

초임계 이산화탄소에서의 유기인 일리드와 카르보닐 화합물의 반응

정경일 · 김학도 · 심재진[†] · 나춘섭^{*}

영남대학교 화학과 · 기초과학연구소

[†]영남대학교 응용화학공학부

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Reaction of Phosphorus Ylides with Carbonyl Compounds in Supercritical Carbon Dioxide

Kyung Il Jeong, Hak Do Kim, Jae-Jin Shim[†], and Choon Sup Ra^{*}

Department of Chemistry and Institute of Natural Sciences, Yeungnam University, Gyongsan 712-749, Korea

[†]School of Chemical Engineering and Technology, Yeungnam University, Gyongsan 712-749, Korea

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요 약. 초임계 이산화탄소 용매에서의 (벤질렌)삼페닐 인 일리드 화합물의 카르보닐 화합물과의 Wittig 반응을 연구하였다. 소량의 조용매 (THF, 5%)를 첨가한 이산화탄소 (24 mL 용기)에 녹인 (벤질렌)삼페닐 인 일리드 (약 1 mmol)를 여러 방향족 알데히드와 초임계 조건(80 °C, 2,000 psi)에서 2시간 반응시켜 올레핀 화합물을 좋은 수율로 얻을 수 있었다. 새로운 조건에서의 반응은 기존 용매 (THF)에서의 반응보다는 약간 느리게 나타났으나 생성물의 (E)-와 (Z)-이성체 비율에 차이가 있었다. 두 이성체가 함께 생성되는 반응의 경우 (Z)-이성체의 비율이 증가하였다. 반면 t-butylcyclohexanone과 같은 케톤과의 반응은 두 조건에서 모두 낮은 전환을 보였다. 이 연구를 통하여 이산화탄소에서의 Wittig 반응이 초임계 조건에서 좋은 수율로 이루어지며 이 새로운 용매의 사용으로 반응선택성의 변화가 가능할 수 있다는 초기 결과를 얻었다. 이 결과는 Wittig 반응과 같은 유용한 유기반응을 친환경 용매 (이산화탄소)에서 수행할 수 있도록 전환하는데 좋은 자료가 될 수 있다고 본다.

주제 어: 초임계, 이산화탄소, 포스포란, 유기인 일리드, Wittig 반응

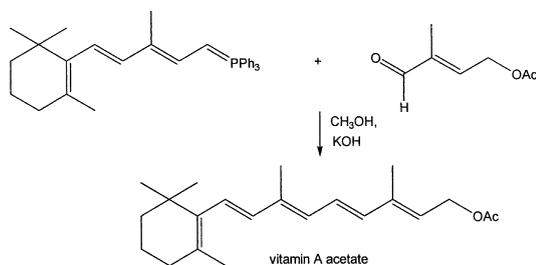
ABSTRACT. The condensation reaction of (benzylene)triphenylphosphoranes with carbonyl compounds in supercritical carbon dioxide was examined. Reactions of (benzylene)phosphoranes (*ca.* 1 mmol) with several benzaldehydes in a supercritical carbon dioxide (80 °C, 2,000 psi) containing THF entrainer (5%) in a 24 mL reactor proceed smoothly to yield olefination products in fairly good to excellent yields but slower, compared to reactions in a conventional THF solvent. Generally, phosphoranes that are not substituted with a nitro group show more (Z)-selective reactions with aromatic aldehydes under scCO₂ condition than in THF. The reaction of (benzylene)triphenylphosphoranes with 4-*t*-butylcyclohexanone gave the corresponding olefin compounds with a low conversion under both the supercritical carbon dioxide and the organic THF solvent. Our preliminary study showed the Wittig reaction carries out smoothly in supercritical carbon dioxide medium and also a possible tunability of this reaction pathway by adding an entrainer. The results would be useful for devising a novel process for the environmentally friendly Wittig reaction.

Keywords: Supercritical, Carbon dioxide, Phosphoranes, Phosphorus Ylides, Wittig reaction

INTRODUCTION

Condensation of the phosphorus ylides with carbonyl compounds discovered in 1953¹ and now named as the Wittig reaction has become one of the most important and useful methods in preparing alkenes with usually high level of geometric control.² The range of products derived from the reaction of the ylides is enormous: from simple alkyl- and aryl-substituted ethylene derivatives to α,β -unsaturated carbonyl compounds and carboxylic esters as well as vinyl halides and vinyl esters. The potential of this reaction for the industrial process was soon recognized³ and the commercial synthesis of medicinally important natural products such as vitamin A acetate by the BASF group (Scheme 1) and β -carotenes is the well-known example.

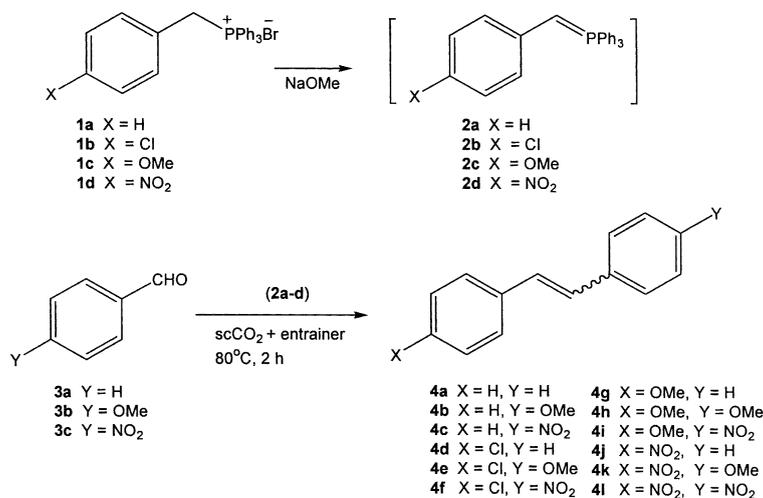
Experimentally a phosphorus ylide prepared in a solution state from the corresponding phosphonium salt by the treatment with a suitable base is condensed with a carbonyl compound to produce a double bond, eliminating triphenylphosphine oxide. Recent two efforts of changing this conventional concept are quite interesting in the use of the phosphorus ylides: a catalytic process⁴ and a solvent-free condition.⁵ The latter involves the employment of phosphorus ylides in a solid state generated by mechanical milling of phosphonium salts with an excess of potassium carbonate, and the ylides are effective for the Wittig-type olefination with carbonyl compounds in a high yield. This process can be particularly useful for the chemical industry that faces an enforcing global control over the use and disposal of hazardous organic solvents. In addition,



Scheme 1. BASF process for the synthesis of vitamin A acetate in 600 ton per year.

the reactive chemicals under a non-conventional state like the phosphorus ylide in a solid state would be very valuable for searching novel chemical phenomena having various advantages which may not be achieved by conventional means. In this respect, chemical systems in a supercritical fluid (SCF) have received significant scientific interests. SCF is considered useful for the replacement of conventional organic solvents. Examples include various organic transformations such as hydrogenation, photochemical and radical reactions, Diels-Alder cycloaddition reactions, oxidations, enzymatic transformations, and polymerization reactions.⁷ Tuning the properties of SCFs by changing the pressure and temperature controls several aspects of the reactions⁸ such as (1) density or cosolvent tuning of reactions for rate, yield and selectivity, (2) improved mass transfer, (3) modifying the local solvating power *via* solute-solvent clustering⁸ and microemulsification.⁹

Our approach to this issue is to investigate reactions usually run in conventional solvents to assess a behavior in SCFs. The condensation reaction of some (benzylene)triphenylphosphoranes with carbonyl compounds in supercritical carbon dioxide ($T_c = 31^\circ\text{C}$, $P_c = 1,074$ psi) was examined. Phosphonium salts are not soluble in carbon dioxide and we needed to dissolve them in a small amount of solvent (THF). Thus, the reactions were actually performed in scCO_2 containing a small amount of cosolvent (THF). Where reagents like many organic compounds have a solubility problem in scCO_2 ,¹⁰ the practice of adding a small amount of polar solvent (entrainer) to SCF is established and tuning of the reaction pathways by the addition of an entrainer is another subject of recent studies.¹¹ In our experiment, the corresponding (benzyl)triphenylphosphonium bromides (**1**) (*ca.* 1 mmol) were dissolved in a small amount of THF (1.5 mL) and treated with 1.5 eq. of sodium methoxide (*ca.* 100 μL , 15 M in methanol) to generate (benzylene)triphenylphosphoranes (**2**). Phosphoranes were introduced into a tubular stainless steel reactor (24 mL capacity), carbonyl compounds (*ca.* 0.9 mmol) were added shortly. Then, the reactor was charged immediately with carbon dioxide by pressurizing. The reaction



Scheme 2. The reactions of (benzylene)phosphoranes (**2**) with aromatic aldehydes (**3**) in scCO₂ and entrainer.

pressure of scCO₂ was monitored by a high precision gauge (Sensotec, TJE model) that is connected with the reactor during the reaction. The reaction mixture was heated at 80 °C with magnetic stirring for 2 h while the pressure was at 2,000 psi. The reactor was cooled, and CO₂ was vented. The residue was dissolved in dichloromethane, concentrated under reduced pressure, and the crude products were submitted to ¹H NMR spectroscopy for determining the isomeric ratios. A further purification of the products was made by column chromatography on silica gel. In the reactions without SCF, phosphoranes generated as before were reacted with carbonyl compounds in a total volume (10 mL) of organic solvents. The reaction of **2** with aromatic aldehydes (**3**) was tested first (Scheme 2).

RESULTS AND DISCUSSION

The condensation of most ylides with benzaldehydes in scCO₂ and entrainer undergoes in high conversion after 2 h (Table 1). The reaction of **2** with benzaldehydes in scCO₂ proceeds more slowly and needs usually a longer reaction period (2 h) to reach a conversion comparable to that without scCO₂ where it is operated for 1 h. Due to their polar character, the reactions of **2** with **3** expect to favor more polar solvent (THF). These results also

Table 1. Compounds Obtained by the Reaction of (Benzylene)-phosphoranes with Aromatic Aldehydes

Compound	scCO ₂ ^a		THF ^b		Reference ^c
	yield, % ^c	<i>E</i> : <i>Z</i> ^d	yield, % ^c	<i>E</i> : <i>Z</i> ^d	
4a	96	1:1.6	82	1:1	13
4b	77	1.3:1	58	1.5:1	14
4c	91	<i>E</i> only	82	<i>E</i> only	15
4d	77	1:2	81	1:2	16
4e	61	1:2.2	72	1:1.1	-
4f	95	<i>E</i> only	70	3:1	17
4g	68	1:1.6	79	1:1	14
4h	37	1:2.7	29	1:1.7	18
4i	73	<i>E</i> only	70	<i>E</i> only	19
4j	60	<i>E</i> only	87	<i>E</i> only	15
4k	40	<i>E</i> only	46	<i>E</i> only	19
4l	5	<i>E</i> only	6	<i>E</i> only	20

^aCondition A: temperature at 80 °C, pressure of CO₂ at 2,000 psi, reaction time for 2 h.

^bCondition B: heating at reflux, reaction time for 2 h.

^cIsolated yields after silica gel column chromatography.

^dThe isomer ratios determined by ¹H NMR spectroscopy.

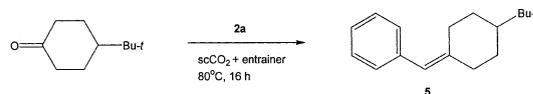
^eReferences used for identification of the compounds.

indicate that modification of the chemical reactivity of **2** caused by the presence of scCO₂ brought a substantial change in *E*:*Z*-isomer ratios. The isomer ratio of **4** determined by ¹H NMR spectroscopy is found to depend on the reaction medium. Generally, phosphoranes that are not substituted with a nitro group (**4a-b**, **4d-e**, and **4g-h**) show more (*Z*-

selective reactions with aromatic aldehydes under scCO_2 condition than in THF. However, in systems having strong electron withdrawing nitro groups (i.e., **4c**, **4f**, **4i-l**), the tendency of (*Z*)-preference was thermodynamically offsetted by a large (*E*)-predominance. The empirical generalization regarding isomeric preferences such as (*Z*)-isomers formation from non-stabilized ylides under salt-free conditions and (*E*)-isomers from stabilized ylides has been well established.^{2d} However, prediction of stereochemistry for semi-stabilized phosphoranes like **2** is less decisive and the ratio of isomeric products may depend on the effect of experimental conditions.² Reactions of (benzylene)phosphoranes **2** in a nonpolar environment as in scCO_2 would proceed through earlier transition state than in THF and would be more selective for (*Z*)-olefins. The configurational assignment of two isomeric products **4** can be made by comparing the ^1H NMR chemical shifts of two distinct olefinic protons. Vinylic protons of (*E*)-isomers resonate at a lower field than those of (*Z*)-isomers; for example, (*E*)-**4a** with $\delta = 6.99$ ppm and (*Z*)-**4a** with $\delta = 6.49$ ppm.¹² The reaction between the least reactive pairs where a nitro group is substituted at the phenyl rings of both the ylide (**2d**) and benzaldehyde (**3c**) was very sluggish. To examine the dependency of the Wittig reaction in scCO_2 on temperature and pressure, we ran the reaction of **2a** with **3a** under various temperatures and pressures. While no significant changes were observed in *E*:*Z* ratios in the reaction of **2a** with **3a** in scCO_2 containing the THF entrainer (*E*:*Z* = 1:1.6 for **4a**) under various temperatures (40, 60, 80 °C) and pressures (1,500 psi to 5,500 psi), the conversion of the reaction consistently increases as the reaction temperature increases (75% at 40 °C, 88% at 60 °C, and 96% at 80 °C after 2 h, respectively). Moreover, the conversion of the reaction very much depends on the reaction time; the production of **4a** smoothly increases as the reaction time when monitored by TLC (20% after 30 min, 50% after 1 h, and 75% after 1.5 h). This result indicates the condensation of the phosphoranes with aldehydes does occur in *not* a pure THF environment but rather a non-conventional reaction medium having

an enhanced solvating power by the addition of THF, tuning the reaction selectivity (i.e., (*E*): (*Z*)-ratio). Tuning of these reactions by using other cosolvent systems is being studied and the results will be presented in due course.

The chemical reactivity of **2** in scCO_2 was further examined by the reaction with a ketone. The reaction of **2** with 4-*t*-butylcyclohexanone gave the corresponding olefin compounds (**5**) in a low conversion (13% for **5a**²¹) even after a long reaction time (16 h). The same reaction in THF gave a higher, but still unsatisfactory yield after heating at refluxing THF for 16 h (38%).



EXPERIMENTAL SECTION

Wittig reaction of **2a** with **3a**. A representative procedure for reactions of **2** with **3/4**.

(Benzyl)triphenylphosphonium bromide (435 mg, 1.00 mmol) was dissolved in anhydrous THF (1.5 mL) and a 15 M solution of sodium methoxide in methanol (100 μL) was added and stirred for 5 min to give a red solution of (benzylene)triphenylphosphorane (**2a**). **2a** was transferred into a tubular stainless steel reactor of 24 mL capacity via a syringe and benzaldehyde (92 mg, 0.87 mmol) were added shortly. Then, the reactor was charged with carbon dioxide by pressurizing initially at 1,300 psi and immersed in the oil bath at 40 °C. The temperature of reaction mixture was raised to 80 °C, while the pressure reached at 2,000 psi. After stirring magnetically for 2 h, the reaction mixture was cooled and CO_2 was vented into dichloromethane. The residue was dissolved in dichloromethane and the organic solvent was evaporated under reduced pressure. The ^1H NMR spectra were recorded for crude products to determine the isomeric ratios, otherwise the residue materials were purified by column chromatography on silica gel (elution with 50 % hexane in benzene then 5 % ethyl acetate in hexane) to give **4a** as two separate isomers; (*E*)-isomer (58 mg, 37 %) and (*Z*)-isomer (93 mg, 59 %).

Other compounds were prepared analogously and spectral data of compounds **4e** which have been not reported, are as follows.

¹H NMR data for **4e**. For (*E*)-**4e** (a white powder); ¹H NMR (CDCl₃, 300 MHz) δ 7.49-7.13 (series of m, 8H), 7.04 (d, J=16.3 Hz, 1H), 6.93 (d, J=16.3 Hz, 1H), 3.84 (s, 3H); IR (KBr, cm⁻¹) 2920, 1585, 1506. For (*Z*)-**4e** (a white powder); ¹H NMR (CDCl₃, 300 MHz) δ 7.45-7.11 (series of m, 8H), 6.90 (d, J=14.4 Hz, 1H), 6.77 (d, J=14.4 Hz, 1H), 3.79 (s, 3H); IR (KBr, cm⁻¹) 2919, 1589, 1505.

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