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First synthesis of 4-chloro-2,2-difluoro[1,3]dioxole[4,5-*c*]pyridine

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ABSTRACT

The 2,2-difluorobenzodioxole moiety has been introduced in medicinal chemistry research as a potential metabolically more stable derivative of the benzodioxole fragment. Herein we present, to the best of our knowledge, the first synthesis of 4-chloro-2,2-difluoro[1,3]dioxole[4,5-*c*]pyridine, a 5-aza-derivative of the 2,2-difluorobenzodioxole, from simple and cheap starting materials. The chlorine atom in position 4 could be useful for further functionalisation by cross coupling reactions.

This Letter describes the synthesis of a novel building block which could be considered very important and useful for medicinal chemistry purposes.

In the literature there are several examples of biologically active drugs and potential drugs, containing a benzodioxole moiety,[1–5] for the treatment of a wide variety of conditions and disorders, including those associated with the dysfunction of the central nervous system (for example unipolar depression, Alzheimer's and Parkinson's diseases).

However it has been hypothesized that the benzodioxole moiety metabolism could be responsible of some Idiosyncratic Adverse Drug Effects (IADE).[6] Therefore, the 2,2-difluorobenzodioxole group has been proposed as a potentially more stable analogue,[7] in order to prevent the metabolism of the oxo-methylene-oxo (OCH_2O) portion, without differing much in terms of steric requirements.

To the best of our knowledge a 5-aza-derivative (Fig. 1) of such moiety has not been described in the literature so far; recently only a 4-aza analogue of the 2,2-difluorobenzodioxole structure has been described.[8]

Therefore we would like to report herein the first synthesis of 4-chloro-2,2-difluoro[1,3]dioxole[4,5-*c*]pyridine.

In a first attempt, the synthesis of the target material **8** was investigated following the route shown in Scheme 1, starting from the easily accessible 3-pyridinol (**1**).

Although the reactions occurred with excellent regioselectivity (confirmed by NMR studies) and fair yields, a lot of work was done in the optimization of the reaction parameters and intermediate recovery. Particular care had to be taken in processing unstable, reactive or volatile intermediates.

The 3-pyridinol **1** was first protected as MOM ether **2**, in order to direct the following lithiation in position 4 and generate the halo-intermediate **3**[9,10] by reaction with either hexachloroethane (X = Cl)[5] or 1,2-dibromotetrachloroethane (X = Br).

As reported in the literature,[9,10] while relatively stable in solution, both those intermediates were unstable once isolated and had to be quickly reacted with MeONa in dry MeOH to give the 3-methoxymethyl-4-methoxypyridine **4**.

Another chlorine atom was selectively introduced in position 2 by further lithiation with BuLi and reaction with hexachloroethane. After that, the protecting groups of the chloropyridine **5**[11] were cleaved with boron tribromide in dry DCM to give the 2-chloro-3,4-dihydroxypyridine **6**.

After careful quenching with MeOH, the recovery in excellent yield of this *water-soluble* diol, from the extremely acidic reaction crude, was performed by removal of the solvent, trituration in AcOEt, filtration and final purification of the isolated solid on an ion exchange cartridge (SCX).

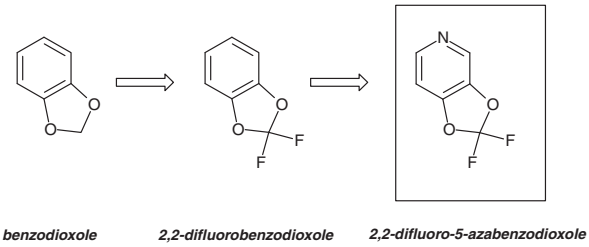

Figure 1. Structural modifications on benzodioxole moiety.

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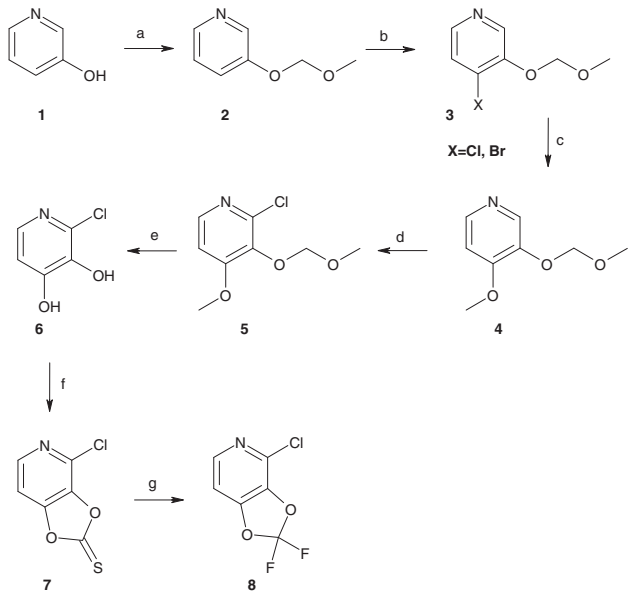
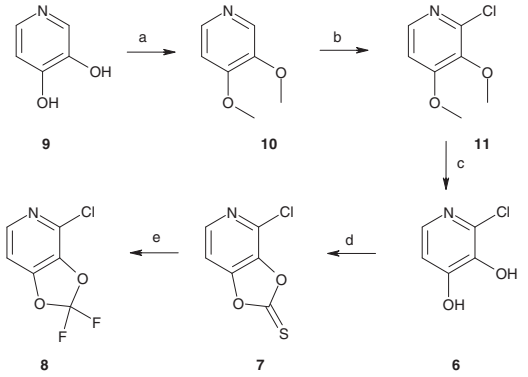


Scheme 1. Reagents and conditions: (a) NaH 60 wt %, DMF, MOMCl, 0 °C, 2 h, *Y* = 81%; (b) *t*-BuLi, C_2Cl_6 or $C_2Cl_4Br_2$, Et_2O, −70 °C, *Y* = 87% or 91%; (c) MeONa, MeOH, 80 °C, overnight, *Y* = 31%; (d) BuLi, C_2Cl_6, THF, −70 °C, 2 h, rt, 1 h, *Y* = 61%; (e) BBr_3 1 M solution in DCM, DCM, 50 min, *Y* = 91%; (f) Cl_2CS, DMAP, DCM, 1 h, rt, *Y* = 79%; (g) HF/pyridine, 1,3-dibromo-5,5-dimethylhydantoin, DCM, −78 °C, 1 h, *Y* = 87%.

Thiocarbamate **7**, obtained[12] by reaction of **6** with thiophosgene and DMAP in dry DCM, proved to be extremely reactive towards weak nucleophiles such as MeOH or even water. Therefore it had to be isolated loading the untreated reaction crude on a silica cartridge and eluting with 100% DCM.

The white solid was then reacted at low temperature with HF/pyridine and 1,3-dibromo-5,5-dimethylhydantoin in dry DCM to give the desired compound **8**.[13,14] In addition to required precautions, when manipulating HF containing mixtures, special care had to be taken in recovering the product, since it proved to be rather volatile. Fortunately all the work up and chromatography could be performed in DCM and it allowed to control solvent evaporation using mild conditions.

In order to devise an alternative synthetic route to access **8,** a shorter and easy strategy was planned, taking advantage of the commercial availability of 3,4-dihydroxypyridine **9** (Scheme 2). The new process avoids the tricky step (b) of chlorination/bromination in Scheme 1, necessary to reach intermediates **3**, both observed to be unstable once isolated.[9,10]



Scheme 2. Reagents and conditions: (a) $TMSN_2$ (2 M hexane solution), DCM/MeOH, 5 h, rt, *Y* = 49%; (b) BuLi, C_2Cl_6, THF, −70 °C, 2 h, rt 1 h, *Y* = 70%; (c) BBr_3 1 M solution, DCM, rt, 3 h, *Y* = 84%; (d) Cl_2CS, DMAP, DCM,1 h, rt, *Y* = 79%; (e) HF/pyridine, 1,3-dibromo-5,5-dimethylhydantoin, DCM, −78 °C 1 h, *Y* = 87%.

The starting material **9** was methylated with TMS-diazomethane to give 3,4-dimethoxypyridine **10**. *ortho*-Directed lithiation with BuLi again occurred in position 2, allowing the formation of the 2-chloro-3,4-dimethoxypyridine **11** by reaction with hexachloroethane. This was then cleaved as previously reported with boron tribromide in DCM, to give the known dihydroxy intermediate **6**. The synthesis then proceeded as described above.

The chlorine atom in position 4 could be useful for further functionalisation by cross coupling reactions, for example the reactivity of the chlorine atom could be tested with the *N*-Boc-piperazine under Buchwald conditions (Pd_2dba, BINAP, *t*-BuOK, toluene)[15] or 1,1-dimethylethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate under Suzuki conditions (Pd tetrakis, K_2CO_3, DMF, microwave irradiation).[16]

In conclusion, the chemistry for the preparation of functionalised 5-aza-benzodioxoles, which could be used as new scaffolds in medicinal chemistry, has been developed, leading also to the first synthesis of 4-chloro-2,2-difluoro[1,3]dioxole[4,5-*c*]pyridine.

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11. BuLi (1.6 M in hexane, 8866 μl, 14.19 mmol) was added, under nitrogen, to dry THF (60 ml) at −70 °C, followed by a solution of 4-methoxy-3-methoxymethoxy-pyridine (Intermediate **4**, 1000 mg, 5.91 mmol) in dry THF (7 ml). After being stirred for 1 h, a solution of hexachloroethane (3079 mg, 13.00 mmol) in dry THF (7 ml) was added to the orange reaction mixture. The temperature of the reaction mixture was kept at −70 °C for 1 h, then at rt for 1 more hour. The reaction mixture was quenched by addition of saturated NH_4Cl and the aqueous phase was extracted with Et_2O twice. The combined organics were washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash-chromatography with Biotage SP4 (silica cartridge), eluting with cyclohexane/EtOAc (from 0% to 60%), to afford **5** (730 mg, 61% yield) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (1H, d, *J* = 5.56 Hz,) 6.83 (1H, d, *J* = 5.56 Hz,) 5.20 (2H, s) 3.93 (3H, s) 3.66 (3H, s). UPLC (IPQC): t_R 0.70 min, *m/z* 204 $[M+H]^{+1}$.
The ^{1}H spectra reported in the paper were obtained in $CDCl_3$ at 25 °C using a Bruker instrument 400 MHz. Chemical shifts are reported in ppm (δ) using the residual solvent line as the internal standard.
Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS AcquityTM system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQTM mass spectrometer operating in positive or negative electrospray ionisation mode [LC/MS—ES (+ or −): analyses performed using an AcquityTM UPLC BEH C18 column (50 × 2.1 mm, 1.7 μm particle size). Acidic conditions: Mobile phase: A—water + 0.1% HCO_2H/B—CH_3CN + 0.06% HCO_2H. Gradient: *t* = 0 min 3% B, *t* = 0.05 min 6% B, *t* = 0.57 min 70% B, *t* = 1.06 min 99%

B lasting for 0.389 min, t = 1.45 min 3% B, stop time 1.5 min. Column T = 40 °C. Flow rate = 1.0 mL/min. Mass range: ES (+): 100–1000 amu. ES (−): 100–800 amu. UV detection range: 210–350 nm.

12. 2-Chloro-3,4-pyridinediol (Intermediate **6**, 2.2 g, 13.60 mmol) and DMAP (6.65 g, 54.4 mmol) were suspended in 60 ml of dry DCM under argon atmosphere. The mixture was cooled at 0 °C and thiophosgene (2.6 ml, 33.9 mmol) was dropwise added. During the addition the formation of a light red precipitate was immediately observed. After 10 min the cooling bath was removed and the mixture was stirred at room temperature for 1 h. The reaction was diluted with DCM and silica was added to the reaction mixture. The solvent was removed under vacuum and the resulting red powder was loaded on a 100 g SNAP silica gel Biotage prepacked column for chromatographic purification. The intermediate **7** was eluted with DCM yielding, after evaporation, 2.02 g of a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.42 (1H, d, J = 5.43 Hz), 7.31 (1H, d, J = 5.43 Hz); UPLC (IPQC): t_R 0.91 min, m/z 188 $[M+H]^+$, 1Cl isotopic pattern.
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14. 4-Chloro[1,3]dioxolo[4,5-*c*]pyridine-2-thione **7** (1.3 g, 6.93 mmol) was dissolved in 40 ml of dry DCM. The solution was cooled with an acetone and dry ice bath and HF/pyridine (Aldrich, HF/pyridine 7/3 wt, 9/1 mole ratio) (13 ml) was carefully added dropwise. Solid 1,3-dibromo-5,5-dimethylhydantoin (6 g, 20.98 mmol) was immediately added portionwise. After 20 min the cooling bath was replaced by one made of ice and NaCl. The mixture was then stirred for 40 min, turning to dark red. After further 20 min, the cold reaction mixture was quenched by careful addition of 130 ml of aqueous ~5 M NaOH. A small amount of solid sodium thiosulphate was added to the mixture. The mixture was diluted with water, a white thick residue was removed by filtration and washed with DCM. The organic layer was separated with a phase separator tube and the aqueous one was extracted with further DCM. The collected organics were carefully evaporated under reduced pressure, keeping the heating bath at 30 °C and working above 300 mbar. The residual liquid was purified by flash chromatography on silica gel, using a 100 g SNAP prepacked Biotage cartridge and eluting with DCM. The product was partially coeluted with a byproduct, so the mixed fractions were carefully concentrated under reduced pressure and again purified by flash chromatography on silica gel, this time using a 50 g SNAP Biotage prepacked column and eluting with DCM. The pure fractions from both purifications were carefully evaporated, to give 1.17 g of compound **8** as a colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (1H, d, J = 5.31 Hz), 7.10 (1H, d, J = 5.31 Hz); UPLC (IPQC): t_R 0.94 min, m/z 194 $[M+H]^+$, 1Cl isotopic pattern.
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