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tert-Butyl 3-Oxo-4-(phenylsulfinyl)-2-(triphenyl-λ^5-phosphanylidene)butanoate: A New Reagent for the Efficient Synthesis of Triphenylphosphorane Ylide Precursors to Vicinal Tricarbonyls from Alkyl Halides

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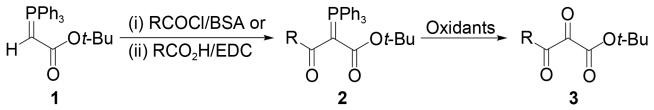
Vicinal tricarbonyl units[1] have been attractive and challenging research topics for synthetic and medicinal chemists not only because of the presence of these units in many bioactive natural products *e.g.*, FK-506,[2a] rapamycin,[2b] eurystatin,[2c] and cyclotryprostatin,[2d] but also because of the superb usefulness of these units for the synthesis of heterocyclic compounds.[3] Therefore, a lot of efforts have been devoted to developing these highly electrophilic units.[4] Wasserman *et al*. reported an unique synthetic route in which triphenylphosphorane ylides **2**, valuable precursors to vicinal tricarbonyls, are introduced in a convergent manner and then oxidized under mild reaction conditions (Scheme 1).[5]



Scheme 1. Wasserman's synthetic route for tricarbonyl units *via* triphenylphosphorane ylide precursors **2**.

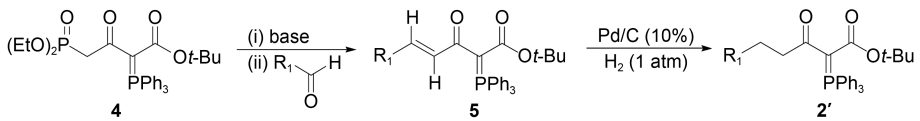
Despite the wide application of this route for the synthesis of complex molecules,[3,6] the key intermediates **2** should have been prepared only from carboxylic acids and acid chlorides. In order to circumvent this limitation and widen the scope, we have recently developed a new synthetic approach to triphenylphosphorane ylides (**5** & **2'**) from carbonyl compounds utilizing a new Horner-Wadsworth-Emmons (HWE) reagent **4** (Scheme 2).[7]

In a related study recently reported,[8] we have devised a new synthetic approach to cyanophosphorane ylides, precursors to α-keto amide/ester in Wasserman's protocol, from alkyl bromides utilizing a new sulfinyl reagent with α-keto cyanophosphorane subunit based on sulfoxide chemistry.[9] As an extention of this strategy for the synthesis of triphenylphosphorane ylide precursors (**5** & **2'**) from chemicals other than carboxylic acids and acid chlorides, herein we wish to report another new synthetic route for triphenylphosphorane ylides **5** from alkyl halides utilizing a new sulfinyl reagent **6** as the key reagent (Scheme 3).

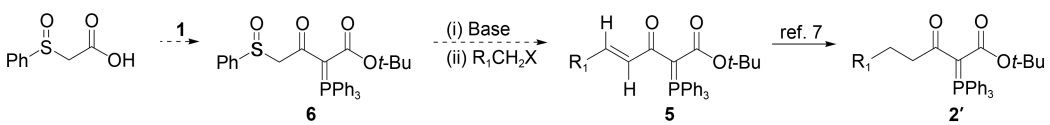
Results and Discussion

The new sulfinyl reagent **6** was prepared successfully from phenylsulfinylacetic acid and commercially available (*tert*-butoxycarbonylmethylene)triphenylphosphorane **1** according to our reported procedure[8] in 81% yield, and the representative results of our new approach using **6** as the key reagent are summarized in Table 1.

To get the optimum reaction conditions, NaH and benzyl chloride were tested first for the alkylation reaction. Although enolization of **6** was accomplished with a little excess of NaH (1.3 eq) in THF under mild conditions (rt, 15 min), alkylation of the resulting enolate with benzyl chloride (1.1 eq) was found to be almost inactive (*ca*. 10% progress) (run 1). Benzyl bromide, however, reacted smoothly with the resulting enolate under the same conditions to provide two diastereomeric alkylated intermediates **7a** (R = -Ph). These diastereomeric alkylated intermediates **7a** were separated by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc = 2/1), and their structure were confirmed by ^{1}H-NMR in which each *methine* proton next to carbonyl and sulfinyl moieties appears in the downfield region of 5.91 ppm (dd, J_1 = 11.2 Hz, J_2 = 3.9 Hz) and 5.97 ppm (dd, J_1 = 11.5 Hz, J_2 = 3.2 Hz), respectively. For the conversion of **7a** to **5a**, **7a** was treated first in refluxing THF for 24 h under Ar. Pyrolysis,

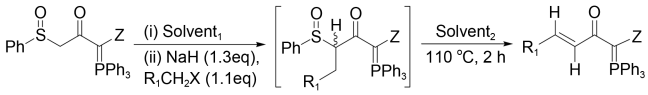


Scheme 2. A new approach to triphenylphosphorane ylide precursors (**5** & **2'**) from carbonyl compounds utilizing a new HWE reagent **4**.



Scheme 3. A new approach to triphenylphosphorane ylide precursors (**5** & **2'**) from alkyl halides utilizing new sulfinyl reagent **6**.

Table 1. Alkylation of **6** (Z = -CO_2*t*-Bu) with alkyl halides and subsequent pyrolysis of **7** to **5** under Ar



6 **7**

Run	$Solvent_1$[a]	R_1	X	$Solvent_2$[b]	**5** (Yield, %)[c,d]
1	THF	C_6H_5-	Cl	-	NA[e]
2	THF	C_6H_5-	Br	THF[f]	**5a** (45)
3	THF	C_6H_5-	Br	Toluene	**5a** (86)
4	THF	2-MeC_6H_4-	Br	Toluene	**5b** (89)
5	THF	4-(*t*-Bu)C_6H_4-	Br	Toluene	**5c** (81)
6	THF	$CH_3(CH_2)_6$-	Br	-	NA[e]
7	THF	$CH_3(CH_2)_6$-	I	Toluene	**5d** (71)
8	THF	$Ph(CH_2)_2$-	I	Toluene	**5e** (80)
9	DMF	C_6H_5-	Br	DMF	**5a** (87)
10	DMF	$CH_3(CH_2)_6$-	I	DMF	**5d** (73)

[a]THF, rt, NaH, 20 min, 0 °C, R_1CH_2X, 0 °C, 30 min, rt, 1 h, Ar or DMF, 0 °C, NaH, 20 min, R_1CH_2X, 0 °C, 30 min, rt, 1 h, Ar. [b]110 °C, 2 h, Ar. [c]Isolated yields after flash chromatography on SiO_2. [d](*E*)-Stereochemistry of **5** was confirmed by coupling constant (ca. 15.1-16.1 Hz) between the two vinylic protons. [e]Pyrolysis was not attempted. [f]Reflux, 24 h, Ar.

however, proceeded partly to afford triphenylphosphorane ylide **5a** in only 45% yield together with unknown by-products (run 2). Upon elevating the reaction temperature to 110 °C by replacing the solvent to toluene, pyrolysis was complete in 2 h in 86% yield (run 3). By following these optimized reaction protocols, various benzyl bromides were transformed cleanly to their corresponding ylides (**5b**, **5c**) in good yields (runs 4, 5).

Several alkyl halides were also examined to determine the scope of these optimized reaction protocols. Alkylation with octyl bromide under the standard conditions was found to be unsuccessful (*ca*. 25% progress) (run 6). Alkyl iodides such as octyl iodide and 1-iodo-3-phenylpropane, however, reacted readily with **6** under the standard conditions to produce the desired ylides (**5d**, **5e**) in good yields (runs 7, 8).

In order to carry out two-step procedure in the same solvent for operational simplicity, we turned our attention to DMF as the common solvent for alkylation and pyrolysis. Alkylations of **6** with benzyl bromide and octyl iodide were successfully accomplished in DMF under mild conditions (0 °C, 20 min, Ar), and also pyrolysis took place smoothly in DMF under the same conditions (110 °C, 2 h) as in toluene to afford the corresponding ylides (**5a**, **5d**) in good yields (runs 9, 10). The reaction patterns and yields of two-step procedure using DMF as the common solvent were almost similar to those of reaction using THF and toluene as each solvent for alkylation and pyrolysis.

The hydrogenation of **5** to **2'** should be straightforward under the standard conditions (Pd-C (10%), (THF/MeOH, 1/1), H_2 (1 atm)) according to our reported procedure.[7]

In summary, we have developed a new synthetic approach to triphenylphosphorane ylides **5**, valuable precursors to vicinal tricarbonyls, from alkyl halides utilizing a new sulfinyl reagent **6** as the key reagent. There are several advantages for this new approach *e.g.*, easy preparation of reagent **6** in good yield, highly stable solid of reagent **6** storable at ambient temperature, mild reaction conditions and good to excellent overall yields. Therefore, this one pot alkylative-elimination procedure could be a method of choice for the synthesis of triphenylphosphorane ylide precursors (**5** & **2'**) from alkyl halides. We are currently applying this new approach to heterocyclic/heteroaromatic/amino acid-derived halides, and the results will be reported in due course.

Experimental Section

General. All reactions were carried out in an oven-dried glassware under Ar. Melting points were determined on an Electrothermal melting-point apparatus and uncorrected. FT IR spectra were obtained on Jasco FT-IR/410 using KBr. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol JNM-EX400 FT NMR spectrometer using $CDCl_3$ as solvent, and chemical shifts (δ) are given in ppm downfield with respect to TMS. Mass spectra were measured with micrOTOF-Q in ESI mode. CHN analyses were done with Vario EL elemental analyzer. Flash column chromatography was carried out on silica gel (Merck, 230-400 mesh) and solvents were reported as V/V ratio mixture. THF was purified by distillation from Na/benzophenone. 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl (EDC), (*tert*-butoxycarbonylmethylene)triphenylphosphorane, NaH (60% in mineral oil), 4-dimethylaminopyridine (DMAP), dry DMF were purchased from Aldrich Chem. Co., and were used directly without further purification. Phenylsulfinylacetic acid was prepared from (phenylthio)acetic acid according to the reported procedure.[10]

***t*-Butyl 3-Oxo-4-(phenylsulfinyl)-2-(triphenyl-λ^5-phosphanylidene)butanoate (6).** To a stirred, precooled (0 °C) solution of phenylsulfinylacetic acid (1.07 g, 5.81 mmol) and (*tert*-butoxycarbonylmethylene)triphenylphosphorane (2.19 g, 1.0 eq) in dry CH_2Cl_2 (30 mL) were added EDC (1.11 g, 1.0 eq) and DMAP (70.9 mg, 0.1 eq), and the resulting mixture was stirred at 0 °C for 1 h, and then at rt for 12 h under Ar. The reaction was quenched by addition of water (20 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The solid residue was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 1/2) to provide **6** (2.55 g, 81%) as a white solid. mp 149-166 °C (decom.); IR (KBr) 3055, 2976, 1648, 1549, 1349, 1104, 1084, 751, 689, 543 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H), 4.44 (d, 1H, *J* = 13.7 Hz), 4.56 (d, 1H, *J* = 13.7 Hz), 7.36-7.60 (m, 12H), 7.63-7.78 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.96, 68.81, 68.89, 71.79, 72.85, 79.30, 124.53, 125.41, 126.34, 128.39, 128.52, 128.65, 128.80, 128.89, 130.34, 131.79, 131.82, 131.88, 131.90, 131.98, 132.08, 133.07, 133.17, 144.95, 166.84, 166.95, 186.31, 186.37; MS (ESI) calcd for $C_{32}H_{31}O_4PS$ $[M+H]^+$: 543.1. found: 543.1; Anal. calcd for $C_{32}H_{31}O_4PS$: C, 70.83; H, 5.76. found: C, 70.70; H, 5.78.

Typical Procedure for 5a using THF and Toluene as for $Solvent_1$ and $Solvent_2$. (i) NaH (11.4 mg, 1.3 eq, 60% in mineral oil) was added to a solution of **6** (119.4 mg, 0.22

mmol) in dry THF (10 mL), and the resulting slurry was stirred at rt for 20 min and cooled to 0 °C under Ar. To this was added benzyl bromide (28.8 μL, 1.1 eq) by syringe, and the resulting mixture was stirred at 0 °C for 30 min and at rt for 1 h under Ar. Evaporation of the solvent from the reaction mixture afforded a solid residue which was subjected to the next pyrolysis reaction without purification. (ii) The solid residue obtained from the alkylation step was combined with dry toluene (5 mL), and the resulting mixture was heated at 110 °C for 2 h under Ar. After removal of toluene under reduced pressure, the yellowish residue was purified by flash column chromatography on SiO_2 (CH_2Cl_2/EtOAc = 15/1) to provide **5a** (95.8 mg, 86%) as an off-white solid. mp 178-179.5 °C; IR (KBr) 1649, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9H), 7.22-7.32 (m, 3H), 7.39-7.59 (m, 12H), 7.68-7.76 (m, 6H), 8.20 (d, 1H, J = 15.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.13, 72.83, 73.54, 78.85, 126.26, 126.32, 126.79, 127.41, 127.97, 128.40, 128.47, 128.56, 131.42, 132.93, 132.99, 136.59, 137.22, 166.99, 167.08, 185.87, 185.89; MS (ESI) calcd for $C_{33}H_{31}O_3P$ $[M+H]^+$: 507.2. found: 507.2; Anal. calcd for $C_{33}H_{31}O_3P$: C, 78.24; H, 6.17. found: C, 78.06; H, 6.15.

Compound 5b: 89%; an off-white solid, mp 69-71 °C; IR (KBr) 1661, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9H), 2.36 (s, 3H), 7.07-7.20 (m, 3H), 7.41-7.55 (m, 9H), 7.66 (d, 1H, J = 15.6 Hz), 7.69-7.78 (m, 7H), 8.11 (d, 1H, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.95, 28.10, 72.50, 73.59, 78.79, 125.85, 126.52, 126.66, 127.39, 127.48, 127.59, 128.26, 128.42, 128.54, 130.22, 131.37, 131.40, 132.90, 132.99, 134.56, 134.59, 135.43, 135.44, 137.22, 166.96, 167.09, 185.94, 185.98; MS (ESI) calcd for $C_{34}H_{33}O_3P$ $[M+H]^+$: 521.2. found: 521.2.

Compound 5c: 81%; a pale-yellow solid, mp 215-217 °C; IR (KBr) 1622, 1549 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (s, 9H), 1.30 (s, 9H), 7.30-7.55 (m, 14H), 7.68-7.78 (m, 6H), 8.15 (d, 1H, J = 16.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.11, 31.18, 34.59, 72.52, 73.62, 78.74, 125.29, 125.38, 125.47, 126.68, 127.62, 127.70, 128.39, 128.51, 131.32, 131.35, 132.87, 132.97, 133.77, 133.77, 137.12, 151.66, 166.91, 167.04, 185.94, 185.99; MS (ESI) calcd for $C_{37}H_{39}O_3P$ $[M+H]^+$: 563.2. found: 563.2; Anal. calcd for $C_{37}H_{39}O_3P$: C, 78.98; H, 6.99. found: C, 78.63; H, 6.94.

Compound 5d: 71%; a white solid, mp 77-79 °C; IR (KBr) 1661, 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, J = 6.9 Hz), 1.06 (s, 9H), 1.20-1.32 (m, 8H), 1.38-1.47 (m, 2H), 2.18 (q, 2H, J = 6.9 Hz), 6.65 (dt, 1H, J_1 = 15.1 Hz, J_2 = 7.0 Hz), 7.37-7.52 (m, 10H), 7.63-7.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.08, 22.62, 28.07, 28.68, 29.13, 29.34, 31.77, 32.46, 78.67, 126.98, 127.60, 128.41, 131.31, 132.91, 132.97, 141.41, 166.99, 167.07, 186.57; MS (ESI) calcd for $C_{34}H_{41}O_3P$ $[M+H]^+$: 529.2. found: 529.2.; Anal. calcd for $C_{34}H_{41}O_3P$: C, 77.24; H, 7.82. found: C, 77.14; H, 7.84.

Compound 5e: 80%; a white solid, mp 46-48 °C; IR (KBr) 1663, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 2.51 (bq, 2H), 2.76 (t, 2H, J = 8.0 Hz), 6.71 (bq, 1H), 7.12-7.30 (m, 5H), 7.39-7.52 (m, 10H), 7.64-7.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.07, 34.36, 35.02, 71.55, 72.65, 78.71, 125.67, 126.73, 127.66, 128.22, 128.33, 128.39, 128.51, 128.85, 128.93, 131.33, 131.35, 132.88, 132.97, 139.95, 141.97, 166.98, 167.12, 186.40; MS (ESI) calcd for $C_{35}H_{35}O_3P$ $[M+H]^+$: 535.2. found: 535.2.

Typical Procedure for 5a using DMF as for Both Solvent$_1$ and Solvent$_2$. (i) To a stirred, precooled (0 °C) solution of **6** (119.4 mg, 0.22 mmol) in dry DMF (5 mL) was added NaH (11.4 mg, 1.3 eq, 60% in mineral oil), and the resulting slurry was stirred at 0 °C for 20 min under Ar. To this was added benzyl bromide (28.8 μL, 1.1 eq) by syringe, and the resulting mixture was stirred at 0 °C for 30 min and at rt for 1 h under Ar. (ii) A round-bottomed flask containing the reaction mixture in DMF was equipped with condenser, and the reaction mixture was heated at 110 °C for 2 h under Ar. Evaporation of DMF under high vacuum afforded a pale-brown residue which was purified by flash column chromatography on SiO_2 (CH_2Cl_2/EtOAc = 15/1) to afford **5a** (97.0 mg, 87%) as an off-white solid. Melting point and other spectroscopic data of this product were exactly matched with those of the same product prepared by using THF and toluene as for Solvent$_1$ and Solvent$_2$.

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