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4-Chromenesulphones: synthesis and transformation to isoflavonoid models†

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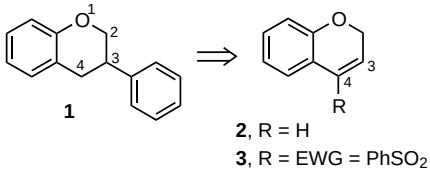
Abstract—Novel sulphones derived from chromenes through substitution at C-4 were prepared. It has been shown that, after conjugate addition of phenyl lithium and sulphone function manipulation on the adducts, these molecules lead to isoflavan, isoflavene and isoflavanone models.

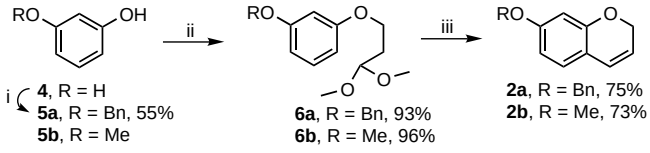
Isoflavonoids constitute quite a large family of natural products.[1,2] Some of these molecules are biosynthesized de novo by plants as a consequence of microorganism invasion. Induced substances which carry antimicrobial activity are known as phytoalexins. Regardless of functional group composition, most isoflavonoids bear basic backbone **1** (Scheme 1).

We wondered whether skeleton **1** might be constructed from chromene **2**. This structure could arguably be harnessed to accept a phenyl nucleophile at C-3. Thus, a temporary electron-withdrawing group (EWG), properly located (as shown by **3**), would render the required electrophlilicity to **2**. Sulphones are well suited for this task. Furthermore, they are recognizably versatile functional groups[3] and could accommodate introduction of different functions at C-4 and/or C-3. Herein, we describe the synthesis of novel substances **3** and report chemical transformations effected on them.



Scheme 1.

We set resorcinol-related chromenes **2** as starting materials (Scheme 2). Among the literature alternatives,[4] we chose to obtain these compounds via acetals **6**,[4a] mainly due to the availability of materials employed in their synthesis. Nevertheless, the initial experiments making use of such a route indicated the opportunity of further development. Firstly, we managed to increase the yields of acrolein-derived acetal chain incorporation on phenols **5** by changing the solvent to DMF. The reaction times were also much shorter (1.5 h) and reaction conditions milder. With regard to preparation of substances **2**, control over the amount of *p*-TsOH (0.05 mol equiv.) and reaction dilution (0.1–0.2 M) was found to be essential to suppress the formation of inseparable 4-methoxy ether, an especially important problem at larger scales, and to bestow a more consistent reaction profile. We observed that, under these conditions, cyclization to chromenes **2** could be accomplished at higher rates (reaction taking 1.5 h instead of 3–6 h). Moreover, we were able to prepare unavailable 3-benzyloxy phenol **5a** from resorcinol **4** in a more straightforward manner.[5] Notwithstanding the moder-



Scheme 2. *Reagents and conditions*: (i) a. BnCl (0.5 mol. equiv.), DMSO, rt; then, 40% aq. KOH (1.3 mol. equiv.), 90°C, 16 h, b. aq. NH_4Cl, rt. (ii) a. NaH, DMF, 0°C, rt, b. $I(CH_2)_2CH(OCH_3)_2$, rt. (iii) *p*-TsOH, dioxane, 110°C.

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† We dedicate this work to the memory of Professor Roderick A. Barnes, a pioneer in Natural Products Chemistry in Brazil.

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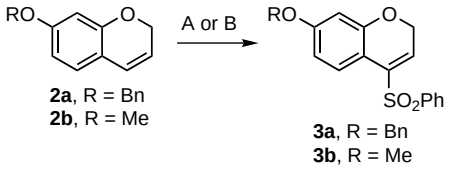
ate yield of **5a** that it provided,[6] this homogeneous-medium procedure made the preparation of multigram quantities (10–20 g) of **5a** easier.

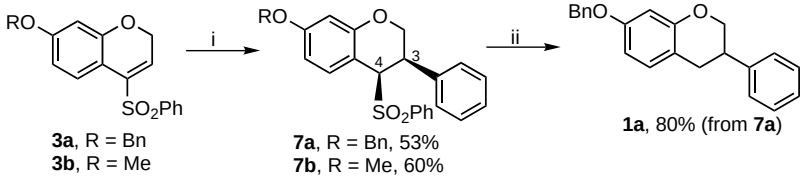
With compounds **2** in hand, we investigated phenylsulphinyl group incorporation and found that Sas-Inomata's procedure[7] proceeded regioselectively to **3** (Scheme 3). By this, chromenes **2** were transformed into β-chloromercury sulphones. Such intermediates were isolated and, in crude form, subjected to rapid HgCl (as Hg^0 and Cl^-) group elimination (20 min). Reproduction of literature stoichiometry (condition A) resulted in slow reaction (24 h) and incomplete conversion to the organomercurial intermediate (55% yield after demercuration). However, we found that higher rates (3 h) and (slightly higher) yields (60%) are attained when a 1.0 mol. equiv. excess of $HgCl_2$ (condition B) is employed. At large scales, condition A is indicated because it prevents final product contamination by mercurial species.



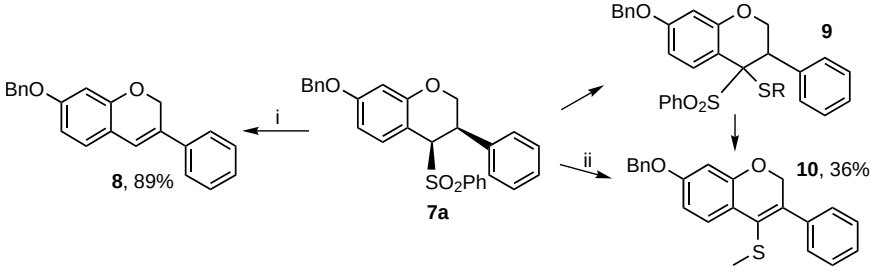
Scheme 3. *Reagents and conditions*: (A) i. $PhSO_2Na$, CH_3OH, CH_2Cl_2; then, $HgCl_2$ (1.0 equiv.), rt, ii. DBU, THF, rt. (B) i. idem, except for: $HgCl_2$ (2.0 equiv.), ii. idem.

Conjugate addition of phenyllithium to vinylsulphones **3** occurred quite cleanly (Scheme 4).‡ Data from NOE diff experiments (6.0–7.7% enhancements following irradiations of C_3/C_4-hydrogens) on adduct **7a** are consistent with the shown *cis* diastereomer.[8] Thus, during work-up (addition of aq. NH_4Cl at −30°C), the proton source approaches the conjugate base of sulphones **7** *anti* to the phenyl group producing kinetic product **7**. Once the electrophilic ability of substances **3** had been established, we set out to study potential manipulations of the sulphone function. Desulphinylation of **7a** was easily accomplished by metal reduction.[9] Isoflavan model structure **1a** was obtained.

Moreover, elimination reaction[10] provided 3-phenyl chromene **8**, a model for isoflavenes (Scheme 5). We also studied conversion of adduct **7a** into its respective ketone via hydrolyzable α-thiosulphone **9**.[11] Attempts to react the conjugate base of **7a** (LDA or LHMDS as base) with $(PhS)_2$ resulted mainly in recovered starting material. Conversely, application of condition ii (Scheme 5) brought about conversion of sulphone **7a** into a high-absorbance (UV) compound in low yield which we identified as methylthiochromene **10**. Naturally, **10** results from the fast in situ elimination of sulphinate from product **9** (R = Me) which leads to a conjugated tetrasubstituted olefin. Hydrolysis of **10** could possibly provide the desired ketone, but because of the low yields of **10**, we sought another means for achieving this transformation.

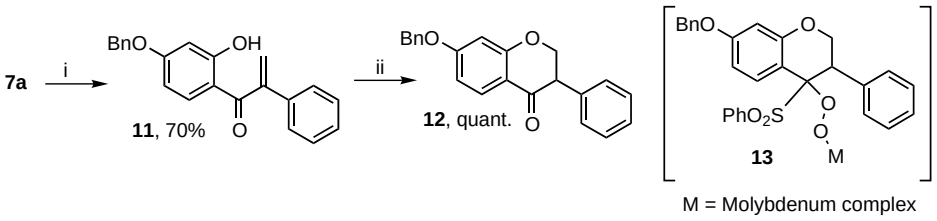


Scheme 4. *Reagents and conditions*: (i) [PhBr–BuLi], THF, −78°C, −30°C. (ii) Na(Hg), MeOH, THF, rt.



Scheme 5. *Reagents and conditions*: (i) ^{t}BuOK, THF, 0°C, rt. (ii) a. LHMDS, THF, −78°C, b. $(MeS)_2$, THF, HMPA, −78°C, −30°C.

‡ Representative procedure: A stirred solution of PhBr (0.124 g; 0.79 mmol) in THF (1.0 mL) at −78°C under Ar was slowly treated with BuLi in hexanes (1.42 M, 0.55 mL). After 20 min, sulphone **3b** (0.16 g; 0.53 mmol) in THF (1.3 mL) was added dropwise to the resulting mixture. The reaction mixture was kept under the same conditions for 30 min and then it was slowly warmed to −30°C. After 2.5 h at −30°C, satd aq. NH_4Cl was added and the cold bath was removed. Product extraction with AcOEt, followed by the usual work-up procedures, led to a brown residue. This material was purified by medium-pressure column chromatography on silica gel (eluting with 10–30% AcOEt/hexanes) to afford pure **7b**.



Scheme 6. *Reagents and conditions*: (i) a. LHMDS, THF, −78°C, b. MoOPH, THF, −78°C. (ii) DBU, THF, rt.

Use of Vedejs' reagent[12] produced α,β-unsaturated ketone **11** (Scheme 6) instead of the desired cyclic compound **12**. After treatment with DBU (but not with either pyridine or Et_3N), enone **11** was converted to **12**. Interestingly, it appears that, during the first reaction, formation of less polar product **11** occurs in the reaction medium (TLC) before the usual reductive work-up. Thus, apparently, the metal peroxide[13] intermediate **13** disproportionates spontaneously in situ producing **12**, which suffers *retro*-Michael-type ring opening under the basic conditions. Ketone **12** represents an isoflavanone model structure.

It is noteworthy that this chemistry enables the preparation of 3-substituted dihydrobenzopyran systems employing phenols bearing free *ortho* positions as starting materials. It renders unnecessary the employment of 2-functionalized phenols, a common feature of the alternative synthetic methodologies.[14]

In summary, a practical synthesis of chromene-based vinyl sulphones has been developed. These novel structures have proven to be quite versatile. Phenyl adducts resulting from these structures may have their sulphone group manipulated to yield isoflavan, isoflavene and isoflavanone models.

Acknowledgements

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