Synthetic Methods and Reactions; 67[1]. One-Step Conversion of Alicyclic Ketones into Lactams with Hydroxylamine-*O*-sulfonic Acid/Formic Acid

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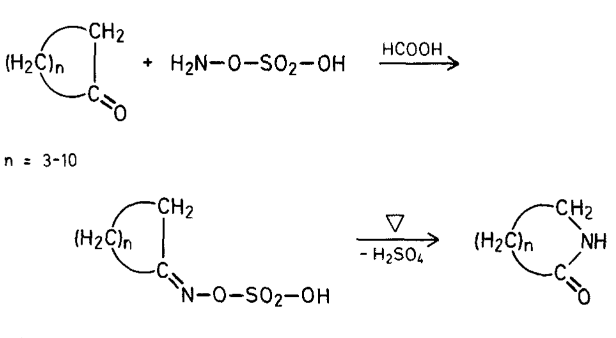
Since its discovery in 1886[2], the Beckmann rearrangement of alicyclic ketoximes to lactams has been extensively studied[3-6]. The reaction has been utilized in synthesis, structure determination, as well as in industrial processes for the manufacture of polyamides, such as Nylon 6.

Methods for simultaneous oximation of ketones and rearrangement to the oximes, in the case of cyclohexanone are known, in the patent literature, either with the use of hydroxylamine and sulfuric acid[7,8], or by employing primary nitroparaffins as a source of hydroxylamine[9,10]. In the former case, generally large excess of concentrated sulfuric acid is required, which subsequently must be neutralized. This process is, thus, unattractive in many cases, particularly in systems sensitive to sulfuric acid, as well as because of the required work up. As the Beckmann rearrangement is frequently used as one of the steps involved in the multistep synthesis of complex natural products, where the involved reaction intermediates can be particularly sensitive to strong acids, there are obvious limitations to its use. There have been reports of the use of the formic acid to bring about the Beckmann rearrangement of certain ketoximes[11-14], although the yield in the case of cyclohexanone oxime was low (42%)[13].

We wish to report now a significantly improved one-step mild conversion of alicyclic ketones into their corresponding lactams, generally in high yields, by simply refluxing in 95-97% formic acid the alicyclic ketone and hydroxylamine-*O*-sulfonic acid, a versatile and readily available reagent[15]. Results are summarized in the Table.

The reaction is suggested to proceed through the following mechanism.



The effect of sulfuric acid, formed *in situ* in the reaction, can be shown when prepared cyclohexanone oxime, itself, was treated with 1 mol-equivalent of sulfuric acid in formic acid. An increased yield of 90% was obtained over the 82% yield of the "one-step" reaction.

Whereas, the method was primarily studied in the reaction of alicyclic ketones, it also seems to be adaptable to the conversion of aryl ketones into amides. Reaction of benzophenone, for example, gave a 68% yield of benzanilide.

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Table. One Step Conversion of Ketones into Lactams

Ketone substrate	Amide product	Reaction time	Yield[a] [%]	b.p./torr or m.p.	
				observed	Lit. value
Cyclopentanone	δ-Valerolactam	4 h	65	94°/0.8	117–118°/6[16]
Cyclohexanone	ε-Caprolactam	3 h	82	83–84°/0.1 68–70°	139°/12[17] 68–70°[18]
Cycloheptanone	2-Azacycloctanone	6 h	75	102–103°/1.2	133–135°/4[19]
Cycloctanone	2-Azacyclononanone	5 h	61	138°/4	150–151°/7–8[19]
Cyclononanone	2-Azacyclodecanone	7 h	83	137–139°	138–139°[20]
Cyclodecanone	2-Azacycloundecanone[b]	3 h	76	163–164°	162°[21]
Cycloundecanone	2-Azacyclododecanone[b]	4 h	77	155–156°	154.2°[22]
Cyclododecanone	2-Azacyclotridecanone[b]	7 h	87	148–149°	150°[22]

[a] Yield of isolated product of ≥99% purity.

[b] Recrystallized from cyclohexane.

General Procedure for Converting Alicyclic Ketones into Lactams:

To a magnetically stirred solution of the corresponding ketone (0.01 mol) and 95–97% formic acid (10 ml) is dropwise added the solution of hydroxylamine-*O*-sulfonic acid (0.015 mol) in 95–97% formic acid (5 ml) at 20° over a period of 10 min. The reaction mixture is then heated under reflux for 3–7 h. After cooling, it is quenched with ice/water, neutralized with 5% sodium hydroxide solution, and then extracted with chloroform (4 × 30 ml). The organic layers are combined and dried with anhydrous sodium sulfate. After removal of the solvent by rotary evaporation, the reaction products are obtained by distillation or recrystallisation. All lactams prepared are known compounds identified by physical properties (m.p. and b.p., I.R. and ^{1}H-N.M.R. spectral characteristics), identical with those reported in the literature and compared with those of authenticated samples.

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