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Water-based conditions for the microscale parallel synthesis of bicyclic lactams

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ABSTRACT

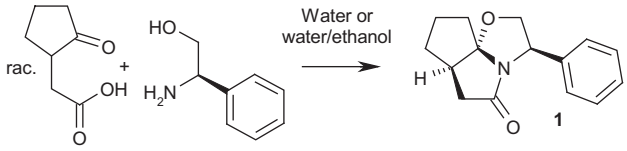
We report efficient miniaturized conditions to prepare arrays of bicyclic lactams for screening. The nature of the solvent is usually an important factor of reactivity. At a small synthesis scale, when automated pipetting devices are required, physical properties of the solvent, such as surface tension and vapor pressure also become very important. After having shown that a complete evaporation of a solution of reagents in water or a mixture of ethanol and water yields the expected lactams, we exemplified the reaction and procedure with the preparation of a library of 80 members. Our synthesis scheme is validated for synthesis scales from 1 to 100 mg. Therefore, it can be used both to produce rapidly test samples for HTS as well as to prepare intermediates for the synthesis of more elaborated nature-inspired compounds.

Meyers' lactamization[1] is a bielectrophile–binucleophile reaction that gives access to complex bicyclic lactams (Scheme 1).[2] It is a well known tool for the synthesis of natural products, especially alkaloids since it allows the formation of key quaternary centers in a stereoselective manner.[3] It is also used for the synthesis of chiral amines in drug discovery.[4] Moreover, the diversity, complexity, and compactness of products obtained make this reaction highly attractive to feed libraries for High-throughput Screening.[2]

In this reaction, a keto-acid reacts with a chiral amino-alcohol. Amino-alcohols are available at low cost and many derive from the chiral pool of natural amino acids. A version of this reaction using other binucleophiles such as diamines has been reported.[5] Usually, γ-keto-acids or esters,[5] δ- or ω-keto-acids constrained or not, are used.[6] Recently, Meyers' lactams were obtained from furans.[7]

Historically, Meyers' lactamization proceeds in toluene, with either an acid catalyst or molecular sieves.[5,8] The synthesis is efficient but reaction times are usually long (12–48 h), and it is usually performed in a Dean–Stark apparatus. In order to reduce the use of solvents such as toluene, we decided to explore the use of solvent-free microwave heating and water-based protocols to access these compounds. To further lessen the environmental impact of parallel synthesis, we also wish to down-size the synthesis.

Solvent-free microwave irradiation has proven to be an efficient environment-friendly procedure for the synthesis of various templates.[9] We have first disclosed a procedure with microwave solvent-free conditions.[10] This procedure allows the synthesis of compounds on a scale from 20 to 100 mg. A solvent-free reaction requires a weighing step that is not easily automated and makes cumbersome the preparation of large arrays of compounds. Therefore, we considered the use of water or water–ethanol mixtures to dispense reagents at low scale (microtiter plates). The use of water as a solvent at lab scale is growing. Indeed, both surface tension and vapor pressure of water make it much easier to handle in pipetting devices than most organic solvents. Also, water is inexpensive, abundant, and nontoxic[11] and water–ethanol mixtures are environmentally sound[12] as opposed to volatile organic solvents. Furthermore, water is already used as a solvent in various lactamization reactions.[13]



Scheme 1. Meyers' lactamization using water media.

We describe in this letter a new water-based synthesis of Meyers' bicyclic-lactams and analogues. Eventually, we disclose the microscale parallel synthesis of a pilot 80-member library compatible with subsequent biological screening.

We previously optimized the reaction conditions in aqueous medium on prototypal compound **1**. In an aqueous solution, total

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URLs: http://www.deprezlab.fr, http://www.drugdiscoverylille.org (Benoit Deprez).

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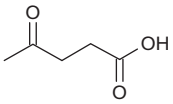
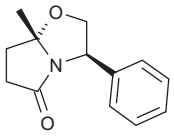
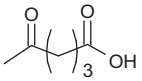
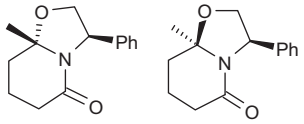
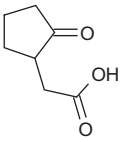
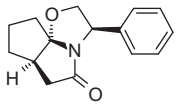
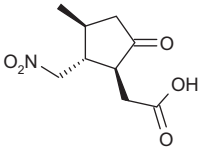
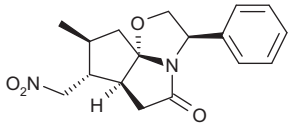
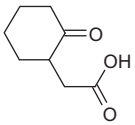
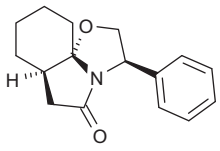
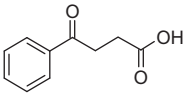
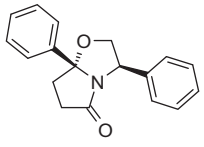
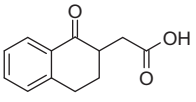
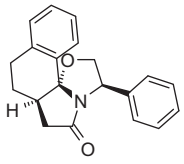
conversion of reagents into **1** requires 16 h of heating allowing a complete evaporation of water.

Selecting and synthesizing precursors

A diverse set of keto-acids was gathered. It included linear (Table 1, entries 1, 2, and 6), cyclic (entries 3–5, 7–10), and aliphatic (entries 1–2) keto-acids. Among the precursors, three are δ-keto-acids (entries 2, 9–10). Two keto-acids present a phenyl ring in alpha of the ketone function (entries 6–7) and two other compounds display a piperidine ring (entries 9–10) among which **3d** bears a positive charge. These piperidines are found in many bioactive compounds and display nitrogen that can be further derivatized. Interestingly, tetralone template (entries 7–8) is found in drug candidates such as serotonine receptor ligands.[4]

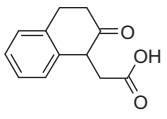
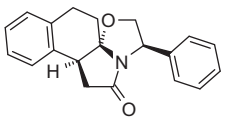
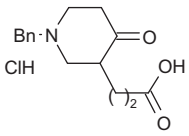
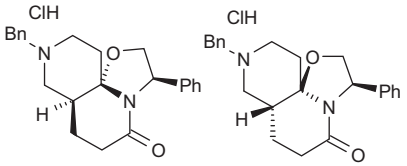
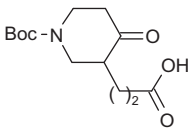
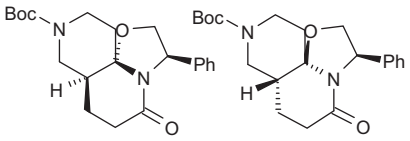
Most of the selected keto-acids were commercially available, others were synthesized **3a–d.** The tetralone derivatives **3a–b** were synthesized from the corresponding ketones (Scheme 2). Keto-acids can also be obtained from the corresponding unsaturated carboxylic acids.[14] The α-tetralone derivative **3a** was synthesized in 2 steps from α-tetralone. For the first step, the use of glyoxalic acid in acidic conditions[15] gave better results than the Knoevenagel reaction in basic conditions. Keto-acid **3a** was obtained from **2a** by reduction using classical conditions.[16] The β-tetralone derivative **3b** could not be obtained by the same procedure as the reduction step led to degradation of the unsaturated intermediate. β-Tetralone was thus reacted with *tert*-butyl bromoacetate in the presence of NaH. The use of unprotected ester was unsuccessful and the use of ethyl ester led to the formation of the unsaturated lactone. The *tert*-butyl moiety was removed with TFA. Piperidone

Table 1
Scope of the reaction with various keto-acids in reaction with *R*-phenylglycinol

Entry	Keto-acid[a]	Lactams	Yield (%) water (solvent-free μwave)
1		 **4**	76
2		 **5a/5b**	79[c]
3		 **1**	97
4		 **6**	86
5		 **7**	55
6		 **8**	59
7	 **3a**	 **9**	8 (5)

(*continued on next page*)

Table 1 (*continued*)

Entry	Keto-acid[a]	Lactams	Yield (%) water (solvent-free μwave)
8	 **3b**	 **10**	73 (5)
9	 **3d**	 **11a/11b**	65[b]
10	 **3c**	 **12a/12b**	80[c]

[a] All chiral keto-acids were used as racemic forms, except for 2-nitromethyl5-oxocyclopentaneacetic acid derivative (entry 4).
[b] Ratio of diastereoisomers 90/10 (before separation) measured by LCMS and NMR.
[c] Ratio of diastereoisomers 80/20, measured by LCMS and NMR.

derivatives **3c–d** were also synthesized. Compound **3c** was obtained as previously described.[17] In **3d**, the Boc group that was used to protect the nitrogen of the piperidone core in **3c** was replaced by a benzyl group. First, 1-benzyl-3-carbethoxy-4-piperidone was reacted with methylacrylate in acetone in the presence of cesium carbonate to give the alkylated intermediate **2d**. Hydrolysis and decarboxylation using 6 N HCl gave **3d** (Scheme 3).

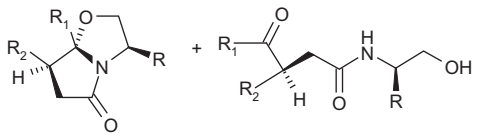
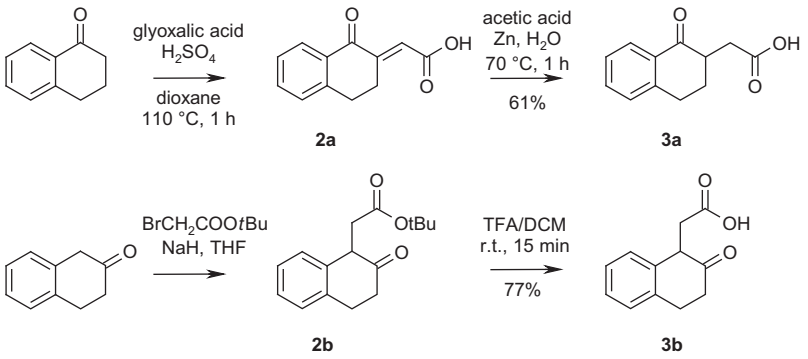
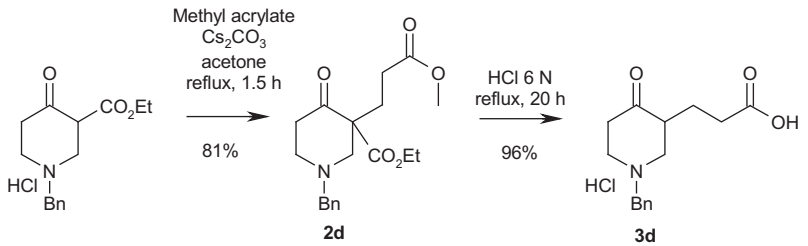


Figure 1. Expected bicyclic lactam and non-cyclic amide by-product.

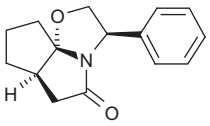
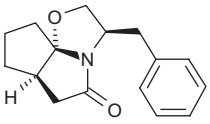
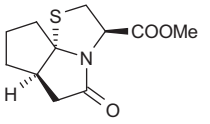
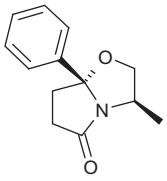
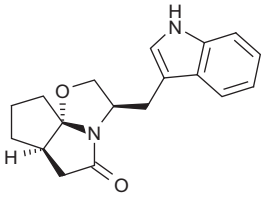
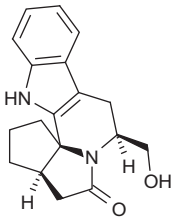
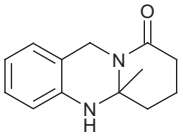
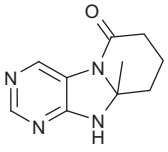


Scheme 2. Synthesis of keto-acid from tetralones.

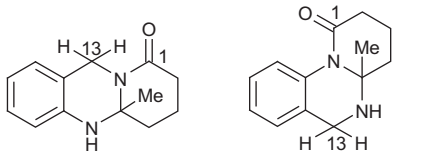


Scheme 3. Synthesis of keto-acid **3d** based on the piperidone template.

Table 2
Scope of the reaction with various binucleophiles[a]

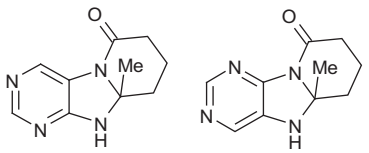
Entry	Binucleophile	Lactams		Yield (%) water (μwave)
1	*R*-Phenylglycinol		**1**	97
2	*R*-Phenylalaninol		**13**	80
3	L-Cysteine methyl ester		**14**	27[b] (97)
4	D-Alaninol		**15**	55 (0[c])
			**16a**	
5	L-Tryptophanol		**16b**	85[d]
6	*o*-Aminobenzylamine[e]		**17**	73
7	Diaminopyrimidine[e]		**18**	66

[a] Compound **1**, **13**–**14**, **16** obtained with 2-oxocyclopentane acetic acid; compound **15** obtained with 3-benzoylpropionic acid; compound **17**–**18** obtained with 4-acetylbutyric acid.
[b] Partial hydrolysis of methyl ester into carboxylic acid was observed.
[c] Only the amide by-product was observed.
[d] Ratio **16a**/**16b** 67/33 measured by LCMS and NMR.
[e] Solubilized in ethanol.



17 **regioisomer not observed**

Figure 2. Structure of **17**.



18 **regioisomer not observed**

Figure 3. Structure of **18**.

Table 3
Quality control of a representative sample of the library[a]

Binucleophile	Keto-acid	MH^+	Purity (%)
R-Phenylglycinol	4-Acetylbutyric acid	232	85
S-Phenylglycinol	4-Acetylbutyric acid	232	85
(1*R*,2*S*)-1-Amino-2-indanol	4-Acetylbutyric acid	244	93
(1*S*,2*R*)-1-Amino-2-indanol	4-Acetylbutyric acid	244	91
D-Alaninol (*R*)	3-Benzoylpropionic acid	218	95
(*S*)-2-Amino-3-methyl-1-butanol	3-Benzoylpropionic acid	246	86
R-2-Amino-3-phenyl-1-propanol	4-Acetylbutyric acid	246	85
R-2-Amino-3-phenylmethoxy-1-propanol	4-Acetylbutyric acid	276	95
L-Tyrosinol(benzyl) (*S*)	4-Acetylbutyric acid	354	85
2-Aminophenol	4-Acetylbutyric acid	204	80
o-Phenylenediamine	4-Acetylbutyric acid	203	88
Diaminopyrimidine	4-Acetylbutyric acid	205	80
o-Aminobenzylamine	4-Acetylbutyric acid	217	92
R-Phenylglycinol	Levulinic acid	218	98
R-Phenylglycinol	2-Oxocyclopentaneacetic acid	244	83
R-Phenylglycinol	3-Benzoylpropionic acid	280	95
R-Phenylglycinol	**3b**	317	91

[a] Purity is determined by LC/MS at 215 nm.

Scope of the reaction

In order to evaluate the scope of the reaction in water, the ten selected keto-acids were reacted with *R*-phenylglycinol (Table 1). All compounds derived from γ-keto-acids gave the pure diastereoisomer as expected.[10] Like other δ-keto-acids,[18] piperidine-based bicyclic lactams **11** and **12** were obtained with good yields (65–80%) as mixtures of 2 diastereoisomers (entries 9 and 10 vs entry 2), with a diastereoisomeric excess of 60%. Bicyclic lactams **4–8** (Table 1) were obtained with yields similar to those obtained using the microwave solvent-free procedure. Tetralone **3a** (entry 7) which ketone is deactivated by the adjacent phenyl is far less reactive than its linear analogue (entry 6). Surprisingly, tetralone **3b** gave the expected compound in water while the solvent-free microwave heating gave mainly the non-cyclic amide by-product (Fig. 1).

To further explore the scope of the reaction, chiral amino-alcohols and more unusual binucleophiles were selected to react with various keto-acids (Table 2). 2-Oxocyclopentanacetic acid reacted with *R*-phenylglycinol and *R*-phenylalaninol (entries 1–2) to give the corresponding lactams in very good yields (80–97%). On the opposite, lactam **14** (entry 3) was obtained from cysteine methyl ester in a low yield due to partial hydrolysis of the methyl ester function. Lactam **15** from D-alaninol and 3-benzoylpropionic acid (entry 4) was obtained in only 55% yield using the aqueous protocol because of the lower reactivity of the keto-acid (already exemplified in Table 2, entry 6). Interestingly, under microwaves, only the amide by-product was obtained. As expected from previous results,[10] L-tryptophanol (entry 5) can give along with the expected lactam **16a**, compound **16b** resulting from cyclization at the C-2 of the indolyl ring to produce the corresponding tetrahydro-β-carboline. Surprisingly, whereas the Pictet–Spengler product **16b** is the major compound (98%) under microwave conditions,[10] it is the minor compound (37%) using water. In all reactions using chiral amino-alcohols, the expected single diastereoisomer was obtained. With diamines (entries 6–7), bicyclic lactams **17–18** were obtained in good yields (66–73%) as racemic mixtures. Two regioisomers could be expected from each of the diamine precursors (Figs. 2 and 3, and Supplementary data). Interestingly, only one regioisomer was isolated in each case. A long distance correlation proton–carbon (HMBC NMR experiment) was observed between the hydrogen atoms at C_{13} in the benzylic position and C_1 from the lactams function. This allowed assigning the structure of **17** (Fig. 2).[5] In the case of **18**, the structure, established by the X-ray crystal analysis (Fig. 3 and Supplementary data) is consistent with the previously published results.[19]

Library synthesis

According to the scope of the reaction (Table 1 and 2), five keto-acids and 16 binucleophiles (Supplementary data) were selected for the parallel synthesis under aqueous conditions of a 80-lactam library. In that case, as reagents are first solubilized in the solvent to be distributed by the liquid handling system, we used either pure water or water/ethanol mixtures (Supplementary data).[20]

Binucleophiles were selected among commercially available compounds on the basis of several criteria: (1) price and availability; (2) solubility in water or water/ethanol mixtures; (3) reactivity (assessed by μmol scale); and (4) chemical diversity. The chemical diversity was assessed by sorting compounds according to the nature of the *R* group (Fig. 1), the nature of the second nucleophilic function, the presence of cycles, and the configuration of the C in the alpha of nitrogen (Supplementary data).

The five ketoacids were selected on the basis of several criteria: (1) reactivity (assessed at μmol scale by reaction with *R*-phenylglycinol); and (2) solubility in water or water/ethanol mixtures (Supplementary data).

All structures were generated using Pipeline Pilot from Accelrys. (Supplementary data). The completion of the reaction was checked by LCMS and the purity of the ready-to-screen library was found to be 80% of compounds above 85% purity (Table 3). The lowest conversions were observed for 2-amino-phenol due to the formation of the amide as a side product (Fig. 1).

In conclusion, we have successfully developed a method useful for the parallel synthesis of bicyclic lactams as water is well suited for the synthesis by the micromole scale using liquid-handling systems. As an example, we synthesized a 80-member library, containing 67% new structures,[21] that can be used for the direct in situ screening, in addition to the new compounds in Table 1.

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Supplementary data

Supplementary data (detailed synthesis and spectral data for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.082.

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20. *Library synthesis (15 μmol-scale).* After checking the solubility of reagents, 0.25 M solutions of keto-acids and binucleophiles are prepared in water or in a mixture of water and ethanol (50/50). The drying-oven is preheated and the reagents stock-solutions are placed on the liquid-handling system. In each well, 60 μL (15 μmol) of the solution of binucleophiles are deposited by the liquid-handling system. CAUTION: It is necessary to change the value of the dispense speed between the solution of water and the solution with ethanol to avoid projections. Tips are then washed. In each well, 60 μL (15 μmol) of the solution of keto-acids are deposited by the liquid-handling system. Then, the 96-well plate is placed on the stove at 100 °C. After 16 h, the plate is removed from the stove. The completion of the reaction is checked by LCMS.
21. Based on a search in Reaxys database as of November 2012. See Supplementary data.