Beckmann rearrangement of ketoximes and deprotection of aldoximes in solvent-free conditions

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Phosphoric acid is an efficient and mild reagent for regeneration of aldehyde from oximes, but ketoximes are converted to amides or lactam by Beckmann rearrangement. The reactions are carried out in solvent-free conditions under microwave irradiation.

Keywords: Beckman rearrangement, ketoximes, deprotection, aldoximes, phosphoric acid amides, lactam, microwave irradiation

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Considerable interests have been grown up in the development of methods for the regeneration of aldehydes from stable and readily prepared oximes. Oximes are not only extensively used for characterization and purification of aldehydes, but also useful as protecting groups in multistep synthesis, as aldehydes are reactive towards a large number of reagents. Regeneration of aldehydes from their oximes under mild conditions is an important process in synthetic organic chemistry. A large number of reagents for the regeneration of ketones from their oximes are known. But, some of the reagents, which regenerate ketones successfully, are not applicable for regeneration of aldehydes, as they either produce aldehydes in low yields or furnish a complex mixture of products. Besides, some of the reagents, viz. thallium (III), lead (IV), chromium (VI), TBHP, which regenerate aldehydes, are toxic. So, the discovery of environment-friendly, high-yielding, inexpensive reagents for the regeneration of aldehydes from oximes, is the goal of the chemists.

Recently, emphasis has been given to use more environment-friendly reagents in organic synthesis, for the growth of green chemistry. Green chemistry approaches hold out significant potential for reduction of by-products, a reduction in the organic solvent waste, a number of which are generally toxic to living beings. Phosphoric acid is an environment-friendly reagent, because pure phosphoric acid is odourless and when diluted, not injurious to health, it is used for the manufacture of certain food stuffs such as gelatin and soft drinks. It is also used in the production of various salts in the fertilizers, detergents and dentrifice industries. The annual output of phosphoric acid is more than ten million metric tons only in USA. Polyphosphoric acid is a common reagent in organic synthesis for cyclizations, acylations, alkylations and Beckmann rearrangements.

However, a little is known in the literature for the use of phosphoric acid in synthetic applications other than its use in dehydrations of 2º and 3º alcohols and very recently regeneration of amino acids from their N-BOC derivatives.

The application of microwave radiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology. The salient features of the microwave application are rapid reaction rates, cleaner products and enhancement in chemical yields. The solvent-free reactions under this condition are especially appealing for providing an environmentally benign system. In order to develop synthetic protocols utilizing microwave radiation, herein we report a facile microwave assisted regeneration of aldehydes in fair to excellent yields and in short time from aldoximes using an environment-friendly and inexpensive reagent, phosphoric acid in solvent-free conditions at ambient pressure in open vessels (thus

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avoiding the risk of high pressure development) (Scheme I). Phosphoric acid regenerates aldehydes from oximes within 35-120 secs in 72-90% yields (Table I). Under similar reaction conditions ketoximes underwent Beckmann rearrangement\(^{22}\) (Scheme II) furnishing amides/lactam in 73-82% yields within 60-180 secs (Table II). There are a number of reagents available to convert aldoximes to the corresponding amides by Beckmann rearrangement\(^{22}\). But in the presence of phosphoric acid, aldoximes are selectively deprotected to form corresponding aldehydes, whereas ketoximes are converted to amides/lactam. To the best of our knowledge, this is the first report of the application of phosphoric acid for the formation of amides from ketoximes by Beckmann rearrangement as well as regeneration of aldehydes from aldoximes. By conventional heating method (110ºC in an oil-bath), the reactions were still incomplete after 4 hr. Recently, amides have also been achieved\(^{23}\) by treatment of ketones with hydroxylamine hydrochloride under microwave irradiation in the presence of silica gel supported NaHSO\(_4\) or HCO\(_2\)H catalyst in good yields.

In conclusion, microwave-assisted solvent-free (under conditions of so-called ‘Green Chemistry’)

![Scheme I](image1)

**Scheme I**

![Scheme II](image2)

**Scheme II**

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<tr>
<th>Table I — Regeneration of aldehydes from aldoximes using phosphoric acid under microwave irradiation</th>
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\(^{a}\)Isolated pure product

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<th>Table II — The Beckmann rearrangement of ketoximes to amides/lactam using phosphoric acid under microwave irradiation</th>
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reactions were employed to synthesize amides from ketoximes and also to deprotect several aldoximes in the presence of phosphoric acid without using hazardous solvents. Advantages of this method include the fact that it is environmentally benign, an economical procedure, has a short reaction time with high yields.

**Experimental Section**

**General procedure.** A mixture of oxime (0.5 mmole) and phosphoric acid (85%, 1 mL) were taken in a 50 mL Erlenmeyer flask, then irradiated inside a BPL-SANYO, 700 T microwave oven for a specified time (Tables I and II). After completion of reaction (monitored by TLC), the product was extracted with ether (3 × 25 mL), combined ether layer washed with brine (25 mL) and then dried over anhyd. Na$_2$SO$_4$. The products from ketoximes were purified by column chromatography over silica gel (EtOAc-

\[ \text{hexane 3:7, for entry 4, 4:6) and characterized spectroscopically and by comparison with reported melting points}^{24}\). The IR absorption bands and $^1$H NMR and $^{13}$C NMR (CDCl$_3$, 300/75 MHz) resonances for a representative products (entry 2, Table II) are as follows: IR (KBr): 3294 (N-H), 1663 (CONH), 1602, 1551, 1493, 755, 698 cm$^{-1}$; $^1$H NMR: δ 8.54 (1H, br.s, NH), 7.52 (2H, d, $J = 8.0$ Hz, H-2 and H-6), 7.23 (2H, t, $J = 8.0$ Hz, H-3 and H-5), 7.08 (1H, t, $J = 8.0$ Hz, H-4), 2.12 (3H, s, CH$_3$); $^{13}$C NMR: δ 168.9 (C=O), 138.1 (C-1), 128.8 (C-3 and C-5), 124.2 (C-4), 120.2 (C-2 and C-6), 24.1 (CH$_3$).

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**References**