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Ultrasound Promoted Efficient Synthesis of some Amides from Nitriles in Ambient Condition

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Some amide derivatives have been synthesized by the reaction of corresponding nitriles with potassium *tert*-butoxide as a nucleophilic oxygen source under ultrasonic irradiation. This new methodology provides good to excellent yields in short reaction times (15-90 min) at room temperature.

Keywords: Ultrasound irradiation, Amide, Nitrile, Synthesis, Room tempereture

INTRODUCTION

Sonochemistry is the application of ultrasound to promote chemical reactions and processes. The chemical and physical effect of ultrasound create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid [1]. The ultrasound leads to changing the reaction pathway, accelerating the rate of the reaction, enhancing chemical reactivity and increasing yield in synthetic organic compounds *via* high local temperatures and pressures produced by cavitation [2-5].

The amide functional groups have important role in chemistry and biology [6], and widely used in industry [7-8]. Initially, amides were prepared from the condensation of carboxylic acids with amines using a variety of coupling agents [9]. The Ritter reaction is an important reaction in organic synthesis that is applied for conversion of nitriles to amides *via* reaction with substituted alkenes or alcohols using concentrated sulfuric acid [10]. One of the most commonly used methods for the synthesis of amides is the hydration of the corresponding nitrile compounds carried out under acid- and base-catalyzed conditions. On this basis, the catalytic hydration of benzonitrile and acetonitrile has been studied by employing different arene-ruthenium(II) complexes with phosphinous (PR_2OH) and phosphorous acid ($P(OR)_2OH$) ligands as catalysts [11]; a transition metal-free process, catalyzed by tetrabutylammonium hydroxide (TBAH), has been developed for the convenient and selective hydration of aromatic, aliphatic, and heteroaromatic nitriles with a wide variety of functional groups to the corresponding amides [12]; freshly prepared nano NiO, NiO supported HAP, TiO_2, ZrO_2 and γ-Al_2O_3 and metal ion substituted nickel oxide ($Ni_{1-x}M_xO$, M = Co, Cu and Mn) have been examined for hydration of aromatic nitriles [13]; a Ru(IV) catalyst is able to promote the selective hydration of nitriles to amides in water, at low metal loadings and under mild conditions [14]; a sustainable flow chemistry process for the hydration of nitriles, whereby an aqueous solution of nitrile is passed through a column containing commercially available amorphous manganese dioxide, has been also reported [15].

Selective hydrolysis of nitriles to corresponding amides is challenging, because amide is more easily hydrolyzed to the corresponding acid than nitrile hydrolyzed to the corresponding amide [16].

Recently, Midya and co-worker reported an efficient metal-free hydration of nitriles using potassium *tert*-butoxide under anhydrous conditions [17]. Although this process offers improved yields and selectivity, this protocol has its own set of disadvantages such as long reaction time (4-36 h). There is a need for the development of an improved reaction condition, which can be performed

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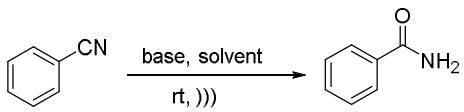
Table 1. Optimization of the Reaction Condition for the Synthesis of Benzamid 2a



Entry	Solvent	Base (equve.)	Time (min)	Yield (%)
1	H_2O	KO^{t}Bu (2)	30	17
2	Glycerol	KO^{t}Bu (2)	60	10
3	PEG	KO^{t}Bu (2)	90	85
4	EtOH	KO^{t}Bu (2)	60	17
5	EtOH	NaOEt (2)	60	5
6	*t*-BuOH	KO^{t}Bu (2)	30	38
7	*t*-BuOH/H_2O (10%)	KO^{t}Bu (2)	30	20
8	*t*-BuOH/H_2O (20%)	KO^{t}Bu (2)	30	15
9	*t*-BuOH/H_2O (2%)	KO^{t}Bu (1)	15	70
10	*t*-BuOH/H_2O (2%)	KO^{t}Bu (2)	20	95

in short reaction time and at room temperature and scalable for industrial applications. As part of our ongoing research program toward the development of economically sustainable green synthetic methodologies [18-20], we herein report a mild synthesis of some amides from nitriles in an ambient condition under ultrasonic irradiation using potassium tertiary butoxide (KO^{t}Bu) as a nuclephilic source of oxygen.

EXPERIMENTAL

Materials

All solvents and starting materials such as Benzonitrile and potassium *tert*-butoxide were obtained commercially (Merck) and used without future purification.

Equipments

The ultrasonic device used was an UP 400 S instrument from Dr. Hielscher GmbH. An S3 immersion horn emitting 24 kHz ultrasound at intensity levels tunable to maximum sonic power density of 460 W cm^{-2} was used. Sonication was carried out at 100% (maximum amplitude 210 mm). A 3 mm long sonotrode (maximum immerse depth of 90 mm) was immersed directly into the reaction mixture. NMR spectra were recorded on a Bruker DRX300 spectrometer. Thin layer chromatography (TLC) was run on silica percolated aluminum plates (Merck Kieselgel F254). Melting points were determined on a Kofler hot-stage apparatus.

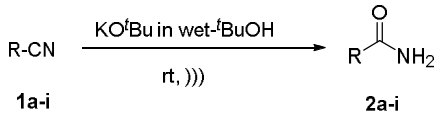
General Procedure for Hydration of Nitriles

To a solution of the appropriate benzonitrile (1 mmol) in dry *tert*-butyl alcohol (4 ml) was added KO^{t}Bu (2 mmol). The reaction mixture was irradiated with ultrasound and progress of the reaction was monitored by TLC. The mixture was poured into water (10 ml) and extracted with chloroform (3 × 8 ml). The organic layer was dried over $MgSO_4$, and the solvent was removed to provide the corresponding amide.

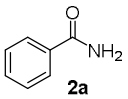
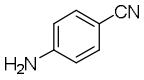
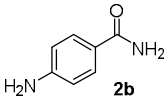
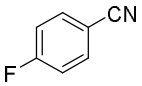
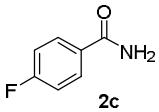
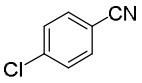
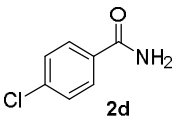
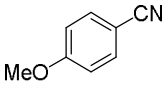
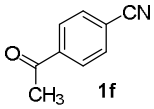
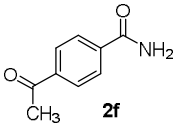
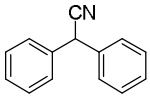
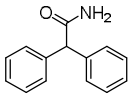
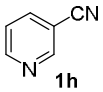
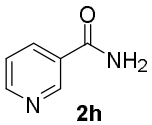
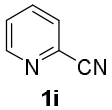
RESULTS AND DISCUSSION

Initially, we optimized the reaction conditions for the synthesis of benzamide 2a using benzonitrile 1a and

Table 2. Synthesis of Amides 2a-i from Corresponding Nitriles 1a-i



1a-i 2a-i

Entry	Nitrile	Product[a]	Time (min)	Yield (%)
1	 1a	 2a	20	95
2	 1b	 2b	60	80
3	 1c	 2c	15	89
4	 1d	 2d	20	90
5	 1e	 2e	65	80
6	 1f	 2f	10	96
7	 1g	 2g	50	90
8	 1h	 2h	90	92
9	 1i	 2i	30	93

[a]All compounds were identified by comparison of their physical and spectral data with those of authentic samples [17].

potassium *tert*-butoxide as a model reaction under ultrasonic irradiation (Table 1). In the first instance, the effect of solvent on the yield of the product was evaluated. Among various solvents tested, PEG and *t*-BuOH/H_2O (Table 1, entry 3 and 10) yielded the best results, whereas H_2O, and *t*-BuOH gave the products in low yields (Table 1, entry 1,6). The reaction gave moderate yield in glycerol and ethanol at room temperature (Table 1, entry 2, 4, 5). Next, we investigated the effect of mole ratio of reactants on the synthesis of benzamide 2a. We found that the yield improves when the reaction of benzonitrile 1a with potassium *tert*-butoxide is carried out in mole ratio of 1:2, respectively (entry 10 in Table 1). The yield was highly dependent upon the sonication time, solvent and the mole ratio of starting materials. The optimum reaction condition for the synthesis of benzamide 2a was found to be: benzonitrile 1a (1 equiv.), potassium *tert*-butoxide (2 equiv.), at room temperature with PEG or *t*-BuOH/H_2O (2.0 ml) as the solvent.

Table 1 summarizes the yield of the reactions using different nitriles in optimized reaction conditions. The expected corresponding amide 2a-i was obtained in high yield. It is clear that hydration of nitriles under ultrasonic irradiation takes place in relatively much shorter reaction times (15-90 min) compared to that reported in the literature [17]. For example, compound 2c (entry 3) was previously prepared in 55% yield in the presence of 3 eq. potassium *tert*-butoxide in tertbutanol at room temperature after 16 h [17], whereas under sonication, 2c was obtained in 80% in the presence of 2 eq. potassium *tert*-butoxidein in wet *tert*-butanol at room temperature within 60 min.

CONCLUSIONS

In conclusion, the use of ultrasound enabled the easy preparation of amides by reaction of corresponding nitrile compounds with potassium *tert*-butoxide as a nucleophilic oxygen source in wet *tert*-butanol. The advantages of ultrasound in hydration of nitriles are shorter reaction times and higher yields.

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