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A NEW ELONGATION REACTION OF THREE CARBON UNITS

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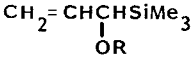
Summary: A new modification of Peterson reaction leading to elongation of three carbon units by treatment of aldehydes with titanium ate complex, prepared from 1-lithio-1-(1-alkoxy)allyltrimethylsilane and titanium(IV) isopropoxide, is described.

Peterson reaction[1] is recognized as an alternative procedure of Wittig reaction in olefin synthesis, and a few examples[2] have been reported using allylsilane carbanions. Nevertheless, these Peterson reactions have a severe limitation, because of difficulty controlling the reaction sites. Recently, Yamamoto,[3] Sato,[4] and coworkers independently reported regiospecific α-attack of allylsilane carbanions on carbonyl compounds, leading to formation of the corresponding dienes. However, no procedure has been reported, which controls the active site of carbanions of α-oxygenated allylsilanes in the reaction with carbonyl compounds. We describe herein that the titanium ate complex, $\mathrm{Li^+(Pr^iO)_4\text{-}Ti^-\text{-}CH_2CH{=}C(SiMe_3)OR}$ (1), prepared from 1-lithio-1-(1-alkoxy)allyltrimethylsilane and titanium(IV) isopropoxide [$\mathrm{Ti(OPr^i)_4}$],[5] has resulted in α-attack on a variety of aldehydes with very high regioselectivity to give the corresponding dienyl ethers in high yields.

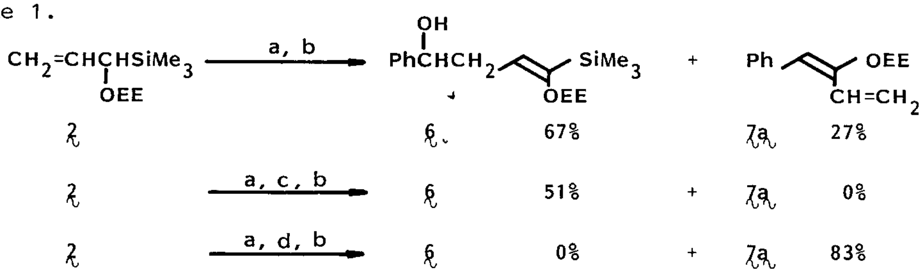
Four allylsilane reagents, 1-(1-ethoxyethoxy)- (2), 1-(1-tetrahydropyranyloxy)- (3), 1-methoxy- (4), and 1-_t_-butyldimethylsilyloxyallyltrimethylsilane (5)[6] were prepared, and their reactivity and selectivity were examined. Treatment of allyl trimethylsilyl ether with _s_-butyllithium (_s_-BuLi) at -78 °C afforded α-trimethylsilylallyl alcohol _via_ Brook rearrangement[7] (73%), which was converted in a usual manner into the desired ethoxyethyl (EE) ether (2)[8] (94%) and tetrahydropyranyl (THP) ether (3) (97%) as mixtures of diastereoisomers, respectively. The corresponding methyl (4) (∿10%) and _t_-butyldimethylsilyl (TBS) ethers (5) (74%) were prepared by _in situ_ reactions of the rearranged alkoxide with respective electrophiles ($\mathrm{Me_2SO_4}$ and TBSCl).


$\mathrm{CH_2{=}CH\underset{OR}{C}HSiMe_3}$

2 R=EE 3 R=THP
4 R=Me 5 R=TBS

The relevant Peterson reaction was examined with the EE ether (2) in details (Scheme 1). Reaction of the carbanion, generated by treatment of 2 with _s_-BuLi in tetrahydrofuran (THF) at -78 °C, with benzaldehyde gave the alcohol

Scheme 1.



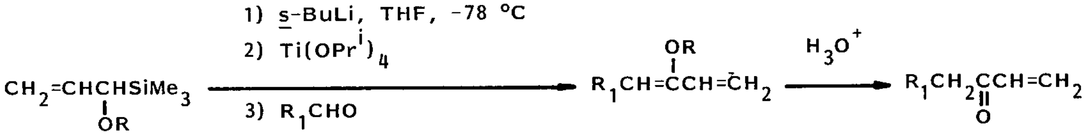
Reagents: a) s-BuLi, THF: b) PhCHO: c) HMPA: d) Ti(OPr^i)$_4$

(6) (67%) and the dienyl ether (7a) (27%), which were formed by γ- and α-attack, respectively. Addition of hexamethylphosphoric triamide (HMPA) to the carbanion led to formation of 6 (51%) as the sole isolable product, any trace amount of 7a being not detected. On the other hand, the ate complex (1, R=EE) prepared by addition of 1 equiv of Ti(OPr^i)$_4$ to the lithio allylsilane solution was treated with benzaldehyde to afford exclusively 7a (83%), no alcohol (6) formed by γ-attack being detected. This new reaction was generalized for various aldehydes (not ketones) (Table 1).

A new modification of Peterson reaction; a general procedure for the EE ether (2): To a solution of 2 (202 mg, 1 mmol) in THF (3 ml) was added a 1.3M solution of s-BuLi in cyclohexane (0.83 ml, 1.08 mmol) at -78 °C under stirring. The resulting dark brown solution was stirred at -78 °C for 30 min. To the solution was added dropwise a solution of Ti(OPr^i)$_4$ (284 mg, 1 mmol) in THF (1 ml), and the mixture was stirred for 45 min, when the color of the solution changed to bright orange. To this ate complex solution was added a solution of aldehyde (0.8 mmol) in THF (0.1 ml), and the reaction mixture was kept at -78 °C for 1 h and warmed gradually to 0 °C during a 3 h period and finally to room temperature during 14 h. The reaction was quenched by addition of water, and resulting precipitates were filtered through Celite and washed with ether thoroughly. The filtrate was concentrated to leave an oily residue, which was poured into saturated brine, and extracted with ether repeatedly. The extracts were washed with water, saturated aqueous NaHCO$_3$, and saturated brine, dried, and evaporated to leave an oily residue, which was separated by chromatography over silica gel (8 g) (1% ethyl acetate-hexanes as eluent) to provide the corresponding dienyl ether (7).

While the less hindered aldehydes (runs 1-3) reacts smoothly with the ate complex (1), reaction with the hindered one such as pivalaldehyde (run 7) proceeds only in poor yield because of steric hindrance.$^{9)}$ It is to be noted that only 1,2-addition reaction occurred in the case of cinnamaldehyde (run 5). Interestingly, the reaction in run 4 offered a single product equivalent

Table 1. A new Peterson reaction and acid hydrolysis



$$CH_2{=}CHCH(OR)SiMe_3 \xrightarrow[3)\ R_1CHO]{1)\ \underline{s}\text{-BuLi, THF, }-78\ °C\quad 2)\ Ti(OPr^i)_4} R_1CH{=}C(OR)CH{=}CH_2 \xrightarrow{H_3O^+} R_1CH_2C(=O)CH{=}CH_2$$

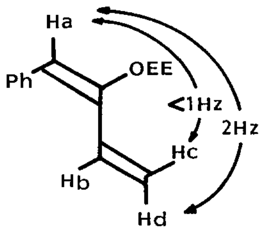
2 R=EE
3 R=THP
4 R=Me

7 R=EE
8 R=THP
9 R=Me

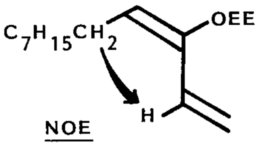
10

Run	reagent	aldehyde (R_1)	dienyl ether[a)]		vinyl ketone[a)]	
1	2	Ph	7a	83%	10a	∿100%
2	2	C_8H_{17}	7b	75%	10b	∿100%
3	2	cyclo-C_6H_{11}	7c	79%	10c	∿100%
4	2	CO_2Me[b)]	7d	68%		
5	2	PhCH=CH	7e	46%	10e	∿100%
6	2	C_4H_3O (furfural)	7f	42%	10f	63%
7	2	$(CH_3)_3C$	7g	0%		
8	3	Ph	8a	78%	10a	37%
9	3	C_8H_{17}	8b	79%	10b	49%
10	3	cyclo-C_6H_{11}	8c	96%	10c	40%
11	3	CO_2Me[b)]	8d	22%		
12	3	$(CH_3)_3C$	8g	0%		
13	4	Ph	9a	46%	10a	∿100%
14	4	C_8H_{17}	9b	32%	10b	∿100%
15	4	cyclo-C_6H_{11}	9c	32%	10c	∿100%

a) Isolated yields. b) T. R. Kelly, T. E. Schmidt, and J. G. Haggerty, Synthesis, 544 (1972).



^{1}H NMR ($CDCl_3$)
δ 1.24 (3H, t, J = 7 Hz)
1.51 (3H, d, J = 5 Hz)
3.5 - 4.1 (2H, m)
5.43 (H_d, dt, J = 11 & 2 Hz)
5.59 (1H, q, J = 5 Hz)
6.10 (H_c, br dd, J = 2 & 17 Hz)
6.31 (H_a, br s)
6.84 (H_b, dd, J = 11 & 17 Hz)



12.7% enhanced

Figure 1. ^{1}H NMR spectra of representative dienyl ethers

synthetically to labile "Nazarov's reagent,"[10] which has been useful in natural product synthesis.[11] It is also emphasized that each of these dienyl ethers is a single isomer concerning the configuration (E) of the newly formed double bond, as indicated by the NMR spectra (Figure 1). This stereochemical homogeneity could be rationalized reasonably by assuming the stereoselective approach of **1** to aldehydes, followed by *syn*-elimination of the resulting adducts with *erythro* configuration concerning the metallated oxygen and alkoxyl groups. While the THP (**3**) and the methyl ethers (**4**) gave the respective dienyl ethers (**8** and **9**) with E-configuration in rather low yields, the silyl ether (**5**) did not afford the expected products, probably because the lithiation of **5** would not occur under the conditions examined.

These dienyl ethers were easily hydrolyzed [2M HCl-THF (1:4), 0 °C, 4 h] to give the corresponding vinyl ketones (**10**) in high yields.[12] This reaction was successfully applied to the first synthesis of (±)-aplysin-20.[13]

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8) **2**: FI-MS, m/z 203 (M^+ + 1), 202 (M^+), 157, and 73; IR, 3080, 1630, 1255, 1130, 1090, 1000, 930, and 910 cm^{-1}; ^1H NMR ($CDCl_3$), δ 0.02 (9H, s), 1.16 (3H, t, J = 8 Hz), 1.27 (3H, d, J = 6 Hz), 3.3-3.7 (2H, m), 3.94 (1H, br d, J = 7 Hz), 4.69 (1H, q, J = 6 Hz), 5.9-6.1 (2H, m), and 5.77 (1H, m).

9) As the sole isolable product in the reactions using pivalaldehyde was obtained (3E,6E)-2,2,8,8-tetramethyl-3,6-nonadien-5-one, mp 57-60 °C, in 28% (run 7) and 12% (run 12) yields, respectively. The ate complexes (**1**) appear to be rather labile on standing at room temperature.

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