Ketone Methylenation Using the Tebbe and Wittig Reagents – A Comparison

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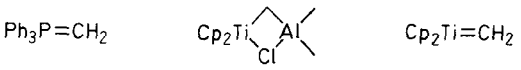
Ketone methylenation has been accomplished using the Tebbe and the Wittig reagents. Comparison of the two reagents for a variety of ketones shows that the Tebbe reagent gives better product yields than the Wittig reagent. This is particularly important when the ketone substrate is hindered. It is also noted that the Tebbe reaction accomplishes methylenation in a non-basic medium, thus racemization does not take place on substrates with enolizable chiral centers.

The simplest Wittig reagent, methylenetriphenylphosphorane (**1**), has seen extensive use for forming terminal alkenes.[1-4] Although other approaches for methylenation have been developed,[5-9] the Wittig procedure and its modifications[10-11] remain the most widely used methods. Following the initial reports by Tebbe and co-workers,[12] we explored the methylenating properties of the titanium–aluminum methylidene complex **2** – the Tebbe reagent.



1 **2** **3**

Our initial efforts addressed ester methylenation[13,14] a process not normally accomplished by the Wittig reagent.[15,16] However, we[14] and others[12,17] also recognized that the titanium methylidene was effective in methylenating the carbonyl groups of aldehydes and ketones.

Carbonyl methylenation by organometallic compounds containing titanium is currently receiving considerable attention.[18-21] However, **2** appears to be the only titanium reagent that has been well characterized. It's activity is associated with the titanium methylidene **3**.[12,19,22]

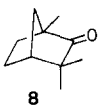
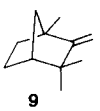
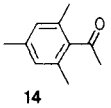
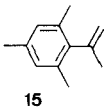
The Tebbe reagent **2** is a deep maroon solid sensitive to air and water. The reagent is soluble in toluene and benzene and stable indefinitely as stock solutions in those solvents. Handling and reactions of the reagent are carried out by standard inert atmosphere methods.[23] Methylenation is accomplished by mixing the reagent solution with the ketone dissolved in tetrahydrofuran.

The Wittig reagent **1** is prepared by adding methyltriphenylphosphonium bromide to sodium hydride in dimethyl sulfoxide. The pure ketone is then added. Reactions are carried out under an inert atmosphere.

Of interest to the synthesis chemist is how a new method compares with established procedures. The Wittig method does have limitations.[1] Specifically, it is of limited utility with hindered substrates[6,24,25] and its basic character often limits the use with enolizable or other base sensitive groups.[1,3,26] Grubbs and co-workers have shown that the latter factor is not a problem using **2** and its metallacycle analog.[17]

The results of methylenation of a series of ketones are recorded in the Table. The data show that in all cases studied, the Tebbe reagent **2** is comparable to or more effective than the Wittig reagent **1**. The value of **2** is particularly obvious when substrates become more hindered. Thus the terpenoid compound fenchone (1,3,3-trimethyl-2-norbornanone, **8**), which is almost unreactive in the Wittig procedure, can be methylenated by **2**. Similarly, the hindered 2,4,6-trimethylacetophenone (**14**) leads to a considerably better yield using **2**. Furthermore, methylenation using the Tebbe reagent is quite rapid; typically the reaction is complete within minutes of mixing the reagent and substrate.

Table. Comparison of Ketone Methylenation using the Tebbe and Wittig Reagents

Ketone	Product	Yield (%)	
		Tebbe	Wittig
 **4**	 **5**	97	89
 **6**	 **7**	96	80
 **8**	 **9**	16	5
 **10**	 **11**	93	90
 **12**	 **13**	98	88
 **14**	 **15**	77	4
 **16**	 **17**	99	89
 **18**	 **19**	98	91
 **20**	 **21**	96	80
 **22**	 **23**	97	46
 **24**	 **25**	63	38

An important example of the advantage of **2** for methylenation has been provided by Ireland and co-workers.[27] They attempted the Wittig methylenation of a carbonyl group adjacent to a chiral center in their synthesis of Lasalocid A. Poor yields of the racemized product were obtained. By contrast, the use of **2** gave a good yield of the desired product without racemization.

One might question the ease of using air sensitive **2** as a general reagent. However, it is similar to handling alkyllithium and Grignard reagents, procedures with which all chemists are familiar. In fact, best results are also obtained for the Wittg reaction when procedures are carried out under an inert atmosphere.[1-4] In this work the Tebbe reagent was prepared by the method of Tebbe.[12] It is also commercially available[28] or it can be prepared by various in situ methods.[29-31]

Reaction solvents toluene, benzene, and THF are dried and deoxygenated by distillation from sodium-benzophenone ketyl. DMSO is distilled from CaH_2. The ketone substrates used in this study are commercially available and are distilled if necessary for purification. They are dried and freed of oxygen by degassing. All reactions are carried out under conditions free of oxygen and moisture in an inert atmosphere dry box or on a vacuum line using Schlenk apparatus.

Product yields are based on isolated material. ^{1}H-NMR spectral data are from a Varian EM-390 spectrometer using CCl_4 as solvent and TMS as the internal standard.

The Tebbe reagent **2** is prepared by the method of Tebbe[12] or obtained commercially.[28] It is used as a 0.5 M solution in toluene or benzene.

The Wittig reagent **1**: NaH (0.24 g, 0.01 mol) is added to DMSO (5 mL) and the slurry heated to 75–80° for 30–45 min. After cooling to r.t., methyltriphenylphosphonium bromide (3.6 g, 0.01 mol) in DMSO (10 mL) is added. After about 1 h, the reagent (0.67 M) is ready for use. It is freshly prepared each day.

The Tebbe Reaction; General Procedure:
To a solution of ketone (0.001 mol) in THF (2–3 mL) at 0 °C is added a toluene or benzene solution of the Tebbe reagent (2 mL of 0.5 M solution, 0.001 mol). The mixture is allowed to warm to r.t. and after about 15 min, Et_2O (15–20 mL) is added. Then 5–10 drops of aq NaOH (0.1 M), is slowly added while stirring the mixture. After gas evolution ceases, the mixture is dried (Na_2SO_4) and filtered using a Celite pad. Rotary evaporation of the solvent provides the crude product which is purified by column chromatography using alumina and an eluent of 2% Et_2O in pentane or petroleum ether. For the more volatile products, gas chromatography separation can be used.

The Wittig Reaction; General Procedure:
The ketone (0.001 mol) is added to the Wittig reagent solution (15 mL of 0.067 M, 0.001 mol). After stirring at r.t. overnight, H_2O (30 mL) and pentane (30 mL) are added and the organic layer separated. After further extraction with pentane and washing with H_2O, the organic layer is dried (Na_2SO_4) and the crude product recovered by rotary evaporation. If necessary, products can be further purified by chromatography as described above.

2,6-Dimethylmethylidenecyclohexane **(5)**: bp 147–148 °C.

HRMS: *m/z*, C_9H_{16}, calc. 124.2254, found 124.1253.

^{1}H-NMR (CCl_4/TMS): δ = 1.0 (d, 6 H, J = 6 Hz, CH_3), 1.3–2.2 (m, 8 H, ring), 4.5 (s, 2 H, $=CH_2$).

2-tert-Butylmethylidenecyclohexane **(7)**[30]:

^{1}H-NMR (CCl_4/TMS): δ = 0.9 (s, 9 H, $C(CH_3)_3$), 1.0–2.2 (m, 9 H, ring), 4.6 (d, 1 H, J = 1 Hz, =CH), 4.7 (d, 1 H, J = 1 Hz, =CH).

1,3,3-Trimethyl-2-methylidenebicyclo[2.2.1]heptane **(9)**[17]:

^{1}H-NMR (CCl_4/TMS): δ = 1.0 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 1.2 (s, 3 H, CH_3), 1.2–1.9 (m, 7 H, ring), 4.4 (s, 1 H, =CH), 4.5 (s, 1 H, =CH).

2-Phenylpropene **(11)**[14]:

^{1}H-NMR (CCl_4/TMS): δ = 2.1 (s, 3 H, CH_3), 5.0 (s, 1 H, =CH), 5.1 (s, 1 H, =CH), 7.0–7.4 (m, 5 H_{arom}).

2-(2-Methylphenyl)propene **(13)**[32]:

HRMS: *m/z*, $C_{10}H_{12}$, calc. 132.2048, found 132.0940.

^{1}H-NMR (CCl_4/TMS): δ = 1.8 (s, 3 H, vinyl-CH_3), 2.1 (s, 3 H, $ArCH_3$), 4.6 (d, 1 H, J = 1 Hz, =CH), 4.9 (d, 1 H, J = 1 Hz, =CH), 6.8 (m, 4 H_{arom}).

2-(2,4,6-Trimethylphenyl)propene **(15)**: bp 192–193 °C.

HRMS: *m/z*, $C_{12}H_{16}$, calc. 160.2584, found 160.1247.

^{1}H-NMR (CCl_4/TMS): δ = 1.9 (s, 3 H, vinyl-CH_3), 2.2 (m, 9 H, Ar–CH_3), 4.6 (d, 1 H, J = 1 Hz, =CH), 5.1 (d, 1 H, J = 1 Hz, =CH), 6.6 (s, 2 H_{arom}).

2-Phenyl-1-pentene **(17)**[33]:

HRMS: *m/z*, $C_{11}H_{14}$, calc. 146.2316, found 146.1096.

^{1}H-NMR (CCl_4/TMS): δ = 0.9 (m, 3 H, CH_3), 1.4 (m, 2 H, CH_2), 2.4 (m, 2 H, CH_2), 5.0 (s, 1 H, =CH)), 5.1 (s, 1 H, =CH), 7.1 (m, 5 H_{arom}).

3-Methyl-2-phenyl-1-butene **(19)**[34]:

HRMS: *m/z*, $C_{11}H_{14}$, calc. 146.2316, found 146.1098.

^{1}H-NMR (CCl_4/TMS): δ = 1.1 (d, 6 H, J = 8 Hz, CH_3), 2.7 (hept, 1 H, J = 8 Hz, CH), 4.9 (d, 1 H, J = 2 Hz, =CH), 5.0 (d, 1 H, J = 2 Hz, =CH), 7.1 (m, 5 H_{arom}).

3,3-Dimethyl-2-phenyl-1-butene **(21)**[14]:

^{1}H-NMR (CCl_4/TMS): δ = 1.1 s, 9 H, CH_3), 4.7 (d, 1 H, J = 2 Hz, =CH), 5.1 (d, 1 H, J = 2 Hz, =CH), 6.8–7.2 (m, 5 H_{arom}).

1,1-Diphenylethene **(23)**[35]:

^{1}H-NMR (CCl_4/TMS): δ = 5.3 (s, 2 H, $=CH_2$), 7.2 (s, 10 H_{arom}).

2-Methyl-3,3-diphenylpropene **(25)**: bp 285–286 °C.

HRMS: *m/z*, $C_{16}H_{16}$, calc. 208.3024, found 208.1251.

^{1}H-NMR (CCl_4/TMS): δ = 1.7 (s, 3 H, CH_3), 4.4 (d, 1 H, J = 1 Hz, =CH), 4.6 (s, 1 H, CH), 5.0 (d, 1 H, J = 1 Hz, =CH), 7.1 (m, 10 H_{arom}).

We gratefully acknowledge support from the following: the Donors of the Petroleum Research Fund, administered by the American Chemical Society; the NIH AREA Program; the NIH Minority Biomedical Research Support (MBRS) Program; and the NIH MARC-Honors Undergraduate Training Program NIGMS.

Received: 14 July 1989; revised: 15 August 1990

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