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LEWIS ACID-CATALYZED FORMYLATION REACTION OF 4-(PIPERAZIN-1-YL)PHENOLS §

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Abstract – The Lewis acid-catalyzed reaction of phenols **1** with paraformaldehyde in aprotic solvents affords good yields of salicylaldehydes **2**.

The introduction of a formyl group in aromatic compounds is an important reaction in synthetic organic chemistry, and can be achieved in many ways.[1,2] On the contrary, few substituted salicylaldehydes are available even though they are useful intermediates in the preparation of a variety of oxygen containing heterocyclic derivatives and biologically active substances.

The direct formylation of phenols is the simplest means of obtaining salicylaldehydes, but there is no method of synthesizing 2-hydroxy-5-(piperazin-1-yl)benzaldehydes,[3-5] which bear a piperazine residue and are used in medicinal chemistry[6] and in the preparation of 5-{4-[4-(5-cyano-1*H*-indol-3-yl-)-butyl]-1-piperazinyl}-2-benzofuranecarboxyamide (*Vilazodone*),[7] a dual serotonin 5-HT re-uptake inhibitor and 5-HT_{1A} receptor agonist. When *Vilazodone* is synthesized,[8] the piperazine residue is introduced *via* a Buchwald-Hartwig amination (BHA) reaction on 5-bromosalicylaldehyde or 5-bromo-2-carbetoxybenzofuran (Scheme 1).

Because of our interest in structurally modifying *Vilazodone*, we prepared 2-hydroxy-5-(piperazin-1-yl)benzaldehydes **2,** using a different approach which, by starting from the corresponding 4-(piperazin-1-yl)phenols **1** and using a direct formylation reaction, avoids the need for an expensive palladium catalyst and phosphine ligands.[8]

§ This paper is dedicated to Prof. Victor Snieckus in the occasion of his 77th birthday.

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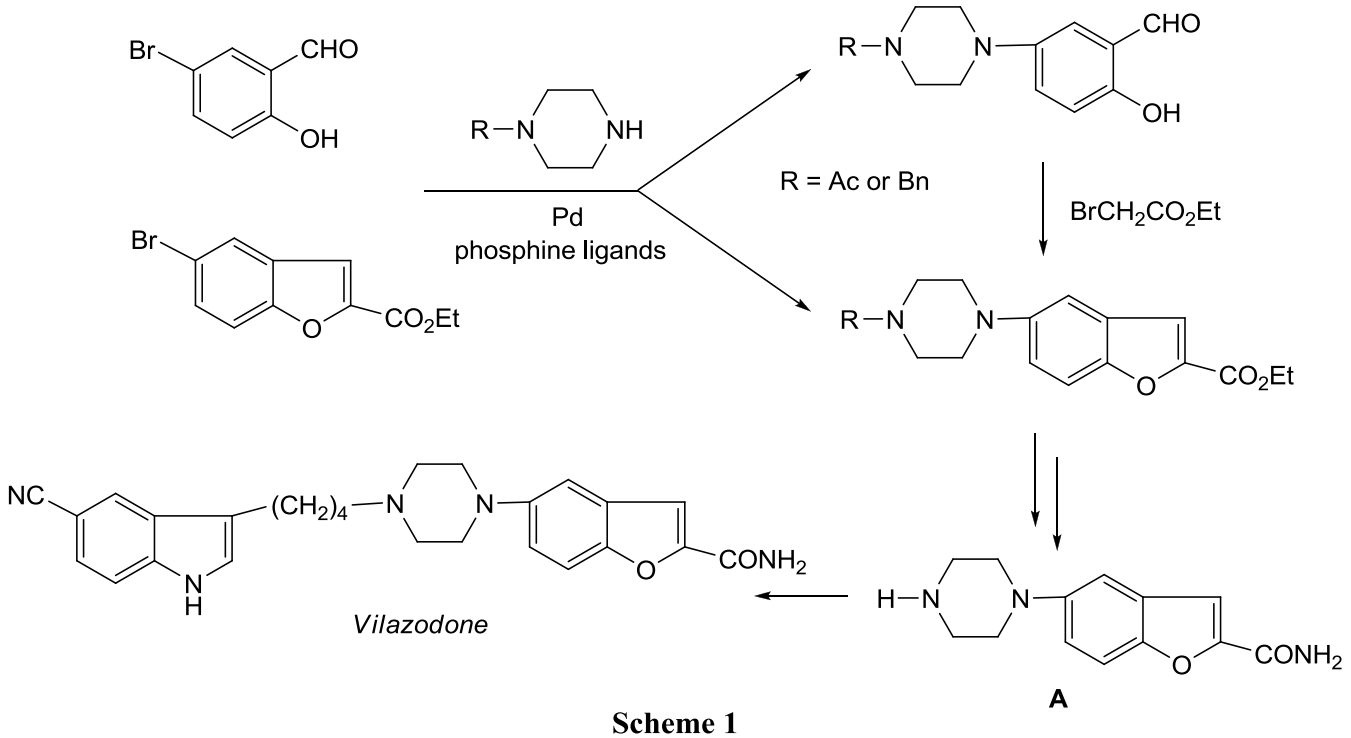
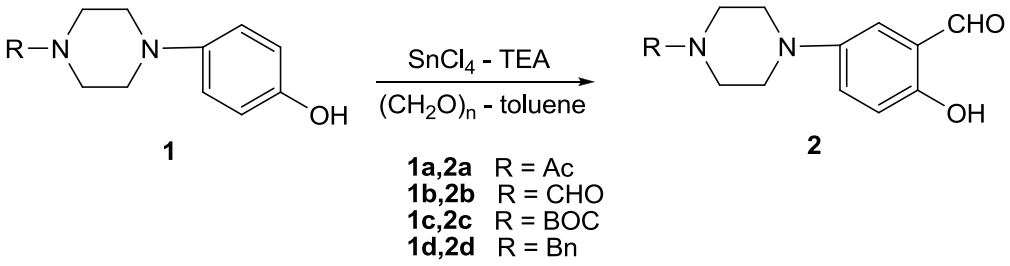


Scheme 1

After a number of trials in basic medium had led to poor results, we decided to test a formylation reaction catalyzed by Lewis acids (Scheme 2).



Scheme 2

The general procedure involves the sequential addition of a Lewis acid, triethylamine and paraformaldehyde to a suspension of phenols **1** in toluene or THF or acetonitrile. As described in the experimental section, the work-up is simple and allows the recovery of products **2a-d** in fair to good yields. The best conversion was reached using the following molar ratios: phenol/Lewis acid/TEA/paraformaldehyde = 1/0.3/1.2/2.

The tested Lewis acids were tin tetrachloride, iron trichloride, aluminium trichloride, silicon tetrachloride and magnesium dichloride, but by far the most satisfactory was tin tetrachloride.

The structural assignments of aldehydes **2a-d** were based on spectral and analytical data, and comparisons with authentic samples. Although the preparation of **2c,d** is reported in a patent,[8] no spectroscopic data are provided.

The formation of **2** can be rationalized on the basis of the behaviour of phenols towards Lewis acids and formaldehyde as previously proposed.[3] This mechanism involves a six-membered tin complex in which the metal co-ordinates the phenol and formaldehyde by directing the reaction to the *ortho*-position. Finally, a tin tetrachloride-assisted redox reaction between a 2-hydroxymethylphenol intermediate and formaldehyde leads to **2**. Also in our case, the mechanism is confirmed by the isolation of the intermediate 4-(4-benzylpiperazin-1-yl)-2-hydroxymethylphenol **3**, (the precursor of aldehyde **2d**), when the reaction time is shortened. As expected, the treatment of **3** with MnO_2 in CH_2Cl_2 solution gives **2d**.

As in the case of the previously procedure,[8] aldehydes **2a,d** could be transferred into 5-(piperazin-1-yl)benzofuran-2-carboxyamide **A**, the key intermediate of *Vilazodone* (Scheme 1).

EXPERIMENTAL

Melting points were determined on a *Büchi* B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department. ^{1}H NMR spectra were recorded in $CDCl_3$ solution (unless otherwise indicated) using a *Varian-Gemini 200 MHz* spectrometer, and chemical shifts are given in ppm relative to TMS. The MS spectra were recorded with a *Thermo-Finnigan LCQ* advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. 4-(Piperazin-1-yl)phenols **1a**,[9] **1b**[9] and **1d**[10] were prepared according to the reported procedures. **1c** is commercially available.

Preparation of aldehydes (2): general procedure. To a stirred suspension of **1** (20.0 mmol) in toluene (40 mL), tin tetrachloride (6.0 mmol) (1M solution in CH_2Cl_2) was added, followed, after 30 min, by TEA (24.0 mmol). The mixture was stirred for 30 min at rt, then paraformaldehyde (40.0 mmol) was charged. The reaction mixture was heated at 110 °C for 7/8 h, then cooled to 80 °C and treated with water (40.0 mL) and AcOEt (20 mL). After stirring for 1 h the mixture was filtered through Celite, the organic layer separated, dried (Na_2SO_4) and the solvent evaporated. The crude residues were purified by column chromatography (SiO_2, AcOEt/EtOH : 90/10) (**2a**,**b**) or by crystallization (**2c**,**d**).

5-(4-Acetylpiperazin-1-yl)-2-hydroxybenzaldehyde (2a). Light yellow solid, mp 120-122 °C (AcOEt). Yield 72%. ^{1}H NMR δ: 2.18 (s, 3H, CH_3); 3.2 (m, 4H, piperazine H-2, H-6); 3.8, 3.9 (m, 4H, piperazine H-3, H-5); 6.8-7.1 (m, 3H, Ar); 9.82 (s, 1H, OH); 10.72 (s, 1H, CHO). MS (EI) *m/z* = 248 [M^+]. *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.66; H, 6.42; N, 11.05.

4-(3-Formyl-4-hydroxyphenyl)piperazine-1-carbaldehyde (2b). Yellow solid, mp 118-120 °C (AcOEt). Yield 76%. ^{1}H NMR δ: 3.0 (m, 4H, piperazine H-2, H-6); 3.5, 3.8 (m, 4H, piperazine H-3, H-

5); 6.8-7.25 (m, 3H, Ar); 8.15 (s, 1H, N-CHO); 9.82 (s, 1H, OH); 10.72 (s, 1H, CHO). MS (EI) *m/z* = 234 [M^+]. *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.48; H, 5.92; N, 11.88.

***tert*-Butyl 4-(3-formyl-4-hydroxyphenyl)piperazine-1-carboxylate (2c).** Solid, mp 82-84 °C (cyclohexane). Lit.[8] 84-86 °C. Yield 78%. ^{1}H NMR δ: 1.5 (s, 9H, *tert*-butyl); 3.08 (m, 4H, piperazine H-2, H-6); 3.62 (m, 4H, piperazine H-3, H-5); 6.9-7.2 (m, 3H, Ar); 9.82 (s, 1H, OH); 10.8 (s, 1H, CHO). MS (EI) *m/z* = 306 [M^+].

5-(4-Benzylpiperazin-1-yl)-2-hydroxybenzaldehyde (2d). Light yellow solid, mp 100-102 °C (*i*-Pr_2O). Lit.[8] 101-103 °C. Yield 80%. ^{1}H NMR δ: 2.6 (m, 4H, piperazine H-3, H-5); 3,12 (m, 4H, piperazine H-2, H-6); 3.58 (s, 2H, CH_2); 6.9-7,4 (m, 8H, Ar); 9.8 (s, 1H, OH); 10.6 (s, 1H, CHO). MS (EI) *m/z* = 296 [M^+].

4-(4-Benzylpiperazin-1-yl)-2-hydroxymethylphenol (3). Following the general procedure for the preparation of aldehydes **2**, the heating was shortened to 4 h. After the work-up described, the crude reaction mixture was chromatographed (SiO_2, AcOEt/EtOH : 90/10) to give **2d** (yield 40%) and **3**. Solid, mp 190-192 °C (AcOEt). Yield 30%. ^{1}H NMR (DMSO) δ: 2.5 (m, 4H, piperazine H-3, H-5); 3.0(m, 4H, piperazine H-2, H-6); 3.49 (s, 2H, CH_2-Ar); 4.4 (d, 2H, *J* = 5.5 Hz, CH_2O); 4.87 (t, 1H, *J* = 5.5 Hz, OH); 6.6-7.0 (m, 3H, Ar); 7.3 (s, 5H, Ar); 8.71 (s, 1H, OH). MS (EI) *m/z* = 298 [M^+]. *Anal.* Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.28; H, 7.42; N, 9.32.

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