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Synthesis of novel 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines as potential new scaffolds for drug discovery: selective introduction of substituents on the pyridine ring

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Abstract—Selective introduction of substituents on 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine at the pyridine ring was achieved using electrophilic aromatic substitution and addition–elimination reactions. In all the examples, functionalization at the 3-position was maintained. For this reason, the products disclosed in this paper could be useful as potential scaffolds for drug discovery and combinatorial chemistry.

Bioisosteric replacement of benzene by pyridine is a classical approach within the field of medicinal chemistry compatible with the maintenance of the biological activity.[1] Using this approach, several 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine derivatives have proved to be active in a wide range of therapeutic areas (Fig. 1), e.g. CNS (compound **1**,[2] 5-HT_{1A} receptor agonists), cardiovascular diseases (compound **2**[3] calcium antagonist) and antibiotics (compound **3**[4]).

Compounds **1**, **2** and **3** have the 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine core, the synthesis of which has been described previously.[5] Moreover, in the literature, few examples of 2,3-dihydro-1,4-dioxino-

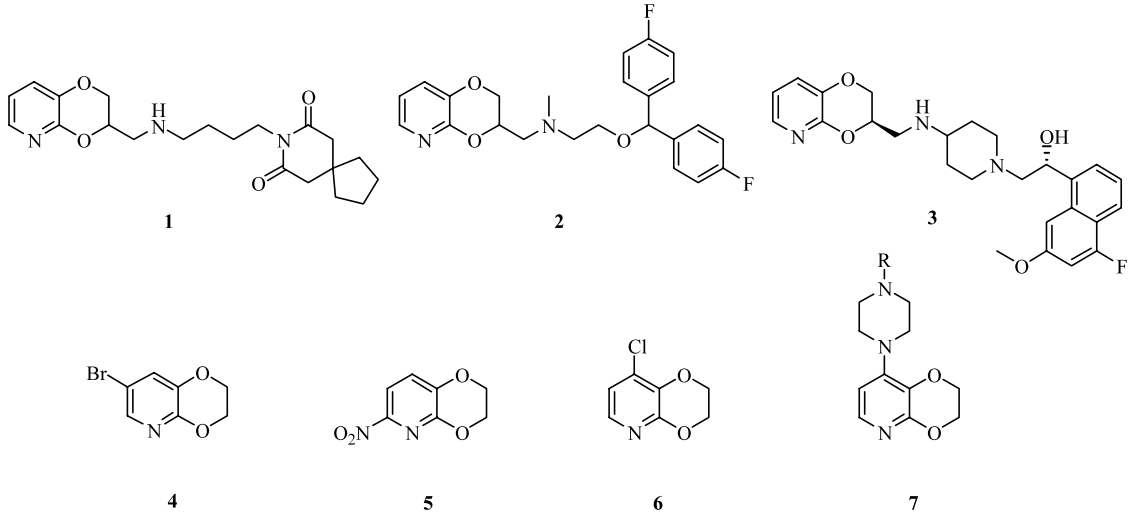

Figure 1.

Keywords: pyridine; heterocycles; 1,4-benzodioxin; 1,4-dioxinopyridine; novel scaffolds.
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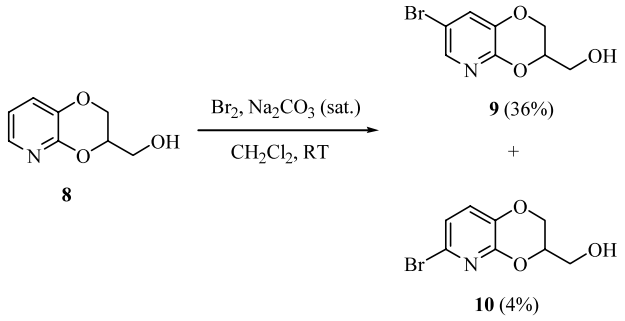
[2,3-*b*]pyridines substituted on the pyridine ring have been reported[6] (compounds **4**,[6a] **5**,[6b] **6** and **7**,[6c] Fig. 1). Despite these two facts and to the best of our knowledge, the simultaneous combination of substituents on both rings in this type of compound still remains undescribed.

As part of one of our drug discovery programs, we were interested in the development of synthetic strategies suitable for the introduction of substituents on the aromatic ring of the 2,3-dihydro-1,4-dioxino[2,3-*b*]-pyridine scaffold, also bearing a moiety at the 3-position that is easy to functionalize. These derivatives could be useful intermediates in the synthesis of bioactive compounds and, with appropriate substituents, for combinatorial chemistry purposes. In the present paper we describe the results of our work that has led to the first synthesis of 3-hydroxymethyl-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines substituted on the pyridine ring.

Substitution on the pyridine ring in examples **4**, **5**, **6** and **7** was achieved using different approaches. For instance, compound **5** was prepared by electrophilic aromatic substitution on the 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine,[6b] whereas compound **6** was prepared both by addition–elimination reaction of the corresponding *N*-oxide and by metallation followed by reaction with hexachloroethane.[6c]

Once antecedents had been considered, our first approach proceeded via electrophilic aromatic substitution. In this way, bromination of compound **8**,[5] using bromine in dichloromethane and an aqueous saturated solution of sodium carbonate as base, afforded the 7-bromo analogue **9**, as the main product, and traces of the 6-bromo derivative **10** were also obtained[7] (Scheme 1). Both compounds were separated by standard column chromatography methods and identified by their ^{1}H NMR data (Table 1). The explanation of the result of this reaction could be found in the balance of the electron-withdrawing effect of the nitrogen atom of the pyridine and the electron-donating effects of the oxygen atoms.



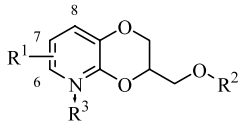
Scheme 1.

For the introduction of substituents at positions 6 and 8, an addition–elimination reaction of the corresponding *N*-oxide was envisaged. According to main principles describing the reactivity of pyridine *N*-oxides, addition–elimination reactions should afford α or γ substituted compounds with re-aromatization and loss of the *N*-oxide function.[8]

To maintain the functionality at position 3, the hydroxy function was protected using either the *tert*-butyldimethylsilyl or methanesulphonyl groups (compounds **11** and **12**).[9] The latter group was chosen to avoid the possible cleavage of the oxygen–silicon bond under acidic conditions. Furthermore, this group can be used as a leaving group for further derivatization. *N*-Oxides **13** and **14** were prepared using standard methodology, *m*-chloroperbenzoic acid in dichloromethane,[10] as described in Scheme 2.

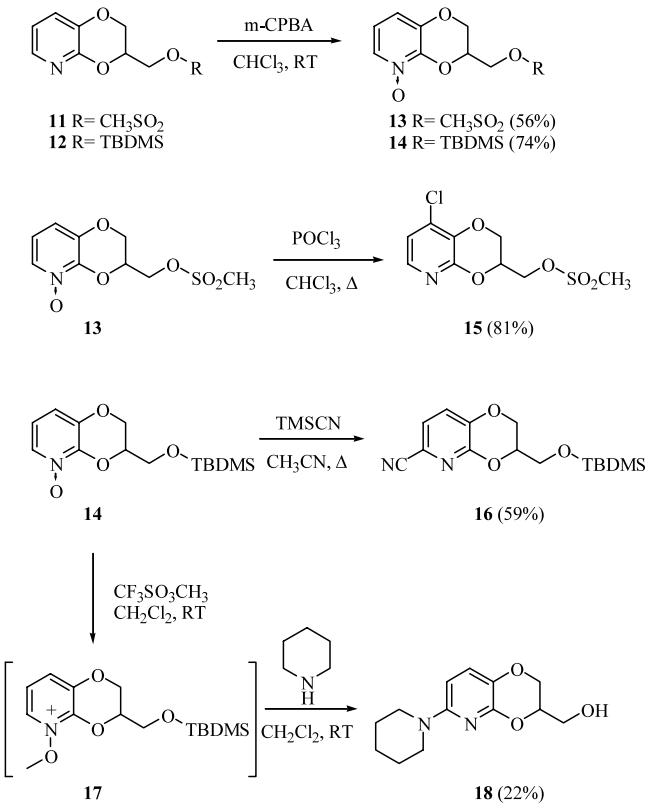
When the reaction of the *N*-oxide **13** with phosphorus oxychloride was performed, 8-substituted compound **15** was obtained with high regioselectivity,[11] (Scheme 2), as confirmed by its ^{1}H NMR (Table 1). This result correlated with that previously described by Guillaumet and

Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) data of azabenzodioxanes **8**–**10**, **14**–**16** and **18**



Compd	R^1	R^2	R^3	$\delta_{H\text{-}6}$[a]	$\delta_{H\text{-}7}$[a]	$\delta_{H\text{-}8}$[a]	$J_{6\text{–}7}$[b]	$J_{7\text{–}8}$[b]	$J_{6\text{–}8}$[b]
8	H	H	–	7.80 (d)	6.87 (dd)	7.20 (d)	4.3	7.8	–
9	7-Br	H	–	7.85 (d)	–	7.34 (d)	–	–	2.1
10	6-Br	H	–	–	7.13 (d)	7.29 (d)	–	8.1	–
14	H	TBDMS	O	7.93 (dd)	6.78 (dd)	6.90 (dd)	6.5	8.4	1.4
15	8-Cl	SO_2CH_3	–	7.72 (d)	6.95 (d)	–	5.2	–	–
16	6-CN	TBDMS	–	–	7.12 (d)	7.21(d)	–	8.5	–
18	6-NC_5H_{10}	H	–	–	6.12 (d)	6.95 (d)	–	8.7	–

[a] δ are given in ppm.
[b] J are given in hertz.



Scheme 2.

co-workers,[6c] and prompted us to consider other addition–elimination reactions in order to find if, in all cases, this type of reaction would consistently result in substitution at the 8-position in 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine scaffolds. For this reason we envisaged two possibilities: first, a one-pot addition–elimination reaction and, second, preparation of the *N*-alkyloxy intermediate and further reaction with nucleophiles, to investigate an intermolecular mechanism.

To check the first possibility, the reaction of pyridine *N*-oxides with trimethylsilyl cyanide was selected. This is a one-pot reaction in which substitution occurs preferably at the α-position with respect to the nitrogen.[12] In our system this result was confirmed and 6-cyano compound **16** was obtained selectively from **14**[13] (Scheme 2). Compound **16** was unambiguously identified by its ^{1}H NMR data (Table 1).

Regarding the second possibility, the *N*-alkoxy quaternary salt **17** was prepared using methyl trifluoromethanesulphonate at room temperature. This compound was very unstable and difficult to isolate. Addition of piperidine as the nucleophile afforded compound **18**,[14] (Scheme 2), according to its ^{1}H NMR data (Table 1). Under these reaction conditions, the oxygen–silicon bond was cleaved, yielding the unprotected hydroxy derivative.

To assign the structures of these compounds ^{1}H NMR coupling constant values were used. For instance, the coupling constant in compounds **10**, **16** and **18**, substituted at position 6, J_{7-8} is about 8 Hz, and in the same range as J_{7-8} in the parent compound **8**.[5] For compound **15**, substituted at position 8, J_{6-7} is 5.20 Hz, and is similar to J_{6-7} in **8**. The results presented in Table 1 match perfectly with the pool of data for pyridines.[15]

In conclusion, the results presented in this work allow the selective introduction of substituents onto the 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine core. Using aromatic electrophilic substitution reactions, compounds substituted at position 7 were readily available. Meanwhile, by addition–elimination reactions, compounds substituted at position 6 were obtained, except when phosphorus oxychloride was used, which afforded compounds substituted at position 8. By this methodology new scaffolds that hold much potential for application in drug discovery have been obtained. Furthermore, compounds **9**, **15** and **16** with two attachment points, could be very useful for combinatorial chemistry purposes. Further research to explain the selectivity detected and to explore these new scaffolds will be the subject matter of future publications.

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7. To a solution of **8** (9 mmol) in dichloromethane (100 mL), 50 mL of a saturated solution of sodium carbonate and bromine (18 mmol) were added. The reaction was stirred overnight at room temperature. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by column

chromatography on silica gel (dichloromethane/methanol 98/2). Affording 0.81 g (36%) of compound **9** and 0.09 g (4%) of compound **10**. ESI-HRMS for both compounds $C_8H_8BrNO_3$ $(M+H)^+$: Calculated: 245.9766. Found: for compound **9** 245.9764, for compound **10** 245.9760. ^1H NMR for both compounds see Table 1.

8. (a) Boulton, J. A.; McKillop, A. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, pp. 29–65; (b) Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, pp. 166–314.
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10. As an example, the preparation of compound **14** is described below: To a solution of **12** (1.7 mmol) in 10 mL of chloroform, was added dropwise a solution of *m*-chloroperbenzoic acid (7.1 mmol) in 10 mL of chloroform at room temperature. The reaction was stirred overnight at room temperature, then 1.0 g of potasium carbonate and 4 ml of methanol were added. The mixture was stirred for 30 min and then filtered. The solid residue was washed with dichloromethane/methanol 9/1 and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol saturated with ammonia 96/4) affording 0.37 g (74%) of compound **14**. ESI-HRMS $C_{14}H_{23}NO_4Si$ $(M+H)^+$: Calculated: 298.1474. Found: 298.1477. ^1H NMR see Table 1.
11. A mixture of **13** (13.8 mmol) and phosphorus oxychloride (69 mmol) was stirred at 100°C for 3 h. The excess phosphorus oxychloride was evaporated and the residue was treated carefully with water and neutralized by addition of solid sodium carbonate. The mixture was extracted with dichloromethane, the organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate 9/1) affording 3.17 g (81%) of compound **15**. ESI-HRMS $C_9H_{10}ClNO_5S$ $(M+H)^+$: Calculated: 280.0046. Found: 280.0041. ^1H NMR see Table 1.
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13. To a solution of **14** (0.5 mmol) in 3 mL of acetonitrile, triethylamine (1.5 mmol) and trimethylsilyl cyanide (2.0 mmol) were added. The reaction was stirred for 24 h at 100°C in a sealed tube. Then, a saturated solution of sodium bicarbonate was added and the mixture was extracted with dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane) affording 91 mg (59%) of compound **16**. ESI-HRMS $C_{15}H_{22}N_2O_3Si$ $(M+H)^+$: Calculated: 307.1478. Found: 307.1482. ^1H NMR see Table 1.
14. To a solution of **14** (1 mmol) in 3 ml of dry dichloromethane, methyl trifluoromethanesulfonate (1.1 mmol) was added under a nitrogen atmosphere at 0°C. The reaction was stirred for 1 h at room temperature. Then piperidine (3 mmol) was added at 0°C and the reaction was stirred overnight at room temperature. This solution was quenched with a saturated solution of sodium bicarbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate 4/1) affording 60 mg (22%) of compound **18**. ESI-HRMS $C_{13}H_{18}N_2O_3$ $(M+H)^+$: Calculated: 251.1395. Found: 251.1398. ^1H NMR see Table 1.
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