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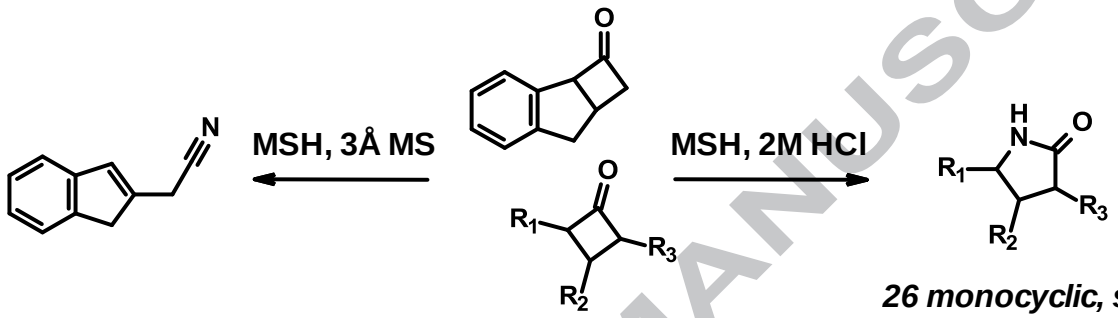

26 monocyclic, spirocyclic, tricyclic examples

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An improved procedure for the Beckmann rearrangement of cyclobutanones

Mathilde Lachia[a]*, François Richard[a], Raphael Bigler[a], Amandine Kolleth-Krieger[a], Michael Dieckmann[a], Alexandre Lumbroso[a], Ulfet Karadeniz[b], Saron Catak[b] and Alain De Mesmaeker[a]*

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ABSTRACT

γ-Lactams are important building blocks for the synthesis of biologically active molecules and can easily be accessed via Beckmann rearrangement of cyclobutanones. However, Beckmann fragmentation is often a competing reaction for these strained ketones. We found that performing the Beckmann rearrangement with Tamura's reagent in the presence of aqueous HCl suppress the undesired fragmentation reaction. This improved procedure was applied to a broad scope of substrates affording monocyclic, bicyclic, tricyclic or spirocyclic lactams.

Our experimental results and DFT calculations suggest that the mechanism of the rearrangement probably involves a tetrahedral intermediate and doesn't proceed via oxime fragmentation as in a classical Beckmann rearrangement.

The acid-mediated rearrangement of oximes to amides was discovered by Beckmann more than a century ago and is one of the oldest and most familiar organic transformations.[1a-c] This reaction is sometimes competing with a Beckmann fragmentation[1d] where the oxime fragments to the corresponding nitrile and olefin. Both reactions have been applied in the synthesis of natural products, but it is quite challenging to control the outcome of the reaction and the regioselectivity of the transformation.[2,3] The Schmidt reaction also faces a similar problem of selectivity between a rearrangement pathway and a fragmentation pathway. Recently, in silico analysis of the Schmidt reaction revealed a late bifurcation after the transition state, making it difficult to predict the outcome of the reaction.[4] In the case of the Beckmann reactions, there have been limited computational studies but steric bulk as for example adjacent quaternary centers, ring strain as for example in four-membered rings or the presence of functional groups which could stabilize a carbocation are known to be factors increasing the fragmentation product.[1c,5]

During the course of our investigation of the synthesis of strigolactones, we have developed a rapid access to tricyclic lactones via a Baeyer-Villiger oxidation of the cyclobutanone **1**.[6-8] In the meantime, we discovered that lactam analogues of strigolactones are very potent germination stimulants of the parasitic weed seeds *Orobanche Cumana*.[9] However, our initial attempts to access the tricyclic lactam skeleton via Beckmann rearrangement of the cyclobutanone **1** were unsuccessful due to competing Beckmann fragmentation (Scheme 1).

We report here our efforts to improve the access to lactams[10,11] via Beckmann rearrangement of cyclobutanones and our investigations to suppress

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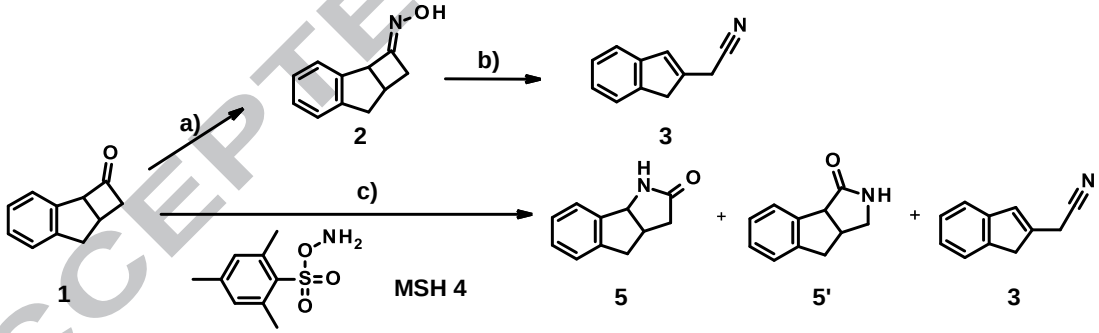
the fragmentation side reaction. We have then applied our optimized conditions to a broad scope of cyclobutanones or other substrates known to be sensitive to fragmentation. Our results also unveiled that the mechanism of the rearrangement probably involves a tetrahedral intermediate and doesn't proceed via oxime fragmentation.

We first investigated the classical Beckmann rearrangement of oxime **2** obtained from cyclobutanone **1**. To our disappointment, only fragmentation product **3** was isolated in 65% yield, even when using mesitylene sulfonyl chloride reported to favor rearrangement.[12,13] There are indeed few examples of rearrangement of oximes derived from cyclobutanones to lactams via Beckmann rearrangement.[14] The rearrangement of cyclobutanone has been mostly reported using *O*-mesitylene sulfonylhydroxylamine (MSH **4**, Tamura's reagent)[15], in particular in the case of fused cyclobutanone similar to our system.[16] Unfortunately, in our case, these optimized conditions gave only 8% of the desired rearranged lactam **5** with the fragmentation still occurring during our first attempt (Scheme 1). This was not totally unexpected as the release of ring strain in the cyclobutanone and the stabilizing effect of the phenyl ring would favor the formation of a benzylic carbocation in the fragmentation pathway. When repeating the reaction, we noticed that the formation of the lactam **5** was highly dependent on the batch of MSH **4**, which is isolated by precipitation from TFA by addition of water followed by filtration.[17] Thus, we suspected that the acid or water present in the MSH might play a key role in the outcome of the reaction.

We investigated the role of water by adding an excess of water or molecular sieves to the reaction (Table 1, entries 1-4). Water was increasing the yield of the lactam whereas anhydrous conditions favored the fragmentation product. We then looked at the effect of different acids (Table 1, entries 5-7). Trifluoroacetic acid or acetic acid didn't reduced the fragmentation but aqueous HCl almost completely suppressed the formation of the undesired nitrile. Finally, the addition of 5 equivalents of 2M HCl provided the desired lactam in 64% yield (Table 1, entry 9) but using more concentrated HCl solution (4M) did not proved to be beneficial (entry 10). Replacing dichloromethane by methanol or THF didn't give any reaction as well as substituting MSH **4** with hydroxylamine *O*-sulfonic acid was not possible (Table 1, entries 11-15).[18]



Scheme 1: Beckmann rearrangement and fragmentation of cyclobutanone **1**. Conditions: a) $NH_2OH.HCl$, NaOAc, MeOH, reflux, 83%; b) $MesSO_2Cl$, LiOH, THF, 65%; c) see Table 1

Table 1. Optimization of the Beckmann rearrangement of cyclobutanone **1.**

Entry	Conditions	Rearrangement **5+5'**[a]	Fragmentation **3**[a]
1	**4**, DCM	35	27
2	**4**, DCM, water (10 equiv)	55	21
3	**4**, DCM, Na_2SO_4	28	38
4	**4**, DCM, Molecular Sieve 3Å	9	68
5	**4**, DCM, TFA (1equiv)	27	9[b]
6	**4**, DCM, AcOH (1equiv)	20	39
7	**4**, DCM, HCl 2M (1 equiv)	60	32
8	**4**, DCM, HCl 2M (2 equiv)	60	14

9	**4**, **DCM, HCl 2M (5 equiv)**	**64**[c]	**6**
10	**4**, DCM, HCl 4M (5 equiv)	50	17
11	**4**, MeOH, HCl 4M (5 equiv)	11	-
12	**4**, THF, HCl 4M (5 equiv)	traces	-
13	**4**, DCM, MS 3Å , Et_3N (1.0 equiv)	-	-
14	NH_2-OSO_3H, DCM, HCl 2M (5 equiv)	-	-
15	NH_2-OSO_3H, DCM	-	-

[a] isolated yield; [b] hydration of the olefin was also observed probably due to a quench of the carbocation (17%); [c] formation of regioisomer **5'** was also observed, Regioisomer ratio (rr) = 11/1.

.

Taken together, these results suggest that the reaction proceeds via the formation of a tetrahedral intermediate **6** that undergoes a rearrangement, similarly to a Baeyer-Villiger reaction (Scheme 2). A similar mechanism was already proposed in the case of camphor.[18] Recently, White *et al*. have also reported the addition of acetic acid to favor the fragmentation of oxime sulfonate during the synthesis of (+)-codeine.[3] In our case, we propose that the acid might promote the addition of MSH to the cyclobutanone **1** and the elimination of mesitylene sulfonic acid, similarly as in a Baeyer-Villiger reaction. Under anhydrous conditions, intermediate **6** eliminates water to give the oxime sulfonate, which undergoes mainly the fragmentation product. Surprisingly, triethylamine completely inhibits the reaction, probably slowing down the addition of MSH to the cyclobutanone **1**. Deactivation of the cyclobutanone **1** due to acetal formation probably explains as well why the reaction doesn't proceed in methanol or THF. Thus, water and acid play an essential role in favoring the formation of **6** and preventing the formation of the oxime sulfonate.

Computational Rationalization

A density functional theory (DFT) approach has been utilized for the computational investigation of the possible reaction mechanisms in Scheme 1. All geometry optimizations and frequency calculations were performed in the gas phase. A meta-GGA functional M06-2X,[19,20] implemented in the Gaussian 09 (G09) program package[21] was utilized, together with the 6-31+G(d,p) basis set, due to its good performance in organic systems with dispersion effects.[22-24] The effect of the solvent environment was taken into account utilizing implicit solvation (IEF-PCM)[25] in water. Moreover, catalytic water molecules were introduced in an explicit manner. Intrinsic reaction coordinate (IRC) analysis were conducted at each transition state to verify the corresponding reactant and product.[26-28] Stationary points were identified as ground state or transition state by normal mode analysis. All free energies were reported at 1 atm and 298 K. The formation of intermediate **6** from reactant **1** and **MSH** as well as the three competing routes leading to oxime sulfonate, and the regioisomeric lactams **5** and **5′**, were computationally modelled and energetically compared to identify the most plausible route (Figure 1).

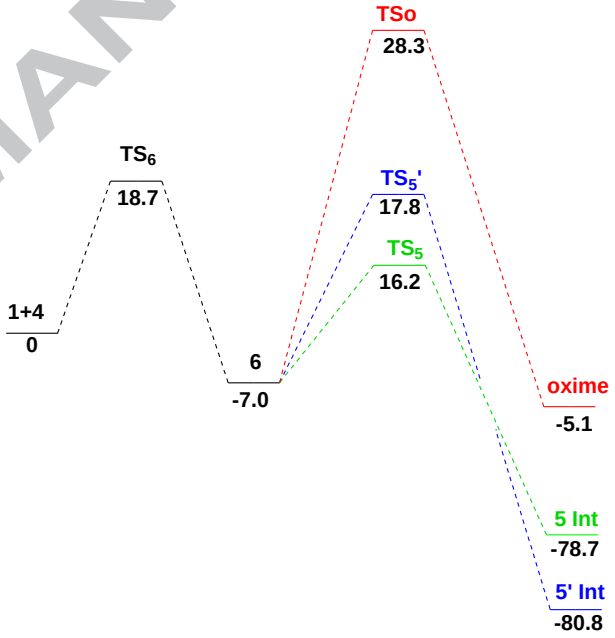
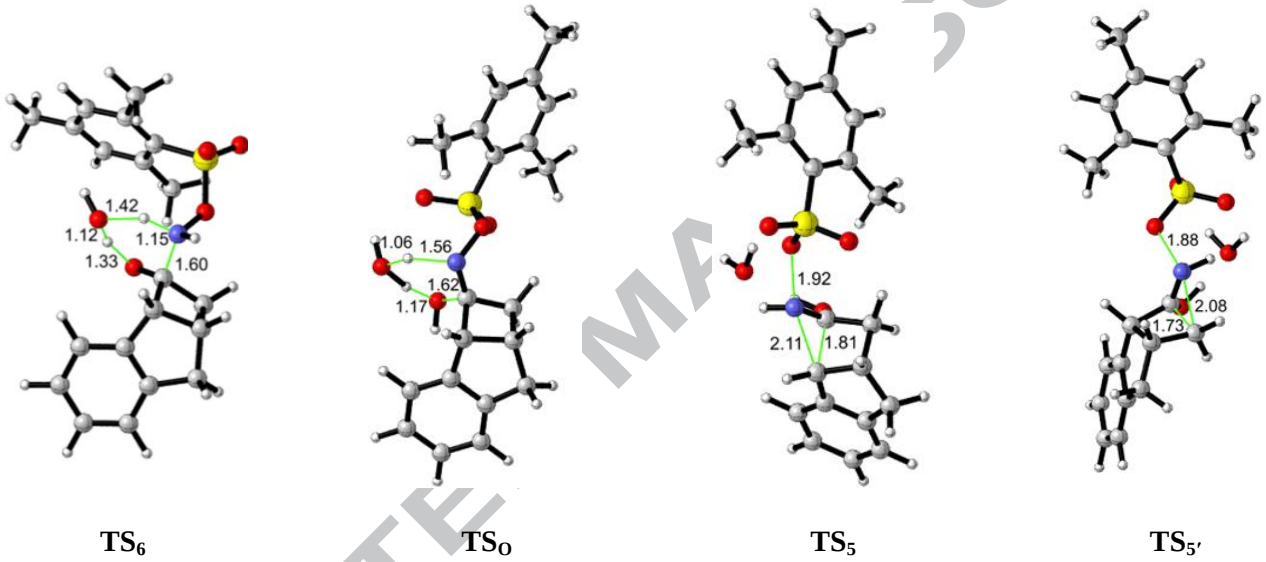


Figure 1. Free energy profile for the water-assisted formation of oxime sulfonate and regioisomeric lactams **5** and **5′** (M06-2X/6-31+G(d,p), IEF-PCM in water, free energies in kcal mol^{-1})

Intermediate **6** was formed through an activation barrier of 18.7 kcal mol^{-1} in a concerted fashion. Whereas the formation of the lactams was shown to proceed through a stepwise mechanism, the first step involving the ring expansion, which is incidentally the rate determining step followed by a second step in which the proton transfer occurs (proton transfer steps not depicted in Fig 1). The oxime sulfonate, however, formed through a concerted mechanism from intermediate **6**. Free

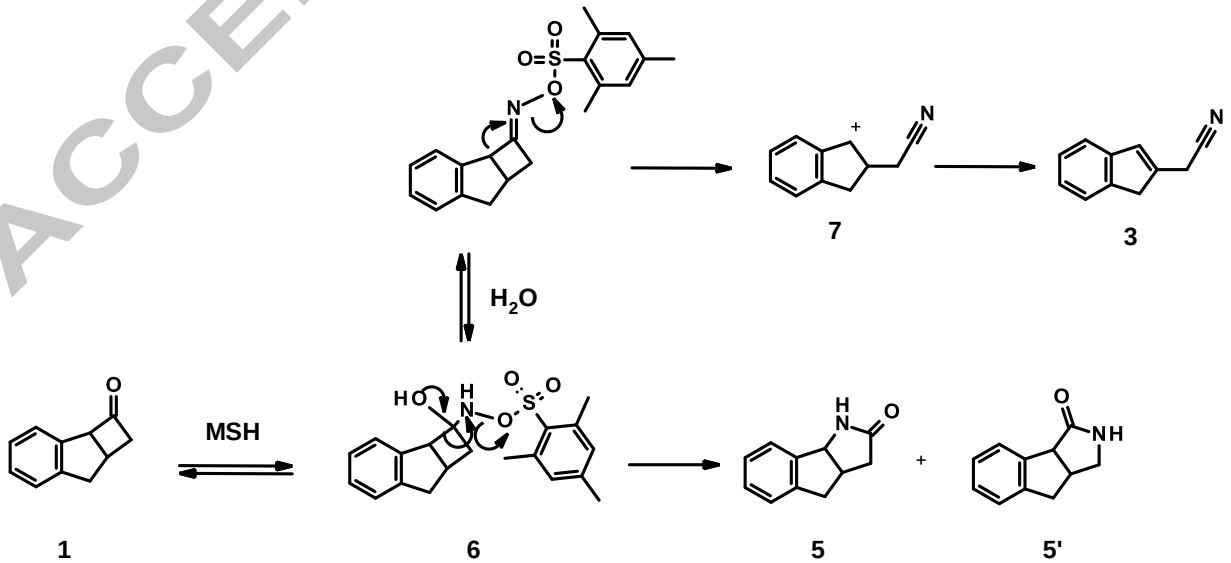
energy barriers depict the favorable formation of regioisomeric lactams **5** and **5′**. The role of water assistance was shown to be crucial in obtaining the rearrangement products. Water molecules act as catalysts, stabilizing transition states (Fig 2) and lowering the activation barriers in favor of the lactam products. These results are in line with experimental findings where anhydrous conditions lead to the fragmentation reaction. The rate determining transition state (TS) structures for the formation of intermediate **6** (TS_6) oxime (TS_O), **5** (TS_5), and **5′** ($TS_{5'}$) are depicted in Figure 2. The results indicate that the formation of the oxime sulfonate is unlikely with a higher free energy of activation when compared to **5** and **5′**. The reactions leading to the lactam were found to be highly exergonic and resulting in very stable products in line with the experiments.

With our optimized conditions in hand, we investigated the rearrangement of other tricyclic cyclobutanones with different electron donating and withdrawing substituents on the aromatic ring (Scheme 3). The cyclobutanones were prepared by intramolecular [2+2]-cycloaddition of ketene-iminium salts generated from the corresponding diisopropyl amides as reported previously.[6,7] (see supporting information)



TS_6 **TS_O** **TS_5** **$TS_{5'}$**

Figure 2. Optimized transition state (M062X/6-31+G(d,p)) structures for the formation of intermediate **6** and three alternative pathways (critical distances in Å).



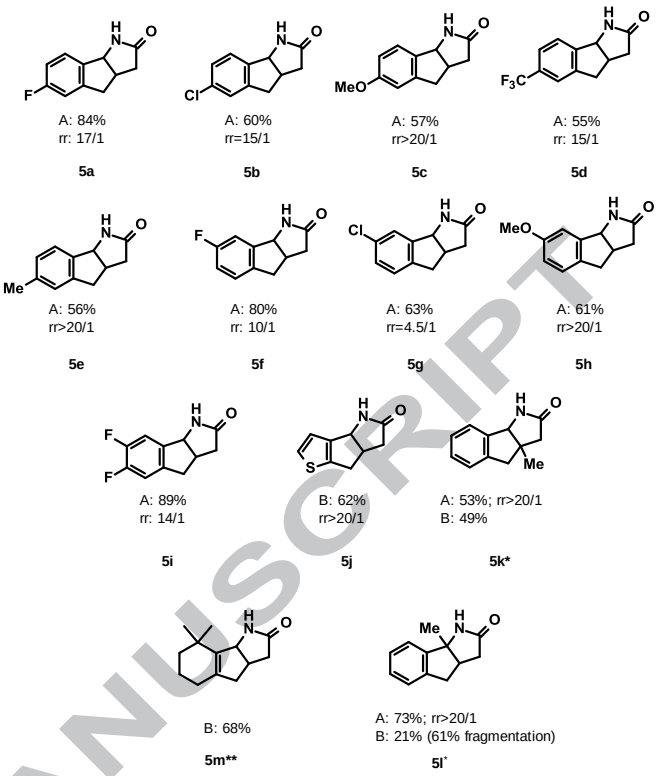
Scheme 2: Proposed mechanism for the ring expansion mediated by MSH

The lactams **5a-5l** were obtained in good yield and good selectivity, the insertion at the benzylic position being electronically favored. It is noteworthy to mention that thiophene derived

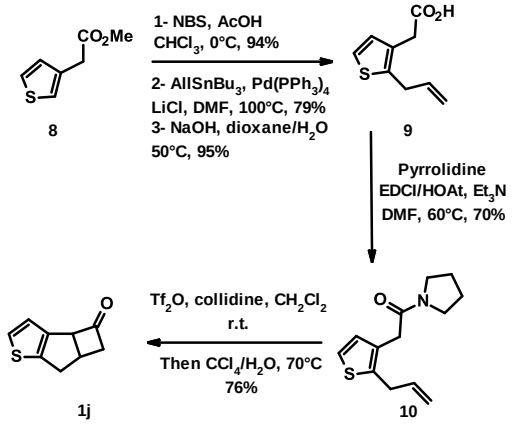
cyclobutanone building block **1j** was efficiently prepared from **8** in 4 steps as depicted in Scheme 4 In the case of electron withdrawing groups on the aryl ring, yields were usually higher but formation of the other regioisomer was increased. Electron donating groups in **5c** and **5e** still gave only the rearrangement product, despite the carbocation **7** being highly stabilized in the fragmentation pathway. In addition, even in the case of hindered cyclobutanone, the desired lactams **5l** was isolated as the only product of the reaction (Scheme 3, method A), whereas the original conditions with MSH in dichloromethane gave mostly the fragmentation compound (Scheme 3, method B).

We then looked at the reaction of different monocyclic or bicyclic cyclobutanones which were either commercially available or reported in the literature (Scheme 5). Lactams **5n-5v** were obtained in good yield and good regioselectivity except in the case of bicyclic lactam **5u** and **5v**. We were pleased to find that the fragmentation didn't occur, even in the case of bulky spiro derivatives **5n, 5o** and **5t** nor in the case of benzylic systems such as **5r** and **5s** where the formation of a carbocation in the fragmentation pathway would be highly favored. Finally, we tested our conditions on the commercial 2,2-dimethylcyclohexanone and 2,2-dimethylcyclopentanone which cleanly gave the corresponding lactams **5w** and **5x** whereas the presence of a quaternary center adjacent to the starting oxime is known to give a substantial amount of fragmentation during Beckmann rearrangement.[1] The conditions of the rearrangement were also compatible with some sensitive functional groups such as ester and Boc protecting group as is **5o**, **5p** and **5t**, respectively.

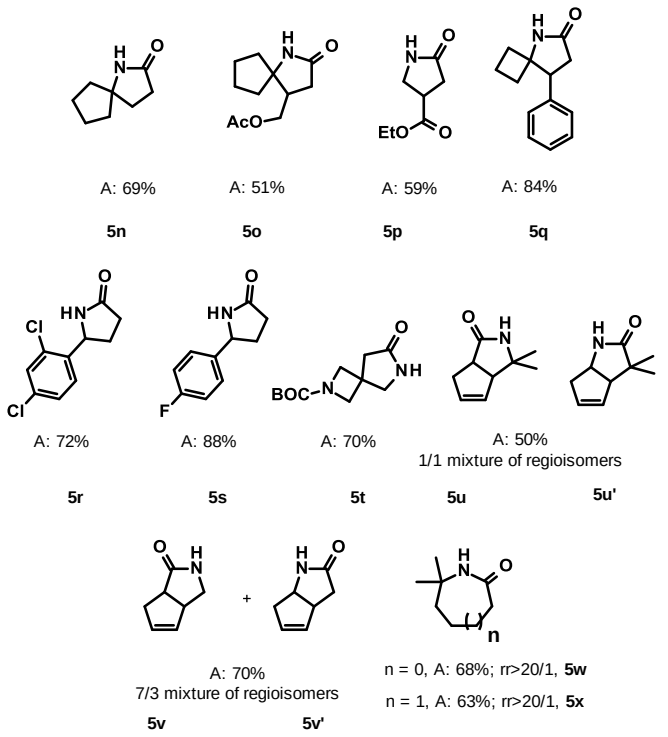
In conclusion, we have identified new and practical reaction conditions for the Beckmann rearrangement of cyclobutanones which reduce or suppress the formation of undesired fragmentation products. The broad scope of these conditions was illustrated on monocyclic, spirocyclic, bicyclic and tricyclic lactams and challenging hindered substrates. We postulate that the reaction proceed mainly via a tetrahedral intermediate and not via the oxime rearrangement.



Scheme 3: Synthesis of different tricyclic lactams from their corresponding tricyclic cyclobutanones via improved Beckmann procedure. Reaction conditions: Method A: MSH **4**, 2 M HCl (5 equiv), CH_2Cl_2, 12 h; Method B: MSH **4**, CH_2Cl_2, 12 h; rr refers to the regioisomeric ratio between the corresponding lactam **5** and **5′**; *Cyclobutanones were prepared as in ref 7; **Cyclobutanone was prepared as in ref 8.



Scheme 4: Synthesis of cyclobutanone precursor **1j**



Scheme 5: Synthesis of different lactams from their corresponding cyclobutanones via improved Beckmann procedure. Reaction conditions: Method A: MSH **4**, 2 M HCl (5 equiv), CH_2Cl_2, 12 h; Isolated yields are reported. A single regioisomer was observed unless mentioned otherwise.

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- An improved procedure for the Beckmann rearrangement of cyclobutanones has been developed

- Experiments and DFT calculation support a rearrangement mechanism involving a tetrahedral intermediate

- The generality of the method has been illustrated on 26 examples.