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THE LITHIATION AND ALKYLATION OF 4-(2'-ALKENESULPHINYL)-MORPHOLINES, A SIMPLE ROUTE TO SUBSTITUTED ALLYLIC SULPHINAMIDES [1]

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Summary: By the reaction with 4-morpholinesulphenyl chloride carried out in the presence of triethylamine, several substituted allylic alcohols have been converted into the corresponding allylic sulphinamides 2. As a complementary method, the new lithio-derivatives II have been prepared and efficiently alkylated with organic halides.

In the course of a survey of the possible uses of unsaturated sulphinamides in organic synthesis, we required various 1',3'-substituted 4-(2'-alkenesulphinyl)-morpholines.

Following a previously reported procedure [2], the nine substituted allylic alcohols (1a-f) were treated with 4-morpholinesulphenyl chloride in the presence of triethylamine and were thus efficiently converted via the transient 4-morpholinesulphenate esters I into the corresponding unsaturated sulphinamides (2a-f) [3,4]. The results are summarised in Table 1, the following features being particularly worthy of comment:

- The yield of sulphinamide 2e was lowered by the presence of the bulky t.butyl group.
- The rearrangement of the morpholinosulphenates examined was found to be regioselective and indeed, the use of secondary alcohols afforded the trans 1'-substituted 4-(2'-alkenesulphinyl)-morpholines 2 exclusively. Furthermore, the styrenic alcohol 1f(E) was converted smoothly into the deconjugated sulphinamide 2f [5].
- The diastereoselectivity of the (2.3)-sigmatropic rearrangement of the intermediates I was generally low, except for compounds 2a, 2a' and 2d', the diastereoisomers A and B [6] of which were formed in different ratios from (E)- and (Z)-olefinic alcohols 1a and 1d respectively [7,8].

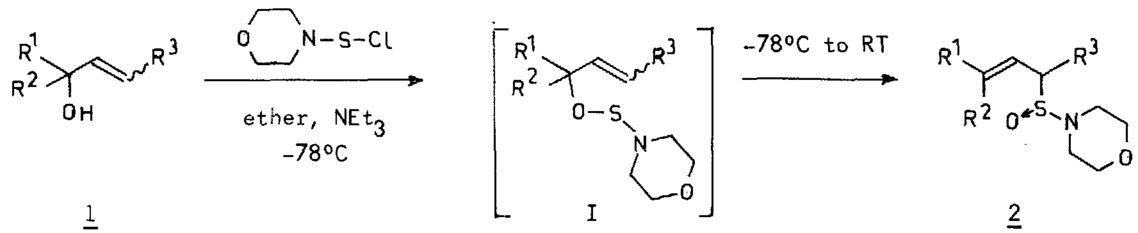

Table 1

Substrate	R^1	R^2	R^3	time (h)	yields (%) of sulphinamides		ratios A:B *
1a (E)	p.Me-C_6H_4	H	Me	1	2a	73	77:23
1a (Z)	p.Me-C_6H_4	H	Me	1	2a'	86	5:95
1b (E)	n.C_7H_{15}	H	Me	4	2b	73	55:45
1b (Z)	n.C_7H_{15}	H	Me	4	2b'	75	53:47
1c (E)	Me	Me	n.C_8H_{17}	4	2c	73	60:40
1d (E)	n.C_7H_{15}	H	i.Pr	4	2d	75	64:35
1d (Z)	n.C_7H_{15}	H	i.Pr	4	2d'	75	20:80
1e (E)	n.C_7H_{15}	H	t.Bu	16	2e	20	60:40
1f (E)	n.C_7H_{15}	H	Ph	16	2f	75	65:35

* The ratios of diastereoisomers are determined by ^1H NMR.

Although the regioselectivity shown in the formation of the above substituted allylic sulphinamides 2 by (2.3)-sigmatropic rearrangement is inherently interesting, a more versatile preparation of such species is required if they are to be of genuine use as synthetic intermediates. According to the initial work of Corey and Durst [9] on the preparation of some lithiated methanesulphinamides and their reaction with carbonyl compounds, it seemed very likely that the allylic sulphinamides 3 [2] could also be lithiated owing to the enhanced acidity of the hydrogens of the allylic methylene carbon adjacent to sulphur. Indeed we found that formation of the allylic carbanions II could be achieved if a solution of the sulphinamide 3 in THF was treated with a slight excess (1,1 eq) of lithium diisopropylamide (LDA) or methyllithium at -78°C for 30 min and the resulting lithio-derivative treated with a variety of organic halides at -78°C or -30°C thus affording the nine 1'-substituted sulphinamides 2.

The results are summarised in Table 2 and there are several noteworthy features:

- The yields of alkylated sulphinamides were generally higher when methyllithium was used as metalating agent.
- The allylic anions derived from sulphinamides 3 were alkylated only α to sulphur with saturated, allylic or benzylic halides to yield the two corresponding diastereoisomers 2 (A and B) with generally a low diastereoselectivity, excepting compound 2a (75:25).
- From the results obtained with the (E)-sulphinamides (3, R^1= alkyl or aryl; R^2=H) no isomerization of the double bond was detected after the lithiation-alkylation process.

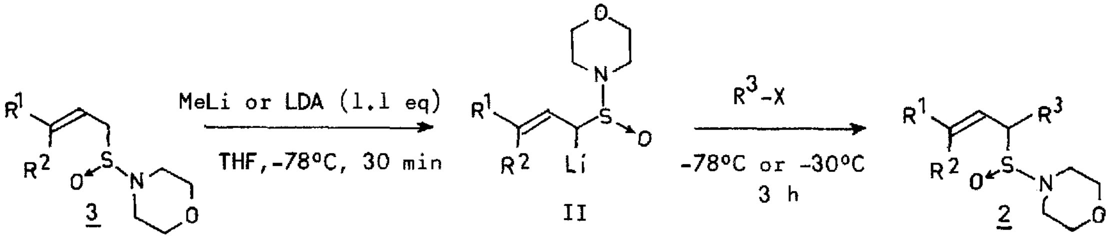

Table 2

Substrate	R^1	R^2	conditions	sulphinamides yields (%)		ratios A:B
3a	p.Me-C_6H_4	H	MeLi; MeI (3 eq); -30°C	2a	84	75:25
3b	H	H	MeLi;p.Me-C_6H_4-CH_2Br (1.1 eq);-78°C	2g	82	60:40
			LDA; idem		34	65:35
3c	n.C_7H_{15}	H	MeLi; MeI (2 eq); -30°C	2b	84	60:40
3b	H	H	MeLi; n.C_8H_{17}I (1.1 eq); -30°C	2h	46	55:45
			LDA; idem		50	idem
3b	H	H	MeLi; $\text{Ph-}\overset{H}{C}\text{=}\underset{H}{C}\text{-CH}_2\text{-Br}$ (1.1 eq);-78°C	2i	78	55:45
			LDA, idem		59	idem
3c	n.C_7H_{15}	H	MeLi; EtI (4 eq); -30°C	2j	90	62:38
3d	n.C_8H_{17}	H	MeLi; MeI (2 eq); -30°C	2k	84	52:48
			LDA; idem		68	55:45
3e	-$(CH_2)_5$-		MeLi; p.Me-C_6H_4-CH_2-Br (1.1 eq);-78°C	2l	88	65:35
3f	$\left\{ \begin{matrix} Me_2C=CH-(CH_2)_2 \\ Me \end{matrix} \right\}$		MeLi; $Me_2C=CH-CH_2$-Br (1.1 eq); -78°C	2m	85	*

* The ratios of the four isomers could not be determined by ^{1}H NMR.

The possibility of efficient alkylation of lithiated sulphinamides has not been heretofore recognized [10] and the reaction of these new allylic carbanions with other electrophiles should extend considerably the range of compounds available for the study of sulphinamide reactivity.

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REFERENCES AND NOTES

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   b) part III: Baudin J.-B., Julia S.A., Tetrahedron Lett., 1988, 29, 3255.
2. Baudin J.-B., Julia S.A., Tetrahedron Lett., 1988, 29, 3251.
3. The identity of all new compounds reported in this communication was established by IR, ^{1}H NMR, ^{13}C NMR and MS. For most of them, the elemental compositions were determined by combustion analysis.
4. The purified allylic sulphinamides can be stored at -20°C during several weeks without notable decomposition.
5. In contrast, the morpholinosulphenate of cinnamyl alcohol after five days yielded a mixture (30:70) of the deconjugated and cinnamyl sulphinamides. Both cinnamyl trichloromethane- and benzene-sulphenates gave only the corresponding cinnamyl sulphoxides: Braverman S., in "The chemistry of Sulphones and Sulphoxides", Ed. Patai S., Rappoport Z., Stirling Ch., J. Wiley & Sons, 1988, chapter 14, p. 717; Baechler R.D., San Filippo L.J., Schroll A., Tetrahedron Lett., 1981, 22, 5247.
6. We have represented the major and minor diastereoisomeric sulphinamides arising from each E-allylic alcohol by A and B respectively.
7. Other examples of diastereoselective (2.3)-sigmatropic rearrangements of some allylic N,N-dialkylaminosulphenate esters have been found in our laboratory; further work is in progress to shed light on their stereochemistry.
8. Cis and trans 2-butenyl p.toluenesulphenates have been reported to rearrange stereoselectively to give a 22:78 and 76:24 mixture of diastereoisomeric α-methyl allyl p.toluenesulphoxides respectively: Rautenstrauch V., J. Chem. Soc. Chem. Commun., 1970, 526.
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