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Expedient Diels–Alder assembly of 4-aryl-4-phenylsulfonyl cyclohexanones☆

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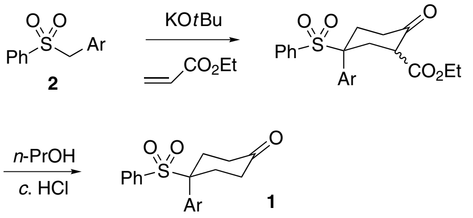
Abstract—The efficient preparation of 4-aryl-4-phenylsulfonyl cyclohexanones, containing a quaternary sulfone-bearing carbon centre, is described. Their synthesis proceeds in 38–78% overall yield by way of three steps: (i) sulfinate alkylation; (ii) methylenation; and (iii) regioselective Diels–Alder condensation with 2-trimethylsiloxybutadiene. The scope and limitations of the one-pot Mannich-type methylenation described were examined.

As part of a drug discovery programme, we required an efficient and scalable synthesis of cyclohexanones with general structure **1** having a quaternary carbon substituted with aryl and phenylsulfonyl moieties. An approach to a related substructure, reliant on a tandem double Michael–Dieckmann cyclisation followed by β-decarboxylation, has been documented (Scheme 1).[1] We found this chemistry to be unacceptable for the benzylphenylsulfones **2** of interest to us, with low yields and attendant poor impurity profiles.[2]

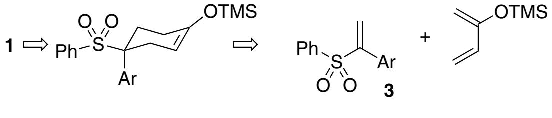
We envisaged an alternative Diels–Alder construction of the cyclohexanone ring by way of the union of a vinyl sulfone **3** with a 2-substituted siloxybutadiene (Scheme 2). Importantly from our perspective, entry to cyclohexanones by 1,4-regioselective [4+2] cycloaddition of this diene type with electron deficient alkenes has been documented.[3] The utility of 1-aryl-1-phenylsulfonyl vinyl sulfones **3** in this context has, however, not been reported.[4,5]



Scheme 1.

In this paper we describe the implementation of this Diels–Alder strategy for the preparation of 4-aryl-4-phenylsulfonyl cyclohexanones **1** proceeding by way of three isolated intermediates. The key steps are Mannich-type methylenation of sulfones **2** to their corresponding vinyl sulfones **3**, followed by thermal Diels–Alder cycloaddition with 2-trimethylsiloxybutadiene. Acid-catalysed hydrolysis of the resultant silyl enol ethers then afforded the desired cyclohexanones **1** in moderate to excellent overall yields.

Construction of ketones **1** began with alkylation of commercially available benzenesulfinate sodium salt with benzyl halides **4** to form the requisite methylene sulfones **2** (Scheme 3). A highly practical procedure was developed, using DMF or DMSO as solvent, which



Scheme 2.

Keywords: Cycloadditions; Diels–Alder reactions; Methylenation; Sulfones.

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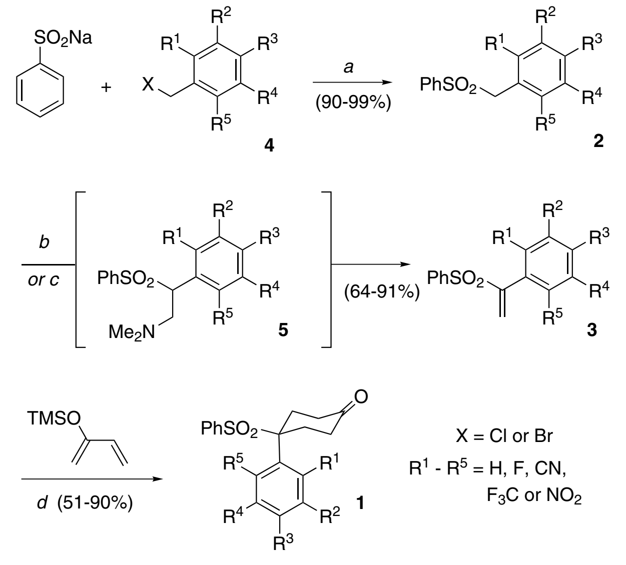


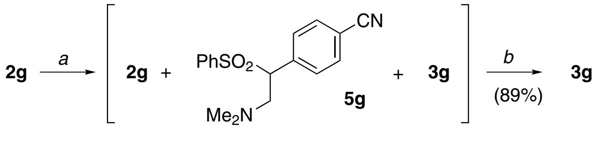
Scheme 3. Reagents and conditions: (a) DMSO or DMF, 60 °C; (b) *n*-BuLi, THF, −35 °C then $(Me_2NCH_2)I$; Ac_2O, PhMe, 85 °C; (c) $Me_2NCH_2NMe_2$, Ac_2O, DMF, 60 °C; (d) *o*-xylene, 130 °C, HCl, THF, rt.

allowed direct crystallisation of sulfones **2a**–**g** in 90–99% yields (Table 1, entries 1–7).[6,7]

Conversion of **2** into the corresponding vinyl sulfones **3** was now required.[8,9] This was achieved by two protocols, dependent on the nature of the substituents (R^1–R^5) pendant to the benzyl moiety of **2**. For sulfones **2a**–**c**, lithiation with *n*-butyllithium and quenching with Eschenmoser's salt afforded the intermediate dimethylamino adducts **5a**–**c** (Scheme 3). Significant amounts (up to 26%) of unconverted sulfones **2a**–**c** were observed in this process, likely due to competing proton transfer from the iminium salt to the lithiated sulfones.[10] However, pH controlled extraction allowed for easy separation of the tertiary amines **5a**–**c** from the sulfones **2a**–**c**. Exposure to acetic anhydride in toluene[11] at elevated temperature then afforded the desired vinyl sulfones **3a**–**c** in moderate overall yields (Table 1, entries 1–3).[12]

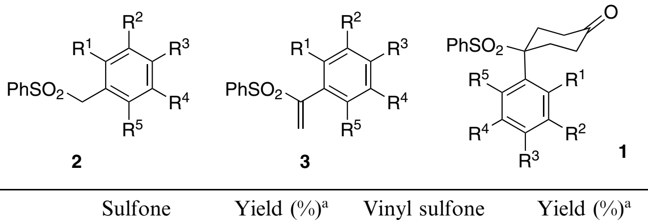
A more practical one-pot procedure was developed for sulfones **2d**–**g** (Table 1, entries 4–7).[13,14] Exposure to *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine (TMMD) and acetic anhydride at elevated temperature in DMF afforded the vinyl sulfones **3d**–**g** directly in good to excellent yields (80–91%). The reaction manifold is illustrated for *p*-cyanobenzyl phenyl sulfone **2g** (Scheme 4). Addition of an initial charge of 1.5 equiv of TMMD and 1.5 equiv acetic anhydride to a DMF solution of **2g** afforded a 49:16:35 mixture[15] of **2g**, the intermediate dimethylamino adduct **5g** and vinyl sulfone **3g** after 2 h at 60 °C. Slow addition of a DMF solution of a further 1.6 equiv of acetic anhydride then led to full conversion to the product **3g**. In the case of nitro-substituted sulfone **2f**, a 71:29 mixture of the dimethylamino intermediate **5f** and vinyl sulfone **3f** was formed after 1 h, with complete consumption of **2f** observed within this time. This reactivity reflects the enhanced electron withdrawing nature of a nitro versus a cyano group, with a predicted lower pK_a for **2f** versus **2g**.[16]

A ^1H NMR study defined the benefit of adding the acetic anhydride in two aliquots (Scheme 5). The iminium salt **6** was rapidly and quantitatively formed from an equimolar mixture of TMMD and acetic anhydride at 0 °C in d_7-DMF. Although this salt was apparently stable at the reaction temperature (60 °C) for up to 2 h, addition of further acetic anhydride triggered degradation over a period of several hours. In the reaction manifold with methylene sulfones **2d**–**g**, slow addition of



Scheme 4. Reagents and conditions: (a) 1.5 equiv $Me_2NCH_2NMe_2$, 1.5 equiv Ac_2O, DMF, 2 h, 60 °C; (b) 1.6 equiv Ac_2O, DMF, 3 h, 60 °C.

Table 1. Synthesis of 4-aryl-4-phenylsulfonylcyclohexanones **1**

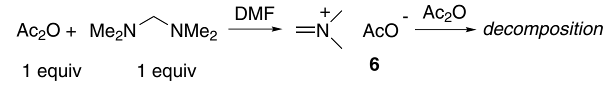


Entry	Substituents	Sulfone	Yield (%)[a]	Vinyl sulfone	Yield (%)[a]	Ketone	Yield (%)[a]
1	R^2–R^5 = H; R^1 = F	**2a**	93	**3a**	64[b]	**1a**	64
2	R^1, R^2, R^4, R^5 = H; R^3 = F	**2b**	90	**3b**	66[b]	**1b**	75
3	R^2, R^3, R^4 = H; R^1, R^5 = F	**2c**	93	**3c**	68[b]	**1c**	51
4	R^2, R^3, R^5 = H; R^1, R^4 = F	**2d**	98	**3d**	82[c]	**1d**	72
5	R^1, R^2, R^4, R^5 = H; R^3 = CF_3	**2e**	99	**3e**	80[c]	**1e**	87
6	R^1, R^2, R^4, R^5 = H; R^3 = NO_2	**2f**	93	**3f**	91[c]	**1f**	89
7	R^1, R^2, R^4, R^5 = H; R^3 = CN	**2g**	98	**3g**	89[c]	**1g**	90

[a] Yields reported are of compounds isolated by chromatography or crystallisation.

[b] *n*-BuLi, THF then $(Me_2NCH_2)I$; Ac_2O, PhMe.

[c] $Me_2NCH_2NMe_2$, Ac_2O, DMF.



Scheme 5.

the second acetic anhydride aliquot allows for preferential conversion of the intermediate dimethylamino adducts **5d–g** to product, whilst reducing degradation of the iminium salt still present in solution. Addition of the full amount of acetic anhydride at the reaction outset invariably led to poor conversion.

The scope of the one-pot methylenation with TMMD and acetic anhydride was found to correlate with the expected acidity of the methylene sulfones **2a–g**.[17] No conversion of monofluorinated sulfones **2a–b**, bearing a 2- or 4-substituent on the benzyl moiety, was observed under these conditions. Whilst 2,5-difluorosubstituted substrate **2d** was consumed in this reaction manifold, the 2,6-difluoro pattern was unreactive, presumably due to the destabilising electrostatic influence of the proximal fluorines.

Diels–Alder reactions of vinyl sulfones **3a–g** with commercially available 2-trimethylsiloxybutadiene[18] proceeded thermally in *o*-xylene as solvent.[19,20] Hydrolysis of the intermediate silyl enol ether was effected with aqueous HCl in THF to afford the product cyclohexanones **1a–g** in moderate to excellent yields (Table 1, 51–90%). Reactivity in the cycloaddition mirrored the substituents attached to the conjugating phenyl ring with conversion of nitro and cyano substrates **3f** and **3g** complete within 3 h at 130 °C, whilst substrates **3a–e** required extended reaction times (up to 16 h). An excess of 2-trimethylsiloxybutadiene was typically used (2–3 equiv), the surfeit of which was removed by distillation prior to hydrolysis of the silyl enol ether intermediate, which minimised deposition and entrainment of polymeric solids resulting from degradation of the butadiene. In all cases, only a single Diels–Alder regioisomer was observed, in accord with previous observations for this diene class.[3c]

In summary, we have developed an expedient synthesis of 4-aryl-4-phenylsulfonyl ketones **1** proceeding by way of three isolated intermediates and in moderate to excellent overall yields (38–78%). Conditions for the one-pot conversion of sulfones **2d–g** to vinyl sulfones **3d–g** were developed and the scope shown to be limited to those substrates bearing strongly electron withdrawing substituents. Subsequent Diels–Alder condensations proceeded thermally affording only a single regioisomeric product.

Acknowledgement

We thank Paul Byway for mass spectrometry analysis.

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14. Representative procedure: Sulfone **2g** (5.2 g, 20.0 mmol) was dissolved in DMF (56 mL) and *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine (3.1 g, 30.0 mmol) added in one portion. Ac_2O (2.8 mL, 30.0 mmol) was then added and the mixture was heated at 60 °C for 2.5 h. A solution of Ac_2O (3.0 mL, 32.0 mmol) in DMF (6.2 mL) was then added via syringe pump over 3 h. The mixture was kept at 60 °C for 0.5 h and then cooled to ambient temperature. H_2O (102 mL) was added dropwise to crystallise the crude product. Purification by chromatography then afforded 1-cyano-4-[1-(phenylsulfonyl)ethenyl]benzene **3g** in 89% yield (4.8 g): ^1H NMR (400 MHz, CD_2Cl_2) δ 7.61–7.57 (2H, m), 7.52–7.47 (3H, m), 7.40–7.34 (4H, m), 6.60 (1H, s), 5.98 (1H, s); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 149.6, 138.3, 137.1, 133.8, 132.1, 129.7, 129.2, 128.3, 127.6, 118.1, 113.2; mp 118–120 °C; MS (ES) 292.10 (79, M+Na), 270.05 (100, M+H).
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20. Representative procedure: Vinyl sulfone **3g** (2.0 g, 7.4 mmol) was heated with 2-trimethylsiloxybutadiene (2.1 g, 14.9 mmol) in *o*-xylene (4.0 mL) at 130 °C for 3 h. The reaction mixture was then allowed to cool to ambient temperature, diluted with *o*-xylene (20 mL) and evaporated in vacuo. The residue was taken up in THF (30 mL) and 2 M HCl (20 mL) added. After 1.0 h at rt, the mixture was filtered through a layer of Whatman Glass Fibre, then extracted with CH_2Cl_2. Evaporation in vacuo followed by chromatography then afforded 4-(4-cyanophenyl)-4-(phenylsulfonyl)cyclohexanone **1g** in 90% yield (2.3 g): ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.75–7.72 (2H, m), 7.64–7.59 (1H, m), 7.52–7.46 (2H, m), 7.45–7.38 (2H, m), 7.24–7.20 (2H, m), 2.80–2.72 (2H, m), 2.40–2.30 (2H, m), 2.21–2.14 (2H, m), 1.99–1.88 (2H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 207.6, 137.2, 135.0, 134.3, 132.6, 131.3, 130.4, 129.5, 118.9, 112.1, 68.9, 36.9, 28.2; mp 221 °C (decomp.); HRMS (CI) calcd for $C_{19}H_{21}N_2O_3S$ (M+NH_4) requires 357.1273; found 357.1265.