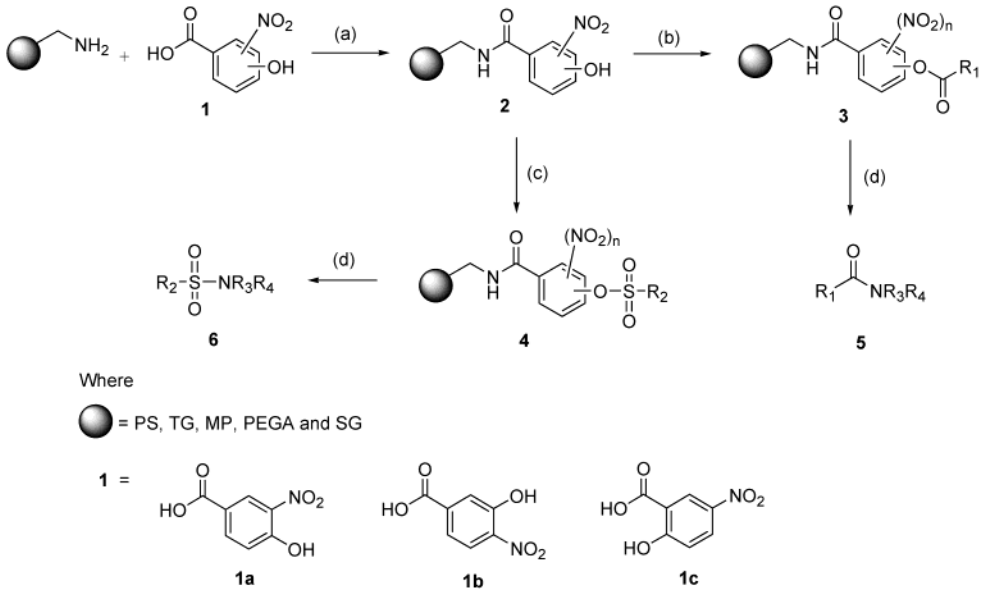
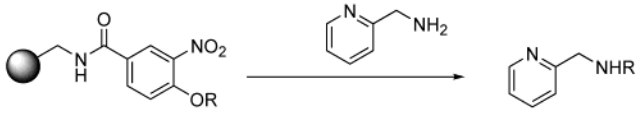
Scheme 1[a]



[a] Reagents and conditions: (a) DIC, HOBt, DMF; (b) R_1COCl, pyridine or R_1COOH, DIC, DMAP in DMF; (c) R_2SO_2Cl, pyridine, THF; (d) R_3R_4NH in various solvents.

Table 1. Representative Amide Synthesis Using Various Activated Esters

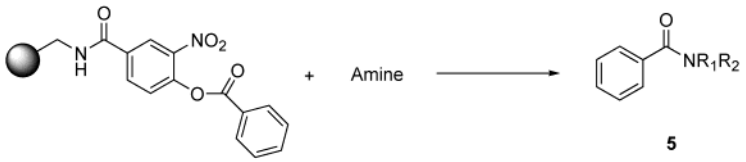


Resin	Structure R	Purity % area at 250nm	Resin	Structure R	Purity % area at 250nm
PS-3a		99	**TG-3a**		90
PS-3a		95	**TG-3b**		91
PS-3a		93	**TG-3b**		92
PS-3a		95	**PEGA-3b**		95
PS-3a		96	**PEGA-3c**		93
PS-3a		97	**MP-3b**		91
PS-3a		97	**MP-3b**		95
PS-3a		99	**SG-3a**		95

position in **8a** and **8c**, but meta in **8b**. In the same condition, PS−TFP gave a k value of 2.00 M^{-1} sec^{-1}.[31] Combining previous kinetics comparisons using different techniques, the reactivity order and relative reaction rate of activated esters are as follows: HOBt (100) ≫ TFP ∼ NHS (1.5−2) > nitrophenol (0.5−1) ≫ Kaiser oxime (0.003).[25,28,31,32]

Another synthetic route was also found utilizing the hydrolysis of chlorobenzene to make nitrophenol resin **2a**. 4-Chloro-3-nitrobenzoyl resin (**7a**) was synthesized using the DIC−HOBt coupling of alkylamino resin with 4-chloro-3-nitrobenzoic acid. A subsequent basic hydrolysis afforded nitrophenol resin **2a** (Scheme 2).[26]

Table 2. Representative Amide Synthesis Using Benzoate Ester Resins (PS−**3**, TG−**3**, PEGA−**3**, MP−**3**, SG−**3**) and Various Amines



PS-3, TG-3, PEGA-3, MP-3, SG-3

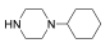
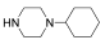
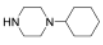
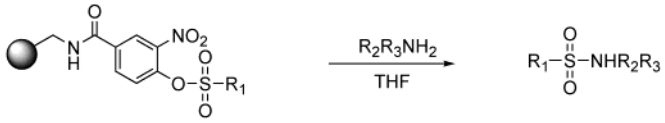
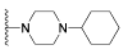
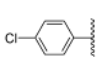
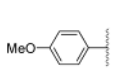
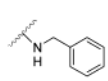
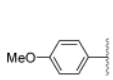
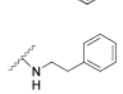
Resin	Amine	Purity (%)	Resin	Amine	Purity (%)
PS-3a		99	**PEGA-3c**		96
PS-3a		98	**MP-3a**		93
PS-3a		96	**MP-3a**		96
PS-3a		99	**MP-3a**		95
TG-3a		94	**MP-3b**		99
TG-3a		97	**MP-3c**		97
TG-3a		98	**SG-3a**		95
TG-3b		97	**SG-3a**		91
TG-3c		97	**SG-3a**		95
PEGA-3b		96	**SG-3a**		94
PEGA-3c		94	**SG-3a**		92

Table 3. Representative Sulfonamide Synthesis Using a Sulfonate Ester Resin (PS−**4**, TG−**4**, MP−**4**) and Various Amines

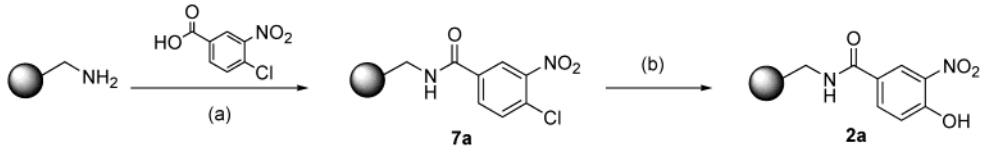


PS-4, TG-4, MP-4

Resin	Structure R_1	Structure R_2R_3	Purity % area at 230nm
PS-3a			95
PS-3a			99
TG-3b			96
TG-3c			93
MP-3c			99

The water compatibility of TG and SG resins allows for amination in aqueous media. Active benzoate esters (TG−**3**, SG−**3**) were prepared, and amidation in aqueous solution was carried out using glycine (0.01−1 M) in 0.1 M $NaHCO_3$ or K_2CO_3. In every case, the desired product was formed as the major component, along with a small amount of

Scheme 2[a]



[a] Reagents and conditions: (a) DIC, HOBt, DMF, rt; (b) $BnMe_3NOH$, H_2O, dioxane, 90 °C, 8 h.

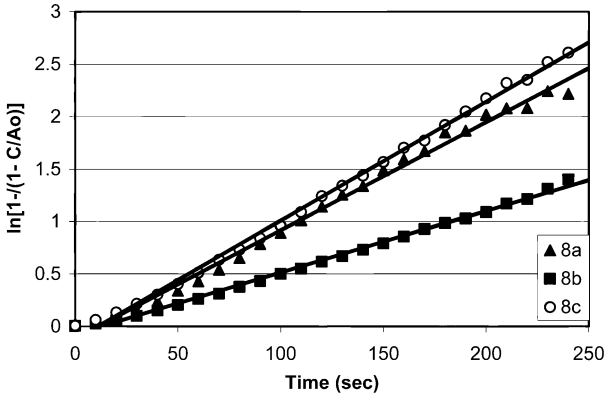
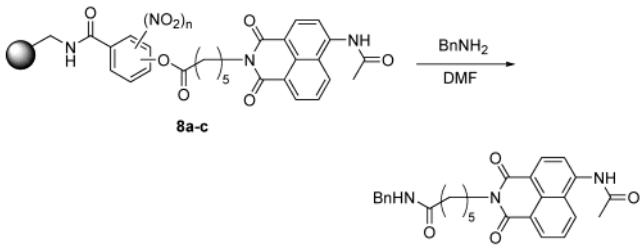


Figure 1. Plot of $\ln[1 - /(1 - C/A_0)]$ vs time for a series of resins **8a**, **8b**, and **8c**. The slope is proportional to the reaction rate constant, *k*. C/A_0 = percent conversion.

Table 4. Second-Order Reaction Constants (M^{-1} s^{-1}) of Three Resins (**8a**−**c**)



	k (M^{-1} s^{-1})	SD
PS−TFP	2.00[a]	0.24[b]
PS−**8a**	1.08	0.11
PS−**8b**	0.51	0.03
PS−**8c**	1.21	0.12

[a,b] Data from ref 31.

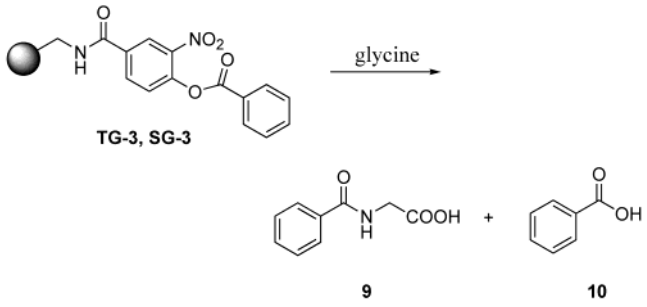
hydrolyzed byproduct. Generally speaking, a higher concentration of glycine gave more of the desired product (Table 5).

In summary, new polymer-bound nitrophenol resins were prepared by coupling alkylamino resin with hydroxynitrobenzoic acid. These active esters and sulfonyl esters will react with a diverse set of amine nucleophiles in various solvent conditions to generate vast arrays of amides and sulfonamides that are useful in drug discovery.

Experimental Section

General. All reagents were obtained from commercial sources and used as received, with the following exception: free trace amine was removed from DMF via the addition of *p*-toluenesulfonic acid resin (Argonaught Tech. Inc. P/N 800287, lot no. 00561) and allowed to stand for a minimum of 5 h. Solid-phase reagents were obtained from the following sources: PS (Argo PS, 1.21 mmol/g, 75−150 μm, Argonaught P/N 800263, lot no. 00265), TG (NovaSyn TG, 0.45 mmol/g, 110 μm, NovaBiochem Catalogue no. 01-64-0144), MP (ArgoPore, 0.99 mmol/g, 106−250 μm, Argonaut P/N 800048, lot no. 104-11), PEGA (0.06 mmol /g, 150−300 μm, Nova Biochem Catalogue no. 01-64-0010), and PS−DIEA (3.72 mmol/g, av 415 μm, Argonaught P/N 800281, lot no. 02158). Silica gel (60 Å, 63−200 μm, standard column grade) was purchased from Sorbent Technology (Catalogue no. 10940-25). Fluorescence spectra were collected using a Jobin-Yvon Horiba Spex Fluoromax-3 equipped with a stirring apparatus, and the temperature was regulated at 25 °C with a Fisher Scientific (model 9101) water circulator. Starna (3-Q-10) and Fisher Scientific (Supracil 3.0 mL) quartz fluorescence cuvettes were used in the fluorescence measurements. Data were obtained using Datamax v. 2.2 software and analyzed using Microsoft Excel. Time-based acquisition experiments were performed in which λ_{ex} = 370 nm and λ_{em} = 455 nm.

Table 5. Amide Formation in Aqueous Media Using Water-Compatible **3a**−**c**



resin	glycine (M)	base (0.1 M)	**9** (%)	**10** (%)
TG−**3a**	1	$NaHCO_3$	97	3
TG−**3a**	0.1	$NaHCO_3$	93	7
TG−**3a**	0.01	$NaHCO_3$	86	14
TG−**3a**	0.1	K_2CO_3	93	7
TG−**3a**	0.01	K_2CO_3	71	29
TG−**3b**	1	$NaHCO_3$	89	11
TG−**3b**	0.1	$NaHCO_3$	90	10
TG−**3b**	0.01	$NaHCO_3$	81	19
TG−**3b**	0.1	K_2CO_3	85	15
TG−**3b**	0.01	K_2CO_3	76	24
TG−**3c**	1	$NaHCO_3$	90	10
TG−**3c**	0.1	$NaHCO_3$	89	11
TG−**3c**	0.01	$NaHCO_3$	88	12
TG−**3c**	0.1	K_2CO_3	86	14
TG−**3c**	0.01	K_2CO_3	86	14
SG−**3a**	1	$NaHCO_3$	87	13
SG−**3a**	0.1	$NaHCO_3$	65	35
SG−**3a**	0.01	$NaHCO_3$	62	38
SG−**3a**	0.1	K_2CO_3	82	18
SG−**3a**	0.01	K_2CO_3	80	20

Representative Preparation of Nitrophenol Resin (PS, TG, MP, PEGA−2). In a 50-mL polystyrene cartridge, to

an amino polystyrene resin (1 g, 1.2 mmol) in DMF (15 mL) were added 4-hydroxy-3-nitrobenzoic acid (**1a**, 1 g, 5.5 mmol), HOBt (1 g, 7.4 mmol), and DIC (1 mL, 6.4 mmol). After overnight shaking, the reaction mixture was washed with DMF (20 mL, 5 times), MC, and methanol (20 mL, 5 times alternatively). To remove any undesirable side product, DMF (5 mL) and piperidine (0.5 mL) were added to the cartridge and allowed to shake for 1.5 h. The resin was filtered and washed with DMF (20 mL, 5 times). The resulting piperidine salt was removed via the addition of a 10% HCl solution (in DMF, 20 mL) and was allowed to shake for 1.5 h. The resin was then filtered; washed with DMF, methanol, and MC (20 mL, 5 times each); and dried by nitrogen gas flow. TG, MP, PEGA, and **1a**−**1c**, were synthesized using the same procedure.The synthesis of SG followed a different procedure.

Representative Preparation of Silica Gel Nitrophenol (SG−2). Silica gel was modified with an aminopropyl group following a slightly modified literature procedure.[33,34] Silica gel (1 g) and 3-aminopropyl-triethoxysilane (1.2 mL, 5.1 mmol) in toluene (10 mL) were refluxed for 6 h. After cooling, the reaction mixture was filtered through a 70-μm, 3-mL filter cartridge and washed thoroughly with hot dioxane (20 mL, 5 times), cold methanol, and MC (20 mL, 5 times each, alternatively). The aminopropyl resin was dried with a nitrogen gas flow.

To the aminopropyl resin resuspended in NMP (10 mL) were added 4-hydroxyl-3-nitrobenzoic acid (2 g, 10.9 mmol), HOBt (2 g, 14.8 mmol), and DIC (2 mL, 12.8 mmol), and the mixture was stirred overnight. The reaction mixture was filtered and washed with DMF (20 mL, 5 times), MC, and methanol (20 mL, 5 times each). The resin was treated with piperidine (0.2 mL) in THF (2 mL) and shaken for 10 min. The resulting SG−**2a** was filtered and washed with hot dioxane (20 mL, 5 times) and MC (20 mL, 5 times) and dried with a nitrogen gas flow. SG−**2b** and **2c** were synthesized using the same procedure.

Representative Preparation of Activated Ester: Example of PS−3a, Benzoate Ester. The nitrophenol resin (PS−**2a**, 100 mg, 0.12 mmol) was suspended in NMP (10 mL), and benzoyl chloride (0.1 mL, 0.86 mmol) and pyridine (0.1 mL, 1.2 mmol) were added to the reaction mixture. The reaction mixture was allowed to shake overnight, and the resins were filtered and washed with DMF (10 mL, 3 times), methanol, and MC (10 mL, 5 times, alternatively) and dried by nitrogen gas flow. All other activated esters were formed using the same procedure.

Representative Preparation of Activated Ester: Example of PS−4a, *p*-Toluenesulfonate Ester. After the nitrophenol resin (PS−**2a**, 1.0 g, 1.2 mmol) was suspended in THF (20 mL), pyridine (1 mL, 12.3 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.3 mmol) were added and agitated vigorously until all of the sulfonyl chloride dissolved. The reaction mixture was then gently agitated for 16 h at room temperature. The resin was filtered, washed with DMF (10 mL, 5 times), methanol, and MC (10 mL, 5 times alternatively), and dried by nitrogen gas flow. All other activated sulfonyl esters were formed using the same procedure.

Representative Synthesis of Amide: *N*-Pyridin-2-ylmethyl Benzamide. A mixture of benzoate ester resin (PS−**3a**, 40 mg, 0.048 mmol) in THF (1 mL) was treated with 2-(aminomethyl) pyridine (2.6 μL, 0.024 mmol) and stirred at room temperature overnight. The reaction mixture was filtered and washed with THF (1 mL, 3 times). The combined filtrate was evaporated and analyzed by LC/MS.

Representative Synthesis of Sulfonamide: *p*-Toluenesulfonyl-4-piperidine. Piperidine (3 μL, 0.03 mmol) was added to a *p*-toluenesulfonate ester resin (PS−**4a**, 50 mg, 0.06 mmol) in THF (1 mL) (3 μL, 0.03 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and washed with THF (1 mL, 3 times). The combined filtrate was evaporated and analyzed by LC/MS.

Representative Synthesis of Amide in Aqueous Solvent: Benzoyl Amino Acetic Acid (9). A solution of glycine (1 M, 0.1 M, 0.01 M) in aqueous sodium bicarbonate or potassium carbonate solution (0.1 M, 0.5 mL) was added to the benzoate ester resin (TG−**3a**, 10 mg), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered and washed with H_2O (0.5 mL, 3 times). The pH of the combined filtrate was adjusted to 4. The filtrate was analyzed by LC/MS, and the data is summarized in Table 5. A few representative large-scale reactions from Table 5 were performed to determine the yield of the reactions through product mass calculations. Most of the cases demonstrated a 90−99% isolated yield. Compound purity was determined by NMR and by LC/MS through comparison of relative peak areas.

Preparation of Fluorescence Activated Ester (8a−c). The nitrophenol resin (PS−**2a**, 100 mg, 0.12 mmol) was suspended in DMF (10 mL), and 4-acetamido-1,8-naphthalimide-caproic acid (100 mg, 0.22 mmol),[25] DIC (100 μL, 0.64 mmol), and DMAP (1 mg) were subsequently added at room temperature. Resin **8a** was filtered and washed with DMF (10 mL, 5 times), THF (10 mL, 10 times), and MC (10 mL, 10 times) and then dried by nitrogen gas flow. Resins **8b** and **8c** were made with the same procedure using PS−**2b** and PS−**2c**.

Kinetics Measurement Procedure. Each activated fluorescence ester resin (**8a**−**c**) was initially suspended in a polypropylene frit-equipped syringe filter set with a 10% acetic acid solution (5 × 5 mL) of the solvent being tested. They were subsequently filtered and thoroughly rinsed (5 × 5 mL) with the solvent being tested (acid-free). DMF (5 mL) was added to the filter syringe, after which 960 μL of the resin-solvent suspension was transferred to the cuvette with an emphasis on taking a minimum number of beads (<10 beads). A UV lamp allowed for enhanced detection of the individual resin beads in suspension. A 1-mL portion of DMF was then added to the suspension in the cuvette. The cuvette was placed in the fluorometer, and 40 μL of a 500 mM solution of benzylamine in the solvent being tested was added to make the final benzylamine concentration 10 mM (total sample volume in the cuvette = 2.0 mL). The fluorometer was immediately triggered upon addition of benzylamine (λ_{ex} = 370 nm, λ_{em} = 455 nm).

Glossary

DIC	1,3-Diisopropylcarbodiimide
DIEA	*N*,*N*- diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMAP	4-(dimethylamino)pyridine
ESI	electrospray ionization
HOBt	1-hydroxybenzotriazole
LC/MS	liquid chromatography/mass spectrometry
MC	methylene chloride
MP	macroporous
NHS	*N*-hydroxysuccinimide
NMP	1-methyl-2-pyrrolodinone
NMR	nuclear magnetic resonance
PEGA	acryoylpoly(ethylene glycol)
PS	polystyrene
SG	silica gel
TFP	tetrafluorophenol
TG	TentaGel
THF	tetrahydrofuran
UV	ultraviolet.

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References and Notes

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