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NEW SYNTHETIC ROUTES TO KETONES, HALOÖLEFINS, AND ACETYLENES USING ALDEHYDES AND PHOSPHONIUM YLIDES

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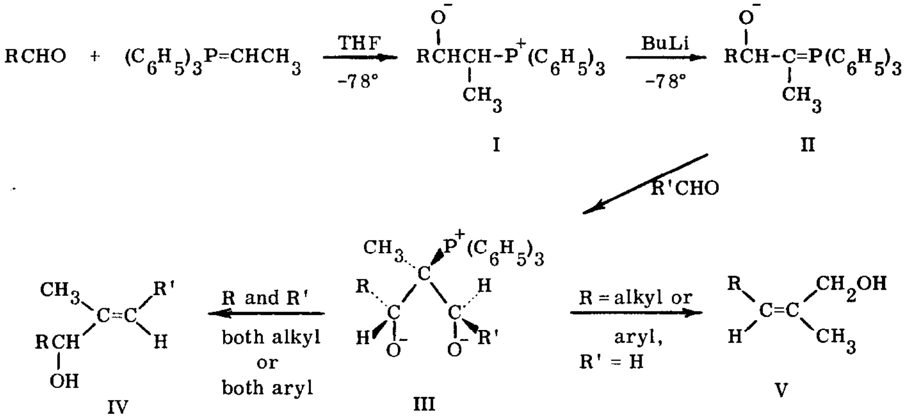
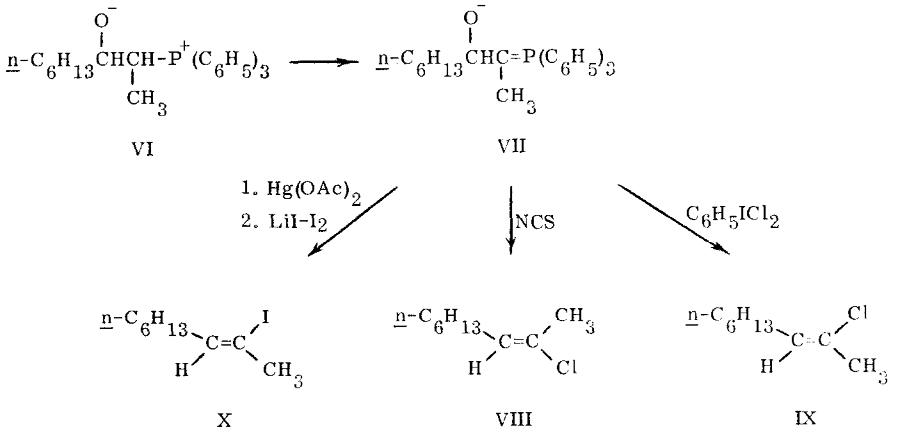
Recent research in these laboratories on the stereospecific synthesis of trisubstituted olefins (1) has yielded a new and extremely promising method (2) which is based on the following reaction sequence (3):



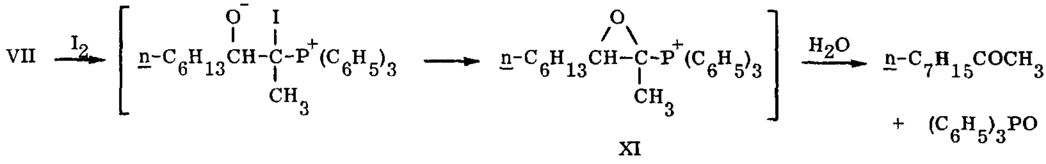
Among the various olefins obtained with high selectivity in a single step in this way were IV, R = R' = $\underline{n}$-C_6H_{13} or C_6H_5; IV, R = CH_3, R' = C_6H_{13}; IV, R = C_6H_{13}, R' = CH_3; and V, R = C_6H_{13} (2). The Wittig betaine I, generated in tetrahydrofuran at -78°, can be converted efficiently by $\underline{n}$-butyllithium at -78° to the corresponding β-oxido ylide II which undergoes a highly selective reaction with an aldehyde to form the β,β'-dioxido phosphonium ion III containing three chiral centers with relative configurations as shown (2). The remarkable stereospecificity and utility of these reactions prompted a study of the reactions of β-oxido phosphonium ylides such as II with other electrophiles which could provide additional routes to trisubstituted olefins. As indicated elsewhere (2), the alkylation reaction of II fails with most halides, and even in favorable cases such as methyl iodide, which affords alkylation product in ca. 50% yield, it is not stereospecific. The failure of the direct alkylation route to trisubstituted olefins suggested an alternative indirect process via iodo- or bromoölefins which can undergo alkyl-halogen replacement using anionic alkylcopper reagents (4). The synthesis of haloölefins by halogenation of β-oxido phosphonium ylides was therefore investigated. Publication of this study is prompted by the appearance of a paper by Schlosser and Christmann which also deals with aspects of the halogenation of β-oxido phosphonium ylides (5).

Reaction of a solution of ethylidenetriphenylphosphorane in tetrahydrofuran at -78° with heptanal for 5 min. (6) produced the betaine VI which was treated with an equivalent of n-butyllithium (in pentane) at -78° to form the deep red β-oxido phosphonium ylide VII. The solution of the ylide VII (which is stable in the range -78 to 0°) was allowed to warm to -30° and added to 1 equiv. of N-chlorosuccinimide at -78° leading to an immediate reaction as evidenced by decolorization of the deep red color of VII. After 2 hr. at -78° and 12 hr. at 30°, the reaction product was isolated (7). 2-Chloro-cis-2-nonene VIII was thereby obtained as the major product (yield ca. 50%) (8). The geometry of the olefinic substituents was established as in VIII by dechlorination of the chloroölefin using sodium in liquid ammonia at -78° to form cis-2-nonene containing only ca. 3% of the trans isomer (using gas chromatographic, infrared, and n.m.r. analysis) (9). Gas chromatographic (g.c.) analysis of the chloroölefin which had been isolated simply by passage over silica gel (solvent, 4 : 1 cyclohexane--ether) showed ca. 95% purity.

Surprisingly, the analogous reaction using iodobenzene dichloride as the reagent for chlorination followed a different stereochemical course. Thus, dropwise addition of the β-oxido ylide VII to a solution of 1 equiv. of iodobenzene dichloride in tetrahydrofuran at -78° afforded as major product (50% yield as determined by g.c.) 2-chloro-trans-2-nonene IX (8), the stereochemistry of which was demonstrated by conversion ($Na-NH_3$) (9) to trans-2-nonene. Analysis by g.c. of the total chloroölefin produced in the reaction of VII with iodobenzene dichloride showed it to contain IX and VIII in a ratio of 95 : 5. The stereochemical result obtained with iodobenzene dichloride corresponds to the course recently reported with this reagent in another case (5).



The reaction of the β-oxido ylide VII with a variety of brominating agents failed to produce appreciable amounts of bromoölefin. Nor did the reaction of VII with iodine lead to iodoölefin. However, in the case of the iodination reaction (at 0°) a pure product could be isolated readily which was shown to be methyl n-heptyl ketone (52% yield) by comparison with an authentic sample. This novel reaction would appear to involve the α,β-epoxy phosphonium derivative XI which could afford the ketone hydrolytically by a number of reasonable paths.



Despite the inaccessibility of iodoölefins from the β-oxido phosphonium ylide VII by reaction with iodine, an indirect, one-step process for preparing iodoölefin from VII could be devised. This consisted of addition of the ylide VII in tetrahydrofuran to a solution of 1.4 equiv. of mercuric acetate at -100° in tetrahydrofuran--hexamethylphosphoramide (10 : 3), warming to 25° and storage for 18 hr. to allow elimination of triphenylphosphine oxide, and finally, treatment of the resulting mixture successively with anhydrous lithium iodide (10 equiv.) and iodine (1.8 equiv.). After 20 hr. at 25° and isolation, 2-iodo-trans-2-nonene X (8) was obtained as the major product in ca. 40% yield. Analysis by g.c. indicated 98% of X and 2% of the geometrical isomer in the reaction product. Reduction of the iodoölefin so formed with sodium--liquid ammonia (9) produced trans-2-nonene and cis-2-nonene in a ratio of 95 : 5 (g.c. analysis). Since the iodine substituent in X is readily and stereospecifically replaced by alkyl using organocopper reagents (4), a new stereoselective route to trisubstituted olefins becomes available.

In summary, it has been shown that cis and trans chloroölefins can be generated stereoselectively by reaction of β-oxido phosphonium ylides such as VII with N-chlorosuccinimide or iodobenzene dichloride. Since such chloroölefins can be converted to acetylenic compounds by reaction with sodium amide in liquid ammonia, a route for the synthesis of acetylenes from aldehydes via Wittig reagents is established which could be useful in complex molecular synthesis. In addition, a novel one-step process has been developed for the conversion $RCHO \rightarrow RCH_2COR'$. Finally, a stereoselective route to iodoölefins and trisubstituted olefins from the joining of an aldehyde and a Wittig reagent becomes available. These new processes provide additional options and possibilities which should be useful in synthesis (10).

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2. E. J. Corey and H. Yamamoto, ibid., in press.
3. Other interesting new approaches to the synthesis of trisubstituted olefins have been described recently; see (a) D. J. Faulkner and M. R. Petersen, Tetrahedron Letters 3243 (1969); (b) S. F. Brady, M. A. Ilton, and W. S. Johnson, J. Am. Chem. Soc. 90, 2882 (1968); (c) R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, ibid. 90, 6224 (1968).
4. E. J. Corey and G. H. Posner, ibid. 89, 3911 (1967); 90, 5615 (1968).
5. M. Schlosser and K. F. Christmann, Synthesis 1, 38 (1969), have described the halogenation of β-oxido phosphonium ylides by perchloryl fluoride, iodobenzene dichloride, and bromine.
6. All reactions were conducted under an inert atmosphere.
7. The procedure involved concentration under reduced pressure, partitioning of the residual material between aqueous potassium carbonate solution (0.5%) and pentane, and drying and subsequent concentration of the pentane extract.
8. Analytical and spectroscopic data were in agreement with the assigned structure.
9. For the stereospecific dehalogenation of the chloroölefins, see M. C. Hoff, K. W. Greenlee, and C. E. Boord, J. Am. Chem. Soc. 73, 3329 (1951).
10. This work was assisted by grants from the National Science Foundation, the National Institutes of Health, and the Hoffmann-La Roche Co.