New reactions of γ-halocarbanions: underestimated reactive intermediates in organic synthesis*

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Short-lived γ-halocarbanions can be trapped by active electrophiles such as aldehydes, imines, and Michael acceptors to give anionic adducts, which undergo intramolecular substitution to give substituted tetrahydrofurans, pyrrolidines, and cyclopentanes. This has underlain a new method for the synthesis of these valuable ring systems. We have determined the acidity of the γ-halocarbanion precursors and have shown that the halogen atoms in the γ-position relative to the carbanion center exert a significant stabilizing effect on the carbanion.

Key words: carbanions, tetrahydrofurans, pyrrolidines, cyclopentanes, cyclizations, pK_a values of carbanion precursors.

Introduction

Carbanions containing halogen substituents are important intermediates in organic synthesis. Due to the presence, in one molecule, of a strongly nucleophilic carbanion center and an electrophilic center connected to a leaving group, such carbanions are able to enter into a variety of reactions. Particularly, α-halocarbanions are widely used as reactive intermediates in numerous processes. The addition of α-halocarbanions to electron-deficient double bonds creates systems with an 1,3-arrangement of the nucleophilic and electrophilic active centers, which usually undergo intramolecular substitution to produce three-membered rings (Scheme 1). Thus, the halohydrin anions formed in the reaction of α-halocarbanions with aldehydes and ketones cyclize to give oxiranes (the Darzens reaction[1]). A similar reaction of α-halocarbanions with Michael acceptors gives substituted cyclopropanes *via* initial adducts, γ-halocarbanions, which undergo intramolecular substitution.[2] The addition of α-halocarbanions to electron-deficient arenes, mainly nitroarenes, gives σ^H-adducts that undergo base-induced β-elimination, the process known as vicarious nucleophilic substitution of hydrogen (see Scheme 1).[3]

Some α-halocarbanions are able to undergo unimolecular dissociation at the carbon—halogen bond, resulting in the departure of the halogen anion to give carbenes.[4] This reaction, often termed α-elimination, usually does not proceed with α-halocarbanions stabilized by electron-withdrawing groups.

The only known transformation of β-halocarbanions is rapid elimination of the halide anion to give alkenes. Therefore, β-halocarbanions generated by deprotonation of β-halo-nitriles, -ketones, -sulfones, *etc.*, are short-lived intermediates in the β-elimination reaction proceeding according to Elcb mechanism.[5] These carbanions can also be generated *via* the addition of anionic nucleophiles to β-halovinyl-nitriles, -ketones, *etc*., being the intermediates in the vinylic nucleophilic substitution proceeding *via* the addition—elimination route[6] (Scheme 2).

γ-Halocarbanions can be generated by three major routes:

(1) deprotonation of appropriate precursors, namely, γ-halonitriles, sulfones, esters, *etc*. by the action of a base;

(2) alkylation of the carbanions formed by methylenic CH acids with 1,2-dihaloalkanes, the initial alkylation products, 2-haloethyl derivatives being rapidly deprotonated to the corresponding γ-halocarbanions; and

(3) the addition of α-halocarbanions to Michael acceptors.

Irrespective of the way of generation, γ-halocarbanions once formed enter into rapid intramolecular substitution leading to three-membered rings, mainly cyclopropanes; this process is often referred to as γ-elimination.[7]

γ-Halocarbanions generated *via* deprotonation of α-halodialkyl ketones cyclize to cyclopropanones, which undergo ring opening in the presence of nucleophiles; this process is known as the Favorsky rearrangement

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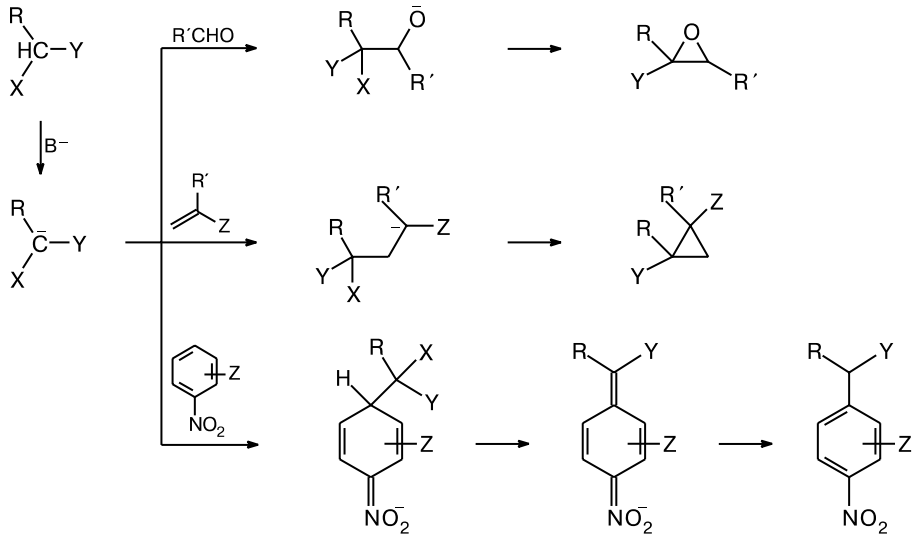
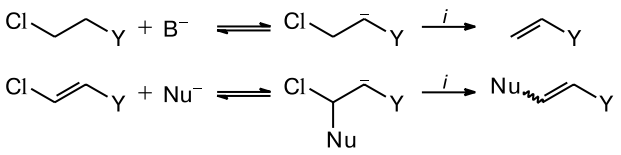
Scheme 1



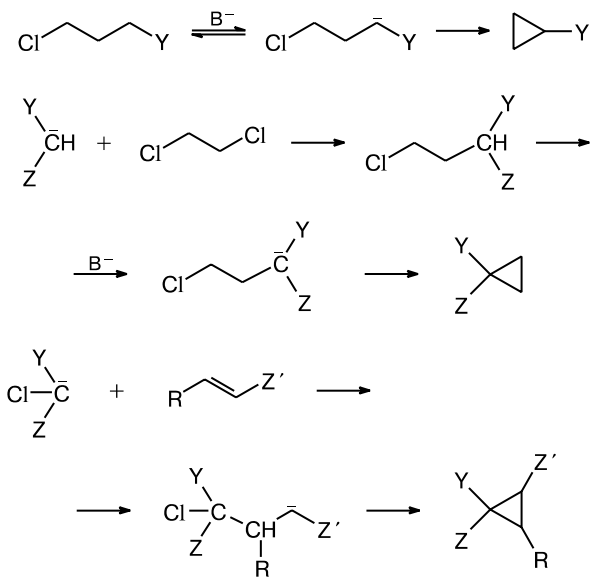
B^- is a base

Scheme 2



i. fast.

Scheme 3



B^- is a base

(Scheme 4, reaction (1)).[7] Similarly, treatment of α-halodialkyl sulfones with a base results in the formation of three-membered dioxathiiranes upon intramolecular replacement of γ-halocarbanions. The dioxathiiranes lose SO_2 to give alkenes; the overall process is known as the Ramberg—Bäcklund reaction[8] (Scheme 4, reaction (2)).

Intermolecular reactions of γ-halocarbanions

By analogy with the reactions of α-halocarbanions, the addition of γ-halocarbanions to electron-deficient C=O, C=N, and C=C double bonds is expected to produce systems with 1,5-arrangement of the active nucleophilic and electrophilic centers, which would cyclize to give five-membered rings (Scheme 5).

These processes, namely, the reactions of γ-halocarbanions with aldehydes, imines, and Michael acceptors, should produce tetrahydrofurans, pyrrolidines, and cyclopentanes, thus being of high value for organic synthesis (Scheme 6).

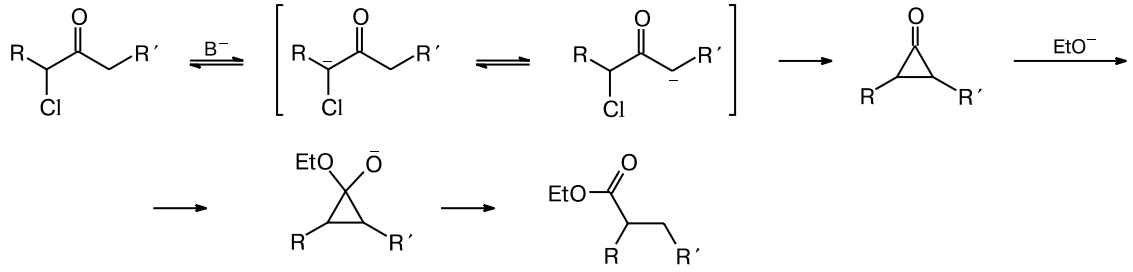
The major problem in the realization of these attractive opportunities is the high rate of intramolecular substitution of γ-halocarbanions (γ-elimination); as a consequence, the intermolecular addition to external electrophilic partners is disfavoured and usually does not occur.

Due to the high rate of γ-elimination, only very few studies on intermolecular reactions of γ-halocarbanions have been reported, the known reactions being limited to the γ-halocarbanions whose specific structural features decelerate the γ-elimination.

The only reported example of intermolecular transformation of γ-halocarbanions susceptible to fast γ-elimi-

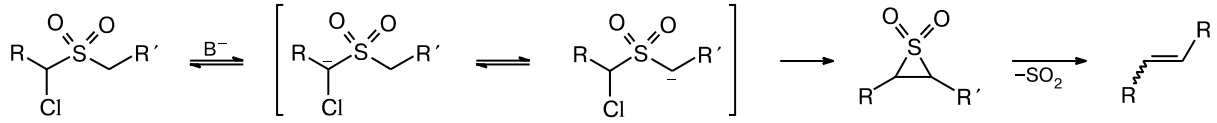
Scheme 4

Favorsky rearrangement



(1)

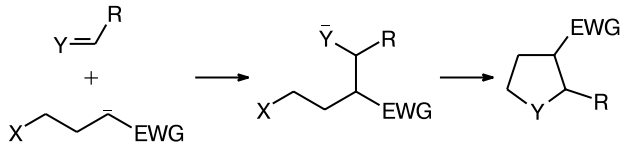
Ramberg—Bäcklund reaction



(2)

B^- is a base

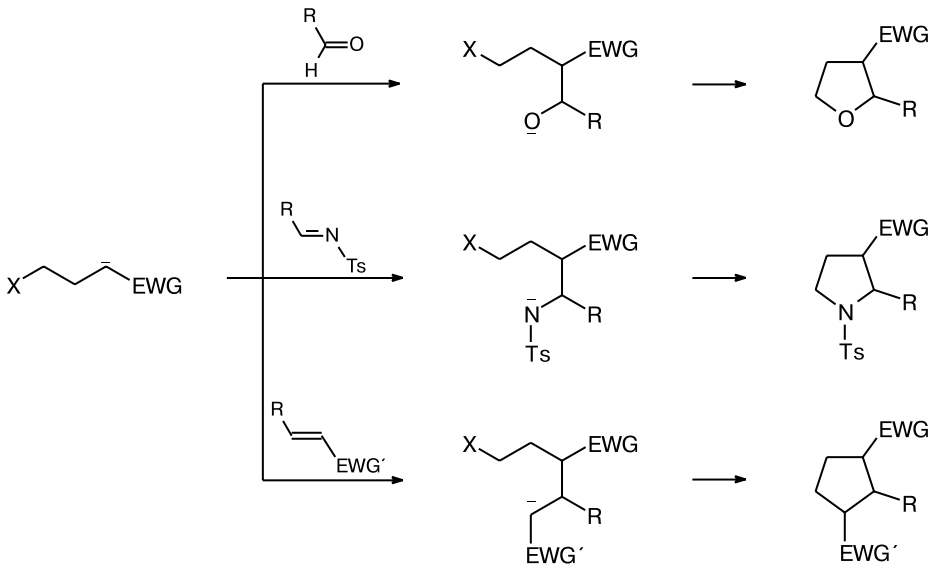
Scheme 5



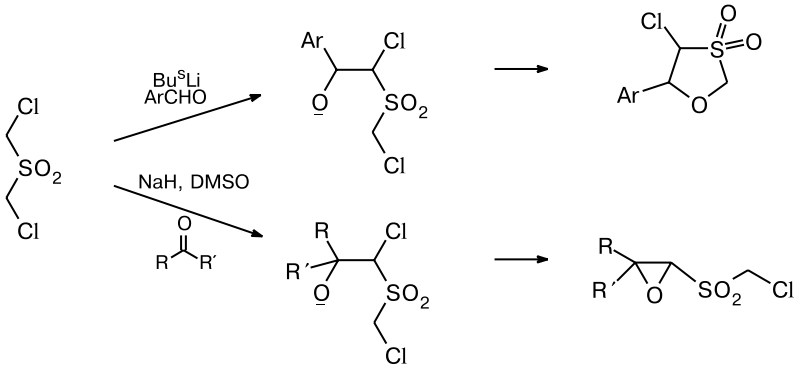
EWG = $ArSO_2$, CN, COOR, ...
Y = O, NTs, C-EWG´
X = Cl, Br, ...

nation is the base-promoted reaction of bis(chloromethyl) sulfone with aldehydes and ketones.[9] Depending on the carbonyl component and the conditions, the initially formed aldol type adducts are converted into three- or five-membered rings *via* 1,3- or 1,5-nucleophilic substitution. Apparently, intramolecular substitution (γ-elimination) in the α,γ-dichlorocarbanion derived from bis(chloromethyl) sulfone is decelerated by the SO_2 group vicinal to the leaving group[9] (Scheme 7).

Scheme 6

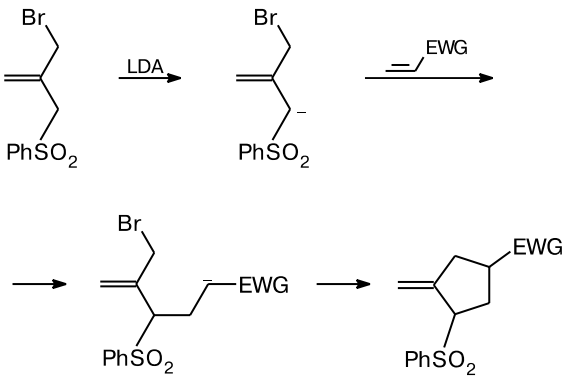


Scheme 7



Examples of intermolecular reactions of γ-halocarbanions unable to undergo γ-elimination due to structural features are reported for 3-bromo-2-methylenepropyl phenyl sulfone. Obviously the rigid methylene moiety with the sp^2 carbon atom keeps the carbanion apart from the electrophilic centers, thus preventing cyclization. In this situation, the carbanion derived from this γ-bromosulfone was successfully trapped by Michael acceptors. The subsequent intramolecular substitution in the resulting adduct anions gave methylenecyclopentane derivatives[10] (Scheme 8).

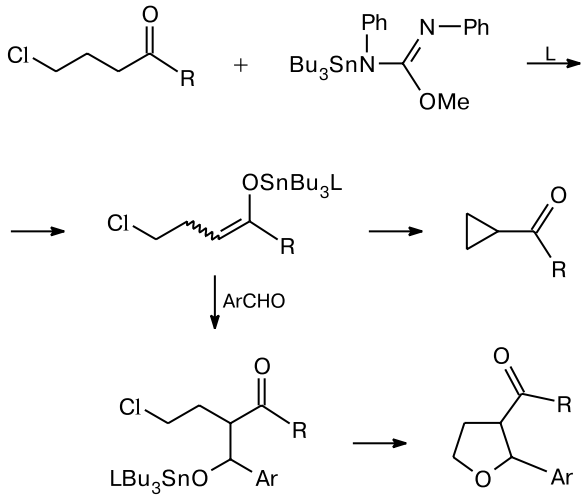
Scheme 8



The possibility of an intermolecular reaction also exists for those γ-halocarbanions that are weak nucleophiles inactive in S_N2-type substitution. Thus the reaction of tin enolate of γ-chlorobutyrophenone with aldehydes results in the formation of substituted tetrahydrofurans, whereas lithium enolate undergoes γ-elimination to give benzoylcyclopropane[11] (Scheme 9).

The nitronate anions generated from γ-halonitropropanes belong to this category. Due to the low nucleophilicity of the nitronate anions, only γ-iodonitropropane slowly cyclizes to nitrocyclopropane when treated with a base.[12] Recently, it was reported that the γ-mesyloxy-

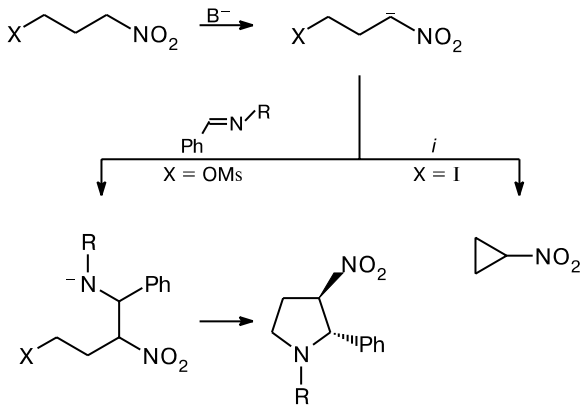
Scheme 9



L = HMPA

nitropropane anion reacts with imines to give substituted nitropyrrolidines[13] (Scheme 10).

Scheme 10



i. slow.

B^- is a base

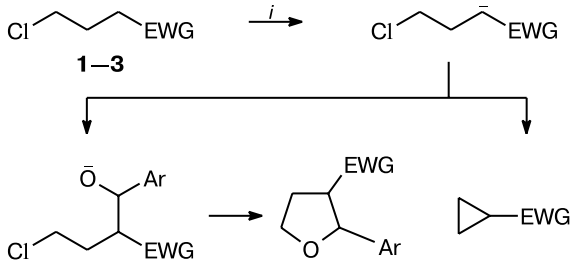
Novel reactions of γ-halocarbanions

Our interest in reactions of γ-halocarbanions came from the observation of facile cyclization of γ-chlorobutyronitrile under conditions of phase transfer catalysis (50% aqueous NaOH and tetraalkylammonium (TAA) catalyst,[14] whereas intermolecular alkylation of butyronitrile with benzyl bromide does not proceed under these conditions. These results can be rationalized in two ways: either the Cl atom in the γ-position of butyronitrile exerts a stabilizing effect on the α-cyanocarbanion and, hence, γ-chlorobutyronitrile can be deprotonated by the aqueous NaOH, or the cyclization (γ-elimination) does not require the formation of kinetically free carbanions. In order to clarify this point, we have carried out the reaction of γ-chlorobutyronitrile under the PTC conditions in the presence of benzaldehyde. Apart from cyanocyclopropane, this reaction gave 3-cyano-2-phenyltetrahydrofuran. We have, therefore, concluded that the halogen atom in the γ-position increases the CH-acidity of γ-chlorobutyronitrile and that the intermediate γ-chlorocarbanion is trapped in the fast intermolecular reaction with benzaldehyde.[15]

Reactions of γ-halocarbanions with aldehydes and ketones

Further studies based on the unprecedented finding that short-lived γ-halocarbanions can enter into intermolecular reactions resulted in the development of a general protocol for the synthesis of substituted tetrahydrofurans *via* the reaction of 4-chlorobutyronitrile (**1**), 3-chloropropylphenylsulfone (**2**), and *tert*-butyl 4-chlorobutyrate (**3**) with aldehydes.[16] The reactions were carried out using Bu^tOK to generate carbanions in the presence of aldehydes in 0.5 *M* THF solutions at −30 °C. Relatively concentrated solutions were used in order to promote the intermolecular reactions (Scheme 11).

Scheme 11



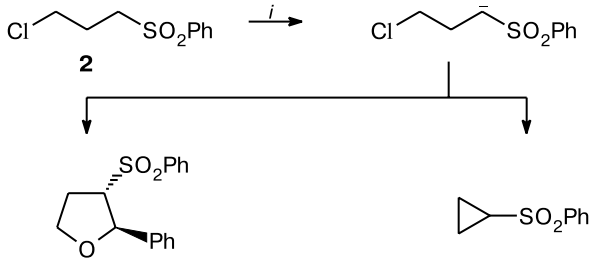
i. ArCHO, Bu^tOK, −30 °C, THF.

Compound	EWG	Ar	Yield (%)	
			I[a]	II[b]
1[c]	CN	Ph	11	78
1[c]	CN	*p*-MeC_6H_4	14	82
1[c]	CN	PhCH=CH	15	76
2[d]	SO_2Ph	Ph	0	95
2[d]	SO_2Ph	*p*-MeC_6H_4	8	88
2[d]	SO_2Ph	*p*-ClC_6H_4	15	83
3[d]	$COOBu^t$	Ph	15	64
3[d]	$COOBu^t$	*p*-MeC_6H_4	32	61

[a] Substituted cyclopropane. [b] Substituted tetrahydrofuran. [c] *trans*/*cis* = 4 : 1. [d] Only the *trans*-isomer.

The effect of the concentration on the competition between the intra- and intermolecular reactions is shown in Scheme 12.

Scheme 12



i. PhCHO, Bu^tOK, −30 °C, THF.

C/mol L^{-1}	Yield (%)	
	I[a]	II[b]
0.5	0	95
0.1	17	79
0.05	22	74

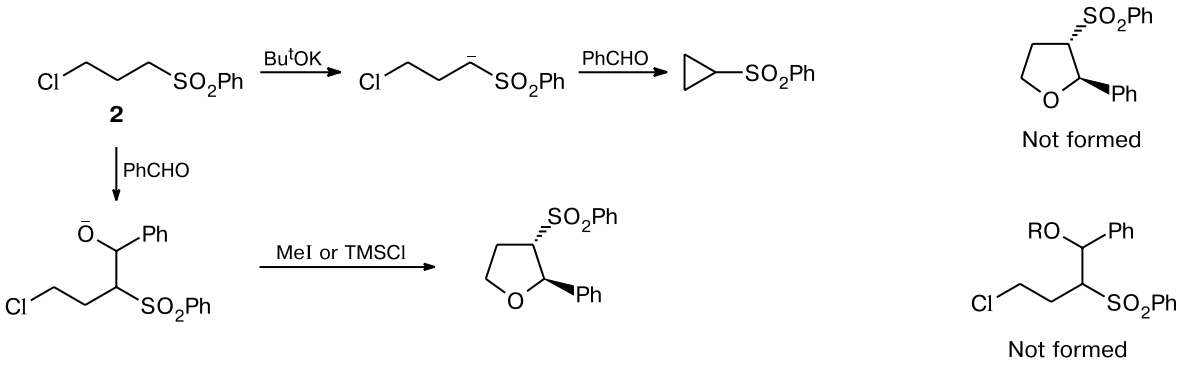
[a] Substituted cyclopropane. [b] Substituted tetrahydrofuran.

Under these conditions, the formation of tetrahydrofurans was the major process, although some amounts of substituted cyclopropanes resulting from competing intramolecular substitution were always formed. Since the reactions of the carbanions of **1** and **2** with aldehydes gave good results, compound **2** was used in further studies as the standard γ-halocarbanion precursor.

2,3-Disubstituted tetrahydrofurans can be formed as *cis*- and *trans*-isomers. The reaction of 4-chlorobutyronitrile (**1**) with aldehydes gives mixtures of *trans*- and *cis*-isomers in ~4 : 1 ratio; it was shown that the stereoisomer ratio is under thermodynamic control. Only the *trans*-isomers of tetrahydrofurans containing more bulky phenylsulfonyl and *tert*-butoxycarbonyl substituents are formed in the reactions of aldehydes with the corresponding sulfone **2** and ester **3**. Estimation of the rates of intramolecular substitution in γ-halocarbanions, their addition to the carbonyl group, and intramolecular substitution within the aldol type adducts to produce tetrahydrofurans are shown in Scheme 13.

The addition of Bu^tOK to a solution of nitrile **1** or sulfone **2** in THF at −70 °C followed immediately

Scheme 13



Conditions: –70 °C, THF.

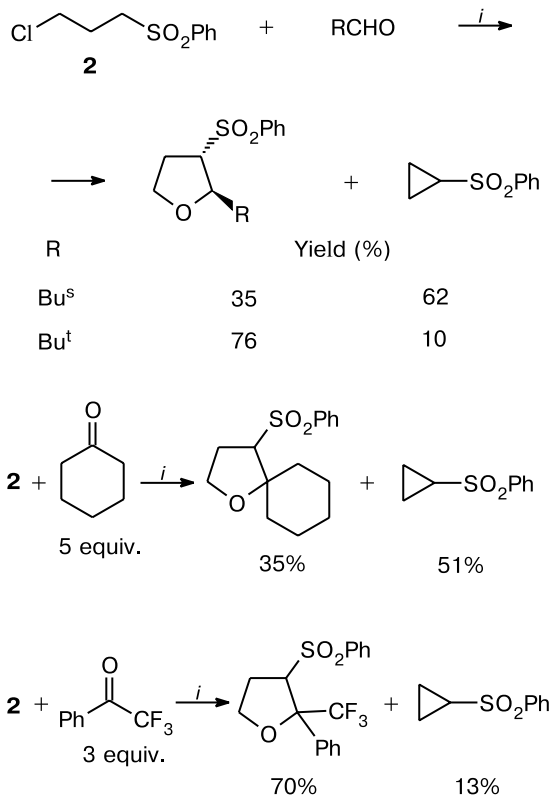
(after 1—2 s) by the addition of benzaldehyde gave only cyclopropanes. The addition of Bu^{t}OK to a THF solution of nitrile **1** or sulfone **2** and benzaldehyde followed by the addition of MeI or Me_3SiCl gave only tetrahydrofurans. Thus, the rates of the reactions under consideration are very high and the carbanions should be generated in the presence of aldehydes.

The extension of this reaction to aliphatic aldehydes is limited because they are relatively strong CH-acids and are deprotonated under the reaction conditions. Therefore, the reaction proceeded satisfactorily only with pivalaldehyde to give *tert*-butyltetrahydrofuran in a good yield.

Due to the lower electrophilicity of the carbonyl group in ketones and some steric hindrance, the reactions of **1** and **2** with ketones are less efficient, although they still can be carried out (Scheme 14).

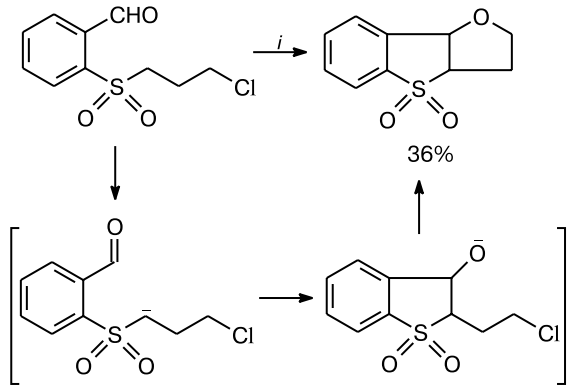
The intramolecular variant of this reaction was performed for the substrate whose molecule contained simultaneously a γ-halocarbanion fragment and an aldehyde carbonyl group* (Scheme 15).

Scheme 14



i. Bu^{t}OK, –30 °C, THF.

Scheme 15



i. Bu^{t}OK, –30 °C, DMF.

The attempts to extend the reactions of carbanions generated from compounds **1** and **2** to other electrophilic partners such as imines and Michael acceptors in the expectation to develop a synthesis of pyrrolidines and cyclopentanes gave initially negative results. The carbanion precursors were mostly converted into cyclopropanes,

* Unpublished results obtained by our research group.

whereas electrophiles decomposed or polymerized under the reaction conditions. It appears that intramolecular replacement of the halogen in the highly nucleophilic carbanions derived from **1** and **2** proceeds faster than the intermolecular addition to these moderately active electrophilic partners.

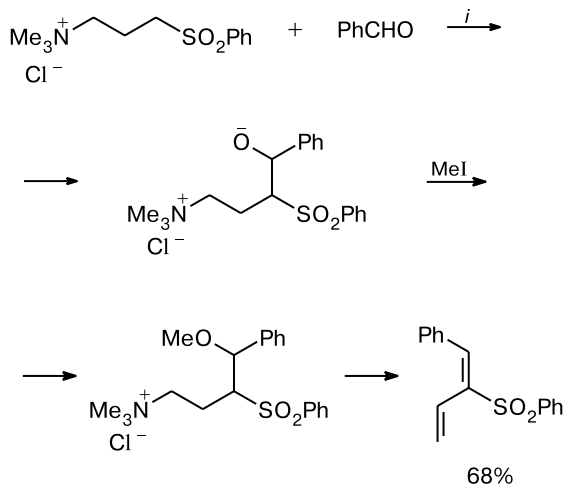
The outcome of the reactions of γ-halocarbanions with electrophilic partners, *viz.*, aldehydes, ketones, imines, electron-deficient alkenes, *etc.*, depends on the relationship between the rates of intramolecular substitution (γ-elimination), the addition to an external electrophilic partner, and the rate of intramolecular 1,5-substitution in the anionic adducts formed. Since the addition is reversible, the final outcome can also be affected by the equilibrium position in the addition reaction.

The effect of the leaving group on the reactions of γ-halocarbanions

The relationship between the rates of intramolecular substitution and intermolecular addition to an external electrophile depends on the type of the leaving group, the nature of the carbanion-stabilizing group, which dictates the precursor deprotonation rate and carbanion nucleophilicity, the substituents in hydrocarbon chain, *etc*. It can be expected that intramolecular substitution would be much faster in γ-bromocarbanions than in γ-chlorocarbanions; nevertheless, the former can be trapped by benzaldehyde taken in an excess to form the corresponding tetrahydrofurans.[16] The nucleophilic replacement of the tetraalkylamonium group usually proceeds more slowly than the replacement of chlorine.[17] Therefore, we have tested reactions of the carbanions derived from 3-cyanopropyl(trimethyl)- and 3-phenylsulfonylpropyl(trimethyl)ammonium chlorides. Treatment of these compounds with a strong base does not induce noticeable intramolecular substitution to form the corresponding cyclopropanes; apparently, the uncontrolled Hoffmann type degradation takes place. Nevertheless, the expected carbanions can be generated and trapped by benzaldehyde, although aldol type anions do not replace trimethylammonium group and give only traces of tetrahydrofurans. Meanwhile, aldol anions can enter into the intermolecular reaction with MeI (or $MeSO_2Cl$) followed by elimination of MeOH (or $MeSO_2OH$) and Me_3N yielding substituted butadienes. This could serve as a useful route to substituted butadienes[18] (Scheme 16).

The ring opening in epoxides on treatment with nucleophiles, which can be considered as an S_N2 type reaction, usually proceeds more slowly than the replacement of chlorine.[19] Thus, the 3,4-epoxybutyl phenyl sulfone carbanion should be a good, slow reacting analog of the γ-halocarbanion. Indeed, treatment of this sulfone with a strong base results in intramolecular ring opening to produce hydroxymethylcyclopropane provided that the

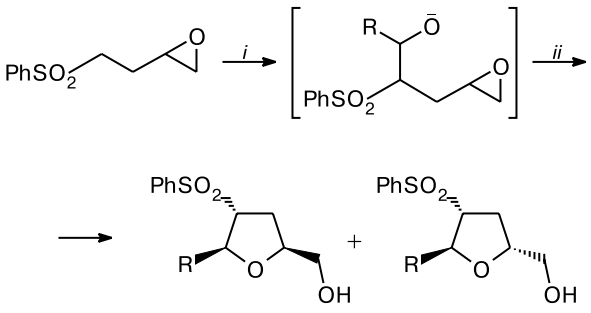
Scheme 16



i. Bu^{t}OK, –30 °C, DMF, <2 min.

oxirane ring is activated by a Lewis acid, *e.g.*, by Li^+ cations.[20] This is not a fast reaction, as the intermediate carbanions are relatively long-lived species and can add to aldehydes giving aldol type adducts, which can be isolated upon protonation or converted *in situ* into hydroxymethyltetrahydrofurans. This process also requires activation of the oxirane ring with Lewis acids. Since this reaction gives rise to three chiral centers, the tetrahydrofurans are formed as mixtures of four diastereomers. We have elaborated conditions that ensure a high overall yield and reasonably high diastereoselectivity of the synthesis of 5-hydroxymethyltetrahydrofurans by the reaction of 3,4-epoxy-1-phenylsulfonylbutane with aldehydes* (Scheme 17)

Scheme 17

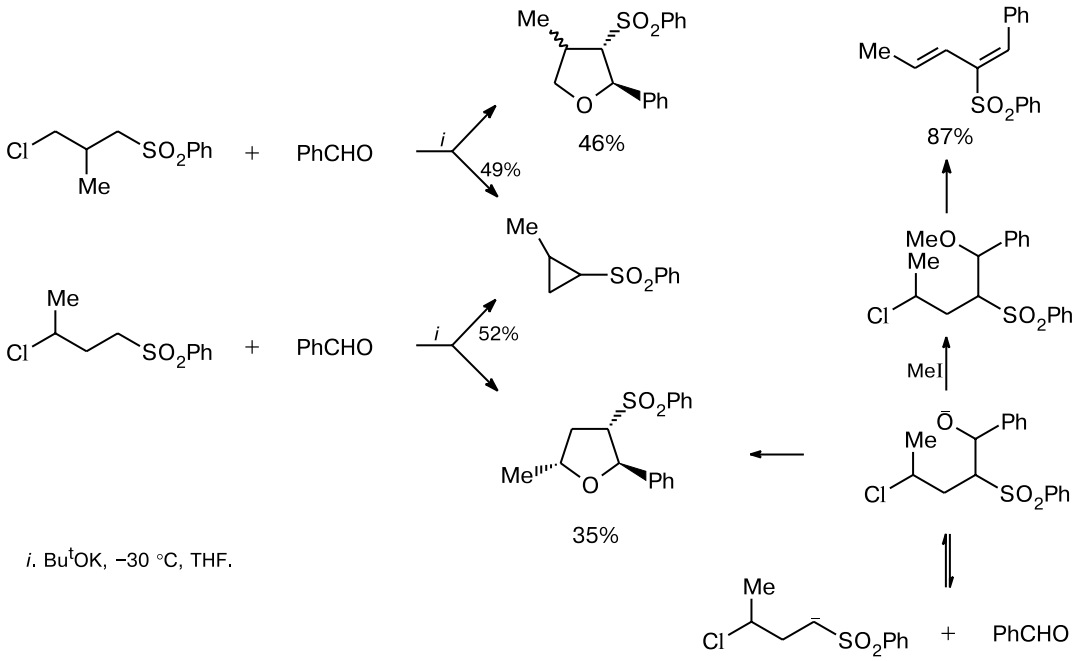


R	Yield (%)	Diastereoselectivity (%)	
Ph	87	77	23
p-MeC_6H_4	90	87	13
2-thienyl	61	81	19
Bu^t	74	53	47

i. RCHO, Bu^{t}OK, Bu^{t}OLi, –78 °C, THF; *ii*. –15 °C, 10 h.

* Unpublished results obtained by our research group.

Scheme 18



Although the initial formation of aldol type adducts is not diastereoselective, fast equilibration caused by reversibility of the addition followed by slower cyclization results in the preferential formation of one diastereomer.

The effect of substituents in the carbon chain

Substituents in the C(1)—C(3) carbon chain of the γ-halocarbanions should exert a substantial influence on their reactivity. An excellent example of this influence is the carbanion derived from 2-methylene-3-bromopropyl phenyl sulfone, which is unable to cyclize to methylenecyclopropane.[10] The phenyl group in 4-chloro-2-phenylbutyronitrile provides additional stabilization of the corresponding carbanion and decreases its nucleophilicity. This effect is expected to decelerate both competing processes, namely, intramolecular substitution and the intermolecular addition to aldehydes. The additional phenyl group in the α-position to the carbanion center causes steric hindrance, which should affect more appreciably the latter process and, hence, hamper the formation of tetrahydrofurans. Indeed, the reaction of 2-phenyl-4-chlorobutyronitrile with benzaldehyde under the standard conditions gave mostly cyclopropane. Some amounts of tetrahydrofurans are formed when benzaldehyde is used in a large excess.[16]

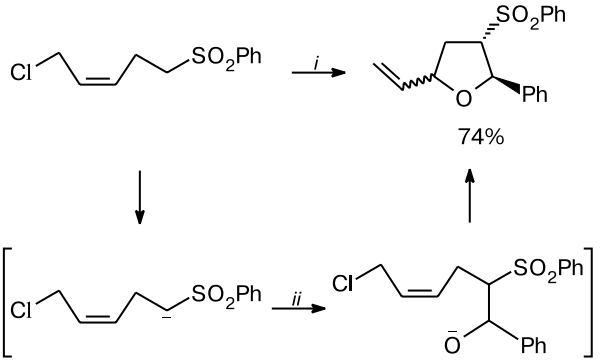
The carbanions generated from 2-methyl- and 3-methyl-3-chloropropyl phenyl sulfones readily cyclize to give the same methylcyclopropane. The cyclization rate of the latter sulfone is substantially lower, because it involves replacement of the halogen atom bound to the secondary carbon atom and, hence, intramolecular substitution is disfavored in competition with the intermolecular addition to benzaldehyde. Therefore, the addition proceeds quantitatively, and, since the intramolecular 1,5-substitution of the aldol type anion for *sec*-halogen is also a slow process, the corresponding alcohol can be isolated upon protonation.* In this situation, the final outcome depends on the interplay of the rates of the 1,3- and 1,5-intramolecular substitution and the position of the addition equilibrium. It was possible to trap the aldol anion with a reactive external electrophile, methyl iodide. The methylation followed by double elimination gave substituted butadiene (Scheme 18).

Allylic halides can react with nucleophiles according to S_N2 and S_N2' mechanisms. On the basis of the vinylogy principle, we can consider that the carbanions formed from 1-chloro-5-phenylsulfonylpent-2-ene and similar structures are analogs of γ-halocarbanions when participate in S_N2' reactions. Due to the stereoelectronic effect, the intramolecular S_N2' substitution in these carbanions is not fast; therefore, the intermolecular addition to aldehydes would compete successfully with intramolecular 1,3- and 1,5-substitution, the latter being feasible only in the case of *Z*-geometry of the double bond. The intramolecular 1,3- and 1,5-substitution in this type of carbanion, proceeding according to the S_N2' and S_N2 mechanisms, respectively, was observed when methylenic carbanions were alkylated with *Z*-1,4-dichloro-2-butene, producing

* Unpublished results obtained by our research group.

1,1-disubstituted 2-vinylcyclopropanes and 1,1-disubstituted cyclopentenes.[21] The aldol type anions resulting from the addition of such carbanions to aldehydes should further react according to the S_N2' 1,5-substitution pattern to give vinyltetrahydrofurans, which was actually observed* (Scheme 19)

Scheme 19



i. 1) PhCHO, Bu^{t}OK, –30 °C, THF, 2) ~20 °C; *ii*. PhCHO.

The effect of the type of the electron-withdrawing group

The relationship between the rates of intramolecular substitution in γ-halocarbanions and intermolecular addition to aldehydes is undoubtedly affected by the type of group stabilizing the carbanion, as the nucleophilicity of carbanions is the function of CH-acidity of the precursors and the charge distribution in the carbanion. In the case of our model compounds **1** and **2**, the high nucleophilicity of the corresponding carbanions limits the scope of intermolecular reactions only to highly reactive electrophiles such as aldehydes. Although structural modifications of the above-mentioned γ-halocarbanions influence the relationship between the rates of the competing intra- and intermolecular processes, the range of this changes is insufficient for our purpose. We have suggested that a moderate change in the acidity of the carbanion precursors should tune the nucleophilicity of γ-halocarbanions and thus enable intermolecular reactions with less active electrophiles. This tuning may take place upon introduction of electron-withdrawing substituents in the benzene ring of compound **2**.

Our first choice was 3-chloropropyl pentachlorophenyl sulfone **4**, which can be easily prepared by alkylation of the corresponding thiophenol with 1,3-bromochloropropane and oxidation of the resulting sulfide. First, we have shown that the lifetime of the carbanion generated from this sulfone is indeed much longer and depends substantially on the counter-cation, as shown in Scheme 20.[22] Thus, the carbanion of **4** can be generated in advance and subsequently introduced in the reactions with electrophiles.

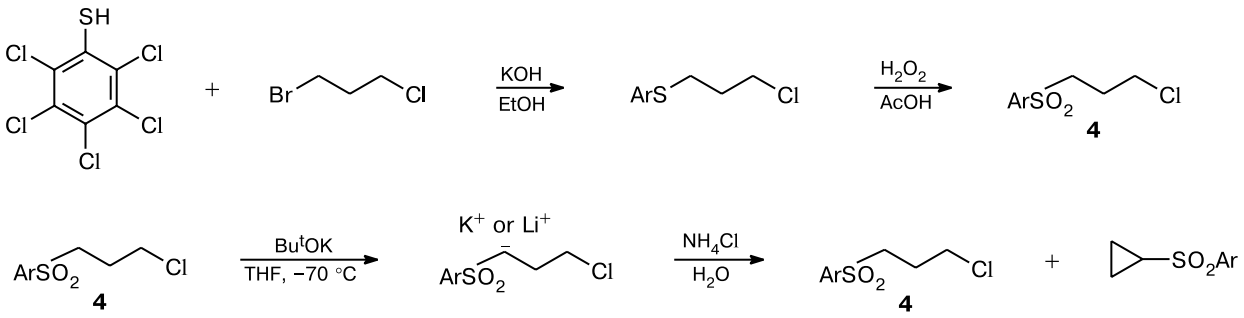
Reactions with imines

Treatment of **4** with LDA produces the lithium salt of the respective carbanion, which reacts, due to the relatively long lifetime, with *N*-benzylidene-*p*-toluenesulfonamide to give the expected substituted pyrrolidine in a good yield. Tosylimines of other aromatic aldehydes behave similarly; therefore, this reaction can be regarded as a general method for the synthesis of substituted pyrrolidines* (Scheme 21).

* Unpublished results obtained by our research group.

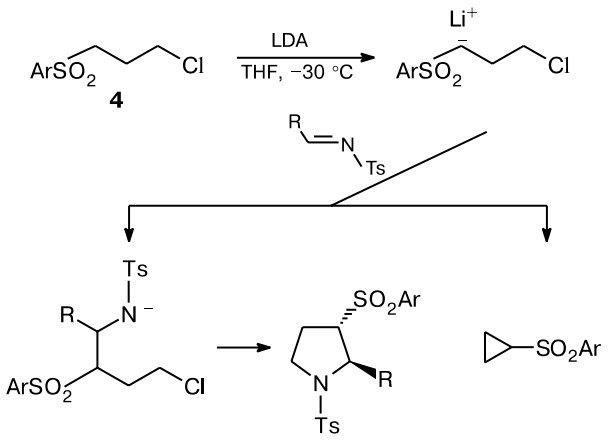
* Unpublished results obtained by our research group.

Scheme 20



Cation	Time before treatment /s	Yield (%)	
		4	SO$_2$Ar
Li^+	15	89	11
	25	78	22
K^+	15	38	62
	25	0	100

Scheme 21



R	Yield (%)	
	I[a]	II[b]
Ph	75	5
p-Tol	73	9
Ph	60	16

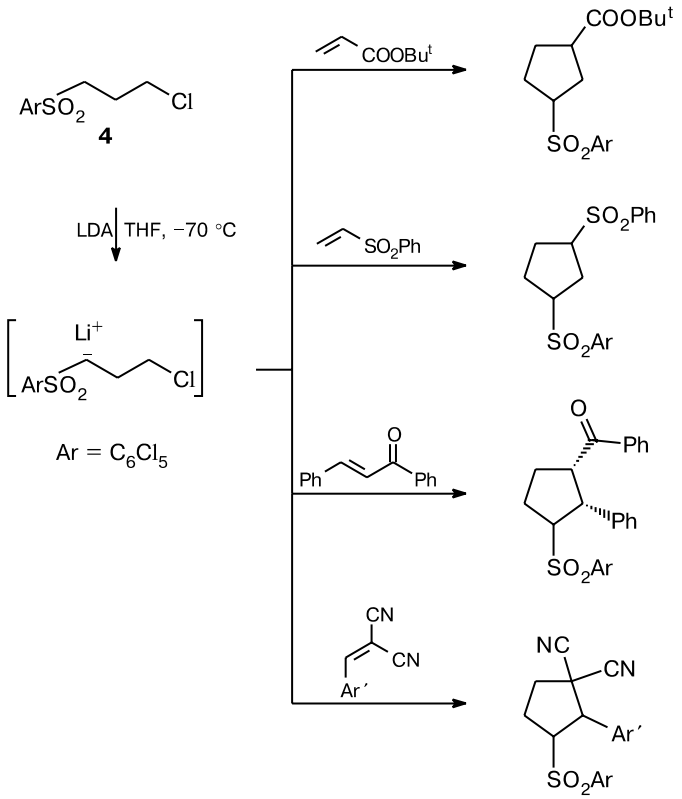
[a] Substituted pyrrolidine. [b] Substituted cyclopropane.

Although the substituted pyrrolidines can be formed as *cis*- and *trans*-isomers, only the *trans*-isomers were formed in our experiments, perhaps, due to the steric interaction of the bulky arylsulfonyl group with the aryl substituents of the imines. This new method for the synthesis of pyrrolidines corresponds to the recently reported reaction of *in situ* generated imines and γ-iodoenolates generated *in situ* by the reaction of cyclopropyl ketones with metal iodides.[23] In this system, fast intramolecular reaction of γ-iodoenolates does not hamper their intermolecular addition to imines and the subsequent formation of pyrrolidines, because of the reversibility of the former process. One can, therefore, consider that the final outcome, the formation of the pyrrolidine ring, is due to the thermodynamic control of the overall multistep process.

Reactions with electron-deficient alkenes

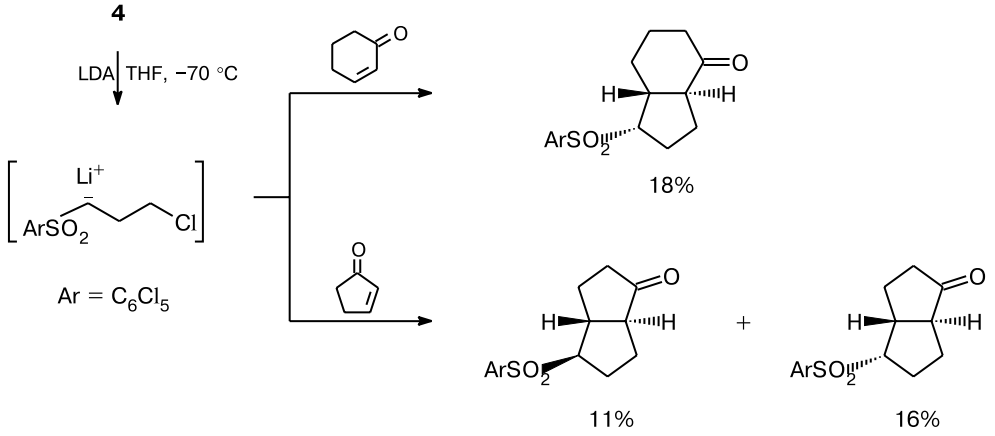
Owing to its longer lifetime, the carbanion generated from sulfone **4** should be a versatile reactive intermediate in the syntheses of substituted cyclopentanes by reactions with Michael acceptors. Indeed, treatment of sulfone **4** with LDA in THF at −70 °C followed by the addition of *tert*-butyl acrylate to the generated carbanion resulted in the formation of *tert*-butyl 3-(pentachlorophenyl)sulfonylcyclopentanecarboxylate as a mixture of *cis*- and *trans*-isomers. A variety of other Michael acceptors react with this carbanion along the same pathway to give cyclopentane derivatives[22] (Scheme 22).

Scheme 22



Ar′	Yield (%)	*cis*/*trans*
Ph	82	44 : 56
o-ClC$_6$H$_4$	70	Only *trans*
2-Furyl	85	66 : 34

Scheme 23



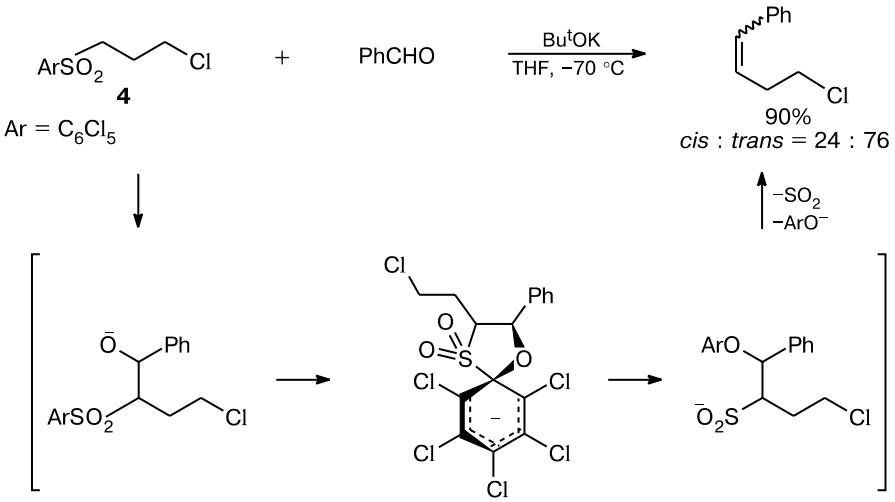
The origin of the stereochemistry of the resulting cyclopentanes is rather complicated. On the basis of preliminary experiments, it appears that it is determined by the addition and substitution steps and, hence, the reaction is kinetically controlled. This aspect, however, requires further studies. The carbanion of **4** reacts also with cyclic Michael acceptors, for instance, with cyclopentenone and cyclohexenone to give fused bicyclic systems[22] (Scheme 23).

Thus, mere modification of the aryl substituent in 3-chloropropyl aryl sulfone provides attractive and versatile possibility for the synthesis of pyrrolidine and cyclopentane derivatives. Surprisingly, the reaction of the carbanion generated from **4** with benzaldehyde followed a different route to give 4-chloro-1-phenylbut-1-ene in high yield rather than the expected substituted tetrahydrofuran. Obviously, the intramolecular S_N2 1,5-replacement of chlorine in the intermediate aldol-type adduct is slower than the intramolecular addition to the electron-deficient aromatic ring to produce the σ-adduct. This adduct undergoes further conversion along the Smiles rearrangement pathway, which is accompanied by expulsion of SO_2 and elimination of pentachlorophenol. The overall process is similar to the one-step variant of the Julia olefination[24] (Scheme 24).

Determination of the acidity of γ-halocarbanion precursors

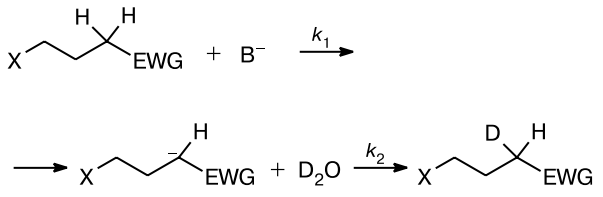
The observation that the halogen atom at the γ-position relative to the potential carbanion site increases the CH-acidity of the carbanion precursor required more rigorous proof. Direct determination of the pK_a value for these compounds is impracticable due to the short lifetime of the carbanions. Thus, only the kinetic acidity can be measured in these cases. This can be done simply by determining the rate of base-catalyzed deuterium ex-

Scheme 24



change under conditions that ensure much faster reprotonation (deuteration) compared to the proton abstraction (Scheme 25).

Scheme 25



$k_2 \gg k_1$

These requirements are met for the deuterium isotope exchange in a dilute solution of NaOD in a mixture of D_2O, EtOD, and DMSO. For convenience, we determined the time of half-exchange using ^1H NMR spectroscopy. The rates of the isotope exchange for the compounds of interest varied over a broad range; hence, measurements under identical conditions were impracticable. In order to avoid these difficulties we have controlled the basicity of the exchange "cocktail" by changing NaOD concentration and the solvent ratio in such a way as to keep the time of half-exchange within a range convenient for measurements. The selected data presented in Table 1 were calculated for identical conditions. From these data, it is evident that the Cl, Br, and F atoms in the γ-position increase substantially the deprotonation rate of 3-halopropyl phenyl sulfones and 4-halobutyronitriles. Under the same conditions, we have measured also the rates of deuterium exchange for some sulfones and nitriles with known pK_a values.[25]

Using the Brønsted equation (1),[26] which relates the rate constants to equilibrium constants and the α values reported for sulfones[27] and nitriles,[28] we calculated the approximate pK_a values for the compounds of interest.

$$\log k = \alpha \log K_a + C \qquad (1)$$

Although the published pK_a values used in our calculations (Table 1) were determined in an aprotic medium (DMSO), while our determination of the isotope exchange rate was done in a protic solvent, these calculations are justified, because the deuterium exchange rates of sulfones and nitriles with known pK_a were determined under identical conditions; thus, the resulting pK_a values are reasonably reliable. These data indicate that the presence of halogens in the γ-position relative to the carbanion-stabilizing groups (SO_2Ph and CN) decreases pK_a by ~2 units. Using the same approach, the pK_a values of γ-halopropyl aryl sulfones, where Ar is a substituted phenyl or hetaryl group, were also measured and calculated.

Table 1. Data of deuterium exchange experiment and calculated pK_a values

Compound		$\tau_{1/2}$/s	k_{obs}/s^{-1}	pK_a (DMSO)
EWG	X			
$PhSO_2$	H	900	$1.1 \cdot 10^{-3}$	31.0
$PhSO_2$	F	43	$2.3 \cdot 10^{-2}$	29.4
$PhSO_2$	Cl	22	$4.5 \cdot 10^{-2}$	29.0
$PhSO_2$	Br	17	$5.9 \cdot 10^{-2}$	28.9
$PhSO_2$	Me_3N^+	1.2	$8.3 \cdot 10^{-1}$ *	27.5
p-$NO_2C_6H_4SO_2$	H	8	$1.3 \cdot 10^{-1}$	28.5
p-$NO_2C_6H_4SO_2$	Cl	0.11	9.1	26.2
2-Pyrimidyl	Cl	1.5	$6.8 \cdot 10^{-1}$	27.6
2-Pyridyl	Cl	0.78	1.3	27.3
2,5-$Cl_2C_6H_3SO_2$	Cl	0.094	11	26.1
$C_6Cl_5SO_2$	Cl	$7.1 \cdot 10^{-3}$	140	24.8
$C_6Cl_5SO_2$	Br	$6 \cdot 10^{-3}$	170	24.7
CN	H	6500	$1.5 \cdot 10^{-5}$	32.5
CN	Cl	320	$3.1 \cdot 10^{-3}$	30.0
CN	Br	250	$3.9 \cdot 10^{-3}$	29.9
CN	Me_3N^+	13	$7.7 \cdot 10^{-2}$ *	28.4

* Salt with the chloride anion.

Conclusion

We have shown that short lived γ-halocarbanions of nitriles and sulfones can be efficiently trapped by active electrophilic partners such as aldehydes. The anionic aldol-type adducts formed initially enter into rapid 1,5-intramolecular substitution giving substituted tetrahydrofurans. This reaction offers a new, convenient and efficient method for the synthesis of these important heterocycles.

The rate of intramolecular substitution (γ-elimination) of the carbanions derived from γ-chloropropyl aryl sulfones can be controlled by varying their nucleophilicity *via* modification of aryl groups. A moderate increase in the acidity of carbanion precursors and, hence, a decrease in the nucleophilicity of γ-halocarbanions increases their lifetime. Hence, they can be trapped by moderately reactive electrophiles such as imines and Michael acceptors. On this basis, new methods for the synthesis of substituted pyrrolidines and cyclopentanes were elaborated.

The isotope exchange rates were measured to determine the kinetic acidity of a series of γ-halobutyronitriles and γ-halopropyl aryl sulfones and to estimate their pK_a values. The results showed that F, Cl, and Br atoms present in the γ-position relative to the carbanion center have a significant stabilizing effect on the carbanions.

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