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Solid and Solution Phase Combinatorial Synthesis of Ureas

José W. Nieuwenhuijzen[◆], Paolo G. M. Conti[❖], Harry C. J. Ottenheijm[❖], Joannes T. M. Linders[❖*]

[❖]Scientific Development Group, NV Organon, PO Box 20, 5340 BH Oss, The Netherlands
[◆]Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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Abstract: An efficient parallel synthesis of ureas based on amino acids is described, both in solution and on solid phase. 1,1'-Carbonylbisbenzotriazole **2** is used as the coupling reagent. The ureas **5** and **10** were obtained in high yield (80-100%) and purity (71-97%).

The use of high-throughput screening in the initial stages of drug discovery has created a demand for large numbers of compounds. The power of combinatorial chemistry techniques for the efficient synthesis of small organic compounds, both on solid phase and in solution, has been demonstrated extensively in recent years.[1]

It has been shown that the activity of a large peptide can be mimicked by a small fragment such as a dipeptide.[2] For example, the decapeptide neurokinin B could be reduced to the dipeptide Boc-Phe-Phe-NH_2. This dipeptide has been the starting point for the development of highly potent antagonists for the tachykinin NK_3 receptor.[3]

We were interested in libraries of unsymmetrical ureas derived from amino acids. These compounds can be viewed as mimics of dipeptides,[4] that lack the metabolically labile amide linkage. Recently, Katritzky *et al.*[5] reported an attractive method for the preparation of unsymmetrical ureas in solution, employing 1,1'-carbonylbisbenzotriazole **2** as the coupling reagent. The authors used this method to synthesize ureas derived from simple amines.

* e-mail: j.linders@organon.oss.akzonobel.nl

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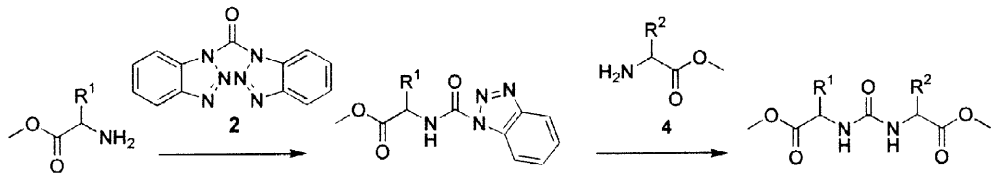
We therefore wondered whether **2** also could be used to prepare our target molecules in a combinatorial fashion. Before we applied **2** in a solid phase approach,[6] we first studied the urea synthesis in solution (Scheme 1).[7]

Solution phase synthesis

Katritzky *et al.* prepared **2** in 85% yield by reaction of benzotriazole with phosgene.[5] We prepared **2** from benzotriazole and the easier to handle triphosgene in THF in the presence of DIPEA, albeit in a somewhat lower yield. The addition of the base was necessary to prevent HCl-mediated cleavage of THF.

The amino acid methyl ester **1** was allowed to react with **2** to form the intermediate benzotriazole urea **3**. As observed by Katritzky, these benzotriazole derivatives are formed selectively, with little or no formation of the symmetrical ureas. Indeed, in pilot experiments we observed that reaction with a second amino acid methyl ester **4** gave the unsymmetrical urea **5** (Scheme 1). Only in the cases where Ser(tBu) or Thr(tBu) were used in the first step, we observed the formation of symmetrical ureas.



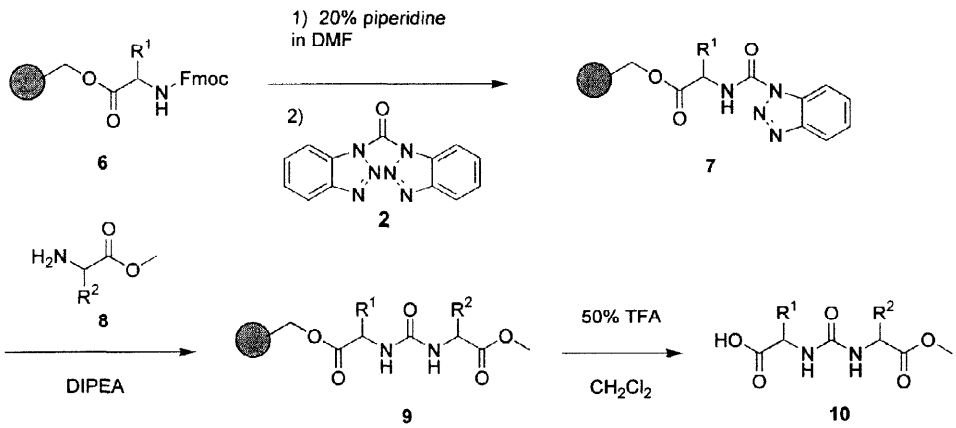
Scheme 1

We applied this method to a semi-automated synthesis which was optimized for the preparation of urea **5a**.[8] The main obstacle we encountered in the work-up was the removal of the benzotriazole formed in the coupling steps. We used a borax buffer (pH 9.2) to extract the benzotriazole (pK_a 8.6). At this pH the methyl esters **5** are not hydrolysed. We performed the work-up procedure in syringes equipped with a PFTE frit. This set-up facilitates the separation of the CH_2Cl_2 layer from the aqueous layer, as the latter remains on top of the filter. The ureas **5** could be isolated in good yield (80-100%) and purity by concentrating the filtrate (Table 1). The products were characterised by MS and NMR.[9] However, the extraction procedure was considered still too tedious for the preparation of large libraries of ureas. Therefore we decided to develop a solid phase method using the same approach.

Solid phase synthesis

An Fmoc-protected amino acid was immobilized on a hydroxymethylene resin to yield **6**, using standard peptide coupling conditions[10,11] (Scheme 2).

Subsequently, the Fmoc protecting group was removed and the free amino acid resin was allowed to react with **2** overnight at RT to give the benzotriazole urea **7**.[11] The second amino acid **8** was allowed to react with **7** yielding the resin-bound urea **9**.[11] Treatment with TFA gave the ureas **10** in high yield (70-100%) and purity (Table 1). The incorporation of secondary amines such as proline (**10g**) required more forcing conditions; for the conversion of **7** into **9** the reaction temperature had to be raised to 60 °C.



Scheme 2

Some representative examples of the ureas **5** and **10**, synthesized by either the solution or the solid phase method, are shown in Table 1. The solid phase synthesis has been used successfully for the preparation of libraries (>100 compounds) of ureas.

Table 1 MS identification and HPLC purities of ureas **5** and **10**

Compound	1st amino acid	2nd amino acid	MS	purity (%)
5a	Phe	Ser(tBu)	380	95[a]
10a	Val	Ser(tBu)	262[b]	74
10b	Met	Leu	320	80
10c	Gln	Arg(NO_2)	405[b]	97
10d	Gly	Trp	319	71
10e	Trp	His(Trt)	399[b]	79
10f	His(Trt)	Glu(OMe)	356[d]	91
10g	Phe	Pro[e]	320	75
10h	Phe	α-HomoPro[e]	334	78

a) NMR purity; b) Protecting group lost upon resin cleavage with TFA; c) Protecting group remains intact upon resin cleavage; d) Trityl group lost upon resin cleavage; e) Resin shaken at 60°C overnight upon addition of secondary amino acid methyl ester **8**.

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8 **Synthesis of urea 5 in solution**: A solution of the amino acid methyl ester hydrochloride **1** (0.2 mmol; 1 eq.) and DIPEA (1.1 eq.) in DMF (1.0 mL) was added to 1,1'-carbonylbisbenzotriazole **2** (1 eq.) in CH_2Cl_2 (1.0 mL) and the resulting mixture was shaken overnight at RT. Then, a solution of the second amino acid methyl ester **4** (0.2 mmol) and DIPEA (1.1 eq.) in DMF (1.0 mL) was added and the resulting mixture was shaken overnight at RT. The samples were concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2, and transferred to syringes equipped with a PFTE frit (Isolute), mounted on a VacMaster. The organic layer was washed with 2x2.0 mL borax buffer (0.1 M; pH 9.2) and 2x2.0 mL 0.2 M HCl. The organic layer was collected in pre-weighed tubes and concentrated to yield the urea **5**.

9 **N-(1-methoxycarbonyl-2-phenylethyl)-N'-(1-methoxycarbonyl-2-*tert*-butoxyethyl)urea (5a):** ^{1}H-NMR: δ 1.1 (s, 9H), 3.1 (d, 2H), 3.65 (dd, 2H), 3.7 (s, 3H). 3.75 (s, 3H), 4.6 (m, 1H), 4.8 (m, 1H), 5.35 (bd, 1H), 5.6 (bd, 1H), 7.1-7.4 (m, 5H). ^{13}C-NMR: δ 27.31 (q), 38.63 (t), 52.30 (d), 53.88 (q), 54.17 (q), 62.56 (t), 127.02 (d), 128.53 (d), 129.44 (d), 136.06 (s), 156.73 (s), 172.09 (s), 173.03 (s).

10 **Synthesis of urea 10 on solid phase**: To hydroxymethylene resin (100 mg; loading 0.87 mmol/g; NovaBiochem) in 1.0 mL dry CH_2Cl_2 was added a solution of the Fmoc-amino acid (3 eq.), TBTU (5 eq.), DIPEA (6 eq.) and DMAP (0.25 eq.) in 1.0 mL DMF and the resulting mixture was shaken overnight at RT to yield **6**. The resin **6** was washed subsequently with DMF, CH_2Cl_2, DMF, and CH_2Cl_2 (2x) and dried *in vacuo* at 40°C. A suspension of resin **6** in 2.0 mL of 20% piperidine in DMF was shaken 1 hr at RT, washed with CH_2Cl_2, EtOH, CH_2Cl_2, EtOH, CH_2Cl_2 (2x) and dried. The free amino acid resin was suspended in 1.0 mL DMF and a solution of 1,1'-carbonylbisbenzotriazole **2** (3 eq.) and DIPEA (5 eq.) in 1.0 mL CH_2Cl_2 was added. The mixture was shaken overnight at RT. The benzotriazole urea resin **7** was washed with CH_2Cl_2, dried and suspended in 1.0 mL CH_2Cl_2. A solution of the amino acid methyl ester **8** (3 eq.) and DIPEA (6 eq.) in 1.0 mL DMF were added to the resin, which was shaken overnight at RT. The urea resin **9** was washed (see above) and dried, suspended in 2.0 mL 50% TFA in CH_2Cl_2 and shaken at RT for 3 hrs. The resin was filtered off and washed with CH_2Cl_2, Et_2O, CH_2Cl_2, Et_2O, CH_2Cl_2 (2x). The filtrate and washings were collected in pre-weighed tubes and concentrated to give the desired urea **10**.

11 The intermediate resins **7** and **9** were characterised by FT-IR and gel-phase MAS-NMR (^{1}H and TOCSY). The products **10** were analysed by MS and HPLC.