Tetrahedron Vol. 34, pp. 2205–2207.

0040-4020/78/0715-2205/$02.00/0

AN EFFECTIVE [1,4]-CHARGE AFFINITY INVERSION OF SULFUR FUNCTIONALIZED ISOPRENES

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(*Received in UK 30 December 1977; Accepted for publication 17 February 1978*)

Abstract—Consecutive [1,2]- and [1,3]-migrations of the sulfur functionality convert the hydroxysulfoxide terpene building block **1a** into the charge affinity inverted synthon **6** or the desulfurized chloro aldehyde **9a**.

Isoprene derived terpene building blocks carrying an activating sulfur functionality at either C atom 1[1] or C atom 4[2] have been used successfully in poly-isoprenoid synthesis. The ready availability of the hydroxy sulfoxide **1a**,[a] which has recently been used in head-extension reactions[1b] tempted us to design an effective [1,4]-migration[b] of the activating sulfur function from the head of the isoprene derivative to its tail. This charge affinity inversion process would allow both head- and tail-extension reactions to be performed starting from the same synthon.

Since to the best of our knowledge no direct method for head to tail [1,4]-migration is described in the literature, we have used two consecutive migrations; a [1,2]-shift (from **1** to **4**, Scheme 1) followed by a [1,3]-shift (from **4** to **6**, Scheme 2). The intermediate tertiary sulfide **4** also gives access to γ-acetoxy tiglic aldehyde (**9b**, Scheme 2), a key-intermediate in the BASF industrial vitamin A synthesis.[5]

Functional group migration

[1,2]- and [1,3]-sulfur shifts are well precedented in the literature. Sulfides with a β-leaving group in general permit [1,2]-shifts of the alkylthio group via thiiranium intermediates.[4a] [1,3]-Shifts are known with sulfides, sulfoxides and sulfones. The mechanism of the [1,3]-allyl sulfide shift is subject to contradictory reports,[4,6] but evidence is accumulating[7] for an associative transition state with a hypervalent S atom by electron donation from the allylic double bond.

The diastereomeric hydroxysulfoxide mixture **1a** must be reduced to a sulfide before the [1,2]-migration can be performed. A Pummerer reaction is very useful to this end.[8] Moreover, the α-carbon is simultaneously oxidized and thus transformed into a masked CO function at C atom 1 of the terpene building block. However, an attempted Pummerer reaction from **1a** to **2** proceeded in a low yield and was accompanied by tar formation.[c] Much better results were obtained after protection of the OH function in the form of its acetate **1b**, by prolonged treatment with acetic anhydride/pyridine.[d] The Pummerer reaction with **1b** gave the sulfide **2** as an almost 1:1 mixture of the diastereomeric racemates in high yield.

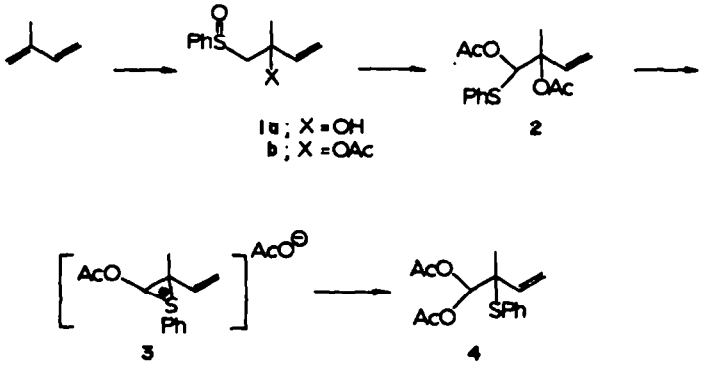
The [1,2]-shift from **2** to **4** is a migration that converts one sulfide with a β-leaving group into another. We expected enough difference in stability between **2** and **4** to lead to domination of the latter under equilibrium conditions; but to our surprise we observed quantitative formation of **4** upon treatment of **2** with acetic anhydride/TsOH at r.t. Since [1,3]-shifts are much slower than [1,2]-shifts[10] compound **4** does not enter into an allylic [1,3]-shift under the mild reaction conditions used.

[a] Prepared from isoprene as a roughly 1:1 mixture of diastereomeric racemates.[3]

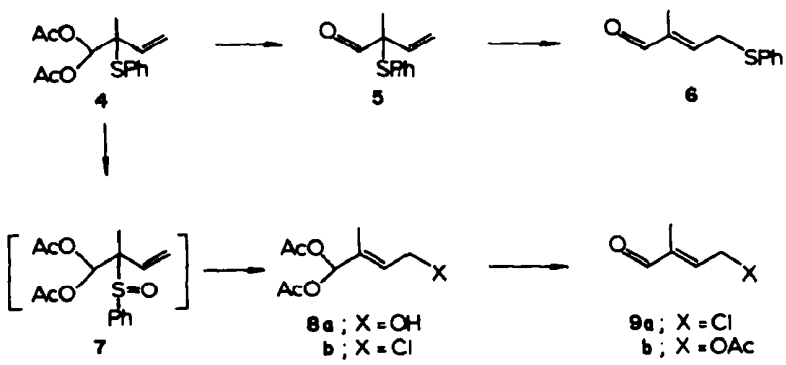
[b] The term migration is used as defined by Brownbridge and Warren.[4]

[c] Possibly the decomposition is initiated by an intramolecular OH attack on the intermediate acetoxy sulfonium group, related to the reaction of β-hydroxy chloro sulfonium salts.[9]

[d] The *in situ* formation of **1b** by gradual heating with Ac_2O/NaOAc[8] gave **2** in only 40%.



Scheme 1.



Scheme 2.

Heating of **4** in order to accelerate the allylic rearrangement results in decomposition into a dark coloured mixture, containing the aldehyde **5**[e] along with unidentified products. However, the [1,3]-migration can be performed smoothly when the *gem* diacetoxy compound **4** is converted to **5** by r.t. treatment with methanolic K_2CO_3. The aldehyde sulfide **5** formed in this way is essentially pure and isomerizes almost completely to the desired (E)-aldehyde sulfide **6** on exposure to daylight (half life time approximately 2 days).

The building block **6** was used in tail-extension reactions after protection of the aldehyde group followed by metallation α to the sulfur function and in head-extensions by Horner–Wittig reaction at the aldehyde group. These applications will be published separately.[11]

Conversion of **4** *to desulfurized five carbon building blocks*

In addition to the above mentioned conversion of **4** to the sulfur functionalized terpene building block **6** we have developed a stereospecific route from **4** to the (E)-4,4-diacetoxy-3-methyl-2-butenol (**8a**) in the following way. Oxidation of **4** to the sulfoxide **7** followed by a [2,3]-sigmatropic shift to the corresponding sulfenate ester gives the allylic alcohol **8a** upon treatment with a thiophilic reagent. A variety of thiophiles has been used in the literature to trap sulfenate esters.[12] Most of them, however, are highly nucleophilic and therefore of no use in the synthesis of compounds possessing electrophilic sites.[f] We found that treatment of the unpurified sulfoxide **7** with water absorbed at nine times its weight of silica affords **8a** in 50% yield after column chromatography. The chloro aldehyde **9a**, a known precursor of **9b**, is obtained from **8a** by reaction with thionyl chloride to **8b** followed by cleavage of the *gem* diacetoxy group.

EXPERIMENTAL

IR, ^1H NMR and ^{13}C NMR were recorded on a Unicam SP 200, a Varian XL-100 and a Varian XL-115 apparatus respectively. GLC analyses were performed on an all glass modified Varian Aerograph series 1700 apparatus, using a 6 ft SE 52 column.

1 - *Phenylsulfinyl* - 2 - *methyl* - 2 - *hydroxybut* - 3 - *ene* (**1a**). Isoprene and thiophenol were co-oxidized with oxygen to give a diastereomeric mixture of hydroxysulfoxide **1a**, as described.[3]

1 - *Phenylsulfinyl* - 2 - *methyl* - 2 - *acetoxybut* - 3 - *ene* (**1b**). A soln of **1a** (6.30 g; 30 mmole) in 40 ml Ac_2O and 40 ml pyridine was stirred during 5 days at 40°. The solvents were distilled off *in vacuo*, toluene was added and distilled from the mixture to remove Ac_2O and AcOH. The residue was dissolved in ether, washed with water and 5% HCl, dried over $MgSO_4$ and filtered through high-flow. After removal of the solvent, the residue was absorbed on silica and eluted with CH_2Cl_2/EtOAc = 1/1 to give the pure acetate as a diastereomeric racemate (6.64 g, 88%). ^1H NMR ($CDCl_3$): 7.40–7.80 (m, phenyl), 5.05–6.50 (m, C_3- and C_4-H), 3.35 and 3.40 (two s, C_1-H), 2.00 and 2.10 (two s, C_2-acetate), 1.75 and 1.80 (two s, C_2-*Me*). IR (neat): 1730, 1230, 1050 cm^{-1}.

1 - *Phenylthio* - 2 - *methyl* - 1,2 - *diacetoxybut* - 3 - *ene* (**2**). A soln of **1b** (5.04 g; 20 mmole) and dry NaOAc (5.0 g; 61 mmole) in 250 ml Ac_2O was refluxed at 130° during 8 hr. The mixture was concentrated *in vacuo*, suspended with cyclohexane and purified by filtration through silicagel. Evaporation of the solvent gave the diastereomeric racemate **2** as a clear oil. (4.88 g, 82%). ^1H NMR (CCl_4): 7.17–7.68 (m, phenyl), 6.50 and 6.60 (two s, C_1-H), 4.95–6.45 (m, C_3-H and C_4-H), 1.87 and 2.00 (two s, C_1- and C_2-acetate), 1.65 (s, C_2-Me). IR (neat): 1740, 1240, 1225 cm^{-1}.

1,1 - *Diacetoxy* - 2 - *methyl* - 2 - *phenylthiobut* - 3 - *ene* (**4**). A soln of **2** (4.00 g; 13.6 mmole) and 200 mg TsOH in 60 ml AcOH and 10 ml Ac_2O was stirred at r.t. during 4 hr. Water (100 ml) and pentane (100 ml) were added and after stirring during another hr the layers were separated and the water layer was extracted 5 times with pentane. The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to give **4** as a pure oil (3.92 g, 98%). Pure **4** decomposes gradually, it cannot be stored at r.t. ^1H NMR ($CDCl_3$): 7.20–7.60 (m, phenyl), 6.96 (s, C_1-H), 4.93–6.06 (m, C_3-H and C_4-H), 2.02 and 2.08 (two s, C_1-acetate), 1.38 (s, C_2-Me). IR (neat): 1740, 1240, 1200 cm^{-1}.

2 - *Methyl* - 2 - *phenylthiobut* - 3 - *enal* (**5**). Compound **4** (485 mg; 1.65 mmole) was dissolved in 15 ml MeOH and K_2CO_3 (683 mg; 4.95 mmole) was added. The mixture was stirred at r.t. during 30 min and poured into water. The water layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated to give 303 mg (96%) of pure **5**. ^1H NMR ($CDCl_3$): 9.38 (s, C_1-H), 7.17–7.45 (m, phenyl), 5.18–6.03 (m, C_3-H and C_4-H), 1.34 (s, C_2-Me). IR (neat): 1720, 1450, 755 cm^{-1}.

(E) - 4 - *Phenylthio* - 2 - *methylbut* - 2 - *enal* (**6**). Compound **5** (300 mg; 1.56 mmole) was exposed to daylight at r.t. The conversion to **6** was monitored by glc (column temp 160°). After 4 days,[g] the conversion was almost complete and **6** (261 mg, 87%) was isolated by column chromatography (silicagel, CH_2Cl_2). ^1H NMR: 9.35 (s, C_1-H), 7.15–7.40 (m, phenyl), 6.43 (t, C_3-H), 4.22 (d, C_4-H), 1.50 (s, C_2-Me). ^{13}C NMR:[h] 194.166 (C_1), 8.953 (C_2-Me). IR (neat): 1690, 1450, 750 cm^{-1}.

(E) - 4,4 - *Diacetoxy* - 3 - *methylbut* - 2 - *enol* (**8a**). Compound **4** (3.31 g; 11.25 mmole) was dissolved in 100 ml CH_2Cl_2 and cooled to −50° using an alcohol-dry ice bath. 85% MCPBA (2.51 g; 12.57 mmole, 1.1 eq.) was added and the mixture was stirred overnight at −20°. The mixture was filtered, allowed to

[e] **4** also decomposes slowly to **5** and Ac_2O when stored at r.t. in the dark. We assume that the equilibrium **4** ⇌ **3** ⇌ **5** + Ac_2O is shifted to the right when Ac_2O is not present in great excess.

[f] Rapid reaction of trimethylphosphite with α,β-unsaturated carbonyl compounds has been observed.[13]

[g] Longer irradiation times led to formation of phenyl disulfide.

[h] Both ^1H NMR[14] and ^{13}C NMR[15] prove the (E)-geometry.

reach r.t. and treated with 100 g silicagel, to which 10 ml water had been added previously. After 1 hr the diacetoxyalcohol (1.73 g, 70%) was isolated by column chromatography (silicagel, CH_2Cl_2). ^1H NMR ($CDCl_3$): 7.07 (s, C_4-H), 5.95 (t, C_2-H), 4.26 (d, C_1-H), 2.12 (s, C_1-acetates), 1.76 (s, C_3-Me). IR (neat): 3400, 1750, 1240, 1200 cm^{-1}. (Found: C, 53.29; H, 7.16; O, 39.55. Calc. for $C_9H_{14}O_5$ (202.20): C, 53.46; H, 6.98; O, 39.56%).

(E) - 1,1 - *Diacetoxy* - 2 - *methyl* - 4 - *chlorobut* - 2 - *ene* (**8b**). To a cooled mixture (0–5°) of 10 ml DMF and 30 ml benzene was added 1.35 g (10 mmole) $SOCl_2$ and 2.02 g (10 mmole) diacetoxyalcohol **8a** each dissolved in 20 ml benzene. The mixture was allowed to reach r.t. and the solvents were distilled off. Distillation (90°, 0.1 mm) of the residue gave pure **8b** (1.87 g, 85%). ^1H NMR ($CDCl_3$): 7.06 (s, C_1-H), 5.96 (t, C_3-H), 4.09 (d, C_4-H), 2.10 (s, C_1-acetates), 1.80 (s, C_2-Me). IR (neat): 1740, 1250, 1210 cm^{-1}.

(E) - γ - *Chloro tiglic aldehyde* (**9a**). Finely powdered NaOH (200 mg; 5 mmole) was added to a soln of **8b** (1.10 g; 5 mmole) in 25 ml MeOH. After stirring for 5 min, 150 ml CH_2Cl_2 was added and the soln was dried over $MgSO_4$. Evaporation of the solvents and distillation gave **9a** (570 mg, 95%), identical in all respects to the substance described by L. Re e.a.[5c]

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