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A NEW APPROACH TO THE BENZOPYRIDOXEPINE CORE BY METAL MEDIATED INTRAMOLECULAR BIARYL ETHER FORMATION

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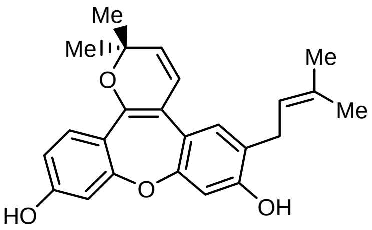
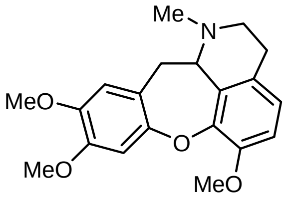
Abstract – This paper presents a concise synthesis of the novel [1,3]dioxo[*d*]benzoxepino[2,3-*c*]-6-bromopyridine **1**. The benzopyridoxepine core has been obtained by intramolecular coupling of a benzopyridylethene that is in turn obtained from the Wittig reaction. Thus, the synthesis was accomplished in a very good yield by implementation of an intramolecular palladium-catalyzed biaryl ether formation (Buchwald-Hartwig type reaction). An alternative approach based on the copper-mediated C-O bond formation (intramolecular Ullmann reaction) was not successful.

INTRODUCTION

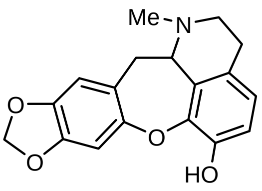
The synthesis of dibenzo[*b*,*f*]oxepine ring was first reported by Manske in 1950 and was later synthesized by Bestmann.[1a] Recently, a large number of dibenzoxepine compounds exhibiting a wide range of biological properties have been reported,[1] and the dibenzo[*b*,*f*]oxepine derivatives containing a fused *N*-heterocyclic ring being the latest studied in this group. This kind of tetracyclic compounds such as maroxepine, savoxepine, beloxepine or ORG 5222 showed an improved tolerance and potent activity compared with other classical antipsychotics.[1d,1e] There are only a few dibenzo[*b*,*f*]oxepine natural products containing a fused heterocyclic ring such as artocarpols or the alkaloids from the cularine group (e.g. cularine, cularimine, cularidine, cularicine). The artocarpol A and other members of this family have notable anti-inflammatory properties.[1f, 2] Some of the alkaloids of the cularine group (e.g. cularine) were found to have significant antifungal activity on Candida albicans and they also exhibited a selective inhibition against the RNA virus Parainfluenza (PI-3).[3a-c]



artocarpol D

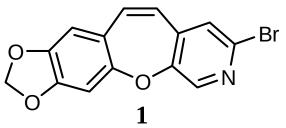


cularine



cularicine

Inspired from the structure of cularicine and other biologically active natural alkaloids possessing a benzodioxol ring in their molecule (e.g. chelerythrine, decarine, fagaridine, nitidine, toddaquinoline, etc.) and taking into account the important role played by the *N*-heterocycle present into the structure of the newly tetracyclic dibenzo[*b,f*]oxepines and the cularine alkaloids mentioned before, we engaged in the synthesis of a tetracycle type **1** planning a challenging approach to benzopyridoxepine ring via a final metal mediated biaryl ether coupling reaction. We engaged in the synthesis of benzopyridoxepine ring with the aim to study the feasibility of benzene-pyridine metal-mediated intramolecular coupling reaction and also to explore their biological properties.



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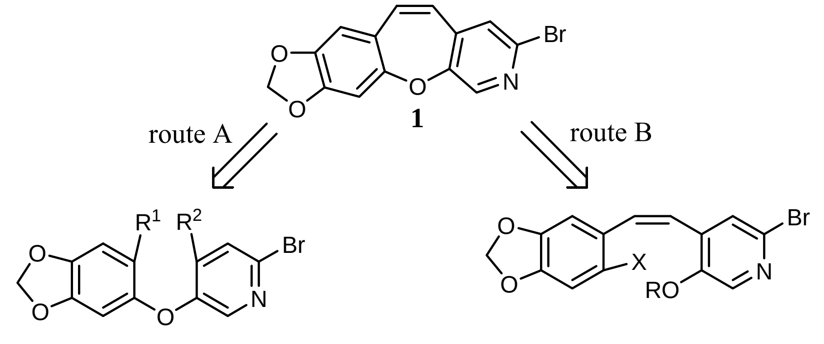
There has been an increased interest in the synthesis of benzopyridoxepines because of their potential application in pharmaceutical industry, as reflected by a large number of patents. In fact, the latest pharmacological tests show that the compounds possessing the benzopyridoxepine core can find application as inflammation inhibitors,[4a-d] chemokine receptor antagonists useful in the treatment of diseases associated with aberrant leukocyte recruitment and/or activation,[4e-f] antiasthmatics and respiratory tract hypersensitiveness inhibitors,[4g] opioid receptor antagonists for the treatment of obesity[4h] or as compounds useful for the treatment of neurological and vascular disorders related to β-amyloid generation and aggregation.[4i]

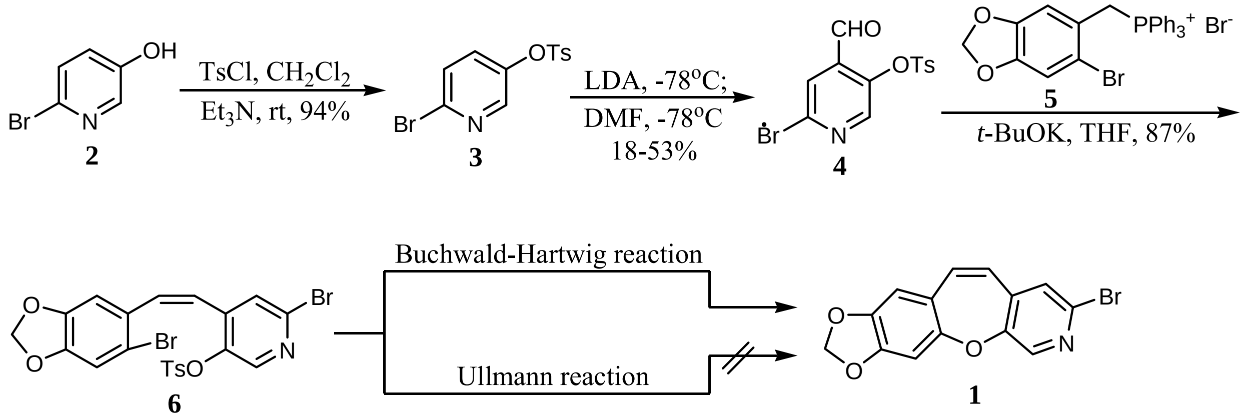
RESULTS AND DISCUSSIONS

The benzopyridoxepine ring could be obtained following two main strategies: synthesis based on the use of starting materials possessing a preformed biaryl ether framework (Scheme 1, route A) and synthesis by intramolecular coupling of benzopyridylethenes that are in turn obtained from the Wittig reaction (Scheme 1, route B). The literature data revealed that the synthesis of benzopyridoxepine derivatives is made by classical method using the route A. Thus, cyclodehydration of phenoxypyridylacetic acid derivatives[4a-4d] or azlactonization of phenoxynicotinaldehyde followed by ring-closure under strongly acidic conditions[4i] are the most commonly used methods for the preparation of benzopyridoxepine derivatives.

The palladium-catalyzed C-O bond forming procedure (Buchwald-Hartwig type reaction) and the copper-mediated C-O bond formation (intramolecular Ullmann reaction) were studied to the preparation of benzopyridoxepine ring **1**. To the best of our knowledge, these methods were not applied yet to the synthesis of benzopyridoxepine ring. The synthetic pathway carried out is outlined in Scheme 2.



Scheme 1. Retrosynthesis of compound **1**



Scheme 2. Synthetic pathway for compound **1**

Thus, the starting material **6** for the intramolecular coupling reaction was synthesized as follows. The *ortho*-lithiation with LDA of 2-bromo-5-hydroxypyridine **2** after protection of hydroxyl group as tosyl[5] followed by electrophilic substitution with DMF provided the aldehyde **4**.[6-8] The formylation of 2-bromo-5-tosyloxypyridine **3** proved to be troublesome in the beginning. Since in our previous studies the formylation of pyridine ring worked very well when 3 eq LDA/4 eq DMF/THF/-78 °C were used,[9] in this case the first trying using the mentioned conditions did not give the expected product except to recover the starting material in a very high yield (table 1, run 1). Even increasing the reaction temperature (-80 °C → -40 °C) did not give a better result (run 2) and increasing the amount of deprotonation agent to

10 eq of LDA, the reaction proceeded in one case (run 3). When the reaction conditions of run 3 were applied again, the result could not be reproduced in the next experiments. Only when a different solvent (THF→ether) and increased amounts of deprotonation agent/formylation agent were used, the formyl compound was obtained in a moderate yield (run 4-6). The position of formyl group of the compound **4** was assigned by one- (^{1}H-NMR, ^{13}C-NMR) and two-dimensional experiments (Heteronuclear Multiple Bond Correlation HMBC). Thus, the ^{1}H-^{13}C long range correlations of compound **4** found by HMBC analysis showed the correlation of formyl hydrogen with C_3, C_4 and C_5 of the pyridine ring.

Table 1. The results of the formylation of compound **3**

Run	LDA (eq/time)	DMF (eq/time)	solvent	temp (°C)	yield (%)	
					3	**4**
1.	3/1h	4/1h	THF	-78	96	-
2.	3/2h	4/1.5h	THF	-40	97	-
3.	10/1.5h	4/1h	THF	-80	-	43
4.	10/1.5-2h	4/1h	ether	-75	43	18
5.	10/2h	6/1h	ether	-78	-	43
6.	10/1.5-2h	8/1h	ether	-80	-	53

After the coupling of the phosphonium salt **5**[10] with the formylpyridine **4** under the standard Wittig conditions, the *Z*-alkene **6** was obtained as a single izomer in a very good yield.

The biaryl coupling reaction of **6** to [1,3]dioxo[*d*]benzoxepino[2,3-*c*]-6-bromopyridine **1** was then examined. In the beginning, we tried to build the C-O bond by intramolecular benzodioxol-pyridine coupling mediated by copper. After screening the utility of copper metal or a few variety of copper derivatives such as cuprous iodidetriethylphosphite complex $CuIP(OC_2H_5)_3$ and copper(I) 2-thiophenecarboxylate CuTC, the intramolecular Ullmann coupling to the benzopyridoxepine ring was not successful (giving only the unreacted starting material or some decomposition products). Even the use of copper(I) 2-thiophenecarboxylate CuTC, which has been reported to promote Ullmann-biaryl coupling at room temperature[11] did not proceed at 100-150 °C and increased temperature to 180 °C was also unsuccessful.

Thus, we tried to apply the palladium methodology in the C-O bond forming (Buchwald-Hartwig type reaction) and the results are summarized in Table 2. It is known that Pd-catalyzed C-O bond forming is a difficult task due to the low nucleophilicity of the oxygen and, therefore, very slow reductive elimination from the arylpalladium alkoxo complex intermediate.[1d] The phenoxides are even less nucleophilic than alkoxides making the intramolecular cyclization more difficult. Anyway, using tricyclohexylphosphine

(Cy_3P) as the ligand and potassium carbonate as the base, the coupling reaction proceeded smoothly to give **1** in 94% yield (run 1) since the change of the base with silver carbonate gave the product **1** only in a moderate yield after a long reaction time (run 2). Using more bulky aryldialkylphosphine chelating ligands such as 2-(di-*t*-butylphosphino)biphenyl **7** (Buchwald's phosphine), the product **1** was obtained in a moderate yield (run 3) and the use of the mixture tri-*n*-butylphosphine (n-Bu_3P) and 1,3-bis(diphenylphosphino)propane DPPP as a ligand did not give the product (run 4). A new procedure using the ligand tri-*o*-tolylphosphine ($(o\text{-}Tol)_3P$ and $Pd(OAc)_2$ in small amounts in the presence of hydroquinone (HQ) as a homogeneous reductant[12] gave the product **1** in a very high yield (run 5). The crucial step of the biaryl coupling reaction, the C-O bond forming reductive elimination from the arylpalladium complex is dependent of the structure of substrate and catalyst chelating ligand as well as the nature/concentration of the base.[1c-d, 13] The monodentate ligands Cy_3P and $(o\text{-}Tol)_3P$ coordinate to palladium to yield the biaryl coupling product in a very high yield, since the bulky ligand 2-(di-*t*-butylphosphino)biphenyl and bidentate ligand DPPP changed the coupling reaction into a sluggish process. Probably the steric hindrance of the *Z*-alkene **6** influences the ability of the bulky and bidentate ligands to promote the reductive elimination step.

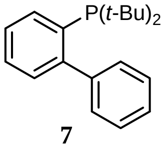


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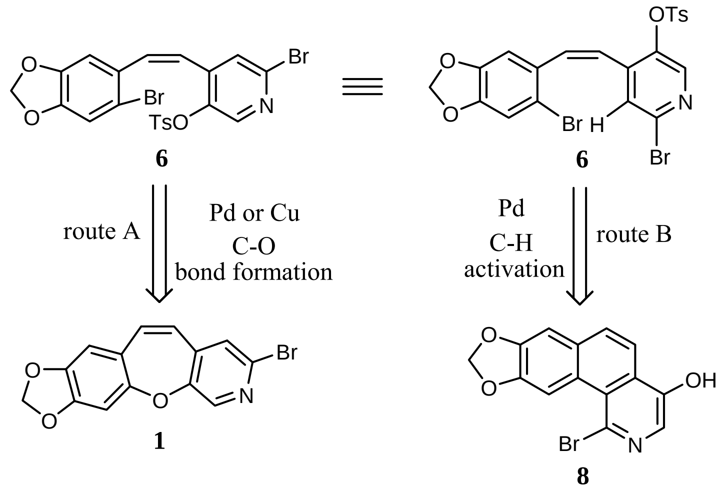
Table 2. The results of Pd reagent mediated intramolecular cyclization

Run	Pd (eq)	ligand (eq)	additive	base (eq)	solvent	temp.(°C)/time (h)	yield
1.	$Pd(OAc)_2$ (0.2)	Cy_3P (0.4)	--	K_2CO_3 (2.0)	DMF	120/2	**1**, 94%
2.	$Pd(OAc)_2$ (0.2)	Cy_3P (0.4)	--	Ag_2CO_3 (2.0)	DMF	120/15	**1**, 49%
3.	$Pd(OAc)_2$ (0.2)	$2(t\text{-}Bu)_2$Pbifenil (0.4)	--	K_2CO_3 (2.0)	DMF	120/3	**1**, 38%
4.	$Pd(OAc)_2$ (1.0)	$(n\text{-}Bu)_3P$ (1.0) DPPP (1)	--	Ag_2CO_3 (2.0)	DMF	120/2.5	many spots
5.	$Pd(OAc)_2$ (0.05)	$(o\text{-}tol)_3P$ (0.05)	HQ (0.5)	Cs_2CO_3 (1.0)	DMF	100/33	**1**, 92%

We have to mention that we chose to study the feasibility of benzene-pyridine metal-mediated intramolecular coupling reaction using the dibromoethene **6** as starting material because of the multiple pathways of cyclization due to the multiple functionalization of the starting material. Thus, the intramolecular cyclization could occur by Pd catalyzed C-O bond formation (Buchwald-Hartwig type reaction) or by Cu-mediated C-O bond formation (intramolecular Ullmann reaction) to give a benzopyridoxepine ring (Scheme 3, route A) but also the intramolecular cyclization could occur by Pd catalyzed C-H activation to give a benzoisoquinoline ring (Scheme 3, route B).



Scheme 3. Possible pathways for cyclization of compound **6**

Since the molecular weight and the elemental analysis of the compounds **1** and **8** are identically, the ^{1}H-NMR and ^{13}C-NMR analysis let us to assign the structure **1** for the cyclization product obtained. The bromine atom present on the structure **1** will be necessary in the next experiments to introduce different functional groups.

In summary, the synthesis of [1,3]dioxo[*d*]benzoxepino[2,3-*c*]-6-bromopyridine **1** was accomplished using a novel methodology for the synthesis of complex fused polycyclic systems employing an intramolecular palladium catalyzed C-O bond formation. The successful experiments were carried out in relatively mild conditions using different chelating ligands: tricyclohexylphosphine (Cy_3P), 2-(di-*t*-butylphosphino)biphenyl, tri-*o*-tolylphosphine ($(o\text{-Tol})_3P$) and different bases: K_2CO_3, Ag_2CO_3, Cs_2CO_3 and gave the product **1** in moderate to very high yield. This method was not applied before and provides a practical alternative to other known methodologies for the preparation of benzopyridoxepine ring.

EXPERIMENTAL

General: Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The ^{1}H-NMR spectra in deuteriochloroform were recorded by a Mercury-300, VXR-500 or Varian Unity INOVA AS600 spectrometer. The NMR spectral data are reported in parts per million downfield from the internal standard (tetramethylsilane, δ 0.0). The FAB-MS were obtained using a VG AutoSpec spectrometer with *m*-nitrobenzyl alcohol as the matrix. The elemental analysis was performed using a Yanaco MT-5 analyzer. Column chromatography was carried out with Merck silica gel (230-400 mesh). The TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates. All the experiments were carried out in an argon atmosphere, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give the purified $Pd(OAc)_2$. The copper was purified by a published method.[14] The cuprous iodidetriethylphosphite complex $CuIP(OC_2H_5)_3$ was prepared by a method from literature.[15]

2-Bromo-5-tosyloxypyridine (3). To a solution of 2-bromo-5-hydroxypyridine **2** (1.5 g, 8.62 mmol) in dry CH_2Cl_2 (65 mL) was added Et_3N (6 mL, 43.1 mmol). The mixture was cooled at 0 °C and *p*-toluenesulfonyl chloride (4.1 g, 21.55 mmol) was added under stirring. The reaction mixture was stirred at rt for 2.5 h, after that was poured over water with ice, neutralized with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the brown residue (5.338 g) was purified by column chromatography on silica gel. Elution with hexane/AcOEt (15:1) gave the tosyloxypyridine **3** (2.678 g, 94%) as colorless prisms, mp 99.5-101 °C (hexane/Et_2O). IR (KBr) cm^{-1}: 1570, 1370, 1180. ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, 1H, Py-H, $J = 2.2$ Hz), 7.70 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.46 (d, 1H, Py-H, $J = 8.4$ Hz), 7.34 (dd, 1H, Py-H, $J = 2.2; 8.4$ Hz), 7.33 (d, 2H, Ar-H, $J = 8.5$ Hz), 2.46 (s, 3H, CH_3). MS (FAB, positive ion mode) *m/z* 328, 330 [$M+1^+$]. *Anal.* Calcd for $C_{12}H_{10}BrNO_3S$: C, 43.92; H, 3.07; N, 4.27. Found: C, 43.98; H, 3.08; N, 4.16.

2-Bromo-4-formyl-5-tosyloxypyridine (4). To a LDA solution prepared from *n*-BuLi (hexane solution, 2 mL, 3.14 mmol) and *i*-Pr_2NH (0.5 mL, 3.55 mmol) in Et_2O (5 mL) at -80 °C for 1 h under Ar atmosphere, 2-bromo-5-tosyloxypyridine **3** (0.1 g, 0.304 mmol) solved in dry Et_2O (8 mL) was added slowly and the mixture was stirred for 1.5-2 h at -80 °C. Dry DMF (0.2 mL, 2.57 mmol) was added drop by drop. After 1 h of stirring at -80 °C, the mixture was hydrolyzed with a 10% degassed aqueous solution of KH_2PO_4 (30 mL) and allowed to warm up to rt and then extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated and chromatographed on silica gel. Elution with hexane/Et_2O (5:1) gave the formylated product **4** (0.057 g, 53%) as colorless prisms, mp 105-107 °C (hexane/Et_2O). IR (KBr) cm^{-1}: 1700, 1590, 1380, 1180. ^1H-NMR (500 MHz, $CDCl_3$) δ: 10.04 (s, 1H, CHO), 8.11 (s, 1H, Py-H_6), 7.86 (s, 1H, Py-H_3), 7.73 (d, 2H, Ar-H, $J = 8$ Hz), 7.39 (d, 2H, Ar-H, $J = 8$ Hz), 2.49 (s, 3H, CH_3). ^{13}C-NMR (600 MHz, $CDCl_3$) δ: 184.98 (CHO), 147.25 (C, C-Ar), 146.53 (CH, C_6-Py), 145.26 (C, C_2-Py), 140.49 (C, C_5-Py), 136.84 (C, C_4-Py), 130.49 (CH, 2C-Ar), 130.26 (C, C-Ar), 128.62 (CH, 2C-Ar), 125.77 (CH, C_3-Py), 21.82 (CH_3). MS (FAB, positive ion mode) *m/z* 356, 358 [$M+1^+$]. *Anal.* Calcd for $C_{13}H_{10}BrNO_4S$: C, 43.84; H, 2.83; N, 3.93. Found: C, 44.19; H, 3.04; N, 3.79.

(*Z*)-5-Tosyloxy-4-[2”-(1’,3’-benzodioxol-6’-bromo-5’-yl)]-1”-ethenyl-2-bromopyridine (6).

Phosphonium bromide **5** (0.234 g, 0.42 mmol) was suspended in dry THF (5 mL) and cooled at 0 °C, then *t*-BuOK (0.048 g, 0.43 mmol) was added and the mixture was let under stirring for 20 min at 0 °C and furthermore for 15 min at rt. After that a solution of 2-bromo-4-formyl-5-tosyloxypyridine **4** (0.05 g, 0.14 mmol) in THF (15 mL) was added drop by drop (25 min, 0 °C) and the mixture was stirred at rt for 3.5 h.

When reaction was finished, water was added and the mixture extracted with Et_2O. The combined organic layers were dried with K_2CO_3 and concentrated in vacuo. The yellow residue (0.356 g) was solved in CH_2Cl_2 and subjected to column chromatography (silica gel, hexane:$CHCl_3$:AcOEt = 50:10:2) to give the cis-isomer **6** (0.068 g, 87%) as colorless plates, mp 175-179 °C (hexane/CH_2Cl_2). IR (KBr) cm^{-1}: 2840, 1600, 1240, 1040, 1580, 1380, 1180. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H, Py-H), 7.79 (d, 2H, Ts-H, J = 8.4 Hz), 7.36 (d, 2H, Ts-H, J = 8.4 Hz), 7.06 (s, 1H, Py-H), 7.05 (s, 1H, Ar-H), 6.77 (d, 1H, =CH, J = 12 Hz), 6.39 (d, 1H, =CH, J = 12 Hz), 6.19 (s, 1H, Ar-H), 5.96 (s, 2H, O-CH_2-O), 2.44 (s, 3H, CH_3). MS (FAB, positive ion mode) *m/z* 552, 554, 556 [M+1$^+$]. HRMS (FAB) calcd for $C_{21}H_{15}Br_2NO_5S^+$: 552.9194 , found 552.9111.

General procedure for the coupling reaction by Pd of (*Z*)-5-tosyloxy-4-[2”-(1’,3’-benzodioxol-6’-bromo-5’-yl)]-1”-ethenyl-2-bromopyridine (6). The dibromopyridine **6** was treated with $Pd(OAc)_2$, a phosphine ligand and a base in dry DMF using $Pd(OAc)_2$, the ligand and the base in the ratios indicated in Table 3. Then, the reaction mixture was extracted with Et_2O, the combined organic layers were washed with brine, dried with K_2CO_3 and evaporated. The residue was solved in CH_2Cl_2 and subjected to column chromatography on silica gel. Elution with hexane/$CHCl_3$/AcOEt (50:10:1) gave the product **1**.

[1,3]Dioxo[*d*]benzoxepino[2,3-*c*]-6-bromopyridine (1) pale yellow powder, amorphous, mp 166-169 °C (Et_2O/hexane). IR (KBr) cm^{-1}: 2860, 1580, 1500, 1250. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15 (s, 1H, Py-H), 7.20 (s, 1H, Py-H), 6.76 (d, 1H, =CH, J = 11.4 Hz), 6.73 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 6.46 (d, 1H, =CH, J = 11.4 Hz), 5.99 (s, 2H, O-CH_2-O). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 152.52 (C), 151.94 (C), 150.01 (C), 145.26 (C), 142.74 (CH), 140.74 (C), 136.94 (C), 135.56 (CH), 126.05 (CH), 124.56 (CH), 122.21 (C), 108.15 (CH), 103.14 (CH), 102.15 (CH_2). MS (FAB, positive ion mode) *m/z* 318, 320 [M+1$^+$]. HRMS (FAB) calcd for $C_{14}H_9BrNO_3^+$: 317.9765, found 317.9788.

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