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# Microwave-assisted transamidation of ureas

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ABSTRACT

An effective microwave-assisted urea formation from cyclopentyl- or isopropyl-substituted ureas is described. This novel transamidation methodology provided ureas **IIa**–**IIq** in good yields via microwave irradiation of the cyclopentyl- or isopropyl-substituted ureas with excess (5–10 equiv) of amines at 150 °C in THF/DMSO.



The urea functional group is a common and useful building block in the preparation of pharmaceutically active candidates and natural products.[1] Ureas are also commonly employed linkages in or between scaffolds as bioisosteres of carbamates or amides in drug discovery. Numerous classical synthetic pathways have been developed to generate ureas through isocyanates,[2a,b] activated carbamate intermediates[3] and carboxylic acid derivaties.[4] The application of microwave-assisted organic synthesis in urea formation via the aforementioned synthetic methods is also well studied. [5a,b] Symmetrical ureas were also generated by reacting aromatic amines with ethyl acetoacetate promoted by zeolite HSZ-360[2c] or by reacting amine using binary $CO_2$/water as reaction media[2d] or by aromatic amines or hydrazines with urea devoid of solvents either under conventional heating in the presence of catalytic zinc chloride[2e,2f] or under microwave irradiation.[2g]

Initially, we planned to form compound **2** via the displacement of 2-Cl-pyridine analog **1**[6a] upon heating pyrrolidine (neat) at 150 °C under microwave irradiation. After 1500 s, the reaction gave an unexpected product **3** (88% yield) with no trace of **2** found (Fig. 1). Compound **3** is a product of both transamidation of cyclopentyl urea with pyrrolidine and displacement of the chlorine atom with pyrrolidine. Herein we report the first synthesis of ureas via transamidation of isopropyl or cyclopentyl urea **I** with excess amines (5–10 equiv) in THF or a 1:1 mixture of THF/DMSO under microwave irradiation at 150 °C (Table 1). Cyclopentyl or isopropyl ureas are final compounds and/or advanced intermediates of two in-house drug discovery programs.[6a–e] The cyclopentyl urea analogs gave good in vitro potency but poor metabolic stability.[6a–c] This methodology allowed us to promptly screen different cyclopentyl urea replacements with structurally diverse amines in a timely fashion.

Table 1 shows the results of primary amines (e.g., entries **4**–**12**) and secondary amines (e.g., entries **13**–**14**) with different bulky groups on one side of the urea group and a cyclopentyl or an isopropyl group on the other side. However, the less bulky group **Ie** in entry **6** also gave the desired product cleanly in good yields. Transamidation also showed good yields with weak amines (calcd. $pK_a = 7$ for entries **4**–**6** and $pK_a = 6$ for entry **8**). Under microwave irradiation, the chirality of the structure remains unchanged based on the chiral purity analysis of **IIa** in entry **4**. All reactions were performed in 1500 s. For reactions with isolated yields under 70% (e.g., entry **4**), the only other side product observed from LCMS of the reaction mixture was the unreacted starting cyclopentyl urea **Ib**. Increasing the temperature or prolonging the reaction irradiation time could lead to completion of reaction.

Upon obtaining good yields for the transamidation of ureas with primary and secondary amines, we conducted a few studies on the scope of the transamidation reaction. For example, using

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0040-4039/

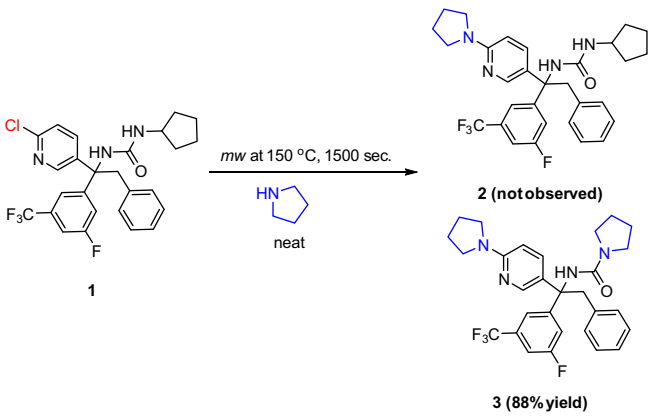



**Figure 1.** Discovery of transamidation of urea **1** to urea **3**.

5–10 equiv of morpholine, urea **1** selectively underwent transamidation reaction without displacing the chlorine atom (entry **15**, Table 2). Functional groups such as carboxylic acid (entry **16**), alcohol (entries **17** and **19**), and dihydrofuran-2(3*H*)-one (entry 18) were also tolerated.

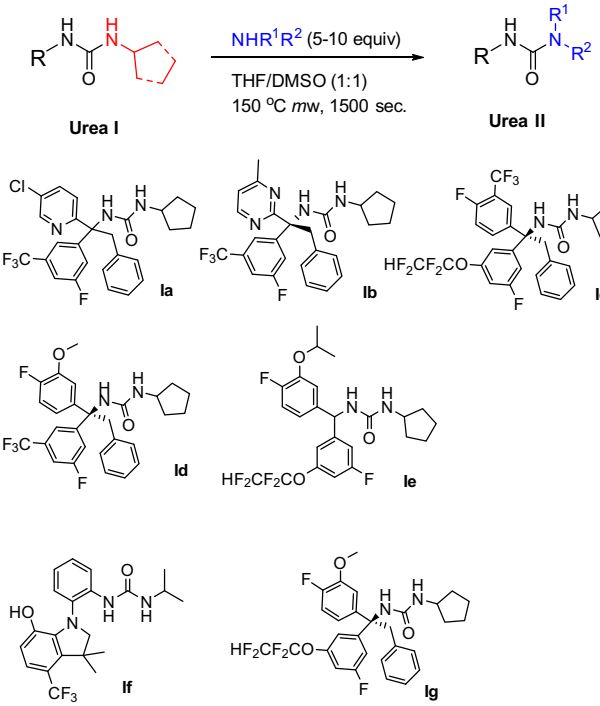
Therefore, in contrast to the classical stepwise synthetic pathway to urea formation, we utilized isopropyl or cyclopentyl ureas as stable intermediates for the transamidation, thereby providing a rapid method for high-throughput synthesis and optimization. Although the mechanism of the transamidation of ureas was not studied, we propose that microwave irradiation facilitated the bond-breaking process of the presumably weaker C–N bond, which was on the less hindered urea side, and thus formed an isocyanate intermediate that contained the relatively bulky group. In fact, LCMS showed a small amount of the corresponding isocyanate formed when heating **Ia** in the absence of an amine under the same reaction conditions (described in Table 1). Interestingly, no un-reacted starting ureas were identified by LCMS after 1500 s. in any of the reactions except entry **4** shown in Tables 1 and 2. Microwave irradiation is the key for these high-yielding transamidation reactions. For example, under conventional heating at 150 °C for 4 h, urea **Ia** reacted with 5–10 equiv of 2,2,2,-trifluoroethanamine to give only 11% of the transamidated product. After heating for 12 more hours, 41% of the transamidated product was formed along with 45% of the cleaved bulky left-hand amine (R-$NH_2$) and 14% of unreacted urea **Ia**. Increasing the temperature to 200 °C under conventional heating led to decomposition.

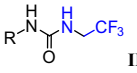
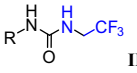
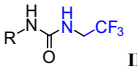
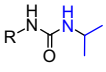
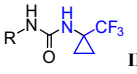
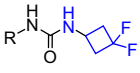
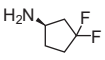
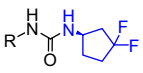
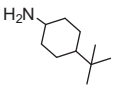
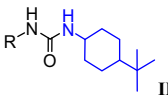
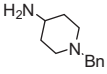
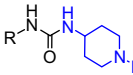
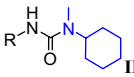
In summary, we described a novel one-step synthesis of ureas via the transamidation of the cyclopentyl or isopropyl ureas with excess amines (5–10 equiv) under microwave irradiation at 150 °C. Moreover, amines can be elaborated with functional groups such as carboxylic acid and alcohol with no putative effect. Generalization of this methodology and study of the reaction mechanism and scopes such as using aryl/heteroaryl amines will be investigated.

## Acknowledgements

The authors would like to thank Dr. Feng Qiu for structural confirmation of compound **3** and Dr. Ruth R. Wexler for reviewing the manuscript and valuable suggestions.

**Table 1**
Transamidation of ureas **Ia–g** with primary and secondary amines under microwave irradiation

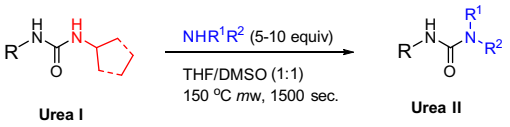


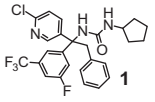
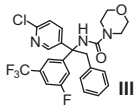
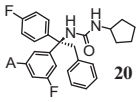
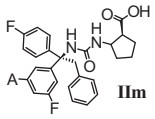
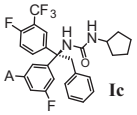
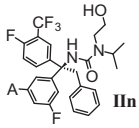
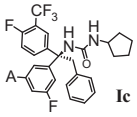
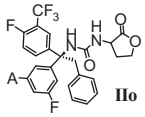
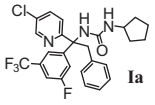
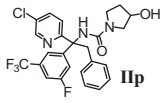

| Entry | Urea I | $R^1R^2NH$ | Urea II | Isolated yield[*,a] (%) |
|---|---|---|---|---|
| **4** | **Ib** |  |  **IIa** | 60 |
| **5**[8] | **Ig** |  |  **IIb** | 78 |
| **6** | **Ie** |  |  **IIc** | 81 |
| **7** | **Ic** |  |  **IId** | 85 |
| **8** | **Id** |  |  **IIe** | 77 |
| **9** | **Id** |  |  **IIf** | 79 |
| **10** | **Id** |  |  **IIg** | 80 |
| **11** | **If** |  |  **IIh** | 93 |
| **12** | **If** |  |  **IIi** | 98 |
| **13** | **Ia** |  |  **IIj** | 84 |
| **14** | **Ia** |  |  **IIk** | 88 |

[*] Yields refer to isolated and chromatographically pure products. All products exhibited spectral data and HRMS consistent with their structures.

[a,7] General reaction method—urea precursor **I** (1 equiv), amine (5–10 equiv), THF/DMSO (1:1, 0.12 M), 150 °C *mw*, 1500 s.

**Table 2**
Transamidation of ureas with functionalized amines under microwave irradiation




| Entry | Urea I | $R^1R^2NH$ | Urea II | Isolated yield[a] (%) |
|---|---|---|---|---|
| 15 |  1 |  |  III | 81 |
| 16 |  20 |  |  IIm | 88 |
| 17 |  Ic |  |  IIn | 74 |
| 18 |  Ic |  |  IIo | 73 |
| 19 |  Ia |  |  IIp | 86 |

A = $-OCF_2CF_2H$.
[a] General reaction method—urea precursor (1 equiv), amine (5–10 equiv), THF/DMSO (1:1, 0.12 M), *mw* 150 °C, 1500 s.

## Supplementary data

Supplementary data (spectroscopic data for compounds **IIa–IIq**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.103.

## References and notes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7. *General procedure for urea transamidation:* In a 2-mL Personal Chemistry Smith Process conical vial, cyclopentyl urea was mixed with amine (5–10 equiv) in a mixture of THF/DMSO (1:1, v/v). Microwave reactions were carried out in a Personal Chemistry Emrys Optimizer model microwave reactor. Typical reactions were run using 300 W of power for 150–300 s. and approximately 100 W of power until the final experiment time reached 1200 s. The temperature was measured with an IR probe and maintained at 150 °C. The resulting mixture was diluted in EtOAc, washed with 1 N HCl and filtered. Solvents were evaporated under vacuum, and the residue was purified by chromatography or preparative HPLC.
8. Typical procedure exemplified by the synthesis of 1-[(1*R*)-1-(4-fluoro-3-methoxyphenyl)-1-[3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl]-2-phenylethyl]-3-(2,2,2-trifluoroethyl)urea (**IIb**, Table 1, entry **5**): In a 2 mL Personal Chemistry Smith Process conical vial, 3-cyclopentyl-1-[(1R)-1-(4-fluoro-3-methoxyphenyl)-1-[3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl]-2-phenylethyl] **Ig** (20 mg, 0.035 mmol) was mixed with 2,2,2,-trifluoroethanamine (19.48 mg, 0.177 mmol) in a 1:1 mixture of THF/DMSO (0.3 mL). The reaction mixture was stirred for 1500 s. under microwave irradiation at 150 °C. The reaction mixture was diluted with EtOAc (2 mL) and washed with 1 N HCl (1 mL), then dried over $Na_2SO_4$. The solution was filtered and the solvent was evaporated under reduced pressure. The crude product was purified via silica chromatography using hexane/EtOAc as the mobile phase to provide the desired product **IIb** as a white solid (18 mg, 78% yield). HRMS: $C_{26}H_{21}F_9N_2O_3$ calcd for [M+H]: 581.14815, found: 581.14771. $^1$H NMR (500 MHz, METHANOL-$d_4$) $\delta$ 7.26–7.13 (m, 3H), 7.10 (d, $J$ = 9.9 Hz, 1H), 7.06–6.94 (m, 3H), 6.82–6.73 (m, 4H), 6.70 (br. s., 1H), 6.46–6.14 (m, 1H), 4.03 (d, $J$ = 12.7 Hz, 1H), 3.93–3.74 (m, 3H), 3.70 (s, 3H). $^{13}$C NMR (125 MHz, METHANOL-$d_4$): $\delta$ 164.04 (d, $J$ = 244.40), 158.85 (m), 152.83 (d, $J$ = 245.8 Hz), 152.40 (d, $J$ = 7.9 Hz), 150.71 (d, $J$ = 11.8 Hz), 148.51 (d, $J$ = 10.9 Hz), 142.38 (m), 137.85, 132.28, 128.79, 127.79, 126.36 (q, $J$ = 278.5 Hz), 120.60 (d, $J$ = 6.6 Hz), 118.12 (tt, $J$ = 271.8, 28.5 Hz), 117.74 (m), 116.42 (d, $J$ = 18.8 Hz), 114.14, 113.78 (d, $J$ = 23.5 Hz), 109.49 (tt, $J$ = 250.1, 40.8 Hz), 108.86 (d, $J$ = 25.8 Hz), 65.74 (m), 56.72, 44.80, 41.90 (q, $J$ = 34.7 Hz). Anal. Calcd for $C_{26}H_{21}F_9N_2O_3$: C, 53.80; H, 3.61; F, 29.46; N, 4.83. Found: C, 53.88; H, 3.60; F, 27.43; N, 4.86.