Regioselective Protonation of Allyllithium Compounds☆

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By varying the general acid, the regioselectivity of the protonation of (triphenylsilyl)allyllithium (**1**) in diethyl ether in the presence of HMPT can be changed from 9:1 to 1:9 at room temperature. When other aprotic solvents are used, the nature of the lithium salt changes, and the selectivity decreases.

The regioselectivity of the protonation of the dithio-stabilized allyllithium **4** by water is highly dependent on the age of the allyllithium solution with α/γ ratios varying from 2.7:1 to 1:3.5.

The protonation of organometallic compounds is a frequently used reaction in organic chemistry. But the selectivity of this reaction is little understood. While promising results have been found for the protonation of prochiral organometallic compounds (enantioselectivity)[1], the diastereo- and regioselectivity[2] of such a protonation is even less understood.

In this work we have investigated the protonation of allyllithium compounds which are ambident systems. They can be protonated in α or γ position. If they are substituted unsymmetrically, protonation will lead to isomers.

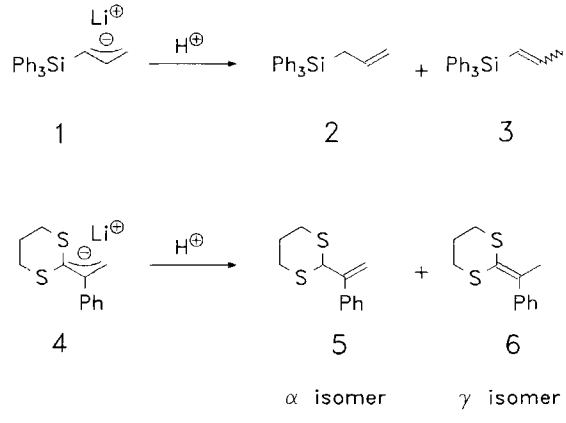
By using acids which are strongly sterically shielded, for instance concave acids[3], it is conceivable that this reaction may be sterically controlled. The α/γ selectivity of an α-substituted allyllithium should then be shifted towards γ protonation.

Two restrictions have to be obeyed. The substitution pattern of the allyllithium should be such that the accessibility of the α and γ position differs with the α position still being accessible to ordinary acids[4,5]. Furthermore, an acid-depending regioselectivity will only be observed when reagent-controlled protonation takes place. The alternative mechanism is a protonation via a protonated solvent molecule (a shuttle mechanism). In this case, the role of the acid is to protonate the solvent, in order to establish a high proton concentration. The protonating acid will always be the same, the protonated solvent.

In acid catalysis, these two types of mechanisms are well-known and are called specific and general acid catalysis[6]. Analogously, we therefore suggest the terms *specific* and *general protonation* by general and specific acids, respectively, to distinguish a reagent-controlled protonation from a protonation by protonated solvent molecules.

In this work, we have investigated the protonation of two allyllithium compounds **1** and **4**[7] by acids with different sterical demands in various solvents at room temperature[8]: (triphenylsilyl)allyllithium (**1**) and 2-(1-phenylethenyl)-1,3-dithian-2-yllithium (**4**)[9]. They are generated by reaction of allyltriphenylsilane (**2**)[10] and 2-(1-phenylethylidene)-1,3-dithiane (**6**)[11,12], resp., with *n*-butyllithium. The completeness of the deprotonation is checked by deuteration.

Scheme 1. The protonation of the allyllithium compounds **1** and **4** leads to the formation of α isomers **2** and **5** and γ isomers **3** and **6**, respectively. The structure of the allyllithium compounds is solvent-dependent (see below), they are therefore only depicted as ion pairs, although η^1 or η^3 binding of the lithium ion should be possible[13,14,15]



In principle, the protonation of (triphenylsilyl)allyllithium (**1**) can give three different products: α protonation will give the allyl, the 2-propenyl derivative **2**, whereas γ protonation will give the *trans*- and *cis*-1-propenyl, the methylvinyl derivative **3**[16]. Table 1 shows the α/γ ratios found for the protonation of **1**.

When the α/γ ratios of the protonation of the silyl-stabilized allyllithium **1** by varying proton sources in diethyl ether are compared, three classes of proton sources can be identified: (i) diethyl malonates prefer to protonate the α position by a factor of 9, (ii) the α/γ ratio is reversed to 1:9 when

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2,6-di-*tert*-butylphenol is used as acid, and (iii) with most proton sources, α/γ ratios between 2:1 and 1:2 are found. The nature of these proton sources is manifold: they are OH and CH acids, strong and weak ones.

Table 1. α/γ ratio (**2**:**3**) of the protonation of (triphenylsilyl)allyllithium (**1**) in diethyl ether in the presence of two equivalents of HMPT at 25°C

Acid	α/γ ratio [a, b] **2** : **3** [± 5]
Diethyl malonate	90 : 10
Diethyl methylmalonate	90 : 10 [c]
Diethyl ethylmalonate	84 : 16
Malononitrile	48 : 52
Triphenylmethane	47 : 53
H_2O	60 : 40
H_2SO_4	47 : 53
$F_9C_4SO_3H$	35 : 65
tert-Butyl alcohol	49 : 51
Phenol	50 : 50
2,6-Di-*tert*-butylphenol	10 : 90

[a] The reactions have been carried out with solutions of the acids but also in acidic buffers. These have been generated by addition of 0.2 equivalents of *n*-butyllithium to the acid solution. No change in α/γ ratio has been found. – [b] Determined by GC. – [c] At 20°C.

An explanation for the preference of the γ protonation by 2,6-di-*tert*-butylphenol may be the sterical shielding of the proton in this acid because with unsubstituted phenol a 1:1 ratio is found. The α selectivity found with the malonates is not obvious: only malonates show high preference to an α protonation whereas malononitrile gives a 1:1 ratio. Coordination between the allyllithium **1** and the carbonyl groups of the esters by the lithium atom may be the reason for this selectivity.

If steric reasons explain the preferred γ selectivity in the case of 2,6-di-*tert*-butylphenol, concave acids (or protonated concave bases, respectively)[3] should also lead to a small α/γ ratio. But in diethyl ether these proton sources are hardly soluble.

Therefore, a solvent change has been necessary. But the change from diethyl ether to other aprotic solvents influences the α/γ selectivities strongly. Table 2 shows the α/γ selectivity of the protonation of **1** in various solvents by those two proton sources which are the most selective ones in diethyl ether (see Table 1).

The largest range of selectivity (10:90 to 85:15) is obtained in diethyl ether. Especially the preference of the γ protonation by 2,6-di-*tert*-butylphenol vanishes when diethyl ether is replaced by other solvents.

When allyllithium **1** is generated in diethyl ether and then added to a proton source in dimethoxyethane, the results are not reproducible. Therefore, **1** has also been generated in dimethoxyethane and in other ethers (THF, dioxane). While a solution of **1** in diethyl ether is yellow, in all other solvents the solutions are red, indicating that the organolithium compounds probably form different aggregates[13,14,15]. The color change from yellow to red can also be achieved when more than two equivalents of HMPT is used in diethyl ether, suggesting a weaker covalent bonding in the red allyllithium compounds. In order to obtain high yields of γ protonated **3**, compound **1** has therefore to be protonated in diethyl ether, and concave acids cannot be used.

Table 2. α/γ selectivity (**2**:**3**) of the protonation of (triphenylsilyl)allyllithium (**1**) generated in diethyl ether in the presence of two equivalents of HMPT with 2,6-di-*tert*-butylphenol and diethyl ethylmalonate in various solvents at 25°C

Solvent	**2** : **3** [a] (2,6-di-*tert*-butylphenol)	**2** : **3** [a] (diethyl ethylmalonate)
Acetonitrile	75 : 25	90 : 10
THF	30 : 70	70 : 30
DMSO	66 : 34	78 : 22
Dioxane	15 : 85	70 : 30
Dimethoxyethane	15 : 85 [b] - 52 : 48 [c]	84 : 16 [b] - 53 : 47 [c]
Diethyl ether	10 : 90	85 : 15

[a] Determined by GC. – [b] The α/γ ratios are not reproducible. – [c] The anion solution has been prepared in dimethoxyethane instead of diethyl ether.

Besides the silyl-stabilized allyllithium **1** also the dithio-stabilized allyllithium **4** has been investigated in protonations by general acids. The reaction has been studied in various solvents including diethyl ether, but the measured α/γ selectivities of protonation are not reproducible. A more careful investigation of the protonation of **4** in THF by water reveals that the regioselectivity of the protonation depends on the age of the solution. Table 3 lists the α/γ ratios obtained for solutions of **4** as a function of time.

Table 3. Time dependence of α/γ ratios (**5**:**6**) and yields (**5** + **6**) after protonation of a HMPT-containing THF solution of **4** with water at 25°C

Age [min]	α/γ ratio [a] **5** : **6**	Yield [%] [a] **5** + **6**
40	73 : 27	69
60	53 : 47	62
130	36 : 64	51
185	29 : 71	44
240	22 : 78	44

[a] Determined by GC.

Although the α and γ products **5** and **6** are produced in ratios varying from 3:1 to 1:3.5, this time-dependent regioselectivity can hardly be exploited because the yield of **5** plus **6** was also time-dependent (69–44%). But the decreasing yield cannot explain the broad α/γ selectivity. If the decrease in yield of 25% is only attributable to the loss of one regioisomer, the 3:1 ratio (50% α, 19% γ) can only change to 1.3:1 (25% α, 19% γ). But a complete reversal of the α/γ selectivity is found. Therefore, also in this case it is probable that the aggregation of the organolithium compound determines the α/γ selectivity, and the time-depen-

dence of the selectivity should be caused by a change of the nature of the allyllithium aggregates with time.

Thus, α or γ regioisomers of **2** or **3** and **5** or **6** can be obtained in excess by a variation of the general acid and the reaction conditions (see Tables 1 and 3). But for a deeper understanding and a prediction of the regioselectivity of such protonations, the structures of the allyllithium compounds must be determined.

Experimental

Generation of Allyllithium Compounds **1** *and* **4**: Under nitrogen, 0.33 mmol of the starting materials **2** or **6** was deprotonated with 0.82 mmol of *n*-butyllithium at −70°C in the presence of HMPT in 5 ml of dry solvent. After 30 min at −70°C, the mixture was stirred at room temp. for additional 10−30 min or as listed in Table 3. The solution of **1** was clear and yellow when two equivalents (0.66 mmol) of HMPT were used in diethyl ether. With four equivalents (1.32 mmol) in diethyl ether or with two equivalents in DMF, dioxane, or THF, red solutions were formed. For the experiments listed in Table 3, **4** was generated in THF (1 h at −70°C, 30 min at room temp.).

Protonation of **1** *and* **4**: 0.50 mmol of the proton source was dissolved in 1.0 ml of the solvent listed in Table 2. In the experiments of Tables 1 and 3, diethyl ether was used. Under nitrogen at 25°C, 150 µl (10 µmol) of the allyllithium solution (see above) was added with stirring. The solution became colorless immediately. 1 ml of diethyl ether and 1 ml of a saturated sodium hydrogencarbonate solution were added, and the aqueous layer was extracted three times with diethyl ether. After concentration of the combined ethereal layers to dryness, the residue was dissolved in diethyl ether and analyzed by GC (OV 17/35 m, 200°C for 25 min, then heating at 10°C/min to 250°C).

When the yields were determined prior to deprotonation ca. 10 mg of trieicosane was added as internal standard. Unused allyllithium solutions were treated with D_2O to check completion of deprotonation by ^{1}H-NMR analysis (minimal degree of deuteration: **1** 90%, **4** 85%).

☆ Dedicated to Prof. *W. Tochtermann* on the occasion of his 60th birthday.

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[7] Whereas the allyllithium compounds **1** and **4** are formed by deprotonation with *n*-butyllithium, 9-ethenylidenefluorene cannot be deprotonated to give the allyllithium, but an *n*-butyl moiety is added to the alkene. This addition also occurs when *tert*-butyllithium is applied. Therefore, protonation experiments have only been carried out with the allyllithium compounds **1** and **4**.

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[16] In almost all investigated protonations only the *trans*-1-propenyltriphenylsilane (*trans*-**3**) has been found. 1.5−3% of *cis*-**3** are detected when amines are used as proton sources. In this case, amide anions are formed which probably are responsible for a *trans*/*cis* isomerization.

[176/94]