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Cavitational chemistry: A mild and efficient multi-component synthesis of amidoalkyl-2-naphthols using reusable silica chloride as catalyst under sonic conditions

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ABSTRACT

An efficient and direct procedure for the synthesis of amidoalkyl-2-naphthol derivatives has been described. The process employs a three-component cyclocondensation reaction in one-pot using β-naphthol, aromatic aldehyde and acetamide or benzamide in the presence of silica chloride accelerated by ultrasound giving the product in excellent yield in very short duration.

1. Introduction

Devising reactions that achieve multi-bond formation in one operation is becoming one of the major challenges in step-economic synthesis. Multi-component reactions (MCRs) in which three or more reactants are combined in a single chemical step to produce products that incorporate portions of all the components comply with many of the stringent requirements for an ideal synthesis [1]. *o*-Quinone methides (*o*-QMs) have emerged as interesting molecules due to their toxicological properties against both normal and cancerous cells and also for their proposed intermediacy in the formation of many biologically important polymers [2]. *o*-QMs also act as intermediates for the synthesis of antitumor agents [3]. Freccero's group [4] and Kresge's group [5] have reported significant findings on the generation of *o*-QMs by photochemical and thermal activation. *o*-QMs mainly involve [4 + 2]-cycloadditions with a wide range of dienophiles and have also been used in many MCRs [6]. We have already reported from our laboratory, the '*in situ*' generation of *o*-QMs which further combine with a molecule of β-naphthol to give dibenzo[*a,j*]xanthenes [7]. One of the tandem reactions involves the '*in situ*' generation of *o*-QMs and its reaction with acetamide or benzamide to give amidoalkyl-2-naphthols, and a considerable number of protocols for the synthesis of amidoalkyl-2-naphthols have been reported in the literature [8–16]. After consulting the literature, we observed that, the synthesis of amidoalkyl-2-naphthols is generally carried out at very high temperatures, and silica sulfuric acid takes about 2 h at 25 °C. Other disadvantages include use of non-reusable and expensive catalysts, or unsatisfactory yield. Hence, we feel that, there is still scope for further investigation towards milder reaction conditions, shorter reaction durations and better yields, which can possibly be achieved using ultrasound as energy source for this MCR, since ultrasound provides very high temperature and pressure within seconds.

Ultrasonic irradiation was first discovered by Sir John I. Thornycroft and Sydney W. Barnaby in 1894 [17], and the chemical ultrasonics began in 1927, when the acceleration of a conventional reaction was reported by Richards and Loomis [18a]. Ultrasound provides an unusual mechanism for generating high-energy chemistry due to the immense temperature, pressure and the extraordinary heating and cooling rates generated by the cavitation bubble collapse [17]. In some cases, it can also increase the chemical reactivities by nearly a million-folds [17]. Frequencies below 50 kHz are generally preferred for the heterogeneous systems due to the more intense mechanical effects [18b]. Hence, we selected 35 kHz for maximum sonication, and from our laboratory we have already reported the use of ultrasound in various reactions like synthesis of δ-chloroesters [19] and β-iodoesters [20]; reduction

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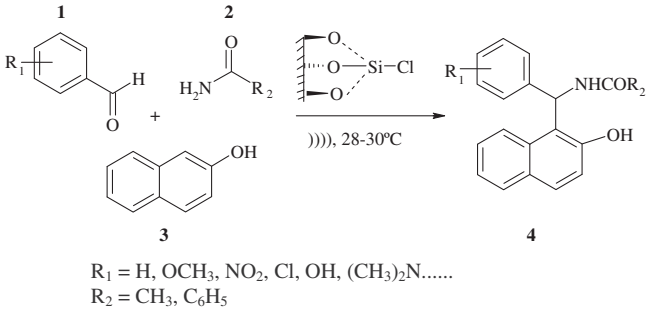

Scheme 1. Synthesis of amidoalkyl-2-naphthols using silica chloride.

of nitroarenes into arylamines [21] and reduction of aryl nitro compounds to azo arenes or arylamines [22] Li et al. have reported a Biginelli-type reaction to synthesize the 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under sonic condition [23].

On the other hand, solid supported reactions have been explored way back from 1960's. The core structure of the library molecule resides in use of solution phase technique and use of solid-phase reagents to facilitate the reaction [24]. The solid-phase reagent can be filtered and washed for reuse. Thus, a reliable technique would be the application of ultrasonic irradiation involving use of heterogeneous and reusable catalysts in a suitable medium. When acoustic cavitation occurs near an extended liquid–solid interface, markedly asymmetric bubble collapse occurs, which generates a high-speed jet of liquid directed at the surface. The impingement of this jet and related 'shockwaves' can create localized erosion, causing particle fragmentation and improved mass transport [25]. In continuation of our recent studies to develop mild and environmentally friendly procedures for the synthesis of bio active molecules using green protocols, we herein, report the synthesis of a small library of amidoalkyl-2-naphthols *via* an ultrasound assisted MCR (Scheme 1).

2. Methods

2.1. Materials and instruments

All starting materials were commercial products, and all were used without further purification except liquid aldehydes, which were distilled before use. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Chennai, Indian make melting point apparatus. Nuclear magnetic resonance spectra were obtained on a 400 MHz Bruker AMX instrument in DMSO-d_6 using TMS as a standard. LC–Mass spectra were performed on an Agilent Technologies 1200 series instrument and GC–Mass spectra were obtained using a Shimadzu GC–MS QP 5050A spectrometer equipped with a 30 m long and 0.32 mm dia BP-5 column with the column temperature 80–15–250 °C. Infrared spectra were recorded using Shimadzu FT-IR-8400s spectrophotometer as KBr pellets. Silica chloride was obtained according to the method reported in the literature [26]. All the reactions were studied using SIDILU, Indian make sonic bath working at 35 kHz (120 W) maintained at 28–30 °C without mechanical stirring.

2.2. Typical procedure for the synthesis of silica chloride

To a well-stirred silica gel (20 g) in CH_2Cl_2 (50 ml), was added $SOCl_2$ (20 g) drop wise at 25 °C. Evolution of copious amounts of HCl and SO_2 occurred instantaneously. After stirring for another hour, the solvent was removed to dryness under reduced pressure.

2.3. Typical procedure for the synthesis of amidoalkyl-2-naphthols

A mixture of aromatic aldehydes (5 mmol), β-naphthol (5 mmol), acetamide or benzamide (5 mmol) and silica chloride (0.1 g) was sonicated in a sonic bath working at 35 kHz (constant frequency) maintained at 28–30 °C (by circulating water). For solid aldehydes DCE (1 ml) was added to the mixture. After completion of the reaction (monitored by TLC), product was taken into ethyl acetate (10 ml) and the catalyst was filtered and washed with chloroform for reuse. The organic layer was washed successively with water (5 ml), sat. $NaHCO_3$ (5 ml), water (5 ml) and then dried over anhydrous sodium sulfate to get the crude compound in almost pure form. The analytical grade of the product was obtained by recrystallization from aq. ethanol.

The spectral data of the novel compounds are

2.3.1. Compound 4m

White solid, IR (KBr, ν_{max}) 3421, 3209, 1650, 1577, 1512, 1438, 1369, 1276, 945, 818 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.650 (s, 1H, NH); 8.756 (s, 1H, OH); 8.414–8.393 (d, 1H, J = 8.4 Hz, ArH); 7.906–7.886 (d, 1H, J = 8.0 Hz, ArH); 7.807–7.734 (m, 2H, ArH); 7.390–7.353 (m, 1H, ArH); 7.282–7.199 (m, 2H, ArH); 7.035–7.013 (d, 1H, J = 8.8 Hz, ArH); 6.824(s, 1H, OH); 6.637–6.616 (d, 1H, J = 8.4 Hz, CH); 6.531–6.508 (m, 1H, ArH); 3.677 (s, 3H, OCH_3); 1.955 (s, 3H, CH_3) ppm. MS *m/z*: 337.

2.3.2. Compound 4v

White solid, IR (KBr, ν_{max}) 3500, 3406, 3121, 2944, 1627, 1571, 1512, 1436, 1348, 1274, 1035, 935, 850, 819, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.298 (s, 1H, OH); 9.029 (d, 1H, J = 8.8 Hz, NH); 8.841 (s, 1H, ArH); 8.116 (d, 1H, J = 8.8 Hz, ArH); 7.859–7.776 (m, 4H, ArH); 7.570–7.454 (m, 4H, ArH); 7.333–7.296 (d, 1H, J = 7.2 Hz, CH); 7.296–7.196 (m, 2H); 6.981 (s, 1H, OH); 6.673–6.628 (t, 2H, J = 9.0 Hz, ArH); 3.664 (s, 3H, OCH_3) ppm. MS *m/z*: 399.

3. Results and discussion

Silica chloride (SiO_2-Cl) is an inexpensive heterogeneous reagent, which can be prepared easily by treating thionyl chloride with silica gel [26]. Ease and safety in handling, rate enhancement, high yields, easy work up procedures for reuse, and economy are the properties which made us to use this interesting reagent as a catalyst. To the best of our knowledge there are no reports on the applicability of silica chloride for the synthesis of amidoalkyl-2-naphthols in the literature.

In an initial endeavor, a mixture of same equivalents of benzaldehyde, β-naphthol and acetamide was taken and sonicated at 28–30 °C for 9 min (TLC) in an ultrasonic bath [27]. As expected, high yield of the product was obtained. When we extended the reaction to *m*-nitrobenzaldehyde, to our surprise only 65% of the product was obtained even after sonicating for 1 h. To improve the yield of the target product, we carried out the reaction in presence of various solvents and the results are presented in Table 1. As can be seen from this table, dichloroethane (DCE) accelerated the reaction and therefore high yields were obtained for all solid aromatic aldehydes including *m*-nitrobenzaldehyde (DCE has the cavity intensity of 39% compared to that of water (std. 100%) [18b]). We wanted to optimize the amount of catalyst used for this cyclocondensation, hence, we carried out the reaction with different amounts of catalyst, but it was observed that, the best result could be obtained with 0.1 g of the catalyst. The same reaction was carried out three times consequently to check the reproducibility and it was found that, all the three times, it gave same yield of the product (±1%).