Kurzmitteilungen / Short Communications

Reductive Lithiation of Sulfides and Sulfones – A Novel Entry into [2,3] Wittig Rearrangements

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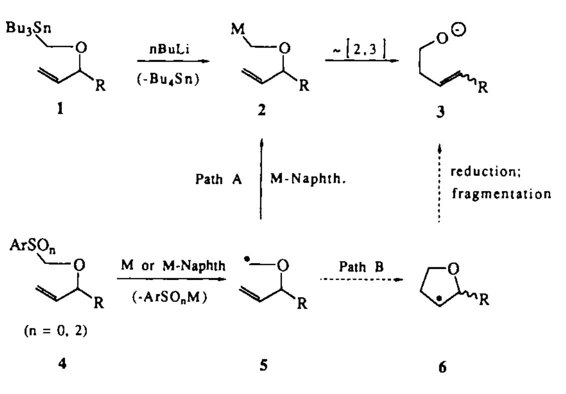
The reductive cleavages of allyl [(phenylthio)methyl] ethers (**8**, **11**) and an allyl [(tolylsulfonyl)methyl] ether (**14**) with lithium naphthalenide in THF furnish homoallylic alcohols (**9**, **12**). The steric course of these transformations (*E/Z* selectivity in the case of **9**, *syn/anti* selectivity for **12**) is very similar to that of analogous Wittig-Still rearrangements.

[2,3] Wittig rearrangements of metalated allyl ethers are increasingly used in stereoselective synthesis[1]. The Wittig-Still rearrangement of stannylated ethers **1**, for example, furnishes homoallylic alcohols **3** with preponderant or exclusive *Z* configuration[2]. A number of explanations for this unusual selectivity, which ranges unique among [2,3] sigmatropic shifts, have been suggested[2a,3]. None of them, however, considers the possibility that *the counterion* – i.e. lithium – biases the transition state towards the *Z* geometry. Such a role of the counterion should be more readily recognizable if one were to prepare metalated ethers **2** with M $\neq$ Li, to submit them to the [2,3] Wittig rearrangement, and to compare stereoselectivities for **2** (M $\neq$ Li) vs. **2** (M = Li). *This is the goal of a program that we have launched recently.*

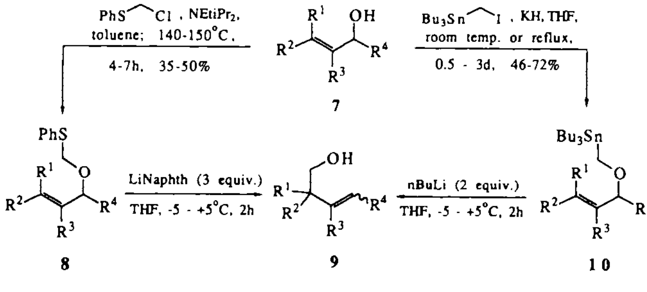
Scheme 1. Counterion variation in the [2,3] Wittig rearrangement



The reductive metalation of [(arylthio)methyl] ethers **4** (*n* = 0) or [(arylsulfonyl)methyl] ethers **4** (*n* = 2) appeared to us a potentially versatile access to the desired species **2** (cf. Scheme 1). Reductive *lithiations* of this kind are known from the work of Cohen[4] and Sinaÿ[5].

Here, we wish to disclose our first results. They indicate that reductive metalations of sulfides and sulfones *are* a viable entry into [2,3] Wittig rearrangements. As a start, we employed lithium naphthalenide as reductant (i.e. postponed the incorporation of metals *other* than Li into the Wittig rearrangement intermediate **2**). This choice was made to compare the stereoselectivities of the *novel* [2,3] Wittig rearrangements with results obtained from analogous Wittig-Still rearrangements. The fact that *E/Z* and *syn/anti* ratios (for **9** and **12**, respectively; vide infra) were essentially independent from the type of rearrangement used, makes a *common intermediate* – the lithiated ether **2** – highly probable, i.e. supports the mechanism "Path A" of Scheme 1. In principle, radical intermediate **5** of the *novel* rearrangement could have cyclized to give the tetrahydrofuranyl radical **6** instead of forming the metalated ether **2**; electron transfer to **6** followed by fragmentation of the resulting carbanion would have given the observed product **3**, too ("Path B" in Scheme 1). Then, however, one should have observed *different* stereoselectivities starting from sulfides vs. stannanes.

Scheme 2. Reductively initiated [2,3] Wittig rearrangements vs. Wittig-Still rearrangements

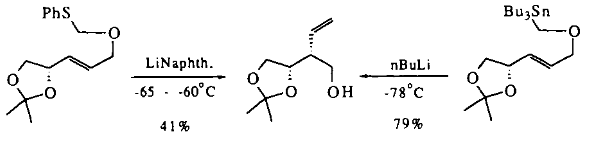


8-10	R^1	R^2	R^3	**9** from **8**: % yield	**9** from **8**: *E*:*Z*	**9** from **10**: % yield	**9** from **10**: *E*:*Z*
a	H	H	H	91	25 : 75	67	30 : 70
b	H	H	Me	85	0 : 100	83	0 : 100
c	Me	H	H	78	86 : 14	60	89 : 11
d	H	Me	H	97	30 : 70	94	37 : 63
e	Me	Me	H	45	100 : 0	61	100 : 0

(R^4 = p-MeO-C_6H_4-CH_2-CH_2-)

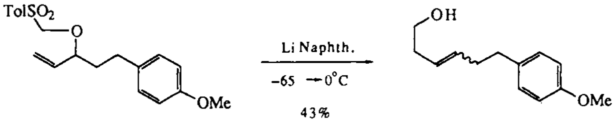
[(Phenylthio)methyl] ethers **8** were obtained from allylic alcohols **7** in moderate yields by reaction with $PhSCH_2Cl$[6] and $NEtiPr_2$ at elevated temperature (toluene, 140–150°C)[7]. Stannylated ethers **10** were prepared from **7** by alkylation with Bu_3SnCH_2I and KH (method: ref.[2a]). Sulfur- *and* tin-containing ethers were rearranged in THF at –5 to +5°C upon treatment with 3 equiv. of LiNaphth or 2 equiv. of *n*BuLi, respectively. The rearrangement products **9a–d** were obtained from the sulfides in good to excellent yields

(78–97%) and in slightly lower yields (60–94%) from the stannanes. Homoallylic alcohol **9e**, the formation of which is hindered due to the formation of a quaternary carbon center, resulted in 45% and 61% yields from the novel and the Wittig-Still route, respectively. In other words, the prospect that reductively initiated [2,3] Wittig rearrangements might become as synthetically useful as the Wittig-Still process, looks favorable[8]. Notice that *E*:*Z* selectivities[9] in both types of rearrangements are *close to identical* (Scheme 2). This is, as mentioned above, a necessary corollary of mechanism "Path A" for the sulfide reaction (Scheme 1).



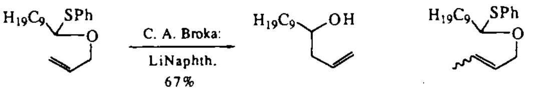
11 *syn*-**12** **13**

Earlier, we reported the occurrence of stereocontrol through asymmetric induction in the Wittig-Still rearrangement **13** → *syn*-**12** (ds = 93:7)[10]. The *same* diastereoselectivity (ds = 90:10) was observed when our reduction/rearrangement protocol served to convert sulfide **11** into *syn*-**12**[9].



14 **9a** (*E* : *Z* = 36 : 64)

The [(allyloxy)methyl] *sulfone* **14** underwent a reductively initiated [2,3] Wittig rearrangement, too, albeit less efficiently than its sulfide analog **8a**: Alcohol **9a** was isolated in 43% yield as a 64:36 mixture of *cis* and *trans* isomers (−60 → 0°C; **8a** → 91% of a 75:25 mixture at −5 to +5°C). Sulfones like **14** are readily accessible[11].



15 **16** *E*- and *Z*-**17**

While the present work was underway, Broka described the first reductive entries into the [2,3] Wittig rearrangement[12]. He generated *secondary* oxyanions from sulfides **15** and **17**, respectively, and rearranged them under conditions similar to ours.

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Experimental

^{1}H NMR spectra: Bruker AC 300; tetramethylsilane as internal standard in CDCl$_3$; integrals in accord with assignments; coupling constants in Hz. – All reactions were performed in oven-dried (100°C) glassware under dry N$_2$. Compounds were purified by flash chromatography[13] on Merck silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh ASTM). – Yields refer to analytically pure samples (analyses compiled in Table 1).

The *sulfides* **8a–e** were prepared from the corresponding alcohols according to the procedure exemplified for **11** in yields of 43%, 35%, 41%, 50%, and 44%, respectively. – The *stannanes* **10a–e** were obtained by etherification of alcohols **7a–e** in 51%, 53%, 46%, 72%, and 68% yield, respectively, following the procedure of ref.[2a]. – *Wittig-Still rearrangements* were performed according to ref.[2a] at −5 to −5°C; 1 equiv. of TMEDA was added in the reaction of **10e** (yields: Scheme 2). – The *reductively initiated rearrangements* of sulfides **8a–c**, **8e**, **11** were performed at −5 to +5°C as exemplified for **8d** (1 equiv. of TMEDA was added in the reaction of **8e**); sulfone **14** was rearranged similarly, but at −65 → 0°C (yields: *cf.* Theoretical Part). – The rearranged alcohols *syn*- and *anti*-**12** were described earlier[10]. – *Sulfone* **14** was obtained from 5-(*p*-anisyl)-1-hexen-3-ol and tosyldiazomethane by the procedure described in ref.[11] (55%).

Table 1. Combustion analyses of compounds **8–11** and **14**

Compound	Empirical formula (Mol. mass)	Found (calcd.) C	H
8a	$C_{19}H_{22}O_2S$ (314.5)	72.77 (72.57)	7.05 (7.05)
b	$C_{20}H_{24}O_2S$ (328.5)	72.24 (73.13)[a]	7.50 (7.36)
c	$C_{20}H_{24}O_2S$ (328.5)	73.10 (73.13)	7.40 (7.36)
d	$C_{20}H_{24}O_2S$ (328.5)	73.14 (73.13)	7.30 (7.36)
e	$C_{21}H_{26}O_2S$ (342.5)	73.18 (73.64)	7.37 (7.65)
9a	$C_{13}H_{18}O_2$ (206.3)	75.38 (75.69)	8.76 (8.80)
b	$C_{14}H_{20}O_2$ (220.3)	76.40 (76.33)	9.27 (9.15)
c	$C_{14}H_{20}O_2$ (220.3)	76.45 (76.33)	8.92 (9.15)
d	$C_{14}H_{20}O_2$ (220.3)	76.28 (76.33)	9.50 (9.15)
e	$C_{15}H_{22}O_2$ (234.3)	76.94 (76.88)	9.60 (9.46)
10a	$C_{25}H_{44}O_2Sn$ (495.3)	60.71 (60.62)	8.86 (8.95)
b	$C_{26}H_{46}O_2Sn$ (509.4)	61.58 (61.30)	8.92 (9.10)
c	$C_{26}H_{46}O_2Sn$ (509.4)	61.58 (61.30)	9.20 (9.10)
d	$C_{26}H_{46}O_2Sn$ (509.4)	61.17 (61.30)	9.17 (9.10)
e	$C_{27}H_{48}O_2Sn$ (523.4)	62.29 (61.96)	9.35 (9.24)
11	$C_{15}H_{20}O_3S$ (280.4)	64.62 (64.25)	7.27 (7.19)
14	$C_{20}H_{24}O_4S$ (360.5)	66.92 (66.64)	6.92 (6.71)

[a] No correct elemental analysis could be obtained.

(4S)-2,2-Dimethyl-4-[(E)-3-(phenylthiomethoxy)-1-propenyl]-1,3-dioxolane (*E*-**11**): (*E*)-3-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-propen-1-ol (0.633 g, 4.00 mmol), NEt*i*Pr$_2$ (1.55 g, 12.0 mmol, 3.0 equiv.), PhSCH$_2$Cl[6] (1.74 g, 10.8 mmol, 2.7 equiv.), and toluene (4 ml) were heated at 150°C for 4.7 h. Dilution with petroleum ether (25 ml) and ether (25 ml), removal of the precipitated solid by filtration, and flash chromatography [petroleum ether/ether (10:1 → 8:1)] afforded *E*-**11** (0.623 g, 56%). – $[\alpha]_D^{20} = 21$ (CH$_2$Cl$_2$, $c = 1.9$). – ^{1}H NMR: $\delta = 1.38$ and 1.42 [2s, 2-(CH$_3$)$_2$], 3.57 (dd, $J_{gem} = J_{5a,4} = 7.9$, 5-H$_a$), 4.08 (dd, $J_{gem} = 8.2$, $J_{5b,4} = 6.2$, 5-H$_b$), 4.16 (br. d, $J \approx 6$, OC*H*$_2$–CH=), 4.51 (br. ddd, all *J* values ca. 7, 4-H), AB signal ($\delta_A = 4.99$, $\delta_B = 5.00$, $J_{A,B} = 11.7$, OCH$_2$S), AB signal ($\delta_A = 5.71$, $\delta_B = 5.85$, $J_{A,B} = 15.5$, in addition split by $J_{A,4} = 7.1$, $J_{A,3'} = 1.3$, $J_{B,3'} = 5.5$, $J_{B,4} = 0.7$, A = 1′-H, B = 2′-H), 7.20–7.30 and 7.44–7.47 (2m; 3 and 2 Ar-H, respectively).

Wittig Rearrangement of (E)-6-(4-Methoxyphenyl)-4-[(phenylthio)methoxy]-2-hexene (**8d**) [^{1}H NMR: $\delta = 1.72$ (dd, $J_{1,2} = 6.4$, $J_{1,3} = 1.6$, 1-H$_3$), superimposing in part 1.69–1.94 (m, 5-H$_2$), 2.46–2.64 (m, 6-H$_2$), 3.78 (s, OCH$_3$), 4.12 (m$_c$, 4-H), AB signal ($\delta_A = 4.85$, $\delta_B = 5.13$, $J_{A,B} = 11.7$, OCH$_2$S), 5.28 (ddq, $J_{trans} = 15.3$, $J_{3,4} = 8.5$, $J_{3,1} = 1.6$, 3-H), 5.60 (dq, $J_{trans} = 15.0$, $J_{2,1} = 6.6$, 2-H), 6.77–6.81, 7.01–7.06, 7.17–7.32 and 7.45–7.50 (4m, 2, 2, 3, and 2 Ar-*H*, respectively)]: At −5 to +5°C, **8d** (0.110 g, 0.334 mmol) in THF (3 ml) was added during 5 min to LiNaphth (1.2 mol/l in THF; 0.85 ml, 1.0 mmol, 3.1 equiv.). The mixture was quenched with H$_2$O (3 ml) after 2 h, extracted with Et$_2$O (3 × 30 ml), and dried with $MgSO_4$. Flash chromatography [ether/petroleum ether (1:10 → 1:3)] furnished *6-(4-methoxyphenyl)-2-methyl-3-hexen-1-ol* (**9d**) as a 30:70 mixture of *E* and *Z* isomers (0.071 g, 97%). – ^{1}H NMR: *E*-**9d**: $\delta = 0.95$ (d, $J_{Me,2} = 6.8$, 2-CH_3), 1.25 (br. s, OH), 2.22 – 2.43 and 2.55 – 2.69 (2m, superimposed by *Z*-**9d**, 2-H, 5-H_2, 6-H_2), 3.21 – 3.48 (m, superimposed by *Z*-**9d**, 1-H_2), 3.79 (s, OCH_3), 5.21 (ddt, $J_{trans} = 15.3$, $J_{3,2} = 8.0$, $J_{3,5}$ ca. 1, 3-H), 5.54 (dtm$_c$, $J_{trans} = 15.4$, $J_{4,5}$ ca. 6, 4-H), AA′BB′ signal centered at $\delta = 6.83$ and 7.08 (C_6H_4OMe). – *Z*-**9d**: $\delta = 0.87$ (d, $J_{Me,2} = 6.8$, 2-CH_3), 1.25 (br. s, OH), 2.22 – 2.43 and 2.55 – 2.69 (2m, superimposed by *E*-**9d**, 2-H, 5-H_2, 6-H_2), 3.21 – 4.48 (m, superimposed by *E*-**9d**, 1-H_2), 3.79 (s, OCH_3), 5.14 (ddm$_c$, $J_{cis} = J_{3,2} = 10.2$, 3-H), 5.50 – 5.59 (m, superimposed by *E*-**9d**, 4-H), AA′BB′ signal centered at $\delta = 6.83$ and 7.10 (C_6H_4OMe).

CAS Registry Numbers

7a: 122410-18-8 / **7b**: 122410-19-9 / **7c**: 122410-20-2 / **7d**: 122410-21-3 / **7e**: 122410-22-4 / **8a**: 122410-11-1 / **8b**: 122410-12-2 / **8c**: 122410-13-3 / **8d**: 122410-14-4 / **8e**: 122410-15-5 / (*E*)-**9a**: 122410-01-9 / (*Z*)-**9a**: 122410-02-0 / (*Z*)-**9b**: 122410-03-1 / (*E*)-**9c** [≡(*E*)-**9d**]: 122410-04-2 / (*Z*)-**9c** [≡(*Z*)-**9d**]: 122410-05-3 / (*E*)-**9e**: 122410-06-4 / **10a**: 122410-07-5 / **10b**: 122410-08-6 / **10c**: 122410-09-7 / **10d**: 122410-09-7 / **10e**: 122410-10-0 / **11**: 122410-16-6 / **12**: 122422-95-4 / **13**: 122422-94-3 / **14**: 122410-17-7 / PhSCH$_2$Cl: 7205-91-6 / Bu$_3$SnCH$_2$I: 66222-29-5 / 5-(*p*-Anisyl)-1-hexen-3-ol: 122410-23-5 / Tosyldiazomethane: 1538-98-3 / (*E*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-propen-1-ol: 79060-23-4

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[8] We are currently trying to improve the yields for the *preparation* of sulfides **8**.

[9] *E*/*Z* ratios of **9** and *syn*/*anti* ratios of **12** were determined by capillary GLC. *E*/*Z* assignments are based on the magnitude of the olefinic coupling constant $^3J_{H,H}$ or on NOE difference spectra (**9b**).

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