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A versatile and concise route to carbocycles using a 1,6-electrocyclic reaction†

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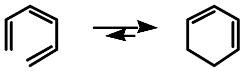
The viability of the 1,6-electrocyclic route to 1,3-cyclohexadienes has been significantly increased by using a phenylsulfonyl substituent in a multi-purpose (≥3) role.

The synthetic construction of aliphatic carbocyclic six-membered rings in suitably substituted or functionalised forms is an important part of preparative organic chemistry. Reactions driven by anions,[1] cations[2] or radicals[3] as well as Diels–Alder reactions[4] have proven useful as have various cyclisations of alkenes/alkynes mediated by transition metal compounds.[5]

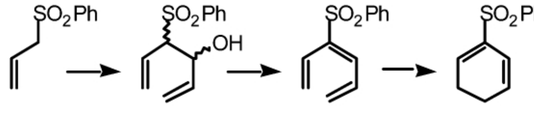
Another route to six-membered ring carbocycles is the electrocyclic ring-closure of 1,3,5-trienes to form 1,3-cyclohexadienes.[6] This reaction typically proceeds at convenient rates at 100–150 °C and gives high yields. It can also be carried out photochemically.[7] Despite extensive phenomenological studies, mainly in the 1970's, the thermal 1,6-electrocyclic reaction of trienes has been little used in synthesis.[8] Two main reasons for this can be seen.



Firstly, the preparation of trienes with the required *cis* configuration of the central double bond has not been straightforward.[9] Reduction of acyclic dienynes has met with only moderate success,[8s,9] and Wittig reactions involving triphenylphosphoranes show low *Z*-selectivities.[10,11] In many of the previous cyclisations the configuration problem was solved or avoided by the central double bond being part of a ring.[6,12]

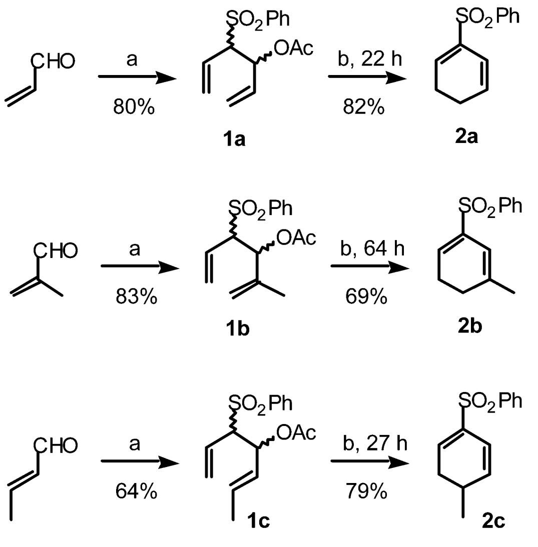
Secondly, and perhaps even more limiting, when a subsequent transformation of the diene moiety of the cyclisation product is required, regioselectivity problems can be foreseen since reactivities of the two double bonds may be too similar.

These problems have now been simultaneously eliminated by the introduction of a suitably placed phenylsulfonyl group (Scheme 1). This strategy enables facile convergent $C_3 + C_3$ synthesis of the C_6 skeleton by the condensation of an allylic sulfone and an α,β-unsaturated aldehyde. In the subsequent elimination to form a triene the sulfone group governs the configuration of the central double bond in the triene.[13] It also creates a difference in the reactivity of the two double bonds in the cyclisation product due to its electron-attracting character.[14]



Scheme 1

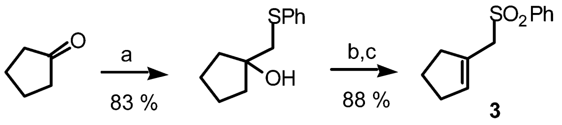
In the first version of our route to carbocycles, lithiated allyl phenyl sulfone was allowed to react with three different α,β-unsaturated aldehydes; these reactions were quenched by acetic anhydride to produce β-acetoxy sulfones **1a–c** as mixtures of diastereomers (3–7 : 1, Scheme 2). Such compounds are intermediates in the Julia–Lythgoe olefination.[13] Elimination of acetic acid to produce a vinylic sulfone has previously been carried out using KOBu^t, NaOH, LDA or DBU.[13] We found that Na_2CO_3(s) in hot toluene directly converted **1a–c** to 2-phenylsulfonyl-1,3-cyclohexadienes **2a–c** (Scheme 2). The carbocyclic products **2a–c** were thus formed in two steps starting from allyl phenyl sulfone. They were indistinguishable from those prepared by other methods.[14a,14d,15] Fortunately, products **2a–c** proved relatively stable during the heating process. In contrast, 2-phenylsulfonyl-1,3-dienes unsubstituted in the 1-position undergo Diels–Alder dimerisation even at room temperature.[14a]



Scheme 2 *Reagents and conditions*: [a] allyl phenyl sulfone + BuLi, then Ac_2O; [b] Na_2CO_3, refluxing toluene.

Allylic sulfones and α,β-unsaturated aldehydes are available by a number of synthetic methods. The example shown in Scheme 3 is a slight modification of a literature procedure.[16] Since it was also of interest to study the formation of sulfonyltrienes and their ring-closure separately, the allylic sulfone **3** was converted to the bicyclic dienyl sulfone **7** in a stepwise fashion (Scheme 4). In the condensation of **3** with methacrolein *ca*. 18% of **3** was recovered in two slightly different runs; this suggested a somewhat unfavourable condensation equilibrium due to the highly branched nature of the lithium salt of **4**. Similarly to other 1-alken-3-ols,[17] **4** reacted with $SOCl_2$–pyridine to exclusively give a rearranged, primary chloride (**5**). Elimination of HCl at 67 °C afforded triene **6** in high isomeric purity (> 95%). On heating at 110 °C **6** underwent ring-closure to **7** (97%).

As shown in our last example (Scheme 5), the electrocyclic reaction is capable of providing six-membered ring carbocycles in



Scheme 3 *Reagents and conditions*: [a] $PhSCH_3$ + BuLi + DABCO; [b] MCPBA; [c] HOTs, Δ.

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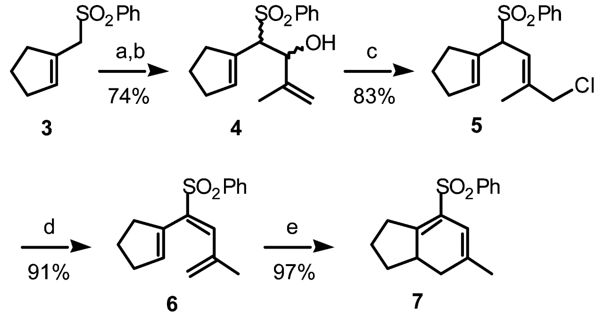
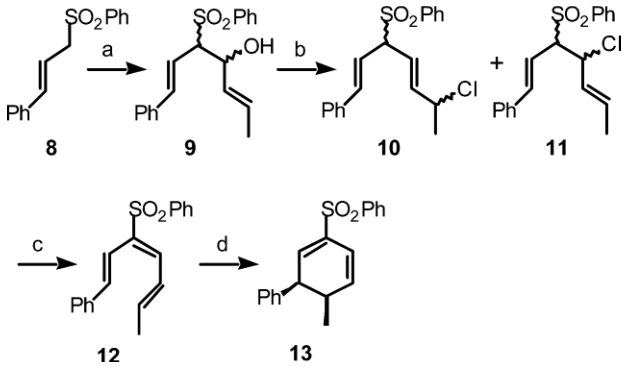
† Electronic Supplementary Information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b3/b311815k/



Scheme 4 *Reagents and conditions*: [a] BuLi; [b] methacrolein; [c] $SOCl_2$, pyridine; [d] Cs_2CO_3, THF, Δ; [e] toluene, 110 °C, 3 h, argon.



Scheme 5 *Reagents and conditions*: [a] BuLi, then 2-butenal; [b] $SOCl_2$, pyridine, 84% from **8**; [c] Cs_2CO_3, THF, Δ, 1 h, $>80\%$; [d] toluene, 110 °C, 5 h, argon, $>90\%$.

which every position in the ring is either substituted or derivatised to enable subsequent substitution. Alcohol **9**, as a *ca*. 3 : 1 mixture of diastereomers, was converted ($SOCl_2$–pyridine) to a mixture of at least four isomeric chlorides; ratio **10** : **11**, *ca*. 10 : 1.

Elimination of HCl gave a mixture of triene isomers which was unstable in air. Besides the major isomer **12** isomers with *Z* configuration either at the central double bond ($<2\%$) or at the methyl-substituted double bond (11%; ^{1}H NMR) were also produced. The ring-closure of **12** was monitored by ^{1}H NMR spectroscopy and a half-life $t_{1/2}$ = 0.9 h was found when the reaction was run in toluene at 100 °C. The two minor triene isomers gave no or little ring-closure. The product expected[7] from **12** was the *cis*-isomer **13**. The product obtained showed a ^{1}H NMR signal at δ 0.66 (d, 3H) which seems consistent with a *cis* configuration and a shielding effect exerted by the adjacent phenyl group.[18] Although ^{1}H NMR analysis indicated high yields in the two steps from (**10** + **11**) to **13**, only 47% of **13** was isolated after purification on silica gel. The loss is probably due to the instability of both **12** and **13**. No instability in air was noticed for the carbocycles **2a–c** and **7** which lack a phenyl substituent.

In summary, the synthetic utility of the 1,6-electrocyclic reaction of 1,3,5-trienes, leading to 1,3-cyclohexadienes, has been significantly increased by using an auxiliary phenylsulfonyl group. This group is used a) in the assembly of the carbon skeleton, b) to obtain the required configuration of the triene, and c) in one or more regioselective manipulations[14] of the 2-phenylsulfonyl-1,3-cyclohexadiene. Finally, the phenylsulfonyl group can be detached either by substitution, elimination, reduction or oxidation, *i.e.* also in a constructive step.[19]

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