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Electrocatalytic reactions: anion radical cyclobutanation reactions and electrogenerated base reactions

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Dedicated to Professor Nathan L. Bauld on the occasion of his retirement from the University of Texas at Austin

Abstract

Intermolecular anion radical [2+2] cyclobutanation reactions have been observed between vinyl sulfones and vinyl/propenyl ketones. The products are novel and formed electrocatalytically, although yields are at best modest (11–45%). Competing mechanisms are discussed. Additionally, the electrochemical reduction of vinyl alkyl sulfones in acetonitrile leads to near quantitative formation of cyanomethylation product cyano-sulfones. The single step approach has electrocatalytic factors in excess of thirty.

Keywords: Cyclobutanation; Cyanomethylation; Phenyl vinyl sulfone; Electrocatalysis; Electrogenerated base

1. Introduction

Cyclobutanation reactions of the cation radicals of alkenes with neutral alkenes have become rather commonplace and are characterized by high cycloaddition rates and low activation barriers, especially in comparison to the corresponding thermal reactions.[1] There have been some recent indications that this extensive body of cation radical cyclobutanation chemistry may have a close counterpart in the domain of anion radical chemistry. Specifically, the reduction of phenyl vinyl sulfone under electrochemical conditions (mercury pool cathode) has been reported to yield *trans*-1,2-bis(phenylsulfonyl)cyclobutane.[2] Subsequently, the cyclo-dimerizations of a variety vinylpyridines and vinylquinolines under similar conditions have also been established.[3]

A variety of intramolecular anion radical cyclobutanations of tethered bis(enones) have been previously described.[4] This work has looked at competitive anion radical chemical methods,[5] the scope, limitations, and mechanisms involved,[6] and an intriguing diastereotopic electrolyte effect.[7] These systems are of special interest because they represent rare examples of inter- or intramolecular anion radical cycloaddition, rather than the more common electrohydrocyclization/dimerization (EHC or EHD).[8] This Letter intends to expand this field, into vinyl ketone cross-cyclization with phenyl vinyl sulfone.

The [2+2] cross-cyclobutanation is assumed to proceed via anion radical to neutral substrate coupling, with rapid subsequent cyclization via a distonic anion intermediate. This is based upon an electrochemical/computational study of phenyl vinyl sulfone cyclodimerization,[9] and also the previous ability to trap the distonic anion radical of the analogous intramolecular enone case.[6]

The electrogenerated formation of cyanomethyl anions, and subsequent addition reactions, was first reported thirty years ago.[10] This initial work expanded to a number of systems where electroreduction of aromatic carbonyl compounds lead to base formation, such that the substrates were themselves in situ pro-bases (PB), analogous to a previously published allyl phenyl sulfone system. The

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difference lies in the lack of a readily removed proton from the substrate, such that the substrate PB deprotonates the acetonitrile solvent, giving a CH_2CN carbanion.[11] This reactive species is then seen to undergo nucleophilic attack, in the published case, upon the carbonyl group of the substrate.[12] An identical observation is made here, where alkyl vinyl sulfones act as in situ PB's to give simple cyano sulfones in a single step with near quantitative yield and high electrocatalytic values.

2. Cyclobutanations

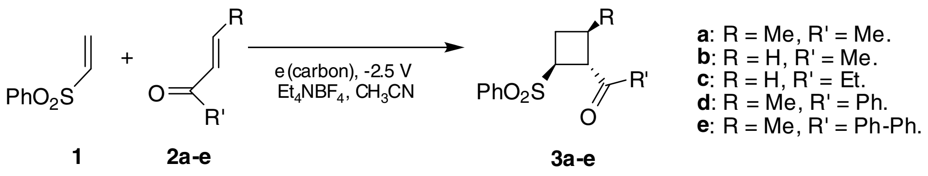
The electrocyclobutanation of phenyl vinyl sulfone (**1**) is well established,[2,9] yet other vinyl compounds are not seen to electrocyclobutanate (see Supplementary data). This maybe due to polymerization or an EHD, however, reaction with **1** may prevent further reactivity, due the relative polymeric passivity of **1**. Therefore, mixed cyclobutanation products should be feasible with vinyl compounds containing electron withdrawing groups (see Scheme 1). While a large variety of substrates were studied, the only class of substrates that proved successful were ketones. The yields are generally modest (Table 1), and appear to be depressed by a variety of competing mechanisms (such as polymerization, and the mechanisms highlighted below). The cross-cyclobutanes formed are however novel, and crystal structures of several are presented. While reactions are electrocatalytic in nature, the true extent of catalysis is not well defined. Competing mechanisms in solution, such as oligomerization or base generation, also consume charge. This leads to a given experiment apparently requiring more charge than is strictly used by cyclobutanation. Thus, the catalytic factors given are likely to be somewhat lower than those specifically engendered by the cross-cyclobutanation. This is particularly suggested by the more efficient cyclobutanation of **1** alone, where a catalytic factor of around ten is quoted for a near quantitative reaction,[2,9,13] and side (charge consuming) reactions are minimized.

2.1. *Phenyl vinyl sulfone* (**1**) *and 3-penten-2-one* (**2a**)

The mixed-cyclobutanation of 3-penten-2-one (**2a**) and phenyl vinyl sulfone (**1**) occurs readily, to give **3a** (Fig. 1), when a variety of substrate ratios are used. The nominal peak mixed-cyclobutane yield occurs with a slight **2a** excess, although there is no real variability (19–26%) in yield from a 3.5-fold **2a** excess to the reverse threefold **1** excess (Supplementary data). These results do not therefore suggest an appropriate route for yield improvement, and that a yield of around 25% may be maximal for this system. This could be due to the electroreactivity of **2a** under all conditions, such that oligomerization limits substrate availability. The dephenylsulfonylation of *trans*-1,2-bis(phenylsulfonyl)cyclobutane (**5**), to yield **6** (Fig. 2), is a clear indication of the presence of electrogenerated bases (EGB's). Indeed, added pro-bases, which form EGB's upon reduction, have been used to produce good yields of **6** from **5**.[15] EGB's also lead to the formation of the minor product **7a** (<5% yield) via deprotonation of **2a** and subsequent addition to two moles of **1**, analogous to chemistry seen before for allyl phenyl sulfone.[16]

2.2. *Methyl vinyl ketone* (**2b**) *and ethyl vinyl ketone* (**2c**)

The reactions of two alkyl vinyl ketones with phenyl vinyl sulfone were also investigated (Table 1). Unsurprisingly, the methyl and ethyl vinyl ketones behaved near identically, with cross-cyclobutane yields of around 30%.



Scheme 1. The intermolecular cyclobutanation reaction between phenyl vinyl sulfone and various vinyl ketones.

Table 1
Summary of the yields and catalytic factors of cyclobutanes (**3**) formed from cross-reaction of vinyl sulfones (**1**, **4**) with ketones (**2**)

Sulfone	Ketone	Reaction ratio	% Yield	Catalytic factor[14]
1: Phenyl vinyl	**2a**: 3-Penten-2-one	**1**:**2a** = 1:1.7	**3a**: 26	6
1: Phenyl vinyl	**2b**: Methyl vinyl ketone	**1**:**2b** = 1:2.9	**3b**: 28	5
1: Phenyl vinyl	**2c**: Ethyl vinyl ketone	**1**:**2c** = 1:2.9	**3c**: 32	9
1: Phenyl vinyl	**2d**: Phenyl propenyl ketone	**1**:**2d** = 1:4.0	**3d**: 45	2
1: Phenyl vinyl	**2e**: Biphenyl vinyl ketone	**1**:**2e** = 1:4.0	**3e**: 28	6
4: Divinyl	**2e**: Biphenyl vinyl ketone	**4**:**2e** = 4.0:1	**3f**: 11	2

Experimental: 100–200 mg of two substrates, in the described mole ratio are electrolyzed at −2.5 V versus Ag wire, in 0.1 M Et_4NBF_4 acetonitrile, using a reticulated vitreous carbon working electrode. Consumption of the starting materials was tracked by TLC, recording the amount of charge required. The products are obtained by extraction and PTLC separation. See Supplementary data for more information.

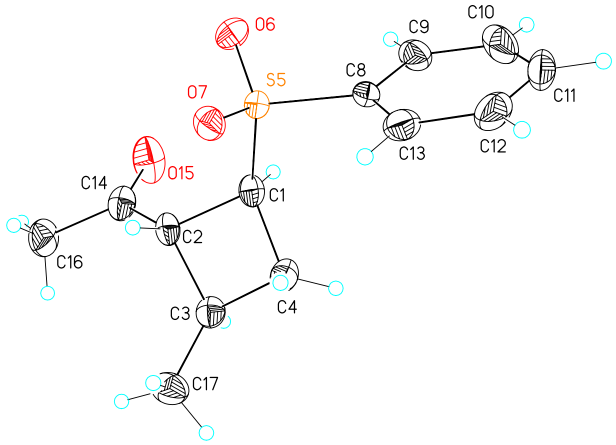


Fig. 1. View of **3a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Deposited as CCDC 659007.

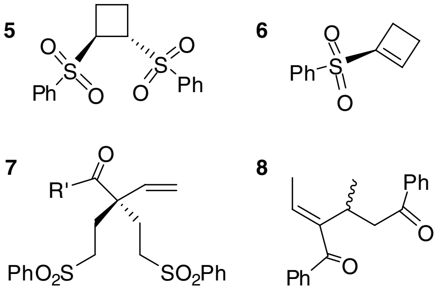


Fig. 2. Product **6** is the dephenylsulfonylation product of **5**. Minor products **7** and **8** are formed via the presence of electrogenerated base, where R′ = Me (**7a**), Ph (**7d**) and Ph–Ph (**7e**).

Increases in the excess of **1** boost yield, form ~10% at 1:1 to ~30% at 3:1 (Supplementary data). A fivefold excess reaction actually led to no cyclobutane products, suggesting a limit to this approach. The excess of phenyl vinyl sulfone readily dimerizes under these conditions (**5**), and leads to the formation of the minor dephenylsulfonylation product, **6**, via EGB.

2.3. Phenyl and biphenyl propenyl ketones (**2d** *and* **2e**)

The reactions of phenyl vinyl sulfone with phenyl propenyl ketone represent the best cross-cyclobutanation yield obtained, at 45% (see Fig. 3). It is thought that the reaction proceeds via reduction of **2d**/**2e**, and subsequent addition to a neutral molecule of **1**, due to the lower reduction potential of **2d**/**2e** and the observation that a 2:1 excess of **2d** over **1** gave polymeric products. However, increasing the excess of **1**, above twofold, gives only a slight increase in cross-cyclobutane yield, from 37% to 45% at a fourfold excess (Supplementary data).

Cyclobutanation was considered rather unlikely between propenyl compounds, for steric reasons, so it was not extensively studied. However, electrolysis of **2d** did give a modest 23% yield of an interesting EGB promoted product. This product, **8**, is formed via EGB deprotonation of the substrate to give a carbanion, which then adds to another mole of substrate, effectively giving a dimer. Again, this mechanism is entirely analogous to the self addition reaction observed for allyl phenyl sulfone.[16]

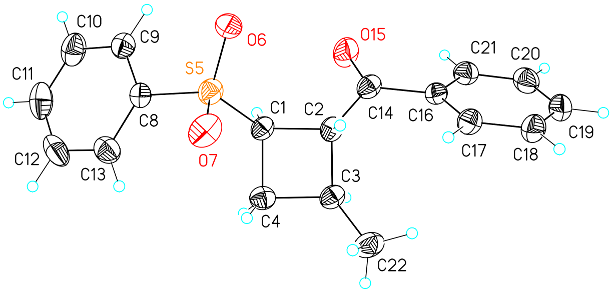


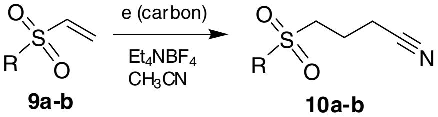
Fig. 3. View of **3d** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Deposited as CCDC 659006.

2.4. Divinyl sulfone (**4**) *and biphenyl propenyl ketone* (**2e**)

The reaction between divinyl sulfone and biphenyl propenyl ketone, using a 4:1 excess of **4**, lead to a rather modest 12% yield (Table 1) of the cross-cyclobutane **3f**. While attempts to improve upon this yield were unsuccessful, this small yield does represent the only non-phenyl vinyl sulfone cyclobutanation obtained in this work, although a vinyl sulfone moiety is still involved.

3. Cyanomethylation

The reduction of two alkyl vinyl sulfones leads to effectively quantitative cyanomethylation (Scheme 2), to give the corresponding cyano sulfones, with large catalytic factors of around 35 (Table 2). These products have been synthesized by non-electrochemical means, in multi-step



Scheme 2. The cyanomethylation reaction, cyano sulfones, **10**, formed via single step where R = Me (**10a**) and Et (**10b**). Procedure is altered for R = Ph (**10c**, see text).

Table 2
Yields of cyanomethylation of selected vinyl sulfones

Substrate	Yield of **10**	Catalytic factor
9a: Methyl vinyl sulfone	**10a**: 94	38
9b: Ethyl vinyl sulfone	**10b**: 96	36
1: Phenyl vinyl sulfone[a]	**10c**: 31	5

[a] Not directly reduced, added to reduced diphenyl sulfone solution.

processes, with 30% yield of **10a**[17] and a better 87% yield of **10b**.[18]

The process for cyanomethylating phenyl vinyl sulfone (**1**) was necessarily different, as reduction yields the cyclobutane dimer, **5**. Initially a pro-base, diphenyl sulfone was co-reduced, yet this did not disrupt the anion radical cyclobutanation process. However, by reducing this pro-base in isolation, ex situ EGB generation, and then adding **1**, appeared to give only **10c**. Separation gave a rather modest yield below the published value of 70%,[18] although that was via a multi-step synthesis. This pre-generation of base may well be a way to access a variety of cyanomethylation reactions that would not normally occur, due to the substrates given electroreactivity.

4. Summary

The mixed reactant approach has lead to modest to reasonable yields of novel ketone/sulfonyl cyclobutanes. These compounds have been synthesized via an electrocatalytic mechanism. While this synthetic method may have limited range, the use of more complex vinyl/propenyl ketone compounds, with aroyl and alkyl variation may expand the examples shown here. The presence, possibly unavoidable, of electrogenerated bases in these reactions is also confirmed. Indeed, electrogenerated bases are shown to promote successful reactions in their own right.

Acknowledgments

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Supplementary data

Crystallographic data (excluding structure factors) for **3a** and **3d**, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 659007 and CCDC 659006, respectively. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.171.

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