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Tetrahedron Letters 44 (2003) 6931–6935

TETRAHEDRON LETTERS

A novel solid-phase synthesis of di- and trisubstituted *N*-acyl ureas

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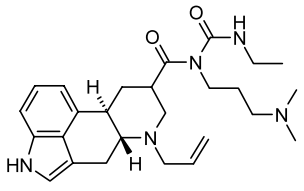
Received 29 April 2003; revised 23 June 2003; accepted 3 July 2003

Abstract—A novel, mild method for the synthesis of di- and trisubstituted *N*-acyl ureas on solid support is described. Addition of carboxylic acids to a resin-bound carbimidoyl chloride gave, initially, an *O*-acyl isourea which subsequently rearranged to the corresponding *N*-acyl urea. Trisubstituted *N*-acyl ureas were assembled on a Wang resin from a wide range of Fmoc amino acids, secondary amines and carboxylic acids. Acid mediated cleavage yielded the products in good yields and excellent purities. In addition, the regioselective synthesis of disubstituted *N*-acyl ureas is demonstrated with four examples.

During the last decade, solid-phase synthesis has proved to be a highly effective technology for the rapid generation of large collections of compounds incorporating a wide variety of pharmacophore elements. This success relied on the development of highly efficient and selective reactions. In our continuing search for small and simple scaffolds for lead identification we were interested in the synthesis of substituted *N*-acyl ureas, preferably on solid support. The *N*-acyl urea substructure has several agrochemical[1] and medicinal applications. One such example thereof is the dopamine D2 agonist Cabergoline,[2] (Fig. 1) which was launched in 1993 as an *anti* Parkinson's agent.

Solution-phase synthesis of *N*-acyl ureas typically involves the reaction of substituted ureas with acyl chlorides at elevated temperatures[3] or from the rather slow reaction of amides with isocyanates.[4] Recently, methods starting from the corresponding acyl isothiocyanate have also been reported.[5] To the best of our knowledge no solid-supported methodology for the synthesis of *N*-acyl ureas has been reported so far. Therefore, we would like herein to report a novel, mild and efficient method for the synthesis of di- and trisubstituted *N*-acyl ureas on solid-support.



Cabergoline

Figure 1.

In a recent report from our laboratories the use of triphenylphosphine dichloride for the desulphurization of thioureas was described in the synthesis of substituted guanidines.[6] The same approach was adopted in the present study employing resin-bound thioureas. The reaction between triphenylphosphine dichloride and a substituted thiourea generates either a carbimidoyl chloride or a carbodiimide, depending on the number of substituents (Fig. 2). Generally, the carbimidoyl chloride is formed from trisubstituted thioureas. The addition of a carboxylic acid to a carbodiimide gives, initially, an *O*-acyl isourea intermediate which can rearrange to an *N*-acyl urea or react with a second molecule of acid to give the corresponding urea together with a symmetric anhydride. We reasoned that carbimidoyl chlorides generated from trisubstituted thioureas may react with carboxylic acids to give the same *O*-acyl isourea intermediate and then rearrange to the trisubstituted *N*-acyl ureas.

In order to explore this strategy the resin-bound tri- and disubstituted thioureas **1** and **3** were chosen as model systems (Scheme 1). A freshly prepared solution

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0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01676-9

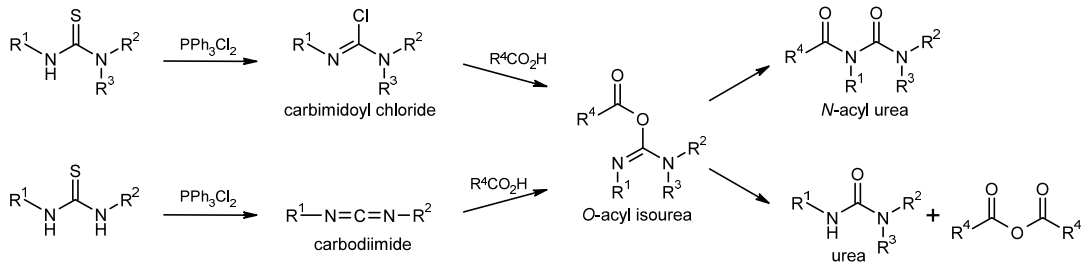
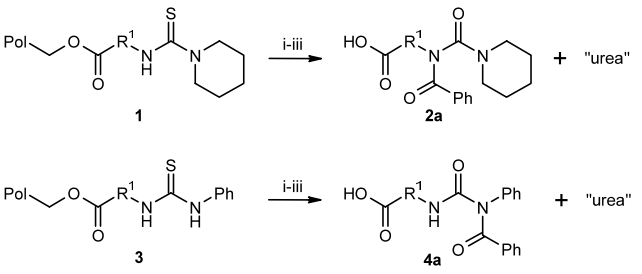


Figure 2.



Scheme 1. Pol = Wang PS, R^1 = 4-$CH_2(C_6H_4)CH_2$. *Reagents and conditions*: (i) C_2Cl_6, PPh_3, dry THF, 20°C, 5 h; (ii) $PhCO_2H$, *solvent* (see Table 1), 20°C, 16 h; (iii) TFA/DCM (1:1, v/v), 20°C, 1 h.

of triphenylphosphine dichloride in dry THF was reacted with **1** and **3** to generate the carbimidoyl chloride and carbodiimide, respectively, which were further reacted with 10 equiv. of benzoic acid in different solvents with or without triethylamine. The products were cleaved from the resin with 50% TFA in dichloromethane and the amounts of *N*-benzoyl ureas **2a** and **4a** and the corresponding non-benzoylated ureas were estimated by LC–MS analysis of the crude mixtures. The results for each system are shown in Table 1.

The addition of benzoic acid without base yielded only the non-benzoylated urea byproducts with no detectable amount of *N*-benzoyl ureas, irrespective of the system or solvent used. The addition of triethylamine to the reaction mixtures dramatically changed this picture and now only small amounts of the non-benzoylated ureas were isolated using dichloromethane, dimethylformamide, tetrahydrofuran or 1,4-dioxane as

Table 1. Product distribution with different solvents in step (ii) (Scheme 1)

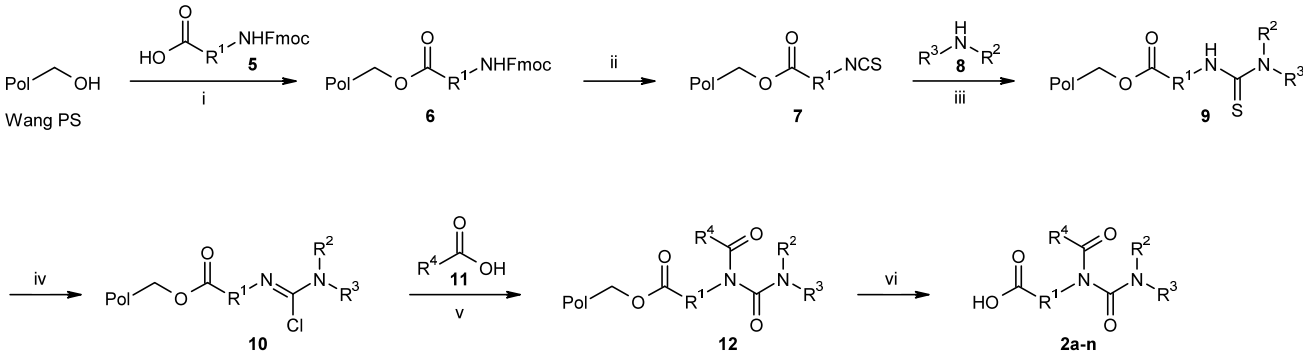
Solvent	**2a**: 'urea'[a]	**4a**: 'urea'[a]
CH_2Cl_2	0:100	0:100
DMF	0:100	0:100
THF	0:100	0:100
1,4-Dioxane	0:100	0:100
CH_2Cl_2, Et_3N	95:5	97:3
DMF, Et_3N	95:5	94:6
THF, Et_3N	96:4	97:3
1,4-Dioxane, Et_3N	*100:0*	*100:0*

[a] Ratios are estimated from ELS peak integration.

the solvent. The latter solvent was superior, since none of the urea byproducts were observed with **1** or **3** as the starting material. Therefore, this protocol was employed in the following studies. Variations in temperature, reaction time and amount of benzoic acid added were also explored but these variables did not influence the outcome significantly (results not shown). The ability of tertiary amines to promote the formation of *N*-acyl ureas from *O*-acyl isoureas has been observed and studied before,[7] but the results of these studies were inconclusive. Nevertheless, these previous findings correspond well with the results for **3** as the addition of a carboxylic acid to a carbodiimide is well-known to give an *O*-acyl isourea both with and without the presence of base. In the case of the trisubstituted carbimidoyl chloride (from **1**) this probably coincides with the ability of triethylamine to deprotonate the acid—a deprotonation most likely required for the addition of a carboxylic acid to a carbimidoyl chloride. In fact, experiments indicated that benzoic acid does not react with the carbimidoyl chloride in the absence of any base, and by the addition of triethylamine before cleavage it was still possible to isolate the *N*-benzoyl urea.[8]

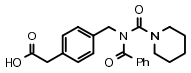
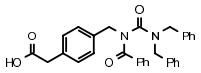
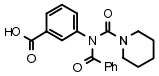
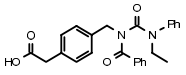
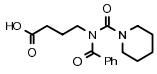
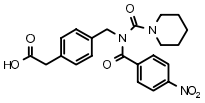
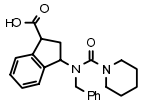
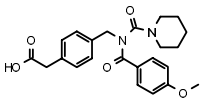
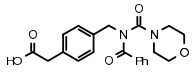
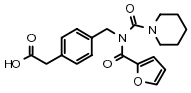
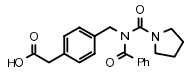
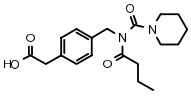
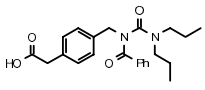
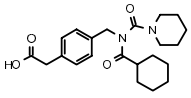
Having established the optimal reaction conditions for the generation of *N*-acyl ureas from thioureas the scope of the method was explored using various building blocks for the synthesis of trisubstituted *N*-acyl ureas. The overall synthesis strategy is outlined in Scheme 2. Polystyrene 4-benzyloxybenzyl alcohol (Wang) resin[9] was loaded with Fmoc protected amino acids **5** using *N*,*N*-diisopropylcarbodiimide and a catalytic amount of *N*,*N*-dimethylaminopyridine. Removal of the Fmoc group was then achieved with piperidine in NMP. Treatment with di-(2-pyridyl)thionocarbonate (DPT) in dichloromethane converted the primary amines to the corresponding resin-bound isothiocyanates **7** after which the addition of secondary amines **8** in NMP gave the trisubstituted thioureas **9**. Conversion of **9** to *N*-acyl ureas was achieved using the optimized protocol described above. Cleavage with 50% TFA in dichloromethane gave the target products **2**.[10,11] A wide range of Fmoc amino acids, secondary amines and carboxylic acids were employed to evaluate the scope of the method and the results are shown in Table 2.

Generally, the *N*-acyl ureas were isolated in good yields and were of high purities. Both aliphatic and aromatic substituents are tolerated in all building blocks, although an aromatic secondary amine gave a slightly lower yield and purity (**2i**). In most cases the corre-



Scheme 2. *Reagents and conditions*: (i) (a) DIC, DMAP, DMF, 20°C, 16 h; (b) 5% Ac_2O, DCM, 20°C, 15 min; (ii) (a) piperidine/NMP (1:4, v/v), 20°C, 20 min; (b) DPT, DCM, 20°C, 4 h; (iii) NMP, 20°C, 16 h; (iv) C_2Cl_6, PPh_3, THF, 20°C, 5 h; (v) Et_3N, 1,4-dioxane, 20°C, 16 h; (vi) TFA/DCM (1:1, v/v), 20°C, 1 h.

Table 2. Yields and purities of *N*-acyl ureas **2a**–**n** synthesized as outlined in Scheme 2

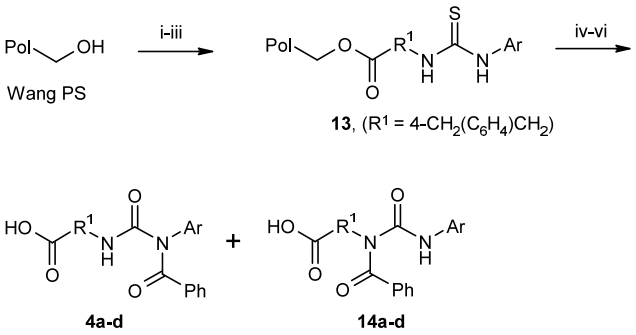
	Structure	Yield (%)[a]	Purity (%)[b]		Structure	Yield (%)[a]	Purity (%)[b]
2a[11]		89	98	**2h**		45	86
2b		74	88	**2i**		30	70
2c		70	>99	**2j**		53	90
2d		53	97	**2k**		30	>99
2e		73	96	**2l**		77	>99
2f		51	96	**2m**		82	99
2g		62	86	**2n**		72	99

[a] Yields are calculated from NMR analysis of the crude products using 2,5-dimethylfuran as an internal standard. [b] Purities are estimated from ELS peak integration.

sponding non-acylated urea represented the major impurity. However, it should be noted that Fmoc-α-amino acids could not be incorporated, since the corresponding thiourea was cleaved through an intramolecular cyclization to give a 2-aminothiazol-5-one.

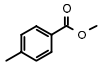
All the examples in Table 2 incorporate secondary amines and the *O*-acyl isourea can therefore only rearrange to give one regioisomer. Initial experiments employing primary aliphatic amines resulted in two isomers with no regioselectivity. Khorana[12] has reported that *N*-cyclohexyl-*N*′-phenylcarbodiimide reacts with benzoyl-glycylglycine (Z-Gly-Gly-OH) to give only one regioisomer of *N*-acyl urea with the acyl group attached to the less basic aniline nitrogen. We have investigated this strategy to synthesize *N*,*N*′-disubstituted benzoyl ureas as outlined in Scheme 3.

N-Benzoyl-*N*-aryl ureas **4**,[13] containing varying small amounts of the regioisomer **14**, were synthesized from resin bound amino acids by reaction with aromatic isothiocyanates and subsequent conversion as before. In Table 3, the results for four different aromatic



Scheme 3. *Reagents and conditions*: (i) (a) $FmocNHR^1CO_2H$, DIC, DMAP, DMF, 20°C, 16 h; (b) 5% Ac_2O, DCM, 20°C, 15 min; (ii) piperidine/NMP (1:4, v/v), 20°C, 20 min; (iii) ArNCS, NMP, 20°C, 16 h; (iv) C_2Cl_6, PPh_3, dry THF, 20°C, 5 h; (v) $PhCO_2H$, Et_3N, 1,4-dioxane, 20°C, 16 h; (vi) TFA/DCM (1:1, v/v), 20°C, 1 h.

Table 3. Yields, purities and regioselectivities in the synthesis of *N*-benzoyl-*N*-aryl ureas **4a–d**

Compound	Ar	Yield (%)[a]	Purity (%)[b]	**4**:**14**[b]
4a[13]		74	97	100:0
4b		69	98	100:0
4c		52	87	95:5
4d		47	68	99:1

[a] Yields are calculated from NMR analysis of the crude product using 2,5-dimethylfuran as an internal standard. [b] Purities and ratios are estimated from ELS peak integration.

isothiocyanates are shown. The regioselectivities were estimated by LC–MS and ^1H NMR in which a characteristic coupling between N–*H* and CH_2 established the identity of the major products **4**. Generally very good selectivities were achieved.

In conclusion, we have developed a novel method for the synthesis of tri- and disubstituted *N*-acyl ureas utilizing resin-bound carbimidoyl chlorides and carbodiimides respectively. Trisubstituted *N*-acyl ureas were assembled on Wang resin from a wide range of Fmoc amino acids, secondary amines and carboxylic acids. Subsequent cleavage from the resin gave the products in good yields and excellent purities. The regioselective synthesis of disubstituted *N*-acyl ureas was also demonstrated with four examples. In accordance with literature reports the acyl group preferably rearranged to the aniline nitrogen while only minute amounts of the regioisomer formed by migration to the other nitrogen was observed.

Acknowledgements

The authors would like to thank Corporate Research Affairs at Novo Nordisk A/S and The Danish Academy of Technical Sciences for financial support and Helle Demuth for LC–MS analysis.

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8. Alternatively, the *N*-benzoyl urea might be the result of acylation of the urea with benzoic anhydride generated concomitantly. However, no such acylation was observed after overnight treatment of a resin bound trisubstituted urea with benzoic anhydride and triethylamine.
9. Wang polystyrene resin (100–200 mesh, 1% DVB, 1.07 mmol/g) was purchased form BACHEM, Switzerland.
10. *General procedure*: Resin **9** was synthesized by the same procedure as reported in Ref. 6. All washings were performed with 5 mL of solvent. To a solution of hexachloroethane (404 mg, 1.71 mmol) in dry THF (5 mL) was added triphenylphosphine (448 mg, 1.71 mmol) and the mixture was stirred for 30 min and then added to resin **9** (300 mg, 0.171 mmol) preswelled in dry THF. The resin was shaken for 5 h and then filtered and washed with dry THF (5×). A solution of benzoic acid (209 mg, 1.71 mmol) and triethylamine (0.33 mL, 1.71 mmol) in dry 1,4-dioxane (5 mL) was added and the mixture shaken for 16 h. After filtration, the resin was washed with DCM (3×), DCM/MeOH (3×), AcOH/MeOH/THF 1:2:7 (1×) and DCM (5×) and the product was cleaved from the support by treatment with TFA/DCM 1:1 for 1 h. The solvents were evaporated under reduced pressure and the residue was dissolved in acetonitrile. A small portion was removed for concentration studies and LC–MS and the remainder was purified by preparative HPLC.
11. **(4-([Benzoyl-(piperidine-1-carbonyl)-amino]-methyl)-phenyl)-acetic acid** (**2a**) White solid. LC–MS (ESI): *m*/*z* 381

(M+H)$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (4H, br s), 1.25 (2H, br s), 2.80 (2H, br s), 3.36 (2H, br s), 3.54 (2H, s), 4.79 (2H, s), 7.24 (2H, d, J 8.1 Hz), 7.32 (2H, d, J 8.1 Hz), 7.45 (2H, m), 7.51–7.56 (3H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.5, 25.0, 40.7, 49.0, 127.8, 128.6, 128.7, 129.8, 131.8, 134.7, 135.4, 135.6, 155.9, 158.4, 173.0.

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13. **(4-[3-Benzoyl-3-phenyl-ureidomethyl]-phenyl)-acetic acid** (**4a**) White solid. LC–MS (ESI): m/z 389 (M+H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.55 (2H, s), 4.28 (2H, d, J 6.0 Hz), 7.14–7.38 (12H, m), 7.47 (2H, m), 8.99 (1H, br t, J 6.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.5, 44.6, 126.82, 126.2, 126.7, 126.8, 127.3, 127.7, 128.2, 129.5, 132.6, 134.9, 135.8, 138.3, 153.9, 157.1, 157.5.