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ORGANIC REACTIONS AT HIGH PRESSURE. WITTIG REACTION OF HINDERED KETONES WITH NONSTABILIZED YLIDES.[1]

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Abstract: The Wittig reaction between n-butylidenetriphenylphosphorane and a series of cyclohexanones of increasing steric hindrance around the carbonyl group has been studied at 7 kbar and 15 kbar pressure (0.75-1.5 GPa) and at 40 °C. In all cases, except 2,2,6,6-tetramethylcyclohexanone and fenchone, 45-60% yields of olefins were obtained, in contrast to poor to no yields which were obtained under ambient conditions.

The application of high pressure to the Wittig reaction sequence, from formation of the alkyltriphenylphosphonium salt[2] to the reaction of the ylide with the carbonyl acceptor,[3] has been shown to strongly accelerate the rates of both reaction steps. In addition, the volume of activation of the Wittig reaction has been shown to be between -20 to -30 cm^3 mol^{-1} which suggests that Wittig reactions of slowly reacting ketones should be accelerated under high pressure conditions.[4] Recently, the study of the reaction of stabilized ylides with a variety of ketones at 9-10 kbar pressure showed that such reactions were accelerated under high pressure.[5] This report has prompted us to report a study of the reaction of non-stabilized ylides with a series of cyclohexanones which have increasing steric congestion around the carbonyl group and a diminution in reactivity.[6-9]

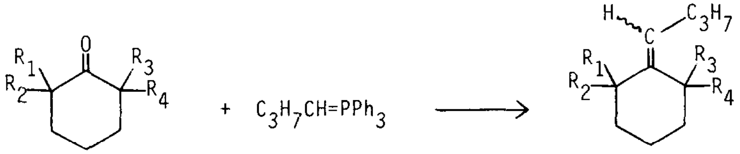
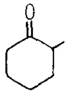
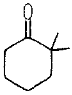
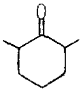
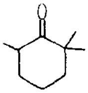
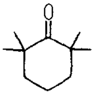
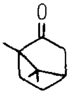
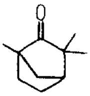


Table I

Wittig Reaction of Hindered Ketones with
n-Butylidenetriphenylphosphorane at High Pressure

Ketone	Reaction Conditions and Product Yields		
	1 bar, 48 h reflux	7 kbar, 48 h 40 °C	15 kbar, 48 h 40 °C
 1	35/35[a,b]	--	50/35
 2	35/40	--[c]	60/35
 3	5/65	50/20	45/25
 4	2/65	10/65	55/35
 5	--[c]	--[c]	5/85
 6	2/95	50/45	55/30
 7	--[c]	--[c]	5/80

[a] All reaction products gave satisfactory spectral and analytical data. [b] All yields quoted as % olefin/% starting material recovered. [c] All such entries mean reactions not run under listed conditions.

The series of ketones 1-7 has been studied with n-butylidenetriphenylphosphorane at low (1 bar) pressure in refluxing tetrahydrofuran and at high (7 kbar and 15 kbar) pressure in tetrahydrofuran at 40 °C. The starting reaction mixture was prepared by addition of 1.1 mL of 1.0 M potassium t-butoxide in THF to a suspension of 1 mmol of n-butyltriphenylphosphonium bromide in 1 mL of dry THF and the mixture stirred, under N_2, at room temperature for 10 min. A solution of 1 mmol of ketone in 1 mL of dry THF was added to the ylide mixture In the 1 bar experiment, the mixture was heated under reflux for 48 h. In the pressure experiments, the ylide-ketone mixture was transferred by syringe to a 8 x 1 cm Teflon® tube, the tube sealed, under N_2, by a clamp, and the tube placed in the high pressure reactor at 40 °C for 48 h. The processed reaction mixture was analyzed by capilliary gas chromatography and then separated by flash chromatography. The results are summarized in Table I.

Within the time period for the Wittig reaction studied, it was found in all cases there was a definite advantage in using high pressure. Even in the less hindered 2-methylcyclohexanone (1) and 2,2-dimethylcyclohexanone (2) which do react at ambient pressure, at 15 kbar the reaction yield is doubled. The more hindered ketones (3-7) basically showed little or no reaction at 1 bar conditions. At the 15 kbar conditions, 2,6-dimethyl- and 2,2,6-dimethylcyclohexanone (3 and 4) reacted well as did camphor (6).[10] The extremely hindered 2,2,6,6-tetramethylcyclohexanone (5) and fenchone (7) reacted only to the extent of a few percent and upon longer reaction time (72 h) the yield only increased negligibly.

Presently, high pressure reactors fall into the 7 kbar and the 15 kbar range, and thus, the effect at these pressures was evaluated.[11] In the cases of the hindered ketones 4, 5, and 7 which went well at 15 kbar, further study at 7 kbar pressure showed that 2,6-dimethylcyclohexanone and camphor reacted well at either pressure, but 2,2,6-trimethylcyclohexanone gave only a 10% yield at 7 kbar as compared to 56% at the higher pressure.

This problem of little or no reactivity of ylides with hindered ketones has also been studied by other investigators. It has been shown by the utilization of α-lithiomethylenetriphenylphosphorane[6,7] at low temperature (-20 °C to +25 °C) or by the employment of high temperatures (90-130 °C) with the ylides derived from potassium bases,[8] the methylenation reaction proceeds in excellent yield. These procedures have not been reported using other alkylidene ylides. To compare the low temperature procedure with the present high pressure results, n-butyltriphenylphosphonium salt was allowed to react under the Corey conditions[6,7] and the ylide derivative was allowed to react with 2,2,6-trimethylcyclohexanone. No olefin product was formed and mainly ketone was recovered. Under the same conditions, methyltriphenylphosphonium bromide and 2,2,6-trimethylcyclohexanone gave 25% of olefin and 50% of starting ketone.

The present study clearly shows that Wittig reaction of nonstabilized ylides run under high pressure conditions adds a new dimension to the utility of the synthetic sequence.

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References and Notes

1. This research was supported by National Science Foundation Grant No. CHE-8401434.
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10. An interesting, but expected, finding was the ratio of the two isomeric olefins in relation to the hindrance in the ketone. For 2-methylcyclohexanone the ratio was 70:30 while for 2,2-dimethylcyclohexanone and for camphor the ratio was 90:10. These ratios were determined by capilliary gas chromatography but the individual isomers could not be separated on a preparative scale. The epoxides obtained form the olefin mixture could be separated but the stereochemistry of these derivatives has not been able to be determined by standard NMR techniques.
11. For a similar study on other organic reactions, see Dauben, W. G.; Gerdes, J. M.; Look, G. C. *Synthesis* **1986**, 532.

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