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1. One pot synthesis of amides from ketones and hydroxylamine hydrochloride using p-toluenesulphonic acid over CTAB under microwave irradiations.

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Papers presented in conferences:

1. Deoximation of carbonyl compounds with new reagents.

2. Regeneration of carbonyl compounds from aldoximes and ketoximes over ceric sulphate.
One Pot Synthesis of Amides from Ketones And Hydroxylamine Hydrochloride Using P-Toluenesulphonic Acid Over CTAB Under Microwave Irradiation

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ABSTRACT

One pot synthesis of amides from variously substituted ketones and hydroxylamine hydrochloride has been carried out in an aqueous medium under microwave irradiation upon treatment with p-toluenesulphonic acid monohydrate (TsOH.H₂O) over phase transfer catalysts N-cetyl-N,N,N-trimethylammonium bromide (CTAB) in 54-60% yield. This catalytic system has been proved to be very efficient for the preparation of amides from ketones in good yield.

Keywords: Amides; Ketones; P-Toluenesulphonic Acid Monohydrate, CTAB, MW.

INTRODUCTION

The amides of various ketones have been prepared by the Beckmann rearrangement reaction of their oxime intermediates, under different reaction conditions. As it is an acid catalyzed reaction therefore, it has been carried out in the presence of a variety of inorganic acids[1]. However, in view of the harsh reaction conditions, limited yields of amides and production of environmentally harmful products etc., there is still a need for developing new eco-friendly methods for this reaction. In recent times, organic synthesis under solvent-free conditions using microwave irradiations has become increasingly popular. Major advantages of the use of MW irradiations for conducting organic reactions include avoiding the use of organic solvents leading to clean, eco-friendly and efficient reactions. Because of our interest in carrying out organic reactions in dry media conditions by utilizing microwave energy[2-6], we report herein the rapid one pot synthesis of amides from ketones and hydroxylamine hydrochloride in an aqueous medium with the help of an easy to handle organic acid, p-toluenesulphonic acid monohydrate (TsOH.H₂O) over N-cetyl-N,N,N-trimethylammonium bromide (CTAB).

MATERIALS AND METHODS

Ketones were purchased from Sigma-Aldrich and Fluka Goldie. p-toluenesulphonic acid monohydrate was purchased from Fluka Goldie and CTAB was purchased from Loba Chemie. Reactions were monitored by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). Visualization of the resulting chromatograms was done by
looking under iodine chamber followed by dipping in a solution of carbon tetrachloride (CCl₄) and ethylacetate. ¹H-NMR was recorded on a 400MHz spectrometer (Bruker Avance II 400). The chemical shifts were determined using Tetramethylsilane (TMS) as internal standard at δ 0.0 or to the signal of residual CDCl₃ δ 7.26. ¹³C-NMR (100MHz) was recorded using CDCl₃ as solvent.

General procedure for the synthesis of amides from ketones: p-Toluenesulphonic acid monohydrate (0.200 g, 1.05 mmol), CTAB (0.100 g) and benzophenone (0.182 g, 1mmol), were mixed thoroughly with hydroxylamine hydrochloride (0.085g, 1.23 mmol) and distilled water (0.5 mL) at room temperature in a 10ml Pyrex beaker and irradiated at a temperature of 54°C. Reaction was monitored by TLC after intervals of 10 sec. when the reaction was found to be completed in 60 sec. The product was extracted with ether, filtered and the solvent evaporated off under reduced pressure to yield the N- phenylbenzamide (0.109 g, 60%). Same procedure was followed for the preparation of amides of other ketones at the identical medium. Accordingly, when the reaction was carried out without microwave irradiation, in an open vessel, the desired amide product was formed, but it was obtained in low yield of 12%. However, when the reaction was carried out in the presence of a mixture of TsOH.H₂O and CTAB (1:0.5, w/w), the product was obtained in about 40% yield under the same reaction conditions. Therefore, in order to increase the

RESULTS AND DISCUSSION

To start with, p-toluenesulphonic acid monohydrate alone was used to explore the formation of the desired product, N- phenylbenzamide from benzophenone and hydroxylamine hydrochloride in an aqueous medium. Accordingly, when the reaction was carried out under microwave irradiation, in an open vessel, the desired amide product was formed, but it was obtained in low yield of 12%. However, when the reaction was carried out in the presence of a mixture of TsOH.H₂O and CTAB (1:0.5, w/w), the product was obtained in about 40% yield under the same reaction conditions. Therefore, in order to increase the
yield of product we decided to increase the ratio of TsOH.H₂O and CTAB to 4:2 (w/w). Under these reaction conditions the desired amide was formed in 60% yield in about 2 min at a temperature of 54°C which was discovered to be the optimum temperature.

To examine the scope of the newly developed procedure, structurally diverse arylketones were selected. The synthesis of amides of acetophenone and its derivatives with electron withdrawing and donating groups such as p-nitro acetophenone, p-chloro acetophenone, p-hydroxy acetophenone and p-methoxy acetophenone was attempted under the same reaction conditions and obtained 55- 60% yield of product (Table-1). Synthesis of ε-caprolactam from cyclohexanone was also carried out and the product was obtained in 54% yield.

**Table –1. Rapid synthesis of amides from variously substituted ketones in the presence of hydroxylamine hydrochloride using p-toluenesulphonic acid and CTAB at 54°C.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reactants</th>
<th>Products</th>
<th>Yield (%)</th>
<th>Time (sec.)</th>
<th>M.P.(°C) Obs.</th>
<th>Lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzophenone acetophenone</td>
<td>N-phenylbenzamide</td>
<td>60</td>
<td>90</td>
<td>163</td>
<td>164</td>
</tr>
<tr>
<td>2</td>
<td>p-hydroxyacetophenone</td>
<td>N-(4-hydroxyphenyl)acetamide</td>
<td>57</td>
<td>90</td>
<td>170</td>
<td>169</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexanone</td>
<td>caprolactam</td>
<td>54</td>
<td>95</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>p-nitroacetophenone</td>
<td>N-(4-nitrophenyl)acetamide</td>
<td>55</td>
<td>90</td>
<td>213</td>
<td>215</td>
</tr>
<tr>
<td>5</td>
<td>p-chloroacetophenone</td>
<td>N-(4-chlorophenyl)acetamide</td>
<td>58</td>
<td>90</td>
<td>177</td>
<td>179</td>
</tr>
<tr>
<td>6</td>
<td>p-methoxyacetophenone</td>
<td>N-(4-methoxyphenyl)acetamide</td>
<td>57</td>
<td>95</td>
<td>128</td>
<td>129</td>
</tr>
</tbody>
</table>

**APPLICATIONS**

The amides have significant pharmacotherapeutic profile. Amides are found in important drugs. Acetaminophen is an analgesic. Phenacetin is another drug that is found in APC. Meprobamate is a tranquilizer. Some amides act as insect-repellant. Amides also form important synthetic fibers such as Nylon 66[8-11].

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Regeneration Of Carbonyl Compounds From Their Oximes Using P-Chloroperbenzoic Acid

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ABSTRACT

Rapid deoximation of aldoximes and ketoximes, substituted with different electron withdrawing and donating groups, has been achieved in excellent yields in the presence of p-chloroperbenzoic acid in dry-media conditions. Oximes of some steroidal compounds have also been deoximated. The method is highly efficient and the work-up is very simple.

Keywords: p-chloroperbenzoic acid, Aldehydes, Ketones, Steroids, Deoximation, Dry-media, Microwave assisted reactions.

INTRODUCTION

Carbonyl compounds are very useful starting materials for various transformations in organic synthesis. Therefore, it becomes necessary to protect them and to deprotect them as well, when required. One of the simplest potential routes is to convert them into oximes [1]. Oximes are significant derivatives of carbonyl compounds with C=N–OH functional group. Oximation represents a classical method for purification, characterisation and protection of carbonyl compounds. Many methods for the regeneration of carbonyl compounds from oximes have been reported. These include the hydrolytic method, oxidative cleavage or reductive cleavage [1]. However, in view of some limitations like use of harsh reaction conditions, limited yields of carbonyl compounds and production of environmentally harmful by-products etc., there is still a need for developing new, more efficient and eco-friendly protocols for deoximations.

In recent times, organic synthesis under solvent-free conditions using microwave irradiations has become increasingly popular [2-6]. Major advantages of the use of MW irradiations for conducting organic reactions include avoiding the use of organic solvents leading to clean, eco-friendly and efficient reactions. Because of our interest in carrying out organic reactions in dry media conditions by utilizing microwave energy [2-6], we report herein the rapid deoximation of aldoximes and ketoximes in the presence of p-chloroperbenzoic acid under solvent-free conditions.

MATERIALS AND METHODS

General: The aldehydes, ketones and steroidal compounds were purchased from Sigma-Aldrich and Fluka. The reactions were monitored by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). 1H-NMR was
recorded on a 400MHz spectrometer (Bruker Avance II 400). The chemical shifts were determined using Tetramethylsilane (TMS) as internal standard at δ 0.0 or to the signal of residual CDCl₃ δ 7.26. ¹³C-NMR (100MHz) was recorded using CDCl₃ as solvent. Oximes of all carbonyl compounds were prepared according to reported procedure [6].

**Procedure for the deoxidation of oximes**: p-Chloroperbenzoic acid (100 mg) and the oxime (1 mmol) were mixed thoroughly in a 10 mL beaker and microwaved with discontinuous heating at 35°C. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ether, filtered and the solvent evaporated off under reduced pressure to yield the corresponding product, benzophenone. Same procedure was followed for the regeneration of other carbonyl compounds from their oximes under the identical reaction conditions. The products were identified on the basis of comparison of their melting points/boiling points and spectroscopic data with those of the authentic samples and found in good agreement with literature.

**Data analysis**

**Benzophenone (1a)**: M.P. 49 °C. ¹H NMR: δ 7.806 (d, J = 8.5 Hz, 2H), 7.579 (t, 1H), 7.470 (t, 2H). ¹³C NMR: δ 196.78, 137.60, 132.96, 130.08, 128.31.

**Acetophenone (1b)**: B.P. 197 °C. ¹H NMR: δ 7.961 (m, 2H), 7.509 (m, 3H), 2.605 (s, 3H). ¹³C NMR: δ 199.12, 136.21, 133.11, 128.51, 128.22, 27.59.

**4- nitroaceto phenone (1c)**: M.P. 75 °C. ¹H NMR: δ 8.224 (m, 4H), 2.702 (s, 3H). ¹³C NMR: δ 197.36, 150.46, 141.52, 129.39, 122.86, 26.91.

**4- methoxyacetophenone (1d)**: M.P. 39 °C. ¹H NMR: δ 7.929 (d, J = 7.2 Hz, 2H), 6.929 (d, J = 7.1 Hz, 2H), 3.863 (s, 3H), 2.546 (s, 3H). ¹³C NMR: δ 196.41, 163.49, 130.52, 130.37, 113.67, 55.34, 26.14.

**Cyclohexanone (1e)**: B.P. 157 °C. ¹H NMR: δ 2.335 (m, 4H), 1.862 (m, 4H), 1.728 (m, 2H). ¹³C NMR: δ 211.03, 42.02, 27.09, 25.03.

**4- hydroxyaceto phenone (1f)**: M.P. 109 °C. ¹H NMR: δ 8.502 (s, 1H, OH), 7.915 (d, J = 8.0 Hz, 2H), 8.098 (d, J = 8.5 Hz, 2H). ¹³C NMR: δ 199.53, 162.12, 130.45, 128.20, 115.77, 26.25.

**4- nitrobenzaldehyde (2a)**: M.P. 103 °C. ¹H NMR: δ 10.128 (s, 1H), 8.337 (d, J = 8.5 Hz, 2H), 8.098 (d, J = 8.5 Hz, 2H). ¹³C NMR: δ 192.36, 150.48, 139.90, 130.40, 123.91, 39.56.

**2- nitrobenzaldehyde (2b)**: M.P. 41 °C. ¹H NMR: δ 10.521 (s, 1H), 7.904 (m, 4H). ¹³C NMR: δ 188.21, 150.57, 135.16, 133.73, 131.35, 129.56, 124.49.

**2, 4- dimethoxybenzaldehyde (2c)**: M.P. 68 °C. ¹H NMR: δ 10.257 (s, 1H), 7.787 (m, 1H), 6.529 (m, 1H), 6.471 (m, 1H), 3.889 (s, 3H), 3.864 (s, 3H). ¹³C NMR: δ 188.14, 166.27, 163.68, 130.53, 119.03, 105.96, 97.87, 55.60.

**4- chlorobenzaldehyde (2d)**: M.P. 46 °C. ¹H NMR: δ 9.962 (s, 1H), 7.801 (d, J = 9.0 Hz, 2H), 7.485 (d, J = 9.0 Hz, 2H). ¹³C NMR: δ 190.77, 140.91, 134.82, 130.89, 129.45.

**4- hydroxybenzaldehyde (2e)**: M.P. 114 °C. ¹H NMR: δ 10.241 (s, 1H, OH), 9.815 (s, 1H), 7.789 (d, J = 8.9 Hz, 2H), 6.965 (d, J = 8.8 Hz, 2H). ¹³C NMR: δ 191.26, 161.65, 132.56, 129.94, 116.06.
4- bromobenzaldehyde (2f): M.P. 57 °C. $^1$H NMR: δ 9.964 (s, 1H), 7.702 (d, $J$ = 9.0 Hz, 2H), 7.621 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR: δ 190.96, 135.13, 132.44, 130.94, 129.72.

Testosterone propionate (3a): M.P. 154 °C. $^1$H NMR: δ 5.731 (s, 1H), 4.614 (t, 1H), 2.414 (m, 6H), 2.192 (m, 1H), 2.013 (m, 1H), 1.837 (m, 2H), 1.691 (m, 2H), 1.562 (m, 3H), 1.359 (m, 2H), 1.227 (m, 4H), 1.156 (t, 3H), 1.072 (m, 2H), 0.959 (m, 1H), 0.839 (s, 3H). $^{13}$C NMR: δ 199.48, 174.52, 170.99, 123.95, 82.22, 53.69, 50.24, 42.51, 38.60, 36.63, 35.69, 35.39, 33.93, 32.74, 31.48, 27.80, 27.52, 23.48, 20.52, 17.39, 12.03, 9.27.

trans - androsterone (3b): M.P. 181 °C. $^1$H NMR: δ 0.694 (m, 1H), 0.865 (m, 6H), 0.995 (m, 2H), 1.132 (m, 1H), 1.309 (m, 6H), 1.567 (m, 4H), 1.737 (m, 3H), 1.816 (m, 3H), 1.950 (m, 1H), 2.088 (m, 1H), 2.470 (m, 1H), 3.598 (s, 1H, OH). $^{13}$C NMR: δ 221.48, 71.13, 54.44, 51.43, 47.82, 44.84, 38.05, 36.95, 35.86, 35.65, 35.05, 31.56, 31.42, 30.90, 28.40, 21.78, 20.51, 13.82, 12.31.

α - tetralone (3c): B.P. 114 °C. $^1$H NMR: δ 7.95- 7.25 (m, 4H), 2.61 (m, 2H), 2.57 (m, 2H), 1.89 (m, 2H). $^{13}$C NMR: δ 198.8, 139.9, 138.8, 133.4, 129.6, 128.5, 126.6, 42.3, 25.5, 31.8.

**RESULTS AND DISCUSSION**

Cl-C$_6$H$_4$COOOH (p-CPBA) was thought to be a good and mild organic acid, which is easy to handle as well. Reactions were carried out under microwave irradiations at 35 °C. The deoximation of benzophenoxime occurred within 82 seconds and the product, benzophenone was obtained in 88% yield as shown in scheme-1.

![Scheme-1](Image)

Deoximation worked well for different ketoximes with variously substituted groups and deoximated products were obtained in high yields under these mild conditions as recorded in table-1.

**Table-1.** Rapid deoximation of variously substituted ketoximes in dry-media in the presence of p-chloroperbenzoic acid.

<table>
<thead>
<tr>
<th>SUBSTRATE (Oximes)</th>
<th>YIELD (%)</th>
<th>TIME (Sec.)</th>
<th>PRODUCT (Ketones)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="Image" alt="Image" /></td>
<td>88</td>
<td>82</td>
<td><img src="Image" alt="Image" /></td>
</tr>
<tr>
<td><img src="Image" alt="Image" /></td>
<td>87</td>
<td>75</td>
<td><img src="Image" alt="Image" /></td>
</tr>
</tbody>
</table>

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Our next attention is towards deoximation of aldoximes using the same approach. A noteworthy feature of the above transformation is that the presence of the electron withdrawing groups such as -NO₂, -Br, -Cl or electron releasing groups such as -OH, -OMe on the aromatic ring of aldoximes did not affect the efficiency of catalyst as shown in table-2.

**Table-2.** Rapid deoximation of variously substituted aldoximes in dry-media in the presence of p-chloroperbenzoic acid.

<table>
<thead>
<tr>
<th>SUBSTRATE (Oximes)</th>
<th>YIELD (%)</th>
<th>TIME (Sec.)</th>
<th>PRODUCT (Aldehydes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HON</td>
<td>81</td>
<td>80</td>
<td>2a</td>
</tr>
<tr>
<td>HON</td>
<td>80</td>
<td>82</td>
<td>2b</td>
</tr>
<tr>
<td>HON</td>
<td>83</td>
<td>92</td>
<td>2c</td>
</tr>
<tr>
<td>HON</td>
<td>88</td>
<td>75</td>
<td>2d</td>
</tr>
<tr>
<td>HON</td>
<td>86</td>
<td>85</td>
<td>2e</td>
</tr>
<tr>
<td>HON</td>
<td>82</td>
<td>83</td>
<td>2f</td>
</tr>
</tbody>
</table>
Another peculiar feature of the catalyst is that the oximes of steroidal compounds having ketonic group like testosterone propionate and trans-androsterone also underwent deoximation under the identical reaction conditions and gave the corresponding product in 80-85% yield, without any effect on the rings of the steroidal compound. Deoximation of oxime of 1-tetralone, a sterically hindered compound, has also been done with the same procedure and the expected product was obtained in good yield as shown in Table-3.

Table-3. Rapid deoximation of oximes of sterically hindered compounds in dry-media in the presence of p-chloroperbenzoic acid.

<table>
<thead>
<tr>
<th>SUBSTRATE</th>
<th>YIELD (%)</th>
<th>TIME (Sec.)</th>
<th>PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
<td>70</td>
<td>3a</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>75</td>
<td>3b</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>80</td>
<td>3c</td>
</tr>
</tbody>
</table>

APPLICATIONS

Oximes have great biological and pharmacotherapeutic profiles. Perillartine, an oxime of perillaldehyde is used as an artificial sweetener, being 2000 times more sweet than sucrose[7]. Oximes also act as antidotes for nerve agents[7]. Oximes find a great application for the conversion of cyclohexanone into its oxime. About half a billion kilograms supply of cyclohexanone is converted into its oxime annually in the world[7].

CONCLUSIONS

In conclusion, the deoximation of compounds having carbonyl group with p-CPBA under microwave irradiations in dry-media conditions is a rapid, manipulative, simple and selective protocol in comparison to the conventional solution phase reactions which suffer from the use of organic pollutant solvents, long reaction times and low yields. The prominent advantage of the catalyst is that it affected only C=N bond of the oxime group while other functional groups remained intact.
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REFERENCES