

Ultrasound-Promoted Synthesis of Aryl amides from Isocyanides and Carboxylic Acids under Ambient Conditions

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Abstract: The synthesis of aryl 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, Aryl amides, Carboxylic acid, Isocyanide

INTRODUCTION

The amide linkage is present in many important molecules including natural products, proteins, glycoconjugates and pharmaceuticals¹. Amide derivatives were associated with broad spectrum of biological activities including antituberculosis², anticonvulsant³, analgesic anti-inflammatory⁴, insecticidal⁵, antifungal⁶ and antitumor⁷ properties. The importance of the amides in drug discovery has been recently highlighted by Carey and co-workers⁸. In this article, it is reported that 66% of the acylation reactions performed in the pharmaceutical industries and medicinal chemistry laboratories are towards the preparation of amides. Besides, just in 2003, at least 9 out of 53 drugs whose sales exceeded 1 billion dollars possessed the amide group. The use of amides as synthetic intermediates and also in material chemistry has been described⁹⁻¹⁴. Some biologically active compounds presented a clear relationship between the presence of the amide moiety and their biological activities. For example, lysergic acid diethyl amide (LSD) provokes psychic alterations and hallucinations in humans while the acid itself is inactive¹⁵. Furthermore; another amide, oleamide, induces physiological sleep in animals while its corresponding carboxylic acid has presented no such activity in comparative assays^{16,17}. Normally, amides are synthesized by the reaction of carboxylic acids and amines in the presence of coupling reagents such as: dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), chloroformates, mesyl chloride, *etc.*^{18,19}. Microwave promoted reactions have been also used in the synthesis of amides from carboxylic acids and their esters²⁰⁻²³.

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^{24,25} and papers²⁶ 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 irradiation²⁷⁻³². The chemical application of ultrasound (sonochemistry) has become an exciting field of research during the last few years. Ultrasound has been utilized to accelerate a number of synthetically useful reactions. Examples include the Biginelli-type reaction, Suzuki cross-coupling in ionic liquid, organometallic reactions, metal-catalyzed hydrogenation, phase transfer, polymer synthesis, reactions in aqueous solution and heterocyclic synthesis³³⁻³⁵.

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 isocyanidebased organic reactions. Isocyanide-based organic reactions have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds³⁶⁻³⁸.

As part of our continuing interest to develop more efficient and convenient benign methods in organic synthesis³⁹⁻⁴¹ and as part of our program aimed at developing new ultrasound-promoted isocyanide-based multi-component reactions⁴²⁻⁴⁴ herein, I wish to report a fast and efficient one-pot two-component synthesis of aryl amides (**3**) from isocyanides (**2**) and carboxylic acids (**1**) under ultrasound irradiation (Scheme 1).

EXPERIMENTAL

Materials and Methods

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 with 20 kHz processing frequency, a nominal power 250 W, uniform sonic waves.

Typical Procedure for the Preparation of NCyclohexyl- 3-nitrobenzamide under Ultrasound Irradiation (3a)

Cyclohexyl isocyanide (0.11 g, 1 mmol) was added to a mixture of 3-nitrobenzoic acid (0.17 g, 1.0 mmol) in MeOH (20 ml) 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 TLC. After completion of the reaction as indicated by TLC, the solvent was

removed under vacuum and the solid residue was washed with diethyl ether and the product **3a** was obtained as a white powder. The product was found to be pure and no further purification was necessary.

RESULTS AND DISCUSSION

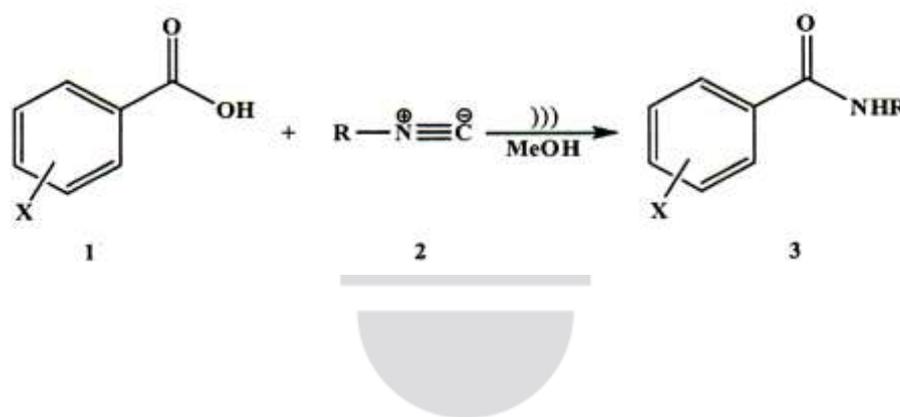
Table 1 provides the details of the reagents and products including the latter's m.p.s. and yields. The sound-wave activated reaction of carboxylic acid in methanol and isocyanides gave the desired products in good to excellent yields (78-95%). The protocol has worked well with aromatic carboxylic acids (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)⁴⁵ 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 and spectroscopic data [FT-IR] with the ones previously reported [45].

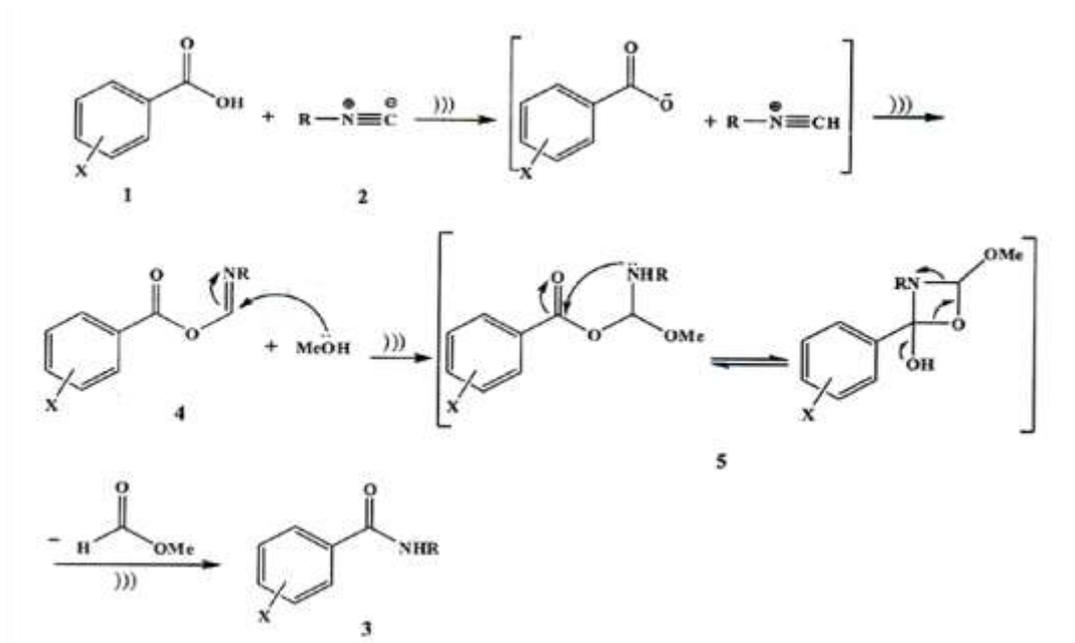
Scheme 1. One-pot synthesis of arylamides under ultrasound irradiation

Table 1. Comparison of the Times and Yields of the Reactions with or without Sonication for the Synthesis of Aryl Amides

Compound	X	R	M.p (oC)					
			Found	Reported	with sonication ^a		Without sonication ^b	
					Yield (%) ^c	Time (Min)	Yield (%) ^c	Time (h)
3a	3-Nitro	Cyclohexyl	217-218	218-220 ⁴⁵	88	135	80	24
3b	4-Nitro	Cyclohexyl	203-205	204-206 ⁵²	84	150	78	24
3c	3-Chloro	Cyclohexyl	185-187	184-186 ⁴⁵	89	120	85	24
3d	4-Methyl	Cyclohexyl	161-162	162-164 ⁴⁵	87	135	83	24
3e	H	Cyclohexyl	152-154	152-154 ⁵²	78	150	65	24
3f	3-Nitro	<i>tert</i> -Butyl	228-230	228-230 ⁴⁵	93	120	86	24
3g	3-Chloro	<i>tert</i> -Butyl	223-224	223-225 ⁴⁵	93	120	90	24
3h	H	<i>tert</i> -Butyl	221-223	223-224 ⁴⁵	88	120	85	24
3i	3-Nitro	1,1,3,3-Tetramethyl butyl	205-207	205-207 ⁴⁵	95	120	92	24

^a Reaction condition: Reaction of benzoic acid derivatives and isocyanide in MeOH under ultrasound irradiation. ^b Reaction condition: Reaction of benzoic acid derivatives and isocyanide in MeOH at room temperature under high stirring condition. ^c Yields of isolated products.





Scheme 2. Proposed mechanism for the synthesis of aryl amides under ultrasound irradiation

The benzoic acid derivative (1) and isocyanide (2) in methanol (MeOH) as solvent under ultrasonic irradiation at room temperature afforded one product in each case (as evidenced by TLC) (Scheme 1). The reaction proceeds fast and cleanly under ultrasonic irradiation and no side reactions were observed. The mechanism of the reaction between the benzoic acid derivative (1) and isocyanide (2) has not been established experimentally. However, a possible explanation is proposed in Scheme 2. On the basis of the well established chemistry of the reaction of isocyanides with acids [46] it is reasonable to assume that protonation of the isocyanide by the carboxylic acid produces O-acylimine (4) which on quenching with methanol rearranges to generate intermediate (5) [47]. Finally elimination of methyl formate from intermediate (5) produces amide (3).

Cavitation is the origin of sonochemistry [48,49]. As ultrasound passes through a liquid, the liquid can produce bubbles. These bubbles can undergo a violent collapse, which generates very high pressures and temperatures, inducing molecular fragmentation, and highly reactive species are locally produced. The implosion of cavities reportedly established an unusual environment for reactions. The gases and vapors inside the cavity are compressed, generating intense heat that raises the temperature of the liquid immediately surrounding the cavity and the high temperature and pressure produced during cavitation break their chemical bonds, short-lived chemical species are returned to the bulk liquid at room temperature, thus reacting with other species [48-51]. With this case in mind, I turned my attention to the reaction mechanism and the role of ultrasound irradiation played in the reaction. I believed that there were two main reasons for the acceleration in the present work. One was the physical aspect of ultrasound which leads mixing aryl carboxylic acid and isocyanide very well and so fast in methanol, another was the chemical aspect of ultrasound which has accelerated the reaction. As known, in these type of reactions, deprotonation of the acid and the formation of O-centered nucleophiles occur very slowly in the absence of ultrasound conditions. The ultrasonic irradiation plays an important role in the formation of O-centered nucleophile while this may be the rate-determining step in the reaction. Also ultrasound waves lead to the stronger attack to the Oacylimine. In fact, localized “hot spots” generated from a violent collapse of the bubbles creates a transient high temperature and pressures, inducing molecular fragmentation, and highly reactive species are locally produced. We think that in the presence of ultrasound irradiation, producing of the conjugate base of acid (1) goes faster. Table 1 shows the obvious difference in the reaction efficiencies with or without sonication. For example the yield of the related reaction to synthesize (3a) is up to 88% under ultrasound condition, whereas the yield of the reaction without sonication is 80%, and the reaction time under sonication is reduced from 24 h to 135 min. Thus, ultrasound was found to have beneficial effect on the synthesis of aryl amides 3a-i (Table 1) in which the time of above reactions is decreased from 24 h in conventional procedure to less than 2.5 h, and also, a noticeable improvement in yields of reactions is observed under ultrasonic irradiations.

In summary, under ultrasound irradiation the reaction is simple to execute and the products are isolated in good yields. It is apparent that ultrasound irradiation can accelerate the reaction significantly to give better yield in shorter period. The results in Table 1 show that ultrasound is much more efficient than magnetic stirring. Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of aryl amides which are produced through time consuming procedures in conventional conditions. The work-up is very simple. The reaction time is short (less than 2.5 h) and the products are obtained in excellent purity.

To the best of my knowledge, this new procedure provides the first example of an efficient and two component method for the synthesis of aryl amides under ultrasound irradiation using isocyanides. This method, based on two component free-catalyst reaction under ultrasonic irradiation, is the most simple and convenient and would be applicable for the synthesis of different types of aryl amides.

CONCLUSIONS

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

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