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Bioorganic & Medicinal Chemistry Letters 17 (2007) 453–455

Bioorganic & Medicinal Chemistry Letters

Conversion of indanone oximes into isocarbostyrils

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Received 11 September 2006; revised 5 October 2006; accepted 10 October 2006
Available online 12 October 2006

Abstract—New and effective method for the Beckmann rearrangement of indanone oxime mesylate is described, in which a selective and controlled production of the isomeric isocarbostyrils is achieved.

The versatile utility of Beckmann rearrangement (BR) in organic synthesis has been manifested in the form of various applications as seen in the volumes of Organic Reactions as well as many textbooks.[1] As a typical example of BR in medicinal chemistry research, tetralone oximes are converted with good regioselectivity into the corresponding benzazepinone derivatives in reasonable yields under mild conditions by the simple treatment with conventional acids (e.g., polyphosphoric acid: PPA, and related reagents).

On the other hand, the reaction of indanone oximes (IO) reveals a completely different aspect; the reported yields are mostly moderate (<50%) at best, with disappointingly poor regioselectivity (resulting in a mixture of isomers). We and others have thus concentrated on the discovery of mild reaction conditions for BR of indanone oximes into carbostyrils.

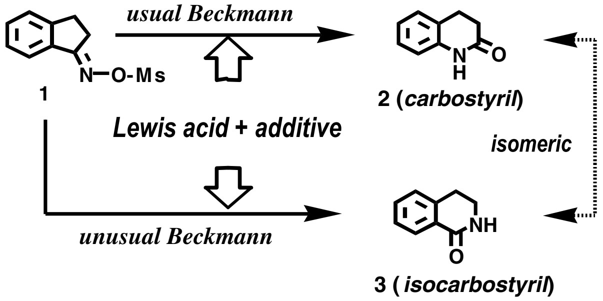
Under these circumstances, we have disclosed a new reagent combination for the BR of IO mesylates into carbostyrils by employing the mixed Lewis acid system ($BF_3{\cdot}OEt_2$–$ZrCl_4$).[2] In this transformation, excess $BF_3{\cdot}OEt_2$ worked as a polar solvent.[3] This indicates to us that a careful combination of reagents may probably offer a new protocol that will avoid notorious solvents and also tedious sequence of extraction and purification (e.g., chromatography).

With some mechanistic insights into the BR of IO, we subsequently disclosed the use of methanesulfonyl chloride (MsCl) as another beneficial additive in BR. The simple combination of MsCl with Lewis acid thus offers a new avenue in the classical Beckmann pathway.[4]

We now report herein our most recent progress toward the inversion of the regiochemistry of the BR of IO, in which the unfavorable conversion into the isomeric isocarbostyrils is selectively carried out under very mild conditions with MsCl as a key additive. Recent publications of Paquette[5] and others[6] have prompted us to disclose our own progress during our process research on the isocarbostyril derivatives.

Focus on the promoter. In the hope of amplifying the versatility of BR, our investigation on the control of BR focused on the conversion of IO into isocarbostyril. While no reports have dealt with this chemoselective transformation in IO, selection of a key promoter for general BR can effect selective (thus two directional) transformation from the single oxime, as noted by Paquette and others.[5]

More precisely, and in a mechanistic sense, key to the success for unusual Beckmann pathway (see Scheme 1)



Scheme 1. Two directional Beckmann rearrangement.

Keywords: Indanone; Oxime; Beckmann rearrangement; Isocarbostyril; CPME.

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doi:10.1016/j.bmcl.2006.10.022

is a selection of mild promoter that is capable of driving isomerization of the oxime double bond prior to the rearrangement.

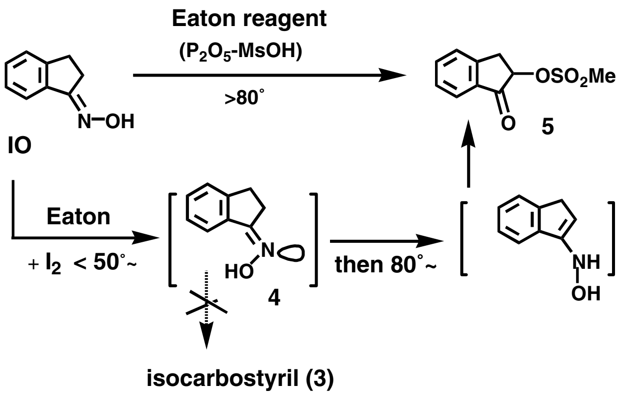
Isomerization of free oxime. We felt it easy to effect the isomerization of free IO with Eaton reagent or PPA, which leads to the production of isomeric BR product (**3**) as indicated previously.[5] It was found that these reagents can effect the isomerization as shown below, producing the isomeric free *Z*-IO easily, while these isomeric IO (**4**) could not easily afford the isocarbostyril (**3**) under same mild reaction conditions. Instead, under these conditions, the conversion into undesired products was observed as a major side reaction, which has already been identified in the previous report by us.[2]

Same isomerization with PPA was also feasible, but only sluggish conversion to isocarbostyril (**3**) was observed (<20%). This prompted us to employ other mild Lewis acids (i.e., not protic acids) such as $TiCl_4$ (Scheme 2).

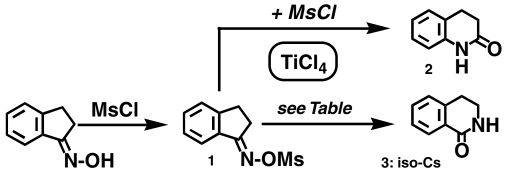
Additive controlled reaction with $TiCl_4$. Non-protic acid $TiCl_4$ is selected as a suitable promoter for both oxime isomerization and subsequent rearrangement under mild conditions, while not many applications by this reagent have so far been mentioned, with almost no applications to the indanone oximes. $TiCl_4$ is a cheap liquid Lewis acid and capable of usual BR in some polar reaction media.

Initial key finding with $TiCl_4$ had emerged in that an effective transformation of the IO mesylate into carbostyrils occurred smoothly, in the solvent system of ethylene dichloride (EDC–$ClCH_2CH_2Cl$) plus MsCl as additive as shown in Scheme 3.

In order to derail (control) this usual Beckmann pathway into the unusual direction, we added another mild Lewis acid or Lewis bases to this mixture of $TiCl_4$. After abortive trials, we found a new and relatively mild condition with BF_3MeOH as a key additive,[4] in which IO was very effectively converted into unusual isocarbostyril in very good yields (nearly quantitative), as far as being judged by NMR. The resulting reaction mixture was nearly homogeneous in NMR (thus almost quantitative conversion).



Scheme 2. Initial attempt at isomerization of IO.



oxime mesylate		conditions	isolated Y
1.0g	BF_3MeOH: 0.8 mL $TiCl_4$: 0.5 mL/	in EDC, rt, 15hr *then* *NMR analysis*	3 : ~100%
1.0g	BF_3OEt_2: 0.5 mL $TiCl_4$: 0.5 mL/ Pivalonitrile:0.2mL	in EDC, rt, 24hr *then* *NMR analysis*	3 : ~100%

Scheme 3. Attempts at isomerization of IO mesylates.

Another useful combination of the reagents was also found, in which addition of pivalonitrile (PN: a weak Lewis base) could effect the isocarbostyril formation albeit in a slow conversion (24 h vs 15 h). When PN was used as a sole solvent, only sluggish reaction was observed with $TiCl_4$. With some tertiary amines or pyridines, it is also possible to carry out same transformation, but oftentimes required large excess Lewis acid until complete conversion. So far, PN is most reliable additive to tune up the Lewis acidity for unusual BR. Use of toluene or CH_3CN as additive or solvent offered no obvious advantages. Further optimization with commercially available $TiCl_4$ solution (in toluene or CH_2Cl_2) gave inferior results.

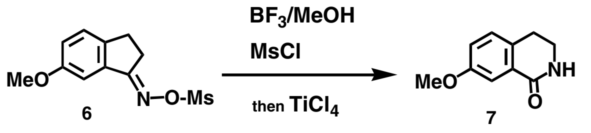
While we selected $ZrCl_4$ as a suitable promoter in the previous report for carbostyril synthesis, this acid was not so effective for the conversion to isocarbostyril under identical conditions, partly because of insoluble nature. Addition of pyridine derivatives, however, can tune up the sluggish reactivity of $ZrCl_4$ to some extent, but solubility problem was an inherent one, that must be overcome especially in a larger scale operations.

Through these investigations, we tentatively concluded that the promoter Ti Lewis acids ($TiCl_4$ and $TiBr_4$) and suitable additive (BF_3MeOH or PN) can play a key and indispensable role for the control of the reaction pathway of BR of IO mesylate.

One application. In order to further cultivate the versatility of the new protocol for isocarbostyril synthesis, we then studied with another important oxime substrate (**6**) bearing methoxy (OMe) substituent. The reaction conditions shown in the following scheme clearly indicate the usefulness and potential of the new protocol, furnishing the product in a satisfactory way (Scheme 4).

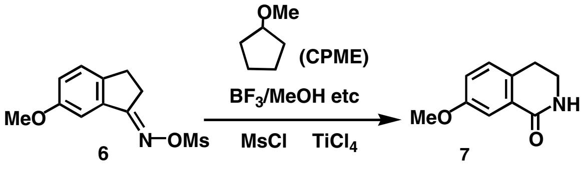
As far as we surveyed this time and previous time, EDC was seemingly the most suitable solvent of the BR of IO mesylate, resulting in the fast and clean reaction.

Solvent optimization. We now move to the solvent optimization for this BR of IO derivative to open another frontier, in which an interesting utilization of new ether solvent cyclopentylmethyl ether (CPME) is investigated briefly;[7] here, CPME does supplant EDC in nearly same



reagent composition	conditions	isolated Y (chromato)
BF_3MeOH-MsCl-$TiCl_4$ (1:1:1) in EDC ($ClCH_2CH_2Cl$)	rt, 4 hr	7: 75%

Scheme 4. BR with methoxy derivative.



reagents	conditions	isolated Y (chromato)
BF_3MeOH-MsCl-$TiCl_4$ (1:1:1.2)	rt, ca. 6hr	*7: 80%*
PivCN -MsCl-$TiCl_4$ (2:1:2)	rt, ca. 12 hr	*7: ~75%*
MsCl-$TiCl_4$ (1:2)	rt~60°C, ca. 6 hr	*7: minor product; < 30%*

Scheme 5. New combination with CPME.

composition of the reagents for BR of IO mesylate as shown in Scheme 5.

Furthermore, it was also found that often-mentioned benzotrifluoride (BTF) was not easily applicable to such acidic transformations, because it slowly reacted with $TiCl_4$ itself (presumably because of a conversion into benzotrichloride).[8]

The conditions with PN are of particular applicability, because it neither requires halogenated solvent (EDC) nor fluorinated reagents, which themselves require particular reaction vessels for protection from fluorine.

In conclusion, we have thus described our progress toward the control of the regiochemistry of the BR of IO, in which the unfavorable conversion into the isomeric isocarbostyrils (such as **3**, **7**) is now feasible under very mild conditions.

These investigations clearly indicate the usefulness of $TiCl_4$ as a promoter of BR of IO, which can exert two directional Beckmann pathways by careful choice of the additives and solvents.

The progress by us along with others now indicates the nicely controlled pathways for general BR for many other synthetic operations. Further applications of these two directional BR tactics to the more demanding substrates are now under active investigation in this laboratory and the progress will be reported in due course.

Acknowledgment

We thank Prof. Veejendra K. Yadav of Indian Institute of Technology at Kanpur, India, for his helpful suggestions and critical reading of the manuscript.

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