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[2,3]-THIA-WITTIG REARRANGEMENTS WITH A MARKED STARTING MATERIAL DEPENDENCE OF STEREOSELECTIVITY

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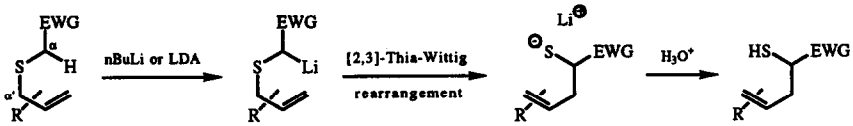
Abstract: [2,3]-Thia-Wittig rearrangements were initiated (a) by Sn,Li exchange of stannyl sulfides type **5** (X = S) and (b) by reductive lithiation of S,S-acetals type **6** (X = S). Homoallyl thiols were obtained in yields between 49 and 96%. *E*:*Z* selectivities of these rearrangements were low while *syn*:*anti* selectivities could be high. Extent and sense of both kinds of stereocontrol depended on whether procedure (a) or (b) was employed.

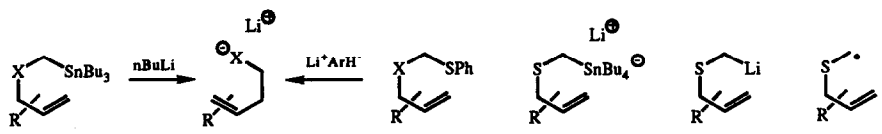
[2,3]-Wittig rearrangements of metalated allyl ethers furnish homoallyl alcohols, often with stereocontrol [1]. Similarly, [2,3]-*Thia*-Wittig rearrangements of lithiated allyl *sulfides* **2** lead via homoallyl thiolates **3** to homoallyl thiols **4** [2-6]. Organolithium compounds **2** suited for such rearrangements were obtained from allyl sulfides **1** in which an electron withdrawing group (EWG) acidifies the neighboring α-hydrogen sufficiently that *it* rather than the allylic α'-hydrogen is abstracted upon addition of BuLi or LDA.



1 **2** **3** **4**

(EWG = -HC=CMe$_2$ [2], -Ph [2], -CO$_2$Me [3], -SMe [4], -S(=O)Me [5], -CN/-SMe [6])

The present paper extends the scope of [2,3]-Thia-Wittig rerrangements to allyl sulfides without an activating EWG group: Allyl tributylstannyl sulfides **5** (X = S) and *n*-BuLi give homoallyl thiolates **3'** in THF at dry ice temperature within 5 min as do the mixed S,S-acetals **6** (X = S) when they are treated with >2 equiv. of lithium naphthalenide (LiNaphth). This means that such [2,3]-Thia-Wittig rearrangements may be performed in essentially complete analogy to the protocols of Still [7] (**5**→**3'**, X = O), Broka [8], and ourselves [9] (**6**→**3'**, X = O) developed in [2,3]-Oxa-Wittig rearrrangement chemistry.

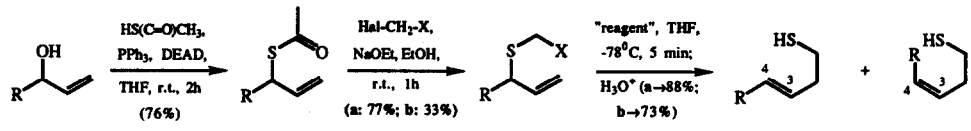


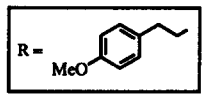
5 **3'** **6** **7** **2'** **8**

X = O: ref. [7]
X = S: this work

X = O: ref. [8,9]
X = S: this work

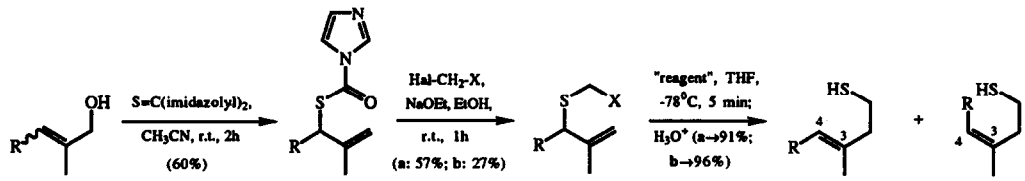
The rearrangement precursors were prepared from allyl alcohols by two routes. In the first, the OH group of compound **9** was subjected under Mitsunobu conditions to a regioselective substitution by thioacetate [10,11] (→**10**). Ethanolysis of **10** in a NaOEt/EtOH mixture liberated a sodium thiolate which was alkylated either with Bu_3Sn-CH_2-I [12] giving stannyl sulfide **11a** or with PhS-CH_2-Cl [13] giving S,S-acetal **11b**. Allyl sulfides **17** and **20** were prepared by the same methods.

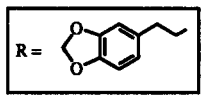




Hal	X	11	reagent			
I	$SnBu_3$	a	nBuLi	1	:	1
Cl	SPh	b	$Li^+Naphth^-$	4	:	1

The second route to rearrangement precursors relied on an S_N'-type conversion of allyl alcohols into allyl thiols [14] realized by the facile [3,3] sigmatropic shift of the alkoxythiocarbonyl imidazolide obtained from alcohol **13** and thiocarbonyl diimidazolide [15]. Basic ethanolysis of the rearrangement product **14** and alkylation of the resulting thiolate yielded stannyl sulfide **15a** and S,S-acetal **15b**.



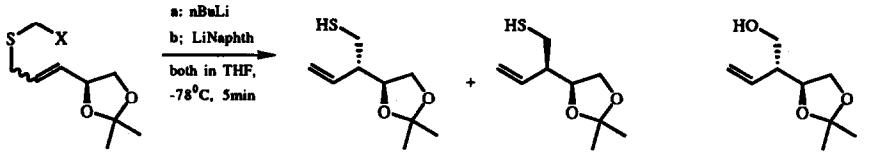


Hal	X	15	reagent			
I	$SnBu_3$	a	nBuLi	1	:	4
Cl	SPh	b	$Li^+Naphth^-$	4	:	1

The stannyl sulfides **11a** and **15a** underwent [2,3]-Thia-Wittig rearrangements within 5 min when treated with a slight excess of nBuLi in THF at -78°C. Aqueous workup provided the rearranged thiols **12** and **16** in 88 and 91% yield, respectively. The same rearrangement products were obtained in 73 and 96% yields, respectively, when the S,S-acetals **11b** and **15b** were lithiated reductively by the addition of >2 equiv. of LiNaphth [16].

Surprisingly, the configuration at the stereogenic C=C double bond of rearrangement products **12** and **16** depended markedly on how lithium was introduced into the molecule: Sn,Li exchange in **11a** provided **12** as a 1:1 *cis*:*trans* mixture whereas the LiNaphth mediated reaction of **11b** led to a 4:1 *trans*:*cis* preponderance (^{13}C NMR) [17]. Similarly, the *E*:*Z* ratio in homoallyl thiol **16** changed from 1:4 observed following Sn,Li exchange in **15a** to 4:1 after LiNaphth treatment of **15b** (^1H NMR) [18]. We cannot exclude rigorously that PhSLi - the by-product of the LiNaphth induced reactions - gave PhS radicals during the workup procedure which then erased an initially possibly identical stereochemical outcome of *both* rearrangement types through rapid *cis*→*trans* or *Z*→*E* isomerizations, respectively. Yet, the different stereoselectivities appear to have a different reason. This may be inferred from [2,3]-Thia-Wittig rearrangements where the

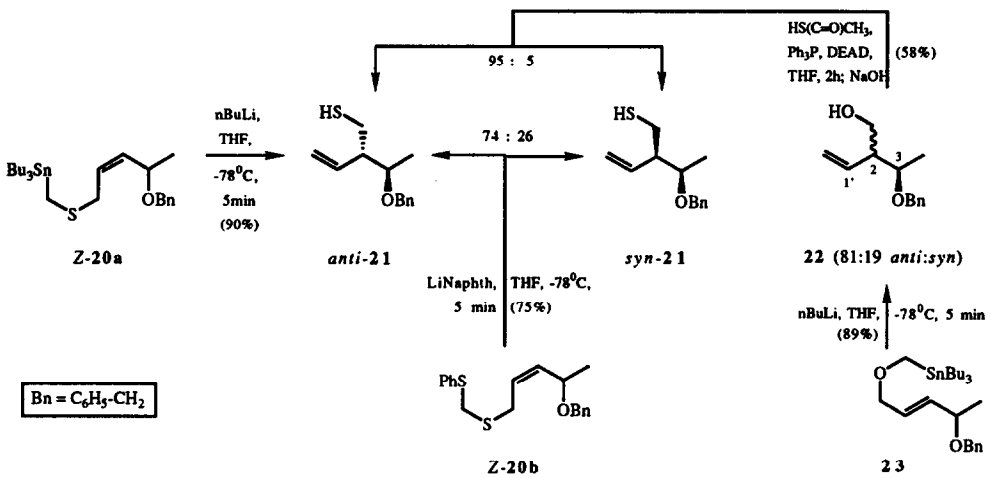
initial isomer distribution - the *anti*:*syn*-**18** and *anti*:*syn*-**21** ratios - would be preserved no matter whether PhS radicals were present or not. There, starting material dependent selectivities were observed once again:



E,*Z*-17a,b	X	Yield	*anti*-18		*syn*-18
E-17a	$SnBu_3$	68%	94	:	6
E-17b	SPh	66%	54	:	46
Z-17a	$SnBu_3$	83%	98	:	2
Z-17b	SPh	49%	35	:	65

19

Stannyl sulfides *E*- and *Z*-**17a** gave the diastereomeric homoallyl thiols **18** with high (94:6, GLC) and very high (98:2, GLC) *anti*-selectivity, respectively, after short BuLi treatment at dry ice temperature [19]. Thus, the kind of stereocontrol through asymmetric induction found in [2,3]-Oxa-Wittig rearrangements of substrates containing an allylic stereocenter [21] rules the stereochemistry in the Thia-series equally and equally well. On the other hand the corresponding S,S-acetals *E*- and *Z*-**17b**, after regioselective cleavage of one of their C-S bonds with LiNaphth, led to the same homoallyl thiols **18** with very low *anti*- (54:46, GLC) and even *syn*-preference (65:35; GLC), respectively.



Starting from another set of precursors containing an allylic oxygen-bearing stereocenter, we obtained similar results: Stannyl sulfide *Z*-**20a** and *n*-BuLi rearranged to *anti*-**21** with high diastereoselectivity (*anti*:*syn* 96:4, GLC) whereas the corresponding S,S-acetal *Z*-**20b** and LiNaphth gave a 74:26 *anti*:*syn*-**21** mixture (GLC) [22].

The starting material dependent stereoselectivities of the [2,3]-Thia-Wittig rearrangements of the present study contrast sharply with the virtual absence of such an effect in related [2,3]-Oxa-Wittig rearrangements [9]. Interestingly, in control experiments the *anti*-selectivity of the reaction of BuLi with stannyl sulfide *E*-**17a** was unaltered in the presence of naphthalene (2.0 equiv.) or both naphthalene and LiSPh (2.0 and 1.0 equiv., respectively). Similarly, the BuLi mediated rearrangement of stannyl sulfide *Z*-**17a** remained *anti*-

selective when LiSPh (1.1 equiv.) was present. Finally, stannyl sulfide *E*-**17a** and LiNaphth (!) gave also only *anti*-configurated [2,3] rearrangement product although in poor yield (33%). This means that the low *syn*-selectivity of the [2,3] rearrangements of the *S,S-acetals E-* and *Z*-**17b** could not be mimicked starting from *stannylated precursors*.

Whether the stereochemical discrepancies between the two [2,3]-Thia-Wittig rearrangements types presented here are due to different mechanisms is not clear. Alternatives to the normally plausible concerted sigmatropic bond shift in a *common* lithio sulfide **2'** intermediate might be a [2,3] shift in the ate-complex **7** for rearrangements starting from organotin compounds or a *5-endo-trig* cyclization of radical **8** followed by electron transfer and ß-elimination for rearrangements starting from S,S-acetals.

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17. The configuration of *trans*-**12** follows from the olefinic coupling constant $J_{3,4}$ = 15.3 Hz (250 MHz ^{1}H-NMR spectrum, $CDCl_3$).
18. The C=C bond configurations were assigned by 400 MHz ^{1}H-NMR spectroscopy ($CDCl_3$): Irradition of 3-CH_3 (δ 1.67 ppm) led to enhanced absorption (3%) at δ 5.28 ppm in the isomer assigned *Z*-**16** while irradition of 3-CH_3 (δ 1.54 ppm) left the olefinic absorption (δ 5.23 ppm) unchanged in the isomer designated *E*-**16**.
19. The configuration of compound *anti*-**18** was proven by an independent synthesis from the known [20] alcohol **19** (MsCl, NEt_3, CH_2Cl_2, -6°C, 1h; excess KHS in EtOH, room temp. → 50°C; 53% overall).
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22. For structural assignment, a 95:5 *anti,syn* mixture of thiols **21** was synthesized independently from the 81:19 *anti*:*syn*-**22** mixture obtained in analogy to precedent [20] by Wittig-Still rearrangement of the stannylated ether **23**. *Anti-* and *syn*-**22** were distinguished by their 500 MHz ^{1}H-NMR spectra (C_6D_6) using the criteria established earlier [20] for such compounds (note that in this reference the *anti*/*syn* designations were defined differently): δ(1'-H) = 5.78 (*anti*) vs. 5.50 (*syn*); $J_{2,3}$ = 3.2 (*anti*) vs. 7.7 Hz (*syn*).

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