JOURNAL OF combinatorial CHEMISTRY

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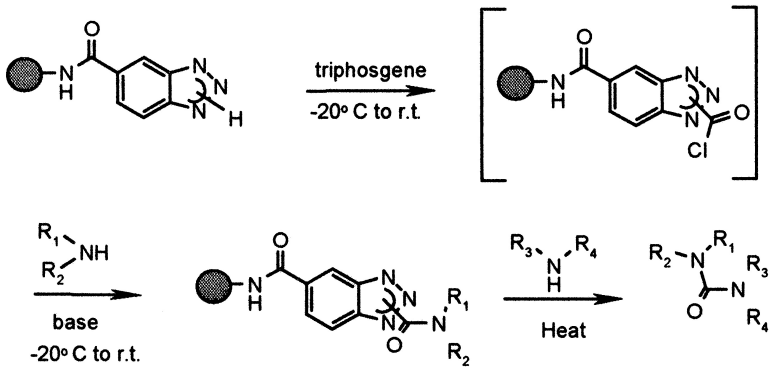
J. Comb. Chem., **2001**, 3 (4), 354-359• DOI: 10.1021/cc000108a • Publication Date (Web): 08 June 2001



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Solid-Supported Benzotriazoles. 2. Synthetic Auxiliaries and Traceless Linkers for the Combinatorial Synthesis of Unsymmetrical Ureas

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Received December 29, 2000

Resin-bound benzotriazole chemistry applied to the solid-phase synthesis of arrays of unsymmetrical aryl ureas is described here. The chemistry assessment process, the monomer rehearsal, the preparation of a discrete library by automated parallel synthesis, the parallel purification protocol employing solid-phase scavenging, and the complete analytical characterization of the library components are also presented.

Introduction

The application of combinatorial chemistry methodologies, both on solid and in solution phase, for the preparation of small druglike molecules has increased exponentially in the past decade.[1] Among the reported libraries of ureas, the chemical functionality found in many compounds endowed with biological activity,[2] arrays have been prepared by using various synthetic methodologies.[3] Linders[4] has recently reported the application of 1,1′-carbonyl-bis-benzotriazole[5] for the preparation of ureas by either solution- or solid-phase synthetic procedures. On the basis of this work and our own previous experience on supported benzotriazole chemistry[6] and considering our interest in biologically active urea derivatives, we developed a novel method for producing combinatorial libraries of unsymmetrical ureas, continuing our exploitation of resin-bound benzotriazole chemistry.

The benzotriazole nucleus acting as either an electron donor or an electron acceptor group is extensively used as a synthetic auxiliary in organic synthesis.[7] The capability of retaining these properties when supported on a polystyrene-based resin and the ability to work as a new recyclable traceless linker have recently been demonstrated.[6,8,9] The present work constitutes a further advancement in this area.

The reaction at room temperature between the chlorocarbonyl derivative of supported benzotriazole (as the most probable reactive species generated in situ) and primary or secondary anilines provokes the attack by the amine of the acyl benzotriazole moiety with formation of an intermediate supported urea (Figure 1). The nucleophilic displacement of the benzotriazole leaving group by a second amine takes place at higher temperatures and releases in solution the desired unsymmetrical urea.

Herein we disclose our results of the solid-phase synthesis of arrays of unsymmetrical aryl ureas by using supported benzotriazole derivatives, which can be easily prepared in one step from commercial sources. The chemistry assessment phase, the successful transfer from manual to automated solid-phase synthesis conditions (ACT-496 synthesizer), the library preparation by automated parallel synthesis, and the final purification of the compounds by using solid-phase scavenging reagents[10] are herein reported.

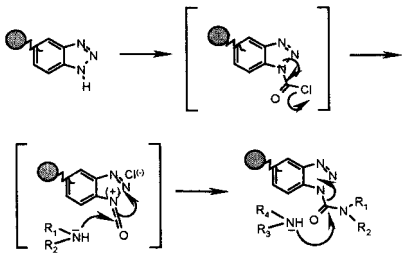
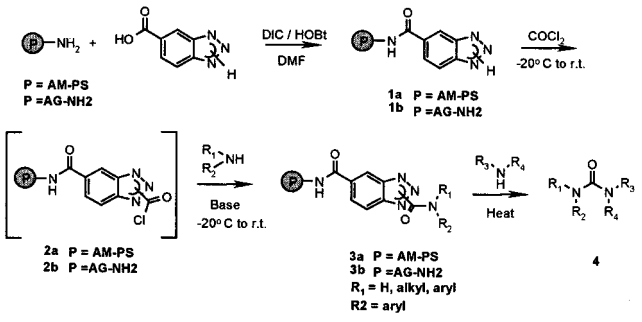


Figure 1. Preparation of unsymmetrical ureas via resin-bound benzotriazoles.

Results and Discussion

1. Preparation of Resin-Bound Benzotriazoles 1a and 1b (Scheme 1). The synthesis of resin-bound benzotriazoles has already been reported,[6,8,9] and different routes may be followed. We recently developed a new method that employed the commercially available benzotriazole-5-carboxylic acid without the need of any protection at the reactive nitrogen.

Scheme 1



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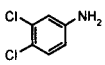
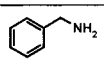
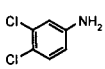
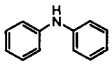
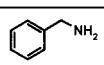
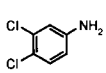
10.1021/cc000108a CCC: $20.00
Published on Web 06/08/2001

Table 1. Chemistry Assessment: Preliminary Experiments

entry	R_1R_2NH	R_3R_4NH	AM-PS		AG-NH_2	
			yields[a]	purity[b]	yields[a]	purity[b]
1			50	87	>100	58
2			76	96	>100	94
3			34	86	81	26
4			46	78	>100	35
5			69	92	55	97
6			19	85	17	42
7			33	-	>100	-
8			10	5	>100	-
9			14	-	98	-

[a] % w/w, exceeding quantitative yield justified by the experimental evidence that AG-NH_2 released impurities during the high-temperature cleavage step. [b] % a/a by HPLC/MS-DAD analysis after SCX purification.

Commercially available benzotriazole-5-carboxylic acid reacted with polystyrene-polyoxyethylene-amino (AG-NH_2) or aminomethyl-polystyrene (AM-PS) resins in the presence of diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in dimethylformamide, providing respectively the supported compounds **1a** or **1b** (Scheme 1) with complete conversion as monitored by means of the colorimetric Kaiser test.[11] The supported benzotriazole derivatives showed ^{1}H magic angle spin (MAS) NMR and FTIR spectra (see Supporting Information for details) identical to the ones prepared with the previously reported method.[6]

2. Synthesis of Unsymmetrical Ureas 4 (Scheme 1). Treatment of polymer-bound benzotriazoles **1a** or **1b** with 5 equiv of phosgene (20% solution in toluene) provided the supported carbonyl chlorides **2a,b**. Arylamines (15 equiv) were reacted in situ with **2a,b** in the presence of pyridine (15 equiv), yielding the supported urea derivatives **3a,b** that can be stored at room temperature for weeks. The reaction has been monitored by ^{1}H MAS NMR spectroscopy (see Supporting Information for details). Treatment of **3a,b** with an excess of amine (5 equiv) either at 75 °C in dioxane or at 100 °C in chlorobenzene for 18 h led to the formation of the desired urea derivatives **4**, which are released in solution. The complete release either at 75 °C in dioxane or at 100 °C in chlorobenzene was confirmed by ^{1}H MAS NMR carried out on the residual resins. In view of the transferring of the chemistry route on an automated device, a solvent with a boiling point at least 40 °C higher than the reaction temperature would have been advisable. Hence, chlorobenzene was selected as the solvent of choice for the last step of the synthesis.

The isolation of the final urea from the reaction solution was performed by trapping the excess of amine on a strong cationic exchanger (SCX) adsorbent by solid-phase extraction (SPE). This protocol provided good to moderate yields and good purity (Table 1) of the final ureas. Possible side reaction of phosgene derivatives with the amide anchorage was not noticed or at least did not affect the course of the main reaction.

In Table 1 a summary of our initial results is reported. In the formation of the supported ureas **3a,b**, a good general reactivity was observed for two out of three anilines tested (entries 1−6). *N*,*N*-Diphenylamine (entries 7−9) gave only traces of the final ureas most likely because of either the low reactivity or the steric hindrance. In the second displacement step the amines tested showed good (benzylamine, piperidine) to moderate (3,4-dichlorophenylamine) reactivity, affording the desired final unsymmetrical urea with variable yields (70−20%) and high purities (>80% a/a) after the SCX cartridge purification.

The two supports displayed different behavior. AG-NH_2 released polyoxyethylene residues most likely during the cleavage step at 100 °C in chlorobenzene as monitored by LC−MS. AM-PS resin undoubtedly performed better in terms of quality of the final urea as observed after SCX purification.

3. Definition of a Synthetic Protocol Suitable for Automation. In view of an automated library synthesis on the ACT-496 synthesizer, the assessment of robust and reproducible experimental conditions starting from the initial manual method was undertaken. The key steps toward the process optimization are described here.

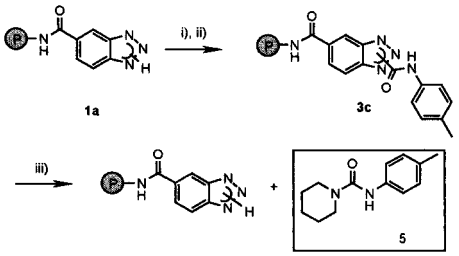
N-(4-Methylphenyl)tetrahydro-1(2H)-pyridinecarboxamide **5** was considered as the standard compound for carrying out the optimization work (Scheme 2). Different reaction parameters including phosgene derivatives, bases, solvent mixtures, reagents addition protocols, cleavage, and purification conditions were taken into account.

Table 2. Summary of Chemistry Assessment Experiments[a]

entry	phosgene source	% Y (w/w)	HPLC−MS (% a/a)[b]	i	ii	iii
1	A	76	96	−20 °C to room temp, 2 h	−20 °C to room temp, 18 h	100 °C, 18 h
2	A	35	87	−20 °C to room temp, 2 h	−20 °C to room temp, 18 h	100 °C, 18 h
3	B	19	81	−20 °C to room temp, 2 h	−20 °C to room temp, 18 h	100 °C, 18 h
4	C	23	77	−20 °C to room temp, 2 h	−20 °C to room temp, 18 h	100 °C, 18 h
5	C	80	96	room temp, 2.5 h	−10 to 4 °C, 18 h	90 °C, 18 h

[a] (i) phosgene (A), diphosgene (B), or triphosgene (C), THF. (ii) *p*-Tolylamine, pyridine, DMF. (iii) Piperidine, chlorobenzene. [b] % a/a by LC−MS (DAD) after SCX purification.

Scheme 2[a]



[a] (i) Phosgene(A), diphosgene (B), or triphosgene (C), THF. (ii) *p*-Methylphenylamine, pyridine, DMF. (iii) Piperidine, chlorobenzene, 100 °C.

3.1. Use of a Safer Phosgene Source. We started from a 20% solution of phosgene in toluene for generating the activated carbamoyl chloride derivatives **2a,b** (Scheme 1), and variable results were obtained (Table 2, entries 1 and 2). The use of a safer and more readily quantifiable phosgene source such as the trichloromethylchloroformate (diphosgene, entry 3) or, even better, the bis(trichloromethyl)carbonate (triphosgene, entries 4, 5) was desirable considering both the preclusion to perform the automated library synthesis in a dedicated "safe" laboratory and the uneven reproducibility of the phosgene-based method. For these reasons triphosgene was selected at the end of the optimization work (Table 2, entry 5), and it gave reproducible results using safe experimental protocols.

3.2. Use of Different Bases vs Pyridine. A study aimed to identify a base that could afford a soluble ammonium salt in the reaction solvent mixture was carried out. A biphasic reaction mixture (resin/homogeneous reactants solution) would have been preferred over a triphasic (resin/reactants solution/insoluble ammonium salts) mainly to facilitate the washing protocol at the end of the reaction. When *n*-tributylamine and *n*-trihexylamine were used, soluble salts were indeed obtained, but lower reaction yields were calculated compared with the original method using pyridine as base. Therefore, the use of soluble ammonium salts was not pursued further.

3.3. Reaction Solvents. The use of solvent different from DMF was tried to avoid the known Vilsmeier reactant that may originate from DMF in the presence of acyl chloride-like reagents that could affect the reaction yields. The use of THF and DCM in combination with bases affording soluble ammonium salts in these solvents was tried. No results were obtained in terms of isolated yields.

The final selected conditions after the optimization study are reported in Table 2 (entry 5).

3.4. Purification of the Final Urea. A scavenger resin added to the chlorobenzene solution of the crude urea in order to remove the excess piperidine (second amine monomer) at the end of the synthetic sequence would have simplified the whole process if compared to a SPE cartridge in view of transferring this chemistry to an automated device. The purification of the crude urea with a scavenger resin (MP-TsOH, Argonaut Technologies) was therefore attempted; the quality of the final compounds was comparable with that from the SPE cartridge purification (Table 3, entries 1, 2), and the experimental protocol was reproducible (Table 3, entries 2, 3). Therefore, the use of scavenger resin for the purification of the final ureas was adopted.

Table 3. Optimization of Crude Urea Purification Procedure

entry	purification method	yield (% w/w)	purity (% a/a)[a]	% yield (corrected)
1	SCX	57	94	54
2	MP-TsOH	64	99	63
3	MP-TsOH	53	88	47

[a] % a/a by LC−MS (DAD) after purification.

3.5. Validation of the ACT-496 Synthesizer. The optimized conditions obtained during the manual assessment, namely,

(a) in situ formation at room temperature of the chlorocarbonylbenzotriazole derivative by addition to the resin of a THF solution of triphosgene (7 equiv) and mixing at room temperature for 2 h,

(b) cooling at −15 °C and addition of a DMF/pyridine solution of *p*-methylphenylamine (first monomer, 20 equiv), followed by mixing at 0 °C for 18 h and workup at room temperature by a cycle of washings with DMF and DCM, and

(c) addition of a chlorobenzene solution of piperidine (second monomer, 5 equiv) and heating at 90 °C for 18 h followed by workup at room temperature by a cycle of washings with DCM and resin-scavenging purification,

were run on the ACT-496 synthesizer to prepare first the standard urea **5**.

If proved successful, the same automated method would have been used for the monomer rehearsal and the library production. However, a series of problems involving the drain of solvents through the steps and leakage from the bottom frits during the cleavage step were noticed using the synthesizer at high temperatures in its conventional setup (reaction block combined with the waste collection block).

To circumvent these inconveniences, we decided to carry out the high-temperature cleavage step, assembling the ACT-496 reaction block with the cleavage block out of the synthesizer and then heating them in an oven. This change combined with the reduction of the cleavage time (2 vs 18

Table 4. Optimization of Cleavage Time

entry	reaction time (h)	yield (% w/w)	purity (% a/a)	% yield (corrected)
1	18	57	81	46
2	6	56	93	52
3	4	55	93	51
4	2	57	94	54

h at 90 °C; see Table 4 for the optimization study) solved the problem of leakage/drain through the frits. The only drawback of such a modification was that the final reaction mixtures had to be filtered manually rather than automatically.

4. Monomer Rehearsal and Library Preparation on the ACT-496. Arylamines (first monomer set) and generic amines (second monomer set) were selected from ACD[13] by similarity to the fragments contained in ureidic hits from HTS campaigns on our biological target. The lists were profiled with EasyFilter (an in-house-developed computational chemistry software), discarding diamines, dianilines, and other problematic products. With the resulting monomers a virtual library was created that was in turn profiled on the basis of physicochemical cutoff filters (molecular weight, ClogP, and number of H bond donors and acceptors, of rotatable bonds, of aromatic rings, and of charges). A list of 13 representatives for the first monomer set and 21 for the second monomer set resulted from this process and were rehearsed. The structures of some representative selected monomers from these lists are reported in Figure 2.

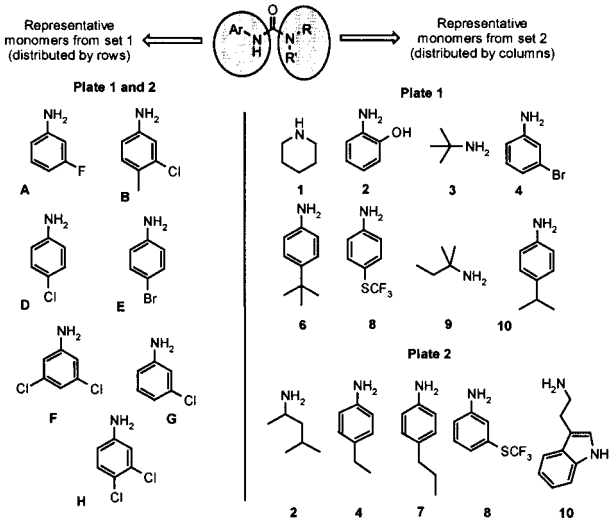


Figure 2.

p-Methylphenylamine was used as the first monomer to rehearse the second set, and piperidine was used as the second monomer to rehearse the first set. The crude products were analyzed by HPLC−MS, which confirmed 32 out of 34 final ureas. A total of 23 final ureas showed a purity profile greater than 80% a/a by LC−MS/diode array detector (DAD) analysis (Table 5) and the corrected overall yields ranged from 40 to 90% w/w.

On the basis of the rehearsal results and according to the availability in our laboratory, 8 monomers from the first set and 20 from the second one were selected and used to prepare the scheduled library (8 × 20 compounds). The library QC

Table 5. Monomer Rehearsal: QC Summary

a/a %	no. of compds
<10	1
10−50	1
50−80	5
>80	23

Table 6. Final Library: QC Summary

% a/a	no. of compds	% of compds
<50%	7	4
50−70%	11	7
70−80%	20	13
80−90%	60	38
>90%	58	36

results are summarized in Table 6. A total of 156 out of 160 compounds were confirmed by flow injection MS analysis, and 138 compounds (74% of the library components) had a purity profile greater than 80% a/a. Details of the QC (LC-MS/DAD spectra) of 20 representative library members are in Supporting Information.

Conclusions

In summary, we have developed an efficient method for the automated synthesis of unsymmetrical aryl ureas. This work represents a further successful application of resin-bound benzotriazoles as supported synthetic auxiliaries and as novel traceless linkers. During chemistry validation, all the reaction parameters were evaluated in order to assess a robust and reproducible process amenable to parallel automated synthesis. The application of solid-supported quenching reagent technology for the final library purification was also successfully applied, and a high-quality library of unsymmetrical aryl ureas (8 × 20 discretes) was prepared, applying resin-bound benzotriazole chemistry on the ACT-496 synthesizer.

Experimental Section

1. Materials. All the individual solid-phase reactions were carried out in glass vials (Wheaton), and the resin washings were carried out on Extract Clean Tube syringes (Alltech or IST). Reagents were purchased from Aldrich, Sigma, Fluka, Acros, or Janssen and used without further purification. The SCX cartridges were purchased from Varian, and the microtiter plate Bioplate SPE-SCX was purchased from Whatman. Both were preconditioned with methanol before use. Polystyrene resins were purchased from Polymer Laboratories, while polystyrene-polyoxyethylene resin was purchased from Argonaut Technologies, Inc.

2. General Methods. All the solid-phase reactions at low temperature were carried out in glass vials without stirring. The reaction mixtures at room temperature were stirred on an orbital shaker unless otherwise stated, and those that required heating were performed in a heating block (PLS 4 × 6 organic synthesizer from Advanced ChemTech). The automated parallel synthesis steps from low temperature to room temperature were carried out on the ACT-496 synthesizer from Advanced ChemTech, while the high-temperature steps were carried out in an oven using the ACT-496 reaction block clamped with the cleavage block. Concentration of the

cleavage solutions after purification protocols was performed on a Speed Vac Plus SC210A (Savant).

Infrared spectra were recorded on a FTIR spectrophotometer in film phase, while for resins they were recorded on single beads with the ATR microscope technique. They are reported in wavenumber (cm^{-1}). All the NMR spectra were acquired at 25 °C, referenced to the residual solvent line, and reported in ppm. ^1H NMR spectra were obtained in $CDCl_3$, unless otherwise stated, at 500 MHz, while ^1H MAS NMR spectra were obtained in CD_2Cl_2 at 400 MHz using Nano-Probe.

HPLC−MS data were obtained using the HP1100 liquid chromatography system equipped with diode array detector (Hewlett-Packard, Germany) coupled to the mass spectrometer Platform II (Micromass Ltd., UK). The autosampler was a Gilson 233XL (Gilson, France). All samples were analyzed by flow injections mass spectrometry and by liquid chromatography mass spectrometry (HPLC−MS), both performed with the same equipment. Flow injections analyses were obtained, infusing 20 μL of each sample into the mass spectrometer by autosampler. The mass spectrometer worked both in positive and in negative electrospray ionization mode (ES^+, ES^-). The mobile phase was water/acetonitrile, 50/50, with 0.1% TFA, and the flow rate was 25 μL/min. The mass range 80−800 amu was scanned in compressed centroid acquisition mode with a 5.0 s scan time. The chromatographic separations were obtained using a Supelcosil ABZ+ Plus (Supelco), 3.3 cm × 0.46 cm, 3 μm. The mobile phase was water (A) and acetonitrile (B), varying from 20% to 90% of B in 8 min and then at 90% of B in 5 min. The reequilibration time between two injections was 3 min. The flow rate was 0.8 mL/min. All samples were injected using a Gilson XL233 autosampler. The injection volume was 20 μL. Diode array chromatograms were collected using a large bandwidth (from 220 to 350 nm).

The mass spectrometer was set in positive and negative electrospray ionization modes (ES^+, ES^-). The mass range 170−800 amu was scanned in compressed centroid acquisition mode with 2.0 s scan time for each ionization mode. All acquired data were processed using the MassLynx software (version 3.2) with the OpenLynx Diversity tools (Micromass Ltd., U.K.).

3. Supporting Benzotriazole-5-carboxylic Acid. 3.1. General Procedure for Preparation of Benzotriazole-5-carboxylic Acid Resin-Bound Amides 1a,b. Benzotriazole-5-carboxylic acid (7.42 g, 45.5 mmol) and HOBt (6.15 g, 45.5 mmol) were suspended in DMF (50−80 mL). DIC was added (3.56 mL, 22.75 mmol), and the mixture was stirred at room temperature for 1 h. AM-PS (aminomethylpolystyrene from Polymer Laboratories, 75−150 μm, 1% cross-linked, batch AMS032, loading 0.91 mmol/g, 5.00 g, 4.55 mmol) or AG-NH_2 (Argogel amino from Argonaut Technologies, 120−230 μm, batch 00043, loading 0.41 mmol/g, 11.1 g, 4.55 mmol) was added, and the mixture was shaken at room temperature for 18 h. The mixture was then filtered and rinsed with DMF, DCM, diethyl ether, and DCM for three repeating cycles, then filtered and rinsed with diethyl ether and DCM for four repeating cycles, and then dried under vacuum.

3.2. Benzotriazole-5-carboxilyc Acid Polystyrene-Bound Amide 1a. After workup, the resulting light-brown resin **1a** revealed no blue beads at the colorimetric Kaiser test. It was characterized by FTIR (1647 cm^{-1}, C═O), ^1H MAS NMR (CD_2Cl_2), δ 7.87 (bs), and elemental analysis (N, theoretical 4.45%, found 4.42%, yield >99%).

3.3. Benzotriazole-5-carboxilyc Acid Argogel-Bound Amide 1b. After workup, the resulting light-brown resin **1b** revealed no blue beads at the colorimetric Kaiser test. It was characterized by FTIR (1657 cm^{-1}, C═O); ^1H MAS NMR (CD_2Cl_2) δ 8.41 (bs, 1H arom), 7.91 (bm, 1H arom), 7.53 (bs, 1H arom)); and elemental analysis (N, theoretical 2.17%, found 2.15%, yield >99%).

4. General Optimized Manual Procedure for the Synthesis of Unsymmetrical Aryl Ureas. 4.1. Preparation of Resin-Bound 1(2)-(4-Toluidinocarbonyl)benzotriazole-5-carboxylic Acid 3c. Polystyrene-bound benzotriazole **1a** (100 mg, 0.80 mmol/g, 0.08 mmol) was swollen with dry THF (1.0 mL) under nitrogen atmosphere. Triphosgene (40 mg, 0.133 mmol, 5 equiv of $COCl_2$) was rapidly added, and the mixture was shaken for 2 h. After the mixture was cooled at −10 °C, pyridine (100 μL, 1.24 mmol, 15.5 equiv) was added; precipitation of salts was immediately noticed. A solution of *p*-methylphenylamine (129 mg, 1.20 mmol, 15 equiv) in dry DMF (0.70 mL) was slowly added to the reaction mixture, which turned orange-red. After being shaken vigorously for a few minutes, the mixture was allowed to reach +4 °C and to react for 18 h, and then the mixture was filtered. The resin was rinsed with DMF and DCM for four repeating cycles, then rinsed with diethyl ether and DCM for four repeating cycles, and then dried under vacuum. ^1H MAS NMR (CD_2Cl_2): δ 9.15−7.49 (m, 3H), 2.27 (m, 3H)).

4.2. Preparation of *N*-(4-Methylphenyl)tetrahydro-1(2H)-pyridinecarboxamide 5. Piperidine (21 μL, 0.216 mmol, 5 equiv) was added to **3c** (60 mg, 0.043 mmol), which was previously swollen with dry chlorobenzene (0.65 mL). The mixture was shaken and heated at 90 °C by means of a PLS-4X6 organic synthesizer (Advanced ChemTech) for 18 h. After cooling to room temperature, the mixture was taken up with methanol (0.7 mL), poured into an SPE cartridge (1.0 g of SCX, 0.75 mequiv/g), and eluted with DCM (1.0 mL) and MeOH (3.0 mL). After concentration at reduced pressure, *N*-(4-methylphenyl)tetrahydro-1(2H)-pyridinecarboxamide **5** (7.5 mg, 80% w/w yield) was recovered as a white solid. ^1H NMR: δ 7.23 (d, 2H), 7.08 (d, 2H), 6.25 (bs, 1H), 3.43 (m, 4H), 2.29 (s, 3H), 1.62 (m, 6H). FTIR (film): 3299 cm^{-1}, N−H, 1637 cm^{-1}, C═O. MS: *m*/*z* 219 $[M + H]^+$. LC−MS (DAD): 96% a/a purity.

5. General Procedure for Automated Synthesis. 5.1. First Step. A suspension of benzotriazole-5-carboxilyc acid polystyrene-bound amide **1a** in a 1/1 mixture DMF/DCM (12 mL/g of resin) was dispensed in the ACT-496 synthesizer reaction block (25 mg of resin/well, 0.8 mmol/g, 0.02 mmol). The resin was rinsed with DCM and drained, preswollen with dry THF, and drained under nitrogen pressure, and then a total of 250 μL of dry THF was dispensed. A 0.47 M triphosgene solution in dry THF (1.42 N, 100 μL, 0.047

mmol, 7 equiv) was added in each well. The reaction block was then shaken for 2 h at room temperature.

5.2. Second Step. A total of 200 μL of a solution of each amine of the first monomer set (2.08 M, 0.416 mmol, 20.8 equiv) and pyridine (2.08 M, 0.416 mmol, 20.8 equiv) in dry DMF were added to the resin suspensions at −20 °C. After the mixtures reached 0 °C, the reaction block was shaken overnight. The resins were rinsed with DMF, DCM, and diethyl ether and were drained under nitrogen pressure.

5.3. Third Step. A 0.34 M solution of the monomers of the second set (for poorly soluble amines, a few drops of DMF were added) in chlorobenzene was added (290 μL, 0.10 mmol, 5 equiv) to resin **3a**, preswollen with chlorobenzene, and drained under nitrogen. The reactions within the clamped reaction/cleavage blocks were performed at 90 °C for 2 h in an oven without stirring. After the blocks reached room temperature, the resins were filtered and rinsed with DCM (6 × 0.5 mL).

5.4. Library Purification. The cleavage solution was purified from excess amine, adding a scavenger resin (MP-TsOH, Argonaut Technologies Inc., 160 mg, 1.5 mmol/g, 0.24 mmol, 2.4 equiv) to the filtrate in the vials of the ACT-496 synthesizer cleavage block and shaking for 1 h. The mixtures were filtered manually and rinsed with DCM (4 × 0.4 mL), and the solution was concentrated in a vacuum to obtain the desired ureas in variable yields and high purity.

Acknowledgment. The authors thank Dr. Aldo Feriani and Dr. Giovanna Tedesco for the computational chemistry work, Dr. Elisabetta de Magistris and Dr. Andrea Missio for helpful discussions, and finally Dr. Alessio Zaramella, Dr. Nadia Conti, and Dr. Carla Marchioro for the analytical support.

Supporting Information Available. ^{1}H MAS NMR of **1a 1b**, and **3a**, ^{1}H NMR of **5**, FTIR spectra of **1a, 1b,** and **5**, LC−MS/DAD spectra of 20 representative compounds from the library QC. This material is available free of charge via the Internet at http://pubs.acs.org.

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