Solvent-free microwave-assisted Meyers' lactamization†

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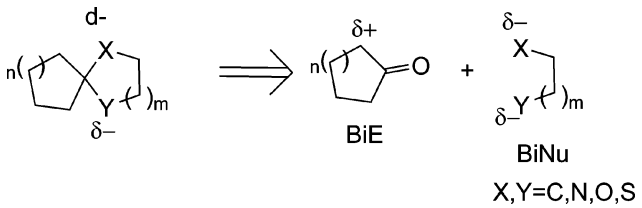
Microwave solvent-free conditions developed for Meyers' lactamization, a typical bielectrophile-binucleophile reaction that produces quaternary centers in a stereoselective manner, give access to Meyers' chiral lactams in good yield and high diastereoselectivity in short times.

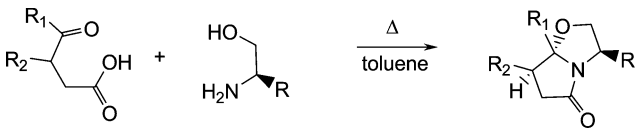
Meyers' lactamization is a typical bielectrophile-binucleophile reaction (BiE-BiNu reaction) that produces quaternary centers, most of the time in a stereoselective manner (Scheme 1).[1] It is a well known tool for the synthesis of natural products, especially alkaloids. This stereoselective reaction is the first step to access *Erythrina* and Amaryllidaceae alkaloids.[2,3]



Scheme 1

Generally speaking, the bicyclic or tricyclic lactams, obtained through Meyers' reaction, are of high synthetic interest.[4] Apart from natural product synthesis, they are useful intermediates for the synthesis of chiral amines in drug discovery.[5] Meyers' lactamization proceeds through the reaction of a keto-acid with an amino-alcohol (usually chiral) (Scheme 2). Many chiral amino-alcohols are readily available at low cost and many of them derive from the chiral pool of natural aminoacids. These enantiomerically-pure building blocks can be assembled into the desired chiral product.

Interestingly, a procedure for deracemization of β-amino-alcohols using a sugar auxiliary was recently published.[6] This could be useful for β-amino-alcohols that are only available as racemates. Keto-acids used in Meyers' reaction are usually γ-keto-acids or esters.[7] Recent examples were also reported for δ- or ω-keto-acids, constrained or not.[8]



Scheme 2

Most of the time, Meyers' lactamization is performed in toluene, with or without a Dean–Stark apparatus.[9,10] Some teams report the use of either an acid catalyst (CSA, PTSA, *etc.*) or molecular sieves.[7,11] Though the synthesis is efficient, reaction times are usually long (12–48 h) and the use of Dean–Stark apparatus prevents the automation of the synthesis. In order to reduce reaction times we decided to explore the use of microwave heating.

Microwave irradiation is now a common alternative to conventional heating and shows clear benefits in terms of yield and kinetics for many chemical transformations. Previous attempts to use toluene and microwaves for lactamization were encouraging.[12] We then decided to shift to solvent-free procedures to get rid of toluene which is always used in large amounts in these kinds of reactions because of the low solubility of precursors (concentrations usually do not exceed 10 mM).[13] Solvent-free microwave irradiation has proven to be an efficient environment-friendly procedure for the synthesis of various templates.[14] We describe here the first solvent-free microwave-assisted synthesis of Meyers' bicyclic-lactams.

In a first step we optimized the irradiation parameters (Table 1). To explore these parameters, we studied the synthesis of known Meyers' lactam **1** obtained from *R*-phenylglycinol with 2-oxocyclopentaneacetic acid. This compound is obtained in 12 h with a 94% yield in refluxed toluene (Dean–Stark) (entry 12).[15] In this solvent, under microwaves, with a temperature set at 110 °C, condensation is completed in 10 min (entries 10–11).

For solvent-free conditions, at the same temperature, reaction time from 2 to 6 min and power from 50 to 150 W were needed. A power of 50 W proved to be insufficient (entries 1–3). Best conversions, above 90%, were obtained for a minimum reaction time of 4 min, with power sets to 100 or 150 W. Nevertheless, in the latter condition, yields were lower due to harder purification of crude product. Thus conditions chosen to explore the scope of this protocol were 110 °C, 4 min and 100 W (entry 5).

The keto-acid set for Meyers' lactamization was explored using *R*-phenylglycinol, the most widely used amino-alcohol for asymmetric synthesis (Table 2). Expected products were

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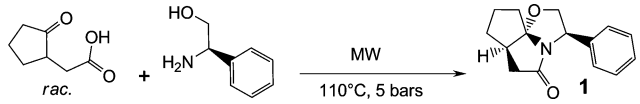
† Electronic supplementary information (ESI) available: Compound characterization and NMR spectra. CCDC reference numbers 749287 and 749288. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924111f

Table 1 Optimisation of irradiation for solvent-free reactions.



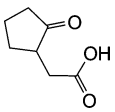
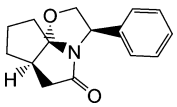
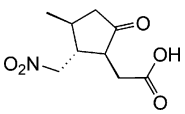
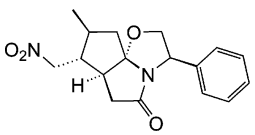
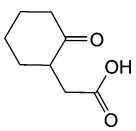
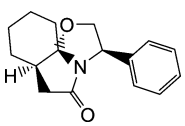
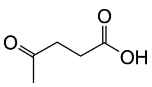
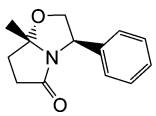
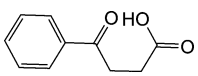
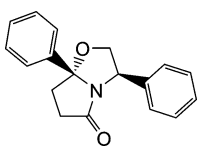
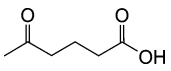
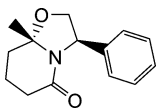
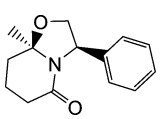
Eentry	Time/min	Power/W	Conversion (%)	Yield (%)
1	2	50	30	27
2	4	50	49	45
3	6	50	54	48
4	2	100	90	89
5	4	100	100	96
6	6	100	100	91
7	2	150	95	88
8	4	150	100	90
9	6	150	100	82
10[a]	5	100	18	—
11[a]	10	100	100	93
12[b]	12 h, toluene, Dean–Stark	94		

[a] In toluene 0.18 M. [b] See ref. 14.

obtained with excellent yields (84–97%) and good diastereoisomeric excess without any other work-up than extraction. The lowest yield was obtained for compound **5** due to a less reactive ketone leading to the presence of the non-cyclic amide byproduct.[16] For γ-keto-acids (entries 1–5), excellent diastereoisomeric excess was obtained. For entry 6, as reported earlier for δ-keto-acids, diastereoisomeric excess was 60%.[17,18]

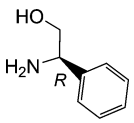
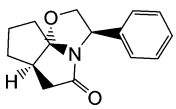
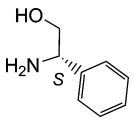
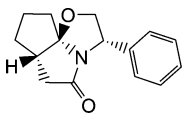
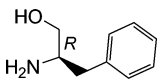
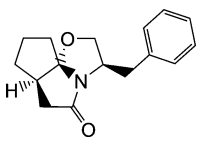
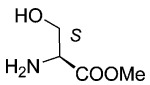
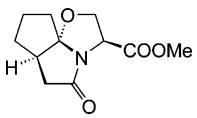
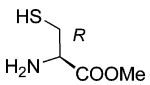
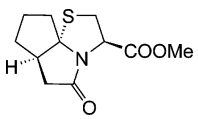
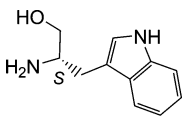
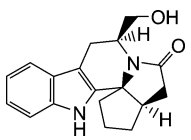
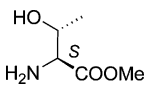
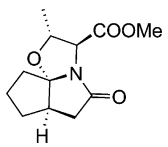
We next turned our attention to examining the scope of the reaction between the 2-oxo-cyclopentaneacetic acid and several amino-alcohols (Table 3). Excellent conversions were observed for various amino-alcohols (entries 1–5). Lower yields were obtained for the serine derivative because of lower thermal stability of serine leading to reactive by-products. Interestingly with serine, only one diastereoisomer was obtained in contrast to results with refluxed toluene conditions. This may be due to the shorter reaction time under microwave irradiation that could avoid the racemisation of the Cα in serine.[7] X-Ray diffraction of crystals of threonine derivative **12** confirmed the stereochemistry of the reaction (Fig. 1).[19]

Table 2 Performance of various keto-acids in reaction with *R*-phenylglycinol. here

Entry	Keto-acid	Product	d.e. (%)[a]	Yield (%)
1			100	96
2			100	97
3			100	84
4			100	94
5			100	69
6			60	68 (**6a**)
				17 (**6b**)

[a] d.e.: diastereoisomeric excess measured by HPLC or NMR.

Table 3 Performance of various aminoalcohols in reaction with oxo-cyclopentanoic acid

Entry	Amino-alcohol	Product	d.e. (%)[a]	Yield (%)
1			100	96
2			100	98
3			100	95
4			100	85
5			100	91
6			100	98
7			100	93

[a] d.e.: diastereoisomeric excess measured by HPLC or NMR.

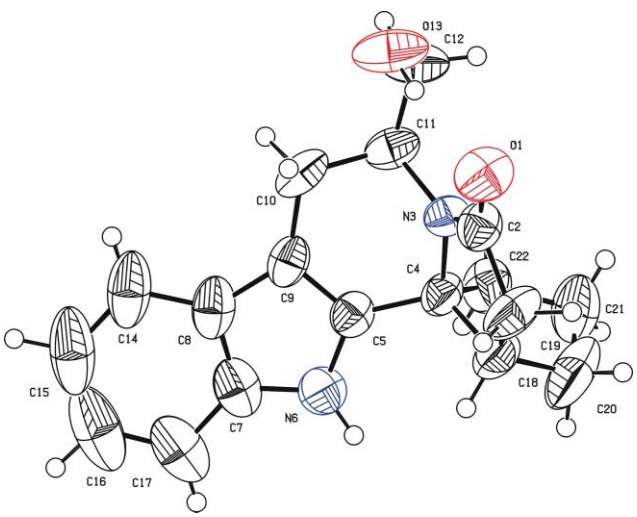


Fig. 1 ORTEP diagram of **12**.

Surprisingly with tryptophanol (entry 6), the expected product was not obtained. NMR analysis revealed that cyclization occurred with the C-2 of the indolyl ring to produce the corresponding tetrahydro-β-carboline **11**. This hypothesis was confirmed *via* X-ray diffraction (Fig. 2).[19]

A similar reaction between a keto-acid and tryptophanol has been previously reported in toluene with 55% yield.[20] Here, the microwave conditions seem to favor the reaction of the C-2 of the indole ring and the formation of the tetrahydro-β-carboline quantitatively.

Conclusion

In summary, general microwave conditions were found to access chiral lactams in good yield, high diastereoselectivity in short times. Work-up was reduced to a simple extraction. This microwave-assisted solvent-free procedure proved to be an excellent alternative to classical Meyers' condensation using a Dean–Stark apparatus, though slightly different regio- and

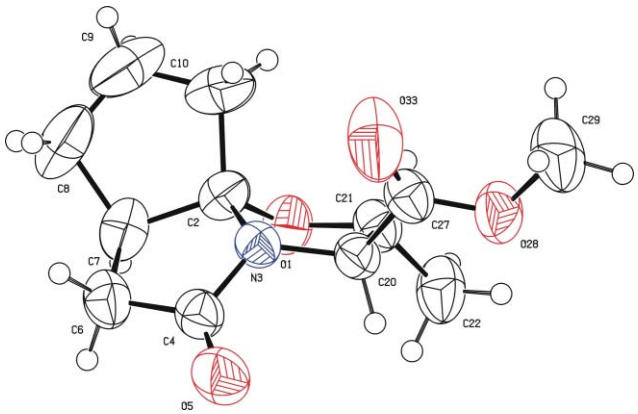


Fig. 2 ORTEP diagram of **11**.

stereo-selectivities were observed. These new conditions are particularly attractive for the synthesis of bicyclic lactams from poorly toluene-soluble keto-acids or amino-alcohols.

Experimental

General procedure

The amino-alcohol (0.32 mmol, 1 eq.) and the ketoacid (0.32 mmol, 1 eq.) were mixed in a capped 10 mL microwave-vessel (reactions were performed using a Discover™ microwave from CEM™). The mixture was heated at 110 °C at least 5 min (average effective ramp time = 1 min). The power was set at 100 W and the pressure was set at 15 bar (average effective pressure = 3 bar). The conversion was directly determined from HPLC-MS analysis. The crude product was dissolved in the minimum DCM (5–10 mL). The organic layer was washed with 1 N HCl (5 mL) and $NaHCO_3$ sat. (5 mL), and dried over $MgSO_4$. Solvent was removed under reduced pressure. Purity (%) was determined by reversed phase HPLC, using UV detection (215 nM).

(3*R*,5a*R*,8a*S*)-3-Phenyl-hexahydro-1-oxa-3a-aza-cyclopenta-[c]pentalen-4-one (1). Yield (409 mg, 94%); off-white crystals; mp = 44–45 °C; $[\alpha]_D$ −163° (c2, CH_2Cl_2); purity: 100%; δ_H (300 MHz; $CDCl_3$) ppm 7.35–7.23 (m, 5 H), 5.13 (t, J = 7.8 Hz, 1H), 4.57 (t, J = 8.7 Hz, 1H), 3.95 (t, J = 7.8 Hz, 1H), 2.88 (dd, J = 17.1, 10.2 Hz, 1H), 2.74–2.64 (m, 1H), 2.45 (dd, J = 17.1, 6.6 Hz, 1H), 2.05-1.87 (m, 2H), 1.81-1.64 (m, 3H), 1.58–1.48 (m, 1H). δ_C (50 MHz; $CDCl_3$) ppm 24.6, 32.3, 36.6, 40.7, 41.4, 57.9, 73.5, 110.9 (Cq), 125.6, 127.4, 128.8, 139.7 (Cq), 180.3 (Cq); rt(LCMS) = 5.22 min; $(M + H^+)$ = 244.

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