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Synthesis of five- and six-membered lactams via solvent-free microwave Ugi reaction

Mouhamad Jida, Sandra Malaquin, Rebecca Deprez-Poulain *, Guillaume Laconde, Benoit Deprez *

Biostructures and Drug Discovery, INSERM U761, Faculté de Pharmacie, Université Lille Nord de France, Lille F-59006, France
PRIM Pôle de Recherche Interdisciplinaire sur le Médicament, Lille F-59000, France

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ABSTRACT

Five- and six-membered lactams were synthesized via a 4-center 3-component Ugi reaction by combining amines, isocyanides, and ketoacids under solvent-free microwave conditions. The reaction was carried out in much shorter times and the yields were improved in comparison to classical conditions.

The number of publications reporting solvent-free conditions for the heterocyclic synthesis has increased rapidly in recent years.[1] One advantage of solvent-free reactions, in comparison to the reaction in molecular solvents, is that the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography. The solvent-free heterocyclic syntheses have been extended to a large number of heterocyclic rings. Many solvent-free reactions are performed under microwave irradiation.[2] Microwave irradiation usually reduces the reaction times and increases product yields. The availability of single-mode microwave reactors, which enable the precise control of the reaction conditions, has widened the use of microwave-assisted methods in the parallel synthesis.

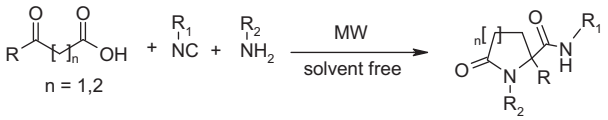
The Ugi reaction is arguably one of the most important multicomponent reactions (MCR).[3–5] It is widely used in the pharmaceutical industry for preparing libraries of compounds. Recent examples include pyrazinones, β-turn mimics, and 4-aminopiperidine-4-carboxylic acid derivatives.[6–8]

The synthesis of five- and six-membered lactams via the intramolecular 4-center 3-component Ugi reaction (U-4C-3CR) is a reaction that produces useful intermediates.[9] Classically, the reaction was performed at room temperature in methanol with reaction times of up to 48 h.[10–12] A variation of this methodology, using microwave irradiation, was reported by Tye et al. only for the synthesis of the five-membered lactams derived from levulinic acid (**1a**).[13] This allowed shorter reaction times of 30 min.

We report here an efficient solvent-free microwave-assisted synthesis of the five- and six-membered lactams via a 4-center 3-component Ugi reaction (Scheme 1) from levulinic acid (**1a**) or 5-ketohexanoic acid (**1b**), isocyanide (**2**), and amine (**3**).

In order to optimize solvent-free-microwave irradiation parameters, we chose levulinic acid (**1a**), benzylisocyanide (**2a**), and benzylamine (**3b**) as the precursors (Fig. 1) for the synthesis of the prototype five-membered lactam (**4a**). The results are shown in Table 1.

All the precursors were used in equimolar proportions. We first evaluated the effect of changes at 100 °C during 5 min (entries 1–3). Total conversion was not achieved with 50 W. Nevertheless, the yield was already better than the published procedure which used methanol at room temperature under classical heating (62%).[10] For 100 W the yield was 88%, due to the degradation of the product. An excellent yield of 95% was obtained for 75 W. Temperature decrease to 80 °C resulted in lower yields (entries 4



1c-a **2c-a** **3e-a** **4a-o** **5a-i** **6**

Scheme 1. U-4C-3CR from ketoacid, isocyanide and amine.

* Corresponding authors. Tel.: +33 3 20964947; fax: +33 3 20964709.
E-mail addresses: rebecca.deprez@univ-lille2.fr (R. Deprez-Poulain), benoit.deprez@univ-lille2.fr (B. Deprez).

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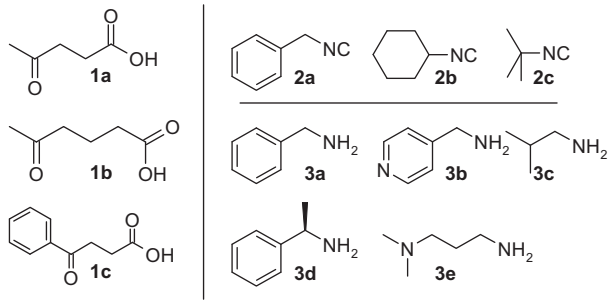


Figure 1. Sets of ketoacids, isocyanides and amines to study the scope of the reaction.

Table 1
Screening irradiation parameters for the synthesis of **4a**

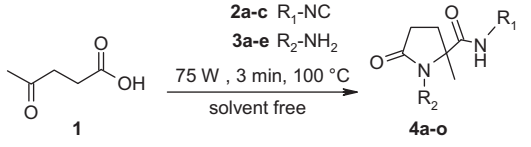
Entry	Power (W)	Temperature (°C)	Time (min)	Conversion (%)	Yield (%)
1	50	100	5	87	76
2	75	100	5	100	95
3	100	100	5	100	88
4	75	80	5	93	81
5	75	80	10	100	84
6	75	100	2	100	91
7	75	100	3	100	97
8	75	100	4	100	96

and 5). Shorter reaction times (entries 6–8 vs 2) allowed **5a** in shorter times and in better yields than the published procedure using methanol and microwave irradiation (90%).[13] A reaction time of 3 min, a temperature of 100 °C, and a power of 75 W proved to be the best conditions (entry 7).

The scope was first explored by using a range of isocyanides **2a–c** and the amines **3a–e** as inputs with levulinic acid **1a** (Fig. 1). The results are shown in Table 2.

The reactivity of different isocyanides with various amines was found to be efficient affording the corresponding lactams in excellent yields (83–97%). For each isocyanide, the best results were obtained for amines **3a–c**. Interestingly, **3e** reacted very well without

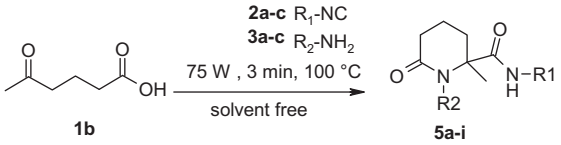
Table 2
Results of Ugi reaction for levulinic acid **1a**



Isocyanide (R_1–NC)	Amine (R_2–NH_2)	Product	Yield (%)
2a	**3a**	**4a**	97 (90[a])
2a	**3b**	**4b**	87
2a	**3c**	**4c**	96
2a	**3d**	**4d**[b]	83
2a	**3e**	**4e**	86
2b	**3a**	**4f**	95 (68[a])
2b	**3b**	**4g**	91
2b	**3c**	**4h**	95
2b	**3d**	**4i**[b]	86
2b	**3e**	**4j**	87
2c	**3a**	**4k**	96
2c	**3b**	**4l**	88
2c	**3c**	**4m**	94
2c	**3d**	**4n**[b]	90
2c	**3e**	**4o**	91

[a] Yields in parenthesis were obtained in MeOH under microwave irradiation. See Ref. 13.
[b] Mixture of diastereoisomers (50/50).

Table 3
Results of Ugi reaction for 5-ketohexanoic acid (**1b**)



Isocyanide (R_1–NC)	Amine (R_2–NH_2)	Product	Yield (%)
2a	**3a**	**5a**	88 (62[a])
2a	**3b**	**5b**	89
2a	**3c**	**5c**	90
2b	**3a**	**5d**	92
2b	**3b**	**5e**	80
2b	**3c**	**5f**	94
2c	**3a**	**5g**	92
2c	**3b**	**5h**	84
2c	**3c**	**5i**	91

[a] Yield obtained in MeOH after 48 h at room temperature. See Ref. 10.

the need for neutralization of the tertiary amine. This solvent-free procedure gave **4a** and **4f** with better yields compared to the microwave procedure with the solvent (97% vs 90% and 95% vs 68%). Though amine **3d** is α-substituted it reacted well with *tert*-butyl isocyanide (**2c**) which is the most reactive isocyanide.[14]

Given these excellent yields obtained with our solvent-free procedures on the synthesis of the five-membered lactams **4a–o**, we next focused on the synthesis of the six-membered lactams via microwave heating. This has never been explored before. 5-Ketohexanoic acid (**1b**) was used as the prototype ketoacid. Classically, the synthesis of six-membered lactams via U-4C-3CR gives the products only in moderate yields in comparison to the five-membered lactams.[15] Indeed, with a γ-ketoacid the transition state is a six-membered ring whereas for a δ-ketoacid (like **1b**) a less favourable seven-membered ring transition state is obtained.[16]

We chose the same isocyanides **2a–c** and amines **3a–c** to study the scope of the reaction, (Table 3).

The results showed the excellent reactivity of the 5-ketohexanoic in these solvent-free microwave conditions. The yields for these reactions range from 80% to 94%. The dibenzyl lactam **5a** was obtained in 88% yield in 3 min in comparison to 62% yield in 48 h at room temperature in methanol.[10]

In summary, we developed a rapid solvent-free microwave synthesis of the five- and six-membered lactams via a 3C-Ugi reaction.[17] These reactions are performed neat at 100 °C for 3 min under 75 W. A set of structurally different amines and isocyanides were combined with either levulinic or 5-ketohexanoic acid under optimized conditions to give 24 structurally different lactams.[18,19] Interestingly, this procedure was successfully applied to the synthesis of lactam **6** from the bulkier 3-benzoylpropionic acid (**1c**) (Fig. 1), isocyanide **2c,** and benzylamine **3a** in 70% yield in 3 min.[20]

This work is the first disclosure of a synthesis of the six-membered lactams assisted by microwave heating and proved to be much better than the classical methods in the literature.

Acknowledgments

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Supplementary data

Supplementary data (Characterization of compounds and NMR Spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.021.

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16. The Ugi transition state is the result of a rearrangement classically referred to as the Mumm-rearrangement. For a discussion on the Ugi intermediates see: Quast, H.; Aldenkortt, S. *Chem. Eur. J.* **1996**, *2*, 462–469.
17. The synthesis of seven-membered lactams is very difficult and depends on the choice of the precursors. In that case, our solvent-free microwave Ugi procedure did not improve the reported yields (0–70%).[10,11]
18. *General reaction protocol*: In a capped 10 mL MW-vessel, the ketoacid (0.5 mmol for **1a**–**c**), the isocyanide (0.5 mmol **2a**–**c**), and the amine (0.5 mmol **3a**–**e**) were mixed. The power was set at 75 W and the pressure at 17 bar (average effective pressure = 4 bar). The mixture was heated at 100 °C for 3 min. After completion the conversion was directly determined by HPLC–MS. The crude product was dissolved in the minimum DCM (10 mL). The organic layer was washed with 1 N HCl (5 mL), and satd aq $NaHCO_3$ (5 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure.
19. Characterization data for selected compounds: *N-tert-Butyl-1-benzyl-2-methyl-5-oxopyrrolidine-2-carboxamide* (**4k**): Yield 138 mg, 96%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (s, 9H); 1.32 (s, 3H); 1.80–1.87 (m, 1H); 2.13–2.20 (m, 1H); 2.32–2.39 (m, 2H); 4.18 (d, J = 15.0 Hz, 1H); 4.45 (d, J = 15.0 Hz, 1H); 5.36 (br s, 1H, NH); 7.14–7.24 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.2; 28.0; 29.3; 33.8; 44.5; 50.9; 67.9; 127.8; 128.4; 128.9; 137.9; 172.3; 176.4 ppm. [(M+H$^+$)] m/z = 289.
N-Cyclohexyl-1-isobutyl-2-methyl-5-oxopyrrolidine-2-carboxamide (**4h**): Yield 133 mg, 95%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72 (d, J = 4.5 Hz, 6H); 0.90–1.26 (m, 5H); 1.37 (s, 3H); 1.39–1.56 (m, 3H); 1.66–1.83 (m, 4H); 2.10–2.26 (m, 3H); 2.56 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H); 3.14 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H); 3.52–3.62 (m, 1H); 6.15 (d, J = 8.1 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.3; 20.7; 23.3; 24.8; 24.9; 25.3; 27.8; 29.6; 32.6; 32.7; 33.0; 48.6; 48.7; 67.5; 172.3; 175.9 ppm. [(M+H$^+$)] m/z = 281.
N-Benzyl-2-methyl-5-oxo-1-[(pyridin-4-yl)methyl]pyrrolidine-2-carboxamide (**4b**): Yield 141 mg, 87%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (s, 3H); 1.75–1.95 (m, 1H); 2.18–2.31 (m, 3H); 3.81 (d, J = 16.2 Hz, 1H); 4.13–4.29 (m, 2H); 4.68 (d, J = 16.2 Hz, 1H); 6.98 (d, J = 6.0 Hz, 2H); 7.03–7.13 (m, 5H); 7.60 (t, J = 5.7 Hz, 1H, NH); 8.30 (d, J = 6.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.4; 29.4; 32.8; 43.6; 44.0; 67.6; 122.4; 127.3; 127.5; 128.5; 138.4; 147.1; 149.7; 172.8; 176.2 ppm. [(M+H$^+$)] m/z = 324.
N-tert-Butyl-1-benzyl-2-methyl-6-oxopiperidine-2-carboxamide (**5g**): Yield 139 mg, 92%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (s, 9H); 1.42 (s, 3H); 1.75–1.80 (m, 3H); 2.18–2.29 (m, 1H); 2.55–2.59 (m, 2H); 4.24 (d, J = 15.6 Hz, 1H); 4.96 (d, J = 15.6 Hz, 1H); 5.61(br s, 1H, NH); 7.20–7.30 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.6; 24.7; 28.4; 32.3; 36.5; 47.8; 51.5; 67.1; 127.0; 127.1; 128.7; 138.5; 172.0; 172.5 ppm. [(M+H$^+$)] m/z = 303.
N-Cyclohexyl-1-isobutyl-2-methyl-6-oxopiperidine-2-carboxamide (**5f**): Yield 138 mg, 94%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, J = 6.6 Hz, 6H); 1.08–1.16 (m, 3H); 1.30–1.39 (m, 3H); 1.55 (s, 3H); 1.71–1.86 (m, 7H); 2.01–2.10 (m, 1H); 2.20–2.26 (m, 1H); 2.44–2.60 (m, 3H); 3.73–3.80 (m, 2H); 5.62 (d, J = 7.12 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8; 20.5; 20.8; 24.7; 25.3; 25.6; 28.6; 32.5; 32.8; 33.2; 36.6; 48.7; 51.6; 66.5; 172.2; 175.7 ppm. [(M+H$^+$)] m/z = 295.
N-benzyl-2-methyl-6-oxo-1-[(pyridin-4-yl)methyl]piperidine-2-carboxamide (**5b**): Yield 150 mg, 87%. Yellow oil (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H); 1.72–1.79 (m, 3H); 2.22–2.41 (m, 3H); 3.78 (d, J = 16.8 Hz, 1H); 4.27–4.46 (m, 2H); 5.19 (d, J = 16.8 Hz, 1H); 7.00 (d, J = 6.0 Hz, 2H); 7.33–7.18 (m, 6H); 8.47 (d, J = 6.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.4; 25.3; 32.3; 36.2; 44.0; 47.6; 66.9; 121.6; 127.6; 127.9; 128.6; 138.3; 147.7; 149.8; 171.9; 172.9 ppm. [(M+H$^+$)] m/z = 338.
N-tert-Butyl-1-benzyl-2-phenyl-5-oxopyrrolidine-2-carboxamide (**6**): Yield 56 mg, 67%. Colorless oil. (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03 (s, 9H); 2.63–2.42 (m, 3H); 2.96–2.90 (m, 1H); 3.77 (d, J = 15.3 Hz, 1H); 4.79 (d, J = 15.3 Hz, 1H); 5.48 (br s, 1H, NH); 7.34–7.15 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.0; 29.5; 35.1; 45.6; 51.6; 75.3; 127.7; 128.0; 128.5; 128.9; 137.5; 138.8; 170.1; 176.9 ppm. [(M+H$^+$)] m/z = 351.
20. The synthesis of lactams from 3-benzoylpropionic acid using classical conditions in methanol gives the desired compounds in 20–75% yield in 48 h (and requires heating to achieve good yields).[10,11]