

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

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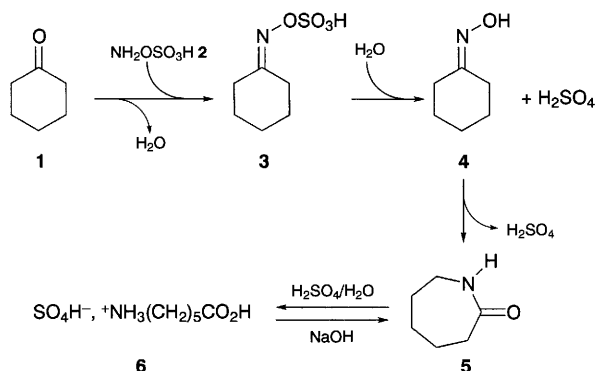
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Hydroxylamine-*O*-sulfonic acid reacts with alicyclic ketones over SiO₂ under microwave irradiation to give an amino acid salt, which cyclises in high yield to the corresponding lactam after work up in basic medium.

In 1979, Olah¹ 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, Sato² catalysed the rearrangement of oximes by the combined use of tetrabutylammonium perrhenate(VII), trifluoromethane sulfonic acid and hydroxylamine hydrochloride at reflux in MeNO₂.

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 SiO₂ (2 g). After leaving to



Scheme 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, ¹³C NMR spectroscopy.

stand for 2 h at room temp., H₂O (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 (CH₂Cl₂) lead to crystalline caprolactam **5** in 86% yield.

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

Cyclohexanone and HOSA are mixed with anhydrous MgSO₄. Extraction with acetone and evaporation gave **3**, characterized by ¹H, ¹³C NMR and HRMS. As expected, **3** is the primary product of the reaction, isolated for the first time. Over SiO₂ in the presence of the condensation water, **3** gives oxime **4** together with H₂SO₄. This second step is demonstrated in the following way: cyclohexanone and HOSA are absorbed over SiO₂ 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 H₂SO₄ 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 SiO₂ with H₂SO₄ and H₂O affords a quantitative yield of **6**. The addition of H₂O (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.

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