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Phosphonium supported triphenylphosphine reagent: an improved access to α-fluoro-α,β-unsaturated esters

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Abstract—α-Fluoro-α,β-unsaturated esters **2** were efficiently synthetized via diethylzinc-promoted Wittig reaction using a phosphonium-supported triphenylphosphine SCG–PPh_3 **1**, which possesses similar reactivity as its parent analog triphenylphosphine. The main advantage of this system is the use of a novel low-molecular-weight support that is soluble in solvents of medium polarities for the attachment of reagents and insoluble in solvents of low polarities.

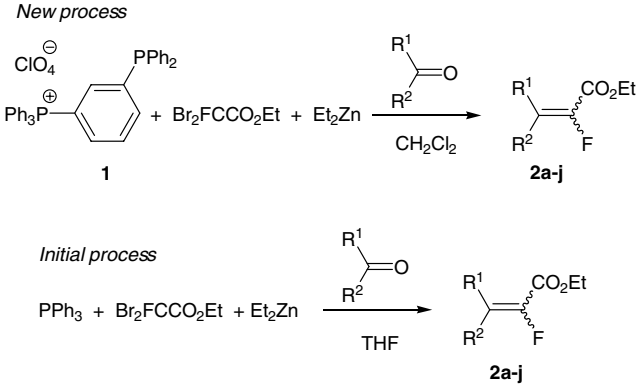
1. Introduction

Very important efforts have been devoted during the past few decades towards the development of novel supports to facilitate organic synthesis. This research area includes the development of insoluble[1] or soluble polymers[2] as solid supports, silica-bound scavengers or reagents.[3] Other approaches such as the use of ionic liquids[4] and fluorous phases[5] have been applied with success in organic synthesis.

One of us recently described the synthesis of new stable entities which are soluble in well-defined solvents but that precipitate completely with a minimum amount of an orthogonal solvent.[6] Tetraarylphosphonium salts can be used effectively as solubility control group (SCG). SCG–PPh_3 **1**, which has been synthesized, is totally insoluble in diethyl ether, is robust and possesses similar reactivity as its parent analog triphenylphosphine. Another unique property of **1** is its little propensity to trap organic compounds upon precipitation.

We also recently described an efficient synthesis of fluoroolefins via diethylzinc-promoted Wittig reaction.[7] In particular, we developed an efficient synthesis of α-fluoro acrylates from aldehydes or ketones using triphenylphosphine, ethyl dibromofluoroacetate and diethylzinc. The main drawback of such a process is the difficult separation, in some cases, of triphenylphosphine and triphenylphosphine oxide from the expected α-fluoro acrylate. We report herein the use of SCG–PPh_3 **1** for the synthesis of α-fluoro-α,β-unsaturated esters (see Scheme 1).

The initial process for the synthesis of such compounds was carried out in THF but SCG–Ph_3 **1** presents low solubility in such a solvent. As **1** is soluble in solvents



Scheme 1.

Keywords: Phosphonium-supported triphenylphosphine; Wittig reaction; Diethylzinc; Fluorine.
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Table 1. Synthesis of α-fluoro α,β-unsaturated esters using SCG–PPh_3**1**

Entry	Compound	R^1	R^2	Phosphine	Yield (%)[a]	Z/E[b]
1	**2a**	4-MeO–C_6H_4	H	PPh_3	91[c]	68/32
2	**2a**	4-MeO–C_6H_4	H	PPh_3	89[d]	68/32
3	**2a**	4-MeO–C_6H_4	H	SCG–PPh_3**1**	93	68/32
4	**2b**	Ph	H	SCG–PPh_3**1**	92	70/30
5	**2c**	C_6H_5–CH=CH	H	SCG–PPh_3**1**	93	70/30
6	**2d**	$CH_3(CH_2)_4$	H	SCG–PPh_3**1**	90	60/40
7	**2e**	Ph–CH_2–CH_2	H	SCG–PPh_3**1**	92	85/15
8	**2f**	4–MeO_2C–C_6H_4	H	SCG–PPh_3**1**	95	70/30
9	**2g**	Ph–CH_2	CH_3	SCG–PPh_3**1**	90	55/45
10	**2h**	Ph	CH_3	SCG–PPh_3**1**	78	60/40
11	**2i**	$(CH_2)_5$		SCG–PPh_3**1**	85	—
12	**2j**	BnO–C_6H_4	C_2H_5	SCG–PPh_3**1**	88	80/20

[a] Isolated yield, product characterized by ^1H, ^{13}C, ^{19}F NMR, IR and mass spectroscopies.[7]
[b] Ratio determined by ^{19}F NMR.
[c] In THF (initial process).
[d] In CH_2Cl_2.

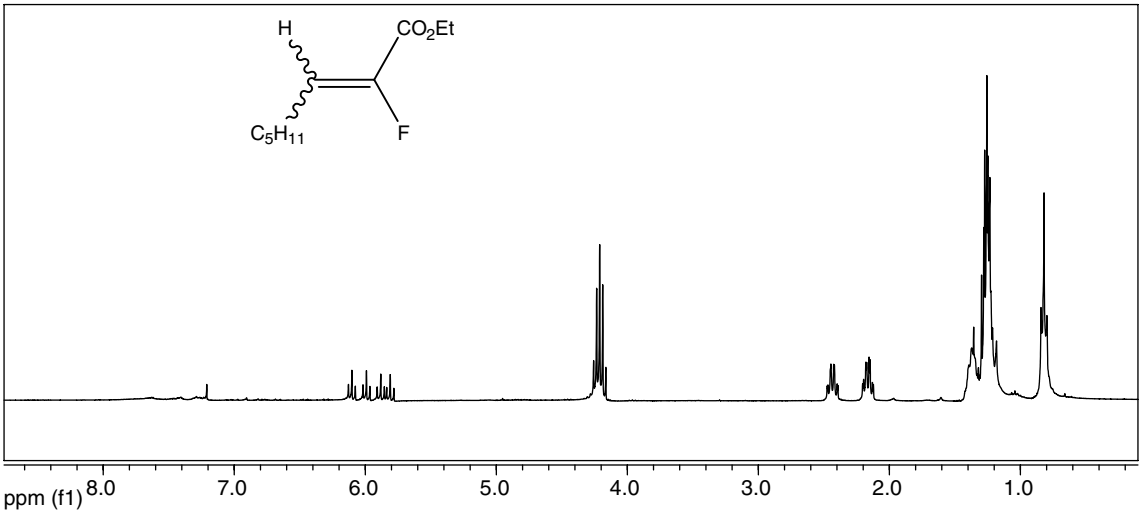

Figure 1. Crude ^1H NMR spectrum of α-fluoro α,β-unsaturated ester **2d**.

of medium polarities (CH_3CN, DMSO, CH_2Cl_2, etc.), we first tested our process using triphenylphosphine in dichloromethane. A similar yield was obtained (Table 1, entry 2). SCG–PPh_3**1** was mixed with ethyl dibromofluoroacetate and diethylzinc in dichloromethane prior to the aldehyde addition. Under these conditions, high yields of α-fluoro-α,β-unsaturated esters were obtained (Table 1). In all cases, equal efficiency was obtained either using triphenylphosphine or SCG–PPh_3 **1**. Various aldehydes were subjected to the optimized reaction conditions, giving the expected fluoroolefins **2** in high yields (Table 1, entries 1–8). We also applied such a process successfully to unactivated ketones (Table 1, entries 9–12).

When the reaction was completed,[8] ethanol was added, and the resulting solution was concentrated under reduced pressure. The residue was diluted with dichloromethane, filtered on Celite to remove zinc salts, and the addition of diethylether to the filtrate allowed complete precipitation of the SCG–PPh_3 oxide by-product, which was removed by filtration leading to a phosphine/phosphine oxide-free organic layer. Concentration under reduced pressure afforded a quantitative recovery of a very clean crude product for which the NMR analysis did not show any traces of phosphonium salts (Fig. 1).

In conclusion, we performed the application of SCG–PPh_3 to the synthesis of α-fluoro-α,β-unsaturated esters via diethylzinc-promoted Wittig reaction. The main advantage of this system is the use of a novel low-molecular-weight support that is soluble in solvents of medium polarities for the attachment of reagents and insoluble in solvents of low polarities.

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8. General procedure: To a solution of SCG-PPh_3 **1** (2 mmol 4 equiv, 1.2 g) and ethyl dibromofluoroacetate (1 mmol, 2 equiv, 140 μL) in dichoromethane (5 mL) was rapidly added diethylzinc (1 M solution in hexane, 2 mmol, 2 equiv, 2 mL) under argon. The reaction was then stirred at room temperature for 10 min and then the appropriate aldehyde or ketone (0.5 mmol, 1 equiv) was rapidly added. The reaction mixture was then stirred for 10 min. The resulting solution was then quenched with ethanol (5 mL) and the solution was concentrated under reduced pressure. The residue was diluted with dichloromethane (2 mL) and filtered on a small pad of *celite* to remove zinc salts. Diethylether (25 mL) was then added to the filtrate that induced the precipitation of the phosphonium salt. The mixture was filtered on a pad of celite. The organic phase was concentrated in vacuo to afford the nearly pure compound. A quick flash chromatography on silica gel (10% ethylacetate/cyclohexane) gave the expected α-fluoro α,β-unsaturated ester. $R_f = 0.5$ (cyclohexane–EtOAc, 9:1). (*Z*) and (*E*) 3-pentyl-2-fluoroacrylic acid ester: 60/40 (**2d**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.05$ (dt, $^3J_{H-H} = 8.0$ Hz, $^3J_{H-F} = 33.3$ Hz, 0.6H, H_{3Z}), 5.85 (dt, $^3J_{H-H} = 8.3$ Hz, $^3J_{H-F} = 21.6$ Hz, 0.4H, H_{3E}), 4.20–4.10 (m, 2H, H_9), 2.40 (dq, $J = 1.7$ Hz, $J = 8.6$ Hz, 0.8H, H_{4E}), 2.15 (dq, $J = 2.2$ Hz, $J = 7.2$ Hz, 1.2H, H_{4Z}), 1.40–1.20 (m, 9H, $H_{5,6,7,8}$), 0.83 (t, 3H, $J = 6.8$ Hz, H_{10}). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 161.1$ (d, $J = 36$ Hz), 161.0 (d, $J = 26$ Hz), 148.0 (d, $J = 255$ Hz), 147.0 (d, $J = 250$ Hz), 123.8 (d, $J = 18$ Hz), 121.0 (d, $J = 12$ Hz), 61.5, 61.3, 31.4, 29.0 (d, $J = 2$ Hz), 29.0 (d, $J = 2$ Hz), 25.5 (d, $J = 5$ Hz), 24.2 (d, $J = 2$ Hz), 22.5, 22.4, 14.1, 14.0. ^{19}F NMR (282.5 MHz, $CDCl_3$): $\delta = -123.2$ (d, $J = 21.5$ Hz, 0.4F), −131.6 (d, $J = 33.3$ Hz, 0.6F). IR (neat): 2960, 2932, 1732, 1678, 1467, 1373, 1309, 1261, 1201, 1148, 1089, 765 cm^{-1}. MS (EI): $m/z = 188$ (M^+), 91, 41.