



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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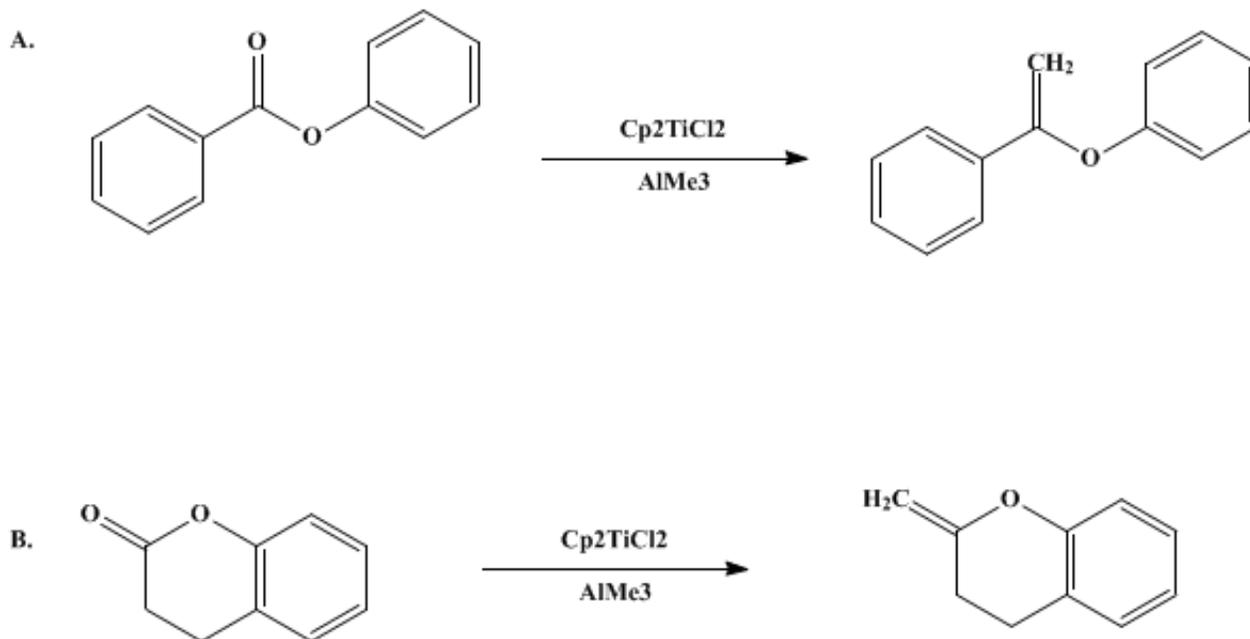
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

ENOL ETHERS BY METHYLENATION OF ESTERS: 1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-2H-1-BENZOPYRAN

[Ether, phenyl 1-phenylvinyl and 2H-1-benzopyran, 3,4-dihydro-2-methylene-]



Submitted by Stanley H. Pine¹, Gia Kim², and Virgil Lee.
Checked by Roger B. Ruggeri and Clayton H. Heathcock.

1. Procedure

Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011]

A. *1-Phenoxy-1-phenylethene*. To a 250-mL round-bottomed flask (Note 1) equipped with a magnetic stirring bar is added 5.0 g (20.0 mmol) of titanocene dichloride [bis(cyclopentadienyl)titanium dichloride] (Note 2). The flask is fitted with a rubber septum through which a large-gauge needle is passed to flush the system with dry nitrogen. After the vessel has been thoroughly purged, the nitrogen line flowing to the needle is opened to a mineral oil bubbler and 20 mL of a trimethylaluminum solution (2.0 M in toluene, 40 mmol) is added by a nitrogen-purged syringe (Note 3). Methane gas evolved by the reaction is allowed to vent as the resulting red solution is stirred at room temperature for 3 days. The Tebbe reagent³ thus formed is used in situ by cooling the mixture in an ice-water bath (Note 4), then adding 4.0 g (20 mmol) of phenyl benzoate (Note 5) dissolved in 20 mL of dry tetrahydrofuran (Note 6) by syringe or cannula to the cooled stirring solution over 5–10 min. After the addition, the reaction mixture is allowed to warm to room temperature and is stirred for about 30 min. The septum is removed and 50 mL of anhydrous diethyl ether is added. To the stirring reaction mixture is gradually added 50 drops of an aqueous solution of 1 M sodium hydroxide over 10–20 min (Note 7). Stirring is continued until gas evolution essentially ceases; then to the resulting orange slurry are added a few grams of anhydrous sodium sulfate to remove excess water. The mixture is filtered through a Celite pad on a large coarse frit using suction and liberal amounts of diethyl ether to transfer the product and rinse the filter pad.

Concentration of the filtrate with a rotary evaporator (Note 8) to 5–8 mL provides crude product, which is purified by column chromatography on basic alumina (150 g) eluting with 10% diethyl ether in pentane (Note 9). Fractions that contain product (Note 10) are combined and evaporated to give 2.69–2.79 g (68–70%) of the desired enol ether (Note 11) as a pale-yellow oil.

B. *3,4-Dihydro-2-methylene-2H-1-benzopyran*. Formation of the *exo*-methylene enol ether with dihydrocoumarin is carried out as in the foregoing procedure except that the reaction solution is cooled with a dry ice–acetone bath before addition of the lactone. From 3.0 g (20 mmol) of dihydrocoumarin (Note 5) is obtained 1.85–1.97 g (63–67%) of the product (Note 12) as a pale-yellow oil, after column chromatography on basic alumina (150 g) eluting with 5% diethyl ether in pentane.

2. Notes

1. The checkers found that the acid ability of the enol ether products requires rigorous treatment of all glassware used for the reaction in order to avoid migration of the double bond in susceptible cases (e.g., dihydrocoumarin in Preparation B). Satisfactory results were obtained by treating the glassware sequentially with ethanolic 0.5 M solutions of hydrogen chloride and potassium hydroxide for approximately 1 hr, thoroughly rinsing with distilled water after each treatment, and finally oven-drying. This protocol is also effective for removing stubborn deposits on the glassware used for the reaction.
2. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc. and used without further purification. This compound is normally obtained as bright red crystals. If its purity is in question Soxhlet extraction using dichloromethane is usually effective; titanocene dichloride is slightly soluble in dichloromethane and slowly dissolves from insoluble materials present.
3. Trimethylaluminum was purchased from Aldrich Chemical Company, Inc. and obtained as a 2.0 M solution in toluene sealed under nitrogen in a Sure/Seal bottle. Trimethylaluminum is pyrophoric and reacts violently with water and air; the syringe and needle used should be rinsed with toluene or hexanes immediately after addition. Note that the rinse, although dilute, contains pyrophoric material and should be handled accordingly.
4. Reaction with the ester is relatively exothermic. Sensitivity of the substrate product to heating varies and should be considered for each particular compound. Phenyl benzoate can be methylenated at room temperature with no significant decrease in product yield. By contrast, dihydrocoumarin (Preparation B) gives no product under these conditions and must be methylenated at -78°C to obtain a good yield. For most substrates it is satisfactory to carry out reactions at 0°C .
5. Substrate esters were purchased from Aldrich Chemical Company, Inc. and used without further purification.
6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
7. Evolution of methane can be quite vigorous so that the reaction vessel must be large enough to prevent bubbling over. If the aqueous solution is delivered slowly in 10-drop increments over the addition period, a controlled quench of the reaction mixture is possible. Cooling slows gas evolution, but also greatly prolongs the hydrolysis step.
8. Methylene enol ethers are usually lower-boiling than their ester precursors. Low-molecular-weight products can be easily lost in evaporation; therefore, the toluene must be removed with care.
9. The checkers used Fisher Scientific basic alumina, Brockman activity I, 80–200 mesh. Neutral alumina and silica gel have also been used. Basic alumina minimizes the potential hazards of hydrolysis or proton-catalyzed isomerization of the carbon–carbon double bond in susceptible enol ethers. Gaseous trimethylamine has also been added to the eluent to minimize these problems during purification.
10. The checkers eluted the columns with a slight positive air pressure on the solvent reservoir to prevent formation of gas bubbles and cracks in the chromatographic medium. Fractions were collected in 25-mL test tubes (Note 1), analyzed by TLC on silica gel, eluting with the column solvent, and visualized with a phosphomolybdic acid solution. The checkers observed a nonvolatile hydrocarbon material (not substrate related) which was eluted in the fractions just prior to the products, which are quite nonpolar themselves and are eluted in the early fractions, ahead of any unreacted ester. Colored, metal-containing components usually remain near the top of the column, although some colored material may accompany the product if much toluene remains in the sample or if the sample is applied to the column in a more polar solvent.
11. The spectral properties for 1-phenoxy-1-phenylethene are as follows: IR (film) cm^{-1} : 1600, 1495, 1290, 1230; ^1H NMR (250 MHz, CDCl_3) δ : 4.45 (d, 1 H, $J = 2.3$), 5.05 (d, 1 H, $J = 2.3$), 7.06–7.11 (m,

3 H), 7.29–7.38 (m, 5 H), 7.66–7.70 (m, 2 H).

12. While the submitters observed no complications, the checkers were unable, even after many trials, to obtain the [dihydrocoumarin](#) adduct completely free of what appears to be the product of double bond migration to give the endocyclic enol ether. Initial results were quite erratic. However, use of the glassware treatment described in Note 1, suggested by Professor Pine, has consistently provided the desired compound contaminated with only a few percent of the unwanted isomer. Spectral properties for the [3,4-dihydro-2-methylene-2H-1-benzopyran](#) are as follows: IR (film) cm^{-1} : 1665, 1595, 1500, 1470, 1250, 990, 770; ^1H NMR (250 MHz, CDCl_3) δ : 2.57 (t, 2 H, $J = 6.5$), 2.80 (t, 2 H, $J = 6.5$), 4.14 (s, 1 H), 4.55 (s, 1 H), 6.85–6.92 (m, 1 H), 7.03–7.07 (m, 1 H), 7.11–7.18 (m, 1 H); impurity (partial) δ : 1.88 (bs, 3 H), 3.39 (bs, 2 H), 4.70 (bs, 1 H).

The submitters suggested that the use of CDCl_3 as the NMR solvent may be the cause of the appearance of unwanted double-bond isomer; they recommend CCl_4 as the solvent of choice.

3. Discussion

The formation of carbon–carbon bonds through the condensation of carbonyl compounds with phosphoranes (the Wittig reaction) is a very useful method in organic synthesis.^{4 5} Allowing the convergence of a wide variety of substrates enables this reaction to provide considerable flexibility in product design. Yet, with limited exceptions,^{6 7 8} this process has not been effective for the transfer of methylene or alkylidenes to the carbonyl group of esters or other carboxylic acid derivatives. However, reaction of the [titanium–aluminum](#) complex (the Tebbe reagent)³ described here does transfer a methylene to the carbonyl group of esters, effecting the conversion of an ester to an enol ether.^{9 10}

The Tebbe reagent functions as a nucleophilic carbenoid in its reactions with carbonyl groups. The carbenoid is activated in the presence of a Lewis base that presumably complexes with the [aluminum](#) atom. [Tetrahydrofuran](#) is the Lewis base in the reactions described above. If the reaction is performed in the absence of added [tetrahydrofuran](#), the carbonyl oxygen atom can function as a weak Lewis base, although the methylenation process is considerably slower.

Vinyl ethers have also been prepared by addition of alkoxides to [acetylene](#),^{11,12,13} elimination from halo ethers and related precursors,^{11,13} and vinyl exchange reactions.¹³ Reaction of an electrophilic tungsten carbenoid with a [methylene phosphorane](#) or [diazomethane](#) also produces vinyl ethers.¹⁴ Enol ethers have resulted from the reaction of some tantalum and niobium carbenoids with esters,¹⁵ and the reaction of phosphoranes with electrophilic esters.^{6,7,8}

Methylenation using the [titanium–aluminum](#) complex converts a variety of esters to enol ethers in good yields.^{9,10} Lactones are converted to synthetically useful *exo*-methylene enol ethers. Carbon–carbon double bonds do not interfere with the methylenation reaction, although functional groups containing acidic hydrogen atoms do consume the reagent and should be protected. The carbonyl group of aldehydes and ketones reacts in preference to the ester carbonyl group in the methylenation process,¹⁰ but those groups can also be selectively protected.

Because of the expense of obtaining the Tebbe reagent in its pure form,¹⁶ an in situ method for its preparation and use was developed.¹⁷ The presence of the excess Lewis acidic by-product, [dimethylaluminum chloride](#), in the in situ preparation may cause reactivity at other sites in the substrate or lower yields of desired products (e.g., 70 vs. 94% for Preparation A, and 65 vs. 85% for Preparation B).¹⁰ However, the overall simplicity of the method can be advantageous with readily obtained substrates.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 10, 355](#)

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

sodium ketyl of benzophenone

titanocene dichloride [bis(cyclopentadienyl)titanium dichloride

acetylene (74-86-2)

hydrogen chloride (7647-01-0)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum (7429-90-5)

methane (7782-42-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

Trimethylamine (75-50-3)

Diazomethane (334-88-3)

phenyl benzoate (93-99-2)

Tetrahydrofuran (109-99-9)

phosphomolybdic acid (51429-74-4)

trimethylaluminum (75-24-1)

titanium (7440-32-6)

1-Phenoxy-1-phenylethene,
Ether, phenyl 1-phenylvinyl (19928-57-5)

Titanocene dichloride (1271-19-8)

dihydrocoumarin (119-84-6)

methylene phosphorane (61183-53-7)

dimethylaluminum chloride (1184-58-3)

3,4-Dihydro-2-methylene-2H-1-benzopyran,
2H-1-benzopyran, 3,4-dihydro-2-methylene- (74104-13-5)