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Beckmann Rearrangement of Oximes under Very Mild Conditions

Lidia De Luca, Giampaolo Giacomelli,* and
Andrea Porcheddu

Dipartimento di Chimica, Università degli Studi di Sassari,
Via Vienna 2, I-07100 Sassari, Italy

ggp@uniss.it

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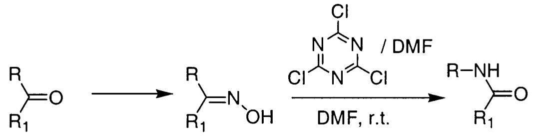
Abstract: A variety of ketoximes, easily prepared from the corresponding ketones, undergo the Beckmann rearrangement upon treatment with 2,4,6-trichloro[1,3,5]triazine in *N*,*N*-dimethylformamide at room temperature in excellent yields. This procedure can be applied to aldoximes for obtaining the corresponding nitriles.

The rearrangement of ketoximes to the corresponding amide, known as the Beckmann reaction, is a common method in organic chemistry[1] and is a topic of current interest. It accomplishes in one stroke both the cleavage of a carbon−carbon bond and the formation of a carbon−nitrogen bond. It represents a powerful method particularly for manufacturing ϵ-caprolactam in the chemical industry. The reaction generally requires high reaction temperatures and strongly acidic and dehydrating media.[1] Thus, the reaction can lead to large amounts of byproducts and preclude its application to sensitive substrates. On these bases milder conditions were tried and several interesting variants developed.[2,3] Recently the Beckmann rearrangement was reported to occur in ionic liquids at room temperature.[4] Nevertheless until now the occurrence of mild conditions was related to the use of rather toxic solvents and expensive reagents or solvents.

As part of an ongoing program directed to the development of efficient reagents for use under mild conditions and following our latest interest in the use of [1,3,5]-triazine derivatives in organic synthesis,[5] we report a very mild and selective procedure for the quantitative conversion of ketoximes into the corresponding amides.

SCHEME 1



The procedure is based on the reaction of a complex formed by 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT), a very inexpensive reagent, and DMF,[6] with a DMF solution of 1 mol equiv of the ketoxime (Scheme 1).[7]

The complex is easily prepared by dissolving the TCT in the least volume of commercial DMF at room temperature,[8] followed by the addition of the oxime[9] in DMF, after disappearance of free TCT (TLC monitoring). The mixture is stirred at room temperature for the required time and then quenched with water. The triazine byproducts are then removed by aqueous workup. The corresponding amides can be recovered chemically pure in high yields (Table 1) without any purification.

The reaction is reasonably fast (less than 4 h) only with acetophenone and cyclohexanone oximes and requires almost 24 h for completion in most of the cases. However, this method can be successfully applied on a large scale. Moreover no deoximation of the oximes to carbonyl compounds occurs.

On examination of Table 1 some observations can be made. In all cases only one of the two possible amides were recovered. Contrary to what was observed in most of the conventional Beckmann rearrangement,[1] electron-donating groups on the aromatic ring seem to reduce the reaction rate, in particular when the substituent is on the ortho−para positions (runs 2, 3, and 4). Generally, migration of an aryl group predominates over that of an alkyl group. However, in the case of both *tert*-butyl phenyl ketone oxime and the oxime of 3,3-dimethylbutan-2-one (runs 8 and 9) the rearrangement gives rise to migration of the *tert*-butyl group. Moreover the results obtained suggest that the stereochemistry of the oximes has very little effect on the reaction as in other Beckmann rearrangements.[10]

The results obtained with the oximes of cyclic ketones are noteworthy and indicate a simple and mild approach to lactams[11] which are particularly important molecules as synthetic intermediates for biologically important compounds.[12] The conversion of the cyclohexanone oxime

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[1] Gawly, R. E. *Org. React.* **1988**, *35*, 1 and references therein. Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; p 1415 and references therein.

[2] Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311. Kikugawa, Y.; Tsuji, C.; Miyazawa, E.; Sakamoto, T. *Tetrahedron Lett.* **2001**, *42*, 2337. Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* **2000**, *41*, 5427. Sato, H.; Yoshioka, H.; Izumi, Y *J. Mol. Catal. A: Chemical* **1999**, *149*, 25. Laurent, A.; Jacquault, P.; Di Martino, J. L.; Hamelin, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1101.

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

[4] Peng, J.; Deng, Y. *Tetrahedron. Lett.* **2001**, *42*, 403. Ren, R. X.; Zueva, L. D.; Ou, W. *Tetrahedron. Lett.* **2001**, *42*, 8441.

[5] (a) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. (c) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275. (d) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519. (f) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (g) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907. (h) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553. (i) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, in press.

[6] (a) Gold, H. *Angew. Chem.* **1960**, *72*, 956. (b) Gupton, J. T.; Colon, C.; Harrison, C. R.; Lizzi, M. J.; Polk, D. E. *J. Org. Chem.* **1980**, *45*, 4522.

[7] No reaction was observed operating with solvents different from DMF, such as dichloromethane or THF. Furthermore, the reaction rate decrease noticeably operating with a reduced amount of TCT with respect to the oxime.

[8] No gas evolution (CO_2) was noted.

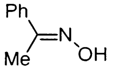
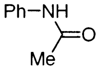
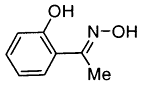
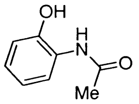
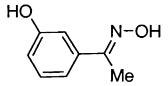
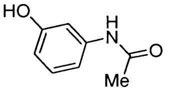
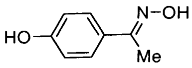
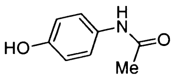
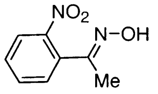
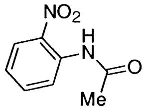
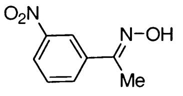
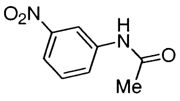
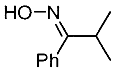
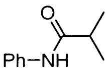
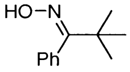
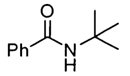
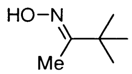
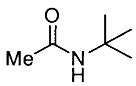
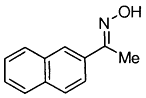
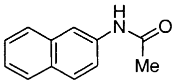
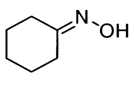
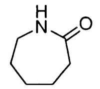
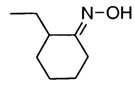
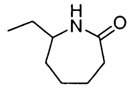
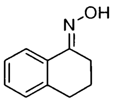
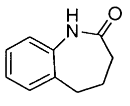
[9] The oximes were either obtained from commercial sources or prepared by standard procedures. No separation of the *E*:*Z* isomer was made.

[10] Probably the *E*- and *Z*-oximes interconvert under the reaction conditions (see also ref 13).

[11] Evans, P. A.; Modi, D. P. *J. Org. Chem.* **1995**, *60*, 6662.

10.1021/jo025960d CCC: $22.00

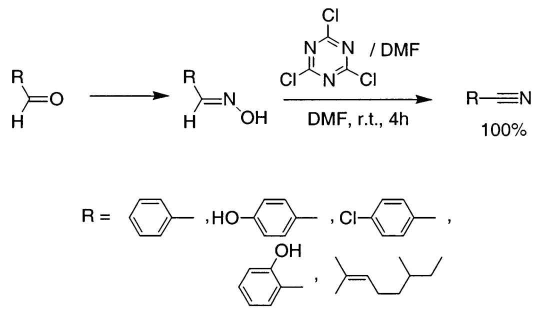
TABLE 1. Conversion of Ketoximes into Amides

entry	oximes	amide	reaction time	conv. (%)
1			6 h	100
2			12 h	75
3			6 h	100
4			6 h	80
5			12 h	60
6			12 h	80
7			12 h	85
8			24 h	91
9			24 h	92
10			12 h	100
11			3 h	100
12			8 h	100
13			12 h	83

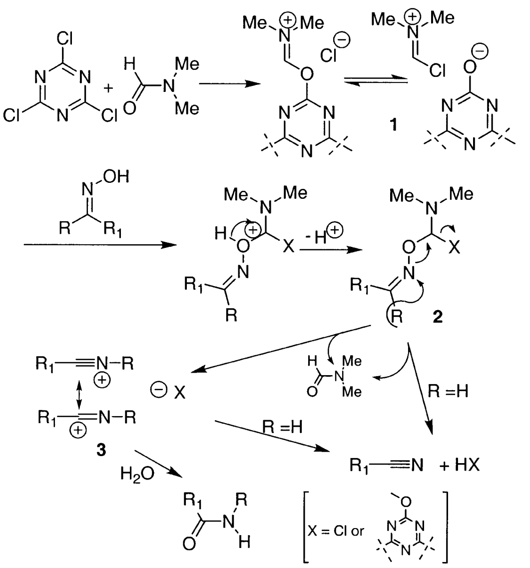
is rapid under the conditions reported and pure ϵ-caprolactam is recovered in a quantitative yield (run 11).

Aldoximes seem apparently to show a different reaction trend. Under the same conditions, treatment of the aldoximes with the TCT/DMF complex in DMF affords rapidly and quantitatively the corresponding nitrile (Scheme 2). The reactions are rapid and quantitative, the nitrile being the only product recovered from the reaction mixtures.

SCHEME 2



SCHEME 3



Although conversion of aldoximes to nitriles, through dehydration, using TCT is already documented,[13] this reaction should not proceed through dehydration sequences,[14] as no added base is present in the reaction medium that is acidic.

Therefore the results obtained may be consistent with the mechanism depicted in Scheme 3. The Vilsmeier–Haack-type complex **1** should add the hydroxyl group of the oxime to form the cationic species **2**.[5h] The subsequent rearrangement to adduct **3** should then afford directly the nitrile, in the case of aldoximes, or the amide upon hydrolitic workup. The conversion of **2** to **3** should occur through a concerted 1,2 intramolecular shift or more presumably via formation of an intermediate nitrilium ion[15] that rearranges to **3**. This last hypothesis could explain the formation of nitriles from aldoximes even though hydrogen very seldom migrates in the conventional Beckmann rearrangement.

In conclusion, this new procedure for the Beckmann-type reaction offers simple and easily reproducible tech-

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(12) Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*; Katritsky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 7, p 491.

(13) Chakrabarti, J. K.; Hotten, T. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1226.

(14) Even in this case, no reaction was observed when dichloromethane was used as solvent of the TCT/DMF complex.

(15) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279.

nique for amides and nitriles. The method seems to be convenient with respect to other reports and can be used as a valid alternative, thus avoiding tedious purifications or the use of more toxic or expensive reagents.

Experimental Section

All solvents and reagents were used as obtained from commercial sources. The oximes were prepared according to standard methods and their purities were established before utilization by melting point. Standard ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75.4 MHz, from $CDCl_3$ solutions. All runs were conducted at least in duplicate. The structures of the acyclic amides were confirmed by saponification and identification of the acid and/or amine components. The nitriles were identified by comparison with samples prepared according to known procedures too.[13]

General Procedure. The procedure for the preparation of 7-ethylazepan-2-one (run 12) is representative. 2,4,6-Trichloro-[1,3,5]triazine (1.83 g, 10.0 mmol) was added to DMF (2 mL), maintained at 25 °C. After the formation of a white solid, the reaction was monitored (TLC) until complete disappearance of TCT, Then 2-ethylcyclohexanone oxime (1.41 g,10.0 mmol) in DMF (15 mL) was added. After the addition, the mixture was stirred at room temperature, monitored (TLC) until completion (8 h). Water (20 mL) was added then the organic phase washed with 15 mL of a saturated solution of Na_2CO_3, followed by 1 N HCl and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated to yield 7-ethylazepan-2-one that was isolated without other purifications (1.41 g, 100%): mp 91 °C;[16] ^{1}H NMR δ (ppm) 6.28 (bs, 1H), 3.15 (m, 1H), 2.37 (bd, 2H), 1.96−1.68 (m, 4H), 1.46 (m, 2H), 1.21 (m, 2H), 0.89 (t, 3H); ^{13}C NMR δ (ppm) 174.9, 55.2, 36.6, 34.9, 29.5, 28.8, 23.1, 10.4.

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Supporting Information Available: Physical and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Gol'dfarb, Ya. L.; Fabrichnyi, B. P.; Shalavina, I. F. *Tetrahedron* **1962**, *18*, 21.