Tetrahedron Letters 52 (2011) 1074–1077

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient catalytic method for the Beckmann rearrangement of ketoximes to amides and aldoximes to nitriles mediated by propylphosphonic anhydride (T3P®)

John Kallikat Augustine [a,*], Rajesha Kumar [a], Agnes Bombrun [b], Ashis Baran Mandal [a]

[a] Syngene International Ltd, Biocon Park, Plot Nos. 2 & 3, Bommasandra IV Phase, Jigani Link Road, Bangalore 560 099, India
[b] Merck Serono SA, 9 Chemin des Mines, 1202 Geneva, Switzerland

ARTICLE INFO

Article history:
Received 10 November 2010
Revised 10 December 2010
Accepted 18 December 2010
Available online 29 December 2010

Keywords:
Beckmann rearrangement
Propylphosphonic anhydride
Ketoximes
Acetanilides
Nitriles

ABSTRACT

An efficient method for the Beckmann rearrangement of ketoximes to amides mediated by a catalytic amount (15 mol %) of propylphosphonic anhydride (T3P®) is described. Aldoximes underwent second order Beckmann rearrangement to provide the corresponding nitriles in excellent yields on reacting with T3P (15 mol %) at room temperature. The main advantages of this environmentally friendly protocol include procedural simplicity, and particularly ease of isolation of the products.

The rearrangement of ketoximes to the corresponding amides/lactams is a prevailing method in organic synthesis[1] and is known as the Beckmann rearrangement. One of the most important applications of this reaction involves the commercial process for the production of nylon-6 and nylon-12.[2] In general, it requires a strong acid and a relatively high reaction temperature, and generates a large amount of ammonium sulfate as a byproduct. Development of this significant process promoted by a catalytic amount of mild reagents has been strongly desired for a long time. Many catalytic methods in vapor phase,[3] liquid phase,[4] supercritical water,[5] and ionic liquids[6] have been reported until now. Liquid-phase catalytic Beckmann rearrangement under mild conditions has become a topic of current interest due to its advantages such as easy work-up, and industrial practicability. The milder conditions developed until now were essentially related to activating the oxime by using acidic reagents such as sulfamic acid,[4d] chloral,[7] chlorosulfonic acid,[4e] cyanuric chloride,[4b] anhydrous oxalic acid,[8] bis(2-oxo-3-oxazolidinyl)phosphonic chloride,[9] diethyl chlorophosphate,[10] PTSA-$ZnCl_2$,[11] and triphosphazene.[12] Further, various inorganic catalysts such as $HgCl_2$,[13] $[RhCl(cod)]_2$,[14] $RuCl_3$,[15] and $Yb(OTf)_3$[16] were reported to achieve the Beckmann transformation in good yields. However, due to their high cost, toxic nature, and corrosiveness, these catalysts have found less industrial utilization. Hence, more efficient and less toxic catalytic methods having wide functional group tolerance for the Beckmann rearrangement are highly desirable.

Propylphosphonic anhydride (T3P®) is a mild water scavenger with low toxicity and low allergenic potential.[17] Although T3P has been largely used as a mild coupling reagent in peptide synthesis, new applications have recently been developed for this reagent.[18] Herein, we report our results on the highly effective propylphosphonic anhydride catalyzed transformation of ketoximes to amides/lactams and aldoximes to nitriles. The method is simple; isolation of the product from reaction mixture is easy and the yields are high.

In order to explore the scope and optimal conditions for T3P mediated Beckmann rearrangement, acetophenone oxime **1a** was selected as a model. The reaction of **1a** (1.0 equiv) with T3P (1.0 equiv, 50% solution in EtOAc) in THF at reflux for 2 h provided **2a** in 99% isolated yield (Table 1, entry 1). Further optimization showed that use of T3P (15 mol %) was appropriate for the transformation in quantitative yield (Table 1, entry 3). Decreasing the amount of T3P from 15 to 10 mol % and lowering the reaction temperature from 70 °C to 25 °C prolonged the duration of reaction as well as lowered the amide yield (Table 1, entries 4 and 5).

The influence of various solvents on the Beckmann rearrangement catalyzed by T3P was then studied and the results are summarized in Table 2. While most of the solvents promoted the reaction, THF and DMF were found to be the most suitable reaction medium for T3P catalyzed Beckmann rearrangement (Table 2, entries 1 and 2). As expected, there was no rearrangement when

* Corresponding author. Tel.: +91 80 2808 3131; fax: +91 80 2808 3150.
E-mail address: john.kallikat@syngeneintl.com (J.K. Augustine).

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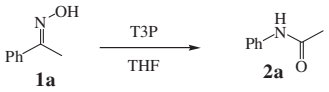
doi:10.1016/j.tetlet.2010.12.090

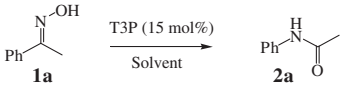
Table 1
Screening optimal conditions



1a **2a**

Entry	T3P (mol %)	Time (h)	Temp. (°C)	Yield (%) **2a**
1	100	2	70	99
2	25	2	70	98
3	15	2	70	98
4	10	5	70	93
5	15	12	25	64

Table 2
Screening optimal solvent



1a **2a**

Entry	Solvent	Time (h)	Temp. (°C)	Yield (%) **2a**
1	DMF	2	80	97
2	THF	2	70	98
3	Toluene	5	100	95
4	$MeNO_2$	5	70	78
5	Dioxane	5	100	84
6	MeCN	5	70	87
7	EtOAc	5	70	76
8	EDC	5	70	61
9[a]	DMF	6	100	NR[b]

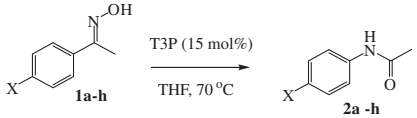
[a] Reaction was performed in the absence of T3P.
[b] No reaction.

the ketoxime was heated at 100 °C in DMF in the absence of T3P (Table 2, entry 9).

With the most favorable reaction conditions (Table 1, entry 3) in hand, we investigated the effect of functional groups on the rate of reaction. The rearrangement of various *para*-substituted acetophenone oximes (**1a**–**h**) into corresponding acetanilides was thus studied (Table 3). As observed by us, the rearrangement of electron rich aromatics was complete within 2 h of reaction at 80 °C in THF (Table 3, entries 2–4), whereas the rate of rearrangement was significantly affected by the presence of electron-withdrawing substituents on the ring (Table 3, entries 5–8).

Having evaluated the electronic parameters of T3P catalyzed Beckmann rearrangement, we proceeded to explore the scope and generality of this reaction. Thus, various ketoximes[19] were treated with T3P under the standard reaction conditions (Table 1, entry 3) to obtain corresponding Beckmann products (Table 4). As summarized in Tables 3 and 4, the reaction tolerated a variety

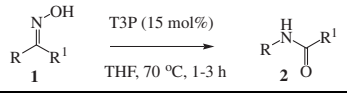
Table 3
Study of electronic behavior



1a-h **2a -h**

Entry	X	Product	Time (h)	Yield (%)
1	H	**2a**	2	98
2	OMe	**2b**	0.5	98
3	NMe_2	**2c**	0.5	95
4	Me	**2d**	2	94
5	F	**2e**	3	95
6	Br	**2f**	2	97
7	COOMe	**2g**	4	92
8	NO_2	**2h**	3	94

Table 4
T3P mediated synthesis of amides from ketoximes

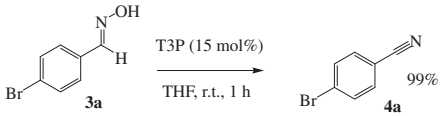


1 **2**

Entry	Substrate	Product	Yield[a] (%)
1	**1i**	**2i**	93
2	**1j**	**2j**	94
3	**1k**	**2k**	89
4	**1l**	**2l**	94
5	**1m**	**2m**	95
6	**1n**	**2n**	91
7	**1o**	**2o**	87
8	**1p**	**2p**	90
9	**1q**	**2q**	92
10	**1r**	**2r**	90
11	**1s**	**2s**	85
12	**1t**	**2t**	84
13	**1u**	**2u**	89
14	**1v**	**2v**	91

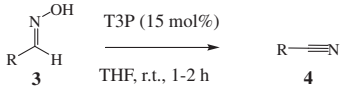
[a] Isolated yields.

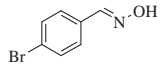
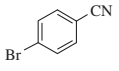
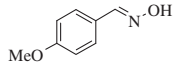
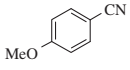
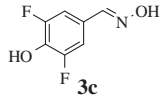
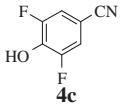
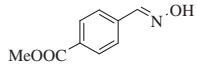
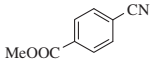
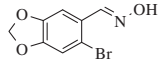
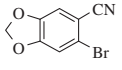
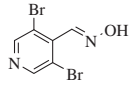
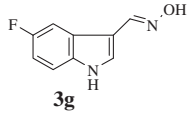
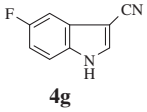
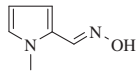
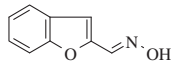
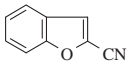
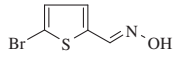
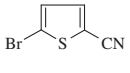
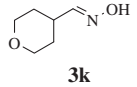
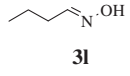
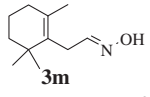
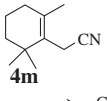
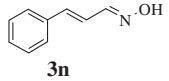
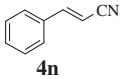
of aromatic, heteroaromatic, and aliphatic ketoximes bearing various functional groups to afford the corresponding amides in good



Scheme 1.

Table 5
T3P mediated synthesis of nitriles from aldoximes



Entry	Substrate	Product	Yield (%)[a]
1	 **3a**	 **4a**	99
2	 **3b**	 **4b**	98
3	 **3c**	 **4c**	94
4	 **3d**	 **4d**	99
5	 **3e**	 **4e**	96
6	 **3f**	 **4f**	96
7	 **3g**	 **4g**	93
8	 **3h**	 **4h**	91
9	 **3i**	 **4i**	95
10	 **3j**	 **4j**	91
11	 **3k**	 **4k**	87
12	 **3l**	 **4l**	95
13	 **3m**	 **4m**	98
14	 **3n**	 **4n**	95

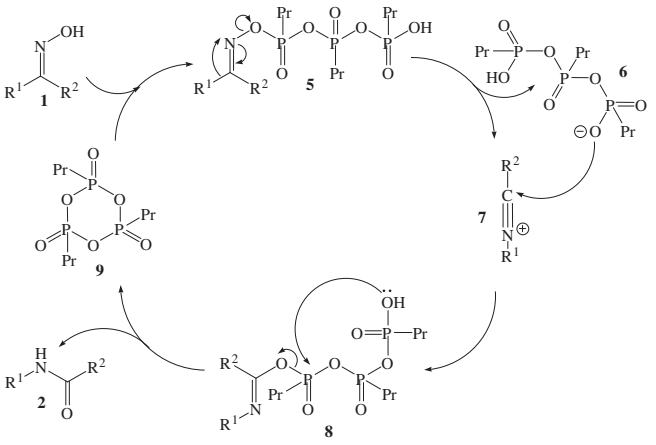
[a] Isolated yields.

yields. It is noteworthy that the reaction tolerated an acid sensitive functional group to provide the Beckmann products in good yields (Table 4, entries 3 and 12). In most cases, the products were isolated after evaporation of solvents such as THF and DMF, washed easily with water, and finally crystallized.

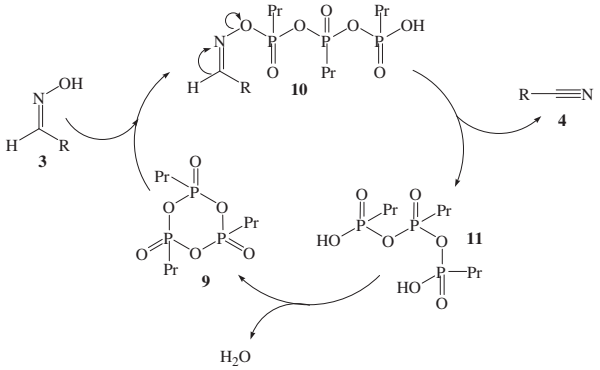
Aldoximes[19] under the new reaction conditions underwent second order Beckmann rearrangement to afford rapidly and quantitatively the corresponding nitriles as sole products. The reaction of **3a** with T3P (15 mol %) in THF at room temperature for 1 h exclusively afforded **4a** (Scheme 1). Further, as summarized in Table 5, the second order Beckmann rearrangement is general in scope among aromatic, heterocyclic, and aliphatic aldoximes to give the corresponding nitriles in excellent yields.

The striking catalytic activity of T3P could be attributed to a possible nucleophilic participation of 'open' hydrated T3P **6** (generated from a concerted 1,2-intramolecular rearrangement of phosphonate intermediate **5**), with nitrilium intermediate **7** to give **8** (Scheme 2). Further, the intermediate **8** cyclizes to regenerate the catalyst **9** (T3P) with the expulsion of amide. The rearrangement should afford directly the nitrile, in the case of aldoximes (Scheme 3).

In summary, T3P has been proven to be an excellent catalyst to access the Beckmann rearrangement. The use of T3P (15 mol %) has resulted in an efficient catalytic method for the synthesis of amides from ketoximes[20] and nitriles from aldoximes.[21] Unlike other reagents, the use of a catalytic amount of T3P is economical. The method seems to be convenient for large scale preparations due to the ease of isolation of products in good purity by simple



Scheme 2.



Scheme 3.

work-up and can be used as a valid substitute for other methods, thus avoiding the use of expensive and more toxic reagents to access amides and nitriles from oximes.

Supplementary data

Supplementary data (characterization data for new compounds, copies of ^{1}H and ^{13}C NMR spectra for **1a–v**, **2a–v**, **3a–n**, **4a–n**, and LCMS report for **2a–v**, and **4a–n**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.090.

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19. All of the oxime substrates used in this investigation were synthesized in quantitative yields by refluxing a mixture of 1 equiv of the corresponding ketones or aldehydes, 1.6 equiv of hydroxylamine hydrochloride, and 2.0 equiv of sodium acetate in aqueous methanol.
20. *T3P catalyzed synthesis of amides/lactams from ketoximes*: To a solution of ketoxime (0.01 mol) in THF (10 mL) was added T3P (15 mol %, 50% soln in EtOAc) and the resulting reaction mixture was stirred at reflux for 1–4 h under nitrogen atmosphere. When the reaction was completed as confirmed by TLC, the solvent was removed under vacuum and the residue was diluted with water (20 mL). The product was extracted with ethyl acetate (2×20 mL) and the combined organic phase was washed with saturated $NaHCO_3$ solution (1×10 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the desired amides in good purity.
21. *T3P catalyzed synthesis of nitriles from aldoximes*: To a solution of aldoxime (0.01 mol) in THF (10 mL) was added T3P (15 mol %, 50% soln in EtOAc) and the resulting reaction mixture was stirred at room temperature for 1–2 h under nitrogen atmosphere. When the reaction was completed as confirmed by TLC, the solvent was removed under vacuum and the residue was diluted with water (20 mL). The product was extracted with ethyl acetate (2×20 mL) and the combined organic phase was washed with saturated $NaHCO_3$ solution (1×10 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford the desired nitriles in good purity.