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Fast, Acid-Free, and Selective Lactamization of Lactones in Ionic Liquids

Kristina M. Orrling, Xiongyu Wu, Francesco Russo, and Mats Larhed*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

mats@orgfarm.uu.se

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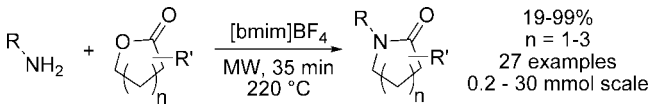

A fast and acid-free one-pot 0.2−30 mmol microwave methodology for direct ionic liquid-mediated preparation of lactams from lactones and primary amines has been developed. The protocol was investigated with a wide range of primary amines and a handful of lactones, including substrates with acid-sensitive substituents. Both γ-lactams and δ-lactams were, despite the complete absence of a Brønsted acid, obtained in useful to excellent yields after only 35 min of microwave processing.

In modern drug discovery chemistry, access to direct synthetic methods for quick and robust generation of new, tunable chemical core structures from commercially available reactants is of great importance.[1] There is also a growing demand for efficient one-pot tandem reactions to quickly prepare target compounds. As such synthetic transformations avoid both time-consuming and costly intermediate purifications and reduce the need for protective groups, they are also inherently more environmentally benign[2] and atom efficient.[3,4]

Microwave heating (MW) using dedicated instrumentation has become an increasingly popular tool due to the fast heating, ease of operation, and high reaction control.[5−8] Since the introduction of 1,3-dialkylimidazolium-based ionic liquids as reaction medium for microwave-accelerated organic synthesis,[9−11] these charged solvents have attracted increasing interest because of their negligible vapor pressure and polar characteristics.[12,13] Due to their charged nature, ionic liquids can provide fast volumetric microwave heating to high temperatures. Ionic liquids of the 1,3-dialkylimidazolium class with non-nucleophilic counterions such as BF_4^- and PF_6^- possess particularly high thermal stability.[14] Furthermore, 1,3-dialkylimidazolium-based ionic liquids display both weak anionic donor and cationic acceptor abilities[15−17] and have been reported to promote acid-catalyzed reactions without addition of an external acid at high temperatures.[18] Since 1,3-dialkylimidazolium cations with non-nucleophilic counterions lack acidic properties, the increased reaction rates might instead be due to their strong polar nature.[19]

In the literature, there are several previously reported procedures to provide lactams from lactones,[20,21] either directly or via hydroxyamide formation, and subsequent substitution of the activated or unactivated hydroxy group. From a synthetic point of view, the available protocols involve either long reaction times at high temperatures,[20,22] harsh reaction conditions using Brønsted acids,[23] or multistep transformations.[24,25] Many of these protocols are run at high temperatures for several days and/or are not compatible with reactive functional groups.

As part of an ongoing medicinal chemistry program, we needed a rapid and smooth method for preparation of a diverse set of *N*-alkylated and ring-functionalized γ- and δ-lactams by direct reaction between a primary amine (**1**) and the corresponding lactone (**2**). Herein we report a fast, acid-free, one-pot, two-step microwave-accelerated lactone to lactam synthesis method in which the 1-butyl-3-methylimidazolium salts [bmim]BF_4 (**3a**) and [bmim]PF_6 (**3b**) promote the ring-closing step. To the best of our knowledge, this ionic liquid-mediated lactamization route provides a unique method for direct synthesis of different γ- and δ-lactams.

As there are previous reports on successful high-temperature synthesis of lactams (**4**) directly from amines and lactones without any additives,[20] it was our original intention to transfer these protocols into a microwave-assisted method in order to facilitate the experimental procedure, to reduce the reaction time, and to improve product purities. Benzylamine (**1a**, 3 equiv) and γ-butyrolactone (**2a**, 1 equiv) served as model substrates in the initial neat experiments (Table 1). All reactions studied were conducted sequentially in disposable borosilicate reaction vessels which were sealed under air and processed with thermocon-

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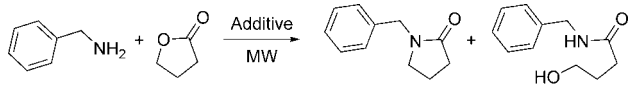
TABLE 1. Microwave-Assisted γ-Lactam Formation. Influence of Reaction Parameters[a]



1a 2a 4a 5a

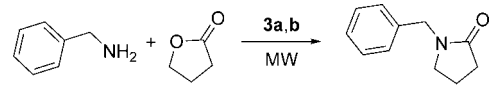
entry	additive **3**	molar ratio (**1a**:**2a**:**3**)	*T* (°C)	time (min)	yield of **4a**[b] (%)	yield of **5a**[b] (%)
1		3:1:0	150	15	8	78
2		3:1:0	220	35	16	47
3		3:1:0	220	420[c]	17	47
4	PTSA[d]	3:1:1	220	35	89	n.d.[e]
5[f]	**[bmim]BF$_4$**	**3:1:1**	**180**	**35**	**82**	**n.d.**[e]

[a] Microwave heating of the reaction mixture on a 2.0 mmol scale using 0.2−0.5 mL sealed tubes. [b] Isolated yield. Purity >95% by GC−MS. [c] 3 × 60 min + 1 × 240 min. [d] In 1 mL of 1,4-dioxane. [e] n.d. = not determined. **5a** <1% according to GC−MS. [f] 1.0 mmol scale in a 0.2−0.5 mL tube.

trolled high-density microwave irradiation. In short, none of the additive-free reactions resulted in complete ring-closure of the readily formed linear hydroxyamide intermediate (**5a**) when heating at 150 or 220 °C (entries 1−3). Increasing the reaction time further than 35 min at 220 °C did not have a positive effect either on the yield (compare entries 2 and 3, Table 1) or on the ratio **4a**:**5a**. These results are consistent with earlier recorded experiments in the literature utilizing classical heating equipment.[26] Inspired by previously reported lactamization procedures,[27−29] attempts were made to promote the cyclization step by including 1 equiv of Brønsted acid in the reaction mixture. Addition of acetic acid at 150 °C gave the opposite effect, and only trace amounts of **4a** was formed although **2a** was almost fully consumed.[30] The use of considerably stronger acids, such as HCl (4.0 M in 1,4-dioxane) and *p*-toluenesulfonic acid (PTSA, **3c**) in 1.0 mL of 1,4-dioxane provided ring-closed **4a** at 180 °C, but still unreacted lactone **2a** remained. At a higher temperature, 220 °C, PTSA promoted the full two-step transformation of **2a** to give **4a** in 89% isolated yield (entry 4, Table 1). However, knowing that polar reaction additives can induce efficient lactamization at high temperatures,[31−34] the highly polar ionic liquid **3a** was evaluated as a ring-closing additive. Rewardingly, **4a** was generated in 82% yield without any traces of **5a** after carrying out the lactam generation in the presence of 1 equiv of **3a** at 180 °C for 35 min (entry 5). Remarkably, no acid was necessary in this one-pot process.

Having identified acid-free conditions for straightforward lactamization, we decided to further improve the protocol, aiming to increase the yield of product **4a** and to evaluate the use of 1,4-dioxane as a cosolvent to improve stirring and solvation of very viscous or solid starting materials. 1,4-Dioxane was chosen on the basis of our experience with the PTSA-catalyzed reaction in Table 1 (entry 4) and because of the need for high thermal stability. The outcome of this cosolvent study and an investigation of other reaction parameters is depicted in Table 2.

TABLE 2. Ionic Liquid-Mediated and Microwave-Assisted γ-Lactam Formation. Influence of Reaction Parameters[a]



1a 2a 4a

entry	ionic liquid **3a**,**b**	molar ratio (**1a**:**2a**:**3**)	*T* (°C)	time (min)	scale (mmol)	yield[b] (%)
1	[bmim]BF$_4$	2:1:1	170	35	1	60
2	[bmim]BF$_4$	2:1:1	180	35	1	77
3	[bmim]BF$_4$	2:1:2	180	35	1	78
4	[bmim]BF$_4$	1:3:1	180	35	1	51
5	[bmim]BF$_4$	5:1:1	180	35	2[c]	n.d.[d]
6	[bmim]BF$_4$	3:1:1	180	60	2[c]	39
7	[bmim]BF$_4$	3:1:1	200	35	2[c]	70
8	**[bmim]BF$_4$**	**3:1:1**	**220**	**35**	**2**[c]	**86**
9[e]	**[bmim]BF$_4$**	**3:2:2**	**220**	**35**	**2**[c]	**99**
10[f]	[bmim]BF$_4$	3:2:2	220	35	0.2	95
11	[bmim]PF$_6$	3:1:1	220	35	2[c]	93
12	[bmim]PF$_6$	3:1:1	220	35	30[g]	88

[a] Microwave heating using a 0.2−0.5 mL sealed tube without a co-solvent. [b] Isolated yield. Purity >95% by GC−MS. [c] Irradiated in 0.5−2.0 mL sealed tube. [d] n.d. = not determined. **4a** not isolated as only ∼50% of **2a** was consumed according to GC−MS. [e] 0.15 mL 1,4-dioxane as cosolvent. [f] 1 mL 1,4-dioxane as cosolvent. [g] Irradiated in a 10−20 mL sealed tube without a cosolvent.

In general, increasing the temperature gave higher yields, but prolonging the reaction time did not improve the preparative outcome (compare entry 5, Table 1, and entry 6, Table 2). It was also found that a 3:1:1 molar ratio of **1a**:**2a**:**3** was preferable and that a greater excess of **1a** resulted in an incomplete conversion of **2a** (entry 5, Table 2). Unfortunately, we were not able to reduce the amount of ionic liquid and retain full transformation of **2a**. The conditions used in entry 8 (220 °C for 35 min) were selected as the most promising neat protocol, providing 86% of product **4a**. Rewardingly, the addition of 1 mL of 1,4-dioxane, together with a reduced excess of **1a**, furnished a quantitative isolated yield of lactam **4a** (entry 9, Table 2). The use of 1,4-dioxane was also important for achieving reproducible results upon reducing the reaction scale down to 0.2 mmol of **2a** (entry 10). The standard ionic liquid **3a** was successfully exchanged to **3b** ([bmim]PF$_6$) (entry 11, Table 2), but the workup of the latter was more complicated due to the solvation properties of [bmim]PF$_6$. The reaction promoted by **3b** was easily scaled-up by 30 times and afforded similarly high isolated yields (entry 12).

The scope of the method was explored with various primary amines (**1b**−**q**) and **2a** to form pyrrolidinones **4b**−**q**, as described in Table 3. Lactamizations were carried out according to either of two protocols, one protocol without any cosolvent, hereafter called method **A** (entry 8, Table 2), or one with the reaction system solvated in 1,4-dioxane, method **B** (entry 9, Table 2).

Using method **A**, less sterically hindered amines, adjacent to primary or secondary carbons, gave γ-lactams in good to excellent yields (entries 1−3, 5, and 6, Table 3). Under the same type **A** conditions, enantiopure **1h** and **1i** were converted into **4h** and **4i** in excellent yields (97−99%) and without any detected racemization. Note also that the acid-sensitive protecting group,

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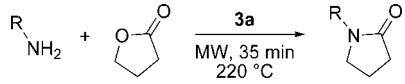
TABLE 3. Direct γ-Lactam Formation From γ-Butyrolactone and Primary Amines[a,b]



1b-r 2a 4b-r

entry		amine	method[b]	product	yield[c] (%)
1	**1b**	*n*-hexylamine	**A**	**4b**	96
2	**1c**	5-amino-1-pentanol	**A**	**4c**	92
3	**1d**	3-chlorobenzylamine	**A**	**4d**	84
4	**1e**	2,2-dimethoxy-ethanamine	**A**[d]	**4e**	54
5	**1f**	isopropylamine	**A**	**4f**	93
6	**1g**	cyclohexylamine	**A**	**4g**	85
7	**1h**	(*S*)-1-phenyl-ethylamine	**A**	**4h**	99[e]
8	**1i**	(*R*)-1-phenyl-ethylamine	**A**	**4i**	97[e]
9	**1j**	1-aminoindan	**A**	**4j**	47
10	**1k**	*cis*-1-amino-2-indanol	**A/B**	**4k**	63/53
11	**1l**	aniline	**A**	**4l**	74
12	**1m**	L-H-*t*-Leu-NHMe	**A/B**[f]	**4m**	38/62
13	**1n**	L-tyrosine ethyl ester	**A/B**	**4n**	19/21
14	**1o**	*tert*-butylamine	**A**	**4o**	30
15	**1p**	1,1,3,3-tetramethylbutylamine	**A**	**4p**	23
16	**1q**	1-adamantanamine	**A**	**4q**	73
17	**1r**	phenylhydrazide	**A**	**4r**	32

[a] All reactions were performed in a 0.5−2.0 mL sealed tube with 2 mmol of **2a** and 2 mmol of [bmim]BF_4 under 35 min of microwave irradiation at 220 °C. [b] Method **A**: 6 mmol of **1** without a cosolvent. Method **B**: 3 mmol of **1** and 1 mL of 1,4-dioxane. [c] Isolated yield. Purity >95% by GC−MS and NMR. [d] The temperature was reduced to 210 °C after 21 min of processing due to high pressure. [e] No racemization as deduced by chiral HPLC and optical rotation measurements. [f] No 1,4-dioxane.

1-phenylethyl,[35] remains intact. To further illustrate the advantage of an acid-free protocol, dimethyl acetal **1e** was used to form lactam **4e** in an acceptable yield (54%), without any detectable formation of the corresponding aldehyde. Although reactions with hydroxy-functionalized *cis*-1-amino-2-indanol (**1k**) did not afford more than 63% and 53% yields employing method **A** and **B**, respectively, 5-amino-1-pentanol (**1c**) furnished 92% of lactam **4c**. The more nucleophilic amino group was found to react exclusively, and no side product from a competing transesterification could be detected. Good results were also experienced with the weak nucleophile aniline (**1l**, entry 11). Solid amino acid derivatives such as L-*t*-leucine methyl amide (**1m**) and L-tyrosine ethyl ester (**1n**) furnished lactams only in low to acceptable amounts, possibly due to the difficult workup and isolation of the highly polar products **4m**,**n** or problems with insufficient magnetic stirring in the microwave vial. It should be noted that hydrolysis of the ethyl ester in **1n**/**4n** occurred only to a very limited extent. Reducing the amount of **1m** increased the yield of **4m** from 38% to 62%, maybe due to a more efficient mixing of the solid amine with the lactone and the ionic liquid. Amines that can form stabilized carbocations, *tert*-butylamine (**1o**) and 1,1,3,3-tetramethylbutylamine (**1p**), furnished *N*-alkylated lactams in lower amounts (entries 14 and 15), and unsubstituted γ-lactam was found as the major side product. The reaction with the cyclic 1-adamantanamine (**1q**), on the other hand, gave **4q** in a good isolated yield of 73% (entry 16). Although phenyl hydrazide only yielded 32% of *N*-(2-oxo-1-pyrrolidinyl)benzamide (**4r**, entry 17), the reaction showed that the protocol could be directly applied with another nucleophile without any further alterations.

To investigate the generality of the methodology with different lactones and ring sizes, we selected benzylamine (**1a**)

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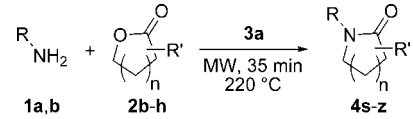
TABLE 4. Direct γ-, δ-, and ε-Lactam Formation from Lactones and Benzylamine or *n*-Hexylamine[a,b]



1a,b 2b-h 4s-z

entry	amine	lactone	method[a]	product	yield (%)[b]
1	**1a**	**2b**	**A**	**4s**	93
2	**1b**	**2b**	**A**	**4t**	91
3	**1b**	**2c**	**A**	**4u**	42
4	**1b**	**2d**	**A/B**	**4v**	56/43
5	**1a**	**2e**	**A**	**4w**	50
7	**1b**	**2e**	**A**	**4x**	65
8	**1b**	**2f**	**A/B**	**4y**	73[c]/0
9	**1b**	**2g**	**A/B**[d]	**4z**	12/30
10	**1b**	**2h**	**A/B**	-	0[e]/0

[a] All reactions were performed in a 0.5−2.0 mL sealed tube with 2 mmol of **2a** and 2 mmol of [bmim]BF_4 under 35 min of microwave irradiation at 220 °C. [b] Method **A**: 6 mmol of **1** without a cosolvent. Method **B**: 3 mmol of **1** and 1 mL of 1,4-dioxane. [c] Isolated yield. Purity >95% by GC−MS and NMR. [d] No saturated lactam **4y** could be isolated. [e] 240 °C and 4 mL of 1,4-dioxane. [f] Only linear hydroxyamide **5#** could be isolated in 89% yield.

and *n*-hexylamine (**1b**) as model reactants. The preparative results are summarized in Table 4.

The reactions with γ-phenyl-γ-butyrolactone **2b** were high yielding with both **1a** and **1b** (entries 1 and 2, Table 4). Even lactones susceptible to side reactions, such as α-methylene-γ-butyrolactone (**2c**) and tetronic acid (**2d**), could be employed to yield satisfactory amounts of lactams **4u** and **4v**, respectively, despite the large excess of basic amine (entries 3 and 4, Table 4). Unfunctionalized δ-lactone **2e** was transformed to products **4w** and **4x** in good yields. The experiment with mevalonic acid lactone **2f** resulted in the α,β-unsaturated lactam **4y** in 73% yield by a concomitant dehydration elimination reaction (entry 8). Thus, no saturated β-hydroxy-β-methyl-δ-valerolactam could

be isolated. *N*-Hexyl-ϵ-caprolactam **4z** was formed in small amounts from **2g** when method **A** was employed. When method **B** was used at 220 °C, **2g** was not fully consumed, but fewer side products could be detected by GC−MS and LC−MS. By raising the temperature to 240 °C and diluting the sample with 4 mL of 1,4-dioxane, thus avoiding extensive polymerization, moderate amounts of product **4z** (30%) could be isolated. As expected, the first step in the reaction of **1b** with 2-coumarone **2h** was straightforward, but the second step, involving intermolecular substitution of the phenol-hydroxy group, did not occur and no lactam product could be detected. Nevertheless, the linear hydroxyamide **5#** was isolated in 89% yield (entry 10, Table 4).

In most cases, method **B** did not prove to be superior to method **A**, although when used, there were less side products in the reaction mixture.

The results presented here demonstrate that ionic liquids **3a**,**b** are useful for promoting the one-pot lactamization process. In an attempt to understand the role of the ionic liquid more in detail, hydroxyamide **5a** was isolated from the product mixture of entry 1, Table 1, and used as the starting material in two model experiments. It was found that 1 equiv of [bmim]BF_4 (**3a**) assisted the ring-formation of purified **5a** under microwave irradiation at 220 °C for 35 min to form lactam **4a** in 90% yield. In contrast, the cyclization reaction was limited to only yield 8% of **4a** in the absence of **3a**. Accordingly, we postulate that under investigated microwave-conditions, the presence of **3a**,**b** is essential for acid-free ring-closing, but not for the preceding lactone-opening step.

The presented direct lactamization of lactones is an expedient procedure that couples the unique capacity of highly polar ionic liquids to mediate sluggish substitution reactions without the addition of acids or bases, with the rapid reaction times associated with microwave methods. In general, the protocol results in very few side products and can be exploited for facile preparation of both γ- and δ-lactams using functionalized aliphatic and aromatic primary amines. Although only a limited number of examples are provided here, we believe that the ease of operation of this one-pot, two-step procedure and, in particular, the suitability of the method for synthesis of γ-butyrolactams carrying sensitive functional groups will prove to be useful for the synthetic community.

Experimental Section

General Experimental Procedure A for Lactam Formation from Lactones and Primary Amines (Tables 3 and 4). A mixture of corresponding lactone **2** (2.00 mmol), amine **1** (6.00 mmol), and ionic liquid **3a** (2.00 mmol, 374 μL) was vortexed in a sealed vessel for 20−30 s prior to microwave irradiation at 220 °C for 35 min. The cold reaction mixture was diluted with 100 mL of ethyl acetate and washed with saturated aq NH_4Cl, concentrated in vacuo, and purified by flash chromatography using silica (isohexane/ethyl acetate/methanol) to afford products **4a**−**z** and **5#**.

General Experimental Procedure B for Lactam Formation from Lactones and Primary Amines (Tables 3 and 4). A mixture of corresponding lactone **2** (2.00 mmol), amine **1** (3.00 mmol), ionic liquid **3a** (2.00 mmol, 374 μL), and 1.0 mL of 1,4-dioxane was treated as previously described under general experimental procedure **A** to afford products **4a**,**k**,**m**,**n**,**v**,**y**,**z**.

1-(3-Chlorobenzyl)-2-pyrrolidinone (4d). Produced according to general experimental procedure **A**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.22 (2H, m); 7.22−7.19 (1H, m); 7.14−7.08 (1H, m); 4.41 (2H, s); 3.28−3.23 (2H, m); 2.47−2.40 (2H, m); 2.05−1.95 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1; 138.8; 134.7; 130.1; 128.2; 127.9; 126.3; 46.8; 46.2; 30.9; 17.9. GC−MS *m*/*z*: 210, 212 ($M + H^+$); 174; 146; 125; 84. Anal. Calcd for $C_{11}H_{12}ClNO \cdot {}^1/_4H_2O$: C, 61.69; H, 5.88; N, 6.54. Found: C, 61.87; H, 5.77; N, 6.87. Pale oil.

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Supporting Information Available: General Experimental Procedure paragraphs, compound characterization data, and copies of spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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