A Simple Method for the Preparation of Di-, Tri- and Tetrasubstituted Non-Symmetrical Ureas

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Abstract: The synthesis of a series of di-, tri- and tetrasubstituted non-symmetrical ureas is described. Di- and trisubstituted ureas are prepared in excellent yield by treatment of a phenyl carbamate in a self-tunable single-mode microwave synthesizer with a primary or secondary amine. The synthetically more challenging tetrasubstituted urea can be prepared using the 4-nitrophenyl carbamate and a secondary amine.

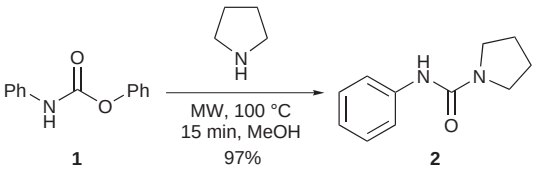
Key words: urea, microwave-assisted synthesis, carbamate

The urea functionality remains an important and common structural motif within many biologically active compounds due to its hydrolytic stability, molecular rigidity and the considerable amount of molecular diversity that can readily be introduced from cheap, commercially available amine starting materials.[1,2] Entrenched methods for their preparation include the use of toxic and highly reactive phosgene[3] and isocyanates.[4] More recently, alternative more controlled protocols have been introduced through the use of 1,1′-carbonylbisbenzotriazole[5] or carbonyldiimidazoles[6] amongst others.[7,8]

Although these newer methods are effective, practical issues and general applicability of the procedures still reveal limitations for the preparation of this crucial and valuable functional group. Of particular note is the need for protection of nucleophilic functional groups such as alcohols in the activated intermediate, which leads to the need for protecting group strategies to be employed which can prove particularly cumbersome, especially when considering the focus on high throughput synthesis within the pharmaceutical industry.[9] Herein, we report a simple and practical, microwave-assisted method for the controlled and reliable preparation of di-, tri- and tetrasubstituted ureas, that proceeds in excellent yields and is tolerant of unprotected alcohols in both amine components, greatly adding to the synthetic utility of the procedure.

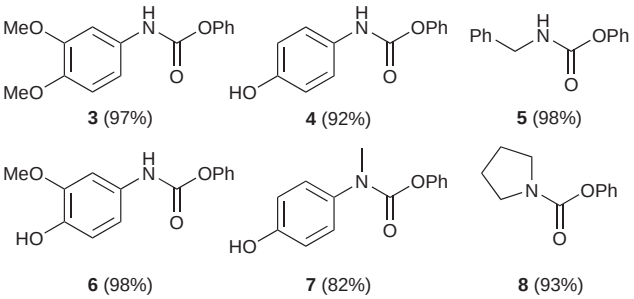
Carbamates are traditionally used as effective protecting groups for the amine functionality and have a well established and reliable reactivity profile, the low electrophilicity of the carbonyl rendering them particularly unreactive to nucleophiles.[10] However, we have found that both phenyl- and 4-nitrophenyl carbamates are effective precursors to the urea motif when treated with either primary or secondary amines under microwave irradiation.

As a starting point we prepared the phenyl carbamate **1** by reaction of 3,4-dimethoxyaniline with phenyl chloroformate in dioxane (97%). Treatment of **1** with one equivalent of pyrrolidine with an initial power of 50 W at 100 °C for 15 minutes in a self-tunable single-mode microwave synthesizer gave the desired non-symmetrical urea **2** in 97% isolated yield without the need for aqueous work up (Scheme 1; see experimental section for full details of reaction conditions).



1 **2**

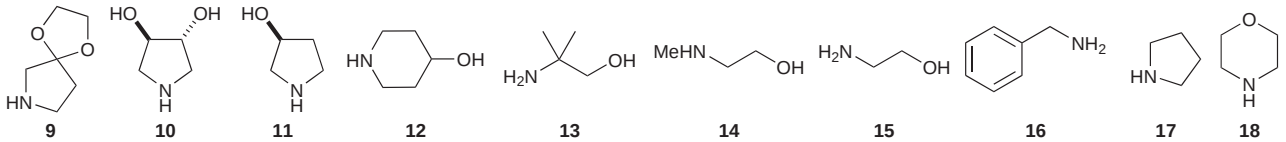
Scheme 1



3 (97%) **4** (92%) **5** (98%)

6 (98%) **7** (82%) **8** (93%)

Figure 1 Phenyl carbamates prepared (yields in parentheses)



9 **10** **11** **12** **13** **14** **15** **16** **17** **18**

Figure 2 Amines used in the preparation of ureas

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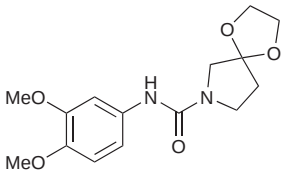
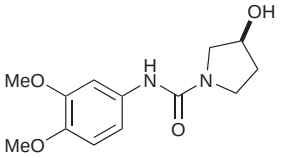
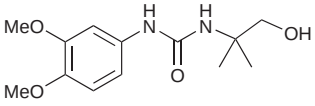
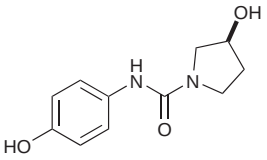
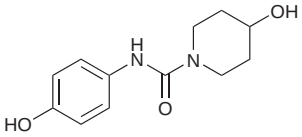
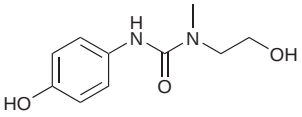
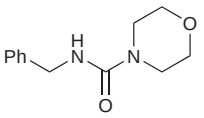
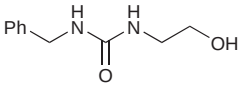
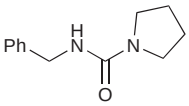
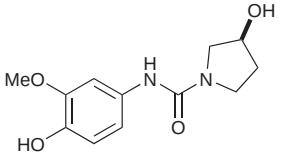
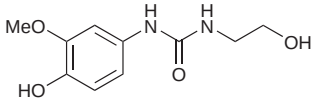
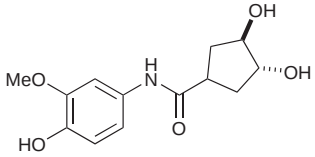
Table 1 Preparation of Non-Symmetrical Di- and Trisubstituted Ureas from Phenyl Carbamates **3**–**6**[a]

Entry	Reaction	Urea	Yield (%)
1	**3** + **9**		96
2	**3** + **11**		90
3	**3** + **13**		92
4	**4** + **11**		93
5	**4** + **12**		95
6	**4** + **14**		94
7	**5** + **18**		95
8	**5** + **15**		96
9	**5** + **17**		96
10	**6** + **11**		92
11	**6** + **15**		90
12	**6** + **10**		93

[a] All reactions performed at an initial power of 50 W for 15 min.

Encouraged by this initial result we went on to investigate whether this was a general method for the preparation of a variety of ureas and prepared the phenyl carbamates **3**–**8** (Figure 1).

The carbamates **3**–**8** were reacted with a series of primary and secondary amines (Figure 2) under our standard reaction conditions to provide, in most cases, the corresponding ureas (Table 1).[11] The reaction worked well for the preparation of disubstituted ureas with the introduction of a variety of amines proceeding smoothly (entries 3, 8, 11 and 12). This was also the case for trisubstituted ureas for aliphatic amines (entry 1) as well as the introduction of amines containing unprotected hydroxyl functionalities (entry 2). Crucially, we were also able to form the desired ureas in the presence of a free hydroxyl on the carbamate moiety, greatly adding to the synthetic utility of this procedure (entries 4–12). We were unable to bring about any reactivity in the reaction of the disubstituted carbamates **7** and **8**, even under more forceful reaction conditions (up to 150 W initial power) with both secondary (pyrrolidine) and primary (benzylamine) amines no observable reaction took place, only starting material being isolated from the reaction mixture. It is probable that with the phenyl carbamates **3**–**6**, the reaction proceeds via an intermediate isocyanate, formed in situ by deprotonation of the carbamate, followed by nucleophilic attack of the amine. This is not possible with the substrates **7** and **8**, whose reaction would have to proceed via a different mechanism.

Comparison of the microwave-assisted and thermal processes revealed the reactions to be more efficient, cleaner and considerably quicker using the microwave-assisted reaction conditions. For example, reaction of carbamate **6** with enthanolamine **15** at room temperature for three days gave the corresponding urea in 64% isolated yield. Heating the reaction at reflux did improve the rate, with the reaction going to completion in 24 hours, however, no real improvement in yield was observed (68%) (cf. Table 1, entry 11: 90% yield, 15 min).

In a search for more reactive substrates to prepare the elusive tetrasubstituted non-symmetrical ureas by a similar method we reasoned that increasing the leaving group ability of the carbamate substituent could lead to an increased electrophilicity of the carbamate carbonyl group, despite the fact that formation of an intermediate isocyanate was not possible from these substrates. We therefore prepared the 4-nitrophenylchloroformate derivatives **19**–**21** (Figure 3) by treatment of the secondary amine with 4-nitrophenylchloroformate, providing the required starting materials for this part of the investigation in excellent yield.[12]

With the more reactive substrates **19**–**21** we found that this proved to be a particularly effective method for the formation of the synthetically challenging non-symmetrical tetrasubstituted urea motif. The results obtained are outlined in Table 2. The method was efficient for the introduction of both acyclic (entries 1, 5 and 6) and cyclic (entries 2–4 and 7, 8) amines, with both alkyl (entries 1, 2) and aryl (entries 4–8) 4-nitrophenyl carbamates.

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Significantly, the reaction was tolerant of nucleophilic hydroxyl groups within the starting carbamate (entries 6–8), which is not the case for alternative methods within the literature,[13] providing a convenient, high yielding and valuable route to this class of compounds. Reaction times varied with this conversion depending on the inherent nucleophilicity of the amine, with cyclic amines typically going to completion in 45 minutes, whereas with the less nucleophilic acyclic amines 90 minutes were required. Increasing the initial power of the microwave irradiation did lead to shorter reaction times but isolated yields fell by 5–10%, leading us to adopt 50 W as the standard reaction power.

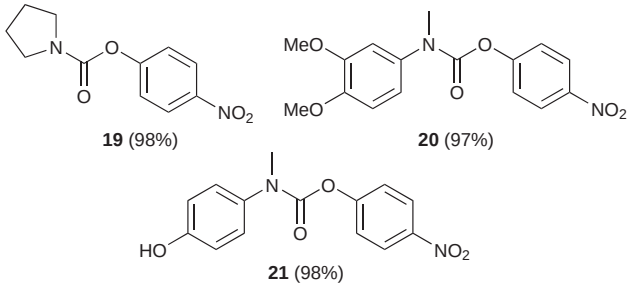
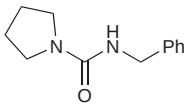
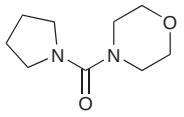
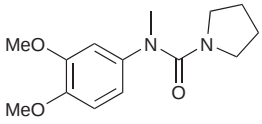
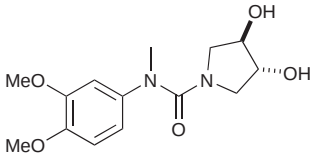
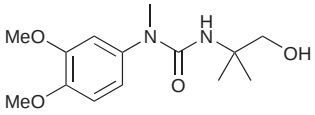
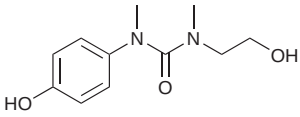
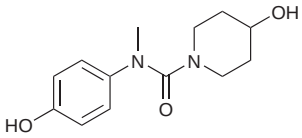
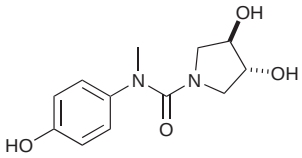


Figure 3 4-Nitrophenyl carbamates prepared (yields in parentheses)

An indication of the increased reactivity that can be obtained by the use of the microwave is exemplified by the fact that no product could be detected in the thermal reaction between the carbamate **20** and pyrrolidine **17**, at reflux, even after 7 days, providing further evidence of the useful modification of reactivity profile that can be obtained using these instruments.

In summary, we have discovered a simple, high yielding method for the preparation of non-symmetrical di-, tri- and tetrasubstituted ureas by the preparation of either the phenyl- or 4-nitrophenyl carbamates, followed by treatment with either primary or secondary amines in a self-tunable microwave synthesizer. The reactions proceed without the need for aqueous work-up and can be purified directly after completion of the reaction.

Table 2 Microwave-Assisted Preparation of Non-Symmetrical Tri- and Tetrasubstituted Ureas from Carbamates **19**–**21**[a]

Entry	Reaction	Urea	Yield (%)
1	**19** + **16**		91
2	**19** + **18**		93
3	**20** + **17**		93
4	**20** + **10**		92
5	**20** + **13**		90
6	**21** + **12**		97
7	**21** + **14**		94
8	**21** + **10**		95

[a] Reactions performed at an initial power of 50 W for 45–90 min.

Typical Experimental Procedure for the Preparation of Trisubstituted Ureas: *N*-[(3*S*)-Pyrrolidinol]-*N*′-(3,4-Dimethoxy)phenyl Urea (Table 1, entry 2)

N-(3,4-Dimethoxyphenyl)-*O*-phenyl carbamate (0.25 g, 0.92 mmol) and 3-(*S*)-pyrrolidinol (0.11 mL, 1.37 mmol) were dissolved in MeOH (3 mL) in a microwave reaction tube. The reaction mixture was stirred in a single-mode microwave reactor for 15 min at 100 °C (initial power 50 W). The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (eluting solvents acetone–hexane, 3:1) to give the title compound (0.22 g, 92%) as a colourless crystalline solid; mp 131–132 °C. HRMS: *m/z* calcd for $C_{13}H_{18}N_2O_4$ $[MH]^+$: 267.1339; found: 267.1341. IR (nujol): ν_{max} = 3508 (NH), 3387 (OH), 1666 (C=O) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.14 (d, *J* = 2.2 Hz, 1 H), 6.92 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 4.47–4.45 (m, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.16–3.55 (m, 3 H), 3.45 (app. br d, 1 H), 2.14–2.05 (m, 1 H), 2.01–1.98 (m, 1 H). ^{13}C NMR (100 MHz, MeOD): δ = 157.9, 150.7, 147.0, 134.9, 115.2, 113.6, 108.4, 71.6, 57.2, 56.7, 55.5, 45.3, 35.0. MS (APcI): *m/z* (%) = 267 (100) $[MH]^+$.

Typical Experimental Procedure for the Preparation of Tetrasubstituted Ureas: *N*-Methyl-*N*-(3,4-dimethoxy)phenyl Pyrrolidine Urea (Table 2, entry 3)

N-(3,4-Dimethoxyphenyl)-*N*-methyl-*O*-(4-nitrophenyl) carbamate (0.25 g, 0.75 mmol) and pyrrolidine (0.13 mL, 1.5 mmol) were dissolved in MeOH (3 mL) in a microwave reaction tube. The reaction mixture was stirred in a single-mode microwave reactor for 30 min at 100 °C (initial power 50 W). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluting solvent acetone–hexane, 1:1) to give the title compound (0.19 g, 93%) as a colourless oil. HRMS: *m/z* calcd for $C_{14}H_{20}N_2O_3$ $[MH]^+$: 265.1547; found: 265.1547. IR (nujol): ν_{max} = 1633 (C=O) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 6.83 (d, *J* = 8.5

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Hz, 1 H), 6.69 (d, *J* = 2.5 Hz, 1 H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.05 (s, 3 H), 2.95 (app. t, *J* = 6.7 Hz, 4 H), 1.62–1.59 (m, 4 H). ^{13}C NMR (100 MHz, MeOD): δ = 162.0, 151.2, 148.6, 140.5, 119.2, 113.3, 111.3, 56.6, 56.6, 56.1, 40.62, 29.5. MS (APcI): *m/z* (%) = 265 (100) $[MH]^+$.

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