The Synthesis of Isoprenoid Ketones[1]

KIKUMASA SATO, SEIICHI INOUE, AND SATOSHI OTA

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Yokohama, Japan

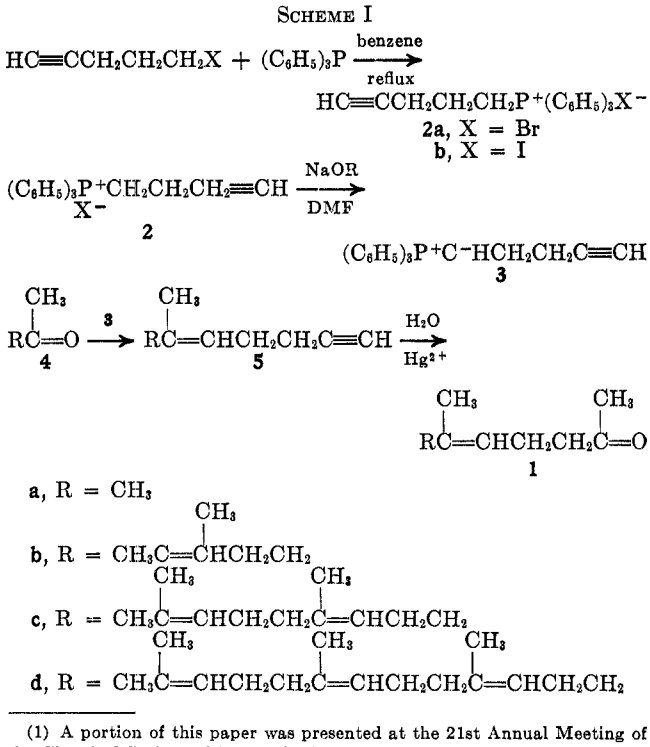
Received June 17, 1969

Pent-4-yn-1-ylidenetriphenylphosphorane (**3**) could be condensed with carbonyl compounds **4** to give the corresponding acetylenes **5**, which were converted by hydration into methyl ketones **1**. Thus, acetone was converted, *via* 2-methylhept-2-en-6-yne, into methylheptenone, which in turn gave, *via* 2,6-dimethylundeca-2,6-dien-10-yne, geranylacetone, and higher isoprenologs were successfully synthesized by this way *via* the intermediary acetylenes. However, stereoisomers on the double bond formed by the Wittig reaction were not separated and the condition for the stereoselective reaction could not be found.

Isler,[2] Kimel,[3] Saucy,[4] and Obol'nikova[5] have reported the syntheses of terpene alcohols and isoprenoid ketones (**1**). In these syntheses, polyprenyl alcohols or isoprenoid methyl ketones were prepared by repetition of many reactions steps. We have found that substituted acetylenes can be obtained from pent-4-yn-1-ylidenetriphenylphosphorane (**3**) and carbonyl compounds by application of the Wittig reaction and that the acetylenes are readily converted into isoprenoid ketones. Thus the synthesis of isoprenoid ketones can be more readily accomplished by Scheme I than by other methods previously described.

The phosphonium salt (**2a**) was initially prepared by the reaction of 5-bromo-1-pentyne with triphenylphosphine; however, both the yield of 5-bromo-1-pentyne by bromination of pent-4-yn-1-ol with phosphorous tribromide[6] and that of the phosphonium salt from the bromide and triphenylphosphine were poor. On the other hand, 4-pentyn-1-yltriphenylphosphonium iodide (**2b**) was obtained quantitatively by the reaction of 5-iodo-1-pentyne[7] with triphenylphosphine in benzene.

SCHEME I



The ylide (**3**) prepared from **2** and sodium ethoxide was not isolated but immediately allowed to react with methyl ketones (**4**) to give acetylenes (**5**). These acetylenes are not only the key intermediates for the synthesis of methyl ketones, but are also important for the stereospecific synthesis of isoprenoid alcohols.[8]

The hydration reaction of acetylenes is generally conducted in an acidic solvent. However, it is known that isoprenoid compounds such as pseudoionone and geranylacetone undergo cyclization by acid catalysis,[9,10] and so the hydration must be achieved under more diluted acidic condition. We have found that **5a–5d** are hydrated in weakly acidic solution to give **1a–1d** in good yield, and that the isomerization did not occur.

The products **5b** and **5c** and the methyl ketones **1b** and **1c** were mixtures of *cis* and *trans* isomers. Since the side chain of coenzyme Q is all *trans*, we attempted to separate the semicarbazones of **1b** and **1c**, but were unsuccessful.

Recently, Schlosser and Christmann[11] have reported conditions for obtaining the *trans* product selectively in the Wittig reaction. Their report includes no example involving the use of an aliphatic methyl ketone. When we applied their modification to the reaction of *n*-butylidenetriphenylphosphorane with methylheptenone, we noted no detectable increase in stereoselectivity. Furthermore, phosphonium salts and carbonyl compounds leading to more stabilized phosphoranes or betaines suitable for our purpose could not be found.

Experimental Section[12]

Starting Materials.—Pent-4-yn-1-ol was prepared by chlorination of tetrahydrofurfuryl alcohol[13] and subsequent treat-

(1) A portion of this paper was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April 1968.

(2) O. Isler and K. Doebel, *Helv. Chim. Acta*, **37**, 225 (1954).

(3) W. Kimel, J. D. Surmatis, J. Weber, G. O. Chase, N. W. Sax, and A. Ofner, *J. Org. Chem.*, **22**, 1611 (1957).

(4) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967).

(5) Geranyl-, farnesyl-, and geranylgeranylacetone were synthesized from methylheptenone, geranylacetone, and farnesylacetone, respectively, using 4,4-ethylenedioxypentyltriphenylphosphonium iodide as a Wittig reagent by Obol'nikova and coworkers [E. A. Obol'nikova, M. T. Yanotovskiĭ, and G. I. Samokhvalov, *Zh. Obshch. Khim.*, **34**, 1499 (1964); E. A. Obol'nikova, L. P. Davydova, L. N. Kaboshina, I. E. Valashek, M. T. Yanotovskiĭ, and G. I. Samokhvalov, *Probl. Org. Sin. Akad. Nauk SSSR, Otd. Obshchi. Tekhn. Khim.* 49 (1965).

(6) M. Olomucki, *Ann. Chim.* (Paris), **5**, 845 (1960).

(7) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(8) E. J. Corey, J. K. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967).

(9) F. Tiemann, *Ber.*, **31**, 807 (1898); H. A. van't Hof, J. U. Veenland, and Th. J. de Boer, *Tetrahedron*, **23**, 3757 (1967).

(10) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); V. A. Smit, A. V. Semenovskiĭ, and V. F. Kucherov, *Vopr. Khim. Terpenov i Terpenoidov, Akad. Nauk Lit. SSR, Tr. Vses. Soveshch., Vilnyus, 1959*. 185 (1960).

(11) M. Schlosser and K. F. Christmann, *Justus Liebigs. Ann. Chem.*, **708**, 1 (1968).

(12) All boiling points and melting points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a JEOL Model C-60H spectrometer as a *ca.* 20% solution in carbon tetrachloride with tetramethylsilane as an internal reference. Gas chromatography was carried out on a Shimazu Model GC-1C gas chromatograph using a 3 mm × 260 cm column of 25% silicon oil on Celite 545 with helium as the carrier gas.

(13) L. A. Brooks and H. R. Snyder, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 698.

ment of the chloride with sodium amide in liquid ammonia.[14] 5-Iodo-1-pentyne, bp 69–71° (30 mm), $n^{20}D$ 1.5358, was obtained from pent-4-yn-1-ol *via* the corresponding tosylate by the method of Eglinton.[7] *trans*-Geranylacetone (**4c**) was prepared by the following method. Geraniol (*trans* form), obtained from the mixture of geraniol and nerol by separating the calcium chloride adduct,[15] was brominated with phosphorous tribromide, and the bromide ($n^{20}D$ 1.4770) was allowed to react with the sodium derivative of ethyl acetoacetate; subsequent hydrolysis and decarboxylation gave *trans*-geranylacetone, bp 80.5–84.0° (0.45 mm), $n^{20}D$ 1.4678.[16] The other chemicals were commercially available.

4-Pentyn-1-yltriphenylphosphonium Iodide (2b).—The mixture of triphenylphosphine (52.5 g, 0.20 mol), freshly distilled 5-iodo-1-pentyne (38.8 g, 0.20 mol), and benzene (100 ml) was heated under reflux for 20 hr with stirring. The mixture was cooled and filtered, and the crystals were washed with benzene and dried *in vacuo*, yield 89.0 g (98%) of **2b**, mp 194–195°. Recrystallization from benzene–acetonitrile raised the melting point to 198–200°. The infrared spectrum showed absorption at 3250 (≡CH), 2100 (C≡C), and 1110 cm^{-1} (C–P).

Anal. Calcd for $C_{23}H_{22}PI$: C, 60.54; H, 4.86; P, 6.79. Found: C, 60.42; H, 5.15; P, 6.90.

4-Pentyn-1-yltriphenylphosphonium bromide (2a) was prepared by the procedure described above: yield 72%; mp 241.5–242.5° from benzene–acetonitrile; ir (KBr) 3170 (≡CH), 2100 (C≡C), and 1110 cm^{-1} (C–P).

Anal. Calcd for $C_{23}H_{22}PBr$: C, 67.49; H, 5.42. Found: C, 67.68; H, 5.69.

2-Methylhept-2-en-6-yne (5a).—N,N-Dimethylformamide (200 ml) was added slowly to sodium ethoxide (6.0 g, 88 mmol) with cooling in an ice bath, and the mixture was stirred until homogeneous. 4-Pentyn-1-yltriphenylphosphonium iodide (40.1 g, 88 mmol) was added to the mixture under nitrogen and the mixture was stirred at 0–2° for 2 hr. To the solution, maintained at 5–10°, acetone (4.6 g, 80 mmol) in N,N-dimethylformamide (20 ml) was added dropwise for *ca.* 1 hr. After the reaction mixture had been stirred at 10° for 2 hr, the mixture was allowed to stand overnight with cooling in an ice bath. The reaction mixture was filtered under suction, and the filtrate was poured into the mixture of ice-cold water (500 ml) and petroleum ether (bp 40–60°) (50 ml). After the petroleum ether had been separated, the aqueous layer was extracted four times with petroleum ether. The extract was washed with water and, after being dried over sodium sulfate, was slowly concentrated. The residue was distilled, giving 6.3 g (72%) of the product: bp 64–66° (80 mm); $n^{20}D$ 1.4450; d^{20}_4 0.7941 [lit.[17] bp 128–129° (760 mm), $n^{19}D$ 1.4418, d_{19} 0.7816]; ir 3300 (≡CH), 2100 (C≡C), and 1670 cm^{-1} (C=C); nmr 1.60 (3 H, *trans* CH_3), 1.67 (3 H, *cis* CH_3), 1.76 (1 H, C≡CH), 2.09 (4 H, CH_2CH_2), and 5.09 ppm (1 H, C=CH).

2,6-Dimethylundeca-2,6-dien-10-yne (5b).—Essentially the same procedure as described above for the preparation of **5a** was employed except that the filtrate of the reaction mixture was condensed under reduced pressure with the bath temperature maintained below 45° before it was poured into water and extracted with petroleum ether. From 24.6 g (54 mmol) of **1b** and 5.7 g (45 mmol) of methylheptenone there was obtained 6.1 g (64%) of **5b**: bp 79–84° (4 mm) [lit.[18] bp 93–99° (11 mm) in *trans* form]; $n^{20}D$ 1.4737; d^{20}_4 0.8344; ir 3300, 2100 (substituted acetylene), and 1670 cm^{-1} (trisubstituted ethylene); nmr 1.59, 1.67 (total 9 H, *trans* and *cis* CH_3), 1.78 (1 H, C≡CH), 1.98–2.03, 2.12 (total 8 H, CH_2CH_2), and 5.06 ppm (2 H, =CH). Gas chromatographic analysis at 100° and 30-ml/min helium flow showed two peaks with retention times of 13.6 (58%, *cis*-**5b**) and 14.9 min (42%, *trans*-**5b**).[19]

2,6,10-Trimethylpentadeca-2,6,10-trien-14-yne (5c) was similarly prepared in 84% yield by using *trans*-geranylacetone as C_{13} ketone: bp 95–100° (0.2 mm); $n^{20}D$ 1.4881; d^{20}_4 0.8550, *cis*/*trans* ratio 59:41.

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.58; H, 11.64.

2,6,10,14-Tetramethylnonadeca-2,6,10,14-tetraen-18-yne (5d) was prepared in 74% yield: bp 108–116° (0.01 mm); $n^{20}D$ 1.5004; d^{20}_4 0.8787.

Anal. Calcd for $C_{23}H_{36}$: C, 88.39; H, 11.61. Found: C, 88.24; H, 11.53.

The above two products showed the expected ir and nmr spectra.

6-Methylhept-5-en-2-one (1a).—To the mixture, maintained at 60°, of mercuric sulfate (0.2 g), sulfuric acid (0.8 g), methanol (30 ml), and water (10 ml), 2-methylhept-2-en-6-yne (2.2 g) in methanol (10 ml) was added dropwise with stirring for *ca.* 1 hr, and the mixture was stirred at 60° for an additional 2 hr. The reaction mixture was cooled to room temperature, diluted with ice–water (60 ml) containing a few drops of sodium bicarbonate, and extracted five times with ether. The extract was washed with water and dried over sodium sulfate. After the solvent had been removed, the residue was distilled at 77–79° (28 mm): yield 2.0 g (76%); $n^{20}D$ 1.4400 [lit.[20] bp 61–62° (12 mm); $n^{20}D$ 1.4408]; ir 2920 and 1710 cm^{-1}. The gas chromatography and the ir spectrum of the product were consistent with those of methylheptenone prepared from citral by heating with aqueous potassium carbonate.

6,10-Dimethylundeca-5,9-dien-2-one (Geranylacetone, 1b).—The hydration of **1b** (the mixture of *cis* and *trans* isomers, 4.4 g) was conducted in methanol (30 ml)–water (20 ml) containing mercuric sulfate (0.15 g) and sulfuric acid (0.3 g) to give geranylacetone: yield 4.0 g (80%); bp 71–74° (0.2 mm); $n^{20}D$ 1.4680 [lit.[21] bp 82–83° (0.8 mm); $n^{25}D$ 1.4658]. Glpc analysis at 180° and 20-ml/min helium flow showed two peaks with retention times of 13.9 (59%) and 14.8 min (41%), the latter being identical with that of authentic *trans*-geranylacetone.

Essentially the same procedure described above afforded the following ketones: **6,10,14-trimethylpentadeca-5,9,13-trien-2-one (farnesylacetone, 1c)**, bp 103–107° (0.1 mm), $n^{20}D$ 1.4835 [lit.[22] bp 107–109° (0.1 mm), $n^{20}D$ 1.4808], yield 83%; and **6,10,-14,18-tetramethylnonadeca-5,9,13,17-tetraen-2-one (geranylgeranylacetone, 1d)**, bp 155–160° (0.01 mm), $n^{20}D$ 1.4947 [lit.[23] bp 95–105° (0.002 mm), $n^{24}D$ 1.4872], yield 60%.

Registry No.—**1a**, 110-93-0; *cis*-**1b**, 3879-26-3; *trans*-**1b**, 3796-70-1; **1c**, 762-29-8; **1d**, 6809-52-5; **2a**, 22842-08-6; **2b**, 22842-09-7; **5a**, 22842-10-0; *cis*-**5b**, 22850-54-0; *trans*-**5b**, 22850-55-1; **5c**, 22842-11-1; **5d**, 22842-12-2.

(14) E. R. H. Jones, G. Eglinton, and M. C. Whiting, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 755.

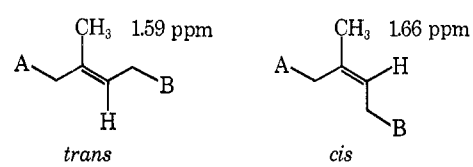
(15) O. Jacobsen, *Justus Liebigs Ann. Chem.*, **157**, 234 (1871).

(16) O. Isler, R. Rüegg, L. H. Chopard-dit-Jean, H. Wagner, and K. Bernhard [*Helv. Chim. Acta*, **39**, 897 (1956)] reported bp 124° (10 mm), $n^{20}D$ 1.465.

(17) G. Gamboni, H. Shinz, and A. Eschenmoser, *ibid.* **37**, 964 (1957).

(18) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *ibid.*, **40**, 1373 (1957).

(19) The *cis*/*trans* ratios were calculated with nmr spectra and gas chromatography. The configuration of trisubstituted olefin cannot be determined except by the nmr spectra. R. B. Bates and D. M. Gale [*J. Amer. Chem. Soc.*, **82**, 5749 (1960)] examined the nmr spectra of isoprenoid compounds; the assigned methyl protons are shown in the following formulas.



trans *cis*

A, B isoprene unit

(20) G. I. Samokhvalov, M. A. Miropol'skaya, L. A. Vakulova, and N. A. Preobrazhenskiĭ, *Zh. Obshch. Khim.*, **25**, 545 (1955); *J. Gen. Chem. USSR*, **25**, 515 (1955).

(21) F. Hoffmann-La Roche, British Patent 788,301 (1957).

(22) J. Weichet, L. Blaha, and V. Kvita, *Collect. Czech. Chem. Commun.*, **25**, 1914 (1950).

(23) O. Isler, R. Rüegg, L. H. Chopard-dit-Jean, A. Winterstein, and O. Wiss, *Helv. Chim. Acta*, **41**, 786 (1958).