Facile Synthesis of Phosphonium Salts Containing Carboxylic Acid Functional Group

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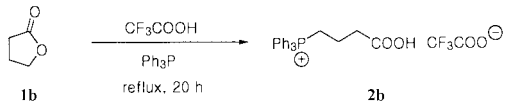
Since its development, the Wittig reaction has remained one of the best routes for the construction of carbon-carbon double bonds.[1] The Wittig reagent needed for the reaction is prepared by deprotonation of the corresponding phosphonium salt generated by the quaternization of a phosphine with organic halides.[2] Synthesis of phosphonium salt often requires forcing conditions. Frequently, the phosphine and organic halide must be heated to reflux for several hours, and in some cases days, to obtain the desired phosphonium salt.[2] In these respects, development of a new methodology for the preparation of phosphonium salt is necessary from alkyl halide[3a] or from other easily available precursors.[3b-e]

Recently we have reported on the reaction of alcohols and triphenylphosphine in a one pot reaction to generate the phosphonium salt.[4] As a continuous work we examined the reaction of lactones **1a-f** and α,β-unsaturated carboxylic acids **1g** and **1h** in order to prepare synthetically useful carboxyl containing phosphonium salts **2a-h**. Carboxyl containing phosphonium salts are important intermediates in organic synthesis such as prostaglandin synthesis.[5] The reaction of lactones and triphenylphosphine hydrobromide has been reported to prepare the carboxyl containing phosphonium salts.[3b,3e] However, some drawbacks in this reaction appeared by the fact that the use of sealed tube or high temperature (160-180 °C) was necessary.

In this paper, we report a facile synthesis of carboxyl containing phosphonium salts **2** by using trifluoroacetic acid and triphenylphosphine.[4] As shown in Scheme 1 the reaction of γ-butyrolactone (**1b**) in the presence of triphenylphosphine (1.1 equiv) in trifluoroacetic acid gave the phosphonium salt **2b** in 74% yield.

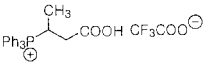
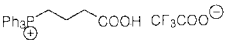
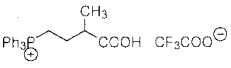
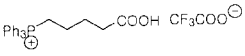
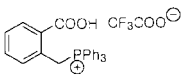
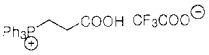
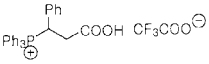
Some representative results are summarized in Table 1, and the following procedure is typical: The reaction mixture of γ-butyrolactone (**1b**, 860 mg, 10 mmol) and Ph_3P (2.9 g, 11 mmol) in trifluoroacetic acid (5 mL) was heated to reflux for 20 h. After cooling to room temperature, the reaction mixture was poured into cold water, extracted with methylene chloride, dried with magnesium sulfate, and evaporated to dryness. Passing through a short silica gel column



1b 2b

Scheme 1

Table 1. Synthesis of Carboxyl Containing Phosphonium Salts **2**

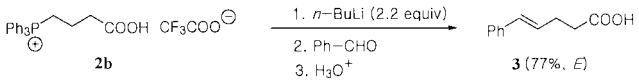
Entry	Subtrate (**1**)	Time	Product (**2**)	Yield (%)
a		12 h		77
b		20 h		74
c		12 h		74
d		7 days	no reaction	–
e		20 h		69
f		3 days		61
g		20 h		72
h		12 h		75

(EtOAc/EtOH, 9 : 1) afforded analytically pure phosphonium salt **2b** (3.42 g, 74%).[6]

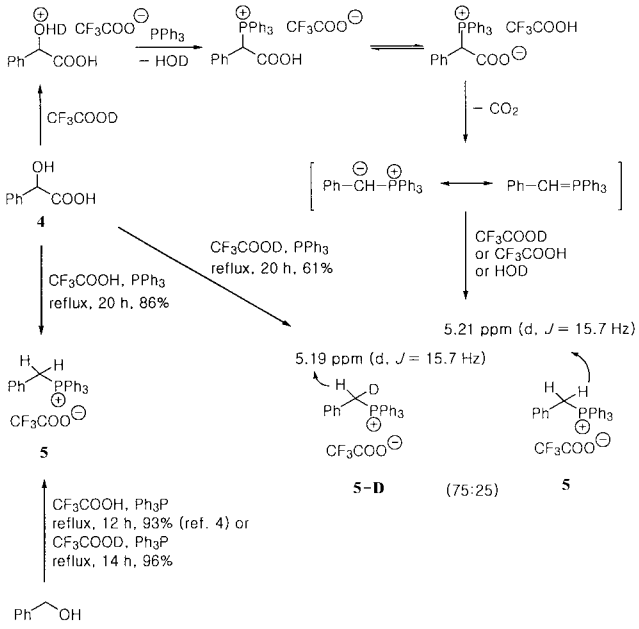
The reaction of β-butyrolactone (**1a**), α-methyl-γ-butyrolactone (**1c**), δ-valerolactone (**1e**), and phthalide (**1f**) in the same reaction conditions afforded the corresponding phosphonium salts in 61-77% isolated yields. In the case of phthalide, somewhat longer reaction time was needed. When we use γ-valerolactone (**1d**), presumably due to the stability of the five-membered lactone ring and the steric hindrance of the methyl substituent, no reaction was observed even after 7 days in our conditions. The use of more reactive tributylphosphine (reflux, 24 h) instead of triphenylphosphine in this case gave no phosphonium salt at all.

The reaction of acrylic acid (**1g**) and cinnamic acid (**1h**) in the same reaction conditions afforded the phosphonium salts **2g** and **2h**, respectively in reasonable yields.

The reaction of **1b** in formic acid (reflux, 48 h) gave the corresponding phosphonium salt in 32% isolated yield, while in acetic acid (reflux, 48 h) no reaction was observed. Moreover the counter anion part, trifluoroacetate, did not show any deteriorative effect in the next Wittig reaction as



Scheme 2



Scheme 3

exemplified by using **2b** for the formation of 5-phenyl-4-pentenoic acid (**3**)[6] in Scheme 2.

By the same analogy, we tried the reaction of DL-mandelic acid (**4**). However, benzyltriphenylphosphonium salt **5** was isolated in 86% yield. The reaction mechanism for the formation of **5** is proposed in Scheme 3. To confirm the mechanism we examined the following two reactions. The reaction of mandelic acid in CF_3COOD gave the deutrium incorporated phosphonium salt **5-D** at the benzylic position (Incoporation of D is about 75% by the integral of ^{1}H NMR spectrum). Two benzylic proton of benzyltriphenylphosphonium salt **5** appeared at 5.21 ppm (d, J = 15.7 Hz) and the one benzylic proton of mono-duterated benzyltriphenylphosphonium salt **5-D** appeared at 5.19 ppm (d, J = 15.7 Hz) in a ratio of about 40 : 60 (determined by the integration in ^{1}H NMR spectrum). The next experiment is the reaction of benzyl alcohol and triphenylphosphine in CF_3COOD (reflux, 14 h, 96%) in order to confirm the possibility of D-incoporation at the acidic benzylic position of the benzyltriphenylphosphonium salt by CF_3COOD. No such D-incoporation (**5-D**) was observed in ^{1}H NMR spectrum at all. From these two separate experiments we could conclude that transient ylide formation in the decarboxylation step was involved for the formation of **5** from DL-mandelic acid (**4**).

In summary, we have disclosed the formation of carboxyl containing phosphonium salts from lactones and α,β-unsaturated carboxylic acids.

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6. Representative spectroscopic data of **2b**: mp 132-137 °C; ^{1}H NMR (DMSO-d_6) δ 1.65-1.81 (m, 2H), 2.43-2.53 (m, 2H), 3.52-3.66 (m, 2H), 7.74-7.95 (m, 15H), 12.50 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ 17.68 (d, J = 3.0 Hz), 19.99 (d, J = 51.0 Hz), 33.53 (d, J = 17.6 Hz), 117.13 (q, J = 298.5 Hz, CF_3COO-), 118.23 (d, J = 84.9 Hz), 130.06 (d, J = 11.3 Hz), 133.34 (d, J = 9.8 Hz), 134.73 (d, J = 3.0 Hz), 157.44 (q, J = 31.0 Hz, CF_3COO-), 172.91 (d, J = 1.3 Hz); IR (KBr) 3427, 3061, 2922, 1728, 1685, 1439 (C-P), 1202, 1130 cm^{-1}.
3: mp 90-91 °C (lit.[7] 90-92 °C); ^{1}H NMR ($CDCl_3$) δ 2.54 (app s, 4H), 6.15-6.26 (m, 1H), 6.45 (d, J = 15.9 Hz, 1H), 7.17-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.91, 33.74, 126.09, 127.18, 128.03, 128.49, 131.22, 137.31, 178.69.
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