Conjugate addition of allylic and prop-2-ynylic alcohols to 3-halogeno-1-phenylsulfonylprop-1-enes; synthesis and radical induced cyclization of 2-alkenyloxy-3-halogenopropylphenyl sulfones

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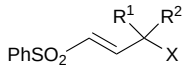
Allylic and prop-2-ynylic alcohols add in a conjugate fashion to 3-halogeno-1-phenylsulfonylprop-1-enes in the presence of KF–basic alumina and the resulting halogenoallyl sulfones can be efficiently cyclized using tributyltin hydride under various conditions.

The ability of vinyl sulfones to act as two carbon acceptors in Michael additions is the basis of their widespread use in synthesis.[1] In this context, 3-halogeno-1-alkenyl sulfones **1**



1a X = Br, R^1 = R^2 = H
b X = Cl, R^1 = R^2 = H
c X = Br, R^1 = H, R^2 = Me
d X = Br, R^1 = R^2 = Me

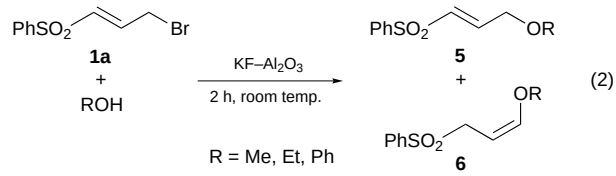
possess two electrophilic adjacent carbon atoms in their structure and therefore conjugate additions would compete with direct S_N2 displacements of the halogen atom. Allylic and aryl Grignard reagents are able to attack the double bond of **1a** and ultimately lead to substituted cyclopropanes *via* a subsequent nucleophilic displacement of the bromide anion.[2] On the contrary, sodium enolates afford direct substitution products when reacted with **1a**.[3]

The behaviour of these systems towards different nucleophiles has been studied in great detail by Bordwell and coworkers.[4] They showed that weakly basic nucleophiles react with primary halogeno derivatives **1a**,**b** giving exclusively direct substitution products arising from an S_N2 process. Michael adducts are obtained only when tertiary halogeno derivative **1d**, which is almost unreactive towards S_N2 substitutions, reacts with sodium methoxide in MeOH.[4b]

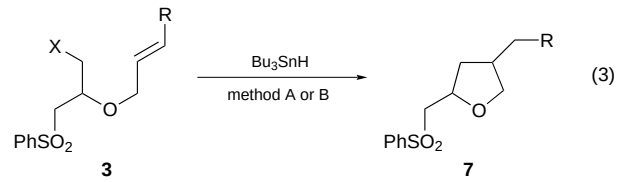
We report here that allylic, prop-2-ynylic and benzylic alcohols efficiently add to the double bond of vinyl sulfones **1a**,**b** in the presence of KF–basic alumina [eqn. (1)].[5] The

reaction is carried out under heterogeneous conditions by simply mixing the vinyl sulfone **1** with the appropriate alcohol and adding the solid base at room temperature.† The corresponding adducts are usually obtained in satisfactory yields upon extraction with CH_2Cl_2 and purification by column chromatography (Table 1).‡ The yields of these adducts obtained starting from bromide **1a** are generally comparable with those attained using chloride **1b**, especially when simple allylic and prop-2-ynylic alcohols are used (Table 1, entries 1–4). Chloride **1b** displays enhanced reactivity towards substituted allylic alcohols (Table 1, entries 8–11) which react poorly with the bromide derivative **1a**. No solvent is required for this procedure, and the presence of solvents as THF, CH_2Cl_2 and Et_2O gives rise to complex product mixtures and prolonged reaction times. Steric crowding around the reaction centre also has a deleterious effect on reactivity. Every attempt to obtain addition products from vinyl sulfone **1c** results in a fast, base-assisted dehydrobromination that produces (*E*)-1-phenylsulfonylbuta-1,3-diene **4** in 40% yield.

A completely different result is observed when short chain alcohol such as methanol, ethanol or phenol are used. In this instance an ordinary direct nucleophilic displacement of the halogen atom occurs, followed by a partial regioisomerisation of the double bond with consequent formation of products **5** and **6** [eqn. (2)].[6]



The allylic ethers **3** prepared by this procedure were recognized immediately as ideal candidates for the synthesis of a tetrahydrofuran moiety *via* a radical cyclization route [eqn. (3)].[7] Ring closure of compound **3** under standard conditions

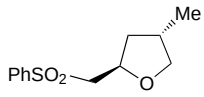
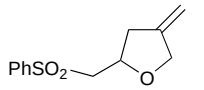
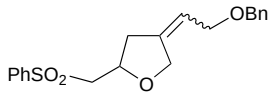
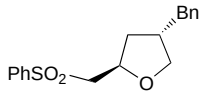
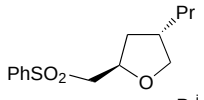
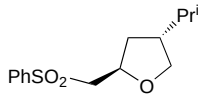


(Bu_3SnH, AIBN catalytic, benzene at reflux)§ gives the corresponding 2,4-disubstituted tetrahydrofuran derivatives **7**

Table 1 Products and yields of the reaction between vinyl sulfones **1** and alcohols **2** in the presence of KF–basic alumina without solvent at room temperature

Entry	Vinyl sulfone	Alcohol **2**	Product	Yield (%)
1	**1a**	CH_2=$CHCH_2OH$	**3a**	80
2	**1b**	CH_2=$CHCH_2OH$	**3b**	75
3	**1a**	CH≡CCH_2OH	**3c**	78
4	**1b**	CH≡CCH_2OH	**3d**	73
5	**1a**	$BnOCH_2C$≡CCH_2OH	**3e**	55
6	**1b**	$BnOCH_2C$≡CCH_2OH	**3f**	71
7	**1a**	BnOH	**3g**	77
8	**1b**	PhCH=$CHCH_2OH$	**3h**	70
9	**1b**	EtCH=$CHCH_2OH$	**3i**	80
10	**1b**	2-(furyl)CH_2OH	**3j**	83
11	**1b**	Me_2C=$CHCH_2OH$	**3k**	65

Table 2 Products and yields of the radical cyclization of unsaturated sulfones **3** in the presence of Bu_3SnH

Entry	Sulfone	Tetrahydrofuran **7**	*trans*:*cis* ratio (method)[a]	Yield (%)
1	**3a**		68:32 (A) 86:14 (B)[b]	92 88
2	**3c**		(A)	88
3	**3e**		55:45 (A)[c] 60:40 (B)[b,c]	50 83
4	**3h**		85:15 (A) 90:10 (B)[b,d]	75 78
5	**3i**		73:27 (A) 80:20 (B)[b]	83 90
6	**3k**		66:34 (A) 77:23 (B)[b]	85 88

[a] Method A: Bu_3SnH, AIBN, benzene at reflux. Method B: Bu_3SnH, Et_3B, O_2, −78 °C. [b] Cyclization is conducted on the iodide obtained by refluxing the corresponding halide with sodium iodide in acetone. [c] This ratio refers to the *E*/*Z* stereoisomers. [d] Reaction conducted at room temperature.

as a diastereoisomeric mixture, usually in good yields (Table 2, method A).‡ These diastereoisomers are inseparable by standard chromatographic techniques, but a survey of available literature data on similar compounds allowed us to assign the *trans* configuration to the major component of the mixture.[8] It is known that radical cyclizations of monohalogeno derivatives of type **7** proceed following a chair-like transition state in which the phenylsulfonylmethyl group and the alkene prefer an equatorial orientation **8** (Scheme 1) that produces the *trans* isomer.[9] The diastereoselectivity obtainable in refluxing benzene is, however, rather poor as witnessed for the cyclization of compound **3a** (Table 2, entry 1, method A, *trans*:*cis* 68:32). Better results are achieved using BEt_3 initiator (Bu_3SnH, BEt_3, O_2, CH_2Cl_2, method B),§ which permits rapid cyclization even at very low temperatures (−78 °C).[10] In this way the diastereoisomeric ratio can be substantially improved for ring closure of **3a** (Table 2, entry 1, method B, *trans*:*cis* 86:14), although in other entries (Table 2, entries 4–6) this gain in diastereoselectivity is rather small, as the isomeric ratio is already quite satisfactory even with method A. The cyclization of alkyne derivative **3e** proceeds with a low degree of stereoselectivity (Table 2, entry 3). This is not surprising since the stereochemistry of compound **7e** is governed by the topicity of the hydrogen abstraction, in which the intermediate alkenyl radical is involved.[11]

In conclusion, a chemoselective conjugate addition of unsaturated alcohols to 3-halogenovinyl sulfones has been accomplished using KF–basic alumina as the basic medium. The resulting adducts can be stereoselectively cyclized by a radical process, affording functionalized 2,4-disubstituted tetrahydrofurans that are suitable for further transformations.

8 **8a**

Scheme 1

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Footnotes and References

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† *Typical experimental procedure for Michael addition*: Vinyl sulfone **1** (5 mmol) was mixed with the appropriate alcohol **2** (15 mmol) and cooled to 0 °C. KF–basic alumina (1 g) was added, the mixture was shaken vigorously for 5 min and then left to stand for 2 h at room temperature. After this time, the mixture was washed with CH_2Cl_2 (5 × 10 ml) and, after evaporation of the solvent at reduced pressure, the crude product was purified by column chromatography.

‡ *Selected data* for **3b**: oil, ν_{max}/cm^{-1} 3060, 1600, 1290, 1130; δ_H (300 MHz, $CDCl_3$) 3.47 (2 H, dd, *J* 1.5, 6.3), 3.66 (2 H, dd, *J* 1.4, 4.5), 3.94–4.05 (2 H, m), 4.12–4.20 (1 H, m), 5.11–5.20 (2 H, m), 5.62–5.78 (1 H, m), 7.52–7.67 (3 H, m), 7.91–7.95 (2 H, m); *m*/*z* 181, 141, 77, 75. For **3c**: oil, ν_{max}/cm^{-1} 3260, 2100, 1290, 1140; δ_H 2.46 (1 H, t, *J* 2.4), 3.49 (2 H, d, *J* 5.1), 3.60 (2 H, d, *J* 4.8), 4.17 (2 H, d, *J* 2.4), 4.32–4.37 (1 H, m), 7.53–7.68 (3 H, m), 7.91–7.96 (2 H, m); *m*/*z* 317 (M^+), 223, 141, 125, 77, 51, 39. For **7a**: mp 39 °C; ν_{max}/cm^{-1} 3050, 1580, 1290, 1130; δ_H 1.00 (3 H, d, *J* 6.8), 1.73–1.90 (2 H, m), 2.28–2.31 (1 H, m), 3.21–3.45 (3 H, m), 3.94–3.92 (1 H, m), 4.35–4.41 (1 H, m), 7.51–7.65 (3 H, m), 7.89–7.92 (m, 2 H); δ_C 17.75, 18.04, 33.38, 33.64, 40.07, 41.38, 61.88, 62.17, 72.98, 73.93. 75.14, 75.48, 128.55, 129.66, 134.17, 140.41; *m*/*z* 240 (M^+), 98, 85, 77.

§ *Typical experimental procedure for ring closure of compounds* **3**: Method A: Bu_3SnH (1.5 mmol) and AIBN (0.15 mmol) were added to a benzene solution (0.06 M) of compound **3** (1 mmol). The mixture was refluxed for 1 h and then the solvent was evaporated at reduced pressure. The oily residue was taken up in Et_2O (40 ml) and washed with aqueous 10% KF. Usual work up gave the crude product, which is purified by column chromatography.

Method B: Bu_3SnH (1.5 mmol) and BEt_3 (0.3 mmol) were added to a CH_2Cl_2 solution (0.05 M) of compound **3**. The mixture was cooled to −78 °C and then O_2 (8 ml) was slowly (45 min) bubbled through the mixture *via* a syringe. After 1 h the mixture was warmed, the solvent was evaporated and the residue was worked up as described in method A.

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