MICROWAVE IRRADIATION SYNTHESIS OF 4-SULFO-1,8-NAPHTHALIMIDE IN $Zn(OAc)_2$/EtOH-H_2O

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ABSTRACT

The synthesis of N-substituted 4-sulfo-1,8-naphthalimide derivatives was performed in microwave reactor. The reaction was conducted in binary solvent mixture (EtOH:H_2O 1:1 v:v) with 4-sulfo-1,8-naphtalic anhydride, the respective primary amine, and $Zn(OAc)_2$ as a catalyst. High yields in a short reaction time were achieved (> 80 % in 5 min). The Lewis acid catalyst and the binary mixture have an important role on the reactivity and time reaction.

Keywords: N-substituted 4-sulfo-1,8-naphthalimides, microwave reactor, Lewis catalysis $Zn(OAc)_2$, H_2O-EtOH binary solvent.

INTRODUCTION

The N-substituted 1,8-naphthalimides are important compounds for application in the technological and biomedical fields. This is due to their physicochemical properties like the planar aromatic p-system, the tunable fluorescence and/or phosphorescence and electron stabilization provision. These features are exploited to create supramolecular building blocks, analytical and optoelectronic devices, smart materials and fluorescent or phosphorescent probes for a set of biological probes and non-biological applications [1 - 12]. Several methods for aromatic naphthalimide derivatives synthesis using protic and dipolar aprotic solvents or alternative routes based on ultrasound, microwave and ionic liquids [13 - 19] are known.

The strategy of aromatic imide synthesis recognizes that the attached substituents exert an important effect on the reaction and the product distribution. In general the electron-withdrawing groups (EWG) accelerate the imidization, while the electron-donnor groups (EDG) slow it down. The electronic conjugation or the inductive effect in the ground state of the EDG´s nonbonding electron pair with the extended p-electron system certainly diminishes the carbonyl electrophilicity of the imide functional group. This effect of electronic delocalization is outlined through the energy decrease of the stretching modes of the carbonylic group [9, 15].

In spite of the imidization favoring reactivity, the presence of EWG may be a problem due to the possible occurrence of a nucleophilic aromatic substitution (S_NAr). When these substituents are *ortho* or *para* positioned in relation to the imide functional group they are strong leaving groups [10, 15]. Thereby, SNAr concurrent reaction can take place leading to undesired secondary products.

Another point is the conducting of a homogeneous or a heterogeneous reaction. This choice can lead to opposite or concurrent pathway reactions producing imidic and/or aromatic substitution products. In this context, the synthesis of sulfo 1,8-naphthalimide acids or salts is representative of this assumption. In a homogeneous solution, i.e. an aqueous medium, there are high odds of displacement of the sulfo ($-SO_3$) and EWG, mainly

when it is at ortho or para position to the imide. The aromatic nucleophilic displacement in the course of a heterogeneous reaction is somewhat blocked irrespectively of the decrease of the imidic condensation rate or the low conversion in some cases [14, 20].

There are studies on microwave-assisted synthesis of 1,8-naphthalimides and 1,4,5,8-naphthalimides [21-23]. In general, a short reaction time is observed and depending on the reaction conditions an imide group is formed in absence of EWG groups' displacement toward primary amines. Thompson et. al. synthesize core-substituted naphthalenediimide with high selectivity under microwave irradiation [24]. Herein, to the best of our knowledge, we report a new synthetic route for 4-sulfo-N-substituted-1,8-naphthalimide derivatives in presence of zinc acetate, $Zn(OAc)_2$ as a catalyst. Microwave irradiation is applied to the heterogeneous medium obtained. The reactions considered proceed with the participation of 4-sulfo-1,8-naphthalic anhydrides and different primary amines in a water-ethanol (H_2O-EtOH) mixture. The respective 4-sulfo-1,8-naphthalimides are obtained with a high yield within a short time reaction time. The use of H_2O-EtOH mixture and the Lewis acid catalyst $Zn(OAc)_2$ is of determining importance for the achievement of an easy-cut reaction and an efficient synthetic methodology. Experiments in absence and presence of a catalyst are carried out.

EXPERIMENTAL

General Procedures

All 1,8-naphthalic anhydrides were purchased from Aldrich. The amines: n-butylamine (Carlo Erba), n-propylamine (Acros), N,N-dimethylethylenediamine (Aldrich), 2-hydroxy-propylamine (Aldrich), Allylamine (Acros), ethylamine as 70 % aqueous solution and methylamine as 40 % aqueous solution (Fluka), sulfanilic acid (Aldrich), nitroaniline (Aldrich) and zinc acetate (Synth) were used as received. Double distilled water was used for the synthesis. The other solvents were of a spectroscopic grade and were introduced without further purification.

1H-NMR spectra were recorded on Varian AC-300 in DMSO-d6. The chemical shifts were reported as parts per million (d, ppm) from TMS as an internal standard. Infrared (IR) spectra were recorded on BOMEM-MB 102-FT-IR spectrometer using KBr plates. Titan MPS-Microwave reactor (PerkinElmer) was used.

The conversion from anhydride to imide was estimated as follows: after separation and drying, 20 mg of the crude products were added to 200 mg of KBr for pellet preparation. The conversion was checked on the ground of the intensity ratio of the carbonyl and anhydride/imide peaks (1780 cm^{-1}/1701 cm^{-1}) in relation to the standard intensity fit of anhydride/imide taken in an anhydride proportion of 100 %, 75 %, 50 %, 25 %, 0 %.

Method A: synthesis in presence of a catalyst

The primary amine (2 mmol) was added to a solution of potassium 4-sulfonic-1,8-naphthalic anhydride (2 mmol) in 50mL of EtOH:H_2O (1:1, v/:v) mixture in an erlenmeyer (150 mL) flask. The catalyst was used in an amount of 10 mol % in relation to the anhydride. The suspensions were put in a sealed and pressurized tube. The reaction was carried out at 100°C at pressure of 1 bar up to 2 bar under microwave irradiation for 10 min. After this period, the precipitation was filtered off and the crude product washed with ethanol (50 ml) and diethyl ether (20 ml). The crude products were dried in a vacuum oven.

Method B: synthesis in catalyst absence

The primary amine (2 mmol) was added to a solution of potassium 4-sulfonic-1,8-naphthalic anhydride (2 mmol) in 50mL of EtOH:H_2O (1:1, v/v) mixture in an erlenmeyer (150 mL) flask. The conditions applied were identical with those described in Method A. The total conversion required 30 min of microwave irradiation.

RESULTS AND DISCUSSION

Fig. 1 illustrates the reaction investigated. Table 1 shows the results of the synthesis of 4-sulfo-1,8-naphtalimide potassium salts in absence and presence of a catalyst. The reaction with $Zn(OAc)_2$ has a high

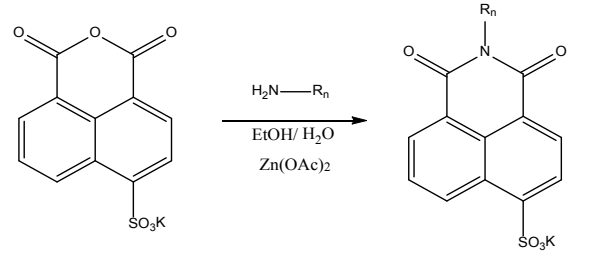
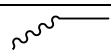
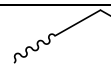
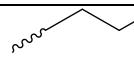
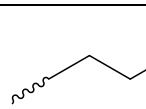
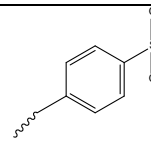
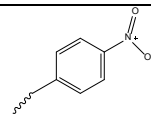


Fig. 1. Imidization from 4-sulfo-1,8-anhydride and amine in H_2O-EtOH solvent.

Table 1. The yields of 4-sulfo-1,8-naphtalimide derivatives obtained by microwave reactor with (method A) and without (method B) $Zn(OAc)_2$ in H_2O-EtOH (1:1). Time of reaction = 10 min.

Entry	Product, N_{imidic}-Rn	Method A yield (%)*#	Method B approximated conversion (%)**
1		95	70
2		92	65
3		70	40
4		90	45
5		95	65
6		92	60
7		95	65
8		88	40
9		90	40

** Yield calculated after washing of the crude product with cold water and ethanol. ** The conversion was stipulated by infrared carbonyl stretching on the anhydride and imide at 1780 cm^{-1} and 1701 cm^{-1}, respectively. # Unpurified Rn = propyl, 70 % is the approximated conversion.*

yield for a short reaction time (10 min). The imide group conversion is total. A few conversions proceed within the same time interval in absence of $Zn(OAc)_2$. Longer time (~ 30 min) is required for the total conversion. These results illustrate the importance of $Zn(OAc)_2$ providing increase of reactivity and selectivity for imidization when compared with aromatic substitution.

A lower yield even under longer microwave irradiation is obtained in the course of the reaction with propylamine (entry **3**). This lack of propylamine reactivity under ultrasound conditions has already been verified [14]. The aromatic amines do not show steric hindrance which could affect the reactivity. Even with few synthetic entries the method is very effective when compared to thermal ethanolic or sonochemical promotion for obtaining 4-sulfo-1,8-naphthalimides whose reaction times are 2 h and 18 h, respectively [14, 20].

The optimal condition refers to the stoichiometric ratio of amine and anhydride (1:1) and the application of H_2O-EtOH heterogeneous medium. This experimental set is very suitable for regiochemistry avoiding nucleophilic displacement of $–SO_3K$ group. Furthermore, the imidization is carried out in H_2O or EtOH solvents which results in side products of S_NAr and a low anhydride-to-imide conversion, respectively. Therefore, in an aqueous medium, most probably due to the better solubility of the sulfo anhydride, there is a greater chance for a displacement reaction while, the low solubility of the 4-sulfo reactant in alcohol refrains the imidic formation.

As mentioned above the S_NAr control is an important issue for all synthetic methods involving aromatic imides having electron-withdrawing groups. In the previous work dealing with imidization of 4-substituted-1,8-naphthalic anhydride derivatives via sonochemical route, the amine nucleophiles are used in a high excess (10 folds) which triggers the S_NAr of the $-SO_3K$ group [14]. In addition, the imidization conducted in an aqueous medium from -Br and $-NO_2$ naphthalimides leads to substitution products when the reaction is promoted by high microwave power [19]. Therefore, the conditions of imidization proceeding are very relevant for the reaction pathways and the corresponding distribution of the products.

The results obtained show that $Zn(OAc)_2$ and H_2O-EtOH play an important role in the present reaction proceeding. Some inferences concerning the possible synthetic gains brought by H_2O-EtOH and $Zn(OAc)_2$ will be drawn out. As reported in a previous work on S_NAr-thiolyses a reaction rate increase is achieved when H_2O-EtOH 1:1 mole ratio is used. This effect is attributed to an enhancement of thio-nucleophilicity and the specific solute/solvent interaction with the leaving group. The EtOH-H_2O 1:1 mole ratio has a lower H-bonding donor solvatochromic property (a) compared to that of water and ethanol [25]. Thereby, the H_2O-EtOH solvent properties should improve the amine nucleophility for the attack at the imidic carbonyl group and the ring-closing imide functionality.

The use of a Lewis acid catalyst for carbonylic ac-

tivation in polar protic solvents is encouraged, although it is not recommended because of the proceeding high coordination with the solvent. There are different modes of carbonyl-Zn interactions which increase the electrophilic character of this organic group [26].

The following mechanistic steps (Fig. 2) are suggested on the ground of results obtained for Lewis acid catalyzed-imidization in H_2O-EOH. In view of the mechanism of imidic condensation, H_2O-EOH medium as a lower H-bonding donor favors preferentially Zn---O=C coordination in order to allow the activated amine-nucleophile attack leading to a ring-opened amic structure. Furthermore, it takes place at the amic intermediate, which in turn facilitates the intramolecular ring-closing condensation to form the imide.

Characterization

The sulfo-compounds match well with those mentioned in ref. [14]:

4-Sulfonic-N-methyl-1,8-naphthalimide potassium salt, yield 95 %; yellow needles, 1:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589, 1349, 1231, 1160, 1067.
^{1}H-NMR d ppm (DMSO-d_6): 2.8 (s, 3H, CH_3), 7.3 (t, 1H, Ar), 7.7–7.8 (m, 1H,
Ar), 8.4 (d, 1H, Ar), 8.7 (d, 2H, Ar), 9.1(d, 1H, Ar).

4-Sulfonic-N-ethyl-1,8-naphthalimide potassium salt, yield 92 %; yellow needles, 2:
IR (KBr) cm^{-1}: 3094, 2970, 2857, 1695, 1640, 1589, 1350, 1231, 1160, 1067.
^{1}H-NMR d ppm (DMSO-d_6): 1.9 (t, 3H, CH_3), 3.1 (t, 2H, CH_2), 7.4 (t, 1H,
Ar), 8.1 (d, 1H, Ar), 8.6 (d, 2H, Ar), 9.3 (d, 1H, Ar).

4-Sulfonic-N-propyl-1,8-naphthalimide potassium salt, yield 70 %; white needles, 3:
IR (KBr) cm^{-1}: 3095, 2962, 2858, 1698, 1644, 1589, 1350, 1232, 1160, 1068.
^{1}H-NMR d ppm (DMSO-d_6): 0.9 (t, 3H, CH_3), 1.6 (sextet, 2H, CH_2), 4.0 (t, 2H,
CH_2), 7.9 (t, 1H, Ar), 8.2 (d, 1H, Ar), 8.5 (d, 2H,Ar), 9.3 (d, 1H, Ar).

4-Sulfonic-N-butyl-1,8-naphthalimide potassium salt, yield 90 %; white powder, 4:
IR (KBr) cm^{-1}: 3093, 2958, 2857, 1705, 1652, 1587, 1348, 1225, 1160, 1077.
^{1}H-NMR d ppm (DMSO-d_6): 0.9 (t, 3H, CH_3), 1.5 (sextet, 2H, CH_2), 1.7 (quintet, 2H, CH_2), 4.2 (t, 2H, CH_2), 7.6 (t, 1H, Ar), 8.1 (d, 1H, Ar), 8.6 (d, 2H, Ar), 9.3(d, 1H, Ar).

4-Sulfonic-N-allyl-1,8-naphthalimide potassium salt, yield 95 %; white needles, 5:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589, 1349, 1231, 1160, 1067,
^{1}H-NMR d ppm (DMSO-d_6): 4.8 (d, 2H, allylic N-CH_2), 5.2 (d, 2H, allylic-CH_2), 5.3 (m, 1H, allylic CH), 7.9 (t, 1H, Ar), 8.4 (d, 1H, Ar), 8.5 (d, 2H, Ar), 9.1 (d, 1H, Ar).

4-Sulfonic-N-(2-hydroxy)-propyl-1,8-naphthalimide potassium salt, yield 92 %; white powder, 6:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589, 1349, 1231, 1160, 1067.
^{1}H-NMR d ppm (DMSO-d_6): 1.1 (d, 3H, CH_3), 4.1 (m, 1H, CH), 4.8 (d, 2H, CH_2), 7.9 (t, 1H, Ar), 8.2 (d, 1H, Ar), 8.4 (d, 2H, Ar), 9.2 (d, 1H, Ar).

4-Sulfonic-N-(N,N-dimethyl)-ethylenamine-1,8--naphthalimide potassium salt, yield 95 %; yellow needles, 7:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589, 1349, 1231, 1160, 1067.
^{1}H-NMR d ppm (DMSO-d_6): 2.4 (s, 6H, CH_3), 3.5 (t, 2H, CH_2), 4.1 (t, 2H, CH_2), 7.9 (t, 1H, Ar), 8.2 (d, 1H, Ar), 8.5 (d, 2H,Ar), 9.25 (d, 1H, Ar).

4-Sulfonic-N-(*p*-sulfonic-benzo)-1,8-naphthalimide potassium salt, yield 88 %; yellow needles, 8:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589, 1349, 1231, 1160, 1067.
^{1}H-NMR d ppm (DMSO-d_6): 7.3 (t, 1H, Ar), 7.7 (d, 1H, Ar), 7.9 (d, 2H,
Ar), 8.2 (d, 2H, Ar), 8.5 (d, 1H, Ar), 9.3 (d, 2H, Ar).

4-Sulfonic- N-(*p*-nitro-benzo)-1,8-naphthalimide potassium salt, yield 90 %; yellow needles, 9:
IR (KBr) cm^{-1}: 3094, 2960, 2857, 1693, 1639, 1589,

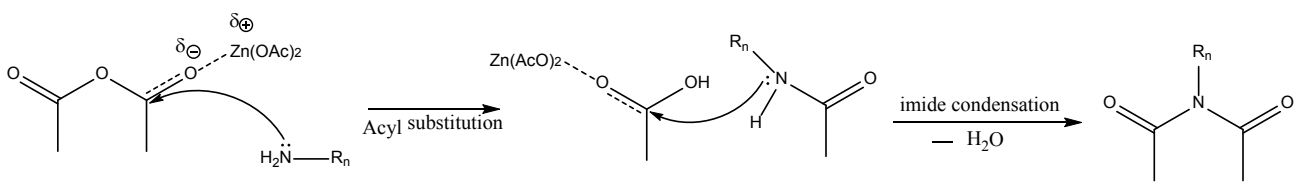


Fig. 2. Carbonyl-Zn$(OAc)_2$ coordination and enhanced-intramolecular N-attack speed up the imidization.

1349, 1231, 1160, 1067.
^{1}H-NMR *d* ppm (DMSO-d_6): 7.4 (t, 1H, Ar), 7.9 (d, 2H, Ar), 8.1 (d, 1H, Ar), 8.7 (d, 2H, Ar), 8.9 (d, 1H, Ar), 9.1 (d, 2H, Ar).

CONCLUSIONS

A versatile methodology for the synthesis of N-substituted 4-sulfo-1,8-naphthalimides by microwave irradiation is developed. The method is very efficient providing high yields and easy treatment. The Lewis acid catalyst $Zn(OAc)_2$ and the mixture of H_2O-EtOH have a key role in determining the reactivity and selectivity of imide condensation carried out in a heterogeneous medium.

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