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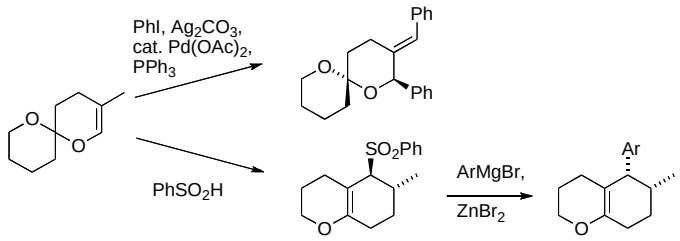

Tetrahedron Letters
journal homepage: www.elsevier.com

Arylation of [6,6]-spiroacetal enol ethers: reactivity and rearrangement

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Spiroacetal
Enol ether
Tetrahydrochroman
Rearrangement
Hexahydrochroman

ABSTRACT

Attempts to selectively arylate [6,6]-spiroacetal enol ethers at the 2-position delivered unexpected results. Palladium-mediated arylation conditions afforded the double-Heck product, whereas reaction with benzenesulfinic acid resulted in a facile rearrangement into the corresponding 5-phenylsulfonyl-3,4,5,6-tetrahydrochromans, providing access to 5-aryl-3,4,5,6-tetrahydrochroman and hexahydrochroman derivatives.

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Spiroacetals[1] are a common structural motif found in many natural products derived from marine organisms, insects, plants, and fungi.[2] These natural products vary greatly in structural complexity and biological activity, acting as insect pheromones, and displaying antibacterial, antifungal, and anti-proliferative properties, among others.[3] Interestingly, of the more than 2500 spiroacetal containing natural products identified to date, only one, integramycin (**1**, Figure 1), incorporates a 2-aryl substituent.[4] Integramycin was first isolated from the fermentation extracts of *Actinoplanes* sp. in 2002, and has been shown to inhibit strand transfer reactions mediated by the viral enzyme HIV-1 integrase, with an IC_{50} value of 4 μM.[3b] Additionally, integramycin exhibits no activity in DNAase assays at 100 μM, implying that it selectively inhibits HIV-1 integrase over other DNA interactive enzymes.

Integramycin poses a challenging synthetic target, comprising thirteen stereocentres and three chemically disparate regions: the aryl spiroacetal, *cis*-decalin and tetramic acid subunits. To date, there have been no reported total syntheses of integramycin, although the aryl spiroacetal subunit and the *cis*-decalin fragments have been synthesized by the groups of Floreancig[5] and Roush,[6] respectively. Floreancig and coworkers employed a ruthenium-mediated hydroesterification and a *C,O*-dianionic addition to a lactone to afford the spiroacetal in their stereoselective synthesis of the aryl spiroacetal subunit.[5] We sought to develop an alternative methodology to access 2-arylspiroacetals, initially focusing on a model system.

Insert Figure 1

We now report our investigation of two strategies for the synthesis of the desired 2-arylspiroacetal motif **2**, *via* a common spiroacetal enol ether **3**: (i) a Heck reaction[7] and subsequent hydrogenation, and (ii) the addition of benzenesulfinic acid across the enol ether double bond, followed by displacement of phenylsulfinate using an appropriate arylzinc reagent.[8] Spiroacetal enol ether **3** could, in turn, be derived from appropriately substituted *exo*-methylene tetrahydropyran **4** and an acrolein derivative **5**, *via* an inverse electron demand hetero-Diels–Alder (HDA) reaction (Scheme 1). The use of an HDA reaction provides a convergent, stereoselective strategy for the synthesis of doubly anomerically-stabilized spiroacetal enol ethers.[9]

Insert Scheme 1

Accordingly, spiroacetal enol ethers **8a** and **8b** were synthesized from tetrahydropyran-2-methanol (**6**) by chlorination,[10] elimination,[11] and HDA reaction with acrolein[12] or methacrolein,[11] respectively (Scheme 2). Initially considering the Heck–hydrogenation strategy, we rationalized that attack of the arylpalladium species should occur from the less hindered β-face, as should subsequent hydrogenation, resulting in the desired equatorial-equatorial stereochemistry (Scheme 3).[13] To investigate this stereochemical hypothesis, the 3-methyl substituted spiroacetal enol ether **8b** was used in our investigation of the key Heck reaction.

Insert Scheme 2

Insert Scheme 3

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Heck reactions of acyclic[14] and cyclic enol ethers[15] have been reported, however, Heck reactions with cyclic olefin substrates have typically resulted in unpredictable isomerization of the resultant product double bond.[16] Larock and coworkers demonstrated that the use of silver carbonate as base and triphenylphosphine as an additive, in conjunction with palladium(II) acetate, almost entirely overcomes unwanted isomerization.[16] With this precedent in mind, we initially sought to exploit these conditions for Heck coupling using spiroacetal enol ether **8b** (Scheme 4).

Insert Scheme 4

Unfortunately, despite attempts to optimize this chemistry for our system, and surveying numerous alternative Heck reaction conditions,[17] the desired product was never obtained. Intriguingly, using iodobenzene with catalytic $Pd(OAc)_2$, Ag_2CO_3 and PPh_3 in 1,4-dioxane afforded spiroacetal **11**,[18] presumably resulting from a second Heck coupling on intermediate *exo*-methylene compound **9a**. Despite significant attempts to curb this undesired reactivity, no desired product was forthcoming, and therefore the alternative arylation strategy was investigated.

Insert Scheme 5

Ley and co-workers have demonstrated that the addition of benzenesulfinic acid to cyclic enol ethers affords the corresponding 2-benzenesulfonyl cyclic ethers.[19] Further reaction with an arylzinc reagent generates the analogous 2-arylcyclic ether.[20] We sought to apply this methodology to our spiroacetal enol ethers (Scheme 5). Reaction of **8b** with benzenesulfinic acid afforded an unexpected product. Instead of the anticipated 2-phenylsulfonylspiroacetal **12b**, 5-phenylsulfonyltetrahydrochroman **13b** was obtained in quantitative yield, solely as the *trans*-diastereomer. The structure of this product was confirmed by X-ray crystallographic analysis,[21] see the Supporting Information for further details.

A mechanistic rationale for the formation of **13b** is illustrated in Scheme 6. Protonation of enol ether **8** and subsequent ring opening of **14** to give **15** would provide aldehyde **16** after loss of a proton. Formation of **17** by intramolecular attack of the enol ether on the aldehyde group and loss of water from **18** would provide conjugated oxocarbenium ion **19** which is trapped by benzenesulfinate to give the sulfone **13**.

Insert Scheme 6

Curiously, subjecting spiroacetal **8a** to the same reaction conditions produced varying results. Initial attempts provided an inseparable mixture of the equatorial[18] 2-phenylsulfonylspiroacetal **12a** and 5-phenylsulfonyl-5,6,7,8-tetrahydrochroman (**13a**) (Scheme 7). This reaction proved particularly capricious, affording highly variable product ratios, ranging from exclusively spiroacetal **12a** to exclusively tetrahydrochroman **13a**. Separate exposure of either **12a** or **13a** to benzenesulfinic acid did not result in interconversion, suggesting the formation of each of these products is irreversible under the reaction conditions employed. In contrast, treatment of **8b** with benzenesulfinic acid under a variety of conditions, reproducibly provides **13b**, with no evidence for the formation of **12b** in any experiment to date.

Insert Scheme 7

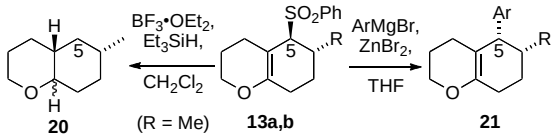
Attempts to direct product formation by varying reaction concentration, temperature, stoichiometry and reaction time, etc. proved unsuccessful. Sulfinic acids are prone to disproportionation and autoxidation to sulfonic acid and thiosulfonate.[22] For this reason, we sought to purify the sulfinic acid immediately prior to use, through complexation/decomplexation with iron(III).[23] Alas, purification of the benzenesulfinic acid had no discernible effect on reaction outcome, using either spiroacetal enol ether **8a** or **8b**. Likewise, substitution of the benzenesulfinic acid with *p*-toluenesulfinic acid did not alter the product outcomes. Other attempts to alter the reaction course by, e.g. the addition of water, the *in situ* generation of the benzenesulfinic acid from the sodium salt, or buffering the reaction mixture with pyridine failed to significantly alter the reaction outcomes. Attempts to convert enol ethers **8a** and **8b** into 2-phenylthio spiroacetals, which could subsequently be oxidized to the desired sulfones, *via* a ceric ammonium nitrate mediated addition of thiophenol[24] were also unsuccessful, leading to decomposition of starting materials in all cases.

Taking the small amount of 2-phenylsulfonylspiroacetal **12a** available to us, we set about reacting it with phenylmagnesium bromide and zinc bromide (Scheme 8).[13] The desired substitution product **10a** was not obtained, and in all attempts at this reaction, a gelatinous precipitate was observed, possibly indicating that 2-phenylsulfonylspiroacetal **12a** binds strongly to the divalent metal ions and is removed from solution.

Insert Scheme 8

Conversely, reaction of the rearrangement products **13a** and **13b** with aryl Grignard reagents in the presence of zinc bromide afforded excellent yields of the corresponding 5-aryl-5,6,7,8-tetrahydrochromans **21a–d** (entries 1–4, Table 1**)**. Disubstituted tetrahydrochromans **21c** and **21d** were each isolated as a single diastereomer, and were tentatively assigned as the *cis*-isomers based on the coupling constant of H-5 (doublet, J = 8.0 Hz), comparison with the absence of H-5 coupling in **13b** (singlet), and the expected inversion of configuration. Reduction of **13b** with triethylsilane–BF_3•OEt_2 was equally successful, affording the fully reduced 6-methylhexahydrochroman **20** in good yield (entry 5, Table 1). The same complexation with magnesium or zinc proposed for **12a** cannot be achieved in this instance, thus allowing the desired reactions to occur. These arylations and the reduction reaction demonstrate high yielding and unprecedented access to several novel chroman derivatives.

Table 1. Synthesis of tetrahydro- and hexahydro-chroman derivatives



Entry	Substrate	R	Ar	Product (yield) [a]
1	**13a**	H	Ph	**21a** (*80%*)
2	**13a**	H	4-$MeOC_6H_4$	**21b** (*74%*)
3	**13b**	Me	Ph	**21c** (*78%*)
4	**13b**	Me	4-$MeOC_6H_4$	**21d** (*82%*)
5	**13b**	Me	–	**20** (*62%*) [b]

[a] Isolated yields.

[b] Separable mix of *cis*- and *trans*-isomers (55:45)

In conclusion, spiroacetal enol ethers **8a** and **8b** were synthesized in excellent yields by HDA reactions under thermal conditions. Attempts to selectively arylate the 2-position of the spiroacetal enol ethers failed to deliver the desired substituted spiroacetals, providing unprecedented alternative products. Heck reaction conditions produced the over-arylated double Heck

product **11**, whilst attempted anomeric sulfonylation resulted in a facile rearrangement to 5-phenylsulfonyl-5,6,7,8-tetrahydrochromans **13a** and **13b**. Conversion of these chroman building blocks into a variety of substituted chroman derivatives was demonstrated.

3-Methyl-1,7-dioxaspiro[5.5]undec-2-ene (8b). A mixture of freshly distilled methacrolein (11.0 mL, 133 mmol), enol ether **7** (14.0 mL, 133 mmol) and K_2CO_3 (20.06 g, 133 mmol) was heated in a base-washed (NaOH) sealed tube at 100 °C for 10 d. The mixture was diluted with Et_2O (200 mL), then washed with dilute HCl (5% aq, 80 mL), water (50 mL), sat. $NaHCO_3$ (50 mL) and sat. NaCl (50 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* and purified *via* flash chromatography (0-5% Et_2O in Pet. Spirits) to afford the title compound **8b** as a colourless oil (18.81 g, 112 mmol, 84%); R_f 0.52 (5% EtOAc in Pet. Spirits); IR (thin film) 2940, 2877, 1680, 1441, 1153, 1100 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.17 (s, 1H), 3.79 (app. dt, J = 10.0, 2.0 Hz, 1H), 3.54 (dd, J = 11.3, 4.7 Hz, 1H), 2.29 (m, 1H), 1.93 (m, 1H), 1.72 (m, 1H), 1.64 (m, 1H), 1.44 (m, 8H), 1.24 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 135.4, 109.2, 94.7, 61.4, 35.0, 32.7, 25.8, 22.7, 19.0, 18.5; MS (EI) *m/z* 168 $[M]^{\bullet+}$; HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^{\bullet+}$ 168.1150, found 168.1150.

(*E*)-3-Benzylidene-2-phenyl-1,7-dioxaspiro[5.5]undecane (11). $Pd(OAc)_2$ (4.5 mg, 20 μmol), Ag_2CO_3 (60.6 mg, 0.22 mmol) and PPh_3 (10.5 mg, 0.04 mmol) were added to a solution of spiroacetal enol ether **8b** (32 μL, 0.20 mmol) and iodobenzene (23 μL, 0.20 mmol) in 1,4-dioxane (5 mL), and the suspension refluxed under an Argon atmosphere for 18 h. The mixture was cooled and diluted with Et_2O (30 mL), then filtered through a pad of Celite to remove inorganic salts. The brown solution was washed with water (10 mL), sat. $NaHCO_3$ (10 mL) and sat. NaCl (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a red/brown oil. Purification by flash chromatography (5% Et_2O in Pet. Spirits) afforded the title compound **11** as a yellow oil (30 mg, 0.092 mmol, 49%); R_f 0.32 (5% EtOAc in Pet. Spirits); IR (thin film) 2946, 2881, 1684, 1436, 1153, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.47 (m, 2H), 7.40 (m, 1H), 7.33 (m, 2H), 7.23 (m, 1H), 7.16 (m, 2H), 5.75 (s, 1H), 5.46 (s, 1H), 3.83 (m, 1H), 3.76 (m, 1H), 2.91 (m, 1H), 2.76 (m, 1H), 1.90–2.04 (m, 2H), 1.76–1.88 (m, 2H), 1.51–1.70 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 140.0, 137.7, 129.1, 128.5, 128.3 (2C), 127.8, 126.6, 125.6, 96.5, 74.8, 61.3, 37.4, 35.7, 25.6, 23.6, 18.9; MS (ESI) *m/z* 321.2 $[M+H]^+$; HRMS (EI) calcd for $C_{22}H_{24}O_2$ $[M]^{\bullet+}$ 320.1776, found 320.1779.

Representative Procedure for the Sulfonylation of Spiroacetal Enol Ethers: 5-(phenylsulfonyl)-5,6,7,8-tetra hydrochroman (13a). Benzenesulfinic acid was prepared by stirring sodium benzenesulfinate (2.05 g, 12.5 mmol) with HCl (10% aq., 40 mL), then extracting with CH_2Cl_2 (3 x 40 mL), drying ($MgSO_4$) and concentrating under reduced pressure. Benzenesulfinic acid (1.779 g, 12.5 mmol) was added to a solution of spiroacetal enol ether **8a** (1.54 g, 10.0 mmol) in CH_2Cl_2 (40 mL) and the solution stirred for 45 min. Sat. $NaHCO_3$ (50 mL) was added the mixture extracted with CH_2Cl_2 (3 x 80 mL). The combined organic phases were washed with sat. NaCl (40 mL), dried ($MgSO_4$), and the solvent removed *in vacuo* to afford a white solid, which was recrystallised (Et_2O/Pet. Spirits) to yield the title compound **13a** as white prisms (2.25 g, 8.1 mmol, 81%), requiring no further purification. R_f 0.18 (20% EtOAc in Pet. Spirits); IR (thin film) 2944, 2875, 1665, 1446, 1302, 1138 cm^{-1}; mp. 104 °C (decomp.); ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 2H), 7.63 (app. t, J = 7.4 Hz, 1H), 7.55 (app. t, J = 7.7 Hz, 2H), 4.06 (m, 1H), 3.97 (m, 1H), 3.67 (m, 1H), 2.64 (m, 1H), 1.89 (m, 7H), 1.70 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 139.1, 133.5, 129.1, 128.9, 97.2, 67.4, 66.1, 27.0, 25.8, 24.4, 22.8, 18.2; MS (EI) *m/z* 278 $[M]^{\bullet+}$; HRMS (EI) calcd for $C_{15}H_{18}O_3S$ $[M]^{\bullet+}$ 278.0977, found 278.0926.

Representative Procedure for the Arylation of 5-(phenylsulfonyl)-5,6,7,8-tetrahydrochromans: 5-phenyl-5, 6,7,8-tetrahydrochroman (21a). Anhydrous zinc bromide (1.0 M in THF, 510 μL, 0.51 mmol) was added to a stirred solution of phenylmagnesium bromide (1.0 M in THF, 1.6 mL, 1.36 mmol) in THF (7 mL) and the resulting suspension stirred for 30 min. Phenylsulfone **13a** (91 mg, 0.34 mmol) was added and the cloudy mixture stirred for 18 h. Sat. NH_4Cl (50 mL) was added and the biphasic mixture extracted with Et_2O (3 x 40 mL). The combined organic phases were washed with sat. NaCl (20 mL), dried ($MgSO_4$), and the solvent removed *in vacuo* to afford the crude product, which was purified by flash chromatography (1% Et_2O in Pet. Spirits) to give the title compound **21a** as a colourless oil (57 mg, 0.27 mmol, 80%); R_f 0.40 (20% EtOAc in Pet. Spirits); IR (thin film) 2930, 2858, 1449, 1173 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.91 (m, 4H), 6.81 (app. t, J = 7.0 Hz, 1H), 3.50 (m, 1H), 3.45 (m, 1H), 2.90 (app. t, J = 5.7 Hz, 1H), 1.89 (m, 2H), 1.55 (m, 1H), 1.37 (m, 1H), 1.25 (m, 5H), 1.11 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 150.3, 146.6, 129.0 (2 x C), 126.6, 105.9, 66.0, 46.4, 33.8, 28.5, 24.6, 23.9, 20.5; MS (EI) *m/z* 214 $[M]^{\bullet+}$; HRMS (EI) calcd for $C_{15}H_{18}O$ $[M]^{\bullet+}$ 214.1358, found 214.1351.

Acknowledgements

We thank the Australian Research Council for funding (DP556187) and Dr Natasha Hungerford for NMR assistance.

Supplementary Material

Experimental procedures and characterization data for compounds not included in the experimental section; X-ray crystallographic data (CIF) for **13b**; ^1H and ^{13}C NMR spectra for all new compounds. This material is available online at doi:

References and Notes

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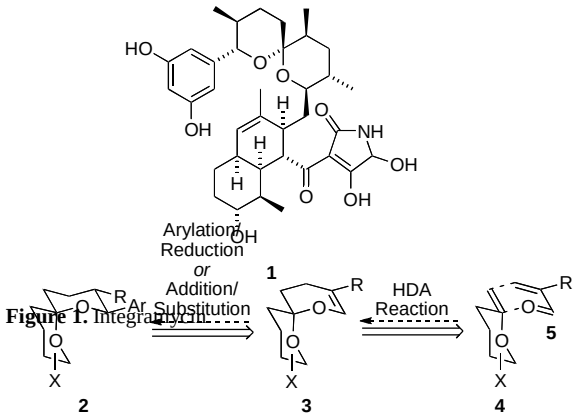
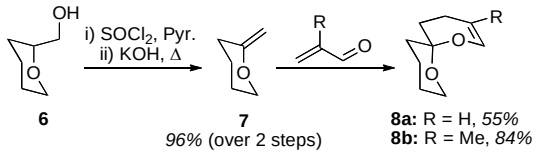
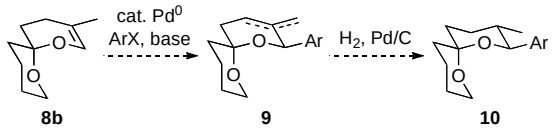


Figure 1. Integrastyn

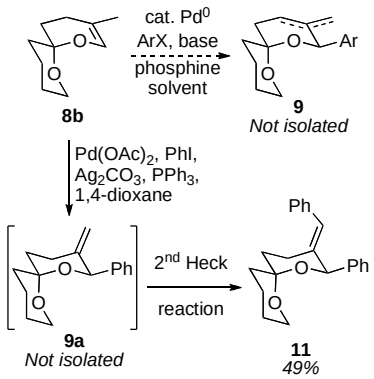
Scheme 1. Strategies for 2-arylspiroacetal synthesis



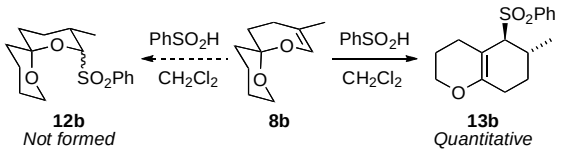
Scheme 2. Synthesis of spiroacetal enol ethers



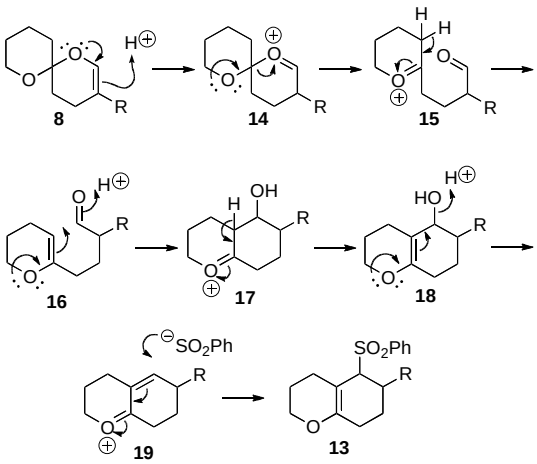
Scheme 3. Heck-hydrogenation approach to 2-arylspiroacetals



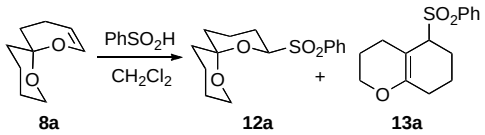
Scheme 4. "Double-Heck" reaction of spiroacetal enol ether **8b**



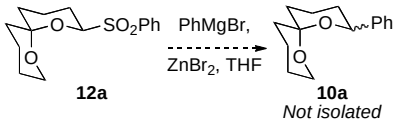
Scheme 5. Reaction of benzenesulfinic acid with **8b**



Scheme 6. Proposed mechanism for the formation of **13**



Scheme 7. Reaction of benzenesulfinic acid with **8a**



Scheme 8. Attempted arylation of **12a**