JOURNAL OF combinatorial CHEMISTRY

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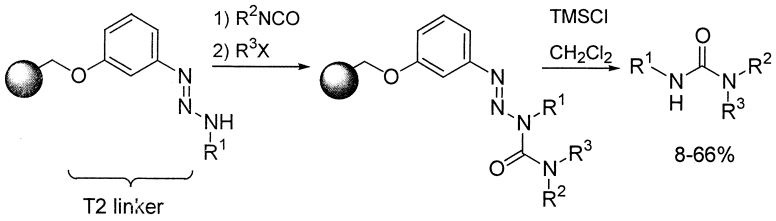
J. Comb. Chem., **2000**, 2 (6), 710-715• DOI: 10.1021/cc000051s • Publication Date (Web): 21 October 2000



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Solid-Phase Synthesis of Urea and Amide Libraries Using the T2 Triazene Linker

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Received June 23, 2000

Starting from Merrifield resin, primary amines were immobilized in two steps by triazene linkage (T2-linker). While reaction with isocyanates gave rise to resin-bound urea derivatives, acylation by acid chlorides or anhydrides furnished amides bound to solid support via the nitrogen atom, therefore representing a novel backbone amide linker. Cleavage from the resin was conducted using dilute trimethylsilyl chloride or trifluoroacetic acid, respectively, to yield ureas and amines/amides in a library format (altogether 60 examples; manual synthesis: 17 ureas, 6 mono-alkylated ureas [including dihydroxylation and ozonolysis/Wittig reaction]; automated synthesis: 15 ureas, 15 amides) in high purities and good overall yields. The synthesis of a small library (4 × 4 member) was successfully conducted on a Bohdan Neptune synthesizer.

Introduction

The solid-phase synthesis of amide containing structures is important to various fields of organic and bioorganic chemistry.[2] Solid-phase peptide synthesis (SPPS) has provided the chemical community with various solutions toward linking, reaction, and detachment of amide structures.[3] In general, these protocols involve the attachment of amine derivatives by their carbon backbone or, in the case of amino acids, by their carboxy functionality. The coupling with carboxyl derivatives proceeds via the free amine. Alternatively, the inverse synthesis of peptides (N to C terminus) has also been reported.[4] Linking by the N−H of the amide bond has been developed, hence leading to so-called backbone amide linkers (BAL). Originally designed for the N−H protection of amide bonds to circumvent β-turns and other problems during peptide synthesis,[5] these amide protecting groups can also serve as linkers for SPPS. Recently, Barany et al.[6] described an application of a backbone amide linker for the synthesis of oligopeptides based on the peptide amide linker (PAL) concept. Similarly, Ellman used this technique in the synthesis of a benzodiazepine library.[7] Other linkers capable of backbone amide linking have been reported recently;[8] however, the benzylamine based linkers, especially, have encountered some problems during cleavage which also caused the fragmentation of the whole linker.[2]

Urea derivatives, which are important biologically active compounds[9,10] and building blocks for organic syntheses, have been synthesized on solid support by various strategies.[2,11] Since urea derivatives are readily accessible from amines and isocyanates, various resins, soluble polymeric supports, and fluorous synthesis techniques[10] have been used for the removal of amines,[10,12] isocyanates,[2,13] and acid[14] derivatives for the automated high-throughput synthesis of ureas in solution.

We have recently developed a method for the attachment and detachment of secondary amines onto solid-support using T2 triazene linkages.[15] We now wish to report the application of the T2 linker for the attachment and modification of primary amines yielding urea and amide derivatives.

Results and Discussion

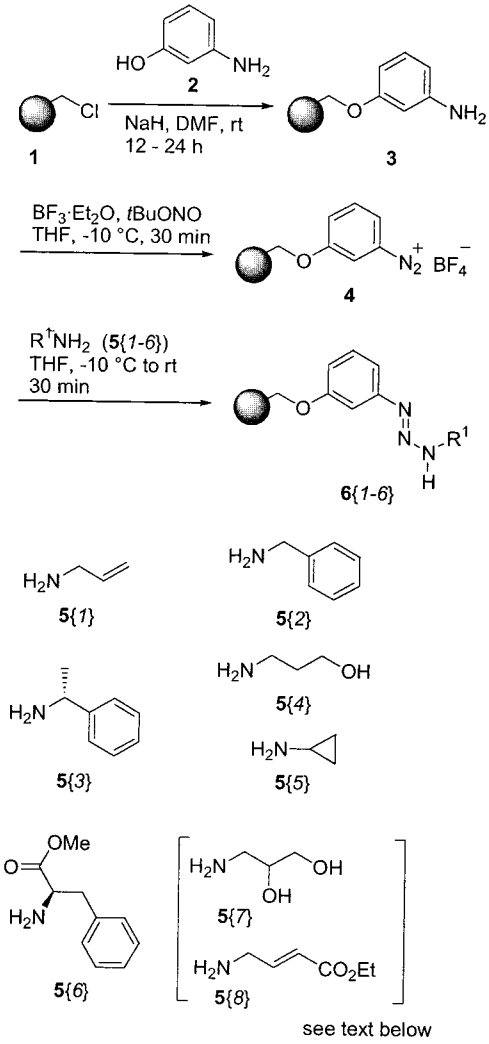
As outlined in Scheme 1, *m*-aminophenol (**2**) was attached to Merrifield resin (**1**) via the phenolic group with the aid of sodium hydride in dimethylformamide (DMF). Improvement of the synthesis led to a loading of nearly 100% as judged by elemental analysis (see Experimental Section)[16] and infrared spectroscopy [disappearance of the C−Cl stretch at 1265 cm^{-1}, literature: ν(Aryl-Hal = 1100−1030 cm^{-1})]. Crucial at this point was an ambient reaction temperature and the exclusion of air in contrast to our first report (80 °C).[15] Hence, resin **3** was obtained as a tan colored product. The reaction proceeded cleanly by O-alkylation rather than N-alkylation, making a protecting strategy unnecessary. Alternatively, potassium *tert*-butoxide as a base may be used for larger scales in order to avoid the formation of hydrogen. *m*-Aminophenol was used as the linker molecule because it is not as easily oxidized as other aminophenols.

Diazotization of the amine resin **3** at −10 °C in THF with *t*BuONO and boron trifluoride etherate yielded a yellowish resin **4**, which was stable for a period of several hours at this temperature. It is possible to obtain a temperature stable diazonium salt by modification of the arene core.[17]

Coupling with various primary amines **5**{*1*−*6*} (Scheme 1) at −10 °C to room temperature led to the formation of a series of new triazene resins **6**{*1*−*6*}. An excess of 5 equiv of the amines **5** was used, initially. However, in the presence of additional bases such as potassium carbonate or, more advantageous in terms of solubility, pyridine, the reaction could be conducted with a slight excess of the primary

10.1021/cc000051s CCC: $19.00
Published on Web 10/21/2000

Scheme 1. Synthesis of Diazenyl-Bound Primary Amines



amines only. As judged by elemental analysis (see Supporting Information) and infrared spectroscopy, an almost quantitative loading was achieved with nearly all free amine bases such as **5**{*1*−*5*}, whereas hydrochlorides such as compound **5**{*6*} are not suitable starting materials. However, the addition of pyridine was beneficial at this point and led to acceptable coupling rates even in these cases. It was pleasing to discover that amino alcohols such as **5**{*4*} can also serve as starting materials.

The triazene resins **6**{*1*−*6*} were indefinitely stable at room temperature. The swelling properties of the triazene resins are comparable to the starting material, reflecting the absence of cross-linking by pentazene formation. The color of the resin is slightly yellow to orange.

Synthesis of a Urea Library

The reactions of the triazene resins **6**{*1*−*6*} with isocyanates **7**{*1*−*8*} were conducted in THF at room temperature with a catalytic amount of triethylamine. The urea resins **8**{*1*−*6*}{*1*−*8*} obtained were fully characterized and showed a characteristic IR stretch of the functional group at 1670 cm^{-1} [lit. ν(NCON) ≈ 1660 cm^{-1})] (Scheme 2).

The cleavage was conducted using trimethylsilyl chloride (TMSCl) in dichloromethane (10%) at room temperature. This silane is by far less expensive than TFA and less corrosive, and the byproducts such as hexamethyldisiloxane (bp 101 °C) can be readily removed by evaporation. It is remarkable that urea derivatives were cleavable under these mild conditions.[15] Presumably, the silicon electrophile is attacked by the lone pair of the nitrogen or oxygen to release the amine from the resin. The involvement of the hydrolysis product of TMSCl, hydrogen chloride, can be ruled out. The resins consistently changed their color after cleavage to deep red, which can be used as a qualitative indicator for detachment. A possible explanation is the formation of azo compounds during cleavage. The ureas **9**{*1*−*6*}{*1*−*8*} prepared were isolated in fair to good yields (see Supporting Information) and excellent purities, which were consistently greater than 92% by judgment of NMR, GC, GC-MS, HPLC (254 nm), and LC-MS. This synthesis was successfully transferred to a Bohdan Neptune station using a prototype solid-phase unit as well as to the Bohdan Miniblock system (see Supporting Information).

Careful examination of the NMR spectra, the HPLC traces, as well as the mass spectra revealed that silylation of the products did not take place. Resin-bound amines, which possess an additional nucleophilic functionality such as amino alcohol **6**{*4*}, react also on this group with the isocyanate giving access to carbamate **9**{*4,1′*}.

The immobilized ureas **8**{*1,1*}{*2,1*}{*5,1*} were modified on the bead by alkylation.[18] Deprotonation with sodium hydride in DMF followed by treatment with benzyl chloride (**10**{*1*}), allyl bromide (**10**{*2*}), methyl iodide (**10**{*3*}), tridecylbromide (**10**{*5*}), and propargyl bromide (**10**{*6*}) proceeded cleanly. The reaction with tosyl chloride (**10**{*4*}), however, occurred sluggish. Cleavage of the solid-bound ureas **11**{*1,1,1*−*3*+*5*}{*2,1,2*−*3*}{*5,1,6*} with TMSCl (10% in dichloromethane) furnished the trisubstituted urea derivatives **12**{*1,1,1*−*3*+*5*}{*2,1,2*−*3*}{*5,1,6*} in good yields and mostly in good purities (seven examples) (Scheme 3).

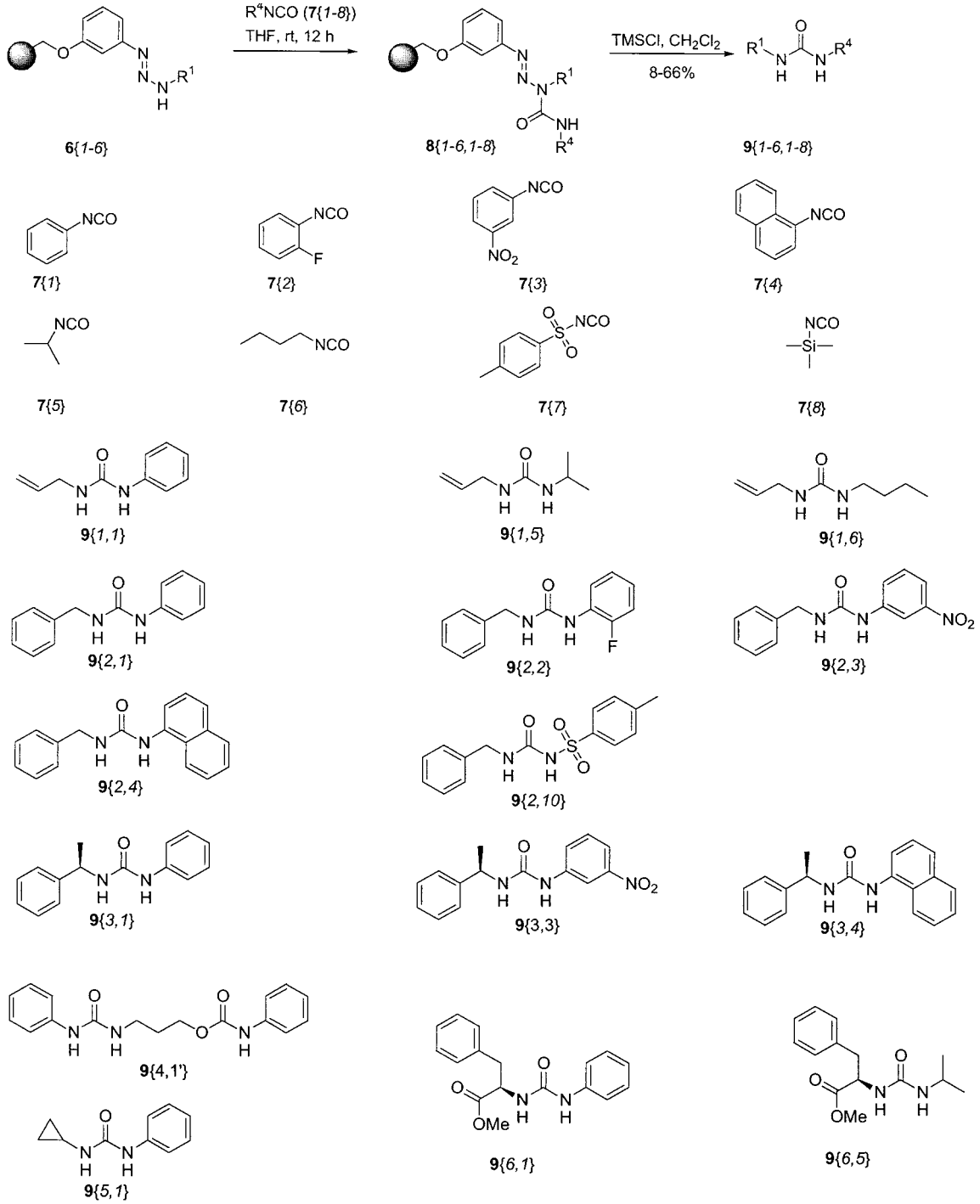
The compatibility of the T2 linker with common organic transformations was further illustrated by double bond functionalization.

Thus, dihydroxylation with osmium tetroxide proceeded smoothly in THF/water with morpholine *N*-oxide as reoxidant (Scheme 4). Cleavage of resins **8**{*1,1*}{*1,5*} provided access to the diols **7**{*7,1*} and **7**{*7,5*} in high purity (95%). The asymmetric variant was conducted with commercially available AD-mix β without any further additives in various solvent mixtures. The optimum mixture was found to be THF and water (v:v 5:1), which apparently favors the swelling properties as well as the dihydroxylation mechanism.[19a]

Ozonolysis of resin **8**{*1,1*} was conducted at −78 °C for 10 min to give an intermediate aldehyde resin. Subsequent Wittig reaction with a stabilized phosphorane gave rise to the formation of the urea **8**{*8,1*}. Cleavage furnished the ester in moderate purities (60%). However, filtration through a short pad of silica gel allowed efficient purification giving pure **9**{*8,1*}.

In summary, this three-component assembly furnished products in good yields without the need for any further protecting group strategy.

Scheme 2. Synthesis of Disubstituted Ureas



Synthesis of an Amide Library

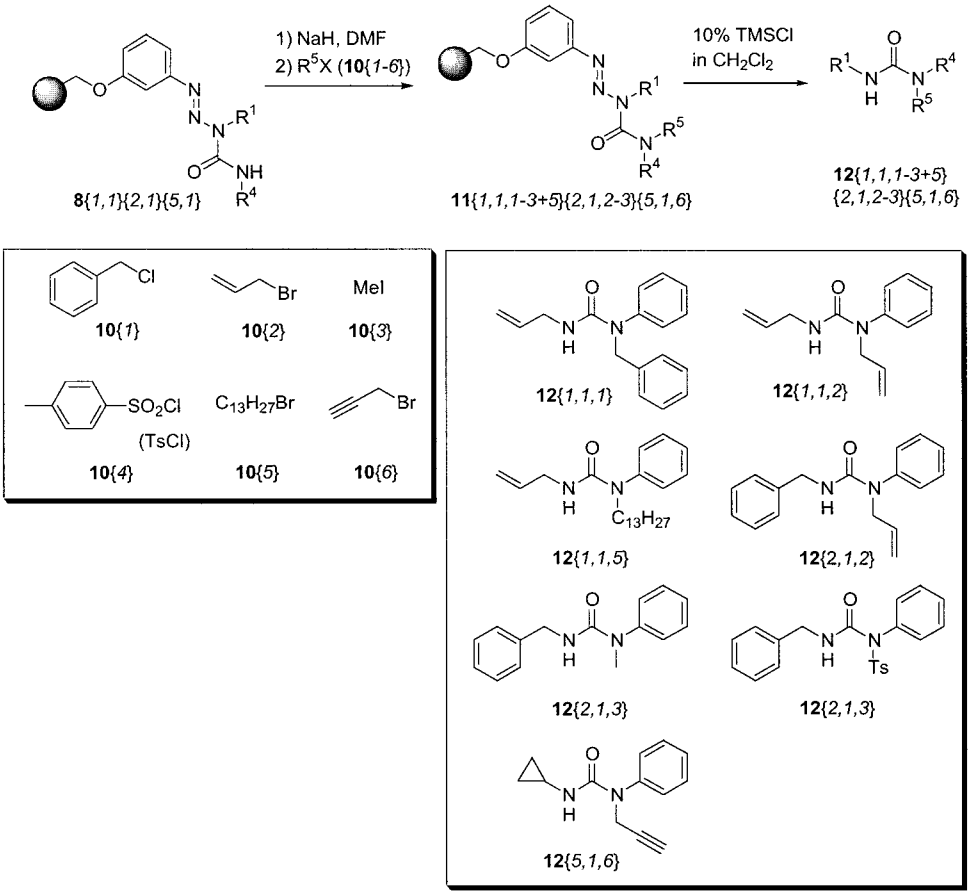
By way of variation, the synthesis of an amide library **15**{*1*−*4*′,*1*−*4*′} was accomplished (Scheme 5).

Thus, reacting the immobilized amines **7**{*1*−*4*} with carboxylic anhydrides or chlorides[19b] **13**{*1*−*4*} in the presence of triethylamine resulted in the formation of diazenyl amides **14**{*1*−*4*′,*1*−*4*}. Judgment from IR shows that the reaction was complete within several minutes; however, extended reaction times ensured quantitative reactions. Cleavage was conducted with trifluoroacetic acid in dichloromethane (5%). As seen before, the resin turned red upon treatment with the acid. The amides **15**{*1*−*4*′,*1*−*4*} obtained were isolated in moderate to good yields and excellent purities. This reaction sequence has also been successfully adopted to automated synthesis (Bohdan Neptune, see Supporting Information). The clean mode of synthesis is in contrast to observation by other groups using acyltriazenes synthesis in solution.[20]

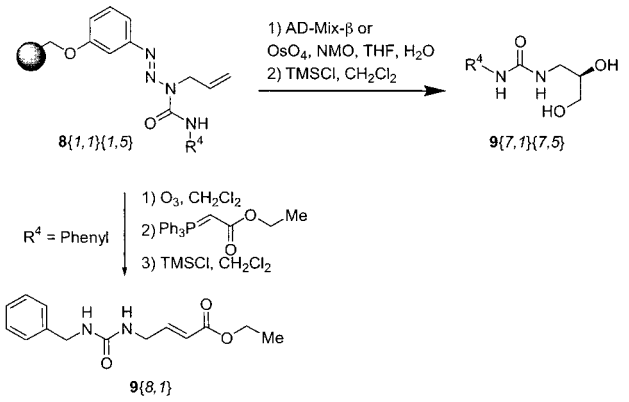
Conclusion

A new and general method for the synthesis of amides and urea derivatives using diazenyl linkers was developed. The ease of construction, high purities and yields, and mildness of detachment in comparison to the well-established benzylamine linkers are important features of this route. The

Scheme 3. Synthesis of Trisubstituted Ureas



Scheme 4. Modification of Resin-Bound Ureas (Dihydroxylation and Ozonolysis/Wittig)



possibility of using automated and parallel synthesis was incorporated.

Since this strategy utilizes backbone amide linkage and protection, the application to peptide synthesis is envisaged. Progress in this area will be reported in due course.

Experimental Section

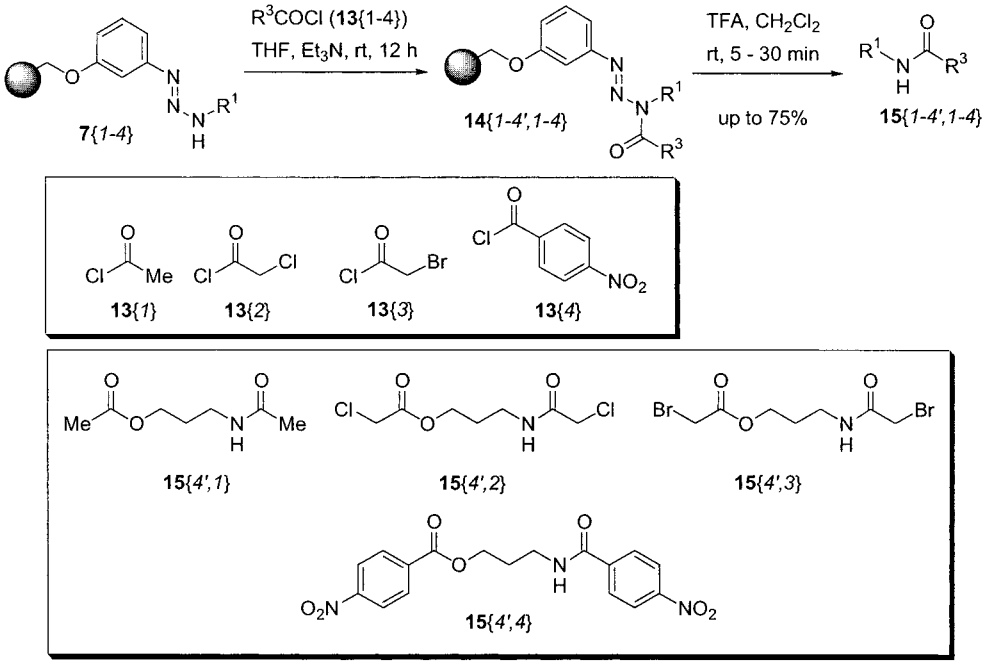
General. Automated procedures were conducted on a Bohdan synthesizer: Bohdan Automation, Inc. Automated RAM synthesizer, software: Bohdan sequencer builder software ver. 3.1 (solid-support unit was prototype), Zymark Turbovap.

Typical Experimental Procedure. 3-Aminophenyl-1-oxymethylpolystyrene (3). A dry 500 mL, three-necked round-bottom flask was fitted with a mechanical stirrer, gas-inlet, and addition funnel. The apparatus was purged with argon and charged with dry 250 mL of DMF and 2.52 g (63.0 mmol, 1.51 g, 60% in paraffin) of sodium hydride. After addition of 20.0 g (12.8 mmol, loading = 0.64 mmol g^{-1}) of Merrifield-resin (**1**), 6.9 g (63 mmol) of *m*-aminophenol (**2**) were added portion-wise (caution: H_2 evolution). After a reaction time of 20 h, the resin **3** was purified according to GP 1. IR (KBr): $\nu = 3390\ cm^{-1}$, 3200, 3080, 3060, 3020, 2910, 2840, 2640, 2600, 2310, 2340, 2380, 2260, 2110, 1940, 1870, 1800, 1710, 1670, 1620, 1590, 740, 690. $C_{125}H_{125}ON$ (1655.0): calcd C 90.63, H 7.55, N 0.85; found C 89.90, H 8.03, N 0.89.

General Procedure for the Work Up of the Resins (GP 1). The resin was washed on an inert gas frit with solvents (three times with each approximately 20 mL for each solvent per 1.00 g of resin): THF, Et_2O, and MeOH. Subsequently the resin was dried in vacuo.

Typical Procedure for the Preparation of Diazonium Salt on the Resin (GP 2). The amine resin **3** (10.0 g, 6.4 mmol) was suspended in dry THF and cooled by means of a cold bath (EtOH/dry ice) to −20 °C. After 20 min, $BF_3 \cdot Et_2O$ (6.9 mL, 7.7 g, 54 mmol) was added, and subsequently after 5 min *t*-BuONO 5.7 mL (5.0 g, 49 mmol) was added. After a reaction time of 30 min, the mixture was collected in an inert gas frit, filtered, and washed with chilled THF (4 × 15 mL/g resin). The further transformations were conducted according to GP 3.

Scheme 5. Application of the Backbone Amide Linker



General Procedure for the Preparation of Amine Resins (GP 3). The resin **4** obtained from GP 2 was swelled in THF (15 mL/g resin) and treated with the amine **5** (5 equiv). After a reaction time of 1 h, a solution of MeOH in THF (50%) was added to quench the reaction. Subsequent work up was conducted according to GP 1.

General Procedure for the Synthesis of Amide Resins (GP 4). The resin obtained from GP 2 was suspended under argon in dry THF (10 mL/g resin) and treated with triethylamine (6 equiv) and the acid chloride (4 equiv). After a reaction time of 1 h, a solution of MeOH in THF (50%) was added to quench the reaction. Subsequent work up was conducted according to GP 1.

General Procedure for the Synthesis of Urea Resins (GP 5). The resin obtained from GP 2 was suspended under argon in dry THF (10 mL/g resin) for 10 min and treated with triethylamine (1 equiv) and the isocyanate (4 equiv). After a reaction time of 1 h, a solution of MeOH in THF (50%) was added to quench the reaction. Subsequent work up was conducted according to GP 1.

General Procedure for the Manual Cleavage of the Resin (GP 6). A filtration setup, consisting of a glass pipet filled with a plug of glass wool, was filled with 100 mg of the resin and treated three times with 1.5 mL cleavage solution (amide: 5% TFA in CH_2Cl_2; urea: 10% TMSCl in CH_2Cl_2) within 5 min at room temperature whereby the resin turns red. The combined filtrates were concentrated in vacuo.

Typical Procedure for the Automated Synthesis on Neptune (GP 7). The resin (1.5 g) was suspended in 7.5 mL of CH_2Cl_2 and 7.5 mL of DMF. In each reaction vessels was distributed 2.5 mL (250 mg, 0.1575 mmol, loading 0.64 $mmolg^{-1}$) of this isopycnic resin suspension. After being filtered, the resin was washed twice with 2.0 mL of THF and finally suspended in 1 mL of THF. The reaction chambers used for the reaction with the acid chlorides were filled with 0.3 mL of triethylamine (0.36 mol L^{-1}, 2 mL, 4-fold excess). The reactants were added, and the reaction chambers were agitated in a parallel compartment overnight at room temperature. The resin was washed (two cycles with each 4.0 mL of CH_2Cl_2 and MeOH, then 4.0 mL of CH_2Cl_2), and the solvent was removed in vacuo. The cleavage was conducted with 10 mL of a 10% TMSCl solution in CH_2Cl_2 under mechanical agitation for 1 h. Subsequently, after filtration and washing of the resin with 1.0 mL of CH_2Cl_2, the combined filtrates were concentrated on a parallel evaporator. The yields were measured automatically. Except for the suspensioning and the weighing process as well as the transport of the shaker unit, all processes have been fully automated.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (BR 1750/2) and the Fonds der Chemischen Industrie (Liebig stipend to St. B.). The companies Bayer AG, Grünenthal GmbH, and CalBioChem-NovaBioChem have to be acknowledged for donations of chemicals. We thank Prof. Dr. D. Enders for the support of our work and for the opportunity using the Neptune synthesizer, M. Reichelt for technical assistance, and C. Pilot for some initial experiments described herein. We thank J. Köbberling for his efforts concerning the automation process.

Supporting Information Available. Detailed characterization (IR, elemental analysis, and, if appropriate, ^1H NMR spectra) of the resins and library compounds, copies of ^1H NMR spectra of unpurified library compounds, and detailed information about automated synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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