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Synthesis of α, β-Unsaturated Ketones Using Allylidenetriphenylphosphorane as a Three-carbon Unit

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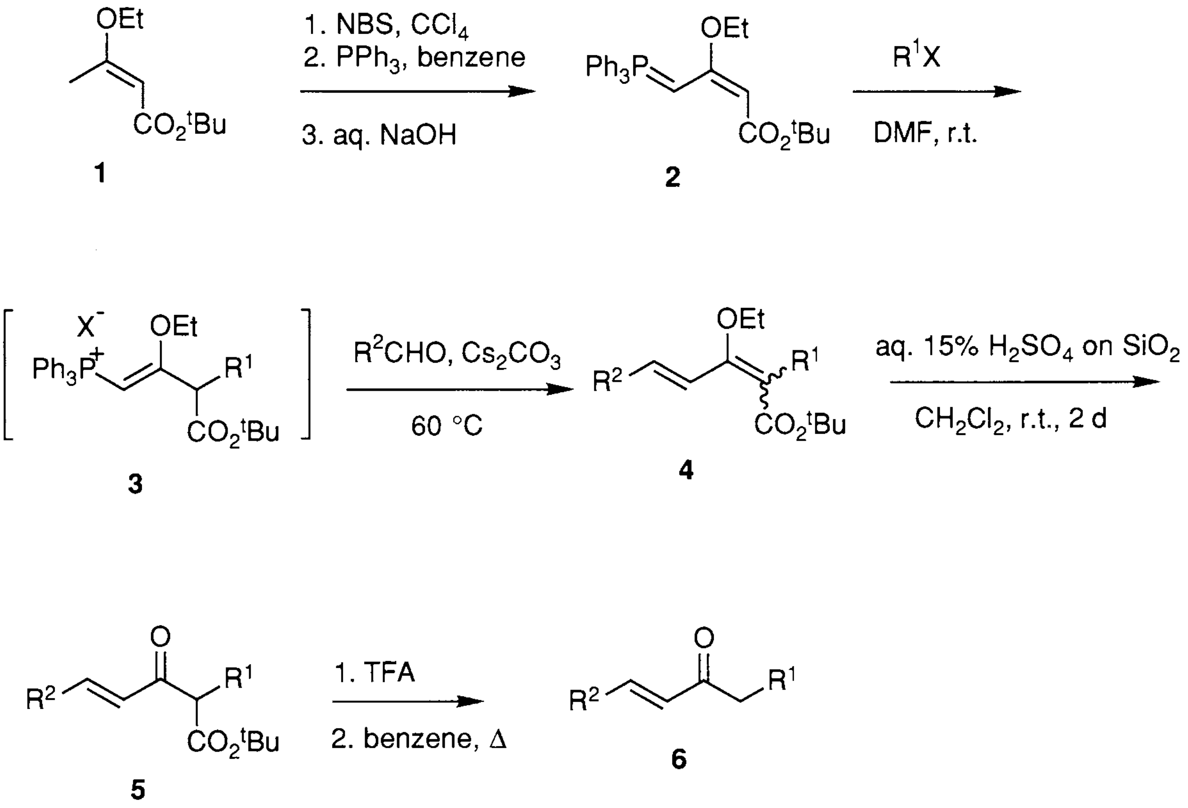
3-Alkoxycarbonyl-2-ethoxy-2-propenylidenetriphenylphosphorane reacts in turn with alkyl halides and aldehydes in the presence of base *via* a one-pot procedure to give moderate to good yields of conjugated enol ethers. Hydrolysis of the conjugated enol ethers and subsequent decarboxylation provide a novel route to α, β-unsaturated ketones.

Allylidenetriphenylphosphoranes react with various electrophiles at the α- or γ-position depending on electrophiles and the substituents of the phosphorane.[1)] However, regioselectivity of alkylation of the phosphorane with alkyl halides remains uncertain because there are only a few precedents.[2)] Recently it was reported that 2-ethoxy-3-ethoxy-carbonyl-2-propenylidenetriphenylphosphorane reacted with α-halo carbonyl compounds leading to the regioselective formation of substituted cyclopentadienes.[3)] In this reaction, initial alkylation takes place preferentially at the γ-position of the phosphorane and subsequent intramolecular Wittig reaction in the presence of base produces the cyclopentadiene. The finding prompted us to investigate carbon elongation at the both ends of the three carbon unit of the phosphorane. This paper describes synthesis of α, β-unsaturated ketones from the allylidenetriphenylphosphorane *via* an alkylation-Wittig reaction sequence.

The allylidenetriphenylphosphorane *t*-butyl ester **2** was prepared from *t*-butyl 3-ethoxy-2-butenoate (**1**) in a straightforward manner *via* bromination and treatment with triphenylphosphine and then aqueous NaOH. Alkylation of **2** with benzyl bromide proceeded smoothly in DMF at room temperature to give the alkylated phosphonium bromide **3** (R^1=CH_2Ph). In a one pot procedure, the reaction mixture was then treated with an equiv of hexanal in the presence of cesium carbonate at 60 °C to give 70% yield of **4a** as a mixture of the geometrically isomeric enol ether. Hydrolysis of the enol ether of **4a** was best carried out by treatment with H_2SO_4 on wet SiO_2 in dichloromethane to give the *trans* ketoester **5a** quantitatively. Treatment of **5a** with trifluoroacetic acid and decarboxylation of the resulting acid furnished *trans* α, β-unsaturated ketone **6a** quantitatively.[4)]

Representative examples are listed in Table 1. These results show that the alkylation



step takes place preferentially at the γ-position of the allylidene phosphorane **2** and finally leads to the formation of various α, β-unsaturated ketones. In an application of this method, shogaol (**9**), the pungent principle of ginger,[5)] was synthesized in 44% overall yield starting from **7**, which was readily prepared from 2-methoxy-4-methylphenol by treatment with *t*-butyldimethylsilyl chloride (imidazole, DMF) followed by bromination (NBS).

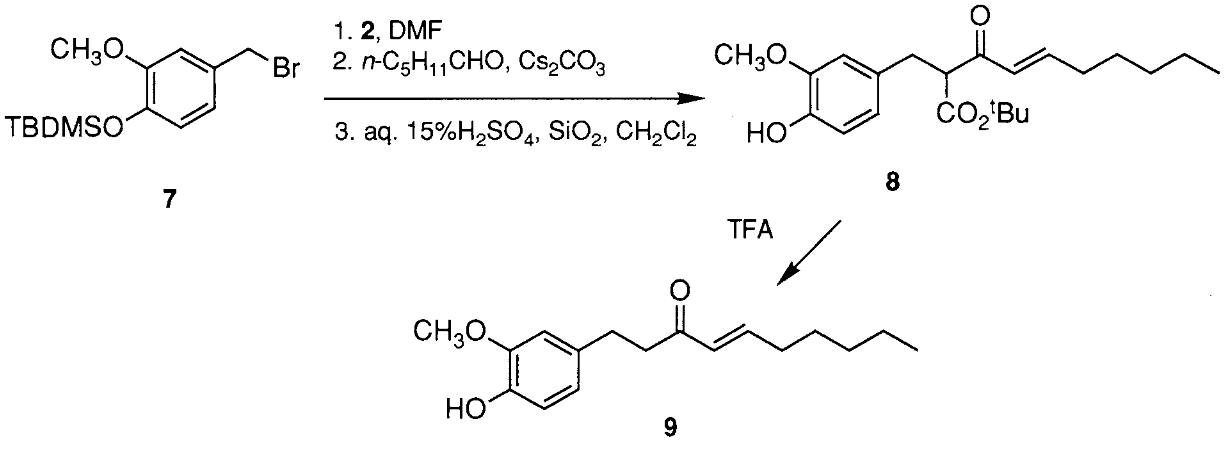


Table 1. Synthesis of α, β-Unsaturated Ketones **6** from Allylidenetriphenylphosphorane **2**

	Starting material		Ketoester **5**		α, β-Unsaturated ketone **6**	
Entry	RX	RCHO	No	Yield[a)]/%	No	Yield[b)]/%
1	$PhCH_2Br$	n-$C_5H_{11}CHO$	**5a**	70	**6a**	99
2	$PhCH_2Br$	PhCHO	**5b**	-	**6b**	85[c)]
3	n-$C_5H_{11}I$	n-$C_5H_{11}CHO$	**5c**	43	**6c**	94
4	n-$C_5H_{11}I$	PhCHO	**5d**	69	**6d**	100
5	C_2H_5I	n-$C_5H_{11}CHO$	**5e**	49	**6e**	81
6	$CH_3O_2CCH_2Br$	n-$C_5H_{11}CHO$	**5f**	68	**6f**	88

a) Isolated yield based on the phosphorane **2**. b) Isolated yield based on **5**. c) Overall yield from **2**; the keto ester **5b** was not isolated and directly treated with trifluoroacetic acid because the crude **5b** contained the corresponding free acid and **6b**.

We believe that the alkylation-Wittig reaction sequence on the allylidenetriphenylphosphorane **2** provides an alternative of the existing methods for the synthesis of *trans* α, β-unsaturated ketones in terms of ready availability of the phosphorane and the mild reaction conditions.

Typical experiments are as follows. *t*-Butyl 2-benzyl-3-oxo-4-decenoate (**5a**): To a solution of the allylidenetriphenylphosphorane **2** (447 mg, 1 mmol) in DMF (2 ml), was added benzyl bromide (0.113 ml, 1.1 mmol) under argon atmosphere. After stirred for 24 h at room temperature, the mixture was treated with Cs_2CO_3 (326 mg, 1 mmol) and hexanal (0.14 ml, 1.1 mmol) and then warmed at 60 °C for 24 h. The cooled reaction mixture was poured into ice-water and extracted with ether. The extract was purified by passing through a short column of silica gel (hexane-ethyl acetate) to give the crude **4a** (322 mg) as an oil which was a ca. 2:1 mixture of geometrical isomers. The whole crude product was treated with 15% aqueous H_2SO_4 solution (0.32 ml) and silica gel (3.2 g)$^{6)}$ in dichloromethane (5 ml) for 2 days at room temperature. Usual work-up and purification by flash chromatography (hexane-ether, 50:1) gave the keto ester **5a** (231 mg, 70%) as an oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.09-1.50 (m, 6H), 1.36 (s, 9H), 2.15-2.23 (m, 2H), 3.15 (d, J=7.5 Hz, 2H), 3.89 (t, J=7.5 Hz, 1H), 6.18 (d, J=15.8 Hz, 1H), 6.91 (dt, J=15.8, 6.9 Hz, 1H), 7.05-7.50 (m, 5H). 1-Phenyl-4-decen-3-one (**6a**): The keto ester **5a** (100 mg, 0.3 mmol) was treated with trifluoroacetic acid (0.22 ml) at 0 °C for 1 h. The mixture was diluted with benzene and evaporated *in vacuo*. The remaining oil was dissolved in benzene and refluxed for 1 h. After evaporation, the residure was purified by flash chromatography (hexane-ether, 50:1) to give **6a** as an oil (69 mg, 99%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.20-1.39 (m, 4H), 1.40-1.50 (m, 2H), 2.15-2.23 (m, 2H), 2.83-2.98 (m, 4H), 6.09 (d, J=15.8 Hz, 1H), 6.82 (dt, J=15.8, 6.9 Hz, 1H), 7.05-7.50 (m, 5H).

References

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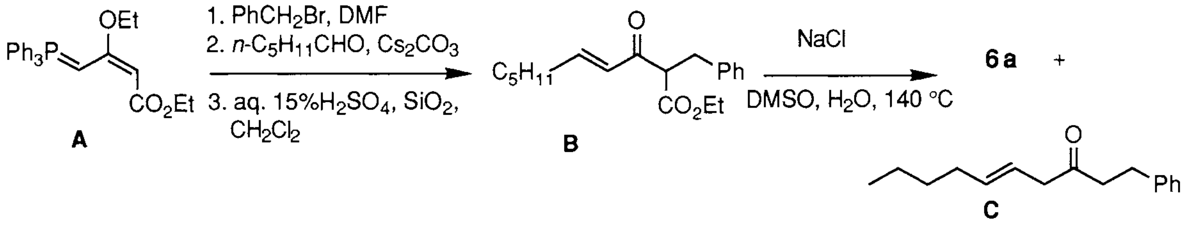
2) For example of alkylation at the γ–position of allylidenephosphorane, see: B. Bogdanovic and S. Konstantinovic, *Synthesis*, **1972**, 481.
3) M. Hatanaka, Y. Himeda, and I. Ueda, *Tetrahedron Lett.*, **32**, 4521 (1991).
4) The ethyl ester **A** also reacted with benzyl bromide and then hexanal in a similar manner to give the keto ester **B** in 91% overall yield after hydrolysis. However, attempted decarboxylation of the ethyl ester **B** by heating with NaCl in wet DMSO at 140 °C led to attendant formation of the β, γ-unsaturated ketone **C** (13%) along with **6a** (40%).



5) The spectral data of **9** were identical with those reported for shogaol; for the isolation and the structure determination of shogaol, see; H. Nomura, *J. Chem. Soc.*, **1917**, 769; *Sci. Rep. Tohoku Imp. Univ.*, **7**, 67 (1918); H. Nomura and S. Tsurami, *ibid.*, **14**, 131 (1925); D. W. Connell and M. D. Sutherland, *Aust. J. Chem.*, **22**, 1033 (1969).
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