Improved Etherification Procedure for the Preparation of Dibenz[*b*,*f*][1,4]oxazepine

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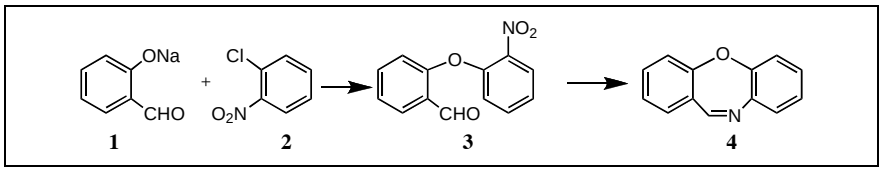

The effect of temperature and catalyst on the yield and rate of the etherification reaction between **1** and **2** was investigated and alternative methods for separation of **3** and **4** from the reaction mixture have been described.

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INTRODUCTION

Dibenz[*b*,*f*][1,4]oxazepine (**4**) is an incapacitating and a lachrymatory agent [1-6]. It is chemically related to *loxapine* (antipsychotic), *amoxapine* (antidepressant) [7] and others substituted dibenzoxazepine compounds that are analgesic or useful for the treatment of various diseases [8-10]. There are different methods for the preparation of this compound [11-19]. Tambute *et al.* described the use of 1-chloro-2-nitrobenzene and salicylaldehyde as starting materials for the preparation of **4** by a two-step reaction [11] (etherification and reductive cyclization) or by a three-step reaction (etherification, ketalization and reductive cyclization) [12].

Aryl etherifications require long periods of heating and several procedures under different conditions [phase-transfer-catalyst, ionic liquid, copper salt catalyst (Ullmann synthesis), *etc*.] have been studied [20-22].

RESULTS AND DISCUSSION

We have preliminary performed the etherification step by refluxing the mixture of salicylaldehyde with **2** (200 mol %) in the presence of K_2CO_3 in DMF (the procedure of Tambute *et al*. [11]) for 6 h and obtained 2-(2-nitrophenoxy)benzaldehyde (**3**) in 15% yield. Even the use of benzyltriethylammonium chloride in conjunction with NaOH in a two-phase solvent system (H_2O/CH_2Cl_2) was unsuccessful for the preparation of **3**. The two-step reaction of sodium salt of salicylaldehyde (**1**) with 1-chloro-2-nitrobenzene (**2**) (etherification and reductive cyclization) for the preparation of **4** was investigated. Special attention was paid to determine optimized conditions (temperature, time of reaction and catalyst) for the etherification step and formation of **3**. The sodium salt of salicyladehyde (**1**) was prepared as a yellow fluorescent solid by the addition of salicylaldehyde to a saturated methanolic solution of sodium methoxide. The etherification of **1** with **2** in equimolar amount was performed in DMSO at different temperatures (T> 200°C) in a pressure glass autoclave and the yield was determined by weighting the crude product after washing the reaction mixture with water and extraction into diethyl ether (Table 1, experiments 1-6). The use of DMSO (bp 189°C) favored completion of the reaction at temperature higher than 200°C using a pressure glass autoclave.

We observed a strong temperature dependence of the etherification reaction rate between **1** and **2**. At temperatures higher than 100°C, a resinous component was formed, the amount of which increased with reaction time. A temperature between 200 and 300°C was favorable for the rapid etherification with high yields. At temperatures lower than 200°C, the reaction rate was very slow and at temperatures higher than 300°C, the reaction mixture decomposed to undesirable components and low yields of **3** was obtained.

Other etherification attempts were studied using CuCl or CuO as catalyst and the yield of **3** was determined by GC (Table 1, Experiments 6-9). CuCl seems to be an adequate catalyst in a reasonable time at 120°C and at reflux temperature with a minor amount of resinous component in the reaction mixture. Compound **1** was thermally unstable and decomposed to a black solid in contact with air moisture and thus should be used freshly prepared and in excess amount in the etherification reaction with **2** at high temperatures.

Separation of **3** from the reaction mixture was achieved either by washing the reaction mixture with water and extraction of **3** from the residue with ether or by addition of the reaction mixture to a large amount of water (10 fold of volume of DMSO used) followed by adjustment of the pH to 9 by addition of 1 mg solid NaOH and separation of the precipitate formed.

Reductive cyclization of **3** (second step) was performed by the classical method proposed by Tambute *et al.* [11]

Table 1

Temperature and Catalytic Effect on the Etherification Reaction Between **1** and **2**.

Expt[a]	Catalyst (mol%)	Temperature (°C)	Reaction time (hr.)	Yield[b] (%)
1	--	200	10	91
2	--	250	5	74
3	--	300	3	86
4	--	350	7	30
5	--	400	1	41
6	CuCl, 10	reflux	3	74
7	CuCl, 10	120	16	86
8	CuO, 10	120	24	50
9	--	120	24	35

a) Equimolar amounts of **1** and **2** (in 0.01 molar scale) with 5 mL of DMSO as solvent were used in all experiments. b) In experiments 1-6, Reaction was performed in a pressure glass autoclave and the yields were expressed as the crude product weighted after washing the reaction mixture with water, extracting **3** with diethyl ether and evaporation of solvent. In experiments 6-9 the yields were expressed as the proportional surface area of **3** after GC analysis of the reaction mixture.

(Experimental Section). Performing the separation of **4** from the reaction mixture, without neutralization of the reaction mixture as suggested by some authors [11], afforded a purer product. Surprisingly, the solvent of choice that caused separation of pure **4** (mp 68°C) was carbon tetrachloride where **3** and resinous residues have low solubility. This property can also be used to obtain purer **3**, free of **2** (which is very soluble in CCl_4), by washing the product obtained in the first step with CCl_4. It is to be noted that the previous reports [11,13] suggested the purification of **4** by distillation [11] (bp 125 °C/0.2 mmHg) or by chromatography on silica gel column using benzene as eluent [13].

The ^{1}H NMR spectra of **3** and **4** are presented in Figure 1. The chemical shift of the aldehyde proton in **3** (at δ 10.5) and the imine proton in **4** (at δ 8.5) are characteristic of these two compounds. We observed distinct signals for the aryl protons of **3**, but the same protons in **4** showed a complex signal between δ 7.13-7.45 in agreement with those reported in literatures [12,13,23].

In summary**,** the effect of temperature and catalyst on the yield and rate of the etherification reaction between **1** and **2** was investigated and alternative methods for separation of **3** and **4** from the reaction mixture have been described. A temperature between 200 and 300°C was favorable for the rapid and high yield etherification between **1** and **2** using DMSO as solvent in a pressure autoclave. CuCl seem to be an adequate catalyst for the etherification reaction between **1** and **2** in a reasonable time at 120°C and at reflux temperature. Carbon tetrachloride is an appropriate solvent to obtain pure **4** and **3** without need of purification procedures (distillation, crystallization or column chromatography).

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 x 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.

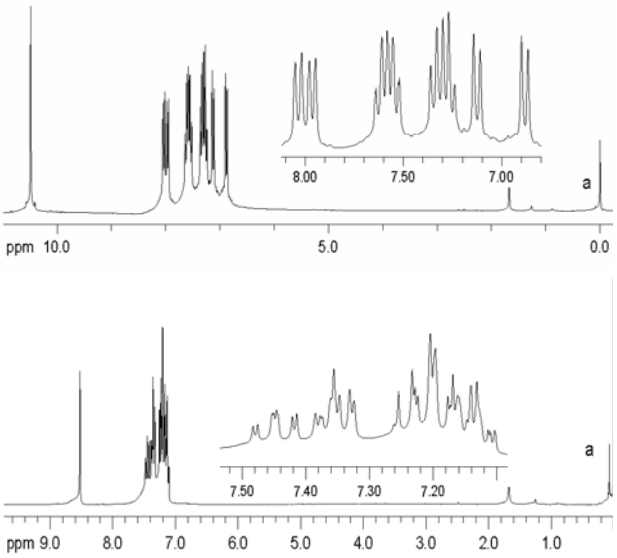

Figure 1. ^{1}H NMR Spectra (in CDCl3) of **3** (a) and **4** (b).

Preparation of 2-(2-nitrophenoxy)benzaldehyde (3). The freshly prepared sodium salt of salicylaldehyde (79 g, 0.55 mol), 1-chloro-2-nitrobenzene (78.5 g, 0.50 mol) and DMSO (200 mL) were placed in a 1000-mL, one-necked flask equipped with a two-inch magnetic stir bar. The mixture was stirred at 120°C for 72 h. After cooling, it was added to 2 L of water and the pH was adjusted to 9 by addition 1 mg solid NaOH. The precipitated brown solid crude product (90.9 g, 75%) was collected and air-dried. Crystallization of the precipitate from *n*-heptane afforded very pure yellow-orange needled solid of **3**, mp 80-81°C, lit. [12] mp 77-78°C . ^{1}H nmr ($CDCl_3$): δ 6.88 (d, $^3J_{H-H}$

= 8.2 Hz, 1H, CH), 7.12 (d, $^3J_{H-H}$ = 8.2 Hz, 1H, CH), 7.27 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 7.33 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 7.55 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 7.61 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 7.96 (d, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 8.35 (d, $^3J_{H-H}$ = 7.5 Hz, 1H, CH), 10.49 (s, 1H, CHO). ^{13}C nmr ($CDCl_3$): δ 118, 121.7, 124.5, 124.8, 126.2, 126.9, 129, 134.7, 135.9, 141.6, 149.4, 158.4, 188.6. GC-ms: retention time: 14.3 min; m/z (intensity (%)): 50 (14), 51 (26), 63 (32), 65 (11), 92 (30), 115 (31), 120 (10), 139 (45), 168 (46), 182 (27), 196 (16), 197 (31), 198 (100), 199 (15), 226 (22), 244 (10).

Preparation of Dibenz[b,f][1,4]oxazepine (4). Sulfuric acid (25%, 100 mL) was added dropwise to a mixture of **3** (10.23 g, 0.07 mol), iron powder (23.1 g, 0.42 mol), methanol (35 mL) and H_2O (35 mL) in a 250-mL, two-necked flask equipped with an addition funnel and a mechanical stirrer. The mixture was stirred at reflux temperature for 6 h and then was extracted by $CHCl_3$ (200 mL). The crude viscous product obtained after vacuum stripping was extracted into CCl_4 (2 x 50 mL) and, after evaporation of solvent, pure **4,** mp 68-69°C was obtained, lit. [13-15] mp 71-72°C, lit. [11] 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 [24]. 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.[25] 139 (25), 167 (52), 195 (100)).

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