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Factorial design study to access the "green" iodocyclization reaction of 2-allylphenols

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Abstract: Iodocyclization of 2-allylphenols is a suitable method to access furans and dihydrofurans with adequate yields. Several methodologies to iodocyclization are reported in the literature; however, since some data about the conditions are conflicting, a more systematic approach is needed to define the best conditions. In this work, we performed a full 2^2 factorial design to study the influence of solvent (water or EtOH:water (1:9) mixture) and the addition of $NaHCO_3$ in iodine-promoted cyclization of 2-allylphenols. The results have shown water as the best solvent to be employed in the cyclization of liquid 2-allylphenols, and the presence of $NaHCO_3$ leads to lower yields. Several examples of 2-iodomethyl-2,3-dihydrobenzofurans preparations are reported using the optimized conditions; however, high yields are only observed when liquid 2-allylphenols were used.

Keywords: dihydrobenzofuran synthesis; factorial design; green chemistry; iodocyclization.

1 Introduction

Benzofuran and dihydrobenzofuran rings are important classes of oxygen-containing heterocycles occurring in a wide variety of biologically active compounds [1]. Several market drugs, such as morphine, citalopram, ramelteon, amiodarone and darifenacin, contain benzofuran or a dihydrobenzofuran moiety (Figure 1). Furthermore, the rings present a bioisosteric relationship with other heterocycles, such as indole, benzimidazole, benzothiazole and others, allowing its exploitation as analogues with possible similar activities [2].

Among the methodologies to prepare benzofurans and dihydrobenzofurans, the iodine-promoted cyclization of 2-allylphenols, sometimes referred to as iodocyclization reaction, is a very attractive strategy. In a previous paper [3], we reported the iodocyclization of 2-allylphenols such as 2-allyl-*p*-guaiacol, 2-allylvanillin, 2-allyl-1-naphthol, 1-allyl-2-naphthol and 3-allyl-2-methyl-4-hydroxiquinoline, besides the 2-allylphenol itself, with good yields. Aside from the iodocyclization of 2-allylvanilin, which used ethanol:water mixture, the reactions were carried out using CH_2Cl_2 as solvent and $NaHCO_3$ as base to deprotonate the phenolic hydroxyl group and neutralize the hydrogen iodide formed.

Fousteris et al. [4] and Chen et al. [5] reported the iodocyclization of 2-allylphenols in procedures slightly different than those reported by us. Fousteris et al. [4] conducted the reaction using a large excess of iodine in water, while Chen et al. [5] employed water:EtOH mixture as solvent. There was no base used in those reactions. However, the yields were quite similar to those obtained in our previously reported procedure [3].

In order to obtain a more efficient and environmentally "green" procedure than the one currently used by our group, we decided to explore more adequate solvents, such as water and ethanol, to conduct this reaction. The factorial design [6] is a widely used approach to explore the influence of several factors in laboratorial and industrial processes, including organic reactions. Accordingly, the objective of this work is to evaluate the influence of the presence of $NaHCO_3$ and the type of solvent by a systematic manner in the reaction of iodocyclization of 2-allylphenols through a complete 2^2 factorial design. Moreover, the conditions defined by this approach were applied to assess several 2-iodomethyl-2,3-dihydrobenzofurans herein.

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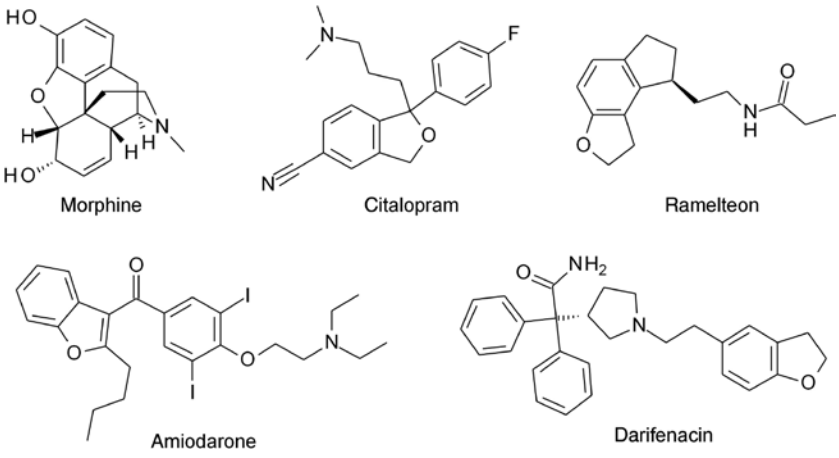

Figure 1: Market drugs containing benzofuran moiety.

2 Materials and methods

All starting materials were commercially available research-grade chemicals (Sigma-Aldrich Co., St. Louis, MO, USA) and were used without further purification. All solvents were dried and distilled prior to use. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX-300 (at 300 MHz for ^{1}H and 75 MHz for ^{13}C) instrument, with tetramethylsilane (TMS) as internal reference and in the indicated solvent; the chemical shifts (δ) from TMS are reported in parts per million. The ^{1}H and ^{13}C-NMR signals reported were obtained at room temperature.

2.1 Factorial design

A full factorial design 2^2 was performed involving the following as variables: (a) the presence or absence of $NaHCO_3$ and (b) solvent used (water or the 1:9 EtOH:water mixture). Experiments were performed in duplicate for all combinations of factor levels. Absence of $NaHCO_3$ and water were defined as categoric low levels (-) and presence of $NaHCO_3$ and EtOH:water mixture as high levels (+). The effects were calculated from equation (1):

$$\text{Effect}(x)=Y_{(x)+}-Y_{(x)-} \quad (1)$$

where $Y_{(x)+}$ and $Y_{(x)-}$ are means of yields obtained with high and low levels, respectively. The symbols (+) and (-) are standard notations in factorial design and their definitions do not affect the interpretation of results. Statistical analysis was carried out using Action free software [7].

In this work the experiments were designed, randomized and performed according to the runs presented in Table 1. Yield determinations were done in duplicate to estimate the standard deviations.

2.2 General procedure for the iodine promoted cyclization of 2-allylphenols (1a–e)

In a 100 ml flask, 3 mmol (0.40 g) of 2-allylphenol and 3.3 mmol (0.84 g) of iodine were added in approximately 20 ml of adequate solvent (water or EtOH:water mixture). When necessary, 3 mmol of $NaHCO_3$ (0.25 g) was also added. The mixture was stirred for 4 h. The aqueous mixture was extracted with 3×15 ml of hexane:AcOEt (9:1), and the combined organic phases were washed with saturated aqueous sodium thiosulfate solution, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography, using hexane:AcOEt (9:1) as eluent. Reaction scheme is shown in Figure 2.

Table 1: Yields for the 2^2 factorial design.

Solvent	Base	Run order	Yield (%)	Average yield (%)	Standard deviation
Water	None	1	86	86.5	±0.71
Water	None	8	87		
EtOH:water	None	3	74	72	±2.83
EtOH:water	None	6	70		
Water	$NaHCO_3$	2	77	78.5	±2.12
Water	$NaHCO_3$	7	80		
EtOH:water	$NaHCO_3$	4	64	62	±2.83
EtOH:water	$NaHCO_3$	5	60		

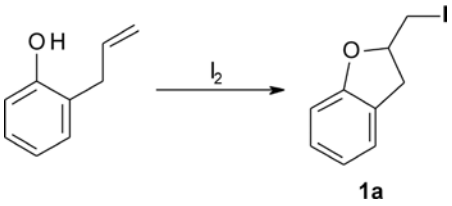

Figure 2: Iodocyclization of 2-allylphenol.

2.2.1 2-Iodomethyl-2,3-dihydrobenzofuran (1a): About 0.40 g of 2-allylphenol resulted in a yellowish oily liquid in the yields summarized in Table 1. ^{1}H-NMR ($CDCl_3$): δ 3.06 (dd, 1H, J=16.1, 6.7 Hz); 3.35–3.58 (m, 3H); 4.83–4.95 (m, 1H); 6.76–6.81 (m, 1H); 6.85–6.93 (m, 1H); 7.10–7.23 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 9.2; 36.3; 81.8; 109.8; 121.1; 125.3; 125.9; 128.4; 159.3.

2.2.2 2-Iodomethyl-7-methoxy-2,3-dihydro-1-benzofuran-5-carbaldehyde (1b): About 0.58 g of 2-allylvanillin yielded 12% of a yellowish oily liquid. ^{1}H-NMR (acetone-d_6): δ 3.13 (dd, 1H, *J*=16.1, 7.0 Hz); 3.50 (dd, 1H, *J*=16.1, 9.1 Hz); 3.64 (dd, 2H, *J*=5.3, 1.1 Hz); 3.93 (s, 3H); 5.00–5.10 (m, 1H); 7.38 (d, 1H, *J*=1.4 Hz); 7.43 (dd, 1H, *J*=2.6, 1.1 Hz); 9.83 (s, 1H). ^{13}C-NMR (acetone-d_6): δ 9.1; 36.2; 56.0; 82.1; 110.5; 126.5; 126.8; 129.1; 149.3; 153.8; 190.7.

2.2.3 2-Iodomethyl-5-methyl-2,3-dihydro-1-benzofuran (1c): About 0.44 g of 2-allyl-*p*-cresol yielded 73% of a yellowish oily liquid. ^{1}H-NMR ($CDCl_3$): δ 2.27 (s, 3H); 3.00 (dd, 1H, *J*=16.0, 6.6 Hz); 3.26–3.48 (m, 3H); 4.79–4.92 (m, 1H); 6.64–7.13 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 8.5; 20.8; 34.3; 81.8; 109.1; 126.5; 128.3; 129.6; 129.3; 157.4.

2.2.4 2-Iodomethyl-5-methoxy-2,3-dihydro-1-benzofuran (1d): About 0.49 g of 2-allyl-4-methoxyphenol yielded 90% of a yellowish oily liquid. ^{1}H-NMR ($CDCl_3$): δ 3.03 (dd, 1H, *J*=16.1, 6.6 Hz); 3.29–3.47 (m, 3H); 3.76 (s, 3H); 4.80–4.92 (m, 1H); 6.62–6.80 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 9.4; 36.5; 56.0; 81.8; 109.5; 111.2; 113.0; 126.8; 153.2; 154.3.

2.2.5 2-Iodomethyl-2,3-dihydro-1-benzofuran-5-carbaldehyde (1e): About 0.49 g of 4-hydroxy-3-allylbenzaldehyde yielded 10% of a yellowish oily liquid. ^{1}H-NMR ($CDCl_3$): δ 3.08 (dd, 1H, *J*=16.3, 6.6 Hz); 3.33–3.50 (m, 3H); 4.92–5.04 (m, 1H); 6.87 (d, 1H, *J*=8.3 Hz); 7.64–7.74 (m, 2H); 9.82 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 8.3; 35.3; 83.0; 109.9; 126.1; 127.4; 130.9; 133.1; 164.5; 190.6.

2.3 General procedure for the synthesis of allyl phenyl ethers (2b–e)

To a solution of 5 mmol of corresponding phenol in 20 ml of EtOH, 5 mmol (0.69 g) of K_2CO_3 and 10 mmol (1.21 g) of allyl bromide ere added and stirred overnight. The mixture was filtered, and the solution was evaporated to dryness. The residue was taken up in 10 ml of hexane and washed with 2×10 ml of distilled water. The organic layer was dried with anhydrous sodium sulfate and evaporated. The oily crude product was then purified by flash chromatography, using hexane:AcOEt (5:1) as eluent.

2.3.1 3-Methoxy-4-allyloxybenzaldehyde (2b): About 0.96 g of vanillin yielded 95% of a yellowish oily liquid. ^{1}H-NMR ($CDCl_3$): δ 3.95 (s, 3H); 4.72 (dt, 2H, *J*=5.4, 1.3 Hz); 5.35 (dq, 1H, *J*=10.4, 1.4 Hz); 5.45 (dq, 1H, *J*=17.3, 1.4 Hz); 5.98–6.21 (m, 1H); 6.98 (dd, 1H, *J*=8.6, 2.7 Hz); 7.40–7.48 (m, 2H); 9.86 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 56.0; 69.8; 109.3; 111.9; 118.8; 126.6; 130.2; 132.2; 149.9; 153.5; 190.9.

2.3.2 1-Allyloxy-4-methylbenzene (2c): About 0.74 g of *p*-cresol yielded 98% of a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 2.28 (s, 3H); 4.51 (dt, 2H, *J*=5.3, 1.5 Hz); 5.27 (dq, 1H, *J*=10.5, 1.4 Hz); 5.40 (dq, 1H, *J*=17.3, 1.4 Hz); 6.05 (ddt, 1H, *J*=17.3, 10.5, 1.4 Hz); 6.76–6.86 (m, 2H); 7.03–7.11 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 56.0; 69.8; 109.3; 111.9; 118.8; 126.6; 130.2; 132.2; 149.9; 153.5; 190.9.

2.3.3 1-Allyloxy-4-methoxybenzene (2d): About 0.82 g of 4-methoxyphenol yielded 97% of a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 3.75 (s, 3H); 4.47 (dt, 2H, *J*=5.3, 1.5 Hz); 5.26 (dq, 1H, *J*=10.5, 1.4 Hz); 5.40 (dq, 1H, *J*=17.3, 1.4 Hz); 6.04 (ddt, 1H, *J*=17.3, 10.5, 1.4 Hz); 6.78–6.89 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 55.7; 69.5; 114.6; 115.7; 117.5; 133.7; 152.8; 153.9.

2.3.4 4-Allyloxybenzaldehyde (2e): About 0.81 g of 4-hydroxybenzaldehyde yielded 90% of a yellowish oil. ^{1}H-NMR ($CDCl_3$): δ 4.63 (dd, 2H, *J*=5.1, 1.3 Hz); 5.33 (dq, 1H, *J*=10.4, 1.3 Hz); 5.44 (dq, 1H, *J*=17.2, 1.3 Hz); 5.97–6.15 (m, 1H); 7.02 (d, 2H, *J*=8.6, Hz); 7.83 (d, 2H, *J*=8.6, Hz); 9.89 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 69.0; 115.0; 118.4; 130.0; 132.0; 132.3; 163.6; 190.8.

2.4 General procedure for the synthesis of 2-allylphenols (3b–e)

In a flask, 3 mmol (0.57 g) of **3** was dissolved in 2 ml of Ph_2O and heated at 180–200°C for 2–6 h. The dark oil was washed with hexane to remove the Ph_2O and then purified by column chromatography, using hexane:AcOEt (5:1) as the eluent.

2.4.1 5-Allyl-4-hydroxy-3-methoxybenzaldehyde (3b): About 0.50 g of **2b** yielded 48% of a yellow solid (m.p. 63–65°C). ^{1}H-NMR ($CDCl_3$): δ 3.49 (dt, 2H, *J*=6.6, 1.4 Hz); 3.98 (s, 3H); 5.07–5.18 (m, 2H); 5.90–6.02 (m, 1H); 6.30 (br.s, 1H); 7.33 (m, 2H); 9.83 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 33.5; 56.3; 107.0; 116.4; 126.1; 128.1; 129.1; 135.6; 146.9; 149.4; 191.2.

2.4.2 3-Allyl-4-methylphenol (3c): About 0.50 g of **2c** yielded 76% of a yellowish liquid. ^{1}H-NMR ($CDCl_3$): δ 2.25 (s, 3H); 3.33–3.39 (m, 2H); 4.96 (br.s, 1H); 5.11 (t, 1H, *J*=1.6 Hz); 5.16 (dq, 1H, *J*=6.9, 1.6 Hz); 5.92–6.05 (m, 1H); 6.66–6.72 (m, 1H); 6.88–6.94 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 20.5; 35.1; 115.7; 116.3; 125.2; 128.3; 130.2; 131.0; 136.6; 151.8.

2.4.3 3-Allyl-4-methoxyphenol (3d): About 0.50 g of **2d** yielded 82% of a yellowish liquid. ^{1}H-NMR ($CDCl_3$): δ 3.35–3.40 (m, 2H); 3.75 (s, 3H); 4.82 (s, 1H); 5.12 (sext, 1H, *J*=1.7 Hz); 5.14–5.19 (m, 1H); 6.00 (ddt, 1H, *J*=17.6, 9.7, 6.3 Hz); 6.64–6.77 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 35.2; 55.8; 112.7; 116.0; 116.5; 126.6; 136.2; 148.0; 153.8.

2.4.4 3-Allyl-4-hydroxybenzaldehyde (3e): About 0.50 g of **2b** yielded 50% of a colorless liquid. ^{1}H-NMR ($CDCl_3$): δ 3.47 (d, 2H, *J*=6.4 Hz); 5.10–5.21 (m, 2H); 5.95–6.10 (m, 1H); 6.95–7.05 (m, 1H); 7.65–7.73 (m, 2H); 9.82 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 34.3; 116.0; 117.0; 217.1; 129.4; 131.0; 132.7; 135.5; 160.7; 192.0.

3 Results and discussion

The iodine-promoted cyclization reaction occurs probably *via* addition of iodine to the olefin, forming the iodonium ion intermediate. Following a regioselective nucleophilic attack from an oxygen atom leads to the opening of the ion ring, forming β-iodoethers (in case of attack by an alcohol) or iodohydrins (in case of attack by water) [8, 9]. To access the dihydrobenzofuran derivatives, intramolecular attack is done by the phenolic hydroxyl

group, generating HI. Literature reports indicate that the attack occurs in a Markovnikov manner, leading to 2-iodomethyl-2,3-dihydrobenzofuran derivatives [4, 5, 9].

The synthesis of 3-ethoxycarbonylpyrroles, benzofurans and naphthofurans through iodocyclization followed by dehydroiodination in alumina was reported previously [3]. The iodocyclization reactions were conducted in CH_2Cl_2, using iodine and $NaHCO_3$ as base to neutralize the formed HI. The obtained yields in these procedures were between 75 and 87%. On the other hand, the iodocyclization of 2-allylvanillin was performed in EtOH:water (1:1) mixture, and the obtained yield was 90%, indicating that the polar solvent could improve the yield.

Fousteris and coworkers [4] presented the iodocyclization of a variety of 2-allylphenols in polar solvents. The reactions were performed varying the iodine amount from 1.0 to 4.0 mol ratios and using water, MeCN, EtOH and the mixture EtOH:water (1:1) as solvents, without any base. The authors obtained lower yields when organic solvents were used, and the best yields were obtained using water as solvent and 4.0 mol ratios of iodine. When the iodine amount was reduced to 1.0 equivalent, the yields decreased significantly [4]. In a recent paper, Chen and coworkers [5] reported the iodocyclization of several 2-allylphenols using iodine in the mixture EtOH:water (1:9) as solvent and without $NaHCO_3$. The yields were in a 60–94% range, very similar to those obtained by Fousteris et al. [4] but using 1.2 equivalents of iodine. Since these data are not conclusive about the best conditions, a systematic investigation is necessary to better evaluate factors that could influence in this reaction.

In order to study the influence of the solvent and the need of $NaHCO_3$, a 2^2 full factorial design was performed, using the 2-allylphenol as reactant to obtain the 2-iodomethyl-2,3-dihydrobenzofuran **1a** (Scheme 1). Several examples of the factorial approach can be found in Fernandes and Felli [10], Britto et al. [11], Trossini et al. [12] and Santos and Castro [13].

In this work, the experiments were designed, randomized and performed according to the runs presented in Table 1. Yield determinations were done in duplicate to estimate the standard deviations. Analyzing standard errors results with a 95% confidence interval, both solvent and presence of $NaHCO_3$ had significant effects ($p<0.05$) on yields (Table 2). However, the interaction effect between the type of solvent and the presence of $NaHCO_3$ was not significant ($p>0.05$), as it can be stated by the nearly parallel fitness of the lines in Figure 3. Accordingly, the interaction effect can be considered negligible.

It was found that the solvent exerts the highest influence on yield. According to the analysis of the data presented in Table 2, the change from water to the EtOH:water (1:9) mixture has a negative effect on yield (about 15.5% lower), as it can be observed in the negative coefficient of the effect. Actually, Fousteris and coworkers [4] observed this effect before, when using EtOH alone or as a cosolvent in 1:1 mixtures with water, which were detrimental to the yields. The use of EtOH in this reaction can promote the ethoxylation as a competing reaction, producing the 2-(2-ethoxy-3-iodopropyl)phenol. This product was detected in TLC plates, developed using hexane:AcOEt (20:1) as eluent, with low R_f (personal data). However, the formation of the iodohydrin 2-(2-hydroxy-3-iodopropyl) phenol was not observed. Since the reactants have low solubility in water, the formation of iodohydrin is less favorable. When the EtOH:water mixture was used, the solubility of the reactants increased significantly, favoring the ethoxylation.

The presence of $NaHCO_3$ had a smaller but significant influence on the yields, as can be observed in data presented in Table 2. However, its influence was also negative

Table 2: Calculated effects and standard errors for 2^2 factorial design.

Effects	Estimate effect	Standard error[a]	p-Value
Global mean	74.8	±0.81	8×10^{-8}
Main effects			
Solvent	-15.5	±1.62	0.0007
Base	-9.0	±1.62	0.0051
Interaction effect			
Solvent×Base	-1.0	±1.62	0.5705

[a]Standard-error of effects were calculated using standard deviations presented in Table 1.

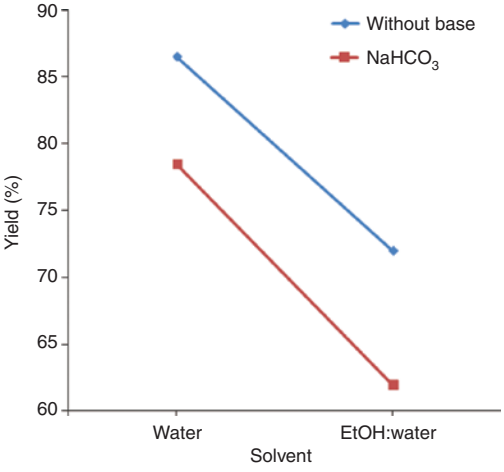

Figure 3: Interaction effect chart between solvent used and presence of base.

(9%). In a previous work [3], we reported the iodocyclization of 2-allylphenols using $NaHCO_3$ in addition to iodine, in CH_2Cl_2, obtaining adequate yields. Although the procedure leads to lower yields than those reported by Fousteris et al. [4] and Chen et al. [5], the nucleophilic attack by EtOH or water is avoided, giving a "cleaner" product. $NaHCO_3$ was added in order to deprotonate the phenolic hydroxyl group, increasing the nucleophilicity of the oxygen and the formation of the 2-iodomethyl-2,3-dihydrobenzofuran under less polar conditions. The use of $NaHCO_3$ in this reaction with polar solvents (such as water and EtOH) had not been reported to date.

The negative effect of the presence of the base can be explained by the increase of elimination rate of hydroiodide. It is well known that alkyl halides can undergo dehydrohalogenation reaction, mainly under basic conditions and mainly in polar solvents [8]. Polar solvents such as water and EtOH can better solvate the iodide ion than solvents such as CH_2Cl_2. Therefore, dehydroiodination is more prone to occur in polar conditions (mainly in protic solvents, such as water and EtOH) than in less polar conditions. The elimination product 2-methylbenzofuran was detected in all runs, but it had a higher relevance in the presence of $NaHCO_3$.

Since the interaction factor was considered negligible, the factors can easily be individually optimized, i.e. the optimized value for the factor "solvent" does not depend on the "base" factor. As can be seen in Figure 4, higher yields can be obtained simply using water as solvent and without $NaHCO_3$. Although it was observed before, Fousteris et al. [4] proposed a procedure using 4.0 equivalents of iodine to achieve 94% yield in 2 h reaction. When 1.0 equivalent of iodine was employed, the reaction time was increased to 4 h, yielding only 80%, and 84% using 1.5 equivalent of iodine. Chen et al. [5] performed the iodocyclization of 2-allylphenol using 1.2 equivalent of iodine and the mixture EtOH:water (1:9) as solvent, obtaining 70% yield in 12 h reaction. All reactions were done under heating (50°C).

In the procedure presented in this work, the iodocyclization of 2-allylphenol to 2-iodomethyl-2,3-dihydrobenzofuran **1a** was done using 1.1 equivalent of iodine, at room temperature in 4 h. With this procedure, we achieved yields varying from 60 to 87%. The highest yield was achieved when water was used as solvent, without $NaHCO_3$. Since less iodine was used, the procedure takes less sodium thiosulfate to reduce the iodine, in addition to room temperature condition, which can promote less energy consumption by avoiding heating and less water consumption regarding solvent cooling system. Thus, the procedure herein presented can satisfy the demands of

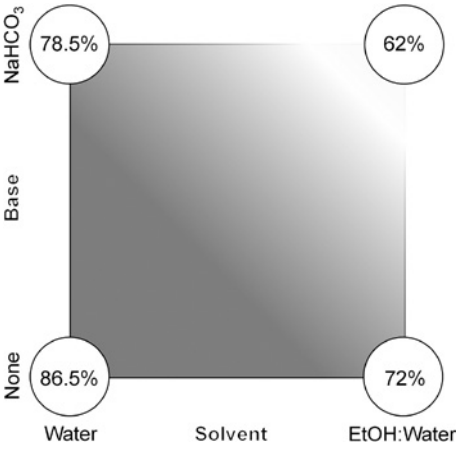

Figure 4: Square plot of the effects of the factors studied. The vertices are the obtained yields in each condition.

environmentally benign "green" chemistry [14] and can be considered very feasible and adequate.

To validate the conditions defined by the factorial design results, we performed the iodocyclization of several 2-allylphenols (**3b–e**) using water as solvent and without base (Figure 5). Using the conditions defined by the results of the factorial design, we achieved the 2-iodomethyl-2,3-dihydrobenzofurans **1b–e** with yields ranging from 10 to 90%. These yields were better when liquid 2-allylphenols were employed as starting materials. On the other hand, solid substrates led to poor yields. This variation can be attributed to the low solubility of the starting materials in water, which allowed adequate reactivity to liquid substrates but not to the solids.

In order to assess this, the iodocyclization reaction of the solid substrates **3b** and **3e** was conducted using the EtOH:water (1:9) as solvent, and the obtained yields were over 80% for both, although considerable amounts of ethoxylated products were found. Anyway, the used solvent mixture is environmentally better than the former used by us (CH_2Cl_2), as well as in absence of $NaHCO_3$ and in shorter reaction time. The synthesis of the allyl phenyl ethers **2b–e** was done using methodology adapted from Larghi and Kaufman [15], using allyl bromide and potassium carbonate in two equivalent molar ratio, which led to excellent yields. The Claisen rearrangement [8] of the obtained allyl phenyl ethers gave the corresponding 2-allylphenols **3b–e** in adequate yields, using Ph_2O as solvent in order to avoid solidification during the reaction course, especially when the desired products are solids. To obtain the liquid 2-allylphenols from the allyl phenyl ethers, the reactions can also be performed in neat conditions, avoiding the use of unnecessary solvents and improving the "greenness" of the whole process.

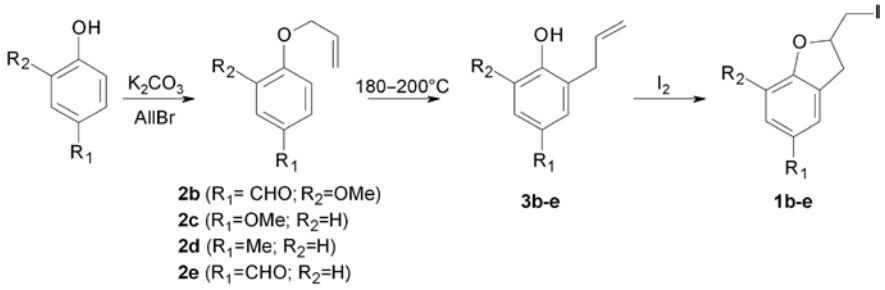

Figure 5: Synthesis of iodocyclized compounds **1b–e.**

4 Conclusion

In conclusion, the factorial design presented here provided a systematic evaluation of a "green" procedure to perform the iodocyclization of 2-allylphenols, saving reagents and energy and redefining the conditions previously reported in literature. The method can be widely applied to access the dihydrobenzofurans in good yields; however, high yields are only possible when liquid 2-allylphenols are used.

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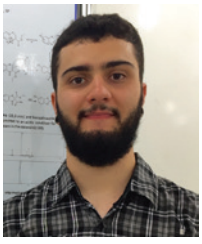

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