Radical Reactions

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Hydrosulfonylation Reaction with Arenesulfonyl Chlorides and Tetrahydrofuran: Conversion of Terminal Alkynes into Cyclopentylmethyl Sulfones

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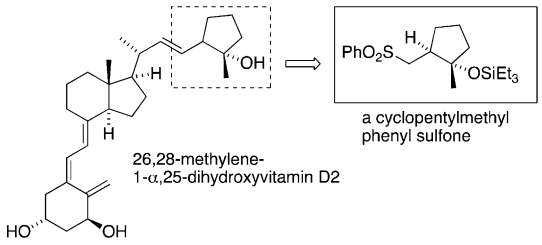
Abstract: *An efficient and simple radical chain reaction to convert terminal alkynes into arenesulfonylmethylcyclopentanes is described. The reaction involves a radical addition–translocation–cyclization process and necessitates solely the use of readily available arenesulfonyl chlorides in tetrahydrofuran. Interestingly, this radical-mediated C–H activation process took place with a high level of retention of configuration when an enantiomerically pure starting material was used.*

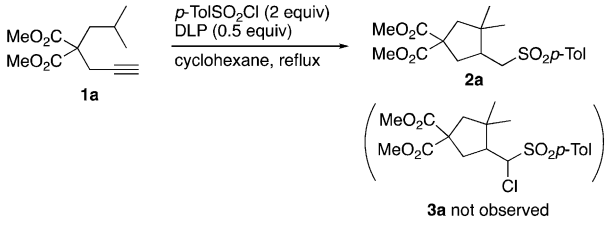
Sulfones are important and versatile compounds in organic synthesis. They are present in natural compounds[1] and analogues[2] presenting biological activity, such as antifungal, antibacterial, and anti-HIV activity. Moreover, several biologically active compounds containing a sulfone functional group are known.[3] Sulfones are also useful building blocks, as illustrated by the preparation of 26,28-methylene-1-α,25-dihydroxyvitamin D2, a drug candidate for the treatment of osteoporosis,[4] on the basis of a Julia olefination process involving a homochiral phenyl cyclopentylmethyl sulfone (Scheme 1). The addition of sulfonyl radicals to alkenes is one of the mildest methods to introduce a sulfonyl group into a molecule. Interestingly, this approach offers unique opportunities for cascade reactions involving, for example, the formation of five-membered-ring systems from dienes and enynes.[5] A variety of precursors, such as sulfonyl halides,[6] sulfonyl selenides,[7] sulfonyl azides,[8] and allyl sulfones,[9] have been used. The use of sulfonyl hydrazides[10] and sulfinates[11] under oxidative conditions has also been reported. Processes involving the addition of a sulfonyl radical and a hydrogen atom to give alkenyl or alkylsulfones (hydrosulfonylation) are much less common and require the use of metal catalysis.[12]



Scheme 1. A cyclopentylmethyl phenyl sulfone building block.

We report herein a hydrosulfonylation procedure based on the use of commercially or readily available arenesulfonyl chlorides and THF as the source of the hydrogen atom, thus avoiding the use of any dedicated reducing agent. The reaction has been used to carry out efficient cascade reactions involving a radical addition–translocation–cyclization (RATC) process leading to the formation of aryl cyclopentylmethyl sulfones from terminal alkynes.[13,14]

The reaction was observed for the first time during an attempt to form a cyclopentane derivative through chlorosulfonylation of alkyne **1a** with *para*-toluenesulfonyl chloride and dilauroyl peroxide (DLP) in cyclohexane at reflux (Scheme 2). In contrast to previously reported radical cascades involving the cyclization of dienes[6a,i,11a,15] and enynes[10c,16] or ring opening of vinylcyclopropanes,[17] no trace of the expected cyclic chlorinated sulfone **3a** was observed. Instead, cyclic compound **2a** resulting from hydrosulfonylation was obtained in 66% yield. A related observation was made by Quiclet-Sire and Zard two decades ago during the study of 1,2-xanthate migration in sugar derivatives, which led finally to an efficient procedure for the preparation of deoxysugars.[18]



Scheme 2. Discovery of the hydrosulfonylation reaction. Tol = tolyl.

Rapid solvent screening showed that weak-hydrogen-atom-donor solvents, such as benzene, acetonitrile, and ethyl acetate, also provided the cyclized product **2a** but in lower yields (Table 1, entries 2–4).[19] 1,4-Dioxane gave results similar to cyclohexane (Table 1, entries 1 and 5). The yield of **2a** was significantly increased to 81% when THF[20] was used as the solvent (Table 1, entry 6).

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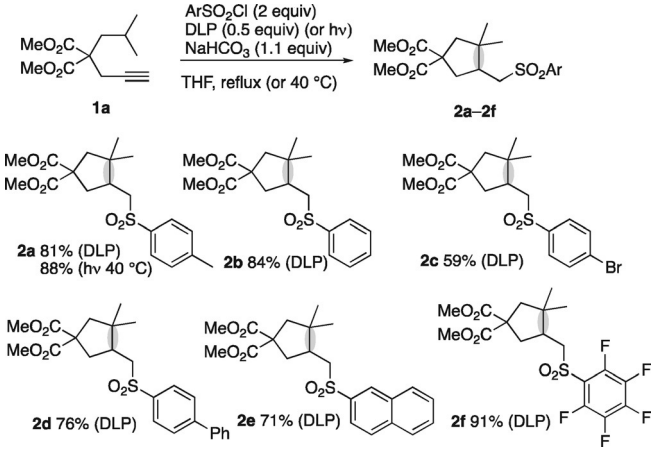
Table 1: Solvent optimization for the reaction of **1a** (Scheme 2).[a]

Entry	Solvent	*T* [°C]	Yield (**2a**) [%]
1	cyclohexane	80	66
2	benzene	80	40
3	acetonitrile	82	19
4	ethyl acetate	77	32
5	1,4-dioxane	101	68
6	tetrahydrofuran	66	81

[a] Reaction conditions: **1a** (1 mmol), *p*-toluenesulfonyl chloride (2 equiv), dilauryl peroxide (DLP; 0.5 equiv).

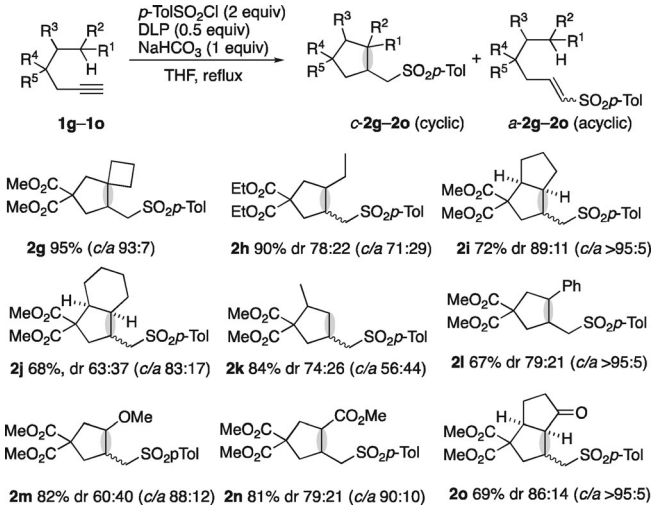
Different arenesulfonyl chlorides were tested and provided the corresponding cyclic sulfones in good to high yields (Scheme 3). Later, it was discovered that initiation of the reaction by simple sunlight irradiation in the absence of DLP afforded the product **2a** in slightly higher yield (88%).[21]



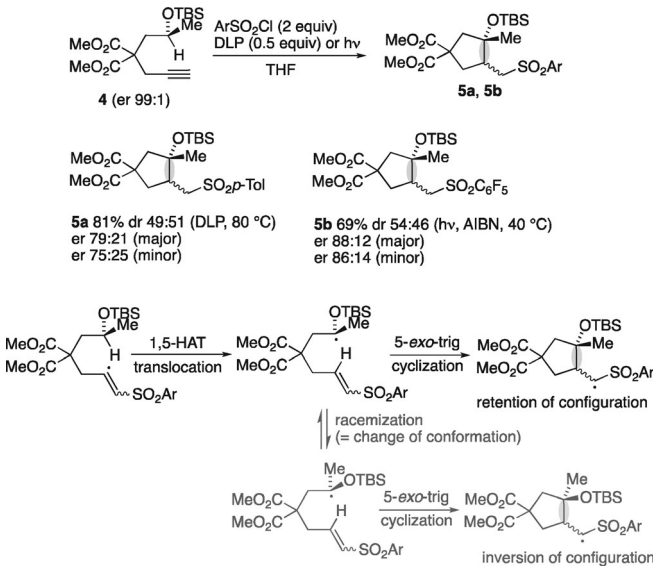
Scheme 3. Reaction of terminal alkyne **1a** with different sulfonyl chlorides.

The reaction was then tested with a variety of terminal alkynes **1g–o** (Scheme 4), and the cyclized product *c*-**2** was obtained as the major product in fair to excellent yields. Translocation processes leading to secondary alkyl radicals are known to be very challenging[13e,22] but take place efficiently under our reaction conditions. The generation of a primary radical from **1k** was even possible and provided a nearly 1:1 mixture of *c*-**2k** and *a*-**2k** in 84% yield. Examples of the activation of such terminal positions are rather scarce.[13e,23,24]

Finally, the reaction was tested for the synthesis of enantiomerically enriched aryl cyclopentylmethyl sulfones related to that used in the preparation of 26,28-methylene-1-α,25-dihydroxyvitamin D2 (see Scheme 1). The strategy was to use a RATC process involving the memory-of-chirality effect discovered by Heiba and Dessau[25] and further studied by Curran and co-workers.[26] Treatment of the enriched silyl ether **4** (er 99:1) with *p*-tolylsulfonyl chloride afforded the expected cyclopentylmethyl sulfone **5a** in 81% yield as a mixture of diastereomers (Scheme 5). Both the major and the minor diastereomer were enantiomerically enriched (er 79:21 and 75:25, respectively). Running the reaction with



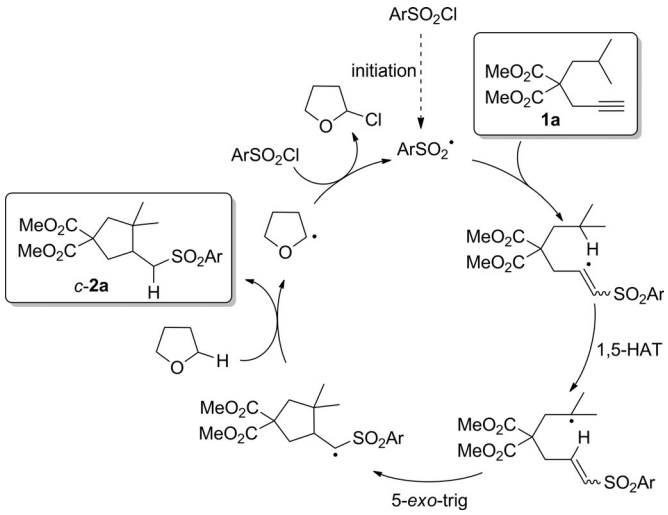
Scheme 4. Scope and limitations of the hydrosulfonylation of terminal alkynes.



Scheme 5. Memory of chirality in the RATC process (gray: racemization process). AIBN = azobisisobutyronitrile, TBS = *tert*-butyldimethylsilyl.

pentafluorobenzenesulfonyl chloride at 40 °C under sun-lamp irradiation afforded **5b** in 69% yield with the highest level of retention of the absolute configuration ever observed for a translocation–cyclization process (er 88:12 and 86:14 for the two diastereomers). The selectivity observed for the formation of the pentafluorinated phenyl sulfone **5b** is best rationalized by favorable electronic effects that increase the rate of cyclization relative to the conformational change involved in the racemization process (Scheme 5, gray part of the mechanism).

To clarify the mechanism, we carried out the reaction of **1h** in THF, [D_8]THF, and cyclohexane (see the Supporting Information for details). The results confirmed that the ratio of cyclic/acyclic products is determined during the translocation step and not during the subsequent very fast cyclization.



Scheme 6. Mechanism: a perfect match of polar effects.

On the basis of these observations, we propose the mechanism depicted in Scheme 6. The starting electrophilic sulfonyl radical adds efficiently to the terminal alkyne to furnish a highly reactive alkenyl radical that is perfectly suitable to abstract a hydrogen atom from an aliphatic C–H bond. Owing to its appropriate conformation and to favorable electronic effects, the translocated radical cyclizes extremely fast. The cyclized α-sulfonyl radical[27] is not chlorinated by $ArSO_2Cl$ owing to unfavorable polar effects[28] but is able to abstract a hydrogen atom from THF (or cyclohexane).[18] This key step is strongly facilitated by polar effects.[18,29] Finally, the nucleophilic 2-tetrahydrofuranyl radical is rapidly chlorinated by $ArSO_2Cl$ owing to favorable polar effects.[28b] Importantly, every single step of this process is favored by polar effects and thermodynamic factors, thus giving rise to an efficient chain reaction.

In conclusion, we have developed an inexpensive method for an unprecedented hydrosulfonylation cascade reaction. The reaction is experimentally very simple to run and affords the desired products in good to high yields. Moreover, the strategy used in this study for the hydrosulfonylation cascade process is expected to be extendable to a large variety of other reactions. Investigations along those lines are currently in progress in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclization · hydrosulfonylation · radicals · sulfonyl chlorides · tetrahydofuran

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