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Synthesis of 6-substituted 5-cyano-7-hydroxy-2-carboxybenzofurans

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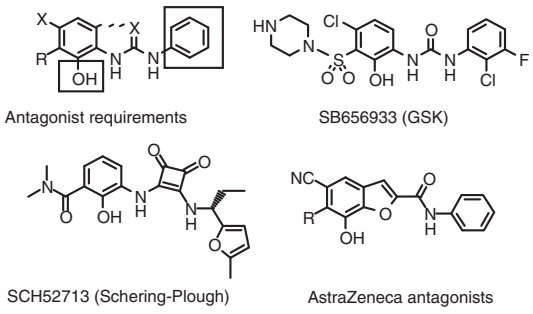
ABSTRACT

Methods for the synthesis of 5-cyano-7-hydroxy-2-carboxybenzofurans bearing a variety of substituents at the 6-position are outlined. The scope and limitations of lithiation processes, electrophilic substitutions, and pericyclic reactions are investigated.

Antagonists of the CXCR2 receptor have a number of potential therapeutic applications.[1] Typically they consist of a phenol connected through a urea to a second aromatic ring.[2] Our in-house program toward antagonists of this receptor used a benzofuran to fix the required groups correctly in space. The synthesis of such heavily substituted benzofurans required the development of a number of novel synthetic transformations which are outlined in this Letter.



Initially, lithiation at the 6-position of 5-cyano-7-methoxybenzofuran[3] **1** (Scheme 1) was investigated. Cyano groups are powerfully *ortho*-directing, though this property is synthetically under utilized. Lithiation dominates over addition to the nitrile when hindered, non-nucleophilic bases are used.[4] It was anticipated that the complexation/chelation of the lithium species by the 7-methoxy group would assist in regiochemical control. The lithiation of **1** failed due to a combination of its insolubility in THF and/or ether at −78 °C and the presence of a moderately reactive 2-furyl ester. These problems were not overcome by using alternative bases such as LiTMP·LiCl or its derivatives. The more soluble and sterically encumbered *t*-Bu ester underwent lithiation and quenched at the 3-position (17% yield plus starting material) using in situ TMSCl, with excess LiTMP as base and allowing the reaction mixture to warm from −78 °C to 0 °C.

The ester moiety was reduced and protected to give **2**. Disappointingly, lithiation and quenching with methyl chloroformate gave a 3:1 mixture of the 4- and 6-methyl esters **3** and **4**. The hoped-for directing effect of the methoxy may be offset by increased steric crowding in this heavily substituted system.

Analogous lithiation applied to the monocyclic system **5**[5] (Scheme 2) cleanly gave the desired lithiation regiochemistry and was quenched with dimethyl disulfide. Demethylation with thiolate gave a difficult to separate mixture of monophenols **7** and **8**. The activating effect of the *para*-cyano function appears to be counterbalanced by the known tendency of 1,2,3-substituted systems to dealkylate regiospecifically at the 2-position.[6] The use of other reagents such as Me_3SiI gave the undesired isomer **7**, regioselectively.

Lithiation and quenching of the silyl-protected ether **9** (Scheme 3) gave the required phenol upon deprotection. Duff formylation gave the aldehyde **11**, annulation with methyl bromoacetate and oxidation gave the sulfoxide **12**. Pummerer rearrangement of this sulfoxide followed by oxidation to the sulfonyl chloride, using chlorine gas in acetic acid gave the sulfonyl chloride **13**. The reaction with Boc-piperidine gave the sulfonamide **14**, possessing a substitution pattern analogous to that found in SB656933. The ester was hydrolysed, coupled with aniline, the methoxy group was converted to the phenol, and the Boc-group was removed to give the required compound **16**.

The sulfonamide could be installed early in the synthesis (Scheme 4) by quenching the anion with sulfur dioxide and converting the intermediate sulfinic acid salt into the benzotriazole sulfonamide **18**.[7] This was converted into stable sulfonamides. However, all attempts at electrophilic formylation of phenol **19**, which possesses two powerful electron-withdrawing groups, resulted in decomposition.

Frustration at our inability to functionalize directly the 6-position in these benzofurans led us to investigate further reactivity in this system (Scheme 5). The profound deactivation exerted by

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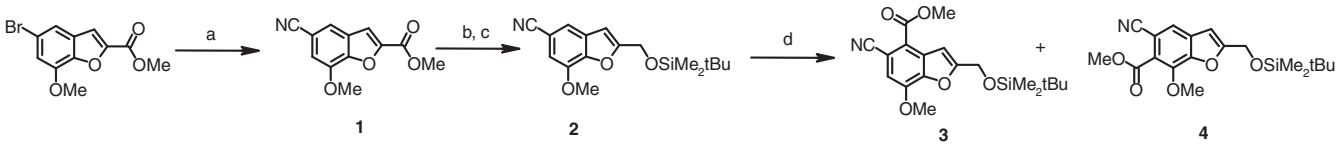
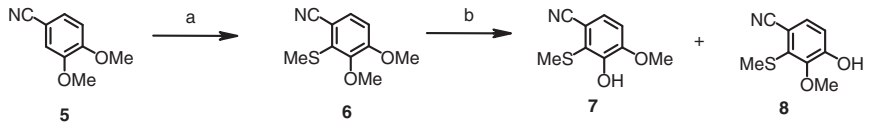
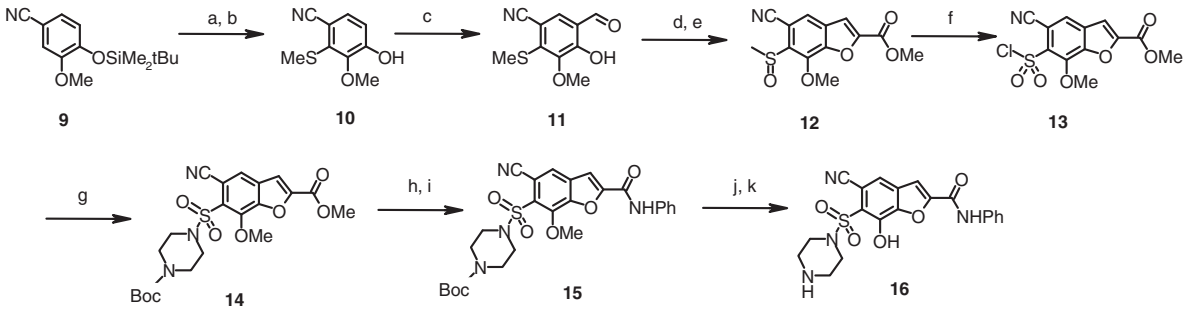


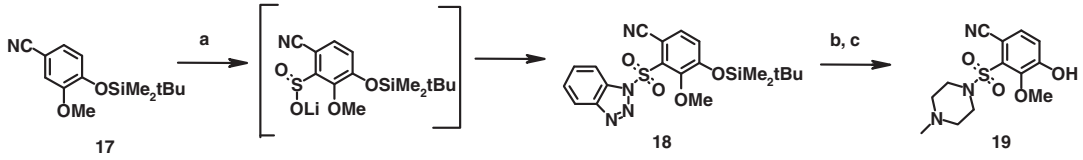
Scheme 1. Reagents and conditions: (a) $Zn(CN)_2$, $(Ph_3P)_4Pd$, N_2, DMF, 85 °C, 70%; (b) $LiBH_4$, THF, 60 °C, 99%; (c) $ClSiMe_2tBu$, DMF, imidazole, 25 °C, 95%; (d) LiTMP, THF, −78 °C then $ClCO_2Me$, 36%.



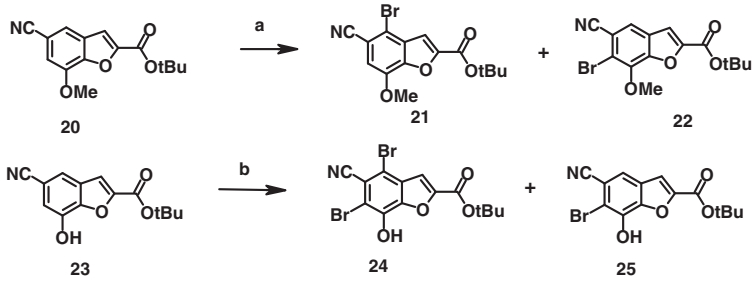
Scheme 2. Reagents and conditions: (a) LiTMP, THF, −78 °C then MeSSMe, 49%; (b) NaSMe, DMF, 50 °C, 74%, 7: **8** = 2:1.



Scheme 3. Reagents and conditions: (a) LiTMP, THF, −78 °C then MeSSMe, 82%; (b) TBAF, THF, 100%; (c) HMTA, TFA, 80 °C, 80%; (d) $BrCH_2CO_2Me$, K_2CO_3, DMF, rt then 100 °C, 70%; (e) mCPBA, CH_2Cl_2, rt, 95%; (f) TFAA then Cl_2, AcOH, 50 °C, 80%; (g) Boc-piperazine, neat, 90%; (h) LiOH, THF, H_2O, 90%; (i) $PhNH_2$, TBTU, DMF, Hünig's base, 70%; (j) LiI, collidine, 120 °C, 70%; (k) TFA neat, rt, 100%.



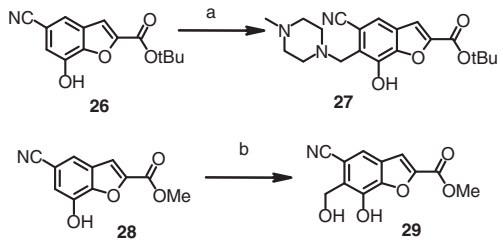
Scheme 4. Reagents and conditions: (a) LiTMP, THF, −78 °C then SO_2 at −78 °C followed by BtCl and warming to 25 °C, 24%; (b) NMe-piperazine, 100%; (c) TBAF, THF, 100%.



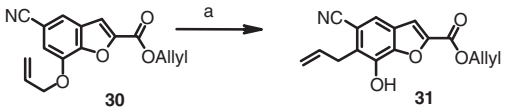
Scheme 5. Reagents and conditions: (a) 3 equiv Br_2, NaOAc, AcOH, 80 °C, 8 h; (b) Br_2, *t*-$BuNH_2$, toluene, CH_2Cl_2, −78 °C, 69% yield for isomer **25**.

the 5-cyano group can easily be underestimated. Forcing conditions and prolonged reaction times are required for mono-bromination of the anisole **20** even with excess bromine. The reaction is selective for the unwanted 4-bromo isomer over the 6-isomer, ratio 3:1. The reactivity of the system can be greatly increased by demethylation to the phenol **23**. Conventional bromination conditions (Br_2, NaOAc, HOAc, 25 °C) gave mixtures of the starting materials together with 6- and 4,6-dibrominated materials. Regioselective *ortho*, mono-substitution in phenols has been extensively investigated.[8] These conditions eventually allowed the production of the required regioisomer **25**, in a good yield. Attempts to introduce a variety of other electrophilic substitutions on phenol **23** using reagents such as $MeSSMe/AlCl_3$, $ClSO_3H$, and HMTA/TFA under a variety of conditions failed.

Remarkably the exceptions to this rule were Mannich processes and hydroxymethylation using paraformaldehyde with a dialkyl



Scheme 6. Reagents and conditions: (a) paraformaldehyde, LiCl, NMP, NMe-piperazine, 50 °C, 43%; (b) Et_2AlCl, paraformaldehyde, DCE, 25 °C, 24 h, 92%.



Scheme 7. Reagents and conditions: (a) xylene reflux, 40 h, 100%.

aluminum Lewis acid catalyst[9] (Scheme 6). The latter may be driven by precipitation of the intermediate aluminate complex. The steric crowding present in this system is demonstrated by the facile loss of the 6-substituent when these products are isolated by concentration from formic- or TFA-containing, reverse phase chromatography fractions, if these had not first been neutralized. Finally the 6-position could be allylated cleanly using the Claisen rearrangement (Scheme 7).

Despite considerable synthetic challenges, we were eventually able to introduce a variety of functional groups into the 6-position of 5-cyano-7-hydroxybenzofurans. These were used to modulate the biological and physical properties of these therapeutically interesting molecules.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.020.

References and notes

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