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An efficient two-step synthesis of mono-, di- and triureas from resin-bound amides

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Abstract

An efficient method for the solid-phase synthesis of mono-, di- and triureas from resin-bound monoamines, diamines and triamines is described. The exhaustive reduction of solid support-bound amides generated the requisite amines, which, following treatment with isocyanates and cleavage, provided the corresponding ureas in high purity and good yields.

Keywords: combinatorial chemistry; solid-phase synthesis; peptidomimetics; urea; diurea; triurea.

Solid-phase parallel synthesis is used worldwide to generate libraries of small organic compounds for the acceleration of the drug discovery process.[1,2] The urea functionality has attracted considerable attention due to its stability compared to the amide bond.[3] Ureas are found in many biological compounds.[4] Included in such compounds are ureas that effect acid gastric secretion and the healing of chronic gastric ulcers induced in rats,[5] inhibitors of acyl-Co:cholesterol *O*-acyl transferase (ACAT),[6] and antioxidant derivatives.[7] Ureas are typically prepared in solution or solid-phase by treatment of isocyanates with amines.[8] We describe here an efficient method for the generation of mono-, di- and triureas from resin-bound amides.

Starting from *p*-methylbenzhydrylamine (MBHA) resin, and following neutralization and acylation of the amine, the resin-bound amide **1** was reduced with borane–THF. The resulting secondary amine **2** is treated with an excess of isocyanate to afford, following HF cleavage, the desired *N*,*N*′-ureas **3** in high purity (Scheme 1). The reduction of amide bonds on the solid support and the use of the resulting amine for the generation of peptidomimetic acyclic and heterocyclic compounds has been previously reported by our laboratory.[9] The feasibility of the reaction was determined by first preparing a small number of individual compounds using the 'tea-bag' method of parallel synthesis.[1b] Twenty-three individual *N*,*N*′-ureas were prepared using nine different carboxylic acids and three different isocyanates. The expected compounds were obtained in excellent purity

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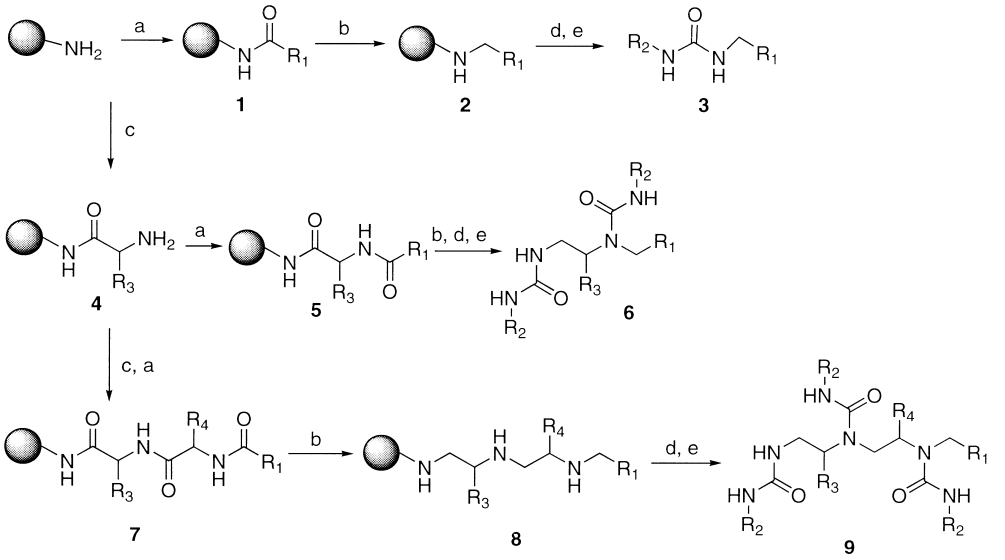
(>95%) and good yields[10] (Table 1). Starting from the same solid support, and following amino acid coupling and acylation, compound **5** was reduced with borane–THF; the resin-bound diamine was then treated with excess of isocyanate to afford, following HF cleavage, the expected diureas **6** in high purity (>95%) (Scheme 1). Four individual diureas were first prepared as controls. The desired compounds were obtained in excellent purity and yields[10] (Table 2). Similarly, treatment of a reduced resin-bound acylated dipeptide **8** with isocyanate (Scheme 1) afforded the corresponding triureas **9** following HF cleavage. Seven individual compounds were synthesized in high purity and good yields[10] (Table 3). In Fig. 1, we show the LC–MS of the triurea **9c**, which is representative of the purities obtained in each case.

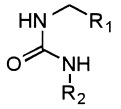


Scheme 1. (a) R_1COOH, DIPCDI, HOBt; (b) BH_3–THF; (c) Xaa–OH, DIPCDI, HOBt; (d) R_2NCO, DMF; (e) HF/anisole

Following the strategy described in Scheme 1, 135 different triureas **9**, in which the individual building blocks were varied while fixing the remaining two positions, were synthesized (48 different amino acids at R_1, 48 different amino acids at R_2 and 39 different carboxylic acids at R_3). Modifications occurring to the amino acid side chains during the reduction steps have been carefully studied. These individual compounds will serve as controls for the synthesis of a large individual or mixture-based triurea library. The library synthesis and screening results for the identification of highly active triureas will be reported elsewhere.

The typical procedure for the synthesis of urea derivatives is as follows: Solid-phase syntheses were carried out using the 'tea-bag' method in which the resin is contained within sealed polypropylene mesh packets.[1b] The completeness of amino acid coupling and *N*-acylation were verified using the ninhydrin test.[11] 100 mg *p*-MBHA resin (0.1 meq/g, 100–200 mesh) was contained within a sealed polypropylene mesh packet. Reactions were carried out in 10 ml polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIPEA) in dichloromethane (DCM), the resin was washed with DCM, and the free amine was either coupled to an amino acid or acylated with a carboxylic acid.

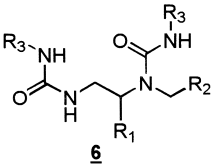
Table 1
Examples of monoureas synthesized. The products were run on a Vydac column, gradient 5 to 95% TFA in CAN in 7 min. The purity was estimated on analytical traces at 214 nm



3

	R_1	R_2	MW (expected	MW (found)	HPLC purity
3a	3-(F)Bn	3-(NO_2)-4(F)Ph	321.2	322.1 (M+H)+	> 95%
3b	4-(CH_3)Bn	3-(NO_2)-4(F)Ph	317.3	318.1 (M+H)+	> 95%
3c	3,5-$(CF_3)_2$Bn	3-(NO_2)-4(F)Ph	439.2	440.0 (M+H)+	> 95%
3d	CH_2CH_2Ph	3-(NO_2)-4(F)Ph	317.3	318.1 (M+H)+	> 95%
3e	CH_2-CH_2-CH_3	3-(NO_2)-4(F)Ph	255.2	256.1 (M+H)+	> 95%
3f	cyclohexyl	3-(NO_2)-4(F)Ph	295.3	296.2 (M+H)+	> 95%
3g	CH_3	3-(NO_2)-4(F)Ph	227.1	228.1 (M+H)+	> 95%
3h	cyclopentyl	3-(NO_2)-4(F)Ph	281.1	282.1 (M+H)+	> 95%
3i	$CH(CH_2CH_3)_2$	3-(NO_2)-4(F)Ph	283.3	284.1 (M+H)+	> 95%
3j	3-(F)Bn	Ph	258.2	259.1 (M+H)+	> 95%
3k	4-(CH_3)Bn	Ph	254.3	255.1 (M+H)+	> 95%
3l	3,5-$(CF_3)_2$BnI	Ph	376.3	377.1 (M+H)+	> 95%
3m	CH_2CH_2Ph	Ph	254.3	255.2 (M+H)+	> 95%
3n	CH_2-CH_2-CH_3	Ph	192.2	193.1 (M+H)+	> 95%
3o	cyclohexyl	Ph	232.3	233.1 (M+H)+	> 95%
3p	CH_3	Ph	164.2	165.1 (M+H)+	> 95%
3q	cyclopentyl	Ph	219.2	219.2 (M+H)+	> 95%
3r	$CH(CH_2CH_3)_2$	Ph	221.2	221.2 (M+H)+	> 95%
3s	3-(F)Bn	n-hexyl	266.3	267.3 (M+H)+	> 95%
3t	4-(CH_3)Bn	n-hexyl	262.3	263.2 (M+H)+	> 95%
3u	3,5-$(CF_3)_2$Bn	n-hexyl	384.3	385.2 (M+H)+	> 95%
3v	CH_2CH_2Ph	n-hexyl	262.3	263.1(M+H)+	> 95%
3w	$CH(CH_2CH_3)_2$	n-hexyl	228.3	229.2(M+H)+	> 95%

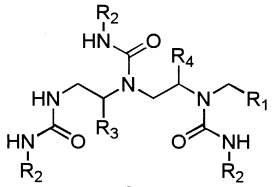
Table 2
Examples of diureas synthesized. The products were run on a Vydac column, gradient 5 to 95% TFA in CAN in 7 min. The purity was estimated on analytical traces at 214 nm



6

	R_1	R_2	R_3	MW (expected)	MW (found)	HPLC purity
6a	Bn	4-(Br)Ph	Ph	571.5	573.0(M+H)+	> 95%
6b	$CH(CH_3)_2$	Bn	Ph	444.5	445.2(M+H)+	> 95%
6c	Bn	4-(NO_2)Ph	Ph	537.6	538.2(M+H)+	> 95%
6d	$CH(CH_3)_2$	4-(NO_2)Ph	Ph	489.5	490.4(M+H)+	> 95%

Table 3
Examples of triureas synthesized (R_2 = Ph). The products were run on a Vydac column, gradient 40 to 95% TFA in CAN in 7 min. The purity was estimated on analytical traces at 214 nm



9

	R_3	R_4	R_1	MW (found)	MW (found)	HPLC purity
9a	Bn	Bn	cycloheptyl	750.9	751.8 (MH+)	> 95%
9b	$CH_2CH_2CH_3$	Bn	CH_2CH_2Ph	696.8	697.6 (MH+)	> 95%
9c	Bn	Bn	$CH_2CH_2(4\text{-}CH_3)Ph$	758.9	759.3 (MH+)	> 95%
9d	CH_3	Bn	CH_2CH_2Ph	668.8	669.6 (MH+)	> 95%
9e	$CH(CH_3)CH_2CH_3$	Bn	CH_2CH_2Ph	710.9	711.7 (MH+)	> 95%
9f	Bn	H	CH_2CH_2Ph	654.8	655.6 (MH+)	> 95%
9j	$CH(CH_3)_2$	Bn	CH_2CH_2Ph	696.8	697.5 (MH+)	> 95%

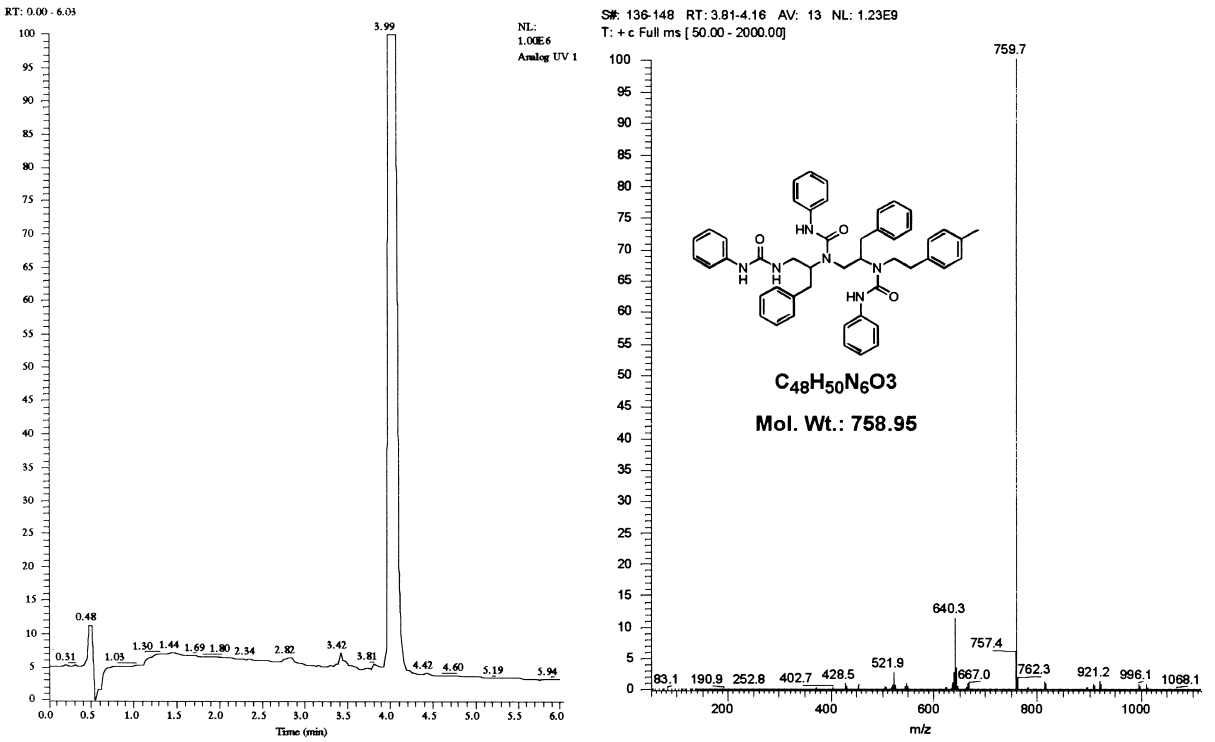


Figure 1. LC–MS of triurea **9c**

Amino acid coupling: The amino acid (Boc-Xaa-OH, 6 equiv.) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 6 equiv.) and diisopropylcarbodiimide (DIPCDI, 6 equiv.) in anhydrous DMF for 60 min. Following removal of the Boc group with 50% trifluoroacetic acid in DCM (2×30 min) and washing with DCM (6×) and 5% DIPEA in DCM (2×), the free amine is then coupled to a second amino acid in the same conditions or acylated with a carboxylic acid.

Acylation: The free amine was *N*-acylated with a carboxylic acid (10 equiv.) in the presence of DIPCDI (10 equiv.) and HOBt (10 equiv.) overnight in anhydrous DMF.

Exhaustive reduction of the amide groups: The reduction was performed in 50 ml kimax tubes under nitrogen. The resin packet and boric acid (15-fold excess over each amide bond) were added to each tube. Trimethyl borate (15-fold excess over each amide bond) was added, followed by 1 M BH_3–THF (40-fold excess over each amide bond). The tubes were heated at 65°C for 72 h, followed by quenching with MeOH at room temperature. The resin was then washed with methanol (4×) and the borane disproportionated by treatment with neat piperidine at 65°C overnight. The resin was then washed with methanol (2×) and DMF (6×) and dried. The completeness of the reaction was verified by cleavage and analysis following reduction.

Urea formation: The resin-bound amines were treated with a seven-fold excess of isocyanate over each amine (0.1 M) in anhydrous DMF overnight. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0°C for 90 min, the desired product was extracted with acetonitrile:water (50:50) and lyophilized.[12]

The described efficient two-step transformation of mono-, di- and triamides to the corresponding mono-, di- and triureas is one of a series of transformations of peptides and peptidomimetics to classic small molecules and heterocyclic compounds. As in earlier studies, the described chemistries will be used to generate individual compounds and mixture-based combinatorial libraries.[13]

Acknowledgements

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