Fast Synthesis of Amino Acid Salts and Lactams without Solvent under Microwave Irradiation

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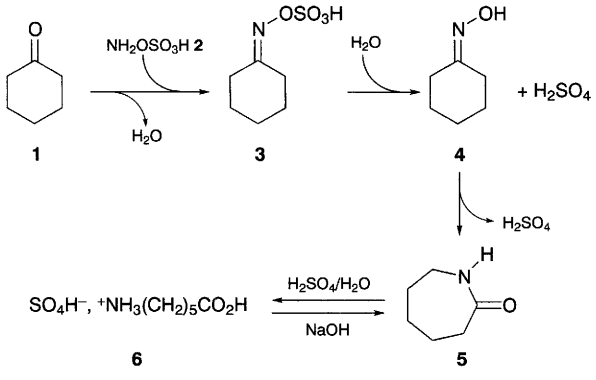
Hydroxylamine-*O*-sulfonic acid reacts with alicyclic ketones over SiO_2 under microwave irradiation to give an amino acid salt, which cyclises in high yield to the corresponding lactam after work up in basic medium.

In 1979, Olah[1] reported a one-step conversion of alicyclic ketones into lactams with hydroxylamine-*O*-sulfonic acid (HOSA) and formic acid under reflux. He suggested that the reaction proceeds through a non-isolated *O*-sulfonic oxime, which decomposes to an oxime and sulfuric acid promoting the Beckmann rearrangement to the lactam. More recently, Sato[2] catalysed the rearrangement of oximes by the combined use of tetrabutylammonium perrhenate(VII), trifluoromethane sulfonic acid and hydroxylamine hydrochloride at reflux in $MeNO_2$.

In connection with our studies related to the condensation of carbonyl compounds with amines, in heterogeneous media under microwave irradiation,[3–5] we report now a new procedure for a fast and efficient synthesis of amino acid salts or the corresponding lactams according to the following mechanism exemplified for cyclohexanone (Scheme 1).

Typical procedure: cyclohexanone **1** (2.5 mmol) and HOSA **2** (1.2 equiv.) are adsorbed over SiO_2 (2 g). After leaving to stand for 2 h at room temp., H_2O (1 equiv.) is added and the mixture is irradiated in a focused microwave oven (PROLABO MX 350)[6] for 10 min at 30 W. Extraction with acetone and evaporation after drying lead to a quantitative yield of ε-amino caproic acid salt **6**. Neutralization of the aqueous solution of **6** (NaOH) and extraction (CH_2Cl_2) lead to crystalline caprolactam **5** in 86% yield.



Scheme 1

The mechanism in Scheme 1 was established by the following experiments.

Cyclohexanone and HOSA are mixed with anhydrous $MgSO_4$. Extraction with acetone and evaporation gave **3**, characterized by ^1H, ^{13}C NMR and HRMS. As expected, **3** is the primary product of the reaction, isolated for the first time. Over SiO_2 in the presence of the condensation water, **3** gives oxime **4** together with H_2SO_4. This second step is demonstrated in the following way: cyclohexanone and HOSA are absorbed over SiO_2 and after 2 h at room temp. the mixture is extracted with acetone to give, after evaporation, a nearly quantitative yield of the oxime **4** together with traces of **3** and **6**. This experiment points out the need of thermal activation to promote Beckmann rearrangement. In the presence of H_2SO_4 and under microwave irradiation, **4** rearranges to **5** which in the reaction conditions hydrolyses to **6**. The following experiment accounts for this last step: irradiation at 30 W during 10 min of pure caprolactam **5** adsorbed over SiO_2 with H_2SO_4 and H_2O affords a quantitative yield of **6**. The addition of H_2O (1 equiv.) before irradiation is necessary because 2 equivs. are required, one for transposition and one for hydrolysis of the lactam. Without this addition of water only 50% yield of **6** is obtained.

This technique was further extended to other alicyclic ketones to prepare the corresponding lactams in good yields as reported in Table 1.

Table 1

Ketone	Lactam **5**	Irradiation time[a]/min	Yield (%)[b]
Cyclopentanone	Valerolactam	15	60
Cyclohexanone	Caprolactam	10	86
Cycloheptanone	2-Azacyclooctanone	20	72
Cyclooctanone	2-Azacyclononanone	15	65
Cycloundecanone	2-Azacyclododecanone	15	72
Cyclododecanone	2-Azacyclotridecanone	20	82

[a] Irradiation at 30 W, the temperatures reached by the reaction mixture are in the range of 100 to 120 °C. [b] All lactams are known compounds, identified by physical properties and ^1H, ^{13}C NMR spectroscopy.

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