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단 신

치환된 Silylpropargylic Alcohol의 Ortho Ester Claisen 재배열반응의 입체 선택성에 관한 연구

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Stereoselectivity of the Ortho Ester Claisen Rearrangement of Substituted Silylpropargylic Alcohols

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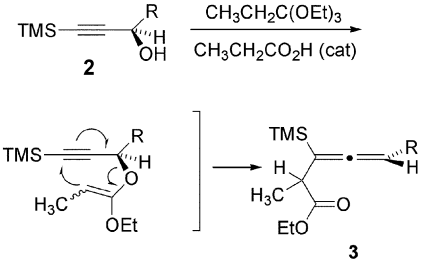
The ortho ester Claisen rearrangement has been very useful synthetic methodology in organic synthesis.[1] The ortho ester Claisen rearrangement of the propargylic alcohols has been very effective method for producing the corresponding allene esters of biologically significant.[2] Particularly the rearrangement involving a β-substituted vinyl participant is a potentially powerful reaction because a diastereomeric allene product may be generated. However, only one example yielding 1,3-disubstituted allenes by ortho ester Claisen rearrangement[3] has been examined using substituted secondary propynyl alcohols by Heathcocks group.[2c] His group was able to obtain high stereoselectivity (80-90% of the *syn* selectivity) of the rearrangement of the propynyl alcohol bearing a bulky alkyl group at C-1 position. The results are noteworthy due to the fact that the diastereoselectivity of the ortho ester Claisen rearrangement is generally moderate or poor because the mixture of E and Z of the vinyl moiety of the intermediate ketene acetal may be generated.[1,2c,4]

The ortho ester Claisen rearrangement of substituted silylpropargylic alcohols might be an efficient route to obtain the stereo-defined substituted silylallenes which has been very useful intermediates in organic synthesis.[5] Therefore, the study on the rearrangement of the 1-alkyl-3-silylpropynol **2** leading to the 1,3-disubstituted silylallenes **3** is reported in this paper.



To investigate the substitution effect of the rearrangement series of silylpropargylic alcohols with various R groups at C-1 position were prepared in good yields by the addition of the corresponding aldehydes to a solution of lithium silylacetylide in THF at -78 °C followed by warming to room tem-

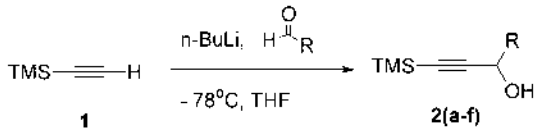


Table 1. Preparation of the silylpropargylic alcohols

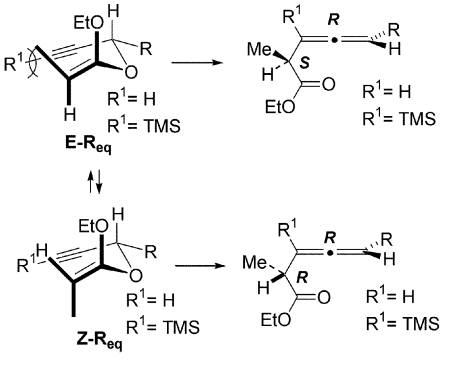
Entry	R group	Product	Yields (%)
1	methyl	2a	60
2	isopropyl	2b	81
3	*t*-butyl	2c	85
4	phenyl	2d	70
5	*p*-methoxyphenyl	2e	76
6	cyclohexyl	2f	91

perature. The results of the addition reactions are described in *Table* 1.

The substituted silylpropargylic alcohols were subjected to the orthoester Claisen rearrangement with triethylorthopropionate in the presence of a catalytic amount of propionic acid. Each was treated with **7** equivalents of triethyl orthopropionate in the presence of a catalytic amount of propionic acid and stirred at 80 to 120 °C. Yields and diastereoselectivities(ds) of the rearrangements are recorded in *Table* 2. The crude reaction mixtures were analyzed by capillary gas chromatography to obtain the ratio of the stereoselectivities. The diastereoselectivities of the ortho ester Claisen rearrangement of the substituted silanynols (entry 1-4) are observed to be poor in general except the cyclohexylynol case (entry 6). The yields of the rearrangement range fair to good except the *p*-methoxyphenyl case, which gave the decomposition compounds.

The result shows an interesting contrast against Heathcocks finding with the 1-alkylsubstituted propynols.[2c] He showed the increasing trend of the diastereoselectivity of the rearrangement as increasing the steric bulkiness at C-1. However, our result implicates that the steric bulkiness does not seem to affect the stereoselectivity with an exception of the cyclohexyl group case in the entry 6. Increasing temperature generally lowers the ratio of the selectivity.

Our results are contrasted with Heathcocks findings; When R^1 is replaced with H, the steric interaction between the two reacting centers of the rearrangement may be small favoring the stable E geometry and the *RS* isomer is produced predominantly as R^1 is more bulky. Comparing with his results, the poor selectivity in the entry 1-4 may be assumed that the transition state of the ketene acetal intermediates disfavors the E isomer (**E-Req**), that results in the mixture of E and Z geometry of the ketene acetals affecting the poor selectivity of the sillyallene esters.



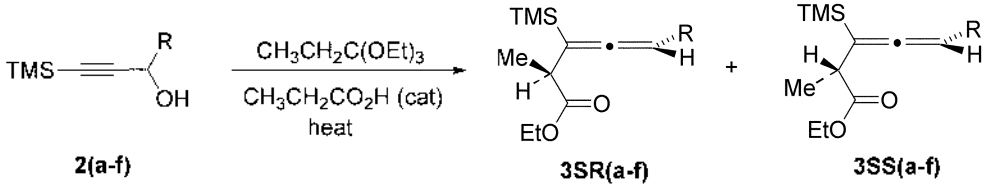
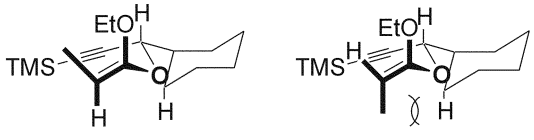


Table 2. The orthoester claisen rearrangement of the silylpropargylic alcohols

Entry	Reactant	R group	Temp (°C)	Time (hrs)	Product	Yield (%)	ds SR:SS
1	2a	methyl	80	12	3a	60	61:39
2	2b	isopropyl	120	4	3b	72	53:47
3	2c	*t*-butyl	80	4	3c	60	60:40
4	2d	phenyl	120	12	3d	56	55:45
5	2e	*p*-methoxyphenyl	80	12	3e	-	-
6	2f	cyclohexyl	80	5	3f	67	93:7

In the case of cyclohexyl substituent the major **3f**(*SR*) was obtained in the 93:7 ratio after 5 hours at 80 °C. Further reaction only resulted in decreasing selectivity. It was found that the selectivity was highly temperature dependent. Reaction at 150 °C for 12 hrs ended up with roughly 1:1 mixture of the diastereomers. The trend was observed in the entry 1-4, but only with a small degree. We are now not sure the origin of the high selectivity in the case of cyclohexyl substituent. We assume that E isomer of ketene acetal ($\mathbf{C_A}$) is probably favored due to the analogy that Z isomer ($\mathbf{C_B}$) might face the steric interaction between the vinyl methyl and cyclohexyl moiety more severely than the cases of other bulky substituents in the entry 1-4.



C_A (E-R_{eq}) C_B (Z-R_{eq})

In summary, these studies demonstrated the synthetic utility of the ortho ester Claisen rearrangement of 1-alkylsubstituted-3-trimethylsilylpropynol providing the corresponding diastereomeric silylallene esters, albeit in a limited scope of selectivity. We observed that TMS group at C-3 generally led to decreasing selectivity of the rearrangement as compared with the results of the corresponding ketene acetals (R^1=H) by Heathcocks group.[2c]

The cyclohexyl group is the most effective in the rearrangement, affording 93:7 ratio of the selectivity. The selectivity of the ortho ester Claisen rearrangement is observed to be highly temperature dependent; lowering temperature causes slightly increasing selectivity in general. The temperature dependence in selectivity is mostly observed in the case of cyclohexyl substituent.

EXPERIMENTAL SECTION

The typical procedure of the preparation of the ynols and the ortho ester Claisen rearrangement

1-Cyclohexyl-3-trimethylsilanyl-prop-2-yn-1-ol (2f). To a solution of 1.00 g (0.01 mmol) of trimethylsilylacetylene in 30 mL of THF was added 4.3 mL (0.011 mol) of 2.5 M n-BuLi in hexanes at -78 °C dropwise. The solution was stirred for 1 hr and 1.3 mL (0.011 mol) of freshly distilled cyclohexanecarboxaldehyde was added in one portion. The mixture was stirred for 1 hr and then allowed to warm to room temperature. Water was added. The organic layer was separated and extracted with ether three times. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with 5% ether in hexanes. Concentration gave 1.95 g (91%) of 2f: IR (neat) 3341, 2926, 2853, 2667, 2171, 1450, 1407, 1379,1250, 1084, 1032 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) 3.95 (1H, d, J=6.0 Hz, methine H), 2.80-1.80 (12H, m, hexyl Hs and OH), 0.12 (9H, s, $Si(CH_3)_3$) ppm;^{13}C NMR (200MHz, $CDCl_3$) 105.8, 90.1, 67.5, 50.0, 43.9, 28.4, 28.0, 26.4, 25.9, 0.01(3).

***rel*-(2S,4R)-5-Cyclohexyl-2-methyl-3-trimethylsilanyl-penta-3,4-dienoic acid ethyl ester(3f).** To 500 mg (2.38 mmol) of the propargylic alcohol **2f** was added 3.40 mL (16.7 mmol) of triethyl orthopropionate and 11 mg (0.14 mmol) of propionic acid. The solution was stirred for 5 hrs at 80 °C. The ratio of the diastereomeric allenic esters was determined by GC analysis (93:7). Ethanol and the excess ortho propionate were removed under reduced pressure. The residue was chromatographed on silica gel with 1% and 2% ether in hexanes to give 470 mg (67%) of allenic ester **3f**: IR (neat) 2926, 2853, 2178, 1937, 1736, 1449, 1248, 1177, 1100, 841 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 5.00 (1H, brt, vinyl H), 4.11 (2H, q, J=7.1 Hz, $-OCH_2CH_3$), 3.0 (1H, m, methine H), 1.00-2.00 (14H, CH_3CH- and hexyl Hs), 1.27 (3H, t, J=7.1 Hz, $-OCH_2CH_3$), 0.11 (9H, s, $-Si(CH_3)_3$)ppm; ^{13}C NMR (80MHz, $CDCl_3$) δ 205.4, 172.0, 128.4, 98.4, 94.7, 60.3, 40.0, 36.8, 33.4, 33.3, 26.2, 17.4, 14.1, 1.1(3); FAB$^+$ mass m/z 294.1.

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6. The major diastereomer of **3f** (91:9 from an attempt) was identified by conversion of **3f** to the alcohol **6** and compared with the alcohol from the Heathcock allene **5**. The direct desilylation of **3f** to **5** only resulted in a diene adduct.