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# Interesting Reaction of the Indanone Oximes Under Beckmann Rearrangement Conditions

Yasuhiro Torisawa,* Takao Nishi and Jun-ichi Minamikawa

*Process Research Laboratory, Second Tokushima Factory, Otsuka Pharmaceutical Co., Ltd, Kawauchi-cho, Tokushima 771-0182, Japan*

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**Abstract**—Attempted Beckmann rearrangement of the 6-methoxyindanone oximes in conventional conditions resulted in the formation of the two kinds of unexpected products: 2-sulfonyloxyindanone and the dimeric product. Related rearrangement was also observed in the reaction with RhCl–trifluoromethansulfonic acid system. © 2002 Elsevier Science Ltd. All rights reserved.

The Beckmann rearrangement has often been recommended as an expedient procedure for the conversion of cyclic ketoximes into the corresponding ring-expanded lactams in a stereospecific manner.[1] By the aid of various acid catalysts, the reaction has found broad application from the manufacturing process to a variety of laboratory scale synthesis. The subtle substituent effect in this robust synthetic process should be noted, especially in view of the practical application. For example, in the reported example of *unsubstituted* indanone oximes, the Beckmann 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, indicating substituents both in the benzene ring and cyclopentane ring of indanone being influencial.[1]

Several years ago, we started a project aimed at elaboration of an optional synthetic pathway to the substituted carbostyril (3,4-dihydroquinolin-2-one) core (**2**) via Beckmann rearrangement of the substituted oxime (**1**). Disclosed herein is the results of our study on the Beckmann rearrangement of methoxyindanone oximes with some conventional acid catalysts (PPA, $P_2O_5$–MsOH, TsCl, $AlR_3$, etc.) and non-conventional promoters [K-10 clay, $Bi(OTf)_3$, transition metal catalysts]. Our study has now revealed the interesting reactivity of 6-methoxyindanone oxime (**3**), which has not been described before. We have also extended our survey to the *unsubstituted* indanone oxime with various catalysts including Rh catalyst.

## Reaction with Eaton Reagent

In order to obtain the ring-substituted carbostyrils (**2**), our search has focused on the oxime bearing alkoxy group (**1**) and adopted the mild catalyst: $P_2O_5$–$MeSO_3H$ (Eaton reagent).

Conversion of some dimethoxyindanone oximes into the isocarbostyril derivatives was reported by this reagent.[1] Thus, we carried out the reaction of **3** by starting at room temperature and slowly heating to 100 °C to observe the behavior of this oxime.[2]

In contrast to our expectations, the major product isolated was the α-sulfonyloxy derivative (**4**, 33%).[3] None of the normal Beckmann products (carbostyril or isocarbostyril) were isolated.

Along with **4**, a polar product (**5**: 13%) was obtained, which was formed after prolonged reaction time. The structure of **4** was determined on the basis of $^1$H and $^{13}$C NMR as shown in Scheme 1.[4]

Further experimentation with the oxime tosylate (**6**) also furnished the same products in a slightly higher yield.[3] Product **4** (50%) lost OTs group of the starting material (**6**), which suggested that the transformation might follow an intermolecular path rather than intramolecular way in the Eaton reagent.

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*Corresponding author. Tel.: +81-88-665-2126; fax: +81-88-637-1144; e-mail: torisawa@fact.otsuka.co.jp

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In order to gain a further insight into the reaction, we next struggled to clarify the structure of the minor product (**5**). The unexpected dimeric structure of **5** (30% from **6**)[5] was deduced on the basis of spectroscopic analysis (as shown in Scheme 2). 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 Beckmann rearrangement. Noteworthy is that the product isolated was an indenone derivative as shown in Scheme 2. Both $^{1}$H and $^{13}$C NMR indicated the indenone skeleton (an olefinic proton at 5.80s which correlates with a carbon at 125.2).

## Reaction with Lewis Acid Catalysts

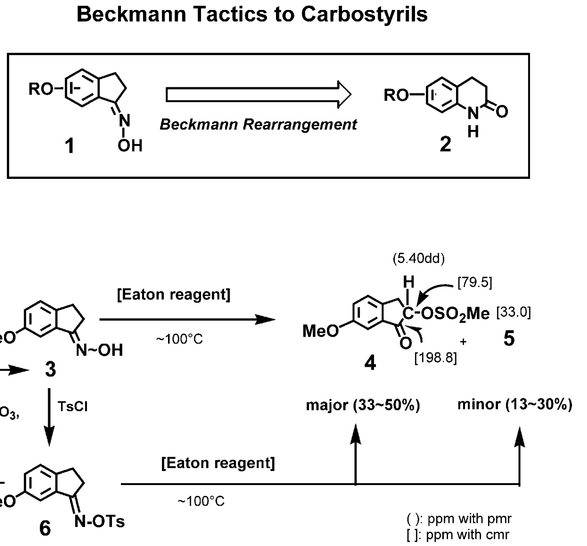
In other reactions with mild promoters ($Al_2O_3$, $SiO_2$, AcOK–aq EtOH, K-10 clay, aqueous sulfuric acid), **6** only returned to **3** via simple hydrolysis. Attempted reactions of **3** with Lewis acid in solvent-free system ($ZrCl_4$, $BiCl_3$, $AlCl_3$, $InCl_3$)[6] resulted in partial demethylation to the phenol and decomposition to base-line products.

Aluminum reagents have also found some utility in the Beckmann rearrangement.[1b,7] However, simple hydrolysis was observed again in the reaction of **3** with excess triisobutylaluminum (TIBAL) at room temperature. DIBAL-H did furnish the rearranged and reduced compound (**7**: 85% from **3**) as a sole product (1,2,3,4-tetrahydroquinoline: **7**; Scheme 2).[8]

## Reaction in PPA System

### 6-Methoxyindanone oxime

We reinvestigated the reaction with PPA, which is the most frequently used reagent for various indanone derivatives.[1] A careful treatment of the oxime (**3**) with PPA (30 wt) at around 100 °C for 1 h produced the dimer (**5**) along with a small amount of recovered starting material (Scheme 2).



Scheme 1.

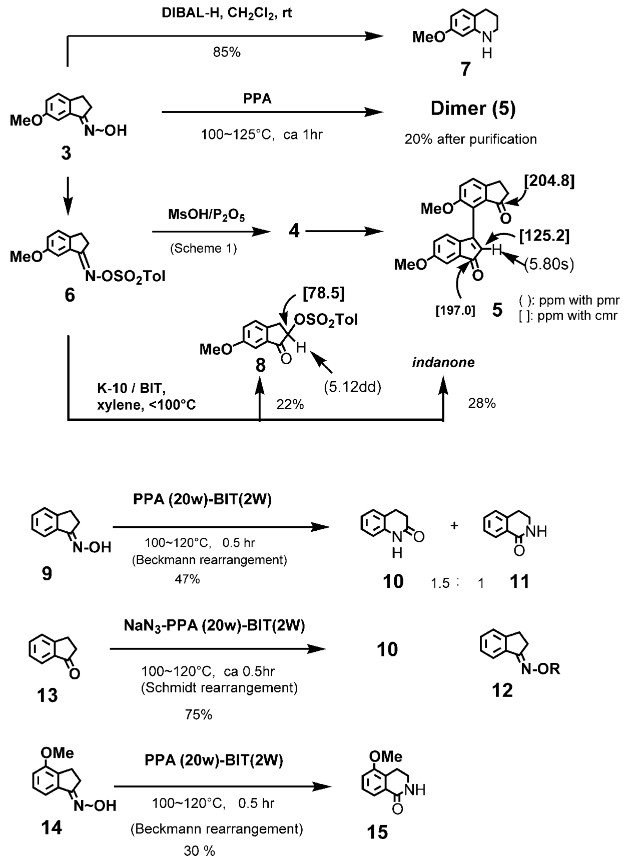
The same reaction of the oxime tosylate (**6**) with PPA was, on the contrary, very sluggish even under heating to ~120 °C. Although we could not detect or isolate any intermediate in the reaction with PPA, an intermediacy of α-oxy-intermediate similar to **4** was speculated.

We further searched for various acid catalysts for **6** and found that K-10 clay in xylene converted **6** into a cleaner mixture than in the reaction with PPA or $Al_2O_3$. The unstable compound (**8**)[9] was isolated from the mixture only in low yield (5–10%).

We were then interested in the effect of the mild acid $Bi(OTf)_3$ (BIT)[10] on this reaction. Fortunately, an improved result was attained by the reaction of **6** with the combined solid acids [BIT/K-10 clay] in xylene at <100 °C for 1 h to give **8** in 22% isolated yield along with the indanone recovered (28%).[11]

### Indanone oxime

Having observed some unprecedented transformation with the 6-methoxyindanone oximes (**3**, **6**), we also surveyed the same reaction with other substrates including other oxime derivatives. The reaction of the indanone oxime (**9**) with PPA was reported to give the carbostyrils (**10** and **11**) in ca. 20% combined yield.[1] We thus treated indanone oxime in our PPA-BIT conditions and found that carbostyril (**10**) was the major component along with the isomeric isocarbostyril (**11**) in 45% combined



Scheme 2.

yield. We could not isolate any dimeric product from the mixtures. The rest of the products were recovered, **9** and **13**. Also surveyed was the reactivity of other indanone derivatives (**12**) towards Beckmann and Schmidt reactions in PPA. In agreement with the old report,[12] the Schmidt reaction of **13** gave the desired carbostyril as the sole product in reasonable isolated yield as shown in Scheme 2.

### 4-Methoxyindanone oxime

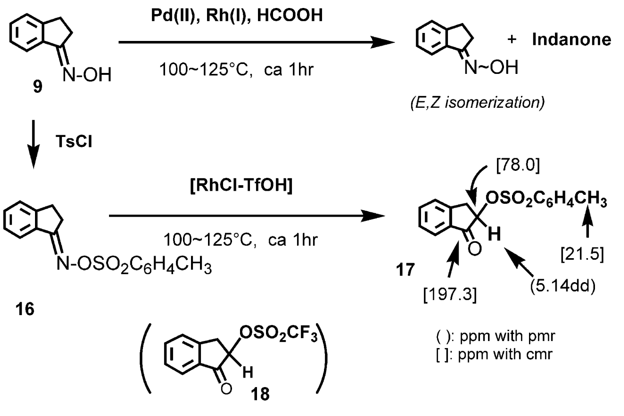
As shown in Scheme 2, reaction of **14** in conventional PPA conditions afforded a black mixture, from which none of the carbostyril structure was isolated. Instead, isomeric isocarbostyril (**15**) was obtained in 5∼10% yields. We could not isolate any dimeric structure corresponding to **5** in this reaction.

Further attempts to improve Beckmann reaction of **14** by the use of PPA-BIT afforded the isocarbostyril (**15**, 30% isolated yields). Isocarbostyrils were obtained predominantly from the reaction by Eaton reagent in the literature. Successful transformation to carbostyril was only possible provided that the 2-position of the indanone oxime was substituted by alkyl groups.[1]

## Mechanistic Speculations

The interesting reactivity of indanone oximes under Beckmann rearrangement conditions described above is particularly intriguing from the mechanistic point of view. We thus focused our attention on the interaction of the oxime double bond with catalytic H-metal species (H-M-X) generated in acidic (protic) media. As shown in Scheme 3, indanone oxime (**9**) itself remained intact with such catalysts as $Pd(OAc)_2$, $RhCl(PPh_3)_3$, $NiCl_2(PPh_3)_2$, in AcOH or $MeSO_3H$ as well as with typical Lewis acids such as $AlCl_3$ and $ZrCl_4$. The only observable phenomena were the *E*,*Z* isomerization of oxime OH and hydrolysis to indanone, as experienced in the previous reaction with Lewis acids.

We, however, observed that the reaction of the indanone oxime sulfonate (**16**) with $RhCl(PPh_3)_3$–TfOH in EDC at reflux gave a single polar product (**17**, 30% isolated yield) containing the OTs group migrated to the 2-position of indanone. The structure is confirmed by the comparison of the previously obtained compounds (**4**, **8**), which clearly distinguished **17** from the OTf derivative (**18**). We further attempted similar transformation with methoxy-substituted indanone oxime tosylates from **3** and **14** and found that the 1,3-rearrangement is a general reaction pathway independent of the position of a methoxy group.[13]



**Scheme 3.**

In the recent report by Yamaguchi, the Rh catalyst system has been successfully employed for the catalytic Beckmann rearrangement of acyclic oximes.[14] It is also proposed that oxidative addition of Rh(I) species to N–OH bond could be most probable.

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

In conclusion, we have surveyed the behaviors of indanone oximes under various Beckmann conditions. The oximes (**3**, **6**, **9**, **12**, **14**) were all sluggish towards conventional Beckmann conditions. Some of them (**3**, **6**) were presumably prone to isomerize, by the action of an acid, and the unexpected dimer **5** was formed through the intermediacy of **4** or **8**. For the intramolecular migration of the oxime sulfonate **6** to **8**, a mild catalyst $Bi(OTf)_3$ played a crucial role.

The dimer formation was characteristic to 6-methoxyindanone oximes (**3**, **6**), and similar dimerization was not observed in other indanone series such as indanone itself and 4-methoxyindanone. We, however, disclosed here a related rearrangement of the oxime tosylate **16** with Rh catalyst in the presence of TfOH. One important conclusion from our survey is that conventional Beckmann protocols are not suitable for practical carbostyril synthesis.

## Acknowledgements

We thank Mr. I. Miura in our laboratory for his helpful assistance in NMR assignment. We also thank Professor T. Ishikawa (Chiba University) for the helpful discussion in manuscript preparation and encouragement.

## References and Notes

1. (a) For recent reviews, see: Gawley, R. E. *Organic Reaction* **1988**, *35*, 1, and references cited therein. (b) Maruoka, K.; Yamamoto, H. *Comp. Org. Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 763.

2. Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

3. General Procedure: **Method A** (Eaton system): To the Eaton reagent (ca. 70 wt to substrate) was added a $CH_2Cl_2$ solution of the oxime (**3**; 250–500 mg) or the oxime tosylate (**6**; 250–500 mg) at room temperature. Resulting mixture was kept at this temperature for 0.5 h before being heated at 100 °C for 2 h. TLC analysis indicated the complete consumption of the starting material. After cooling to room temperature, the mixture was poured into AcOEt–$H_2O$ (1:1), extracted several times with AcOEt and worked up as usual. The crude products were purified by $SiO_2$ column chromatography to afford the products shown in Scheme 1. **Method B** (PPA system): The oxime (**3**) or the tosylate (**6**) was added to PPA (70 wt) under warming (60 °C) to form homogeneous mixture with adequate stirring. The whole mixture was carefully kept at around 100–110 °C (bath temperature) for less than 1 h. The mixture turned to black and TLC indicated the consumption of the oxime (**3**). Then the mixture was cooled to room temperature and diluted with AcOEt and $H_2O$. Crude product obtained after evaporation of the dried organic solvent was purified by chromatography to afford the dimer (**5**) along with a small amount of the recovered oxime (**3**). **Method C** (PPA–BIT): PPA and $Bi(OTf)_3$ was first suspended in $CH_2Cl_2$, to which the oxime was added at room temperature. Solvent was removed by heating to leave an oil, which was gently heated at 100 °C for 1 h. TLC indicated the formation of the polar products. The mixture was worked up as above and purified by column chromatography to afford the products shown. **Method D** (BIT/K-10): A mixture of the oxime tosylate (**6**), K-10 powder (Aldrich, preheated), and $Bi(OTf)_3$ powder in xylene was hated at 90–100 °C (bath temperature) for less than 1 h. TLC indicated the formation of new products. The black mixture was diluted with AcOEt–$H_2O$ (1:1), extracted several times and worked up as usual. The crude products obtained were purified by column chromatography to afford the products shown in Scheme 2.

4. Selected data for **4**: $^{13}$C NMR ($CDCl_3$) $\delta$ 198.8 (C=O); 160.0 (O–C); 142.8; 134.5; 127.5; 125.9; 105.6; 79.4 (O–C); 55.6 (OMe); 39.5; 33.0; $^1$H NMR ($CDCl_3$) $\delta$ 7.38 (d, 1H, $J=5.7$ Hz), 7.25 (m, 1H), 7.17 (d, 1H, $J=0.9$ Hz), 5.34 (dd, 1H, $J=8.0$, 4.5 Hz), 3.83, (s, 3H), 3.63 (dd, 1H, $J=16.8$, 8.0 Hz), 3.31 (s, 3H), 3.21 (dd, 1H, $J=16.7$, 4.5 Hz); MS *m/e* 256 (M +), 160 (base).

5. Selected data for **5**: $^{13}$C NMR ($CDCl_3$) $\delta$ 204.8 (C=O); 197.0 (C=O); 160.5; 157.8; 155.9; 147.2; 137.5; 135.1; 132.5; 127.8; 125.2; 121.2; 119.0; 117.8; 115.8; 109.7; 56.4 (OMe); 55.5 (OMe); 37.1; 24.5; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (d, 1H, $J=8.4$ Hz), 7.25 (d, 1H, $J=8.4$ Hz), 7.07 (d, 1H, $J=2.4$ Hz), 6.65 (dd, 1H, $J=8.0$, 2.4 Hz), 6.50 (d, 1H, $J=7.9$ Hz), 5.80 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.08 (m, 2H), 2.67 (m, 2H); MS *m/e* 320 (M +), 162, 84 (base).

6. Thakur, A. J.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Synth. Commun.* **2000**, *30*, 2105.

7. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

8. Cho, H.; Murakami, K.; Nakanishi, H.; Isoshima, H.; Hayakawa, K.; Uchida, I. *Heterocycles* **1998**, *48*, 919.

9. Selected spectral data for **8**: $^{13}$C NMR ($CDCl_3$) $\delta$ 197.3 (C=O); 159.7 (O–C); 144.9; 142.5; 134.4; 133.0; 129.6; 128.0; 127.2; 125.5; 105.5; 78.5 (O–C); 55.4 (OMe); 33.0, 21.5; $^1$H NMR ($CDCl_3$) $\delta$ 7.91 (d, 2H, $J=8.2$ Hz), 7.37 (d, 2H, $J=8.2$ Hz), 7.31 (d, 1H, $J=8.5$ Hz), 7.22 (dd, 1H, $J=8.5$, 2.3 Hz), 7.13 (d, 1H, $J=2.3$ Hz), 5.12 (dd, 1H, $J=8.0$, 4.5 Hz), 3.80, (s, 3H), 3.55 (dd, 1H, $J=16.8$, 8.0 Hz), 3.12 (dd, 1H, $J=16.7$, 4.5 Hz), 2.45 (3H, s); MS *m/e* 332 ($M^+$), 160 (base).

10. Torisawa, Y.; Nishi, T.; Minamikawa, J. *Org. Process Res. Dev.* **2001**, *5*, 84.

11. The mixed catalyst system (PPA–BIT) was prepared and used as follows; PPA and $Bi(OTf)_3$ was first suspended in $CH_2Cl_2$, to which the oxime was added at room temperature. Solvent was removed to leave an oil, which was gently heated at 100 °C for 1 h and worked up as usual.

12. The Schmidt reaction of unsubstituted indanone in, PPA–$NaN_3$ gave carbostyril as a sole product (60%). See also: Briggs, L. H.; De Ath, G. C. *J. Chem. Soc.* **1937**, *456*.

13. Preliminary experiments showed the 1,3-rearrangement reaction was faster in the methoxy-substituted oxime tosylates. Further investigation revealed that other metal chlorides such as $PdCl_2$, $CoCl_2$ were also effective for this transformation. The scope and limitation of this rearrangement will be reported in due course.

14. Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311.