Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (3): 1007-1010

(International Peer Reviewed Journal)

One Pot Synthesis of Amides from Ketones And Hydroxylamine Hydrochloride Using P-Toluenesulphonic Acid Over CTAB Under Microwave Irradiation

Sharwan k. Dewan* and Priti Sharma

*Department of Chemistry, Maharshi Dayanand University, Rohtak, Haryana-124001, **INDIA**

Email: sharwandewan@rediff.com

Accepted on 8th April 2014

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 ($TsOH.H_2O$) 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 ($TsOH.H_2O$) 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 (CCl_4) and ethylacetate. ^{1}H-NMR was recorded on a 400MHz spectrometer (Bruker Avance Π 400). The chemical shifts were determined using Tetramethylsilane (TMS) as internal standard at δ 0.0 or to the signal of residual $CDCl_3$ δ 7.26. ^{13}C-NMR (100MHz) was recorded using $CDCl_3$ 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 temperature till completion of the reaction. The products were identified on the basis of comparison of their melting points and spectroscopic data with those of the authentic samples and found in good agreement with literature[7-11].

Spectral analysis data*N*- Phenylbenzamide (benzanilide) ^{1}H-NMR ($CDCl_3$) δ 8.10 (br 1H, NH), 7.85 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.25-7.53 (m, 5H), 7.14 (t, J = 7.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 166.1 (C=O), 139.2 (C-N), 134.0, 131.0, 129.3, 128.5, 128.1, 125.3, 120.5.

***N*- Phenylacetamide (acetanilide)** ^{1}H-NMR ($CDCl_3$) δ 8.09 (br 1H, NH), 7.51 (d, *J*=7.10 Hz, 2H), 7.28 (d, *J*=7.8 Hz, 2H) 7.08 (t, *J* = 7.6 Hz, 1 H), 2.13 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.4 C=O), 138.1(C-N), 128.0, 124.5, 120.5, 24.9.

***N*-(4-hydroxyphenyl)acetamide (acetaminophen)** ^{1}H-NMR ($CDCl_3$) δ 9.97 (br 1H, NH), 9.25 (1H, OH), 7.35 (d, *J*=8.9 Hz, 2H), 6.69 (d, *J*=8.7 Hz, 2H), 2.05 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 167.6 (C=O), 131.4 (C-N), 154.1, 120.8, 115.5, 23.5.

1-aza-2-cycloheptanone (caprolactam) ^{1}H-NMR ($CDCl_3$) δ 7.79 (br 1H, NH), 3.13-3.22 (m, 2H), 2.46-2.43 (m, 2H), 1.78-1.61 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 180.2 (C=O), 41.9 (C-N), 37.2, 30.6, 29.7, 24.1.

***N*-(4-nitrophenyl)acetamide (4-nitroacetanilide)** ^{1}H-NMR ($CDCl_3$) δ 10.23 (br 1H, NH), 8.25 (d, *J*=9.3 Hz, 2H), 7.82 (d, *J*=9.2 Hz, 2H); 2.09 (s, 3H), ^{13}C-NMR ($CDCl_3$) δ 169.7 (C=O), 147.8 (C-N), 143.1, 125.9, 119.5, 22.7.

***N*-(4-chlorophenyl)acetamide (4-chloroacetanilide)** ^{1}H-NMR ($CDCl_3$) δ 10.41 (br 1H, NH), 7.65 (d, *J*=7.9 Hz, 2H), 7.35 (d, *J*=7.9 Hz, 2H), 2.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 168.7 (C=O), 139.8 (C-N), 128.9, 127.1, 120.5, 23.7.

***N*-(4-methoxyphenyl)acetamide (4-methoxyacetanilide)** ^{1}H-NMR ($CDCl_3$) δ 7.90 (br 1H, NH), 7.39 (d, *J*=8.9 Hz, 2H), 6.69 (d, *J*=8.7 Hz, 2H), 3.90 (s, 3H), 2.10 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.2 (C=O), 159.2 (C-N), 135.1, 122.2, 114.9, 59.0, 21.9.

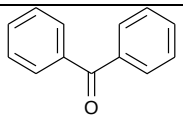
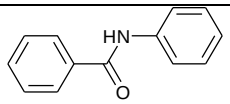
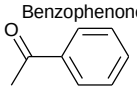
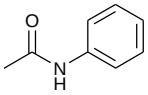
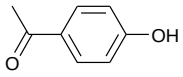
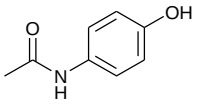
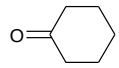
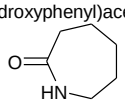
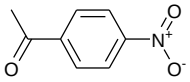
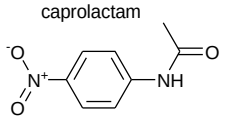
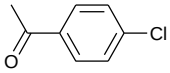
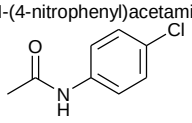
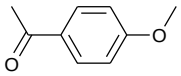
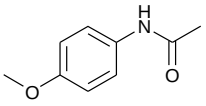
RESULTS AND DISCUSSION

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 $TsOH.H_2O$ 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 $TsOH.H_2O$ 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.

Sr. No.	Reactants	Products	Yield (%)	Time (sec.)	M.P.(°C) Obs.	Lit.
1	 Benzophenone	 N-phenylbenzamide	60	90	163	164
2	 acetophenone	 N-phenylacetamide	59	95	115	114
3	 p-hydroxyacetophenone	 N-(4-hydroxyphenyl)acetamide	57	90	170	169
4	 cyclohexanone	 caprolactam	54	95	68	69
5	 p-nitroacetophenone	 N-(4-nitrophenyl)acetamide	55	90	213	215
6	 p-chloroacetophenone	 N-(4-chlorophenyl)acetamide	58	90	177	179
7	 p-methoxyacetophenone	 N-(4-methoxyphenyl)acetamide	57	95	128	129

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. Meprobromate is a tranquilizer. Some amides act as insect-repellant. Amides also form important synthetic fibers such as Nylon 66[8-11].

ACKNOWLEDGMENT

We would like to thank University Grant Commission (UGC) for financial support.

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