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A Study on the Conversion of Indanones into Carbostyrils

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Abstract—We have surveyed the utility of Beckmann rearrangement for the conversion of indanones into carbostyrils. Initial attempts at the conversion of 6-methoxy indanone oxime under classical conditions resulted in the formation of the two unusual products: 2-sulfonyloxyindanone and the dimeric product. This unusual rearrangement was also observed by the treatment of some metal triflates species. Further investigation has led to the development of reliable conditions starting from oxime mesylate (not oxime tosylate), in which some strong Lewis acid catalyst ($ZrCl_4$) was employed in either a conventional or non-conventional solvent system. The advantage of the new protocol is highlighted by the simple work up and direct isolation of the product in 65% isolated yield.

Some years ago, we started a project aimed at elaboration of a new synthetic pathway to the substituted carbostyril (3,4-dihydroquinolin-2-one, **2**) via Beckmann rearrangement (BR) of the substituted oxime (**1**) (Scheme 1). This new pathway was not only interesting for the process development for our important drug substances but also useful for general medicinal chemistry research.

While the BR has found broad application from the manufacturing process to a variety of laboratory synthesis, not many reports have described the practical synthesis of substituted carbostyrils (CS). One of the problems might stem from the selectivity of this rearrangement.

In the reported example of BR of *unsubstituted* indanone oximes, the products were obtained only in low yield (~20% by PPA). On the other hand, in the *substituted* indanone oximes, yields varied depending on the substituents.[1]

Our investigation has shed light on the unusual reactivity of indanone oximes and further on the reactions of these oxime sulfonates with some metal triflates. Successful transformation to carbostyril was finally made possible by the careful selection of the acid catalysts ($ZrCl_4$) in proper solvent systems.[2]

Reaction with Eaton Reagent and PPA

A conversion of the dimethoxyindanone oximes into the isocarbostyril derivatives (undesired isomer) was reported by the acid catalyst: P_2O_5–$MeSO_3H$ (Eaton reagent).[1a,3] In contrast to this report, reaction of **3** with Eaton reagent gave a mixture of the two polar spots, both of which were unlike the desired CS structure.

The major product was assigned as α-sulfonyloxy derivative (**4**, 33%) as shown in Scheme 1. Along with **4**, a polar product (**5**: 15%) was obtained. Reaction with the tosylate (**6**) also furnished the same products in a slightly higher yield. Product **4** (now 50% from **6**) lost OTs group of the starting material (**6**).

Careful inspection of another product (**5**) revealed its dimeric structure (30% from **6**) on the basis of spectroscopic analysis. Two sets of C=O and OMe are present in one molecule. We have as yet been unable to find another example of such dimerizartion during BR by such classical protic reagents.

The reaction with Eaton reagent must have an intermolecular aspect (reaction with solvent MsOH), since both products incorporated MsO group absent in the

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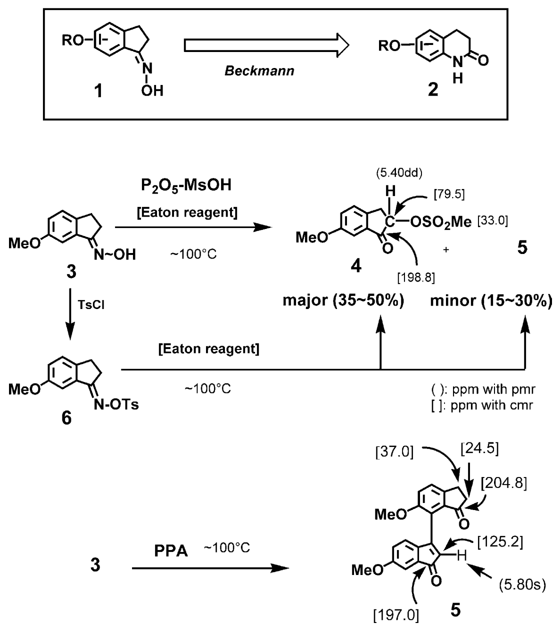


Scheme 1. Initial plan and result.

starting materials. It seems likely that these reactions proceed through the enamine tautomer, and the important aspect is that the OMs group could be introduced by intermolecular addition with concomitant elimination of some leaving group on oxime nitrogen.

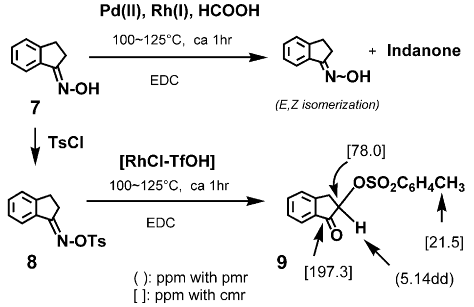
As shown in Scheme 1, the treatment of the oxime (**3**) with PPA at around 100 °C for 1 h produced the dimer (**5**) along with a small amount of indanone and polar materials. Same reaction of the tosylate (**6**) in PPA was very sluggish (mostly starting material and unidentified fragments).

Reaction with Transition Metal Catalysts: Mechanistic Implication

The unusual reactivity under BR conditions described above was intriguing from the mechanistic point of view. Mechanistic speculation strongly suggested the isomerization of oxime double bond to enamine tautomer, and transition metal catalyst was most likely to catalyze such isomerization. Our attention thus focused on the interaction of oxime double bond with other H-metal species (H-M-X), in which the metal is a transition metal.

As summarized in Scheme 2, indanone oxime (**7**) was intact with such catalyst as $Pd(OAc)_2$, $RhCl(PPh_3)_3$, $NiCl_2(PPh_3)_2$ in AcOH or $MeSO_3H$ as with typical Lewis acids. Only observable phenomena were the *E*, *Z* isomerization of oxime OH and hydrolysis to indanone.

We were then interested in the reaction of *transition metal triflate (MOTf)* formed in TfOH. In our previous experiments, some metal triflates such as $Bi(OTf)_3$ and $Hf(OTf)_4$ were actually effective for the conversion of indanone oximes but in very low yield.[2] There was no indication of the use of such transition metal triflate for oxime–enamine interconversions.



Scheme 2. Survey with Rh catalyst.

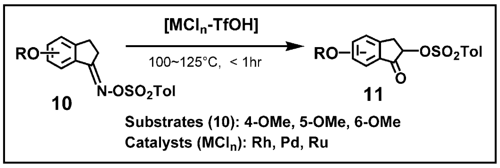
To our delight, however, the reaction of the sulfonate (**8**) with $RhCl(PPh_3)_3$ –TfOH in ethylene dichloride (EDC) at reflux (>80°) gave a single polar product (**9**, 55% isolated yield) containing OTs group migrated in the 2-position of indanone. The results are obviously better than the case of $Bi(OTf)_3$ and $Hf(OTf)_4$.

The 1,3-migration of the sulfonate was very sluggish in CH_2Cl_2, in which typical BR was most frequently carried out.[1] Reaction without TfOH was somewhat slow. The preferable amount of TfOH was 2–4 equiv to the metal catalyst Rh and Pd, so that the active species might form in the following equilibrium in Scheme 3. Reaction with TfOH gave a messy mixture.

We further attempted similar transformation with some methoxy-substituted oxime tosylate (**10**), and found that this 1,3-rearrangement to **11** was a general reaction pathway and independent on the position of a methoxy group. As a metal catalyst, $RhCl(PPh_3)_3$ and Pd(benzonitrile)$_2Cl_2$ were the most effective among examined (with less than 20 mol% catalyst to consume all the starting material) but $RhCl_3$, $RuCl_3$ and $PdCl_2$ were also applicable at higher loading (with more than 20 mol% catalyst). Usually 2–4 equiv of TfOH to metal catalyst was required. Reaction completed within 0.5 h with yields 55 (with **8**) to 75% (with **10**) along with indanone produced through hydrolysis. There was very little influence of the small water present, but a large amount (>1 equiv) of water simply accelerated hydrolysis and no BR product was produced. It should finally be emphasized that the reaction of **10** was much faster than **8**. Generally, reactions with oxime tosylates were faster than those with oxime mesylates.

Another Rh catalyst system has been successfully employed for the catalytic Beckmann rearrangement of acyclic oximes.[4]

$$MCl_n + TfOH \rightleftharpoons H\text{-}M(OTf)_n \rightleftharpoons \begin{matrix} M(OTf)Cl_{n-1} \\ + HCl \end{matrix}$$



Scheme 3. Reaction with transition metal catalysts.

Although we could neither propose a plausible reaction mechanism nor isolate any pivotal intermediates in our studies, we are speculating the interaction between oxime C=N bond and metal (or acid) catalyst to promote isomerization of the C=N bond (from *exo* to *endo*) affording enamine intermediate for the anomalous reaction pathway described above.

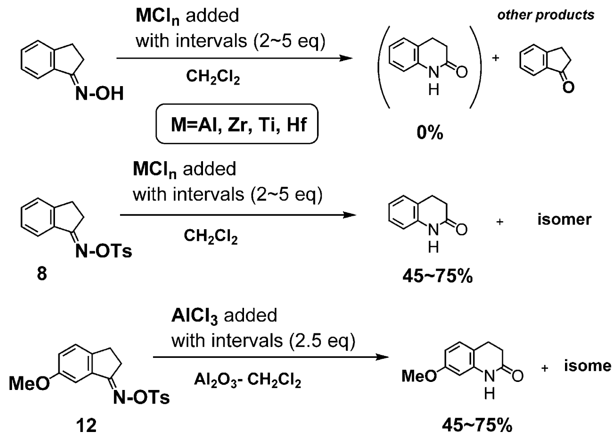
Reaction with Lewis-Acid Catalysts

After these abortive investigations, we have been interested in the BR promoted by strong metal halide catalysts. Although preliminary reactions of **3** with some Lewis acids in CH_2Cl_2 or a solvent-free system[5] led to a mixture through decomposition into unidentified polar products, some literatures precedent indicated the use of $AlCl_3$ in this stubborn rearrangement.[6]

A clue to our pursuit was finally found in the report by Chi, who developed optimized reaction conditions for the indanone oxime tosylate (**8**) with $AlCl_3$ in CH_2Cl_2 under careful temperature control (−40° to rt).[7] This protocol was reproducible in our hands (as summarized in Scheme 4). Fortunately, we found that other Lewis acids ($TiCl_4$, $ZrCl_4$ and $HfCl_4$) were also able to catalyze the reaction. We then attempted to modify Chi's original protocol so as to obtain the product without any chromatographic purification.

We focused on the 4-methoxy series (**13**) after the successful conversion with **12**, particularly in relation to the study for OPC-14523.[8] Fortunately, it was found that the reaction of the oxime *mesylate* (**13b**) was more facile than the corresponding *tosylates* (**8**) towards various Lewis acid catalysts in CH_2Cl_2. For example, the reaction of **13b** with excess $FeCl_3$ or $SnCl_4$ gave nearly 50% yield of the carbostyril (**14**), while the corresponding tosylate (**8**) gave almost recovery of the starting oxime under identical conditions. We then examined various solvent systems other than CH_2Cl_2, and found that ethylene dichloride (EDC) was a superior one to carry out the reaction at around 5–10 °C.

In order to prevent exothermic reaction at the addition of $AlCl_3$, we utilized $ZrCl_4$ for the key catalyst. Reaction was done at 0 °C to rt. with exothermic way in EDC. Simple extractive isolation by AcOEt gave a crude product, which was easily triturated by AcOEt–hexane (or ethylal, see Experimental) to afford a powdered material (**14a**) as a first crop. Further amount of **14a** was recovered from the mother liquor.



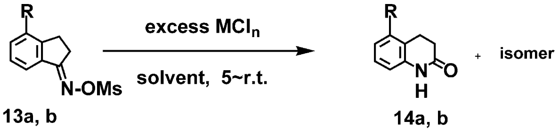
Scheme 4. Reaction with Lewis acids.

Reaction with isomeric **15** was also successful to furnish the corresponding carbostyril. Thus we have established a preferable pathway to carbostyrils by utilizing *oxime mesylate* derivatives of indanones, that is superior to the previous protocol with *oxime tosylate*, which required a tedious chromatographic separation.[7]

To attain more easy and effective work-up, we developed a new set of Lewis acid and solvent combination, in which BF_3OEt_2 was utilized as a solvent in place of EDC. As detailed in Experimental, the new protocol without conventional halogenated solvent (EDC) made it possible to isolate the crude product by simple dilution with water. As a first crop, we isolated **14a** in up to 65% yield, which is superior than the reaction in EDC. This new protocol does not require any extractive operation and amenable to scalable synthesis.

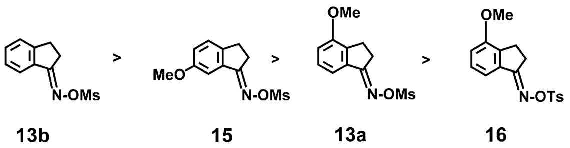
Thus, we have improved the original Chi protocol by employing the mesylate (**13b**) as a substrate with $ZrCl_4$ as a key Lewis acid catalyst. Advantage of the Zr catalysts can be emphasized again in that the reaction was carried out at rt without any cryogenic conditions and no chromatographic purification was required.

As shown in Scheme 5, the novel combination with $ZrCl_4$ in BF_3OEt_2 in place of conventional solvent (EDC) was very useful for further process optimization.



oxime mesylate	Lewis-acids and solvent		isolated Y
13a: R=OMe 4.5g	**$AlCl_3$: 9.0+0.5g EDC: 90ml**	5°~rt: 1 h	**49 % (1st crop)**
13b: R=H 16.0 g	**$ZrCl_4$: 20 g EDC: 300 mL**	10°~rt: 1 h	**72 %**
13a: R=OMe 17.0 g	**$ZrCl_4$: 20+20 g EDC:** 340mL	10°~rt: 1 h	**48 % (1st crop)**
13a: R=OMe 17.0 g	**$ZrCl_4$: 20+20 g BF_3OEt_2:** 60 mL	10°~rt: 1.5 h	**65 % (1st crop)**

order of reactivity:



Scheme 5. Survey with oxime mesylates.

Conclusion

We have demonstrated that $AlCl_3$ and $ZrCl_4$ were the key reagents for the Beckmann rearrangement of indanone oximes. The final conclusion we have shown here is virtually same as those reported by Chi and others.[7] However we had a chance to uncover some novel reactivities of indanone derivatives under classical BR conditions. In our survey, oximes (**3**, **6**, **10**) were all sluggish towards conventional BR conditions. They were presumably prone to isomerize, by the action of an acid, and the unexpected dimer (**5**) was formed through the intermediacy of **4**. For the intramolecular migration of the oxime sulfonate (**10**) to **11**, we developed new effective reagents generated from common Rh or Pd catalyst under the influence of TfOH.

All of these results simply indicated that the selection of acid catalyst is crucial for the conversion of indanone into carbostyrils. The new protocol of carefully optimized conditions using BF_3OEt_2 as solvent catalyst was superior to the classical system. It offers an optional synthetic pathway for carbostyril core of OPC-14523[8] and Aripiprazole,[9] provided that the catalyst-solvent combination is further optimized and starting indanone is obtainable in a reasonable cost as a starting material.

Experimental

General comments. Chemicals were purchased from the commercial firms indicated and used without further purification except for the case of brief drying with MS-4A (solvents) or crushing into fine powder [$ZrCl_4$ and $AlCl_3$] prior to use. TLC analysis was carried out using Merck silica gel 60 F_{254} plate (Art 5715). ^1H- and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, with tetramethylsilane (TMS) as the internal standard. The products of BR reaction were characterized by the comparison with the reported deta.[7]

BR by $ZrCl_4$ in EDC. The oxime mesylate (**13a**) was prepared from the oxime in a conventional way through the treatment of MsCl and Et_3N in CH_2Cl_2 under cooling. The pure oxime mesylate powder (**13a**, recrystallized, 17.0 g, 66.6 mmole) was dissolved in dry EDC (dry 250 mL) and kept at $<10\,°C$ by water-ice bath. To this was added a first shot of $ZrCl_4$ powder (Merck, 20 g initially, 85 mmole) in one portion. A yellow mixture was kept stirring at 10 °C for 10 min before the second shot of $ZrCl_4$ (20 g, 85 mmol) in one portion. After stirring 1 h with water bath temperature, the resulting yellow-brown mixture was slowly poured into ice-water (1 l) and stirred at rt for 1 h. The mixture was then extracted from AcOEt after neutralization by Na_2CO_3 powder (10 g). Crude extracts were filtered through a short pad of Celite to remove polar materials. Resulting filtrate was then concentrated to give crude products, which were triturated by ethylal (TCI, 400 mL) to afford the first crop of the carbostyril (**14a**, 5.7 g, 48%)[7] as a yellow powder.

From the filtrate, a further amount of **14a** (15%) was obtained by a column chromatography (CC) separation from the polar isomer isoCS (ca. 5%). A part of iso-CS was actually elusive in aqueous layer in these work up operations. The average ratio of carbostyril:isomer was usually ∼5:1 in the extractive residue.

If the stirring was inefficient, a large amount of indanone was produced through simple hydrolysis. Addition of toluene as a co-solvent was helpful to obtain less colored mixture. Reaction in CH_2Cl_2 was also successful at 5–10 °C, which gave a dark colored crop (**14a**) in less than 40% yield.

BR by $ZrCl_4$ in BF_3OEt_2. The pure oxime mesylate powder (**13a**, recrystallized, 17.0 g, 66.6 mmol) was stirred in the mixture of BF_3OEt_2 (distilled, 60 mL) and H_2O (0.5 mL) and kept at 10 °C by water-ice bath, while a first shot of $ZrCl_4$ powder (20 g initially) was delivered in one portion. The mixture was kept stirring at 10 °C for 15 min, before the second shot of $ZrCl_4$ (20 g) in one portion. After stirring 1.5 hr without cooling at rt, the resulting mixture was slowly poured into ice-water (1.5 L) and stirred at rt for further 2 h. The mixture was then kept standing overnight to settle the product and further diluted with cold water, before filtration.. Thus the obtained solid product was washed with H_2O to afford the first crop of the carbostyril (**14a**, 65% after drying at rt)[7] as a yellow powder.

From the filtrate, a further amount of **14a** (10%) was obtained by a CC separation from the polar isomer isoCS (ca. 10%).

BR by $AlCl_3$. The oxime mesylate (**13a**, 4.5 g) was dissolved well in dry EDC (90 mL) and kept stirring vigorously under ice-bath cooling (5 °C). The first shot of $AlCl_3$ (Wako, 9.0 g) was delivered in one portion and the resulting mixture was stirred at 5–25 °C for 0.5 h. A further amount of $AlCl_3$ (0.5 g) was delivered to ensure the reaction. The resulting mixture was quenched after TLC analysis and worked up as above. The crude product was triturated from AcOEt–*n*-hexane in the cold to give nearly pure carbostyril (**14a**, 1.5 g, 49%) as a first crop.. Reaction of the tosylate (**16**) with $AlCl_3$ in EDC also gave similar results but we could not obtain a good solid product from the extractive residue as in the case of the mesylate (**13a**).

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