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Improved procedures for the Beckmann rearrangement: the reaction of ketoxime carbonates with boron trifluoride etherate

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Abstract

A variety of ketoxime ethyl carbonates—easily prepared from the oximes and ethyl chloroformate—undergo the Beckmann rearrangement upon treatment with 1 equivalent of boron trifluoride etherate, in dichloromethane solution at room temperature in excellent yields (generally 75–99%).

Keywords: Beckmann rearrangement; boron trifluoride; ethyl chloroformate; oxime carbonates.

The Beckmann rearrangement is a venerable reaction that has not only shaped the development of both synthetic and mechanistic organic chemistry, but also remains a topic of current interest.[1,2] It accomplishes in one stroke both the cleavage of a carbon–carbon bond and the formation of a carbon–nitrogen bond; and the specificity that obtains vis-a-vis both the oxime geometry and the configuration at the migrating centre enhances its value. Classically, the reaction was effected in strongly acidic and dehydrating media, thus precluding its application to sensitive substrates. Milder conditions, of course, were sought, and several interesting variants developed.[1,2] These essentially focused on forming activated oxime derivatives (e.g. the sulphonate esters) which were found to rearrange under relatively mild conditions. However, a drawback in such methods is the inherent instability of the activated oximes, the use of rather toxic solvents (e.g. pyridine), expensive reagents (e.g. the Mitsunobu reagent), etc.;[1,2] all these difficulties preclude scale-up to larger batches. There is, therefore, a need for relatively simple and mild conditions for the Beckmann rearrangement, and the present studies were thus directed.

In fact, a consideration of the mechanism of the Beckmann rearrangement uncovers the following intriguing possibility: since the nucleofuge and the migrating group are mutually *anti*, a nucleofuge carrying a remote nucleophilic moiety should also be able to assist the migration process via

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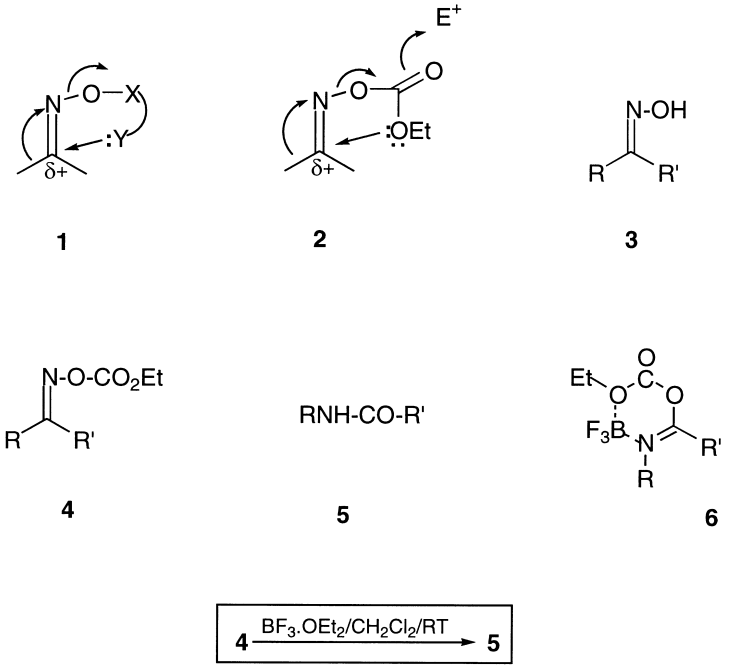
coordination to the developing cationic centre, as shown in the putative transition state **1** (Scheme 1). A very simple system in which such interactions are feasible is that of the oxime carbonate, in which the oxygen atom of the alkoxy group can coordinate as suggested above (**2**). Interestingly, the Beckmann rearrangement of oxime carbonates[3] was apparently unknown, and so a detailed study was initiated.



Scheme 1.

A variety of ketoximes **3** was converted to the corresponding ethyl carbonates **4** relatively simply and in high yields (generally 90–99%), via treatment with ethyl chloroformate in dichloromethane solution, in the presence of 1 equivalent of pyridine at room temperature. Treatment of the oxime ethyl carbonates **4** thus obtained with 1 equivalent of boron trifluoride diethyl etherate in dichloromethane solution, effected the Beckmann rearrangement at room temperature (with one exception). The reaction times varied from 4–18 h, and the yields of the amide or lactam products **5** from 70–99% (with one exception, Table 1). Although the reaction was originally envisaged as being catalytic in boron trifluoride etherate, it was found that a minimum of 1 equivalent was required for complete conversion: the most likely explanation is its complexation with the immediate product of the rearrangement (the iminol carbonate, possibly to form the chelate **6**)—which, of course, leaves it unavailable for the rearrangement itself.

It was also determined that benzophenone oxime acetate also undergoes the Beckmann rearrangement but rather sluggishly, upon treatment with boron trifluoride etherate under the above conditions: this confirms the little literature precedent that does exist.[4–6] Of course, this lends credence to the coordination-assisted transition state **2** envisaged above in the case of the carbonates.

In summary, a set of very mild reaction conditions—with the added virtue of simplicity—has been developed for a two-step process for the Beckmann rearrangement. Further work is planned to extend the above results.

Table 1
The Beckmann rearrangement of the ketoxime carbonates **4**[a] to the amides/lactams **5**

R / R'	Reaction time (h)	% Yield of **5**
Ph / Ph	6	98
$PhCH_2$ / $PhCH_2$	4	78
Ph / Me	18	87
Et / Et	7	77
$Ph(CH_2)_2$ / Me	12	74
p-Cl-C_6H_4 / *p*-Cl-C_6H_4	12	99
p-Me-C_6H_4 / Me	12	76
-$(CH_2)_5$-	10	58[b]
(from camphor oxime)	5	70[c]
(from 2-decalone oxime)	10	83[d]
(from 6-methoxy-α-tetralone oxime)	6 (CCl_4 reflux)	87[e]

[a]The stereochemistry of the oxime employed is as shown in **4;** [b]caprolactam; [c] the fragmention product: 4-cyanomethyl-3,3-dimethyl-1-methylcyclopent-1-ene; [d]mixture of both the possible lactam products; [e]1,2,3,4-tetrahydro-7-methoxy-5*H*-1-benzazepin-2-one, produced by the migration of the aryl ring.

Typical procedures - The oxime ethyl carbonates. The oxime (1 mmol) and dry pyridine (1 mmol) in dry CH_2Cl_2 (3 ml) were treated with ethyl chloroformate (1 mmol) at 25 °C, and the mixture worked up after 3h by washing with water, drying and evaporation of the solvent. The rearrangement. The oxime carbonate (1 mmol) in CH_2Cl_2 (3 ml) was treated with $BF_3.Et_2O$ (1 mmol) at 25 °C. After the indicated time the mixture was worked up as above. All compounds were identified spectroscopically (IR, ^1H and ^{13}C NMR and MS), and known compounds by their physical constants; new compounds generally furnished good elemental analysis.

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