

Ultrasound Synthesis of amides from Isocyanides, Nitrile and Carboxylic Acids under Ambient Conditions

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ABSTRACT

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

The synthesis of amides via the reactions of carboxylic acids and isocyanides in methanol was carried out in 78-95% yields under ultrasound irradiation. The method has wide applicability, and the protocol is mild, fast and efficient compared to the existing methods based on silent conditions.

Keywords: *Ultrasound irradiation, Amide, Nitriles Synthesis, Carboxylic acid, Isocyanide*

INTRODUCTION

Sonochemistry is the application of ultrasound to promote chemical reactions. The chemical and physical effect of ultrasound create, enlarge, and implode cavities in an irradiated liquid [1]. The ultrasound leads to changing the reaction pathway, accelerating the rate of the reaction, enhancing chemical reactivity and increase the yield in synthetic organic compounds *via* high temperatures and pressures produced by cavitation [2-5]. The amide functional groups have an 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 and phosphorous acid ligands as catalysts [11]; a transition metal-free process, catalyzed by tetrabutylammonium hydroxide (, 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. Ru(IV) catalyst is able to promote the selective hydration of nitriles to amides in water, at low metal loadings and under mild conditions [4]; 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 [2]. 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 [10]. Microwave promoted reactions have been also used in the synthesis of amides from carboxylic acids and their esters. Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades. There are many published comprehensive books [3,5] and papers about chemical application of ultrasound irradiation in organic chemistry, which offers an efficient and facile route for a large variety of syntheses. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation [4-9]. The

chemical application of ultrasound (sonochemistry) has become an exciting field of research during the last these years. recently, midya and co-worker reported an efficient metal-free hydration of nitriles using potassium *tert*-butoxide under anhydrous conditions [4]. Although this process offers improved yields and selectivity, this protocol has its 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 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, we herein report a mild synthesis of some amides from nitriles in an ambient condition under ultrasonic irradiation using potassium tertiary butoxide as a nucleophilic source of oxygen.

The great potential of isocyanides for the development of organic synthesis lies in the diversity of bond forming processes available, functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in isocyanide-based organic reactions. Isocyanide-based organic reactions have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [36-38].

Table 1. optimization of the reaction condition for the synthesis of benzamid 2a				
$R-CN \xrightarrow[\text{rt.)))]]{\text{base, solvent}} R-CONH_2$				
Entry	solving	Base	Time(min)	Yield(%)
1	water	Potassium tertiary butoxid	20	11.3
2	glycerol	Potassium tertiary butoxid	50	8.3
3	PEG	Potassium tertiary butoxid	80	75
4	EtOH	Potassium tertiary butoxid	50	14.16
5	EtOH	Potassium tertiary butoxid	50	4.16
6	t-BuOH	Potassium tertiary butoxid	20	25.33
7	t-BuOH/H ₂ O(10%)	Potassium tertiary butoxid	20	13.33
8	t-BuOH/H ₂ O(20%)	Potassium tertiary butoxid	20	10
9	t-BuOH/H ₂ O(2%)	Potassium tertiary butoxid	5	23.33
10	t-BuOH/H ₂ O(2%)	Potassium tertiary butoxid	10	47.5

EXPERIMENTAL

Materials and methods

All solvents and starting materials such as Benzonitrile and potassium *tert*-butoxide were obtained commercially and used without further purification. All reagents were obtained from commercial sources and used without further purification. Infrared spectra were recorded on a Jasco 6300 FTIR spectrometer. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Sonication was performed in a Bandelin SONOPULS ultrasonic homogenizers (made in Germany) with 20 kHz processing frequency, a nominal power 250 W, uniform sonic waves.

Procedure for the Preparation of N- Cyclohexyl-3-nitrobenzamide under Ultrasound Irradiation (3a)

Cyclohexyl isocyanide was added to a mixture of 3-nitrobenzoic acid in MeOH and the reaction mixture was exposed to ultrasonic irradiation for 135 min. The ultrasound waves amplitude in this experiment was kept on 40 and the progress of the reaction was followed by Tin layer chromatography. After completion of the reaction as indicated by Tin layer chromatography, the solvent was removed and the solid residue was

washed with diethyl ether and the product **3a** was obtained as a white powder..

RESULTS AND DISCUSSION

Table 1 provides the details of the reagents and products including the latter's m.ps. and yields. The sound-wave activated reaction of carboxylic acid in methanol and isocyanides gave the desired products in good to excellent yields (78-95%). The protocol has worked well with aromatic carboxylic acids (Compounds 3a-3i). In order to ascertain the efficiency of the acoustic effect in our synthesis, we have compared two separate reactions in methanol one at room temperature (24 h) [11] and the other with application of sound waves. In the first case, the reaction took place with 80% yield, but the second one did indicate to the product in 135 min followed by the almost total transformation of the reactants to the product as evidenced by TLC with 88% yield. Thus, it is obvious that sonication increases the reaction rate by activating the reagents. The structures of all compounds reported in this work have been ascertained by comparison of their melting

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 hendered percent (maximum amplitude 210 mm). A3 mm long sonotrode was immersed directly into the reaction mixture. NMR spectra were recorded on a spectrometer. Thin layer chromatography (Tin layer charomotography) was run on silica percolated aluminum plates. 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 was added KOtBu. The reaction mixture was irradiated with ultrasound and progress of the reaction was monitored by Tin layer charomotography The mixture was poured into water (10 ml) and extracted with chloroform (24ml).The organic layer was dried over MgSO₄, 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 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/H₂O (Table 1, entry 3 and 10) yielded the best results, whereas H₂O, 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.

Table 1.2 synthesis of Amides from corresponding nitriles				
$R-CN \xrightarrow[\text{rt.})]{\text{base, solvent}} R-CONH_2$				
Entry	nitrile	Product	Time(min)	Yield (%)
1			20	95
2			60	80
3			15	89
4			20	90
5			65	80
6				
7			10	96
8			50	90
			90	92

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/H₂O (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 [9]. For example, compound 2c (entry 3) was previously prepared in 55% yield in the presence of 3 eq. potassium *tert*-butoxide in *tert*butanol at room temperature after 16 h, whereas under sonication, 2c was obtained in 80% in the presence of 2 eq. potassium *tert*-butoxide in wet *tert*-butanol

at room temperature within 60 min [8]. Table 1 provides the details of the reagents and products including the latter's m.p.s. and yields. The sound-wave activated reaction of carboxylic acid in methanol and isocyanides gave the desired products in good to excellent yields (78-95%). The protocol has worked well with aromatic carboxylic acids (Compounds 3a-3i). In order to ascertain the efficiency of the acoustic effect in our synthesis, we have compared two separate reactions in methanol one at room temperature (24 h) [5] and the other with application of sound waves. In the first case, the reaction took place with 80% yield, but the second one did indicate to the product in 135 min followed by the almost total transformation of the reactants to the product as evidenced by TLC with 88% yield. Thus, it is obvious that sonication increases the reaction rate by activating the reagents. The structures of all compounds reported in this work have been ascertained by comparison of their melting points.

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. An efficient and convenient procedure for the synthesis of some aryl amides from carboxylic acids and isocyanides has been developed under ultrasound irradiation. This method provides several advantages such as simple work-up procedure, shorter reaction time and higher yield.

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