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Synthesis of 1,2-Diphenyliminoethanols and the Evaluation of Their Possible Biological Activity

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Abstract: The chemical cellular signaling pathway of phosphatidylinositol-3-kinase (PI3K) is crucial in many aspects of cell growth and survival. Genetic alterations such as amplification, mutation and chromosomal transposition can compromise the PI3K pathway, leading to its permanent activation, which results in the alteration of growth control and cell survival mechanisms, favoring competitive growth, metastatic capacity, and often a greater resistance to treatments. Evidence of these destructive genetic modifications has been found in different types of cancer. Recently, a group of researchers found that the structure of benzoin matches the fingerprint of the active PI3K inhibitor. The focus of this work is on the synthesis of substituted benzoins via benzoin condensation in aqueous medium for subsequent reaction with anilines. The aim is to obtain a series of new compounds derived from 1,2-diphenyliminoethanol, which will be sent to a specialized laboratory to evaluate their cytotoxicity on carcinoma cell lines.

Key words: Benzoin, Schiff bases, 1,2-diphenyliminoethanol.

1. Introduction

Benzoin is an organic compound whose chemical structure contains two phenyl, one keto and one hydroxy group.

Benzoins and their derivatives can be obtained in the laboratory. Benzoin condensation is an organic reaction discovered in 1832 by Wöhler and Liebig [1], which generates α-hydroxyketones from aromatic aldehydes by using the cyanide ion as a catalyst, under very controlled conditions. Although initially discovered on aromatic aldehydes, benzoin condensation easily expands to their aliphatic counterparts [1].

The condensation reaction will be symmetric if the substituent R1 is the same as R2. If the substituents in the aromatic ring are different, the condensation will be asymmetric. In cases where two different aldehyde precursors are exposed to the cyanide catalyst, the reaction typically results in a mixture of the four possible products [1].

Other studies indicate that benzoin condensation in water can be performed using an ionic environment [2].

The α-hydroxy carbonyl structural unit is found in many natural biologically active products; and it also represents a versatile class of intermediate compounds in organic synthesis [3]. They have generally been used in the synthesis of quinazolines, imidazoles, pyrazines, indoles and pyrroles [4].

Schiff bases, named after Hugo Schiff [5], are formed when a primary amine reacts with an aldehyde or ketone, which produces a nitrogen analogue of the aldehyde or ketone in which the carbonyl group has been replaced by an imine or azometin group [5]. Compounds containing Schiff's bases have also been used due to their range of biological effects, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral and antipyretic [6]. The imine group in these compounds has proven crucial for their biological effects [7].

The chemical cellular signaling pathway of phosphatidylinositol-3-kinase (PI3K) is crucial in

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many aspects of cell growth and survival. Several genetic alterations such as amplification, mutation and chromosomal rearrangements can compromise the PI3K pathway, leading to its permanent activation. Abnormal activation of the PI3K pathway results in impaired growth control and cell survival mechanisms; which favors competitive growth, metastatic capacity, and often a greater resistance to treatments. Evidence of these destructive genetic modifications has been found in different types of cancer [8]. Recently, a group of researchers using pharmacophore models based on PI3K active inhibitor ligands, and searching the database of the National Cancer Institute, found that the structure of benzoin matches the fingerprint of the active PI3K inhibitor. In order to improve the inhibitory capacity of benzoin against that of PI3K enzyme, compounds have been synthesized from benzoins and aliphatic compounds, without any successful results [9].

Due to their chemical structure, compounds derived from 1,2-diphenyliminoethanols are part of the Schiff base family. These compounds can be synthesized from benzoins and substituted anilines, reacting under acidic conditions, using ethanol, DMF (N,N-Dimethylformamide) and reflux [9]. We consider that the substituted 1,2-diphenyliminoethanols more closely resemble the structure of the PI3K enzyme inhibitors, keeping the benzoin fingerprint in the structure. The focus of this work is on the synthesis of substituted benzoins via benzoin condensation in aqueous medium for subsequent reaction with anilines. The aim is to obtain a series of new compounds derived from 1,2-diphenyliminoethanol, which will be sent to a specialized laboratory to evaluate their cytotoxicity on carcinoma cell lines.

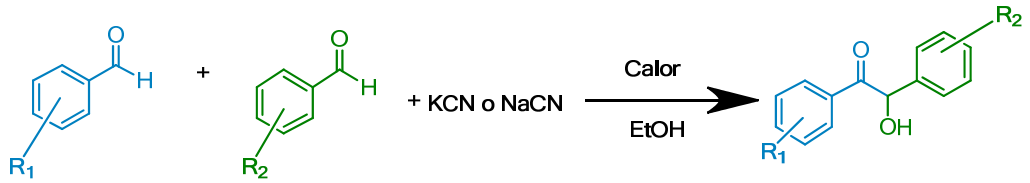
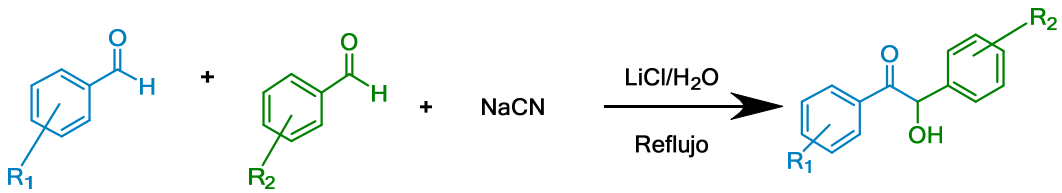


Fig. 1 First reported benzoin condensation reaction.



R_1=R_2= 3,4,5-tri-OCH_3 ; 4-Cl; 4-OH; 4-N$(CH_3)_2$; 4-NO_2; 2,6 di-Cl.

Fig. 2 Benzoin condensation carried out.

Table 1 Benzoin condensation reactions.

No.	R1	R_2	Fusion point (literature) (°C)	Fusion point (experimental) (°C)	Yield[a] (%)
1	3,4,5-trimethoxy		147-148 [10]	137-139	71.3
2	4-chlorine		86-88 [11]	87	69.4
3[b]	4-OH		181-182 [12]	-	-
4[b]	4-dimethylamino		153-156 [13]	-	-
5[b]	4-NO_2		164 [14]	-	-

Reaction conditions: Benzaldehyde 10 mmol, NaCN 30 mmol, LiCl 3 g, water 15 mL, reflux for 3 h.

[a] Yield of the isolated product.

[b] Reaction from which no product was obtained.

2. Results and Discussion

Symmetric benzoin condensation reactions were performed in aqueous medium using LiCl as saline and reflux agent, and taking benzaldehydes as substituted precursors (Table 1). Reactions 1 and 2 were the only ones where any product was obtained. In both cases it was observed that the products achieved a high purity standard after purification by recrystallization. The purity standard was verified by thin layer chromatography, using AcOEt-Hexane as eluent in different proportions. The analysis of the IR and 1H-NMR spectroscopic techniques confirmed the presence of the characteristic bands of the bonds present in the benzoin, so the obtaining of the desired products is confirmed.

In the case of reactions No. 3 and No. 5, a dark brown liquid was obtained. Based on the results of thin layer chromatography, it contained at least a mixture of 3 different products that could not be separated. The reaction No. 4 was followed by running a thin layer chromatography every 3 h for 15 h in total. Its respective raw materials were taken as reference, but in no case was the formation of any product observed, so it was decided to suspend the reaction.

Synthesis reactions of a series of different 1,2-diphenyliminoethanols, and not reported in the literature, were performed. Benzoin and aromatic amines were taken as precursors (Table 2). The reaction No. 1 is the only one that has been reported. We replicated it to verify the method of synthesis. Reactions were carried out with the two previously synthesized benzoins, unfortunately only from hexamethoxybenzoin were products obtained. The reactions No. 6 and No. 7 were followed by running a thin layer chromatography every 4 h for 30 h in total. Its respective raw materials were taken as reference, but in no case was the formation of any product observed, so it was decided to suspend the reaction. The reaction time varies in all cases. The shortest one was from reaction No. 1 (4 h) while reactions No. 4 and No. 5 up to 16 h were required to obtain products. All reactions were followed running thin layer chromatography. It was observed that all the products had a high purity standard, which was verified running thin layer chromatography, using AcOEt-Hexane as eluent in different proportions. The analysis of the IR and 1H-NMR spectroscopic techniques confirmed the presence of the characteristic bands of the bonds present in the benzoin, so the obtaining of the desired products is confirmed. Since most of the compounds are not reported in the literature, the 1H-NMR spectra were simulated, in order to compare the ones that were experimentally obtained with the simulated ones.

Table 2 Synthesis reactions of 1,2-diphenyliminoethanols.

No.	R-1	R_2	R3	Fusion point (literature) (°C)	Fusion point (experimental) (°C)	Yield[a] (%)
1	H	H	H	92-93 [9]	85-86	59.8
2[b]	3,4,5-trimethoxy		H	-	160–164	41.3
3[b]	H	H	4-Cl	-	161-163	49.9
4[b]	H	H	2-NO_2	-	137-138	72.9
5[b]	3,4,5-trimethoxy		4-CH_3	-	162-164	59.5
6[c]	4-Cl		H	-	-	-
7[c]	4-Cl		4-Cl	-	-	-

Reaction conditions: benzion 0.5 mmol, aniline 0.5 mmol, HCl (conc.) 0.4 mL, DMF 2 mL, EtOH 15 mL, and reflux at different time.

[a] Yield of the isolated product.

[b] Not described in the literature.

[c] Reaction from which no product was obtained.

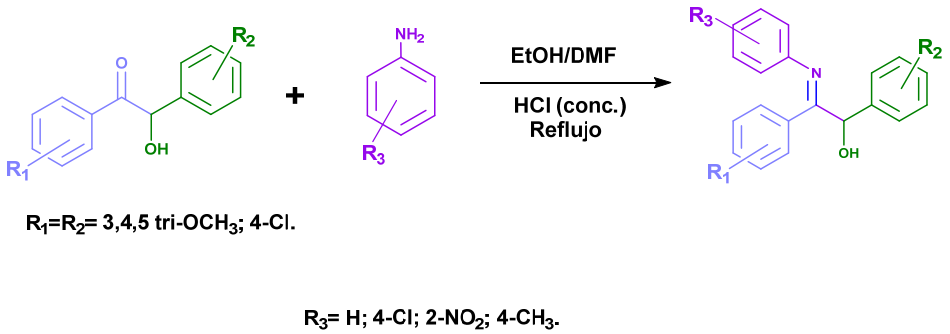


Fig. 3 Synthesis of 1,2-diphenyliminoethanols.

3. Experimental Section

3.1 Synthesis of Benzoins from Substituted Benzaldehydes

In a 100 mL ball flask with ground joint, a magnetic stir bar was placed followed by 30 mmol of KCN, which was dissolved in 15 mL of water. Subsequently, 10 mmol of benzaldehyde and 3 g of LiCl were added. The reaction mixture was left under constant stirring at reflux and the progress of the reaction was followed by running thin layer chromatography. After 3 h of reaction, the presence of a solid product was observed, which was extracted by decantation. Subsequently, the solid was dissolved in 10 mL of EtOH. The solution was transferred to a beaker, which had been placed in an ice bath. Crystallization was induced by carving the beaker's walls with a glass stirrer. The solid was vacuum filtered and it was rinsed 3 times using 5 mL of ice water each time. The product was allowed to dry. Thin layer chromatography was run, using AcOEt-Hex as eluent in different proportions to verify the purity of the product. The melting point was measured and the yield was calculated.

3.2 Synthesis of 1,2-Diphenyliminoethanol

A magnetic stir bar was placed in a 50 mL ball flask with ground joint. Then 0.5 mmol of benzoin and 0.5 mmol of aniline were added. Subsequently, 15 mL of EtOH, 2 mL of DMF and 0.5 mL of $HCl_{(conc.)}$ were added. The reaction mixture was left under constant stirring at reflux. The reaction progress was followed running thin layer chromatography. At the end of the reaction time, the flask was allowed to cool at room temperature, and the reaction mixture was transferred to a beaker containing 5 g of ice. It was confirmed that the reaction mixture had pH = 7.0 using pH testing paper. The beaker was placed in an ice bath and crystallization was induced by carving the beaker's walls with a glass stirrer. The solid was vacuum filtered and it was rinsed 3 times using 5 mL of ice water each time. The product was allowed to dry. Thin layer chromatography was run, using AcOEt-Hex as eluent in different proportions to verify the purity of the product. The melting point was measured and the yield was calculated.

The products obtained were characterized by IR and ^{1}H-NMR spectroscopy.

4. Conclusions

It was concluded that a series of new compounds derived from 1,2-diphenyliminoethanols can be synthesized from substituted benzoins and aromatic anilines, which maintain the fingerprint of the PI3K enzyme inhibitor. These compounds will be sent to a specialized laboratory to evaluate cytotoxicity on carcinoma cell lines.

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Hexamethoxybenzoin. ^{1}H-NMR (90 MHz, $CHCl_3$) δ: 5.02-5.04 (18H, OCH_3), 5.11 (1H, OH), 6.99 (1H, CH), 7.78 (2H, CH), 8.41 (2H, CH); IR (KBr, cm^{-1}):

3,375 (OH), 1,692 (C = O), 1,454, 1,588 (C = C).

1,2-Diphenyliminoethanol. ^{1}H-NMR (90 MHz, $CHCl_3$) δ: 5.38 (1H, OH), 6.01 (1H, CH), 6.60-6.73 (3H, CH), 7.03-7.45 (10H, CH), 7.92-8.03 (2H, CH); IR (KBr, cm^{-1}): 3,344 (OH), 1,662 (C = N), 1,445, 1,595 (C = C).

3,4,5,3',4',5'-Hexamethoxy-1,2-diphenyliminoethanol. ^{1}H-NMR (90 MHz, $CHCl_3$) δ: 4.55-4.67 (18H, CH), 4.72 (1H, OH), 6.61 (1H, CH), 7.40-7.48 (4H, CH), 7.83-8.04 (5H, CH); IR (KBr, cm^{-1}): 3,408 (OH), 1,669 (C = N), 1,415, 1,588 (C = C), 1,126 (OCH_3).

4'''Chloro-1,2-diphenyliminoethanol. ^{1}H-NMR (90 MHz, $CHCl_3$) δ: 5.42 (1H, OH), 5.93 (1H, CH), 6.51-6.64 (2H, CH), 6.97-7.54 (10H, CH), 7.84-8.03 (2H, CH); IR (KBr, cm^{-1}): 3,389 (OH), 1,668 (C = N), 1,447, 1,597 (C = C), 697 (C-Cl).

2-Nitro'''-1,2-diphenyliminoethanol. δ: 4.59 (1H, OH), 5.98 (1H, CH), 7.27-7.50 (10H, CH), 7.85-7.96 (4H, CH); IR (KBr, cm^{-1}): 3,377-3,411 (OH), 1,677 (C = N), 1,448, 1,593 (C = C), 1,335 (C-NO_2).

3,4,5,3',4',5'-Hexamethoxy-1,2-diphenyliminoethanol. ^{1}H-NMR (90 MHz, $CHCl_3$) δ: 2.20 (3H, CH), 3.78-3.90 (18H, CH), 3.95 (1H, OH), 5.80 (1H, CH), 6.57-6.60 (3H, CH), 6.91-7.00 (2H, CH), 7.19-7.26 (3H, CH); IR (KBr, cm^{-1}): 3,401 (OH), 1,668 (C = N), 1,458, 1,586 (C = C).

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