Chemistry of Sulfonate- and Sulfonamide-Stabilized Carbanions − The *CSIC* Reactions[‡]

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Keywords: Carbanions / *CSIC* reactions / Cyclization / Sulfonamides / Sulfur heterocycles / Sultones

In this account we review the varied, but extensively documented reactions affording acyclic alkanesulfonates, alkanesulfonamides, and heterocyclic ring systems (sultones, 1,2-oxathiole *S*,*S*-dioxides, sultams, and 2,3-dihydroisothiazole *S*,*S*-dioxides) from conveniently functionalized alkanesulfonates or alkanesulfonamides, by a general procedure that we have named and classified as *CSIC* reactions both as intermolecular [*C*arbanion-mediated *S*ulfonate (or *S*ulfonamide) *I*ntermolecular *C*oupling] and as intramolecular [*C*arbanion-mediated *S*ulfonate (or *S*ulfonamide) *I*ntramolecular *C*yclization] variants of the conversion.

[‡] CSIC (Consejo Superior de Investigaciones Científicas") is also the acronym for the main Spanish public institution dedicated to basic and applied research in all branches of knowledge and the sciences. By chance, one of the versions of the CSIC reaction ("the nitrile application") was discovered in a CSIC institute where one of the authors (J. L. M.) of this review is carrying out active research on this reaction.

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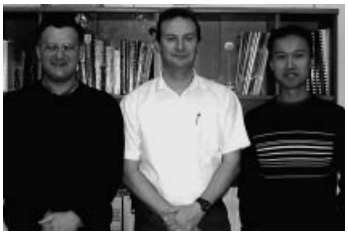
1. Introduction

The reactivity of carbanions[1] stabilized by sulfur-containing functional groups is one of the most useful and widely recognized tools for carbon−carbon bond formation in organic synthesis.

The chemistry of α-sulfinyl,[2] α-sulfonyl,[3] and α-sulfonimidoyl carbanions[4] has been reviewed comprehensively, and is not covered in this account. Here we focus on the known literature pertaining to the synthesis and reactivity of α-sulfonyl carbanions derived from related substrates,



José Marco Contelles (left) studied chemistry at the Universidad Complutense de Madrid (UCM) (graduating with honors), where he obtained his PhD under Professor Benjamín Rodríguez (Instituto de Química Orgánica, Consejo Superior de Investigaciones Científicas, CSIC) in 1984. After two years working as a post-doctoral fellow under Dr. H.-P. Husson (Institut de Chimie de Substance Naturelles, CNRS, Gif-sur-Yvette, France) (CNRS methods in asymmetric synthesis) (1984-85), he worked as an associate researcher under Professor Wolfgang Oppolzer (Département de Chimie Organique, Genève, Suisse) (aldol reaction) (1986) and was a visiting Professor at the Department of Chemistry, Duke University, North Carolina working with Professor Fraser-Reid (free radical chemistry; annulated furanoses; formal total synthesis of phyllathocin). In 1986 he was appointed as Associate Researcher, and in 1992 he was promoted to Research Scientist in the CSIC (Spain). He was Invited Professor at the Université Pierre et Marie Curie, Paris VI (June 2000) and at the Université Jules Verne-Picardie (Amiens, France) (May−July 2003). He is scientific consultant for Specs and BioSpecs. In 2002 he received the French-Spanish award of the French Chemical Society. His present interests include the development of new synthetic methodologies in free radical chemistry, organometallic chemistry (Pauson-Khand reaction, $PtCl_2$-mediated cycloisomerization of polyunsaturated precursors) and synthesis/biological evaluation of heterocyclic systems (CSIC reaction, tacrine analogues).

Denis Postel (center) was born in 1964 in Beauvais (France). He studied chemistry at the University of Picardie-Jules Verne (UPJV) of Amiens (France) where he obtained his his PhD in organic chemistry in 1990 under the supervision of Professor P. Villa working on thio- and azaglyco derivatives. After a year of ATER (Attaché Temporaire d'Enseignement et de Recherche), he assumed the position of Maître de Conférences of Organic Chemistry at the UPJV in 1991 and was appointed as full Professor in 2002 in the Laboratoire des Glucides. His present research interest include the glycochemistry and heterocyclic chemistry applied to glycoaminonitriles and nucleosides and their application for the development of novel Sugar Amino Acids and aza analogs of TSAO.

Albert Nguyen Van Nhien (right) was born in 1974. He received his PhD degree from the Université of Picardie-Jules Verne, Amiens (France). After a postdoctoral position in the group of John A. Murphy (Strathclyde University, Glasgow), he re-joined the UPJV where he is currently Maître de Conférences in the Laboratoire des Glucides working with Professor Postel.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

such as alkanesulfonates and alkanesulfonamides, comparison with electrophilic species, and their respective roles in inter- or intramolecular processes.

In contrast to the number of theoretical studies dedicated to α-sulfonyl carbanions derived from sulfones,[3c,5] the literature regarding related α-sulfonyl carbanions derived from alkanesulfonates and alkanesulfonamides is relatively scarce, and has been concentrated on mechanistic studies concerning the elimination-addition of acyl transfer reactions producing sulfenes.[6] These studies have allowed the determination of the pK_a values of some sultones (15.6) and phenyl phenylmethanesulfonate (18.0) in dimethyl sulfoxide.[7] These show the marked lability of α-hydrogen sulfonyl protons (it is noteworthy that the pK_a values of methyl phenyl sulfone and phenylsulfonylacetophenone are 29.0 and 11.4, respectively).[8] Accordingly, it has been shown that a large range of bases, from *n*BuLi to DBU, are able to abstract protons in positions α to sulfur atoms in alkanesulfonates and alkanesulfonamides to give reactive species that react with various electrophiles such as alkyl halides, sulfonates, either α,β-unsaturated or other unsaturated carbonyl compounds (ketones, esters), nitriles, and aromatic activated substrates, in inter- and intramolecular conversions, to yield substituted alkanesulfonates, alkanesulfonamides, and different types of heterocyclic ring systems [Scheme 1, Equations (1) and (2)].

We have named and classified these transformations as *CSIC* reactions, taken from the initials of the keywords that describe and define the process for the intermolecular [*C*arbanion-mediated *S*ulfonate (or *S*ulfonamide) *I*ntermolecular *C*oupling] and intramolecular [*C*arbanion-mediated *S*ulfonate (or *S*ulfonamide) *I*ntramolecular *C*yclization] conversions.[2c]

In the first part of this account we present examples of intermolecular applications of this chemistry, whilst the second part is concerned with intramolecular examples.

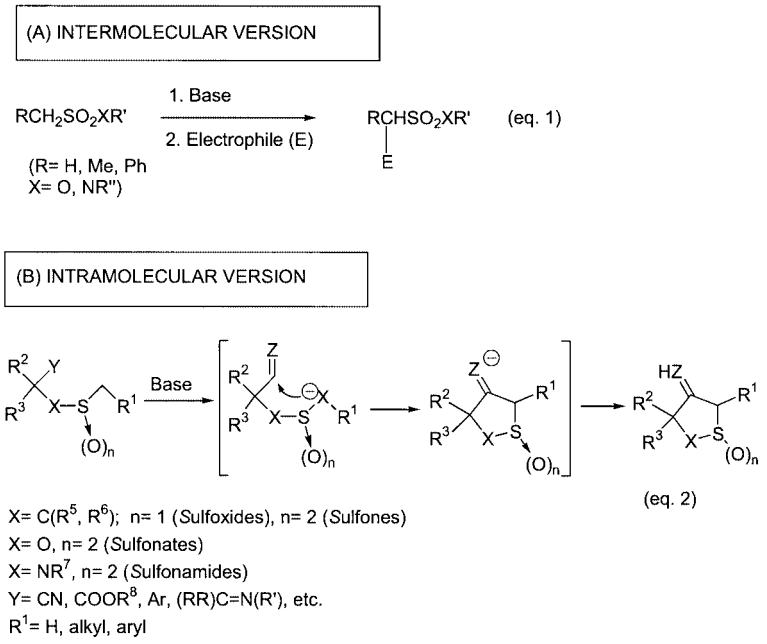
2. *C*arbanion-Mediated *S*ulfonate (or *S*ulfonamide) *I*ntermolecular *C*oupling (*CSIC* Reaction)

2.1. From Alkanesulfonates

The first example of a *c*arbanion-mediated *s*ulfonate *i*ntermolecular *c*oupling (*CSIC* reaction) was communicated in 1966 by Corey and Durst in a footnote in a preliminary communication[9a] and in a full paper[9b] describing the reactivity of dianions of methanesulfinanilides, which states that "the α-lithio derivative of methanesulfonate ($LiCH_2SO_2OCH_3$) is formed cleanly with *n*-butyllithium in tetrahydrofuran at −78 °C, as shown by the isolation of adducts with benzophenone (91%) and cyclohexanone (76%)". However, neither further examples nor detailed studies to explore the potential of this useful transformation [X = O, Equation (1) in Scheme 1] were undertaken.

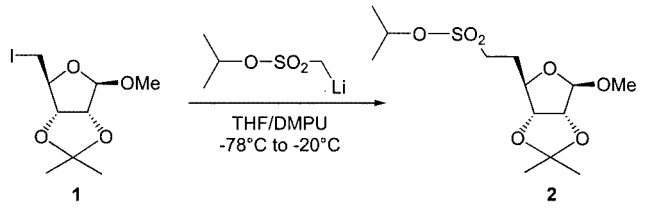
Such an exercise was, however, reported in 1969 by Truce and Vrencur.[10] For instance, they described the α-alkylation of some neopentyl alkanesulfonates[10a] with different alkyl iodides and bromides with KH as base (or, better, either *n*BuLi alone or in the presence of TMEDA in THF at −65 °C) to give the expected products in yields ranging from 40 to 80%.

Several years after these reports, Widlansky[11] reported the α-alkylation of isopropyl methanesulfonate with primary carbohydrate iodides **1**, showing that no alkylation



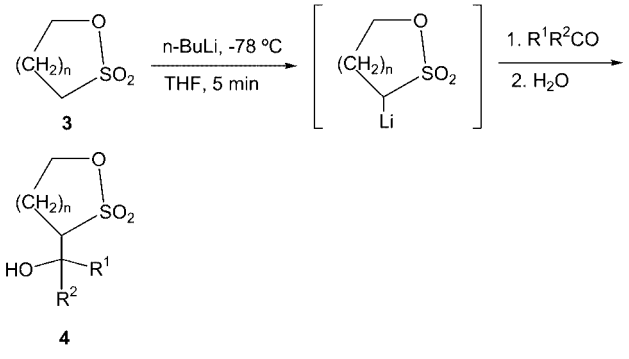
Scheme 1. The reactivity of sulfur-stabilized carbanions (*CSIC* reactions)

was observed under the previously reported conditions.[10] This situation changed dramatically when DMPU was added to the reaction medium, which enabled the alkylated products **2** to be obtained in moderate yields (Scheme 2).[11a,11b] Such chemistry was also applied to primary steroid iodides for the synthesis of steroid sulfonates.[11c]



Scheme 2. α-*C*-Glycosylation of alkanesulfonate

In 1969, Durst found that the known reactivity of sultones **3** with organometallic reagents (*n*BuLi) to give open-chain sulfonic acids could be suppressed by simple temperature control (i.e., by lowering the temperature to −78 °C), promoting the α-metallation, and that subsequent alkylation with electrophilic species such as methyl iodide, benzyl chloride (with less reactive halides the yields were lower), ketones, and aldehydes gave the variously substituted sultones **4** in moderate yields (Scheme 3).[12a] In the case of the ketones, dehydration of the resulting β-hydroxy sultones gave α,β-unsaturated sultones (benzophenone) or β,γ-unsaturated sultones (acetone, cyclohexanone), depending on the ketone used. In other studies Durst showed that there was a marked preference for the introduction of the lithium atom in the equatorial position, as could be observed in subsequent deuteration or alkylation steps.[12b]

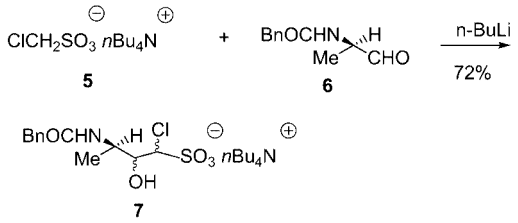


Scheme 3. α-Alkylation of sultones

α,β-Unsaturated sulfonate derivatives have been prepared by treatment of aldehydes with a sulfonyl-stabilized α-phosphonate anion as described by Ghosez.[13]

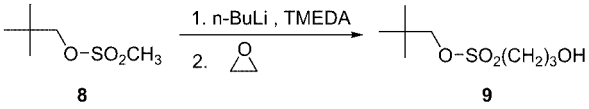
Widlansky reported the synthesis of nucleoside sulfonates by hydrogenation of α,β-unsaturated sulfonates prepared by this procedure.[11d] Widlansky has also described the *CSIC* reaction between an α-sulfonyl carbanion and a ketone in the case of a nucleoside; the resulting β-hydroxy-sulfonate was dehydrated and then hydrogenated to give a series of α-alkylated alkanesulfonates.[11e,11f] α,β-Unsaturated sulfonates are precursors in the synthesis of α,β-unsaturated sulfonamides[14] via the corresponding sulfonyl chlorides.

Ghosez also described the Darzens reaction between aldehydes and the α-chlorosulfonic acid derivative **5** (Scheme 4).[13c] The stereoselectivity of the *CSIC* reaction with D-alanilal (**6**) was poor, but the reaction gave a mixture of *threo* and *erythro* derivatives **7** in good yield.



Scheme 4. Darzens reactions of α-chlorosulfonic acid derivatives

Adamczyk and co-workers performed the first *CSIC* reaction between alkanesulfonates and epoxides. A neopentyl mesylate **8** was deprotonated with *n*BuLi and subsequently treated with ethylene oxide to give a hydroxypropanesulfonate **9** (Scheme 5).[15]



Scheme 5. Synthesis of hydroxypropanesulfonate

Wong and co-workers also reported the synthesis and biological evaluation of a series of alkanesulfonates as inactivators and inhibitors for subtilisin. These alkanesulfonates were obtained by α-alkylation, promoted by *n*BuLi at −78 °C, of methanesulfonate with either benzaldehyde or benzoyl chloride.[16]

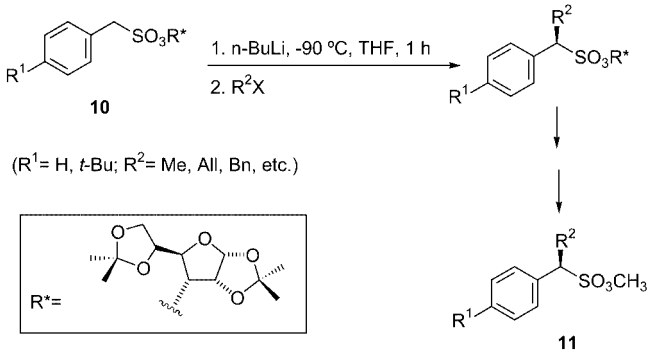
The α,α′-difluorination of arylmethanesulfonates with use of *n*BuLi as base and *N*-fluorobenzenesulfonimide (NFSi) has been described.[17]

In 1983 Zwanenburg reported asymmetric Darzens reactions between enantiomerically pure L-menthyl chloromethanesulfonate and aldehydes or symmetrical ketones.[18] Under phase-transfer conditions (NaOH, TEBA), good yields of the *trans*-epoxysulfonates were obtained, but with very poor diastereoselectivities (around 10%).

Biller and co-workers used a chiral α-phosphono sulfonate with chirality incorporated into the phosphono moiety for the asymmetric synthesis of useful intermediates as inhibitors of squalene synthase.[19]

Enders and co-workers have very recently reported the first example of the α-alkylation of enantiomerically pure alkanesulfonates with 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as a chiral auxiliary,[20a] together with some practical applications for the synthesis of chiral sultones[20b] and Michael addition to nitroalkenes.[20c,20d] In his seminal

studies, Enders found that sulfonates **10** derived from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose could be α-alkylated with active alkyl (methyl, benzyl, allyl) halides by use of *n*BuLi as the base at −90 °C in THF, in high yields and with good stereoselectivities. Simple and efficient non-racemization reaction conditions were employed to give the corresponding enantiomerically pure methanesulfonate **11** (Scheme 6).



Scheme 6. Asymmetric synthesis of α-alkylated alkanesulfonates

2.2. From Alkanesulfonamides

The first case of a *CSIC* reaction from alkanesulfonamides was the reaction between an *N*,*N*-dimethyl-sulfonamide and benzophenone in the presence of potassium hydroxide in diethyl ether, to afford a substituted sulfonamide in 25% yield, as reported by Chodkiewicz et al. in 1958.[21]

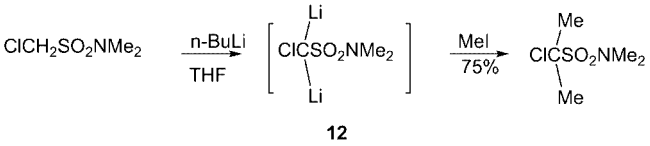
In 1960, Martenson and Nilsson[22] described the α-alkylation, in moderate yields, of *N*,*N*-disubstituted phenylmethanesulfonamides and diphenylmethanesulfonamides with alkyl halides by use of sodium amide as the base, in either benzene or toluene, at high temperatures (around 100 °C).

In 1965, in the context of a detailed account of the generation of the methylsulfinyl carbanion and its synthetic applications, Corey and Chaykovsky reported[9c] high yields (77−97%) for the α-metallation of an *N*,*N*-dimethyl-sulfonamide under milder conditions (*n*BuLi in a cold water bath) with benzophenone, cyclohexanone, and ethyl cyclohexanecarboxylate. Shortly afterwards, in 1969, Truce described the α-nitration of sulfonamides with alkyl nitrates[10d] and *CSIC* reactions (with ketones,[10e,10g] esters,[10e] aldehydes,[10f,10g] imines,[10f] and Michael acceptors[10f]) of lithium α-chloro-sulfonamide carbanions and lithium salts of α-chloro-sulfonates.[10e]

In subsequent communications the reactivity of alkanesulfonamides with these electrophiles (ketones/epoxides,[23] imines,[24] and esters[25]) was also confirmed and expanded upon.

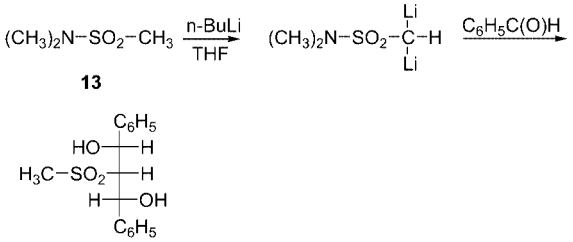
In 1969, Loew and Dowalo also reported the reaction between an α-carbanion of a sulfonamide (prepared by use of potassium hydride in THF) and a nitrite to give α-oxo-imino-sulfonamides.[26]

In 1971, Truce[10h] and Böhme[27] independently reported the preparation of the 1,1-dilithio-α-chloro-*N*,*N*-dimethylmethanesulfonamide (**12**) and their subsequent double α-alkylation (Scheme 7). Similar reactivities and results were published by Makosza several years later; particularly interesting in these examples was the Darzens condensation between aldehydes and α-chloro-sulfonamides to give the expected oxiranes in good yields.[28]



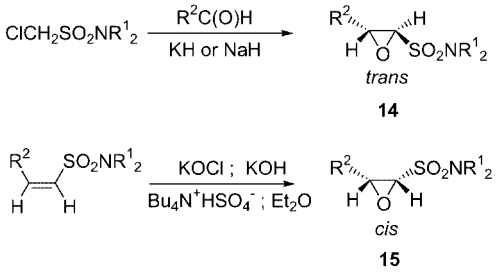
Scheme 7. α-Dialkylation of alkanesulfonamides

Kaiser also reported the preparation of dilithio carbanions, and their transformations, from *N*,*N*-dimethylphenylmethanesulfonamides.[29] Soon afterwards, Umani-Ronchi also communicated that *N*,*N*-dimethylmethanesulfonamide (**13**) are rapidly converted into their 1,1-dilithio salts on treatment with *n*BuLi in THF/hexane. The nature of these species was confirmed by deuteration studies and alkylation with aldehydes (Scheme 8).[30]



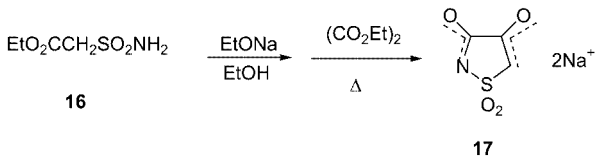
Scheme 8. Alkylation of 1,1-dilithio salts of methanesulfonamide

According to the pioneering studies by Truce[10g] and Makosza,[28] the stereochemistry of the Darzens reaction with α-chloro-sulfonamides under phase-transfer conditions (PTCs) was further carefully investigated.[31] Under the usual conditions the *trans*-epoxy-sulfonamides **14** were obtained by use of either potassium or sodium hydride, while the *cis* isomers **15** were prepared by epoxidation of *cis*-ethenesulfonamides (Scheme 9). It is interesting to note that the use of *n*BuLi as the base[10g] gave exclusively the α-chloro-β-hydroxy-sulfonamides, while use of potassium *tert*-butoxide gave the corresponding epoxy-sulfonamides. Alternatively, the Darzens reaction under PTCs afforded epoxy-sulfonamides directly from the corresponding precursors.[31]



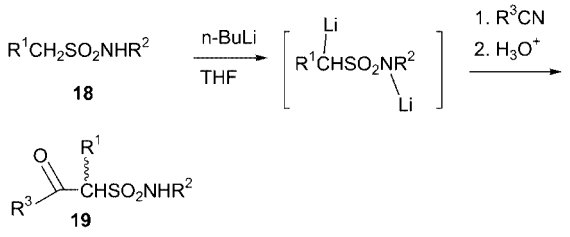
Scheme 9. Darzens reactions with α-chloro-sulfonamides

In 1983, Britcher reported the synthesis of isothiazole *S*,*S*-dioxide (**17**) through condensation between a substituted methanesulfonamide **16** and diethyl oxalate in the presence of sodium ethoxide as a base (Scheme 10).[32]



Scheme 10. α-Alkylation of alkanesulfonamides with esters

In 1984, Thompson noticed that no methodology existed for the selective *C*-alkylation of methanesulfonamides. Consequently, he developed and reported[33a] the first full, systematic analysis of the α-alkylation of mono-*N*-substituted alkanesulfonamides, by use of *n*BuLi (2 equiv.) at −70 to −30 °C, followed by treatment with alkyl or benzyl halides, trimethylsilyl chloride, aldehydes, and ketones. When starting from methanesulfonamide and using such a procedure, a dianion ($LiCH_2SO_2NHLi$) was obtained; this gave a poor yield after reaction with methyl iodide. As an alternative route it was found that *N*-*tert*-butylmethanesulfonamide could be converted into a dilithio derivative that reacted chemoselectively at the carbon atom, presumably due to the location of the greatest charge density at this center. The procedure proved to have general application and gave the expected adducts in good yield. In the cases of aldehydes and substituted methanesulfonamides, low stereoselectivities were reported, the *threo*/*erythro* ratios being 2:1 and 3.6:1, respectively. Such β-hydroxysulfonamides were also transformed into 1,2-thiazetidine *S*,*S*-dioxides and β-styrenesulfonamides. Continuing the research on this topic, in 1988 Thompson reported the *CSIC* reaction between alkanesulfonamides **18** and nitriles as electrophiles to give β-oxo-sulfonamides **19** after acid hydrolysis (Scheme 11).[33b] In addition, it was also reported that *CSIC* reactions involving such nitriles, followed by trapping of the reactive intermediate dianion either with phosgene or with phenyl chloroformate, very cleanly afforded 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxides. Alternatively, the *CSIC* reaction with aldehydes followed by a similar procedure gave 5,6-dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-dioxides.



Scheme 11. α-Alkylation of alkanesulfonamides with nitriles

Thompson's studies[33] have greatly contributed to demonstration of the utility of these synthetic transformations, different authors having used these technologies with advantage in a number of subsequent publications.[34] For instance, the use of *N*-benzylphenylmethanesulfonamides in the *CSIC* reaction with formaldehyde gave the unexpected heterocyclic ring system tetrahydro-1,4,3-oxathiazine 4,4-dioxide in moderate yield.[34a] The α-benzylation of a sulfonamide−proline residue in a peptide derivative[34b] and the α-allylation of an isopropyl α-(sulfonamido)acetate[34c] have also been reported.

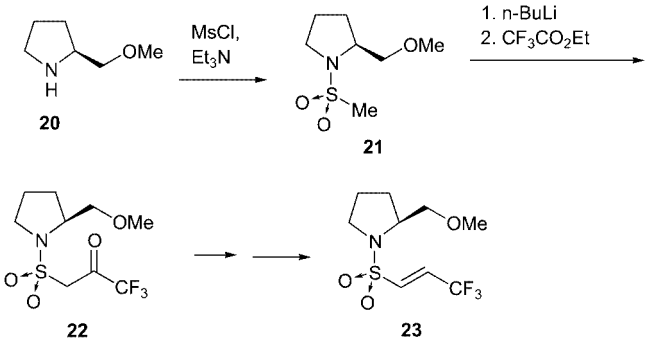
An interesting application of the *CSIC* reaction was shown by Tozer[35] and co-workers in the case of the reaction between tertiary *N*-Boc-protected methanesulfonamides and aldehydes, with basic treatment with potassium *tert*-butoxide, to give a direct route to the synthesis of (*E*)-α,β-unsaturated sulfonamides.[14] It is interesting to point out that in 1975, Oliver and De Milo had already described the synthesis of styrene-ω-sulfoanilides through the *CSIC* reaction between aromatic aldehydes and (phenylaminosulfonyl)acetic acid.[36,37]

In the literature, we have found some notable heterocyclic interconversions.[38] Examples include the transformation of isatoic anhydrides into 2- or 4-oxoquinolines with carbanions of active methylene compounds, such as *N*,*N*-dimethyl-β-oxo-2-thienylethanesulfonamide,[38a] and the synthesis of 1,4-benzodiazepines by ring expansion of 2-chloroquinazolines with stabilized carbanions, such as that derived from an *N*,*N*-dimethyl-sulfonamide.[38b]

Finally, other useful reported transformations include the synthesis of 2′,3′-cyclopropane nucleoside dimers by α,α′-dialkylation of alkanesulfonamides with vinyl selenones,[39a] the reaction with enantiomerically pure tricarbonyl(2-substituted benzaldehyde)chromium complexes,[39b] and the free radical halogenation to yield α-halo-sulfonamides.[39c]

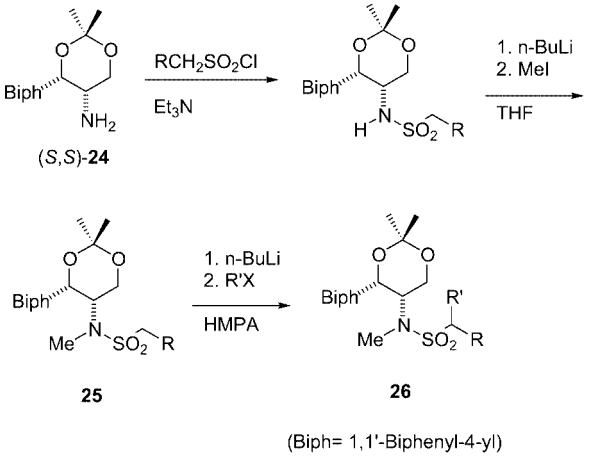
Very surprisingly, no reports relating to the asymmetric α-alkylation of chiral sulfonamides were known until 1985. According to the previous work on the asymmetric Darzens reaction with chloromethanesulfonates (see above),[18] Nkunya and Zwanenburg performed similar studies on α-chloro mono- and disubstituted sulfonamides.[40] (*S*)-(−)-2-(Methoxymethyl)pyrrolidine, (*S*)-(−)-*tert*-butylprolinate, and (+)-ephedrine were each used as chiral inductors. The Darzens reaction with different aldehydes and ketones was conducted under PTC conditions, affording the expected epoxides in good yields but with poor diastereoselection. A detailed discussion interpreting the stereochemical course of this reaction was presented.[40]

In 1997, Eguchi reported[41] the reactions of different α-metallated enantiomerically pure methanesulfonamides, such as the *CSIC* reaction between **21** [obtained from (2*S*)-2-(methoxymethyl)pyrrolidine (**20**)] and ethyl trifluoroacetate (Scheme 12) to give the β-oxo-sulfonamide **22**, which was subsequently converted into the α,β-unsaturated sulfonamide **23**. This product proved to be a versatile substrate for a variety of Michael additions to give useful building blocks.



Scheme 12. α-Alkylation of alkanesulfonamides with ethyl trifluoroacetate

In 1998, Enders also described *CSIC* reactions between chiral sulfonamides and alkyl and benzyl halides.[42] The chiral auxiliaries were the amines (*S*,*S*)-**24** and (*R*,*R*)-**24**, which were treated with the corresponding sulfonyl chlorides under the standard conditions to give the precursors **25**. The α-alkylation, with *n*BuLi as base in diethyl ether as solvent, at −70 °C, afforded the alkylated sulfonamides **26** in good yields and with high stereoselectivities (Scheme 13).



Scheme 13. Asymmetric α-alkylation of alkanesulfonamides with halides

Davis and associates reported on the asymmetric alkylation of the camphorsulfonylimines **A** and **B** (Figure 1).[43] Treatment of camphorsulfonylimine **A** with LDA (2.2 equiv.) at 0 °C afforded the alkylated products *exo*-**A1** and *endo*-**A1**, in good yield but in unfavorable ratios (1:1 or 3:7, depending of the electrophile). Such products have been used for the synthesis of enantiomerically pure (camphorsulfonyl)oxaziridines.[43a] In other studies, this team reported on the synthesis of α-functionalized primary sulfonamides **B2** by acid hydrolysis of the alkylation products **B1** obtained from the compound **B**.[43b]

Finally, we should mention the alkylation studies reported by Huart and Ghosez in the asymmetric synthesis of bicyclic cyclopentenones through stereoselective 1,4-addition of metallated enantiomerically pure sulfonamides to cyclic enones.[44]

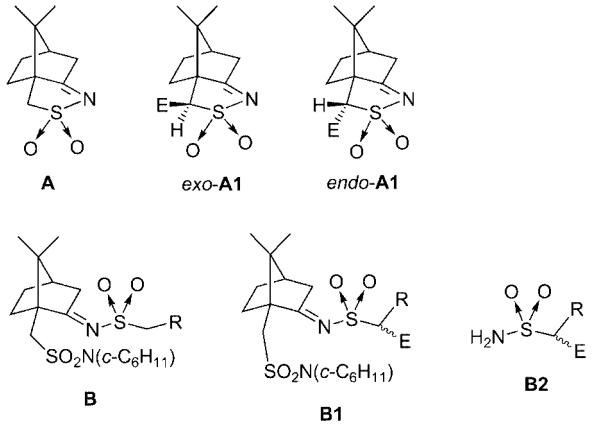
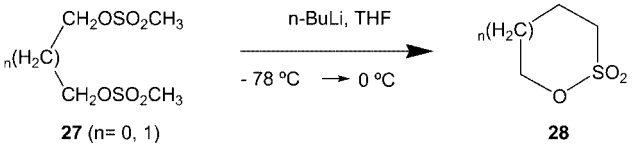


Figure 1. Asymmetric α-alkylation of camphorsulfonylimines

3. *C*arbanion-Mediated *S*ulfonate (or *S*ulfonamide) *I*ntramolecular *C*yclization (*CSIC* Reaction)

3.1. Sulfonates or Halides as Electrophilic Species

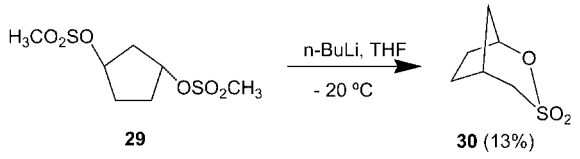
The first example of a *CSIC* reaction was reported in 1970 by Durst and Tin,[12c] following the pioneering studies on the intermolecular reactions between α-metallated species produced from alkanesulfonates or alkanesulfonamides and electrophiles, described by Corey[9] and Truce.[10] Durst and Tin reported the synthesis of five- and six-membered ring sultones through *CSIC* reactions with 1,2-ethanediyl or 1,3-propanediyl bis(methanesulfonates) **27**, promoted by *n*BuLi, at −78 °C with subsequent warming to 0 °C over 30 min, in THF as solvent (Scheme 14).[12c] A detailed study entailing modification of the structure of the precursor was undertaken, giving the expected sultones **28** in yields from 47 to 74%. However, attempts to extend these reactions to the synthesis of seven- or eight-membered ring sultones proved unsuccessful. The authors also described *CSIC* reactions of related chloro- or bromomesylates. The yields for these transformations were low (ca. 30%), and always lower than those obtained with the parent disulfonates. Very interestingly, in no cases were elimination products detected. Sultones are interesting intermediates for the preparation of sulfonic acids, behave as sulfoalkylating agents, and are of considerable industrial and biological interest.[45]



Scheme 14. *CSIC* reactions with bis(methanesulfonates)

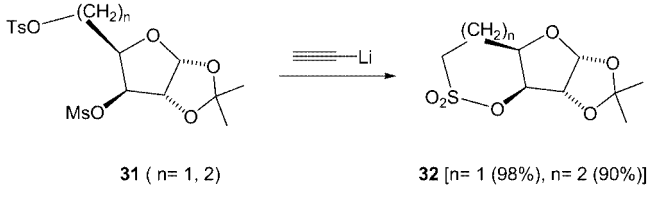
Kobayashi and co-workers showed that the *CSIC* reactions of *N*-(2-bromoalkyl)-*N*-methylalkanesulfonamides, in the presence of *n*BuLi as base at −70 °C, gave the corresponding sultams in moderate yield.[46] Such sultams have also been alkylated. Examples that have been recorded in the literature start with 2,1-benzoisothiazoline 2,2-dioxides and its treatment with 4-fluoronitrobenzene in NaOH/DMSO to give 3-aryl-2,1-benzoisothiazoline 2,2-dioxides in moderate yields.[47a] The preparation and alkylation of β-sultam mono- and dianions has been reported.[47b]

Some years later, in 1977, Pilichowski and Lhomme reported[48] the synthesis of a bridged sultone **30** from a *trans*-cyclopentane-1,3-diylbis(methanesulfonate) (**29**) (Scheme 15), under the same experimental conditions. This product was isolated in low yield, from a complex, incompletely converted reaction mixture. Efforts to improve this result under various experimental conditions (base, solvent, temperature) proved fruitless.



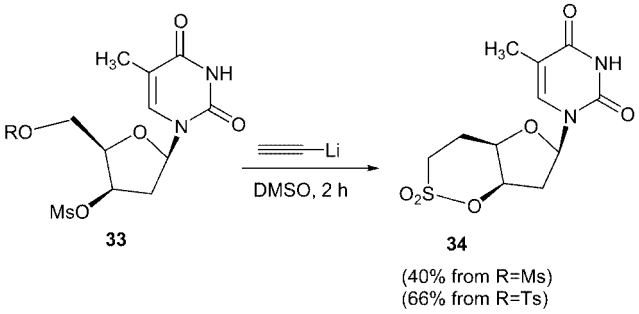
Scheme 15. *CSIC* reaction with a *trans*-cyclopentane-1,3-diylbis(methanesulfonate)

In 1981, Fraser-Reid[49] also reported the synthesis of some six- and seven-membered sultones annulated onto furanose or pyranose templates. In this case the *CSIC* reaction of mixed disulfonates with an *O*-methylsulfonyl moiety at a secondary carbon atom and an *O*-*p*-tolylsulfonyl group at a primary carbon atom, derived from carbohydrates **31**, promoted variously by lithium acetylide/ethylenediamine complex in dry DMSO at room temperature, sodium hydride or the dianion of ethyl acetoacetate, gave the corresponding sultones **32** in good to excellent yields (Scheme 16). As in the previous examples, the mesylate was deprotonated and the resulting carbanion displaced the tosylate to give the desired sultone.



Scheme 16. *CSIC* reactions with mixed disulfonates on carbohydrate templates

More recently Crooks and Reynolds[50] have reported a similar transformation, under the same experimental conditions, but with a nucleoside precursor **33** possessing a bis(methanesulfonate) or a mixed bis(sulfonate) functional group located at a convenient position (Scheme 17). As observed by Durst and Tin,[12c] only the sultone **34** resulting from generation of the carbanion of the 3′-*O*-mesyl group and subsequent displacement of the 5′-*O*-mesyl moiety was observed, and not the compound resulting from attack of the carbanion at the 5′-*O*-mesyl group on the secondary 3′-mesylate. As previously reported by Fraser-Reid,[49] the mixed disulfonate precursor gave the best yields in the *CSIC* reaction with values ranging from 40 to 66%.



Scheme 17. CSIC reactions with mixed disulfonates on nucleoside templates

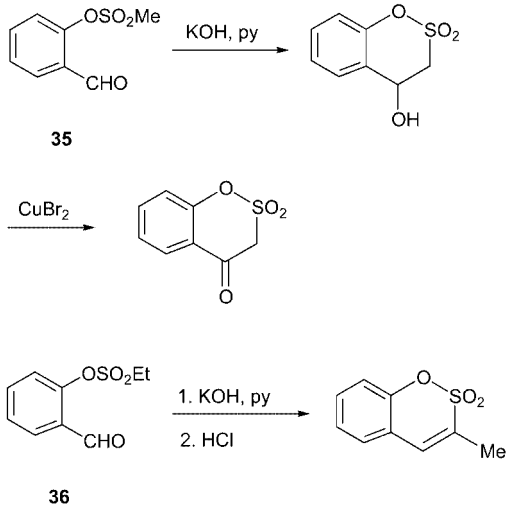
3.2. Carbonyl Groups as Electrophilic Species

3.2.1. Aldehydes as Electrophilic Species

To the best of our knowledge, the only recorded examples with an aldehyde group as the terminal point for the *CSIC* reaction were described in 1972.[51] Such reactions involved (alkylsulfonyl)salicylaldehydes **35/36** and gave the expected sultones, which were used as precursors for a number of different transformations as shown in Scheme 18.

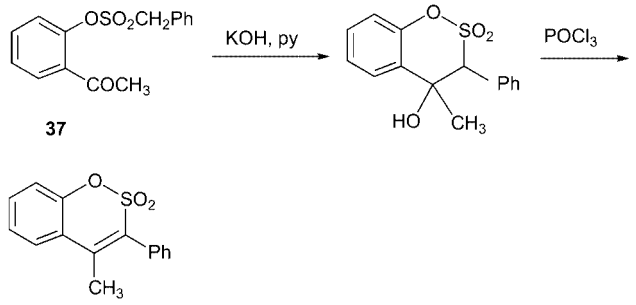
3.2.2. Ketones as Electrophilic Species

Several examples are known. In the first,[52] acetylphenyl methanesulfonate and acetylphenyl phenylmethane-



Scheme 18. *CSIC* reactions with aldehydes as electrophiles

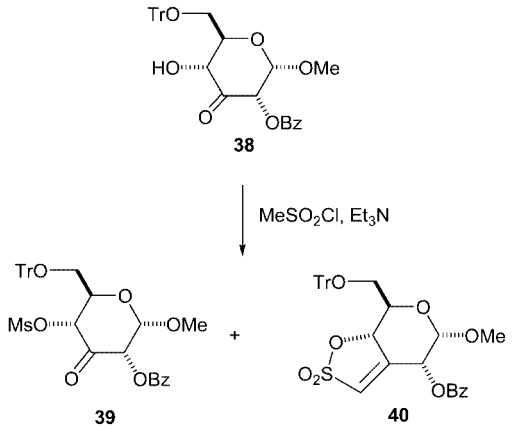
sulfonate) (**37**) were subjected to the *CSIC* reaction conditions in the presence of potassium hydroxide in pyridine to give the corresponding sultones (yields not reported), which were employed as intermediates for various further



Scheme 19. *CSIC* reactions with ketones as electrophiles

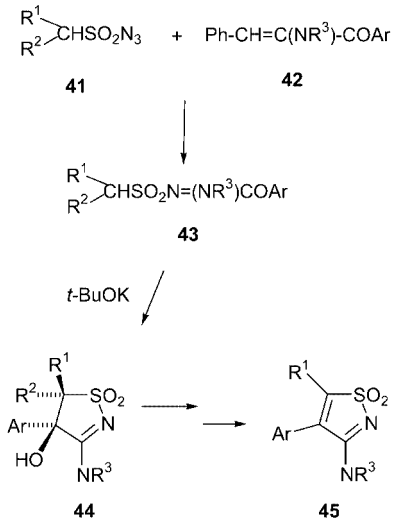
transformations for characterization purposes (Scheme 19).

The second literature example of a *CSIC* reaction involving an oxo group as an electrophile was reported by Fraser-Reid[53] in 1978; the oxo group was part of a carbohydrate molecule. Treatment of the α-hydroxy ketone **38** with methanesulfonyl chloride and triethylamine in dichloromethane gave the expected mesylate **39** and the annulated pyrano-1,2-oxathiole *S*,*S*-dioxide **40**. The yields were variable, in accordance with reaction temperature and ranged from 0% (at −75 °C) to 30−35% (at 40 °C) (Scheme 20). It was observed that compound **39**, under the same experimental conditions, did not afford product **40**, thus ruling out a *CSIC*-type mechanism (Scheme 1). An explanation proposed by the authors for the formation of the product **40** involved the intermolecular aldol-type reaction of an α-metallated methanesulfonate salt in triethylamine with the ketone, followed by *O*-sulfonation of the free vicinal hydroxy group and finally dehydration. No further examples of this interesting reactivity and transformation have been reported.



Scheme 20. *CSIC* reactions with oxo sulfonates on carbohydrate templates

More recently, Clerici has shown that *N*-sulfonylamidines **43**,[54a] prepared by 1,3-dipolar cycloaddition of sulfonyl azides **41** and enamines **42**, upon treatment with a base such as potassium *tert*-butoxide, afforded the isothiazolines **44**, which were subsequently transformed into isothiazoles **45** (Scheme 21).[54b] These isothiazole dioxides[54c] were tested for their ability to inhibit protein farnesyltransferase from the parasite that causes African sleeping disease (*Trypanosoma brucei*).[54d]

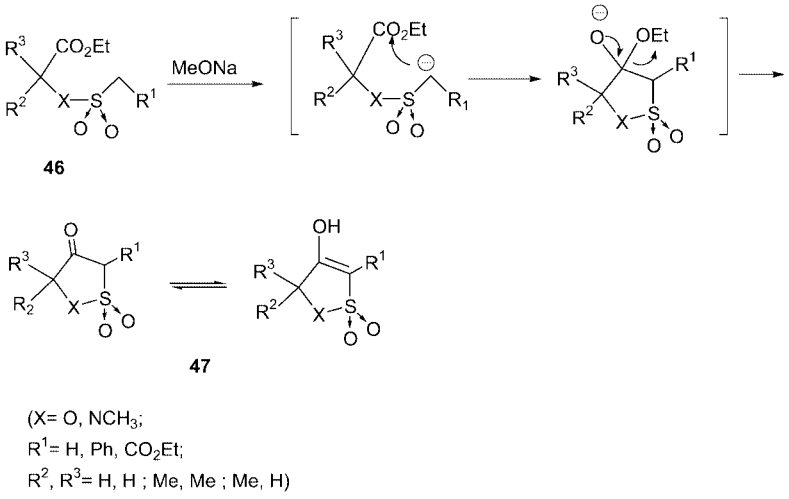


Scheme 21. *CSIC* reactions with β-oxo sulfonylamidines

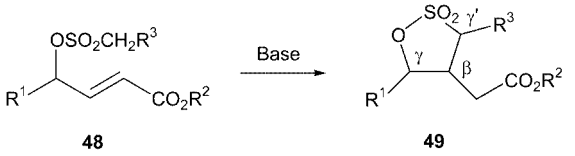
3.2.3. Carboxylic Esters as Electrophilic Species

In 1976 (in a patent[55a]) and in 1985 (as a full paper[55b]), Stachel and Drasch described the first examples of a *CSIC* reaction involving carboxylic esters as electrophiles. The authors synthesized a large range of differently substituted (methane, phenylmethane, and ethoxycarbonylmethane) sulfonates from (unsubstituted, α-mono- and α,α′-dialkylated) α-hydroxy- and α-(*N*-methyl)amino esters **46**. With use of sodium methoxide as base in dry ethanol as solvent, the corresponding sultones (1,2-oxathiolan-4-one 2,2-dioxides) or sultams (isothiazolidin-4-one 1,1-dioxides) **47** were obtained in moderate yields (from 30 to 60%) (Scheme 22). Determination of the pK_a values of the cyclic products showed that they exist mostly as their enol forms. Other authors have also demonstrated the reactivity of these substrates with aldehydes in aldol-like reactions to produce Knoevenagel-type products.[56] Finally, it is interesting to note that similar reactivity was reported by Stachel in analogous esters like *O*- and *N*-methyl phosphonates to give 1,2-oxaphospholan-4-ones and 1,2-azaphospholidin-4-ones, respectively.[55c]

CSIC reactions with γ-alkylsulfonyloxy α,β-unsaturated carboxylic esters **48** have also been reported.[57] After exploratory experiments, either LDA/CuCN or LDA/AgCN were found to be the best choices of base for the cyclization reactions to give sultones **49** in good yields (Scheme 23). In the reactions in which new stereocenters (β, γ, γ′) were formed, poor and variable stereoselectivities were observed in the isomer ratios.



Scheme 22. *CSIC* reactions with carboxylic esters as electrophiles



Scheme 23. *CSIC* reactions with γ-alkylsulfonyloxy α,β-unsaturated carboxylic esters

3.3. Aromatic Rings Substituted with Nitro Groups as Electrophilic Species

Wróbel has described *CSIC* reactions with *N*-alkyl-*N*-(3-nitroaryl)prop-3-enesulfonamides **50**[58a,58b] (Scheme 24). With DBU as base, in the presence of magnesium chloride, tricyclic 1-alkyl-8-X-1*H*-2,2-dioxoisothiazolo[5,4,3-*d*,*e*]-quinolines **51** were obtained in yields ranging from 6% (in acetonitrile) to 64% (in DMSO), with traces of quinoline *N*-oxides **52**. Similar reactivity has also been described for *N*-alkyl-*N*-(3-nitroaryl)phenylmethanesulfonamides.[58c] The mechanism for the formation of these products is still under investigation, but the first step is the deprotonation by DBU at the position α to the SO_2 group, followed by the intramolecular addition of the resulting carbanion to the nitroaromatic part of the molecule.

3.4. Iminium Salts as Electrophilic Species

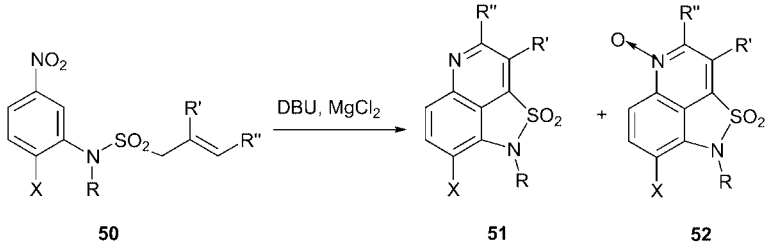
Deniaud and co-workers have very recently reported[59] the first *CSIC* reaction with iminium salts obtained in situ in the reaction between amidines **53** and methane- (or ethane)sulfonyl chlorides, in dichloromethane as solvent and with triethylamine as base. Under these conditions, mixtures of the intermediate **54** and compound **55** were obtained, but it was observed that this mixture, after further treatment with methyl iodide in triethylamine, gave 6,7-dihydrothiazolo[3,2-*b*]-1,2,4-thiadiazine 1,1-dioxides **55** in modest yields (30−40%) (Scheme 25).

3.5. Nitriles as Electrophilic Species

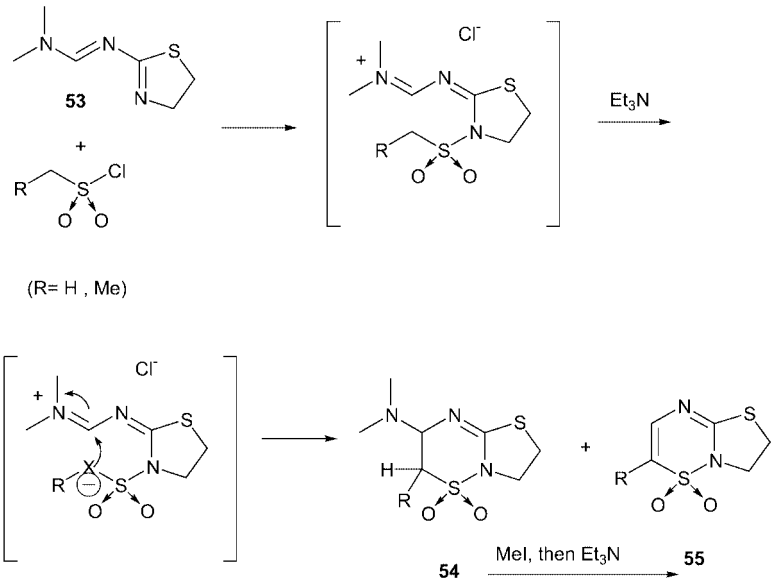
In the same year (1988) that Thompson[33b] reported the intermolecular *CSIC* reaction between alkanesulfonamides and nitriles, Gómez de las Heras reported[60] the intramolecular version of this reaction (Scheme 1, X = N). Subsequent studies from other laboratories, particularly those reported from Marco's and Postel's groups (see below) have greatly contributed to expansion and exploitation of the interest of this synthetic methodology.

3.5.1. Nitriles as Electrophilic Species from Alkanesulfonates

A *CSIC* reaction was observed when DBU was treated with cyanomesylate **56** (Scheme 26) to afford the unexpected product **57** in 89% yield and as the only isolated product.[60a] In this case the intermediate, under mild hydrolysis conditions, gave the imino group, which tautomerized to the more stable enamine function, leaving the *endo*-alkene conjugated with the *S*,*S*-dioxide moiety. Other bases and

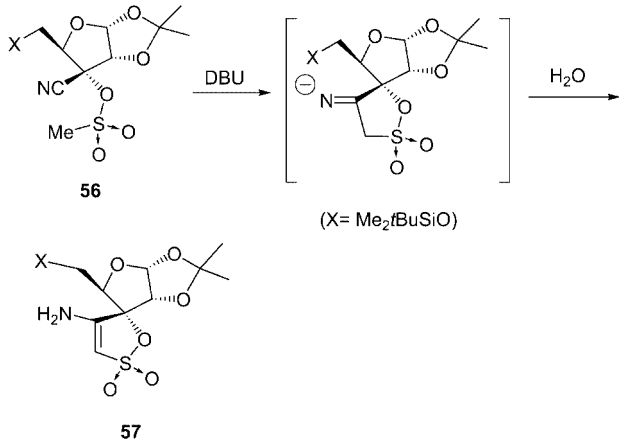


Scheme 24. *CSIC* reactions with *N*-(nitroaryl)prop-3-enesulfonamides



Scheme 25. *CSIC* reactions with iminium salts

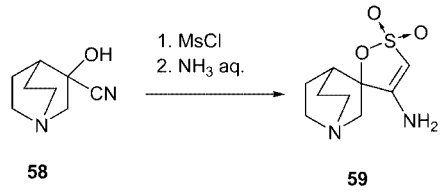
solvents, such as NaOH in acetonitrile or NaH in dimethoxyethane, proved equally efficient in the *CSIC* reaction. In a full paper three years later, the scope of the reaction was analyzed by that preparation of other cyanomesylates in sugar (furanose or pyranose)[60b] and nucleoside templates.[61] Only occasionally has a non-carbohydrate substrate (adamantanone) been used as ketone-containing starting material for the *CSIC* reaction.[62] In summary, a number of enantiomerically pure 4-amino-1,2-oxathiole *S*,*S*-dioxides were prepared in good yields, from complex and highly functionalized precursors by use of this methodology.



Scheme 26. *CSIC* reactions with cyanomesylates in sugar templates

In 1994, Luthman described a *CSIC* reaction with the cyanomesylated quinuclidine **58**, by use of aqueous ammonia as promoting base. The spiro derivative **59** was isolated in 82% yield (Scheme 27).[63]

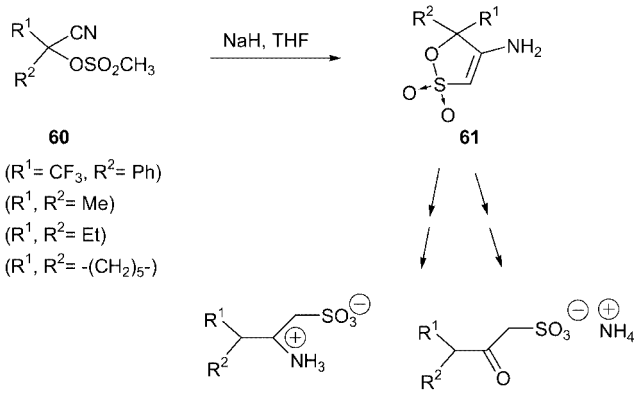
In 1997, Simig[64] and Marco[65a,65b] independently described *CSIC* reactions with simple, readily available alkanesulfonates and nitriles as electrophiles. This obvious and useful chemistry had been neglected in previous studies and by other researchers in the field. These studies contributed to the generalization and expansion of interest in these types of synthetic transformations, showing that *CSIC* reactions with nitriles could be more widely applied to a variety of simple ketones to give a diverse and large array of differently substituted 1,2-oxathiole *S*,*S*-dioxides.



Scheme 27. *CSIC* reactions with cyanomesylates in a quinuclidine substrate

Simig[64] prepared a series of cyanomesylates **60** and subjected them to *CSIC* conditions, with sodium hydride in THF, to give 4-amino-5*H*-1,2-oxathiole *S*,*S*-dioxides **61** in good yields (Scheme 28). These intermediates were transformed into β-amino and β-oxo sulfonic acids.

Similarly, Marco[65a,65b] prepared a series of cyanoalkanesulfonates (R = H, Me, Ph) **62** and used them in *CSIC* reactions involving sodium hydride in THF or DBU in acetonitrile, to give differently substituted 4-amino-5*H*-1,2-oxathiole *S*,*S*-dioxides **63** (Scheme 29). These intermediates were also subjected to acid hydrolysis, transamination, and *N*-acylation reactions. In a subsequent publication, the *CSIC* reaction was studied in more detail by identification of the substrates in cases in which the reaction was unsuccessful, and by showing its application to cyanoalkanesulfonate moieties of *N*-benzyl(or ethoxycarbonyl)piperidones.[65c] An important, and completely unprecedented

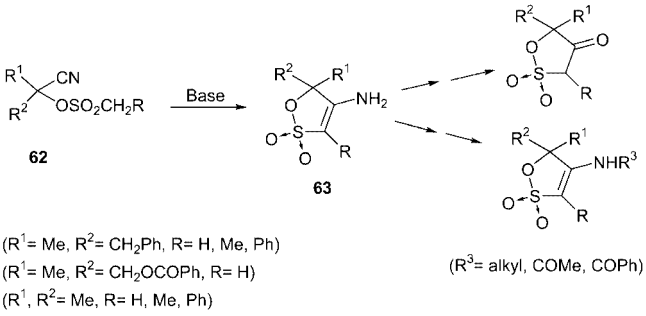


Scheme 28. *CSIC* reactions with cyanomesylates

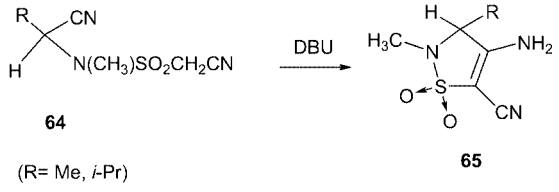
feature, yet to be disclosed, was the potential *CSIC* reaction with conveniently functionalized cyanoalkanesulfonates derived from aldehydes. It was found that suitable derivatives of benzaldehydes failed to afford the expected products, but in contrast, the *CSIC* reaction was successful in the case of cyanoalkanesulfonates obtained from alkyl aldehydes.[65d,65e]

3.5.2. Nitriles as Electrophilic Species from Alkanesulfonamides

In the previously summarized results from Marco's laboratory, similar successful results with alkanesulfonamides were also reported, giving 4-amino-2,3-dihydroisothiazole 1,1-dioxide heterocyclic ring systems.[65a−65c] However, it is interesting to note that cyanoalkanesulfonamides derived from alkyl aldehydes very surprisingly did not afford the expected adducts. This reactivity could be modulated by the incorporation of an additional activating group, such as a nitrile, to enhance the acidity of the α-protons relative to



Scheme 29. *CSIC* reactions with cyanomesylates

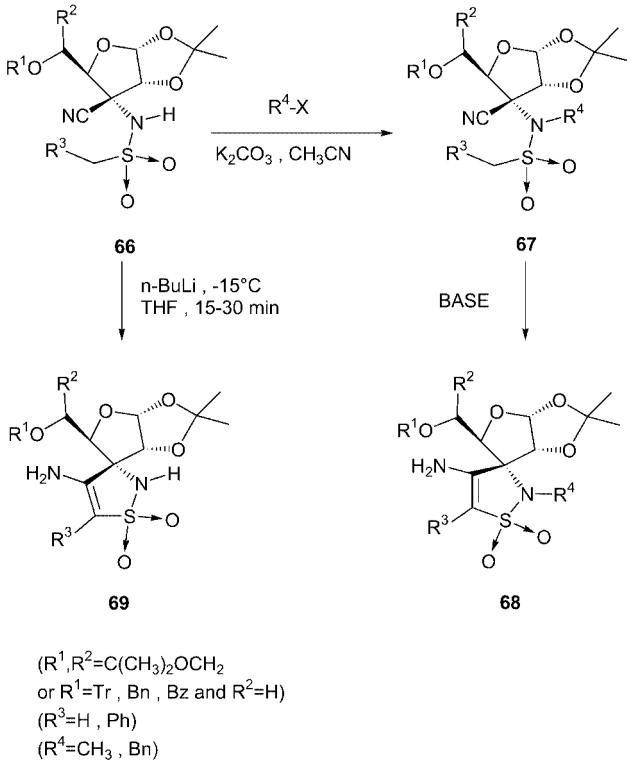


Scheme 30. *CSIC* reactions with cyanomesylates derived from aldehydes

the sulfonyl group. In fact, the newly designed precursors **64** afforded the *CSIC* products **65** very cleanly and in moderate yields (Scheme 30).[65d,65e]

In 2001, Postel's group reported the synthesis and treatment of novel cyanomethanesulfonamides of monosaccharidic and nucleosidic substrates under *CSIC* conditions (Cs_2CO_3 or NaH).[66a] The results demonstrated that these conditions yielded the dihydroisothiazole 1,1-dioxide compounds **68** on a large scale (25−90%) starting exclusively from the *N*-methylated substrates **67**. With a view to increasing the solubility of the salt resulting from the removal of the acidic *N*-hydrogen atom of the unsubstituted alkanesulfonamides **66**, the *CSIC* reaction was performed with lithium bases (*n*BuLi or LDA). The compounds **69** were obtained in good yields in a range of 60−98%.

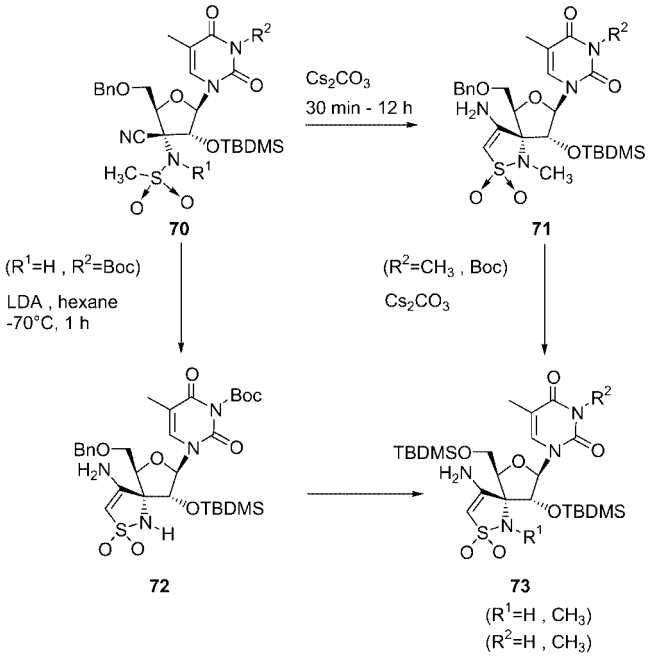
Recently, Marco's and Postel's groups have collaborated efficiently to study the scope and limitations of the *CSIC* reaction in carbohydrate systems. They demonstrated that monosaccharide substrates with various substituents both on the sulfonamide and on the glycone moieties could easily be converted into the corresponding 5′-substituted dihydroisothiazole (Scheme 31). In some cases, the *N*-alkylation conditions were sufficient to induce the removal of the acidic hydrogen atom and subsequent intramolecular cyclization to give the target compound **68** in a one-step procedure.[66b]



Scheme 31. *CSIC* reactions with carbohydrate precursors

Over the last decade, extensive structure-activity relationship studies on TSAO derivatives possessing the 4-amino-5*H*-1,2-oxathiole *S*,*S*-dioxide moiety have been conducted, but surprisingly, no examples of analogues with a 1,2-isothi-

azole ring were reported. Starting from synthetic nucleosides, Postel demonstrated that the *CSIC* reaction could be performed effectively from both free and substituted alkane sulfonamide groups **70** (Scheme 32). However, such reactions were successful only when the nitrogen atom of the base moiety was alkylated or protected with a Boc group, producing the corresponding isothiazole derivatives **71** and **72**. This strategy provided a convenient route to a new range of aza analogues of TSAO nucleosides **73** in moderate yields (35−55%).[66c]



Scheme 32. *CSIC* reactions with nucleoside precursors

4. Conclusions

To summarize, we should like to emphasize the synthetic importance of the α-alkylation of alkanesulfonates or alkanesulfonamides in inter- or intramolecular reactions (chemistry that we have named and propose to the scientific community as the *CSIC* reaction), which has been relatively unexplored. Recent reports have shown the intrinsic value of the *CSIC* reaction and the large scope of opportunities that exist for further exploration and improvement, particularly in the field of carbohydrate chemistry.

Acknowledgments

The authors thank all their co-workers (whose names are in the references) for their collaboration and enthusiasm during these years, and Prof. Graham McKenzie for improving and carefully reading the manuscript. One of us (J. L. M.) would like to thank the CSIC for continuous support and facilities in order to develop and to carry out this and other synthetic ventures. D. P. would like to thank the Conseil Régional de Picardie, the Fonds Social Européen, and the Ministère Français de la Recherche for financial support.

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Received March 12, 2003
Early View Article
Published Online August 14, 2003

