Synthesis of *p*-tolylsulfonyl-substituted dienes *via* radical cyclization of diynes

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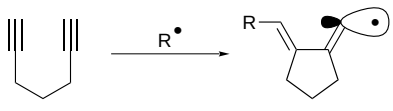
A novel radical cyclization of hepta-1,6-diynes with toluene-*p*-sulfonyl bromide leads to two new classes of electron deficient sulfonyl dienes.

The use of radical cyclizations for the synthesis of five-membered rings has become widespread in organic chemistry and radicals are now regarded as useful intermediates in synthesis.[1] The majority of commonly employed methods use tributyltin hydride (TBTH) to induce homolysis of an organic halide or alcohol derivative to generate the reactive carbon-centred radical species. An attractive alternative is to use the addition of a free-radical to a carbon–carbon π bond in order to generate the radical species; this has the advantage of incorporating some additional functional groups into the product. The synthetic utility of this type of approach using enyne and diene systems has been shown. Seminal work by Stork *et al.* has illustrated the synthetic advantages of using alkynes in radical based transformations.[2] Cyclization of diynes has attracted little attention, which is surprising considering the synthetic potential of the resultant diene.[3] Here we present our preliminary investigations relating to this novel type of radical cyclization (Scheme 1).

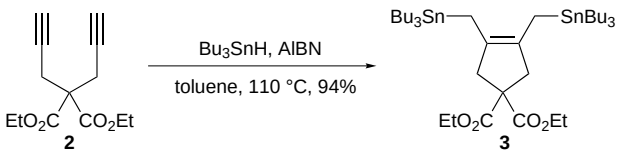
Our initial work illustrated the nature of the problem associated with the radical cyclization of diynes. Treatment of diyne **2** with TBTH under standard free-radical conditions led to the isolation of the bis(stannane) **3** in good yield[4] (Scheme 2).

This type of symmetrical allylic stannane may well be synthetically useful. However, we were never able to isolate a tin-substituted diene, although we note that, with substrate modification, this may be possible.[5] This reductive process is most likely a reflection of the relative rates of addition of the stannyl radical to an intermediate conjugated diene compared to that to acetylenes.† To address this problem we were attracted to the use of sulfonyl radicals which have, surprisingly, gained little use in synthesis.[6] In a diyne to diene transformation, we postulated that initial addition–cyclization would lead to an electronically deficient π-system; further addition would be disfavoured due to the inherent electrophilic nature of sulfonyl radicals.[7]

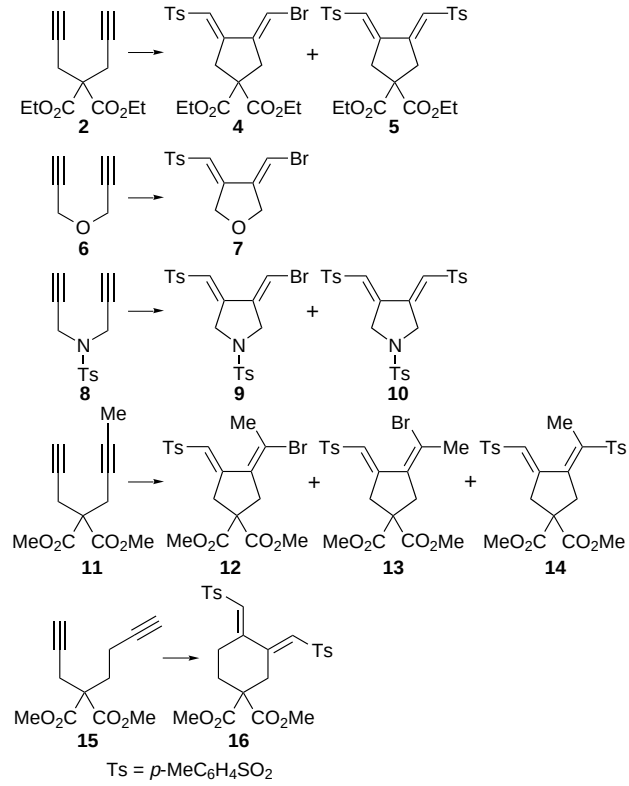
We elected to study the reaction of several readily available diynes with toluene-*p*-sulfonyl bromide (TsBr) under standard free-radical conditions (Scheme 3). Table 1 presents the detailed results of these experiments and several features are worthy of note. Entry 2 shows the optimised transformation of **2** to **4**. When the reaction was carried out under reflux the reaction proceeded with diminished yield and selectivity (entry



Scheme 1



Scheme 2



Scheme 3

Table 1 Reaction of diynes with toluene-*p*-sulfonyl bromide

Entry	Precursor	Products (yield, %)
1[a]	**2**	**4** (46) **5** (18)
2[b]	**2**	**4** (63) **5** (17)
3[c]	**6**	**7** (72)
4[b]	**8**	**9** (34) **10** (22)
5[b]	**11**	**12** (40) **13** (17.5) **14** (13.5)
6[d]	**2**	**5** (91)
7[d]	**8**	**10** (87)
8[d]	**15**	**16** (51)

[a] A stirred benzene solution of diyne (*ca.* 0.04 M), TsBr (1 equiv.), AIBN (0.25 equiv.) under reflux over 24 hr. [b] A stirred benzene solution of diyne (*ca.* 0.04 M), TsBr (1 equiv.), AIBN (0.25 equiv.) (external temp. 63–65 °C) over 72 h. [c] A stirred benzene solution of excess diyne (*ca.* 0.04 M), TsBr (1 equiv.), AIBN (0.25 equiv.) in a sealed tube (external temp. 63–65 °C) with AIBN added portionwise (0.25 equiv.) every 24 h until reaction complete. [d] A stirred benzene solution of diyne (*ca.* 0.12 M), TsBr (3 equiv.), AIBN (0.4 equiv.) in a sealed tube (external temp. 98–100 °C) with AIBN added portionwise (0.4 equiv.) every 24 h until reaction complete.

1). Substrate **6** was the only precursor from which we isolated the bromo sulfone; we suspect that this is a result of the relatively insoluble nature of the bromide **7** (entry 3). In the synthesis of heterocycles there is no evidence of products derived from β-scission or double bond migration to yield the aromatic furan or pyrrole (entries 3 and 4).[8]

Entry 5 is particularly informative; it demonstrates the regio- and stereo-control which can be associated with reactions of this type.‡ The products appear to be uniquely derived from addition of the *p*-tolylsulfonyl radical to the least hindered end of the alkyne; we attribute this to a reversible addition of sulfonyl radicals to acetylenes. The stereochemical outcome of these reactions may be a consequence of the rapid rate of inversion of vinyl radicals.[9] If so, it is likely that the stereochemical course of a particular reaction could be predicted by comparison of the relative sizes of the bromine atom with other proximal substituents.§

Initially our efforts were directed at maximising the yield of bromo sulfone products and we were surprised by the isolation of the bis(sulfones). We assume that these products result from the further addition of toluene-*p*-sulfonyl bromide to the bromo sulfones followed by loss of bromine under radical or electrocyclic conditions. The bis(sulfones) have some obvious synthetic utility[10] and we decided to examine the prospect of transforming the diynes directly into the bis(sulfones) as the sole product. We found that this was possible with representative diynes **2** and **8** by treatment with excess toluene-*p*-sulfonyl bromide (entries 6 and 7). Using these conditions we were also able to prepare the cyclohexane derivative **16** from **15** in reasonable yield (entry 8).¶

We believe that cyclizations of this type can form the basis for a general synthetic methodology, however, if the bromo sulfones are required it is likely that any given example will require a particular set of reaction conditions. The shelf stable bis(sulfones) are likely to find some utility in synthesis as they are now readily available in good yield from the diyne precursor. The work presented here illustrates for the first time that diynes can be transformed into stable cyclic dienes[11] under radical conditions using toluene-*p*-sulfonyl bromide. The isolation of the bromo sulfone as the major product under appropriate conditions may support the original hypothesis that the electron deficient sulfonyl diene is relatively unreactive toward the electrophilic sulfonyl radical. The incorporation of two useful functional groups in the products derived from this and other toluene-*p*-sulfonyl radical mediated cyclizations is a clear advantage over related tin based transformations. Investigations of the synthetic utility of the two new classes of diene presented here are ongoing.

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Footnotes

† The analogous silyl derivative of the intermediate conjugate diene has been successfully synthesised by the use of cuprate methodology, albeit in poor yield: I. Fleming and E. M. deMarigorta, *Tetrahedron Lett.*, 1993, **34**, 1201.

‡ All compounds exhibited data consistent with their formulae (IR, ^{1}H and ^{13}C NMR, MS, HRMS). *Selected data* for **4**: ν_{max}/cm^{-1} 1733, 1673, 1327, 1148; $\delta_H(CDCl_3$; 250 MHz) 1.23 (t, *J* 7.1, 6 H), 2.41 (s, 3 H), 3.04 (d, *J* 2.7, 2 H), 3.66 (d, *J* 2.4, 2 H), 4.17 (q, *J* 7.1, 4 H), 6.39 (t, *J* 2.4, 1 H), 6.78 (t, *J* 2.7, 1 H), 7.32 and 7.8 (AA′BB′, 4 H); $\delta_C(CDCl_3$; 75.5 MHz) 14.37, 22.04, 39.78, 40.26, 57.56, 62.54, 108.53, 121.17, 127.72, 130.35, 138.84, 142.82, 144.97, 150.32, 170.59 [HRMS: (M + H$^+$) $C_{20}H_{24}{}^{81}BrO_6S$ requires 473.0457. Found, 471.0448]. For **5**: ν_{max}/cm^{-1} 1732, 1597, 1332, 1149; $\delta_H(CDCl_3$; 250 MHz) 1.22 (t, *J* 7.1, 6 H), 2.41 (s, 6 H), 3.55 (d, *J* 2.3, 4 H), 4.16 (q, *J* 7.1, 4 H), 6.52 (t, *J* 2.3, 2 H), 7.32 and 7.76 (AA′BB′, 8 H); $\delta_C(CDCl_3$; 75.5 MHz) 14.66, 22.38, 38.05, 58.75, 62.96, 125.87, 128.16, 130.77, 138.24, 154.89, 160.80, 170.71 [HRMS: (M + H$^+$) $C_{27}H_{31}O_8S_2$ requires 547.140. Found, 547.1447].

§ The stereochemistry was determined by NMR experiments (NOE studies) and X-ray crystallography.

¶ We have been unable to isolate and characterise the expected bromo sulfone from the complex mixture which results from treatment of **15** with TsBr (1 equiv.).

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