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Ultrasonic and Microwave Effects on the Benzamide/Sulfuryl Chloride Mediated Benzoylation of Benzene Derivatives Under Vilsmeier-Haack Conditions

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ABSTRACT

Benzamide/ Sulfuryl Chloride (SO2Cl2) reagent has been developed as a Vilsmeier- Haack(VH) reagent for benzoylation of aromatic compounds by using the conventional and ultrasonic sonication (US), and microwave (MW) conditions. Benzoylation is much more competent and faster than the analogous VH ((Benzamide/ POCl3) or (Benzamide/ SOCl2)) reagents and afforded benzoyl derivatives in fairly good yields. Reaction times are moderately less than those observed with [Benzamide/ POCl3] and (Benzamide/ SOCl2) reagents. Reaction times are far less in microwave assisted (MWAR) reactions than ultrasonically assisted (USAS) reactions , which in turn are less than the conventional method with a decreasing trend: MWAR (seconds) << Sonication (minutes) << conventional (hrs). The highly remarkable rate accelerations in MW assisted reactions are attributed to the bulk activation of the molecules; while US assisted reactions could be accounted for cavitation effects.

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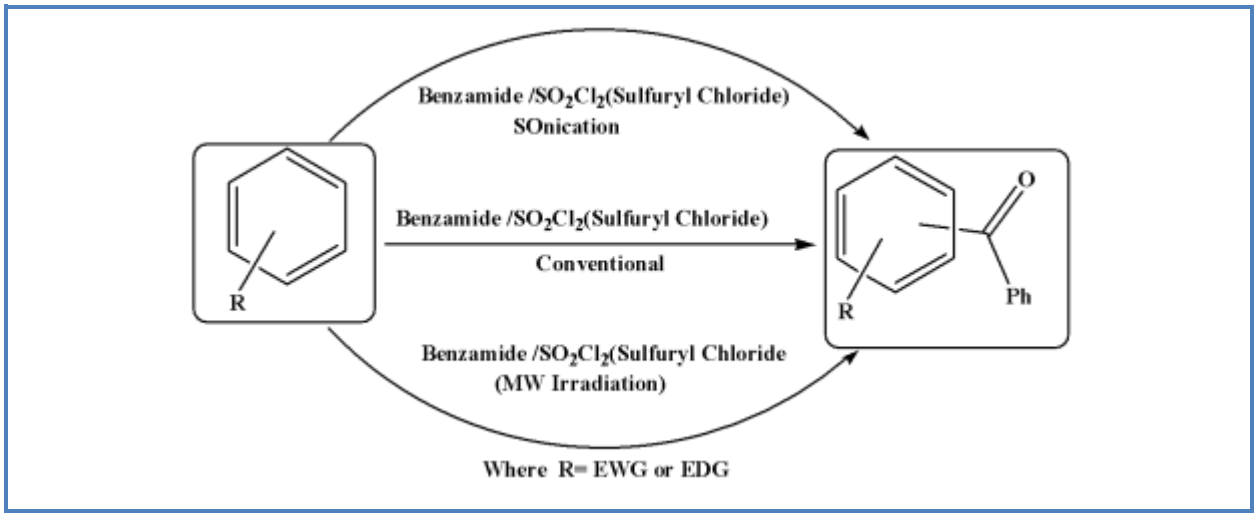
Graphical Abstract



Introduction

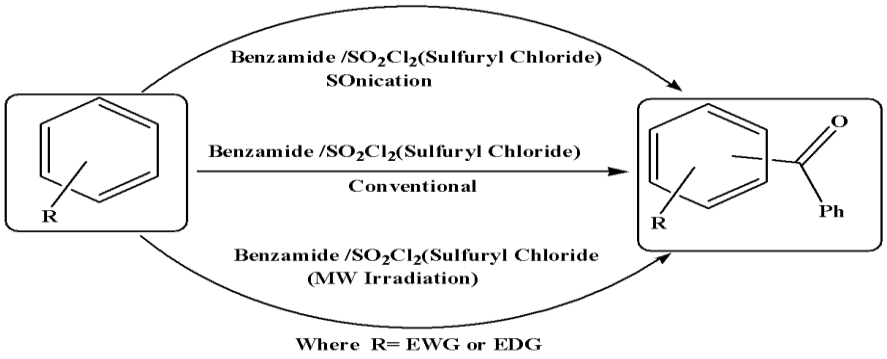
Benzoylation forms an important class among the Friedel Crafts acylation reactions. Benzoylation reaction is generally carried out using benzoyl chloride with a Lewis acid as the benzoylating agent [1, 2]. It is a colorless fuming liquid with an irritating odor, however it is still widely used for producing the peroxides, preparation of dyes, perfumes, pharmaceuticals, and resins. Also, it is commonly used in many laboratories because of its availability and low cost. Besides the benzoyl chloride, a number of reagents such as, benzoic anhydride, benzoyl tetrazole, 2-benzoyl-1-methylpyridinium chloride, S-benzoic-O, O-diethylphosphoro dithoic anhydride, and benzoyl cyanide, could be used for this reaction [3-6]. The reaction is usually catalyzed by the bases such as, pyridine, triethylamine, and sodium hydroxide [7-9]. Recently, Satya Paul *et al.* [8] developed a rapid, economic, and environmentally friendly method for benzoylation of -NH2, -OH and -SH groups by using the PhCOCl-Py/basic alumina. The developed reagent system was found a good alternative to classical method since the benzoylation underwent expeditiously with high yields under the solvent-free conditions. Vasanth Chowdhury et al. [10] investigated the liquid phase benzylation of benzene by benzyl chloride over the Ga_2O_3, In_2O_3, $GaCl_3$ and $InCl_3$ impregnated H_β zeolite catalysts at 60 and 80 ^oC as a function of reaction time has been carried out and the catalysts were compared for their acidity and catalytic performance in the benzylation process. Benzylation and benzoylation of different aromatic compounds (at 80 ^oC) over the (In_2O_3/H_β) catalyst indicated the highest benzene benzylation activity in this study. Benzoylation is one of the most important routes for synthesis of the aromatic ketones owing to its several industrial applications ranging from petrochemicals to pharmaceuticals [1, 2]. Benzophenones are very much useful as dye

intermediates, UV absorbents Also, they have immense importance in perfume industry as an additive. Recent literature reports revealed that a wide number of naturally occurring prenylated and isoprenylated benzophenones act as potent antimicrobial, anticancer, and cytotoxic agents [3]. In addition, they are reported as new class of non-nucleoside HIV reverse transcriptase inhibitors [11- 13].

On the other hand, benzoylation has also been carried out using Benzamide/$POCl_3$, or Benzamide/$SOCl_2$ as Vilsmeier-Haack reagents [14-17]. Over the last few years, with the increasing interest in the application of non-conventional energy sources in organic synthesis, ultrasound and microwave assisted protocols have attracted a great deal of attention from organic chemists. A great number of organic reactions have been carried out under ultrasonic and microwave irradiation to obtain higher yields, with the shorter reaction times or milder conditions [18-22]. Over the last few years, our group has been actively working on exploiting the use of eco-friendly materials such as a micelle forming surfactants and non-conventional energy sources (such as microwave and ultra sound) to serve multitudinous organic transformations [23, 24] including Vilsmeier- Haack reactions [23] and other electrophilic substitution reactions [24]. Sulfuryl chloride is a versatile and potential reagent in organic synthesis, which has been used to produce chlorinate electron-rich aryl and alkyl aryl compounds [25, 26]. Reactions with sulfuryl chloride are generally high yielding when the functionalities are compatible with this reagent. In our previous study, we have explored the use of acetamide/SO_2Cl_2 as an effective reagent for acylation of aromatic compounds under ultrasonic and microwave conditions [27]. Encouraged by the results presented therein, we have embarked on the present study to explore the use of Benzamide/SO_2Cl_2 as a new VH reagent for effective benzoylation of aromatic compounds under conventional and nonconventional conditions. The present developed reagent system is found to be a good alternative to classical method since the benzoylation underwent expeditiously with high yields under the solvent-free conditions.

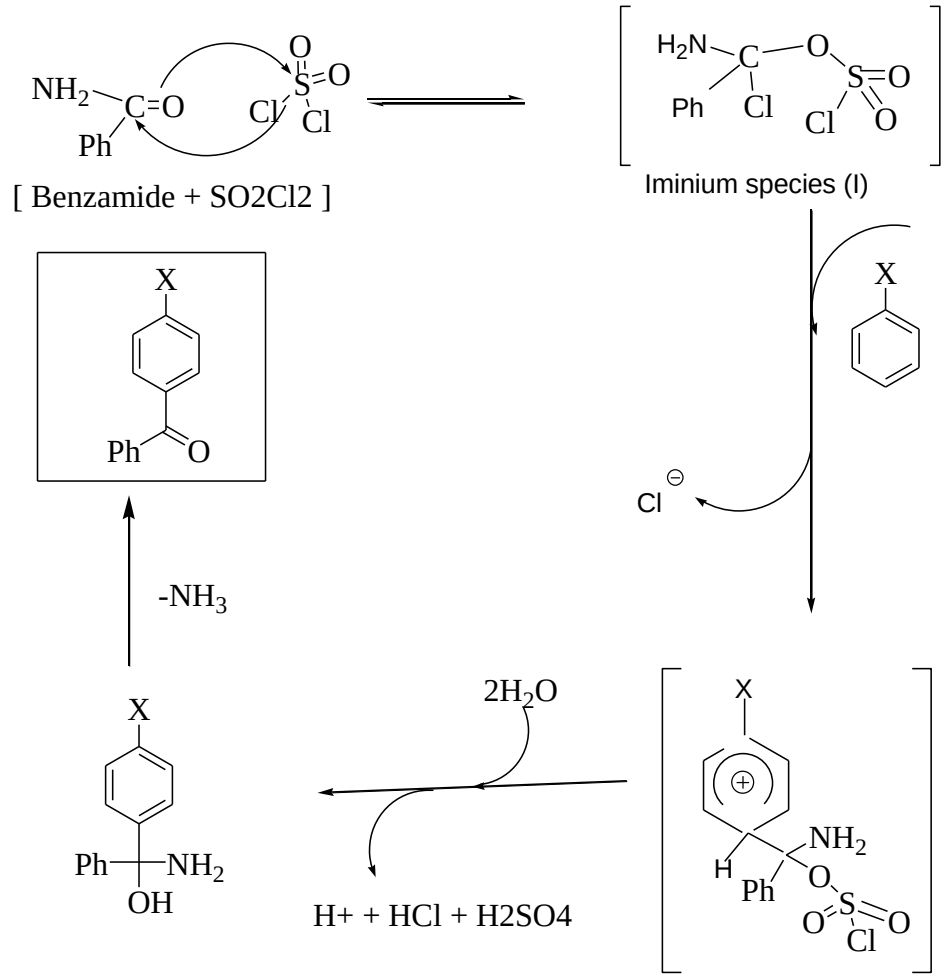
Results and Discussion

Freshly prepared Benzamide/SO_2Cl_2 was used for the benzoylation of aromatic compounds under conventional, ultrasonic, and microwave assisted conditions.



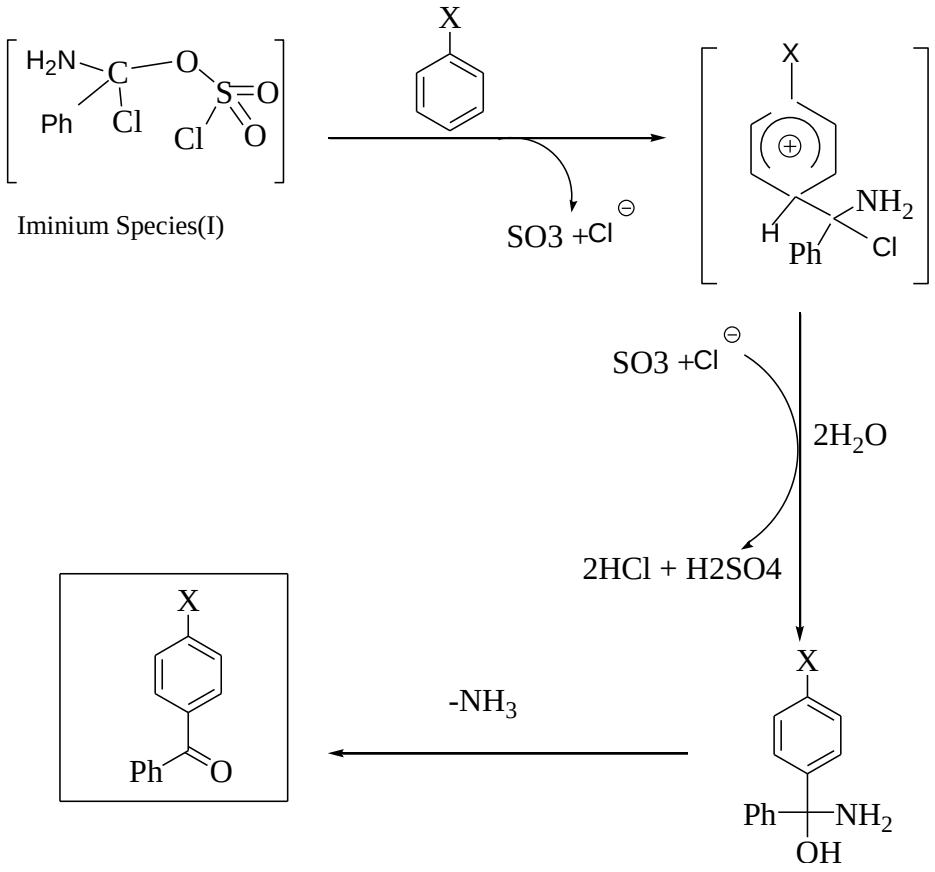
Scheme-1: Benzoylation of Aromatic compounds using Benzamide /SO_2Cl_2(Sulfuryl Chloride)

Aromatic compounds underwent the smooth benzoylation and afforded very good yields of products when treated with Benzamide/SO_2Cl_2, respectively under the conventional and non-conventional conditions (Scheme-1). The reaction times observed with benzamide/SO_2Cl_2 (Sulfuryl chloride) adduct are in the range of 5-8 h These reaction times observed in this study are much less than those observed with benzamide/(thionyl chloride) $SOCl_2$ (10-13h) or benzamide/$POCl_3$ (11-13h) when used as benzoylation agents in our previous study [13]. This trend can be probably attributed to the increased Lewis acid character of SO_2Cl_2 (Sulfuryl chloride) over (thionyl chloride) $SOCl_2$ or $POCl_3$ which favors the formation of a better iminium salt with benzamide than that of the latter oxychlorides. We have successfully extended our study conducted under ultrasonically and microwave assisted conditions. The results are summarized in Table-1. Mechanism of the reaction could be explained through the formation of iminium salt type intermediate in the first step due to interaction of benzamide and sulfuryl chloride, which then converts aromatic compound to benzoyl derivatives followed by the removal of HCl and H_2SO_4 in the fast steps as shown in Scheme-2. Formation of the unstable transient species prior to the acids elimination step could be supported on the basis of our earlier reports [13, 23] in which we have used benzamide and $SOCl_2$ or $POCl_3$ for the formation of iminium species.



Scheme 2: Mechanism of Benzoylation of Aromatic compounds using Benzamide/SO_2Cl_2

Another plausible mechanism could be analogous to a Swern oxidation, in which unstable transient species formed in the first step produces SO3 and Cl-, followed by FC reaction to produce the imminium ion. The iminium ion thus formed upon hydrolysis produce end products (during work-up) as illustrated in Scheme 3.



Scheme 3: Mechanism of Benzoylation of Aromatic compounds using Benzamide/SO_2Cl_2.

Reaction times reduced from 5-8 h (under conventional methods) to 40-60 min (under sonication) and only 4-6 min under microwave assisted conditions. It is earlier reported that sonication of a chemical reaction in solution triggers the formation, growth, and collapse of bubbles, called as acoustic cavitation [17-22]. During sonication, compression of the liquid is followed by the rarefaction (expansion), in which a sudden pressure drop forms small oscillating bubbles, which expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse. This bubble collapse causes intense local heating, and high pressures which are responsible for rate enhancements and shorter reaction times. Acoustic cavitation effects could thus explain the experimental results in this study. On the other hand, microwave irradiation causes enhanced dipole-dipole and ionic interactions apart from direct absorption of the selective microwave energy by the reactive species irrespective of their polar or dipolar nature. This may lead to the bulk activation of molecules which decompose or rearrange to afford the products and bring about highly significant decrease in reaction times and increase in the product yield. Reactions with large activation energies will also be influenced greatly with microwave

irradiation. According to Haile *et al.* [28], microwave assisted reactions get advantages such as volumetric heating, selectivity, rapid kinetics, homogeneity, and energy saving due to the direct absorption of the selective microwave energy. Microwave irradiation also provides pollution free environment since there are no byproducts of combustion. Thus, extremely faster reaction rates in MIR system could be accounted for the bulk activation of molecules rather than random activation.

Table 1: Benzoylation of aromatic compounds under different conditions

Entry	Substrate	Product	Conventional		Sonication		Microwave	
			R.T (hrs)	Yield (%)	R.T (min)	Yield (%)	R.T (min)	Yield (%)
1	Toulene	4- Me Benzophenone	5	72	45	74	4	70
2	Chloro Benzene	4- Cl Benzophenone	4.5	70	40	72	4	70
3	Nitrobenzene	4- NO_2 Benzophenone	4	75	35	78	3.5	73
4	Fluoro Benzene	4- F Benzophenone	5	71	50	74	5	72
5	Anisole	4- OMe Benzophenone	6	74	60	76	5	75
6	Phenol	4- OH Benzophenone	6.5	75	70	77	4.5	78
7	Bromo Benzene	4- Br Benzophenone	4	68	40	70	4	74
8	Naphthalene	2-Benzoyl naphthalene	7.5	65	65	69	6	66
9	Acetophenone	3-Benzoyl acetophenone	7	76	60	80	5	80
10	4-OH acetophenone	3-Benzoyl 4-OH acetophenone	4	76	40	78	4.5	82
11	4-Cl acetophenone	3-Benzoyl 4-Cl acetophenone	5.5	62	45	67	4	69
12	4-NO_2 acetophenone	3-Benzoyl 4-NO_2 acetophenone	4	79	50	80	3.5	82
13	Benzaldehyde	3-Benzoyl Benzaldehyde	7.5	70	60	75	5	78
14	4-Cl Benzaldehyde	3-Benzoyl 4-Cl Benzaldehyde	5.5	74	40	76	4	81
15	4- OMe Benzaldehyde	3-Benzoyl 4-OMe Benzaldehyde	6.5	70	50	75	5.5	79

Data presented in table 1 shows that benzoylation occurred exclusively at the para position to the substituents such as -OMe, -Me, -Cl and -Br in mono substituted benzenes and afforded quantitative yields. However, in cases where the para positions are blocked (Table 1, entries 10,11,12,14 and 15), the benzoyl group is introduced in the *meta* position (3-position). The benzoylation of naphthalene is observed at second position (2 position) of naphthalene with good yield (Table 1,

entry 8). On the whole benzoylation took place efficiently with good regioselectivity in normal as well as ultrasound and microwave assisted reactions.

Experimental

All the chemicals were purchased from Aldrich or Arcos Organics and used without further purification. Analytical TLC was carried out using Merck aluminum- backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230-400mesh). Ultrasonically assisted reactions were performed in a Sonicator bath (KQ-250B, China). A flat transducer with a frequency of 40 kHz and voltage of 220 V (with an output of 100 W electric power rating) was mounted at the bottom of the Sonicator.

Preparation of Benzamide/SO_2Cl_2 (Sulfuryl Chloride) Reagent:

Requisite amounts (equimolar) of benzamide and sulfuryl chloride (SO_2Cl_2) are mixed in acetonitrile under chilled (at -5^oC) conditions for the preparation of benzamide/SO_2Cl_2 (sulfuryl chloride) reagent. The reagent is always prepared afresh before use.

Representative Procedure for Benzoylation using SO_2Cl_2/benzamide Reagent under Reflux condition:

About 0.01mol of aromatic substrate and 0.015 mol of SO_2Cl_2/benzamide reagent and acetonitrile solvent were taken in a clean Round bottom flask and refluxed for about 5 to 8 hours and progress of the reaction was monitored by checked by thin layer chromatography. After completion, the reaction mixture is washed with $NaHCO_3$ solution, followed by the addition of ethyl acetate. The organic layer was separated, dried over Na_2SO_4, under the vacuum to get pure product. The purified products were characterized by ^{1}HNMR and mass spectroscopic technique and also by their physical data, which were similar to our earlier reports [14].

Representative procedure for benzoylation using of SO_2Cl_2/benzamide Reagent under Sonication:

Centimolar (0.01 mol) organic substrate, SO_2Cl_2/benzamide reagent (0.015 mol) and acetonitrile were added in a previously cleaned in a Round bottom flask and clamped in a Sonicator and progress of the reaction is followed by thin layer chromatography. After completion of the reaction, product is separated as described in the preceding section.

Representative procedure for microwave assisted benzoylation using of SO_2Cl_2/benzamide Reagent under microwave irradiation:

A centimolar (0.01mol) aromatic compound, about 0.015 mol of SO_2Cl_2/benzamide, were taken in a cleaned in a Round bottom flask containing acetonitrile and clamped in a laboratory MW oven. Progress of the reaction is monitored by thin layer chromatography. The separation and purification process is by and large similar to the above procedure.

Conclusions

In summary, we have successfully developed a new protocol for benzoylation of aromatic compounds under conventional, sonication and microwave irradiation. Longer reaction times (5-8 hours) under the normal conditions reduced to 40-60 min under sonication, while microwave assisted reactions further reduced the reaction time to only 4-6 minutes. Reactions are conducted with economically cheap and readily available laboratory desktop chemicals with a simple work. Benzoylation occurred with good regioselectivity. Rate enhancements coupled with enhanced reaction yields under sonication and microwave irradiation substantiate that the present work is a good contribution in the area of benzoylation reactions of aromatic compounds with potential biological activity.

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