CARBON-CARBON BOND FORMATION BY O → C REARRANGEMENT OF ALLYLIDENEOXYPHOSPHORANES

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Summary: A new O → C rearrangement reaction, which has been applied to the synthesis of squalene (Scheme I), has been shown to proceed by an intermolecular mechanism (Scheme II).

Reported herein is a novel rearrangement of allylphosphinic esters which proceeds via allylidenephosphorane intermediates with carbon-carbon bond formation, as exemplified by the overall transformation **1 → 2**. The rearrangement in this case was effected simply by sequential treatment of **1** with


1

2 R=H

3 R=CH₃
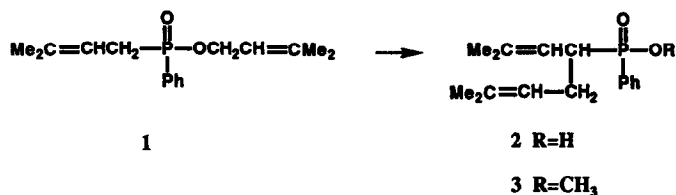
2 equiv of lithium disopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C for 5 min and 2 equiv of triisopropylsilyl (TIPS) triflate[1] at -78 °C for 30 min, and the product (**2**) was isolated extractively after quenching with water and acidification in 81% yield. Reaction of **2** with diazomethane in ether-ethanol afforded ester **3** (93%, as a mixture of two P/C$_\alpha$ diastereomers.[2,3] The following sequence was employed for the synthesis of **1**: [4]

4

1

5
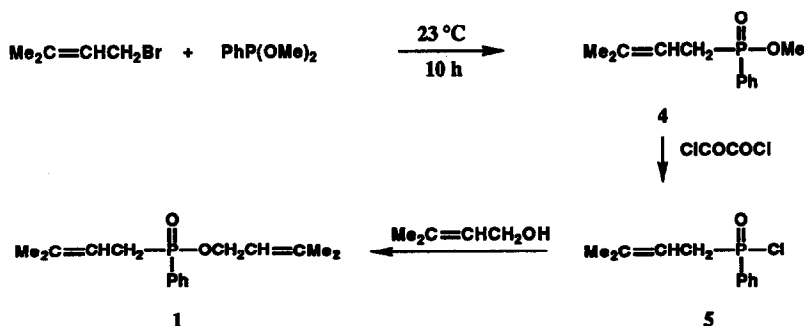
The rearrangement has been applied to a synthesis of squalene from farnesol as shown in Scheme I. Methyl E,E-farnesylphenylphosphinate (6) (from E,E-farnesyl bromide and dimethyl phenylphosphonite[4]) was converted directly to the corresponding acid chloride and thence with E,E-farnesol to 7. Rearrangement of 7 under the standard conditions outlined effected selective C_{15}-C_{15} coupling to form the TIPS ester 8 which was transformed into the corresponding morpholide 9. Although the removal of phosphorus from phosphonic acid derivatives is not well precedented,[5] it was possible to convert 9 to pure all E-squalene under the reductive conditions indicated in Scheme I.[6,7]

The mechanism of this interesting C-C bond forming rearrangement has been clarified by a variety of experiments as outlined in the following sections.

A. Methyl groups can migrate from O to C in the rearrangement. For example, treatment of the methyl ester 11 successively at -78 °C in THF with LDA and TIPS triflate produced the TIPS ester 12 in 91% yield as a mixture of two P/C_α diastereomers.

| 13 | 11 | 12 |
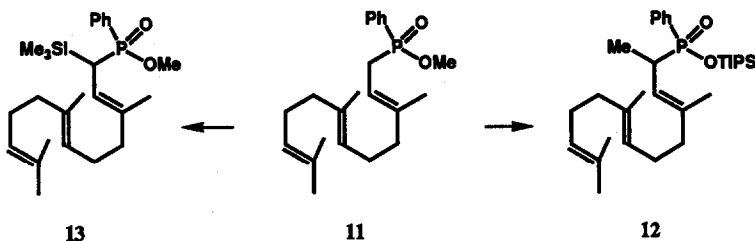
B. The use of trimethylchlorosilane instead of TIPS triflate after α-lithiation of 11 produces only α-silylated product 13. The formation of 13 may proceed by a direct C-silylation process or, more probably, via an initial O-silylation step.

C. Allylic groups migrate *without* allylic transposition. For example, reaction of the specifically dideuterated ester 14[8] sequentially with LDA and TIPS triflate at -78 °C in THF produced rearrangement product 15 exclusively (70% yield) and none of the isomeric 16, as determined by ^{1}H NMR analysis.

| 14 | 15 | 16 |
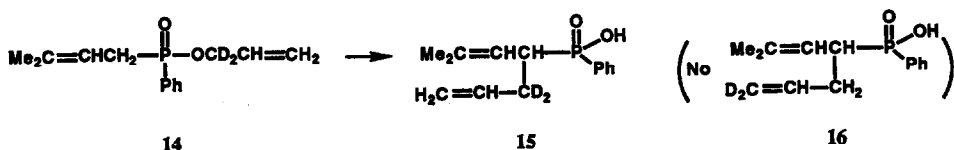
D. The formation of the O → C rearrangement product is not unimolecular as shown by crossover experiments. Thus, when a 1:1 mixture of 6 and 17 in THF at -78 °C was treated successively with LDA and TIPS triflate, there was obtained after hydrolysis, esterification with CH_2N_2 and silica gel chromatography a *ca.* 1:1 mixture of 18, R=CH_3, and 18, R=CD_3, and a *ca.* 1:1 mixture of 19, R=CH_3, and 19, R=CD_3, as determined by mass spectroscopic analysis (chemical ionization using NH_3). From this result it is clear that the migration from O to C is an intermolecular rather than an intramolecular process.

This result is not unexpected since an intramolecular rearrangement of methyl would be tantamount to a frontside S_N2 displacement.

6   17   18   19
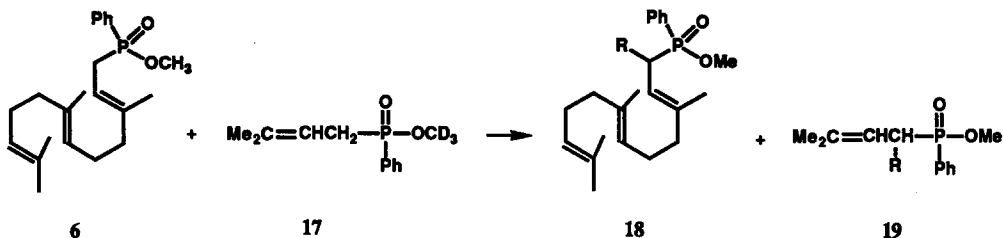
E. Tertiary carbon groups do not undergo O → C migration. Reaction of substrate **20** in THF at -78 °C successively with LDA and TIPS triflate affords only the α-silylated product **21** (as a mixture of two P/C$_\alpha$ diastereomers), possibly the result of O → C silyl migration.


20   21
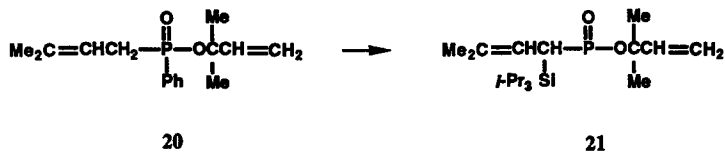
Scheme I
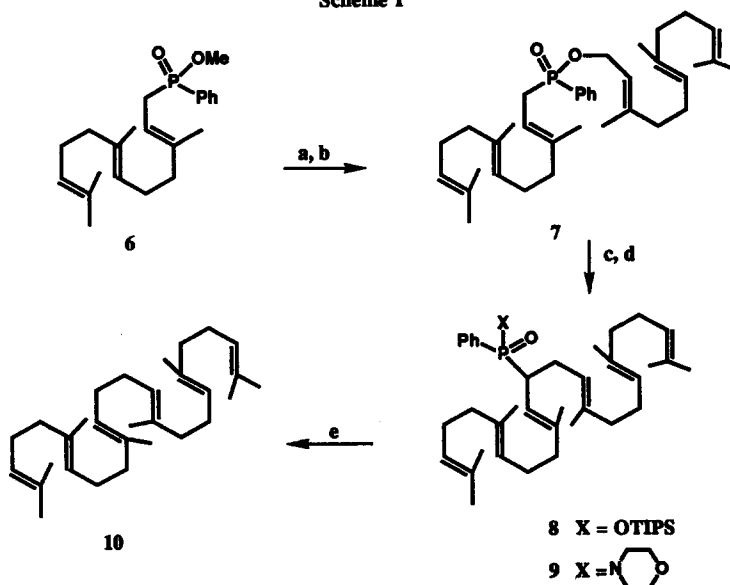
(a) 1.1 equiv of ClCOCOCl, CH$_2$Cl$_2$, 0 °C, 6 h; (b) *E,E*-farnesol (Aldrich Co.), 2 equiv Et$_3$N, CH$_2$Cl$_2$, 0 °C, 4 h (72% of **7**); (c) 2 equiv of LDA, THF, -78 °C, 2 equiv of TIPS triflate (65% of **8**); (d) 1.1 equiv of ClCOCOCl, then excess morpholine, CH$_2$Cl$_2$, 0 °C (73% of **9**); (e) excess Li in EtNH$_2$ - THF - *t*-BuOH, 0 °C 2.5 h (31% of **10** after column chromatography on silica gel).

It is likely that the O → C rearrangement occurs via an O-silyl allylideneoxyphosphorane (**22**, Scheme II) as a bimolecular event, either via the ion pair **23** + **24** or by a concerted double O→ C rearrangement process as symbolized by **25**. Although the latter possibility demands a greater loss of entropy, it cannot now be excluded.

Scheme II
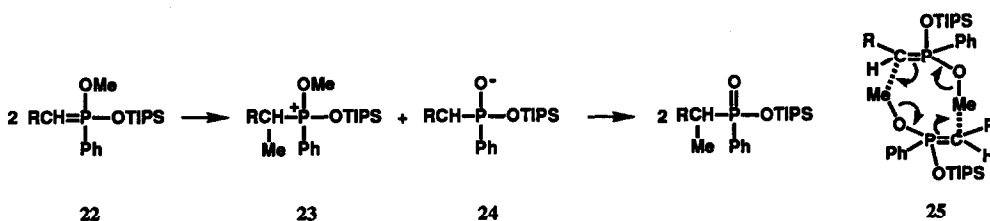
In summary, an interesting and synthetically useful reaction for carbon-carbon coupling is described which depends on the O-silylation of a phosphinate stabilized carbanion and a bimolecular double O → C rearrangement.[9]

References and Notes

1. E. J. Corey, H. Cho, C. Rucker, and D. H. Hua, *Tetrahedron Letters*, **22**, 3455 (1981).

2. Satisfactory ^{1}H NMR, infrared and mass spectral data were obtained for all new compounds using chromatographically purified and homogeneous samples.

3. An authentic sample of **3** was prepared in 61% yield by deprotonation of $Me_2C=CHCH_2$-$P(O)(C_6H_5)OMe$ (**4**) using LDA in THF and alkylation with 3,3-dimethylallyl bromide.

4. (a) A. Michaelis and R. Kaehne, *Chem. Ber.*, **31**, 1048 (1948); (b) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).

5. See (a) L. M. Harwood and M. Julia, *Synthesis*, 456 (1980); (b) L. Z. Avila and J. W. Frost, *J. Am. Chem. Soc.*, **111**, 8969 (1989).

6. Formed in addition to squalene were two dihydro derivatives (23% yield) (MH+ 413 by chemical ionization (NH_3) mass spectral analysis (squalene MH+ = 411)) and an unstable phosphorus-containing polar product (15-20%). R_f values (tlc silica gel, hexane) were 0.30 for squalene and 0.42 and 0.51 for the dihydro derivatives.

7. Squalene prepared from **9** was identical in all respects (IR, ^{1}H NMR, MS, TLC) with an authentic sample (Aldrich Co.).

8. Synthesized from $CH_2=CH-CD_2OH$ which was prepared as described by D. Hasselmann and W. Kirmse, *Chem. Ber.*, **105**, 859 (1972).

9. We are grateful to Ms. Ruth Stanaszek for some of the NMR work (^{13}C, ^{31}P and spin decoupling experiments), to Mr. Steven Cepa for GC-MS data, and to Ms. Mita De for HPLC analysis.

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