

Synthetic and Mechanistic Aspects on the Wittig Reaction.

A Yield Increasing Modification

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In the Wittig reaction between ketones and methylenetriphenylphosphorane in ether, enolization of the ketone is shown to be an important side-reaction that in many cases decreases the yield substantially. To avoid this, repeated additions of stoichiometric amounts of water (to regenerate the ketone) and the phosphorane were made. In a typical example, the yield of olefin was raised from 38 to 89 % by this procedure.

The synthetic usefulness of the Wittig reaction is well documented.¹ In numerous cases however, the reported yields are surprisingly low especially when diethyl ether is used as solvent. For the simplest phosphorane (1), no explanation has been given for this disturbing fact (although in the case of sterically hindered² or highly basic³ phosphoranes, enolization of the carbonyl compound with concomitant aldol condensation has been reported; furthermore, epimerization of bicyclic ketones has been observed on Wittig reaction in DMSO⁴).

Several modifications of the original Wittig procedure have been suggested in order to increase the yields. α -Carbonyl phosphonate ylids have been used to circumvent the low reactivity of the corresponding phosphoranes towards ketones;⁵ Li-ion-free phosphorane solutions have been obtained in different ways and shown to be beneficial;⁶ as described in a recent publication from this laboratory,⁷ HMPA was used as a presumed Li-ion complexing agent, which gave a markedly increased yield in a single case (reaction of a long-chain hydroxy-ketone with methylenetriphenylphosphorane). This observation initiated the present investigation.

Some simple ketones which, according to the literature, gave low yields on reaction with methylenetriphenylphosphorane, were chosen for comparison. It soon turned out that the yields obtained by us in several cases were significantly higher than those reported for the same compounds* (see Table 1), and furthermore that the addition of HMPA had no effect with monofunctional ketones. Moreover, on careful analysis of the reaction mixtures (after aqueous work-up), it was found that formation of the desired olefin was incomplete and that the starting ketone was present^{8i,9} in all cases (roughly equivalent to the theoretical amount of expected non-olefinic material). This can be explained in at least two different ways.**

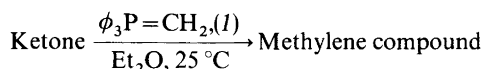
(i) Two competitive reactions can occur between the ketone and the phosphorane, leading to the expected betaine A and the lithium enolate B; the former then collapses to give the desired olefin and triphenylphosphine oxide. (ii) The betaine is stable under dry conditions but breaks down in two ways on addition of water, giving the olefin and regenerating the starting ketone.

The conversion of cyclooctanone to methylenecyclooctane was then chosen as a model system because of the low yield of olefin obtained along with a correspondingly large amount of

* We have no obvious explanation for this; however, we have found that heating of the reaction mixture (which has long been the general practice) gave lower yields than if the reaction was run at, or below, room temperature.

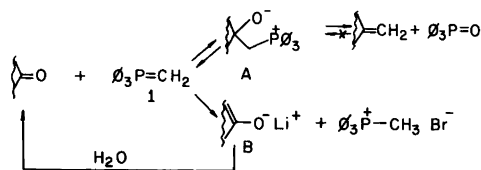
** Stirring methylenecyclooctane and triphenylphosphine oxide in ether at room temperature for 48 h did not yield any cyclooctanone, thus precluding a simple equilibrium condition.

Table 1. Yields in the reaction



Starting ketone	Yield of olefin %		Preparative	Recovered ketone % GLC ^a	Literature yield, % (Ref.)	
	NMR ^a	GLC ^a			GLC	Preparative
3,3-Dimethylcyclopentanone	44	—	27	25		56 (8a) ^b
Cyclohexanone	94	93	80 ^c	5	91 (6b) ^d 71 (8b) ^e	35–40 (8c) 48 (8d)
Cycloheptanone	100	96	72	6	38 (8b) ^e	5–10 (8e) ^f 40 (8f)
Cyclooctanone	38	44	29	55	—	5–10 (8e) ^f
Cyclononanone	—	36	—	54	—	—
2-Octanone	69	60	58	19	—	12 (8g) ^g
8-Pentadecanone	100	—	97	1	—	—
Acetophenone	80	73	62	15	—	74 (8d)
Benzophenone	—	—	99	0	—	84 (8h)
2,3-Benzo-2-cyclohexen-1-one	75	—	—	20	—	—
1,3-Diphenyl-2-propanone	9	—	—	87	—	h (8i)

^aQuantitative analysis with benzaldehyde or nonane as internal standard. ^bLiterature yield for 2,2-dimethyl-1-methylenecyclopentane. ^cContains some benzene. ^d*t*-BuO⁻K⁺ added. ^eNo Wittig reaction; 3-step *N*-ylid method. ^fPreparative GLC. ^gLiterature yield for 2-methyl-1-hexene. ^hThe calculation of the yield is inconclusive. DMSO was used as solvent.



Scheme 1.

“unreacted” ketone (see Table 1). To decide between the two different mechanisms indicated above, some simple experiments were performed:

(i) Low-temperature vacuum distillation of the reaction mixture (ketone–phosphorane, 1:1) before aqueous work-up gave a distillate containing the olefin but no ketone (GLC). The distillate contained the ketone when it was present in excess over the phosphorane. This clearly rules out the possibility that the betaine A is stable under dry reaction conditions as mentioned above.

(ii) Addition of trimethylsilyl chloride to the dry reaction mixture resulted in approximately equal amounts of olefin and 1-cyclooctenyltrimethylsilyl ether (GLC; less than 2% free cyclooctanone was present).

(iii) Reaction with the non-enolizable ketone benzophenone gave a practically quantitative yield of 1,1-diphenylethene.

(iv) On Wittig reaction with enolizable ketones, the re-formed phosphonium salt (*cf.* Scheme 1) was isolated in much higher yield than with benzophenone.

These results clearly indicate that competitive enolate formation is the main reason for the low yields of olefin sometimes encountered in Wittig reactions between ketones and methylenetriphenylphosphorane. Kinetic data on the base catalyzed enolization of ketones in ether may corroborate the present investigation. Unfortunately, no such data seem to be available for the series of ketones used here, but our data are in qualitative agreement with enolization rates for ketones in other solvents.¹⁰

The influence of solvent and temperature was also investigated with cyclooctanone. Running the reaction in tetrahydrofuran or dimethyl sulfoxide (instead of ether) gave no significant change in the yield of either the olefin or the recovered ketone. The reaction temperature turned out to have a slight influence on the olefin yield, showing a rather flat optimum at -10°C .

Since aqueous work-up of the reaction mixture regenerates the ketone (see Scheme 1), the addition of one equivalent of water forms the ketone while maintaining the “dry” reaction conditions.

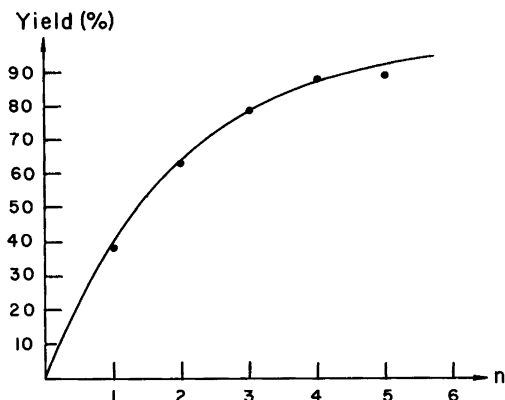
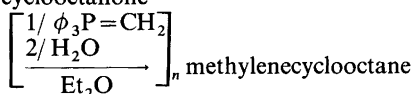


Fig. 1. Yields in the reaction cyclooctanone

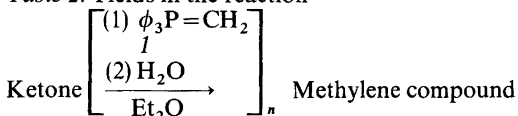


—, Theoretical curve.

●, Experimental values.

Addition of a new portion of the phosphorane gives a new portion of olefin and enolate in the same proportions as originally formed. These sequential water and phosphorane additions can be repeated until practically all of the ketone has been consumed, thus raising the olefin yield asymptotically towards 100% providing that side reactions such as aldol condensations do not interfere. A series of ketones which gave low yields of olefin in the standard procedure (see Table 1 and

Table 2. Yields in the reaction



Starting ketone	Total number of cycles <i>n</i>	Yield ^a of olefin %	Theoretical yield ^b of olefin %	Recovered ketone ^a %
Cyclooctanone	5	89	91	1
Cyclononanone	5	83 (73 ^c)	89	2
3,3-Dimethylcyclopentanone	5	76 ^d	94	0
2,3-Benzo-2-cyclohexen-1-one	3	90	98	4
1,3-Diphenyl-2-propanone	5	35 ^e (28 ^c)	38	55

^a By GLC. ^b Calculated by the mathematical expression shown above; based on the fraction of olefin formed after one cycle (a) as shown in Table 1. ^c Preparative yield. ^d The low yield indicates that a side reaction (probably aldol condensation) has taken place. ^e 15 cycles necessary to get > 75% yield.

the experimental section) were treated according to this method, and in all cases the olefin yield increased dramatically (see Table 2).

The final yield can be calculated using the simple mathematical expression: Yield of olefin (%) = 100[1 - (1 - a)ⁿ]; where *n* = number of cycles and *a* = fraction of olefin formed after one cycle.

Fig. 1 shows an example of the yield of olefin (methylenecyclooctane) after each addition of water - phosphorane. The yield curve follows quite closely the theoretical curve that has been constructed on the assumption that the fraction of olefin formed after one cycle is 0.4.

EXPERIMENTAL

¹H NMR spectra were run in CDCl₃/Me₄Si. IR spectra were run as liquid film. GLC was run on a 50 m SE-30 glass capillary column. High resolution mass spectra were recorded on a Varian MAT 311 instrument (Clinical Chemistry Department, University Hospital, Lund).

Quantitative analyses were performed by GLC and by ¹H NMR. Benzaldehyde (GLC and NMR) or nonane (GLC) were used as internal standards. The GLC data were computed by a Varian CDS 111 electronic integrator.

Standard procedure for the Wittig reaction (cf. Table 1). All equipment was thoroughly oven-dried. A 500 ml three-necked flask with N₂-inlet was charged with a suspension of triphenylmethylphosphonium bromide (30 mmol) in ether (200 ml). Butyllithium (30 mmol in hexane; standardized by the diphenylacetic acid method recently described¹¹) was added dropwise at room temperature with

magnetic stirring which gave a yellow solution of methylenetriphenylphosphorane (this solution is extremely reactive towards air).

The phosphorane formation seemed to be completed after *ca.* 30 min provided that the triphenylmethylphosphonium bromide was well pulverized. The ketone (27 mmol in 10 ml of ether) was added at room temperature after 4 h which gave a heavy precipitate in a slightly exothermal reaction. After 15 h, water (100 ml) was added with a syringe and the phases were separated. The aqueous phase was extracted with ether (2 × 50 ml) and the combined extracts were dried (Na₂SO₄) and filtered. Part of the ethereal solution (10 %) was removed and the internal reference compound (benzaldehyde or nonane) was added. The bulk of the ether was removed by distillation with a 30 cm Vigreux column. The residue was analyzed by GLC and ¹H NMR as described above. The preparative yield was determined by distillation or by column chromatography of the remainder (90 %) of the ether solution. The pure olefins obtained were used for calibration in the GLC and ¹H NMR analyses.

Procedure for the cyclic Wittig reaction (cf. Table 2). Methylenetriphenylphosphorane (12.5 mmol) was prepared in ether (80 ml) as described above and transferred by means of nitrogen pressure into a graduated dropping funnel. The ketone (2.25 mmol) was dissolved in ether (10 ml) in a 100 ml three-necked flask with N₂-inlet and magnetic stirring. Methylenetriphenylphosphorane (2.5 mmol) was added (2 min) to the ketone solution at room temperature (the reaction mixture became slightly yellow due to excess of phosphorane). Water (2.5 mmol) was added with a syringe after 15 min (the yellow colour disappeared) and the reaction mixture was stirred for another 15 min. Methylenetriphenylphosphorane (2.5 mmol) was added as described above, followed by a new portion (2.5 mmol) of water *etc.* When the desired number of phosphorane/water cycles had been performed, the reaction mixture was worked up as described above for the standard procedure.

Treatment of the reaction mixture (from cyclooctanone) with trimethylchlorosilane. Methylenetriphenylphosphorane (5 mmol) and cyclooctanone (4.5 mmol) were allowed to react as described above. The reaction mixture (40 ml) was cooled to -10 °C, and a mixture of trimethylchlorosilane (7.5 mmol) and triethylamine (7.5 mmol) was added. After 10 min, the temperature was raised to 15 °C. After 2 h, the reaction mixture was diluted with cold pentane (0 °C; 40 ml) and washed with cold, saturated NaHCO₃ solution (0 °C, 20 ml) followed by cold, saturated NaCl solution (0 °C, 20 ml). The organic phase was separated, dried (Na₂SO₄) and evaporated. The amounts of 1-cyclooctenyl trimethylsilyl

ether and methylenecyclooctane were determined by GLC.

Low-temperature vacuum distillation of the reaction mixture. A reaction mixture was prepared from cyclooctanone and methylenetriphenylphosphorane as described above and distilled (<0.01 mmHg; -10 °C → room temperature) using a liquid nitrogen-cooled condenser. Equimolar amounts of the reactants gave only *exo*-methylenecyclooctane in the distillate, whereas on using an excess of cyclooctanone, the ketone was also present in the distillate.

Characterization of olefins not previously described in the literature. 3,3-Dimethyl-1-methylenecyclopentane. ¹H NMR δ 4.79 (s, 2H, =CH₂); mass spectrum *m/e* (rel. intensity) 110 (M⁺, 18, C₈H₁₄), 95 (100, base peak), 81 (24). Anal. Calc. for C₈H₁₄: mol wt. 110.1095. Found: mol wt. 110.1085.

Methylenecyclononane. IR ν 3080, 1645, 890, 702 cm⁻¹; ¹H NMR δ 4.88 (s, 2H, =CH₂); mass spectrum *m/e* (rel. intensity) 138 (M⁺, 6, C₁₀H₁₈), 123 (16), 110 (20), 95 (75), 81 (91), 67 (100, base peak), 55 (92). Anal. Calc. for C₁₀H₁₈: mol wt. 138.1408. Found: mol wt. 138.1413.

2-Methyloct-1-ene. ¹H NMR δ 4.60 (s, 2H, =CH₂); mass spectrum *m/e* (rel. intensity) 126 (M⁺, 100, base peak, C₉H₁₈), 111 (97), 98 (96), 84 (89), 83 (81), 68 (77), 67 (74), 53 (80). Anal. Calc. for C₉H₁₈: mol wt. 126.1408. Found: mol wt. 126.1401.

2-Heptylnon-1-ene. IR ν 3080, 1650, 892 cm⁻¹; ¹H NMR δ 4.73 (s, 2H, =CH₂); mass spectrum *m/e* (rel. intensity) 224 (M⁺, 7, C₁₆H₃₂), 140 (18), 125 (53), 112 (44), 97 (47), 84 (95), 83 (76), 70 (78), 69 (100, base peak). Anal. Calc. for C₁₆H₃₂: mol wt. 224.2503. Found: mol wt. 224.2497.

1-Methylene-2,3,4-trihydronaphthalene. IR ν 3100, 3080, 3030, 1695, 1637, 890, 780, 740 cm⁻¹; ¹H NMR δ 5.49, 4.95 (s, 1 H each, =CH₂); mass spectrum *m/e* (rel. intensity) 144 (M⁺, 83, C₁₁H₁₂), 129 (100, base peak), 115 (40). Anal. Calc. for C₁₁H₁₂: mol wt. 144.0939. Found: mol wt. 144.0960.

2-Benzyl-3-phenylpropene. IR ν 3098, 3075, 3040, 1651, 1610, 1502, 1561, 1083, 1039, 903, 755, 706 cm⁻¹; ¹H NMR δ 7.26 (s, 10 H, arom. H), 4.90 (s, 2H, =CH₂), 3.31 (s, 4H, φ-CH₂-); mass spectrum *m/e* (rel. intensity) 208 (M⁺, 48, C₁₆H₁₆), 193 (21), 179 (13), 178 (14), 130 (23), 129 (27), 117 (92), 115 (100, base peak), 91 (88). Anal. Calc. for C₁₆H₁₆: mol wt. 208.1252. Found: mol wt. 208.1216.

Acknowledgements. We are grateful to Professor Börje Wickberg for valuable suggestions. This work was supported by the Swedish Natural Science Research Council.

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Received April 22, 1980.