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Continuing efforts on the improvement of Beckmann rearrangement of indanone oxime

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Abstract—Continuing search for beneficial additive toward the Beckmann rearrangement (BR) of indanone oxime has revealed that common Lewis acid catalyst in methanesulfonyl chloride (MsCl) showed increasing efficiency in this ionic rearrangement. The new protocol with MsCl is superior to the classical phosphorus-based methods such as PPA and Eaton reagent, especially in the reaction of indanone oximes.

With a common acid catalyst in proper solvent, Beckmann rearrangement (BR) has found broad application in the manufacturing process to a variety of bench-size syntheses.[1] BR of indanone oximes (IO) has also been the subject of interest for quinolinone production, and thus investigated in these laboratories with some informative observations.[2]

Improvement of BR from process research viewpoint highlights the two basic aspects; (1) brand-new catalyst for regio-controlled rearrangement and (2) reduction of wastes and solvents.

Thus, mission was given to us to find very mild conditions for BR of ketoximes into lactams with high regioselectivity in the context of process development. Previously, we have disclosed a new reagent system, in which the classical halogenated solvents were eliminated by using the mixed Lewis acid system ($BF_3{\cdot}OEt_2$–$ZrCl_4$).[2] In this transformation, excess $BF_3{\cdot}OEt_2$ worked as a polar solvent.[3] This indicated to us that continuing search will disclose a new protocol (or additive) that will avoid conventional solvents and tedious sequence of isolation (extraction and evaporation of solvent).

We now report herein our progress toward the establishment of a new protocol for BR with common additives. Recent publications of Giacomelli[4] and others[5] have prompted us to disclose our progress during our process research on the carbostyril derivatives.

Reaction with amide solvent. As often noted,[4] the new conditions for BR in recent literatures were mostly related to the use of uncommon reagents that are also expensive in view of process development. Key to success is selection of a polar solvent with a mild promoter that is capable of driving the ionic transformation very effectively.

Recent literature also suggested us to use a polar amide solvent such as dimethylformamide (DMF) and dimethylimidazolidinone (DMI). Giacomelli has reported a new reagent system generated from DMF-trichlorotriazine (TCT).[4] Chlorinated DMF was proposed to be the active species.

On the other hand, Isobe and Ishikawa[6] have developed versatile dehydrating (chlorinating) reagent 2-chloro-1,3-dimethylimidazolinium chloride (DMC) through the chlorination of DMI, as well as its recoverable character as DMI.

In the light of these reports, BR of IO was re-examined. In our pilot experiments, however, the new protocols with polar amide solvents were totally unsuccessful for the conversion of IO as shown below; deoximation and chlorination with excess reagent (TCT) were the noticeable fragments, even with the new protocol by Ishihara and Yamamoto.[7]

Keywords: Indanone; Oxime; Beckmann rearrangement; Methanesulfonyl chloride.

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We further noticed that undesired side reactions were suppressed to some extent by the mixed use of toluene as co-solvent. The conversion, however, was very low.

In addition to these unsuccessful observations, we also attempted catalytic BR using P_2O_5 in ionic liquids (IL)[5,8] that eventually turned useless because of very slow (sluggish and messy) conversion with the high price of IL that was not easily recoverable. We then turned our attention to more conventional sets of reagents, we have investigated earlier, as follows.

New combination with lewis acids. In view of its versatility, a mild Lewis acid such as $ZrCl_4$ seems to be a reagent of choice for the conversion of oxime sulfonate (not free oxime). We thus commenced our solvent optimization using this mild Lewis acid catalyst. Kikugawa has emphasized on the utility of $ZrCl_4$ in some non-classical transformations of *O*-aryloximes.[9] This prompted us to re-investigate the reaction of various oximes with excess $ZrCl_4$ in a specified solvent system (or new solvent-additive combination).

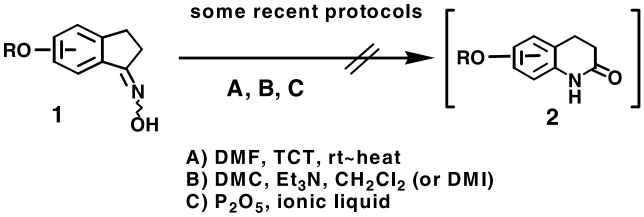
We soon found that mixed Lewis acid system ($BF_3 \cdot OEt_2$ + $ZrCl_4$) in toluene or chlorotoluene was more effective than $ZrCl_4$ itself as summarized in Table 1. It is also noteworthy that mixed Lewis acid system in toluene was more effective than PPA as shown. Usually, the carbostyril was the major product (as in Table 1), while the isomeric isocarbostyril was increased (as in Table 2) with catalysts less acidic than $ZrCl_4$ (i.e., $FeCl_3$).

Reaction with BF_3MeOH also showed a slow conversion and at the same time, a mixture of the products was observed.

The observed regioselectivity of BR was usually governed by the original stereochemistry of the oxime mesylate. Thus, we examined the geometry of the starting indanone oximes (free oxime or its mesylate) by NMR, and found it with mostly in the *E*-configuration.

Some scrambling of the oxime stereochemistry during Lewis acid treatment is most likely to occur with free oxime, when acid catalysts are weak like Eaton reagent, $FeCl_3$ and BF_3MeOH. While such scrambling of free oxime geometry was seen in many other examples of BR of free oxime, it was not so often with oxime mesylates. We then investigated the reaction of the IO-*p*-toluenesulfonate, which also resulted in a conversion to a 3:1 mixture of the two BR products as shown in Table 2, with $ZrCl_4$. With $AlCl_3$ catalyst in CH_2Cl_2, however, the oxime tosylate gave exclusively **5** with trace of **6**. This indicated us Lewis acid strength (coordination) can control the selectivity of BR of IO (Schemes 1 and 2).

From the mechanistic points of view, we can now envisage the two cationic intermediates (**A** and **B** in Scheme 3), which could be involved in the transformation through complexation with the Lewis acid catalyst, resulting in the diverse course of rearrangement as shown. We propose here a 1,2-pinacol rearrangement (rearrangement around single C–N bond) rather than rearrangement *across the oxime double bond* for the formation of the minor isocarbostyril derivative. Interference of water may be possible during reaction and work-up to assist rearrangement.



Scheme 1. Unsuccessful attempts.

A more careful mechanistic inspection of IO-BR has been made by Chi, who also indicated the formation of such cationic species.[10]

MsCl as a new additive. While searching for new conditions with mechanistic inspection, we oftentimes observed that attempted reactions of a *crude mesylate* turned to be faster than those of the pure crystallized material. Examination of the contaminants in the crude mesylate indicated the presence of excess MsCl, accompanied by traces of water (or HCl). We then speculated the effect of MsCl on BR. According to the above reaction scheme, positive interaction of *organic chloride* with the key intermediate was anticipated (through assistance by a chlorine atom as shown). Furthermore, MsCl is considered to be the actual by-product formed after completion of BR.

We were thus interested in BR with MsCl in toluene or chlorotoluene. Experiments shown in Table 3 indicate that addition of MsCl was advantageous in view of the improvement in the low solubility of $ZrCl_4$ and the substrate in toluene, thus facilitating overall conversion.

We next carried out BR in MsCl as the sole solvent. The result collected in Table 3 clearly indicates an efficient transformation and thus, a simple useful protocol was established with common Lewis acid catalysts such as $ZrCl_4$ and $FeCl_3$ in MsCl as a solvent of choice. As for additive, a small amount of water is also recommended for BR. Thus, reaction was carried out in the presence of water (1–2 equiv) in MsCl, and nearly the same conversion was observed.

We speculate here the role of water as shown in Scheme 4. Thus, the reaction course must be more pinacol-like. These results, taken together with the results from other reactions, clearly indicate the advantages of the MsCl protocol, which is also insensitive to the contamination by water.

Addition of MsOH was also beneficial in the same extent, albeit its cost. Fortunately, MsCl is a low-cost material available in bulk. Unlike MsOH, MsCl has low freezing point and can be utilized under cooling conditions. Then a mixture of MsCl and MsOH was found to be effective for the Schmidt reaction (SR) of indanones

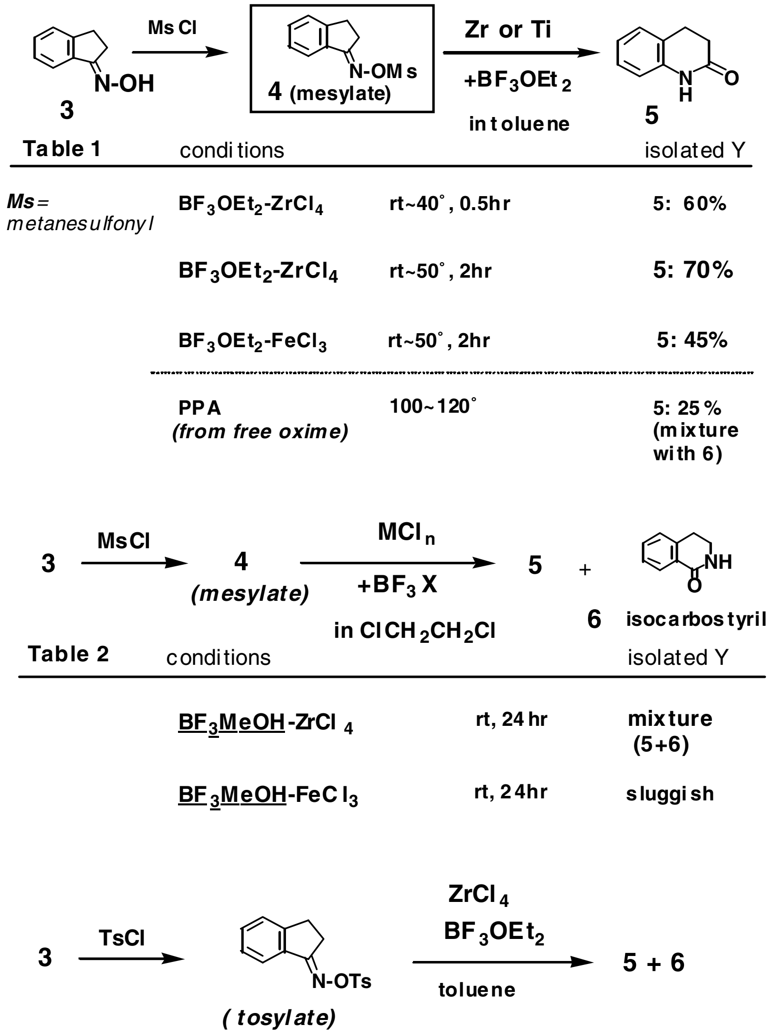
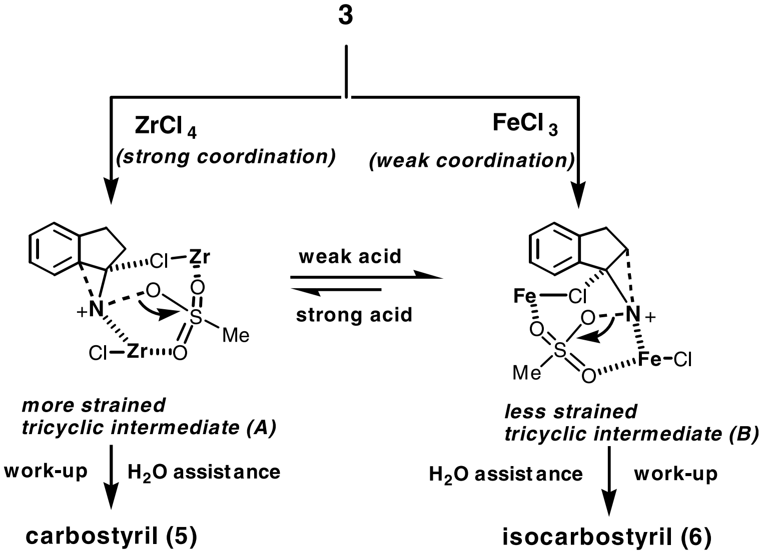


Table 1	conditions		isolated Y
Ms= metanesulfonyl	BF_3OEt_2-$ZrCl_4$	rt~40°, 0.5hr	5: 60%
	BF_3OEt_2-$ZrCl_4$	rt~50°, 2hr	5: 70%
	BF_3OEt_2-$FeCl_3$	rt~50°, 2hr	5: 45%
	PPA *(from free oxime)*	100~120°	5: 25% (mixture with 6)

Table 2	conditions		isolated Y
	BF_3MeOH-$ZrCl_4$	rt, 24 hr	mixture (5+6)
	BF_3MeOH-$FeCl_3$	rt, 24hr	sluggish

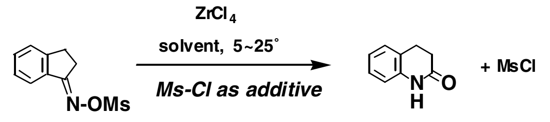
Scheme 2. Reactions with mixed Lewis acids.



Scheme 3. A plausible reaction course.

as shown in Scheme 5. An old report on SR of indanones indicated the unsuccessful reaction with methylenedioxyindanone derivative in the presence of H_2SO_4.[11] This unsuccessful outcome was probably due to the side reaction (sulfonylation by H_2SO_4) of electron-rich aromatic ring.

Table 3. BR in the presence of MsCl



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solvent system		isolated Y
$ZrCl_4$ (3 eq) /toluene-MsCl (1eq)	5°~rt: 1h	5: 75%[a]
$ZrCl_4$ (3eq) toluene-MsCl (2 eq)	5°~rt: 1h	5: 80%[a]
$FeCl_3$ (3eq) toluene-MsCl (2eq)	5°~rt: 2h	5: 60%[a]
$FeCl_3$ (4eq) toluene-MsCl (2eq)	5°~rt: 2h	5: 70%[a]
$ZrCl_4$ in MsCl (5eq)	**5°~rt: 1h**	**5: 80%[a]**

[a] Yield by chromatography.

[b] Yield without chromatography.

In the SR of the two indanones in MsCl–MsOH shown below, no side reactions were observed. Use of a less polar solvent such as chlorotoluene and benzotrifluoride (BTF) also helped to suppress side reaction with dense color formation.

Related reactions for comparison. A brief comparison with the existing methods was carried out, which is summarized below, clearly indicating the effectiveness of the present method.

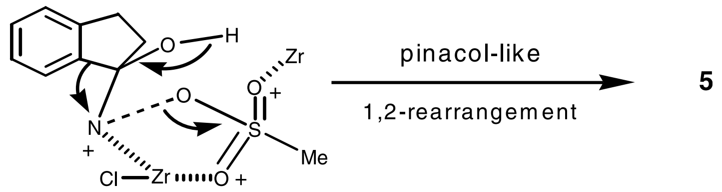
As mentioned earlier, Ishihara and Yamamoto suggested recently that CH_3CN was a solvent of choice for the *catalytic* BR of oximes with the aid of Lewis acid.[7] In our case, however, CH_3CN was not a good candidate as much sluggish reaction was observed with $ZrCl_4$ because of its Lewis basicity of the nitrile function. Reaction with excess $ZrCl_4$ at rt gave a mixture of products with carbostyril as the major component, while isomeric isocarbostyril as a second major compound.

Solvent-free BR in which $FeCl_3$ or $BiCl_3$ is most recommended has also been reported.[12] We attempted such a solvent-free condition for the BR of IO; however only resulting in the hydrolysis product (indanone).

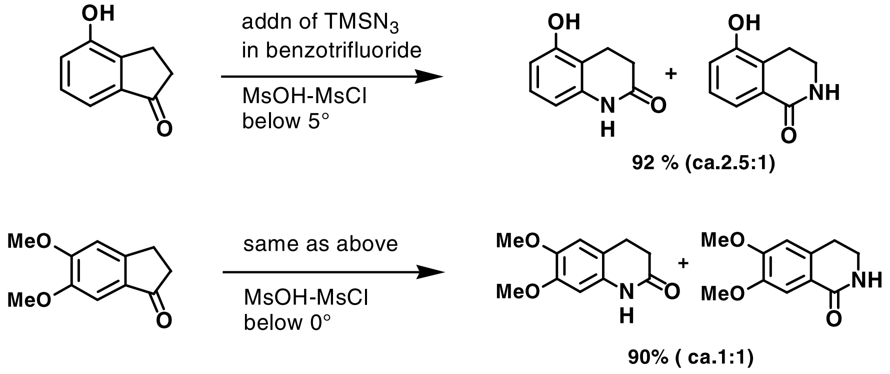
Reaction with oxime mesylate with these acids under heating conditions led mainly to deoximation with only a trace of BR product. These unsuccessful results indicate the importance of proper solvent and key promoter.

Finally, we attempted other sets of protocols reported quite recently by Chandrasekhar,[13] all of which unfortunately led us to some trivial results: attempted reaction with the oxime carbonate and $BF_3{\cdot}OEt_2$ under gentle heating gave no BR product but the free oxime formation (via decarbonylation).

Other attempts along with the more recent protocol[14] with oxalic acid, chloral, sulfamic acids, and TCI as key reagents afforded only a messy mixture containing trace amount of the product (mainly deoxymation). This indicates some inefficiency of the most reagents of current interests, demonstrating the superiority of our simple protocol employing conventional additive for practical applications.



Scheme 4. OH assisted reaction course.



Scheme 5. Schmidt reaction with MsCl.

Extending our reaction conditions to other ketoximes (tertaloneoxime sulfonate or cycloalkanoneoxime sulfonates as general substrates) also led to very satisfactory results with the $ZrCl_4$–MsCl system. However, these reactions offered no particular advantages because the conventional methods (PPA, Eaton reagent, TsCl, and other usual acidic conditions) were proven to be very satisfactory with free oximes under mild conditions. Our protocol was somewhat ineffective with these free oximes, while effective with oxime mesylates.

In conclusion, a very simple and effective method for the BR of cycloalkanone oximes is developed through the elaboration of a suitable solvent promoter, MsCl, with adequate insight into the plausible reaction pathways. The noteworthy aspect is the operational simplicity based on the common Lewis acid catalysts mixed with MsCl without the use of any hazardous halogenated solvent. This precludes tedious extractive work-up, but simple quenching into ice-water to separate the solid product.

The new protocol is superior to the classical phosphorus-based methods such as PPA and Eaton reagent, especially in the reaction of indanone oximes.

Application of MsCl as a preferred co-solvent for Schmidt reaction was also demonstrated briefly. Further application of MsCl as a key solvent for practical synthesis is now under active investigation in our laboratories.[15]

Acknowledgments

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