Antimycobacterial Benzofuro[3,2-f]chromenes from a 5-Bromochromen-6-ol

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Abstract: In the course of our work on the synthesis of analogues of the specific antimycobacterial 3,3-dimethyl-3H-benzofuro[3,2-f]chromene, we prepared the previously unreported 5-bromo-2,2-dimethyl-2H-chromen-6-ol. We wish to report here an original synthetic scheme using this compound. The preparation of various 5-bromo-2,2-dimethyl-6-(aryloxy)-2H-chromenes was first investigated. This was followed by a palladium-catalysed cyclisation reaction, which takes place only in the presence of air, and leads to 3,3-dimethyl-3H-benzofuro[3,2-f]chromenes or 3,3-dimethyl-3H-4,7-dioxa-10-aza-benzo[f]fluorene. The antimycobacterial properties of these analogues have been investigated.

Key words: nucleophilic aromatic substitutions, cyclisations, medicinal chemistry, catalysis, palladium

Tuberculosis figures once again amongst the scourges of humanity. To combat this threat, the design of new anti-tuberculosis drugs acting on novel biological targets is a priority. 2 As previously reported, 3 the dibenzofuran derivatives 1 and 2 (Figure 1) were found to be remarkably selective in vitro inhibitors of mycobacterial growth. This has led us to undertake further investigations. One of our approaches focuses on the synthesis of related compounds, of which it is hoped that this selectivity of action is retained, but with improved activity in vitro and in vivo.

Figure 1

The first element of our structure–activity relationship study was somewhat disappointing, as the ‘easy to make’ analogues of this benzofuro[3,2-f]chromene derivative 1 had lower antimycobacterial activity or were also cytotoxic. 4 On the other hand, the high CLogP value of 1 (5.5 as estimated by calculation) or some of the analogues synthesised led us to investigate original synthetic access to compounds bearing more hydrophilic substituents. The lack of chemical selectivity sometimes encountered in the cyclisation of propargylic ethers into the chromene part of some of the analogues was amongst the difficulties. 4 We have reported an approach addressing this issue, the synthesis of the chromene ring system by an ytterbium triflate catalysed reaction between isobutene and various salicylaldehydes via the corresponding quinonemethides formed in situ. 6 In the course of this work, we observed that 2,5-dihydroxybenzaldehyde gave the corresponding chromene in low yield, along with unidentified side products. We also found more recently that, under the same reaction conditions, the readily available 2-bromo-3,6-dihydroxybenzaldehyde (3) 7 led to the corresponding 5-bromo-2,2-dimethyl-2H-chromen-6-ol (4) in 65% yield. This leads us to suggest that the additional bromine protects the 6-hydroxy moiety from further reactions through the formation of a stabilising internal hydrogen bond. In any case, this regioselective access to compound 4 opens many synthetic possibilities for the preparation of analogues of the antimycobacterial compound 1. Amongst them, the preparation of various 5-bromo-2,2-dimethyl-6-(aryloxy)-2H-chromenes would allow subsequent cyclisation to give the corresponding tetracyclic analogues featuring a central furan ring in only two steps.

After a few trials, it became clear that extensive decomposition along with a quite remarkable rearrangement of compound 4 into its isomer 5 took place under various basic conditions at high temperature. As illustrated in Scheme 1, heating compound 4 in dimethylacetamide at 130 °C for 2.5 hours in the presence of potassium carbonate led to a 3:1 mixture of compounds 4 and 5 along with highly polar material. Further heating, up to 12 hours, led to a 1:1 ratio and even more polar material. Even worse, the addition of copper salts under these conditions led to many other unidentified side reactions. On the other hand, little or no side reactions took place if potassium carbonate was omitted or if the isomerisation was attempted at 80 °C in N,N-dimethylformamide. Although we could not separate compounds 4 and 5, 1H, 13C, and long-distance correlation NMR spectroscopic studies demonstrated beyond any doubt the presence of 5 in the purified mixture (see experimental section).

The reduced chromane 6, selectively prepared under ionic hydrogenation conditions (Scheme 1), 8 was also moni-
tored for this isomerisation reaction. Remarkably, under the conditions described above, this compound does not isomerise. A literature search found previous reports describing related bromine migrations in the case of oxygen-rich aromatic compounds, although only under acidic conditions. We have too little experimental data to suggest a mechanism for this apparent bromine migration. The bromine atom of compound 4 could be displaced sequentially by successive phenolate ions. Unfortunately, its very weak ionisation under air-pressure electrospray ionisation technique precluded conclusive evidence for traces of a hypothetical dibrominated intermediate in the LC/MS analysis of the reaction mixture. Since much decomposition is observed in this reaction, more complex mechanisms cannot be excluded, such as a probably less plausible chromene ring opening/closure process.

Scheme 1
Reagents and conditions: (i) Yb(OTf)3, HC(OMe)3, H2C=CMe2, CH2Cl2, r.t., 60 h; (ii) K2CO3, AcNMe2, 130 °C; (iii) TfOH, TESH, CH2Cl2.

The base-induced isomerisation of 4 somehow limited the possible methods we could use for the synthesis of the corresponding aryl ethers. As depicted in Scheme 2, phenyl ether 7 was prepared in 38% yield by a very mild copper-catalysed coupling method between 4 and phenylboronic acid. In another approach, an aromatic nucleophilic substitution reaction took place between 4 and the reactive 1-fluoro-2-nitrobenzene in N,N-dimethylformamide at room temperature in the presence of sodium hydride to yield 2-nitrophenyl ether 8 in 74% yield (Scheme 2). It is remarkable that 4-chloro- or 4-iodopyridine did not undergo etherification to give 4-pyridyl ether 9 under these conditions, whereas ether 9 could be prepared in 60% yield from 4-iodopyridine by a solvent-free approach at 150 °C in the presence of sodium bicarbonate (Scheme 2).

A fairly simple protocol involving five mol% of palladium acetate and sodium carbonate was used to attempt the palladium-catalysed cyclisation of diaryl ethers 7–9 (Scheme 3). Tetrabutylammonium bromine, which likely acts as a remarkable catalyst stabiliser, was also added. Although we did not attempt to purify the reaction products of this trial, 1H NMR monitoring of the cyclisation of 7 indicated the formation of the expected product 1, but also sizable amounts of the linear isomer 10 as well as traces of the reduced diaryl ether 11 (Scheme 3). These last two unexpected side products were easily identified by 1H NMR spectroscopy, as we had previously obtained them by other, unambiguous synthetic routes. We verified that no isomerisation of 7 took place in boiling N,N-dimethylformamide in the presence of sodium carbonate and tetrabutylammonium bromide, thus confirming the importance of the palladium added. Furthermore, in light of previously reported palladium-promoted dehydrogenative ring closure, palladium-promoted cyclisation of pure compound 11 was attempted under the conditions described above, but resulted in no cyclisation by this pathway.

Palladium-catalysed cyclisations of ethers 8 and 9 into analogues 12 and 13 were achieved (Scheme 3), albeit in low yields, probably because of related side reactions. The

Scheme 2
Reagents and conditions: (i) Cu(OAc)2, H2O, Et3N, CH2Cl2, 4 Å MS, air; (ii) NaH, DMF, 25 °C; (iii) NaHCO3, neat, 150 °C.

Scheme 3
Reagents and conditions: (i) Pd(OAc)2, TBAB, DMF, air, reflux.

side products formed could not be properly separated from the main compounds by chromatography, but recrystallisation of these chromatographic fractions allowed the isolation of pure compounds 12 and 13 (in 17 and 21% yield, respectively). A noteworthy feature of this cyclisation reaction is that the best yields were obtained only if air was allowed into the reaction mixture. Monitoring of reaction trials under an argon atmosphere showed that the reaction would eventually stall prior to the formation of a black precipitate usually characteristic of a palladium deposit. A few trials using a more recently reported method\textsuperscript{34} were also unsuccessful.

Along with the isomerisation of 4, these results rather limited our attempts at the design of a regioselective and efficient route to the angular benzo-furo[3,2-f]chromene derivatives. We also investigated an alternative approach aimed at the preparation of chromane-bearing analogues of compound 2. We thus prepared ethers 14 and 15, in 61 and 43\% yield, respectively, from the more stable chromane 6 and phenylboronic acid and 4-iodopyridine, respectively (Scheme 4). The much improved 61\% yield of ether 14 was encouraging, as it hinted at chromane 6 being more stable than chromene 4 giving phenyl ether 7 in only 38\% yield. However, the cyclisation attempts under the conditions described above in the next step with both compound 14 and 15 were disappointing, as \textsuperscript{1}

H NMR monitoring showed that no reaction took place in the former case and only slow decomposition occurred in the latter.

![Scheme 4](image)

In summary, we have observed that the electron-rich chromene 4 is not very stable under basic conditions and can undergo an unprecedented low-yield rearrangement into 5. The formation of the isomeric cyclisation product 10 during palladium-catalysed cyclisation of 7 also results from some kind of palladium-promoted rearrangement. On the other hand, no base-promoted rearrangement occurred in the case of chromane 6 and the chromane-bearing ethers 14 and 15 did not react under palladium-promoted conditions to cyclise and form 7. One possible hypothesis is that because of lower electron density, the carbon–bromine bond of chromanes 6, 14, and 15 is much less reactive than the carbon–bromine bond of the corresponding chromenes. This remarkable difference in behaviour between biaryl ethers 7–9 and biaryl ethers 14 and 15 leads us to surmise that there is an initial $\pi$-interaction between palladium and the alkene moiety of the chromenes, which would assist the subsequent palladium insertion into the carbon–bromine bond. Again, we have not found a precedent for this putative assisting effect in the literature.

What appears to be less logical is the necessity to run the palladium-catalysed cyclisation reaction of compounds 7–9 in the presence of air, an experimental requirement that has not been reported so far. It is conceivable that a more thorough study of the reaction conditions, especially the use of modern palladium ligands, would allow the cyclisation of compounds 14 and 15. However, the antimonycobacterial activity of compounds 12 and 13 described below has not encouraged us to pursue this. Compounds 12 and 13 were assayed for their antimonycobacterial properties according to a previously described procedure.\textsuperscript{4} Probably because of its lack of solubility, compound 12 was devoid of antimonycobacterial activity, whereas the minimal inhibitory concentration MIC 95 of the much more soluble compound 13 on Mycobacterium smegmatis and Mycobacterium tuberculosis was 8 $\mu$g/mL and 16 $\mu$g/mL, respectively.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (6) are given in ppm relative to the TMS signal. Column chromatography was performed on Merck silica gel 60 (0.035–0.070 mm), and a solvent system consisted of gradients of either H$_2$O and MeCN containing 0.07\% HCO$_2$H or, more often, H$_2$O and MeOH containing 0.07\% ammonium formate. Microanalysis and HRMS were carried at the ICSN, CNRS, Gif sur Yvette, France.

5-Bromo-2,2-dimethyl-2H-chromene-6-ol (4) A previously described procedure was followed.\textsuperscript{5} In a 300-mL thick-walled round-bottomed flask fitted with a PTFE-faced screw-cap, 2-bromo-3,6-dihydroxybenzaldehyde\textsuperscript{7} (3; 4.00 g, 29.0 mmol) was dissolved in CH$_2$Cl$_2$ (185 mL). HC(O)Me$_2$ (4.25 mL, 37.7 mmol) and Yb(O$e$)$_3$·xH$_2$O (0.78 g, 1.3 mmol) were then added. The resulting solution was cooled to 0 °C in an ice bath and 2-methylpropene was bubbled through the solution. The mass added was monitored by periodic weighing, and 6.2 equiv 2-methylpropene (8.70 g) was thus added. The bottle was tightly closed and the soles were stirred at r.t. for 60 h. The resulting solution was cooled to 0 °C before (please note!) the bottle was opened; the contents were then diluted with CH$_2$Cl$_2$ (150 mL) and washed with 1 M NaHCO$_3$ soln (3 × 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated to dryness. The residue was dissolved in toluene (185 mL) and TsOH (0.07 g, 0.4 mmol) was added. The mixture was heated to reflux for 1 h while the MeOH was allowed to distil from the mixture by removal of the condensate in a Dean-Stark apparatus (four times). After the mixture had been concentrated to dryness, the residue was purified by column chromatography (silica gel, cyclohexane–CH$_2$Cl$_2$, 1:1); this yielded compound 4 as an oil which slowly turned deep purple even when stored at 0 °C.

Yield: 4.14 g (65\%).
LC/MS (ES): \textit{m/z} = 253/255 [M – H]⁺. This compound could not be properly ionised for HRMS.

7-Bromo-2,2-dimethyl-6-chromen-6-ol (5)
Compound 4 (0.1 g, 0.39 mmol), K₂CO₃ (0.2 g, 1.5 mmol), and AcNMeff (20 mL) were heated in a sealed tube for 2.5 h at 130 °C. The resulting dark solid was concentrated to dryness, diluted with EtOAc (100 mL) and washed with H₂O (3 x 10 mL). After removal of the solvents, the residue was purified by chromatography (silica gel, cyclohexane–CH₂Cl₂, 1:1); this yielded a mixture of compounds 4 and 5 (3:1) as an oil. (The NMR data for compound 5 given below were obtained by subtracting the NMR signals of 4 from the NMR spectra of this mixture of 4 and 5.)

Yield: 0.03 g (30%).

1H NMR (400 MHz, CDCl₃): δ = 1.44 (s, 6 H, CH₃), 5.09 (s, 1 H, OH), 6.69 (d, J = 9.9 Hz, 1 H, H-3), 6.26 (d, J = 9.9 Hz, 1 H, H-4), 6.68 (s, 1 H-5), 6.92 (s, 1 H, H-8). 13C NMR (100 MHz, CDCl₃): δ = 28.0, 76.6, 109.1, 113.2, 119.5, 122.0, 122.6, 132.8, 146.7, 147.3.

5-Bromo-2,2-dimethylchroman-6-ol (6)
Compound 4 (0.66 g, 2.6 mmol) was dissolved in CH₂Cl₂ (100 mL). TESH (1.65 mL, 10.3 mmol) was added, followed by TIOH (0.91 mL, 10.3 mmol), which was added dropwise. The resulting purple soln was stirred for 3 h, washed with 1 N NaHCO₃ (3 x 10 mL) and H₂O (3 x 10 mL), dried (Na₂SO₄), and concentrated to dryness. The residue was purified by chromatography (silica gel, cyclohexane–CH₂Cl₂, 1:1); this yielded compound 6 as an oil which also slowly darkened over time. (The 1H NMR data are closely related to that reported previously.²⁵)

Yield: 0.39 g (59%).

1H NMR (400 MHz, CDCl₃): δ = 1.44 (s, 6 H, CH₃), 1.83 (t, J = 6.9 Hz, 2 H, CH₃-3), 2.74 (t, J = 6.9 Hz, 2 H, CH₂-4), 5.32 (s, 1 H, OH), 6.72 (d, J = 8.9 Hz, 1 H, H-7), 6.84 (d, J = 8.9 Hz, 1 H, H-8).

13C NMR (100 MHz, CDCl₃): δ = 24.7, 26.7, 33.1, 74.0, 112.7, 114.5, 117.7, 121.3, 146.1, 148.7.

LC/MS (ES): \textit{m/z} = 256, 257, 258, 259 (weak signals; extensive decomposition in the source).

5-Bromo-2,2-dimethyl-6-phenoxy-2H-chromen-6-ol (7)
Compound 4 (0.2 g, 0.78 mmol), PhBH₂(OH)₂ (0.19 g, 1.56 mmol), Cu(OAc)₂·H₂O (0.156 g, 0.78 mmol), and Et₃N (0.33 mL, 2.34 mmol) were mixed in CH₂Cl₂ (10 mL). To this suspension was added 4-iodopyridine (0.20 g, 1.0 mmol), and NaHCO₃ (0.16 g, 2.34 mmol) was added. The mixture was stirred overnight at r.t. and then concentrated to dryness. The residue was dissolved in EtOAc (100 mL) and the organic phase was washed with H₂O (5 x 10 mL), dried (Na₂SO₄), and concentrated to dryness. The residue was purified by chromatography (silica gel, cyclohexane–CH₂Cl₂, 85:15); this gave compound 7 as a yellow solid.

Yield: 0.84 g (74%).

1H NMR (400 MHz, CDCl₃): δ = 1.48 (s, 6 H, CH₃), 5.79 (d, J = 10.0 Hz, 1 H, H-3), 6.70 (d, J = 10.0 Hz, 1 H, H-4), 6.81 (m, 2 H, H-7 and H-8), 6.93 (d, J = 8.7 Hz, 1 H, H-7), 7.15 (m, 1 H, H-Ar4), 7.45 (m, 1 H, H-Ar5), 7.97 (d, J = 8.1 Hz, 1 H, H-Ar3).

13C NMR (100 MHz, CDCl₃): δ = 28.0, 76.8, 115.4, 116.9, 117.9, 121.3, 121.1, 122.6, 123.0, 126.1, 133.5, 134.4, 140.4, 144.5, 151.6, 151.5.

LC/MS (ES): \textit{m/z} = 393/395 [M + NH₄]⁺.


4-(5-Bromo-2,2-dimethyl-2H-chromen-6-ol)pyridine (9)
In a Kugelrohr distillation apparatus, a mixture of 4 (0.25 g, 1.0 mmol), 4-iodopyridine (0.20 g, 1.0 mmol), and NaHCO₃ (0.16 g, 2.0 mmol) was heated at 150 °C for 2 h. The residue was purified by chromatography (silica gel, CH₂Cl₂–EtOH, 99:1); this gave 9 as a brown oil. (Note that 9 could be obtained in similar yield from the commercially available 4-chloropyridine hydrochloride.)

Yield: 0.2 g (61%).

1H NMR (400 MHz, CDCl₃): δ = 1.49 (s, 6 H, CH₃), 5.71 (d, J = 9.9 Hz, 1 H, H-3), 6.60 (d, J = 9.9 Hz, 1 H, H-4), 6.72 (m, 2 H, H-7 and H-Pyr 3 and 5), 6.83 (d, J = 8.7 Hz, 1 H, H-8), 8.38 (m, 2 H, H-Pyr 2 and 6).

13C NMR (100 MHz, CDCl₃): δ = 32.1, 76.9, 111.7, 115.9, 117.0, 121.3, 121.7, 123.0, 133.5, 144.7, 151.7, 151.8, 164.9.

LC/MS (ES): \textit{m/z} = 332/334 [M + H]⁺.


4-(5-Bromo-2,2-dimethyl-2H-chromen-6-ol)pyridine (15)
The procedure described above for the preparation of 9 was used to prepare 15, which was obtained as an oil.

Yield: 43%.

1H NMR (400 MHz, CDCl₃): δ = 1.38 (s, 6 H, CH₃), 1.88 (t, J = 6.8 Hz, 2 H, H-3), 2.80 (t, J = 6.8 Hz, 2 H, H-4), 6.81 (m, 2 H, H-Pyr 3 and 5).
and 5), 6.84 (d, J = 8.8 Hz, 1 H, H-7), 6.95 (d, J = 8.8 Hz, 1 H, H-8), 8.47 (m, 2 H, H-Pyr 2 and 6). To this, Pd(OAc)2 (13.0 mg, 0.058 mmol), TBAB (0.39 g, 1.17 mmol), and K2CO3 (0.4 g, 2.9 mmol) were added. The suspension was heated to reflux atmosphere for 3 h. The solvent was removed under vacuum, the residue was purified by two successive recrystallisations from cyclohexane.


3,3-Dimethyl-8-nitro-3H-benzofuro[3,2-f]chromene (12)

Aryl ether 8 (0.44 g, 1.17 mmol) was dissolved in DMF (30 mL, dried over 4 Å MS). To this, Pd(OAc)2 (13.0 mg, 0.058 mmol), THF (0.9 g, 1.17 mmol), and K2CO3 (0.4 g, 2.9 mmol) were added. The suspension was heated to reflux without (important!) an inert atmosphere for 3 h. The solvent was removed under vacuum, the residue was dissolved in EtOAc (100 mL), and the organic phase was washed with H2O (5 x 10 mL), dried (Na2SO4), and concentrated to dryness. The residue was purified by chromatography (silica gel, cyclohexane–CH2Cl2, 3:1); this gave compound 12, which was further purified by two successive recrystallisations from cyclohexane.

Yield: 0.06 g (17%); mp 174 °C.

1H NMR (400 MHz, CDCl3): δ = 1.53 (s, 6 H, CH3), 5.92 (d, J = 9.8 Hz, 1 H, H-2), 7.05 (m, 1 H, H-10), 7.50 (d, J = 8.7 Hz, 1 H, H-6), 118.25, 118.8 (d), 122.7, 122.9, 128.6, 129.1, 133.5, 134.4, 149.9, 152.1.


3,3-Dimethyl-4,7-dioxa-10-aza-benzo[c]fluorene (13)

The procedure described above for the preparation of 12 was used to prepare 13 from diaryl ether 9; this led to a residue, which was purified by chromatography (silica gel, CH2Cl2–EtOH, 99:1). This fraction was purified further by recrystallisation from cyclohexane.


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