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# Synthesis of 2-Substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine Derivatives

**Mustapha Soukri,[†,‡] Said Lazar,[‡] Mohamed Akssira,[‡] and Gérald Guillaumet*,[†]**

*Institut de Chimie Organique et Analytique associé au CNRS,*
*Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France, and*
*Laboratoire de Chimie Bioorganique et Analytique, FST-Université Hassan II,*
*Mohammedia, BP146, 20650 Mohammedia, Morocco*

*gerald.guillaumet@univ-orleans.fr*

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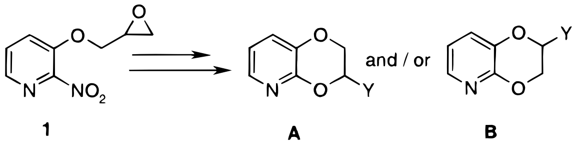
## ABSTRACT



**A variety of 2-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines B have been synthesized from the readily available 2-nitro-3-oxiranylmethoxy-pyridine 1 via a Smiles rearrangement. We demonstrate how variations of reaction conditions affect the product distribution of A and B.**

The 2,3-dihydro-1,4-benzodioxin ring system is present in a large number of structures of therapeutic agents possessing important biological activities.[1] Some of them are antagonists of α-adrenergic receptors, giving them antihypertensive properties.[2−6] Other have affinities with serotonin receptors which are involved in nervous breakdown and schizophrenia[7−12] or represent an attractive therapeutic target for the treatment of glaucoma.[13]

Recently, 2,3-dihydro-1,4-benzodioxins have been developed as inhibitors of 5-lipoxygenase, an enzyme involved in the oxygenation of arachidonic acid to the leukotriens; they are also useful for the treatment of inflammatory diseases such as asthma and arthritis.[14] The occurrence of the 2,3-dihydro-1,4-benzodioxin structure in various naturally abundant compounds has been also reported.[15,16] Paradoxically, despite the considerable development of procedures to efficiently build up the nitrogenated rings, the 1,4-dioxino[2,3-*b*]pyridine skeleton has still remained inaccessible.

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[†] Université d'Orléans.

[‡] FST-Université Hassan II, Mohammedia.

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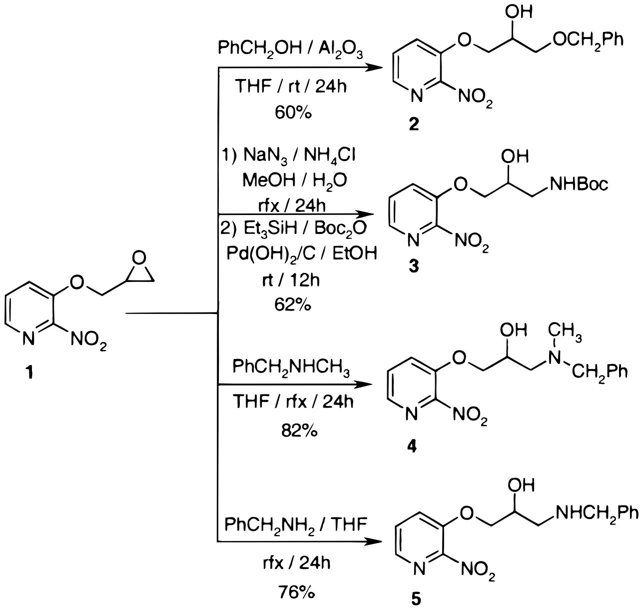
To the best of our knowledge, the only known polyheterocyclic system has been prepared by treatment of 3-hydroxy-2-pyridone with base and 1,2-dibromoethane.[17] This method, unfortunately too restrictive, not only gives unsatisfactory yields but also makes the introduction of various substituents in the six-membered nonaromatic moiety infeasible. The only published work reported on derivatives functionalized at the oxygenated moiety is the result from our laboratory and concerning derivatives **A** with a substituent in position 3 (Figure 1).[18] The compounds **B** substituted in position 2 were mentioned only once and are obtained by a relatively long synthesis implementing starting materials such as 2-chloro-3-pyridinol and 1-acetoxy-3-benzyloxy-2-propanol.[19] In the present Letter, we report a novel and effective route for the synthesis of 2-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines **B**.

**Figure 1.**

Our synthetic approach is based, first, on the formation of the epoxide **1**[20] and then on its opening by appropriate nucleophiles to the corresponding alcohols **2**−**5**. Alcohols **2**−**5** are the key intermediates for the synthesis of the target molecules (Scheme 1). In addition, given the diversity of the possible means of opening of an oxirane, it is possible to prepare compounds with the very diversified substituents on the oxygenated moiety. Several approaches were considered, and in each case nucleophilic attack on the oxirane moiety must occur.

**Scheme 1**



To synthesize the aryl alkyl ether, we found that a stirring slurry of activated commercially available Woelm 200 neutral chromatographic alumina (500 °C, 24 h) catalyzed the regioselective opening of epoxide **1** by benzyl alcohol under mild conditions (25 °C, THF)[21] to give the corresponding functionalized alcohol **2** in good yields.

For the synthesis of alcohol **3**, epoxide **1** was regioselectively opened with sodium azide in the presence of ammonium chloride.[22] The azido alcohol intermediate was transformed to the corresponding *N*-Boc-protected amine in a one-pot step, by using triethylsilane and di-*tert*-butyl dicarbonate in the presence of a catalytic amount of 20% Pd(OH)$_2$/C in ethanol.[23]

The ring opening of epoxide **1** with amines was promoted by use of THF at reflux, affording the corresponding amino alcohols **4** and **5** in excellent yields. The reaction was carried out with only 3 equiv of amines such as *N*-methylbenzylamine and benzylamine.

The second part of our study concerned the cyclization of the alcohols **2**−**5** by intramolecular nucleophilic substitution (SNAr) to afford the 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine **A**.[18d] However, due to the experimental conditions used (e.g., base, solvent, and substarte structure), 2-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines **B** have been isolated in fairly good yields. Formation of the isomers **B** could be explained by Smiles rearrangement.[24]

The Smiles rearrangement, involving attack of an alkoxide on the 3-position of the pyridine ring with displacement of the alkoxide, and the subsequent closure of the delivered alkoxide into the 2-position of the pyridine ring, gives the compounds **B**. The reaction is facilitated by the presence of electron-withdrawing groups in the ortho position of the aromatic ring such as the nitro group, which is also a good nucleofuge.

The relative amounts **A** and **B** are subject to some control by variation of the base and solvent (Scheme 2, Table 1). All ring closures of alcohols **2**−**5** have been carried out under identical conditions, i.e., with sodium hydride and potasium

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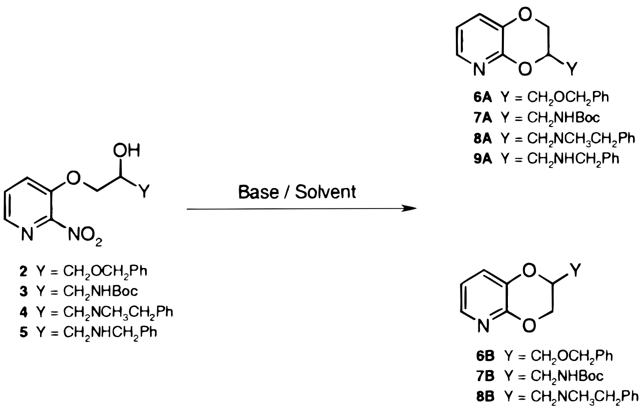
**Scheme 2**



*tert*-butoxide as base associated with ethylene glycol dimethyl ether and *tert*-butyl alcohol as solvent, respectively.

**Table 1.** Conditions of Cyclization Reactions of Alcohols **2**−**5**

| entry | Y | base/solvent | *T*, °C/ *t* (h) | yield,[a] % | ratio[b] A/B |
|---|---|---|---|---|---|
| **2** | $CH_2OCH_2Ph$ | NaH/DME | 80/12 | 98 | 50/50 |
| | | *t*-BuOK/*t*-BuOH | 80/12 | 94 | 40/60 |
| **3** | $CH_2NHBoc$ | NaH/DME | 80/12 | 92 | 100/0 |
| | | *t*-BuOK/*t*-BuOH | 80/12 | 94 | 40/60 |
| **4** | $CH_2NCH_3CH_2Ph$ | NaH/DME | 80/12 | 88 | 70/30 |
| | | *t*-BuOK/*t*-BuOH | 80/12 | 89 | 30/70 |
| **5** | $CH_2NHCH_2Ph$ | NaH/DME | 80/12 | 90 | 100/0 |
| | | *t*-BuOK/*t*-BuOH | 80/12 | 89 | 100/0 |

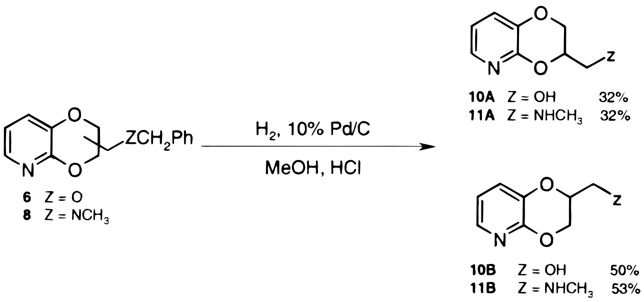
[a] Yields of cyclization reaction after flash chromatography. [b] Ratio of each isomer determinated from $^1$H NMR.[25]

Under various conditions, it was found that the total yield of the reaction of intramolecular cyclization is excellent. Interestingly, when *t*-BuOK/*t*-BuOH was used, the isomer **B** was isolated as a major product, except for alcohol **5** for which only the isomer **A** was obtained.

It would be also necessary, by analogy with work completed in the 2,3-dihydro-1,4-benzodioxin series, to have the methylamine or methyl alcohol at position 2 of 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine. Thus, catalytic Pd/C hydrogenolysis of compounds **6** and **8** in methanol with a few drops of concentrated hydrochloric acid gave debenzylated products **10** and **11** in satisfactory yields (Scheme 3). The obtained structures could present a great affinity for the biological targets after an *O*- or *N*-alkylation. So, to complete our study, it would be useful to regenerate the free amine, (2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin-2-yl)methylamine.

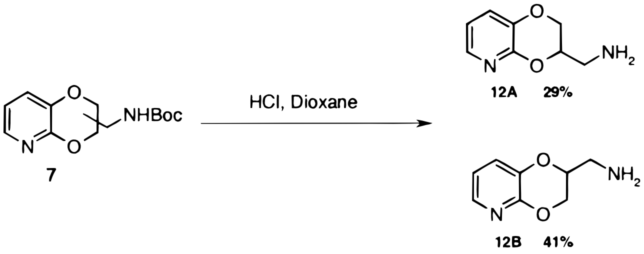
The acidic hydrolysis (4 N HCl in dioxane) of compound **7** afforded the corresponding amines **12A** and **12B** in fairly good yields (Scheme 4).

**Scheme 3**



The isomers **A** and **B** were separated by column chromatography[26] after debenzylation of compouds **6** and **8** or acidic hydrolysis of carbamate **7**, respectively. The yields of isolated products **10A**−**12A** and **10B**−**12B**[27] (Schemes 3 and 4) were

**Scheme 4**



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[25] The ratio of each isomer has been determined by NMR comparison of the chemical shift of the $CH_2$-dioxinopyridine ring, which is, for instance, deshielded for **A** and **B** isomers: (**7A** $\delta$ (ppm) 3.90 (dd, 1H, $J = 7.6$, 11.5 Hz; 7**B** $\delta$ (ppm) 4.10 (dd, 1H, $J = 7.6$, 11.5 Hz). These assignments are in agreement with those already reported for the **A** isomers.[18]

[26] **A** and **B** isomers were separated by column flash chromatography ($CH_2Cl_2$/MeOH: 95/5 to 90/10. For instance: $R_f$ **12A** (0.50) and **12B** (0.45) with a TLC eluent system ($CH_2Cl_2$/MeOH: 95/5).

[27] All compounds were fully caracterized by IR, $^1$H and $^{13}$C NMR, MS, and elemental analyses. Structures of **10B**, **12A**, and **12B** are in agreement with previously published physicochemical data.[18,19] Data for selected compounds follows. **10A**: IR(film) $\upsilon$ 3600−3100 (OH) cm$^{-1}$; $^1$H NMR (250 MHz $CDCl_3$ + $D_2O$) $\delta$ (ppm) 3.84−4.40 (m, 2H, **CH$_2$**OH), 4.14 (dd, 1H, OC**H$_2$**, $J = 8.1$, 11.6 Hz), 4.33 (dd, 1H, O**CH$_2$**, $J = 2.5$, 11.6 Hz), 4.39−4.48 (m, 1H, OC**H**), 6.88 (dd, 1H, **H-7**, $J = 5.0$, 7.8 Hz), 7.20 (dd, 1H, **H-8**, $J = 1.6$, 7.8 Hz), 7.81 (dd, 1H, **H-6**, $J = 1.6$, 5.0 Hz); $^{13}$C NMR (62.9 MHz $CDCl_3$) $\delta$ (ppm) 61.5 (**C**H$_2$OH), 65.1 (O**C**H$_2$), 74.7 (O**C**H), 118.7 (**C**H, **C-8**), 128.9 (**C**H, **C-7**), 139.1 (-**C**-, **C-9**), 140.0 (**C**H, **C-6**), 150.4 (-**C**-, **C-10**); MS *m/z* 168 (M$^+$ + 1). **10B**: $^{13}$C NMR (62.9 MHz $CDCl_3$) 59.5 (**C**H$_2$OH), 66.4 (O**C**H$_2$), 73.6 (O**C**H), 118.8 (**C**H, **C-8**), 126.6 (**C**H, **C-7**), 136.3 (-**C**-, **C-9**), 139.6 (**C**H, **C-6**), 150.2 (-**C**-, **C-10**); MS *m/z* 168 (M$^+$ + 1). **11A**: IR(film) $\upsilon$ 3500−3150 (NH) cm$^{-1}$; $^1$H NMR (250 MHz DMSO-$d_6$) $\delta$ (ppm) 2.46 (s, 3H, C**H$_3$**), 3.02 (d, 2H, C**H**$_2$NH, $J = 5.1$ Hz), 4.06 (dd, 1H, OC**H$_2$**, $J = 7.3$, 11.7 Hz), 4.32 (dd, 1H, OC**H$_2$**, $J = 2.5$, 11.7 Hz), 4.51−4.62 (m, 1H, OC**H**), 6.97 (dd, 1H, **H-7**, $J = 4.7$, 8.0 Hz), 7.32 (dd, 1H, **H-8**, $J = 1.6$, 8.0 Hz), 7.74 (dd, 1H, **H-6**, $J = 1.6$, 4.7 Hz); $^{13}$C NMR (62.9 MHz DMSO-$d_6$) $\delta$ (ppm) 34.9 (**C**H$_3$), 49.6 (**C**H$_2$-NH), 65.5 (O**C**H$_2$), 72.1 (O**C**H), 119.7 (**C**H, **C-8**), 125.7 (**C**H, **C-7**), 139.2 (-**C**-, **C-9**), 140.2 (**C**H, **C-6**), 150.5 (-**C**-, **C-10**); MS *m/z*: 181 (M$^+$ + 1). **11B**: IR(film) $\upsilon$ 3500−3150 (NH) cm$^{-1}$; $^1$H NMR (250 MHz DMSO-$d_6$) $\delta$ (ppm) 2.40 (s, 3H, C**H$_3$**), 2.89 (d, 2H, C**H**$_2$NH, $J = 5.9$ Hz), 4.18 (dd, 1H, OC**H$_2$**, $J = 6.9$, 11.6 Hz), 4.35−4.45 (m, 1H, OC**H**), 4.48 (dd, 1H, OC**H$_2$**, $J = 2.5$, 11.6 Hz), 6.95 (dd, 1H, **H-7**, $J = 4.7$, 7.8 Hz), 7.29 (dd, 1H, **H-8**, $J = 1.6$, 7.8 Hz), 7.74 (dd, 1H, **H-6**, $J = 1.6$, 4.7 Hz); $^{13}$C NMR (62.9 MHz DMSO-$d_6$) $\delta$ (ppm) 35.2 (**C**H$_3$), 49.8 (**C**H$_2$NH), 66.2 (O**C**H$_2$), 71.1 (O**C**H), 118.7 (**C**H, **C-8**), 124.9 (**C**H, **C-7**), 139.3 (-**C**-, **C-9**), 140.4 (**C**H, **C-6**), 150.5 (-**C**-, **C-10**); MS *m/z* 181 (M$^+$ + 1). **12A**: $^{13}$C NMR ($CDCl_3$, 62.9 MHz), 42.5 (**C**H$_2$−NH$_2$), 65.8 (O**C**H$_2$), 75.6 (O**C**H), 118.5 (**C**H, **C-8**), 124.7 (**C**H, **C-7**), 139.0 (-**C**-, **C-9**), 140.0 (**C**H, **C-6**), 150.9 (-**C**-, **C-10**); MS *m/z* 167 (M$^+$ + 1). **12B**: IR (film) $\upsilon$ 3500−3100 (NH) cm$^{-1}$; $^{13}$C NMR ($CDCl_3$, 62.9 MHz), 42.3 (**C**H$_2$−NH$_2$), 66.7 (O**C**H$_2$), 74.4 (O**C**H), 118.5 (**C**H, **C-8**), 124.8 (**C**H, **C-7**), 138.8 (-**C**-, **C-9**), 139.8 (**C**H, **C-6**), 150.9 (-**C**-, **C-10**); MS *m/z* 167 (M$^+$ + 1).

determined from alcohols **2**−**5** after a cyclization reaction and deprotection step.

The obtained compounds **6**−**12** have been fully caracterized by NMR spectroscopy. The NMR data (COSY, HMQC, ...) are in agreement with the proposed structures.

In conclusion, this study reports a convenient and effective synthetic pathway to 2-substituted-2,3-dihydro-1,4-dioxino-[2,3-*b*]pyridines via a Smiles rearrangement. The starting material of this novel approach is readily available, and it is suitable for preparing derivatives having a wide variety of substituents.

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