Design and Synthesis of Naphthol Derivative Using Three Components System and Its Relation with Physicochemical Parameters log P and π

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A naphthol derivative was synthesized using the three-component system (β-naphthol, benzaldehyde and N-(2-aminoethyl)-4-hydroxybenzamide) and characterized by spectral analyses. In order to characterize the structural and chemical requirements of naphthol derivative, some parameters such as log P and π were evaluated. The results showed an increase in the values of log P and π for the compound **4** in comparison with **1**, **2** and **3**. These data indicate a high degree of lipophilicity and steric impediment for compound **4** in comparison with **1**, **2** and **3**.

Key Words: Naphthol, Derivatives, Synthesis.

INTRODUCTION

Aromatic-condensed derivatives are a important hetero-cyclic compounds which induced several biological activities such as antibacterial[1,2] and as material in the production of polyesters fibers and plastics[3]. There are several methods reported for synthesis of aromatic-condensed derivatives, *e.g.*, the synthesis of naphthyl ketone by the reaction of *o*-alkynylbenzaldehydes with alkynes using AuCl₃ as catalyst[4]. In addition, other studies shown the synthesis of 1,3-disubstituted naphthalenes from the Baylis-Hillman acetates with the help of manganese(III) acetate[5]. Other reports indicate the tandem pummerer Diels-Alder sequence for the preparation of α-thio substituted naphthalene derivatives[6]. Additionally, other studies[7] showed the synthesis of 1,8-diphenylnaphtalene and 1-iodo-8-phenylnaphtalene by the reaction of lithium diphenyl cuprate and aryl halides. Other studies by Ganapathy and Viswanathan[8] shown the synthesis of polysubstituted naphthalene derivatives through gallium trichloride catalyzed by alkyne-aldehyde coupling. In addition, some carbamato-alkyl-naphthol derivatives[9] have been synthetized by condensation of β-naphthol, aromatic aldehyde and methyl carbamate in ionic liquid media. All these experimental results show several procedures which are available for synthesis of naphthalene derivatives. Nevertheless, expensive reagents and special conditions are required. Therefore, in this study a naphthol derivative was synthetized using the three-component system [β-naphthol, benzaldehyde and N-(2-aminoethyl)-4-hydroxy-benzamide].

EXPERIMENTAL

N-(2-Aminoethyl)-4-hydroxybenzamide was prepared according to reported method[10]. The other compounds evaluated in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an electrothermal (900 model). Infrared spectra was recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ¹H and ¹³C NMR spectra were recorded on a varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl₃ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. Spectrometer. elementary analysis data were acquired from a Perkin-Elmer Ser. II CHNS/0 2400 elemental analyzer.

4-Hydroxy-N-(2-{[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino}-ethyl)-benzamide (4): A solution of N-(2-aminoethyl)-4-hydroxybenzamide (126 mg, 0.69 m mol), β-naphthol (100 mg, 0.69 mmol), benzaldehyde (70 μL, 0.69 mmol) in 10 mL of ethanol was stirring for 48 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystalli-

zation from methanol: water (4:1) yielding 60 % of product, m.p. 72-74 ºC; IR (KBr, ν_{max}, cm^{-1}): 3630, 3320, 1630 and 1580; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.02 (t, 2H, J = 6.5 Hz), 3.53 (t, 2H, J = 6.5 Hz), 5.07 (s, 1H), 5.16 (broad), 6.82 (d, 2H), 6.96 (d, 2H), 7.06 (m, 1H), 7.11 (m, 2H), 7.20 (m, 1H), 7.42-7.54 (m, 3H), 7.57 (d, 2H), 7.68-7.75 (m, 2H) ppm.^{13}C NMR (74.5 MHz, CDCl$_3$) δ_C: 40.13 (C-15), 53.35 (C-14), 54.43(C-12), 114.38 (C-9), 115.07(C-27, C-29), 121.18 (C-8), 123.47 (C-6), 126.62 (C-7), 126.76 (C-2), 127.25 (C-25), 127.38 (C-22), 128.03 (C-4), 128.94 (C-10), 128.95 (C-26, C-30), 129.52 (C-20, C-24), 129.82 (C-5), 130.07 (C-21, C-23), 138.95 (C-19), 139.01 (C-3), 152.11 (C-1), 160.43 (C-28), 169.53 (C-17) ppm. EI-MS m/z: 412.72 (M$^+$, 12), 231.19, 143.16, 121.11. Anal. calcd. (%) for: $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79; O, 11.64. Found (%): C, 75.68; H, 5.83.

RESULTS AND DISCUSSION

Many procedures for formation of naphthol derivatives are available in the literature. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks; some reagents are of limited stability and preparation can be dangerous[11-13]. Therefore, in this study we report a straight forward route for synthesis of new naphthol derivative using the three-component system [β-naphthol, benzaldehyde and N-(2-aminoethyl)-4-hydroxybenzamide] in ethanol under reflux (Fig. 1). The ^{1}H NMR spectrum of 4 shows signals at 3.02 and 3.53 ppm for protons involved in the arm bound to amide and amine groups; at 5.07 ppm for hydrogen of methylene which is bound to both phenyl and naphthol groups. Other signal at 5.16 ppm for both amino and hydroxyl groups were found. Finally, the spectrum contains several signals at 6.82-6.96, 7.11, 7.20 and 7.57 ppm for phenyl groups; at 7.06, 7.42-7.75 ppm for naphthol group. The ^{13}C NMR spectrum contains peaks at chemical shifts of 42.13 and 53.35 ppm for the carbons of the methylenes involved in the arm bound to amide and amine groups. A signal at 54.43 ppm for methylene bound to phenyl group and naphthol group was found. In addition, several signals at 114.38, 121.18-126.76, 128.03-128.94, 129.82 and 139.03-152.11 ppm for carbons involved in the naphthol group; at 115.07, 127.25-127.38, 128.95-129.52, 130.07-138.98 and 160.43 ppm for carbons of phenyl groups; 169.53 ppm for amide group were found. In addition, the presence of 4 was further confirmed from mass spectrum which showed a molecular ion at m/z 412.72.

Analyses of physicochemical parameters: In order to characterize the structural and chemical requirements of naphthol derivative (4), some descriptors such as log P and π were calculated. log P describes the logarithmic octanol-water partition coefficient; therefore, it represents the lipophilic effects of a molecule that includes the sum of the lipophilic contributions of the parent molecule and its substituents[14]. The difference between the substituted and unsubstituted log P values is conditioned by the π value for a particular substituent[15]. In this work, log P and π parameters were calculated by the method reported by Leo[14] and Mannhold and Waterbeemd[16]. The results (Tables 1-4) showed an increase in both log P and π values of compound 4 with respect to 1, 2
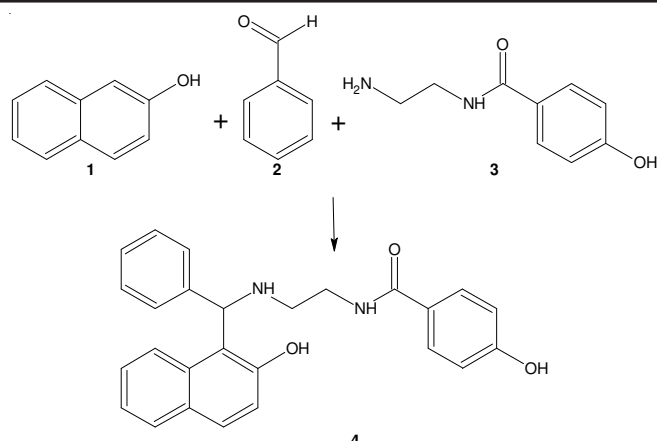

Fig. 1. Synthesis of 4-hydroxy-N-(2-{[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino}-ethyl)-benzamide (4) using the three-component system[β-naphthol (1), benzaldehyde (2) and N-(2-aminoethyl)-4-hydroxybenzamide (3)]

TABLE-1
PHYSICOCHEMICAL PARAMETERS log K_{ow} AND π OF β-NAPHTHOL (1)

Compound	log K_{ow} fragment	Contributions
1	Aromatic carbon	2.9400
	-OH [hydroxy, aromatic attach]	-0.4802
	Equation constant	0.2290
	log K_{ow}	2.6888
	π	-0.4820

TABLE-2
PHYSICOCHEMICAL PARAMETERS log K_{ow} AND π OF BENZALDEHYDE (2)

Compound	log K_{ow} fragment	Contributions
2	Aromatic carbon	1.7640
	-OH [aldehyde, aromatic attach]	-0.2828
	Equation constant	0.2290
	log K_{ow}	1.7102
	π	-0.2828

TABLE-3
PHYSICOCHEMICAL PARAMETERS log K_{ow} AND π OF N-(2-AMINOETHYL)-4-HYDROXYBENZAMIDE (3)

Compound	log K_{ow} fragment	Contributions
3	-CH$_2$ [aliphatic carbon]	0.9822
	-NH$_2$ [aliphatic attach]	-1.4148
	-NH- [aliphatic attach]	-1.4962
	Aromatic carbon	1.7640
	-OH [hydroxy, aromatic attach]	-0.4802
	-C(=O)N [aromatic attach]	0.1599
	Equation constant	0.2290
	log K_{ow}	-0.2561
	π	1.1381

and 3. These results showed that both aliphatic carbon (-CH) and aromatic carbon involved in chemical structure of 4 contribute to the highlipophilicity in comparison with compounds 1, 2 and 3. These data indicate a high steric impediment and different conformationalpreferences and internal rotation of 4 in comparison with 1, 2 and 3. These data are supported by studies of Bryantsev and coworkers[17], who showed that conformational differences between several chemical functional groups have important consequences.

TABLE-4
PHYSICOCHEMICAL PARAMETERS log K_{ow}
AND π OF NAPHTHOL DERIVATIVE (**4**)

Compound	log K_{ow} fragment	Contributions
4	-CH$_2$ [aliphatic carbon]	0.9822
	-NH$_2$ [aliphatic attach]	0.3614
	-NH- [aliphatic attach]	-2.9924
	Aromatic carbon	6.4680
	-OH [hydroxy, aromatic attach]	0.9604
	-C(=O)N [aromatic attach]	0.1599
	Equation constant	0.2290
	log K_{ow}	4.2477
	π	1.5577

Conclusion

In this study, we report an easy methodology for synthesize a naphthol derivative using the three-component system (β-naphthol, benzaldehyde and N-(2-aminoethyl)-4-hydroxybenzamide). In addition, other results indicate a high degree of lipophilicity and a steric impediment of compound **4** in comparison with **1**, **2** and **3**.

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