Reinvestigation of Alternative Method for the Preparation of Dibenz[*b*,*f*][1,4]oxazepine

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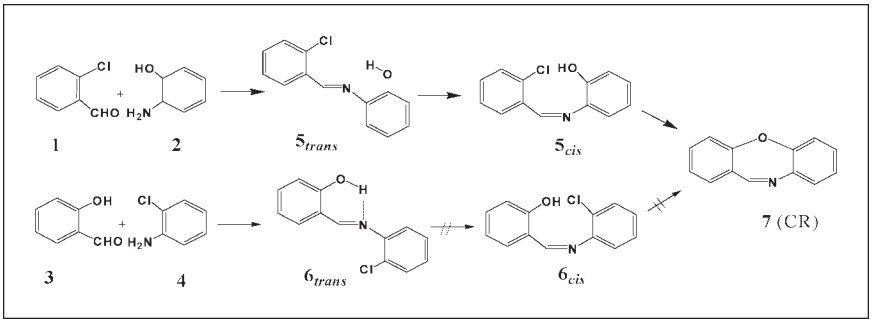

Two distinct alternative methods using different starting materials for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**, CR) were reinvestigated. The possibility of *trans-cis* conversion of the Schiff base **5** (produced from **1** and **2**) is considered the favorable orientation that leads to cyclization (production of **7**). Fluoro derivative of **1** afforded excellent and more convenient conditions for the one pot preparation of high yield pure **7**. The presence of only *trans* configuration for the imine **6** (produced from **3** with **4**) and the impossibility of its conversion to *cis*, makes it inadequate for the preparation of **7**.

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INTRODUCTION

Dibenz[*b*,*f*][1,4]oxazepine (**7**, CR) is an incapacitating lachrymatory agent [1–6] and is an intermediate in the synthesis of *loxapine* (antipsychotic), *amoxapine* (antidepressant) [7], and others substituted dibenzoxazepine compounds that are analgesic or useful for the treatment of different diseases [8–11].

Moreover, reduction of the imine group of dibenz[*b*,*f*][1,4]oxazepine and/or the oxidation of the same group to the imid afforded intermediates in the synthesis of several other compounds effective in the prevention and treatment of circulatory disease and osteoporosis [9,11].

There are different methods for the preparation of **7** [12–24]. Two pathways starting from different raw materials can be considered for the preparation of this compound (Schemes 1 and 2).

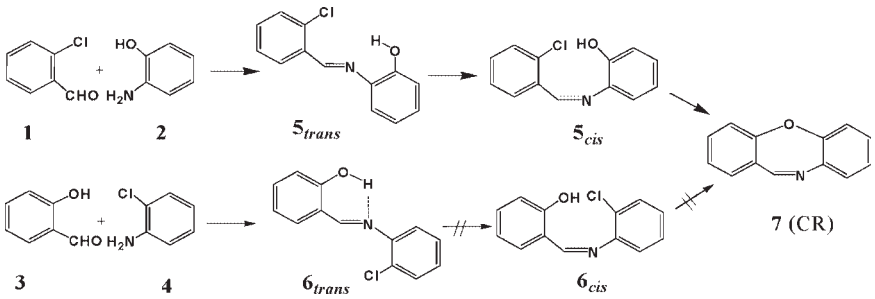
These methods are differentiated in the occurrence of either the imine reaction or etherification in the first step. Thus, in Scheme 1, dibenz[*b*,*f*][1,4]oxazepine is formed by the imine reaction followed by the etherification (cyclization), whereas in Scheme 2, etherification is followed by the imine reaction (cyclization). The two etherification and imine reactions each have limitations that influence the yield of the final product.

Firstly, the method proposed by Tambute [12,13] for the preparation of **7** involves the condensation of salicyl-aldehyde with 2-nitrochlorobenzene (Scheme 2). We have recently reported the effect of temperature and catalyst on the yields and rate of the etherification reaction between sodium salt of salicylaldehyde and 2-nitrochlorobenzene and have emphasized the harsh conditions necessary for the preparation of **7** by this method [22]. We have observed that the etherification reaction of 2-nitrophenol and 2-chlorobenzaldehyde does not occur under the same conditions and requires more difficult circumstances to be performed. This can be rationalized by the electrophilic effect of NO_2 group, which reduces the nucleophilic character of the hydroxy oxygen atom in 2-nitrophenol.

The formation of **7** *via* **1** and **2** (Scheme 1) has been reported recently [19,20], and the kinetic data have been investigated [17,18]. Other attempts to prepare **7** *via* cyclization of 2-[(2-fluorobenzylidene)amino] phenol (fluoro derivative of **5**) in ethanol with excess triethylamine were unsuccessful even after prolonged reflux. In contrast, the preparation of 1,2,3,4-tetrafluorobenzo[*b*,*f*][1,4]oxazepine (**10**) by cyclization of 2-[(2,3,4,5,6-pentaflurobenzylidene)amino] phenol (**8**) (Scheme 3) using the same conditions was successful, whereas the attempts to cyclize **9** into **11** failed [23].

The difference in reactivity between **8** and **9** has been justified by the necessity for the electrophilic arene to be a benzylidene and not a phenyl imine, that is, the

Scheme 1



electron-withdrawing —CH=N substituent enhances the susceptibility of C_6F_5 to nucleophilic attack, whereas the electron-donating —N=CH substituent has the opposite effect [23].

The last report on the synthesis of **7** was consisted in the reaction of 2-fluorobenzaldehyde (fluoro derivative of **1**) with 2-aminophenol using K_2CO_3 in polyethylene glycol (PEG-400) at 100°C, affording 89% of **7** after 8 h [24].

This contribution discussed the feasibility of two distinct pathway methods (Scheme 1) using different starting materials and passing by different intermediates for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**, CR).

RESULTS AND DISCUSSION

The preparation of **7** *via* 2-chlorobenzaldehyde (**1**) and 2-aminophenol (**2**) or salicylaldehyde (**3**) and 2-chloro-aniline (**4**) was reinvestigated (Scheme 1). Imine formation following both methods was nearly quantitative, and the water released in the course of the reaction did interfere with imine formation.

We have reported the results of GC, GC-MS, and ^{1}H NMR analysis of the imine products [25], according to which we have presumed the formation of $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ and only $\mathbf{6}_{trans}$ in solution.

The ^{13}C NMR spectrum $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ were similar and their mixture presented 13 resonances for carbon, but the chemical shift of imine proton (in ^{1}H NMR spectrum) was different. However, their MS fragmentation patterns were completely different (see Experimental Section). It is noteworthy that the X-ray crystallography of **5** indicates a unique *trans* configuration [25].

The retention time in GC and GC-MS, and fragmentation pattern of $\mathbf{5}_{trans}$ and $\mathbf{6}_{trans}$ were nearly similar else the more abundant peak (*m*/*z* (100%); 120 for $\mathbf{5}_{trans}$ and 196 for $\mathbf{6}_{trans}$). The occurrence of $\mathbf{5}_{cis}$ increases at high temperature (> 100°C) and with a catalytic amount of acid (H_2SO_4 98%).

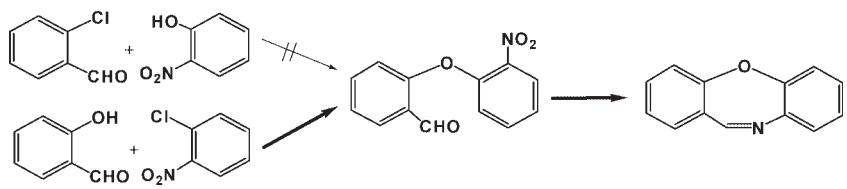
The effect of solvent and UV irradiation in the *trans-cis* transformation were also investigated, but complete conversion of $\mathbf{5}_{trans}$ to $\mathbf{5}_{cis}$ was never observed. In contrast, $\mathbf{6}_{trans}$ was not converted to $\mathbf{6}_{cis}$ under any conditions. The target product (**7**) was never obtained by cyclization of imine **6**. Thus, we presumed that apart from electronic parameters, the prevention of *trans-cis* conversion in **6** is another reason that the target product (**7**) was not obtained by cyclization of imine **6**. In fact, *trans-cis* isomerization can occur through the hemiaminal resulting from attack of the phenolic oxygen to the imine carbon, which is much easier in **5** (five-membered ring) than in **6** (four-membered ring).

The preparation of **7** *via* **1** and **2**, performed following several procedures, afforded different yields (Scheme 4).

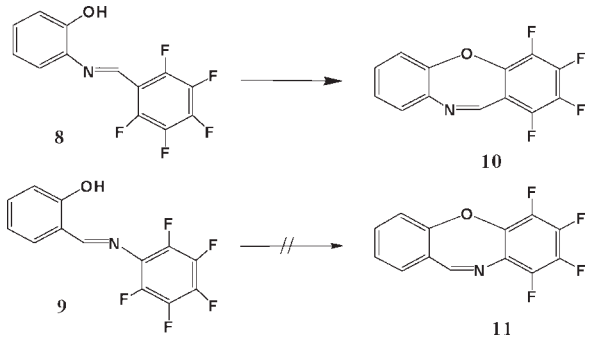
Reaction of **1** with **2** in DMSO at 150°C (the procedure B_1) afforded **7** in 25% yield. Following procedure B_3, the mixture of **1**, **2**, and KOH in CCl_4 are refluxed for 5 h and then after evaporation of solvent, DMSO was added, and the mixture was refluxed for 6 h to afford 50% of **7**.

According to the procedure B_2, when we used xylene as solvent, $\mathbf{5}_{cis}$ and $\mathbf{5}_{trans}$ were formed with proportional amounts of 12 and 88%, respectively. Heating the

Scheme 2



Scheme 3



solution at 120°C for 24 h changed the proportional amount of the two isomers in favor of *cis*, which afforded 75% of **7** after addition of Na and refluxing the reaction mixture. Without heating the solution, the attend product (**7**) was not formed. While when we used DMSO as solvent, prior conversion of *trans* to *cis* was not indispensable and the salt of **5** rearrange for the production of **7**.

Preparation of sodium salt of **2** and its subsequent reaction with **1** in DMSO at 150°C for 6 h (the procedure C) has yielded 47% of **7**.

The reaction conditions following the procedure A are more convenient (the time of reaction and the temperature), and pure products were formed after the first and second steps. In addition to good yield (70%), the formation of **7** following this method can be performed *via* a one-pot procedure (procedure B).

Our last tentative in the preparation of **7** was based on the usage of 2-fluorobenzaldehyde (a fluoro derivative of **1**) in conjunction with polyethylene glycol as was outlined recently [24]. 2-fluorobenzaldehyde is more expensive that **1** (7 fold) but the procedure offered soft conditions to obtain high-yield pure product. Simultaneous mixing of 2-fluorobenzaldehyde, 2-aminophenol (**2**), K_2CO_3 and PEG(300) (as was reported [24]) has not conducted us to the considered results. It seems that simultaneous addition of K_2CO_3 with other reactants causes formation of potassium salt of **2** which alter imine formation and its subsequent cyclization to **7**. In another attempt, 2-amino phenol was first dissolved in PEG(300) at 50°C and after addition of 2-fluorobenzaldehyde, the solution was stirred for 10 h at 50°C to complete imine (schiff base) formation. The production of **7** was accomplished after addition of K_2CO_3 and continuing the reaction for 10 h at 100°C (Scheme 5).

Thus, this procedure is slightly different from which previously proposed [24]. In this manner, the preparation of **7** was performed in one-pot two-step procedure following which preparation of imine in the first step was followed by the potassium salt formation of imine and its cyclization to produce **7** in the second step.

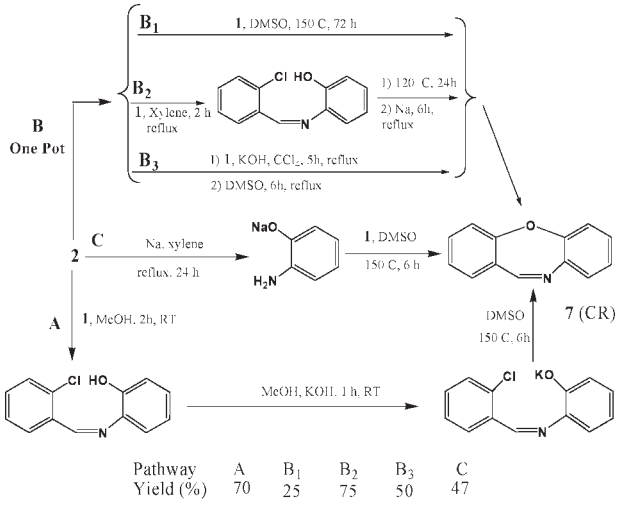
The time of reaction in the second step determined the yield of the final product. In fact, we have found that compound **7** is very temperature sensitive and at temperature higher than 100°C, the target compound decomposed and the yield decreased. Thus the time of reaction and the temperature in the second step should be controlled carefully.

The workup of the reaction mixture to obtain pure **7** was very simplified following this procedure. Effectively, the extraction with ether and several washing of organic phase with water, drying over $CaCl_2$ and striping of solvent afforded very pure product without need of further purification procedure.

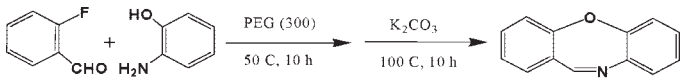
The reaction of **1** with **2** conducted under same conditions with PEG(300) has not afforded **7**. However, the usage of catalytic amount of KF (10 mol%) in the second step (after formation of imine in the first step) favors the formation of **7** (50%) but other experiments should be performed to optimize this method.

In summary, two distinct alternative methods (Scheme 1) using different starting materials for the preparation of dibenz[*b*,*f*][1,4]oxazepine (**7**) were reinvestigated. The imine reaction, according to these methods, occurs readily and yields of Schiff bases (**5**, its fluoro derivative, and **6**) are nearly quantitative. The possibility of *trans-cis* conversion of the Schiff base **5** were considered as favorable conditions that caused its cyclization (production of **7**). This reaction was performed following different procedures and various yields are obtained. The pathway A afforded more convenient and soft conditions for the production of pure **7** and its intermediates. Fluoro derivative of **1** afforded excellent, more convenient and soft conditions for the one-pot preparation of target compound (**7**). The presence of only *trans* configuration for the imine **6** (produced from **3** with **4**)

Scheme 4



Scheme 5



7 (CR), 89%

and the impossibility of its conversion to *cis*, makes it inadequate for the preparation of **7**.

EXPERIMENTAL

NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 62.5 MHz for ^{13}C), and $CDCl_3$ was used as solvent; chemical shifts are reported in δ (ppm) from TMS. Electronic ionization GC-MS spectra were recorded on a Varian (SATURN 4D) spectrometer with capillary column (DB-5MS, 0.1 micron, 30 m × 0.250 mm). Only *m*/*z* values having intensities of more than 10% are given and retention times are reported using temperature programming (100–250°C, 10°C/min) with He flow rate of 10 mL/min. Melting points were obtained on a Mettler FP61 apparatus.

Preparation of 5. 2-Aminophenol (22 g, 0.2 mol) and MeOH (200 mL) were placed in a 300-mL, one-necked flask equipped with a mechanical stirrer. The solution was stirred at 50°C for 30 min. After complete dissolution of 2-aminophenol in MeOH, 2-chlorobenzaldehyde (28 g, 22.5 mL, 0.2 mol) was added, and the mixture was stirred for 2 h at RT. The precipitates formed were filtrated at 0°C and dried to offered 39 g of **5** (84% yield) as an orange solid, mp. 97–99°C.^{1}H NMR ($CDCl_3$): δ 6.89–7.42 (m, 8H, CH), 8.20 (d, $^4J_{H-H}$ = 2.5 Hz, 1H, CHN_{trans}), 8.23 (m, 1H, CHN_{cis}), 9.15 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 115.2, 116.2, 120.2, 127.2, 128.3, 129.5, 130.2, 132.4, 132.9, 135.4, 136.2, 152.6, 153.4. *Anal*. Calcd for $C_{13}H_{10}NOCl$: C, 67.39; H, 4.32; N, 6.05. Found: C, 68.38; H, 4.19; N, 6.18. GC: retention time: 28 min (***5*****$_{cis}$**) and 38 min (***5*****$_{trans}$**). GC-MS of ***5*****$_{cis}$**: retention time: 12.3 min; *m*/*z* (intensity (%)): 50 (11), 63 (51), 64 (25), 75 (11), 92 (13), 166 (19), 201 (25), 229 (100), 230 (20), 231 (38). GC-MS of ***5*****$_{trans}$**: retention time: 13.6 min; *m*/*z* (intensity (%)):50 (13), 51 (16), 63 (19), 65 (29), 75 (11), 89 (11), 93 (16), 102 (10), 120 (100), 196 (24), 230 (18), 231 (33), 232 (25), 233 (18), 234 (12).

Preparation of 6. 2-Chloroaniline (12.8 g, 10.6 mL, 0.1 mol) salicylaldehyde (12.2 g, 10.4 mL, 0.1 mol) and xylene (10 mL) were placed in a 100-mL, one-necked flask equipped with a magnetic stir bar. The mixture was stirred at RT for 12 h. Evaporation of solvent and water afforded 21.9 g of ***6*****$_{trans}$** (95% yield) as a yellow-orange solid, mp. 86.5–87°C. ^{1}H NMR ($CDCl_3$): δ 6.9–7.5 (m, 8H, CH), 8.61 (s, 1H, CHN), 13.2 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 117.5, 119.1, 119.2, 127.7, 127.8, 129.6, 130.2, 132.6, 133.7, 144.8, 161.4, 163.2. GC: retention time: 38 min. GC-MS: retention time: 13.5 min; *m*/*z* (intensity (%)): 50 (13), 51 (21), 63 (12), 75 (22), 77 (12), 111 (14), 167 (16), 168 (14), 196 (100), 197 (15), 230 (11), 231 (57), 232 (40), 233 (25), 234 (13).

Preparation of 7 *via* 5. The sodium salt of **5** (25 g, 0.1 mol)—prepared by addition of **5** (23.2 g, 0.1 mol) to a methanolic solution of KOH (5.6 g, 0.1 mol in 70 mL of MeOH) followed by evaporation of solvent and drying the precipitate formed—and DMSO (100 mL) were placed in a 250-mL, glass pressure autoclave equipped with a magnetic stir bar. The mixture was stirred at 150°C for 6 h. Then the mixture was washed with water (2 × 10 mL) and extracted by toluene (3 × 10 mL). Vacuum stripping of solvent and recrystalization from benzene afforded **7** as an orange solid mp. 67–70°C, lit. [14–16] mp. 71–72°C, lit. [12] mp. 68–74°C. ^{1}H NMR ($CDCl_3$): δ 7–7.5 (m, 8H, CH), 8.52 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$): δ 119.6, 120.3, 124, 124.6, 126.3, 127.7, 128.2, 129, 132.3, 139.5, 151.6, 159.4, 159.5, in agreement with literature [26]. *Anal*. Calcd for $C_{13}H_9NO$: C, 80.00; H, 4.61; N, 7.18. Found: C, 79.23; H, 4.42; N, 7.04. GC-MS: retention time: 10.2 min; *m*/*z* (intensity (%)): 50 (11), 51 (16), 63 (16), 139 (27), 140 (13), 166 (29), 167 (55), 195 (100), 196 (24) (lit.[27] 139 (25), 167 (52), 195 (100)).

One-pot preparation of 7 *via* fluoro derivative of 1. 2-aminophenol (5.5 g, 0.05 mol) and PEG(300) (100 mL) were placed in a 200-mL, one-necked flask equipped with a mechanical stirrer. The solution was stirred at 50°C for 30 min. After complete dissolution of 2-aminophenol in PEG(300), 2-fluorobenzaldehyde (6.82 g, 5.77 mL, 0.055 mol) was added and the mixture was stirred for 10 h at 50°C. Finally, K_2CO_3 (6.9 g, 0.05 mol) was added and the mixture was stirred again for 10 h at 100°C. Extraction with ether (4 × 50 mL), several washing of organic phase with water (5 × 200 mL), drying the organic phase over $CaCl_2$ and evaporation of solvent afforded very pure product **7** (7.8 g, 80% yield) as an orange solid.

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