Intramolecular alkylation of an α-sulfinyl vinylic carbanion without loss of optical purity: a novel access to chiral cyclic vinylic sulfoxides

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Received (in Cambridge, UK) 1st July 1999, Accepted 9th August 1999

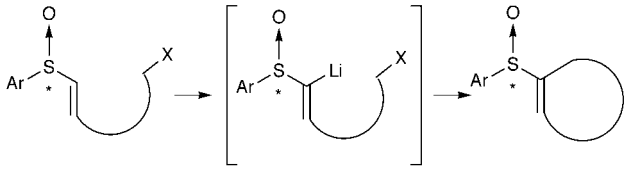
Novel cyclisation *via* intramolecular α-alkylation of vinylic sulfoxides was studied and cyclic vinylic sulfoxides of various ring sizes (5–7) were synthesised from both (*E*)- and (*Z*)-isomers without loss of optical purity.

1-Alkenyl aryl sulfoxides are deprotonated at the α-position and generate vinylic carbanion species, which react with a variety of electrophiles such as alkyl halides, epoxides, aldehydes and ketones.[1] This methodology is very useful for the synthesis of substituted vinylic sulfoxides, which can be transformed into a variety of functional groups and which also have potential use for asymmetric reactions.[2] However, research on the intermolecular reactions of α-lithio vinylic sulfoxides has revealed two problems: (i) contamination of the geometric isomer by isomerisation of its olefin moiety, and (ii) racemisation of the stereogenic center on the sulfur atom during isomerisation.[3] During the course of our research on the reaction of α-sulfinyl carbanions,[4] we have become interested in intramolecular α-alkylation of vinylic sulfoxides, which, to the best of our knowledge, has never been discussed in the literature (Scheme 1). This reaction has two advantages. (i) Not only (*E*)-isomers but also (*Z*)-isomers could be cyclised into the same product *via* rapid isomerisation; this would then provide a cyclic vinylic sulfoxide. Therefore, neither selective preparation of the geometric isomers nor their separation is required. (ii) The loss of enantiomeric excess is expected to be overcome since the intramolecular reaction is generally milder than the corresponding intermolecular version, due to the reduced decrease in the entropy of the intramolecular system.

Here we report a novel cyclisation *via* intramolecular alkylation of α-sulfinyl vinylic carbanions generated from (*E*)- and (*Z*)-isomers; this process provides cyclic vinylic sulfoxides without a subsequent loss of optical purity.

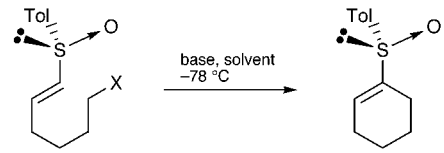
We began our study employing (*E*,*R*)-6-iodohex-1-en-1-yl *p*-tolyl sulfoxide (*E*)-**1a**. On treatment of (*E*)-**1a** with LDA (1.5 equiv.) in THF at −78 °C, rapid cyclisation proceeded to give cyclohex-1-enyl *p*-tolyl sulfoxide **2** in 82% yield; neither elimination of iodide nor the rearrangement of the double bond to the β,γ-position was observed (Table 1, entry 1). The corresponding bromide (*E*)-**1b** also afforded **2** in a comparable yield (79%) (entry 2). On the other hand, the tosylate and mesylate analogues caused the production of many products and therefore resulted in poor results (entries 3 and 4). Variation of the additive, base and solvent used did not improve the yield (entries 5–13).

Next, we examined cyclisation of ω-iodo vinylic sulfoxides (*E*)-**1e**,**f** with different chain lengths. Five- to seven-membered rings were formed in a good yield (79–82%; Table 2, entries 1–3). However, an eight-membered ring could not be formed even under highly dilute conditions (0.001 M), yielding instead many unidentified products together with the dimer **6** (22%) (entry 4). Then, we focused on the intramolecular alkylation of (*Z*)-isomers. As expected, cyclisation of (*Z*)-**1a**,**e**,**f** proceeded *via* isomerisation of their olefin geometry followed by cyclisa-



Scheme 1

Table 1 Intramolecular alkylation of α-sulfinyl vinyl carbanion[a]

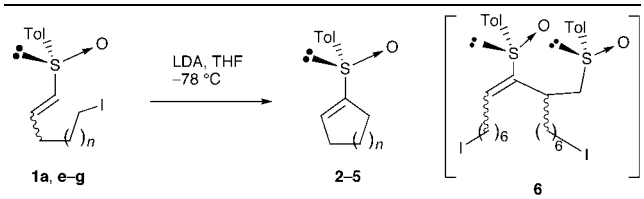


(*E*)-**1a**–**d** **2** Tol = *p*-MeC_6H_4

Entry	Substrate (X)	Base	Additive	Solvent	Yield (%)[b]
1	**1a** (I)	LDA	—	THF	82
2	**1b** (Br)	LDA	—	THF	79
3	**1c** (OTs)	LDA	—	THF	24
4	**1d** (OMs)	LDA	—	THF	complex
5	**1a** (I)	LDA	HMPA	THF	55
6	**1a** (I)	LDA	TMEDA	THF	62
7	**1a** (I)	LICA[c]	—	THF	75
8	**1a** (I)	LTMP[d]	—	THF	65
9	**1a** (I)	NaHMDS	—	THF	complex
10	**1a** (I)	KHMDS	—	THF	complex
11	**1a** (I)	LDA	—	DME	39
12	**1a** (I)	LDA	—	Et_2O	10
13	**1a** (I)	LDA	—	toluene	21

[a] The substrate was treated with 1.5 equiv. of the base at −78 °C under N_2. [b] Isolated yield. [c] LICA = lithium cyclohexylisopropylamide. [d] LTMP = lithium 2,2,6,6-tetramethylpiperidide.

Table 2 Cyclisation of (*E*)- and (*Z*)-**1** and optical purities of the products[a]



1a, **e**–**g** **2**–**5** **6**

Entry	Substrate	Product	*n* (ring size)	Yield (%)[b]	$[\alpha]_D$	Ee[c]
1	(*E*)-**1e**	**3**	1 (5)	81	+57	98
2	(*E*)-**1a**	**2**	2 (6)	82	+9	98
3	(*E*)-**1f**	**4**	3 (7)	79	+10	—
4	(*E*)-**1g**	**5**	4 (8)	0	—	—
5	(*Z*)-**1e**	**3**	1 (5)	66	+57	96
6	(*Z*)-**1a**	**2**	2 (6)	71	+9	98
7	(*Z*)-**1f**	**4**	3 (7)	64	+10	—

[a] The substrate was treated with 1.5 equiv. of the base at −78 °C under N_2. [b] Isolated Yield. [c] Determined by chiral HPLC.

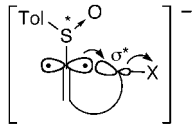


Fig. 1 Reaction mechanism.

tion to give **2**–**4**, respectively, in moderate yield (64–71%; entries 5–7).

Posner reported that α-deprotonation of optical pure (*E*,*R*)-undec-1-en-1-yl *p*-tolyl sulfoxide followed by reprotonation produced no racemisation, whereas similar treatment of the corresponding (*Z*)-isomer produced racemisation (*ca.* 30% loss of optical purity).[3] Therfore, the specific rotations of the cyclised products of intramolecular alkylation from the (*E*)- and (*Z*)-isomers were compared. The cyclic vinylic sulfoxides from the (*Z*)-isomers have almost the same specific rotations as those from the corresponding (*E*)-isomers. Furthermore, the products **2** and **3** prepared from (*E*)- and (*Z*)-ω-iodo vinylic sulfoxides **1a** and **1e** were confirmed to be highly optically pure (≥96% ee) by chiral HPLC (Daisel Chiralcel OB). As we expected, racemisation did not occur appreciably during (*Z*)- to (*E*)-isomerisation with the intramolecular alkylation of α-lithio vinylic sulfoxides.

The mechanism of racemisation in the α-carbanion of the (*Z*)-vinylic sulfoxide has not been revealed. However, the results of Posners' experiments indicate that racemisation occurs during isomerisation because no racemisation occurs in the corresponding reaction of the (*E*)-isomer. This means that the intramolecular alkylation of the (*Z*)-isomer is not a stepwise reaction involving isomerisation and cyclisation. We assumed the concerted mechanism shown in Fig. 1, wherein the σ*-orbital of the internal C–X bond participates in the olefin isomerisation by accepting the carbanion extending through the sp^2 carbon and assists the isomerisation.[1c,5] This interaction with the internal electrophile would prevent the racemisation of the sulfoxide.

A typical experimental procedure is described for the reaction of 7-iodohept-1-en-1-yl tolyl sulfoxide with LDA. A solution of the iodide **1f** (43 mg, 0.12 mmol) in dry THF (2.3 ml) was added to a solution of LDA (1.5 equiv.) [prepared from Pr^i_2NH (25 μl, 0.18 mmol) and 1.58 M BuLi in hexane (115 μl, 0.18 mmol) in dry THF (2.3 ml)]. The solution was stirred at −78 °C under N_2. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The extract was washed with brine prior to drying and solvent evaporation. The crude sample was purified by preparative TLC on silica gel with hexane–EtOAc (2 : 1) to give cyclohex-1-enyl *p*-tolyl sulfoxide (22 mg, 79%).

In summary, we found a ring-forming reaction *via* intramolecular alkylation of the α-lithio vinylic sulfoxides, which proceeded in moderate to good yield. Interestingly, even vinylic sulfoxides with (*Z*)-configuration were cyclised *via* rapid isomerisation; no racemisation occurred at the sulfur atoms. Further study of this method of cyclisation is currently underway.

Notes and references

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Communication 9/05320D