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단신 (Notes)

A New Synthesis of Phosphorane Ylide Precursors to Vicinal Tricarbonyls from Alkyl Halides Utilizing a Novel Phenylsulfonyl Reagent

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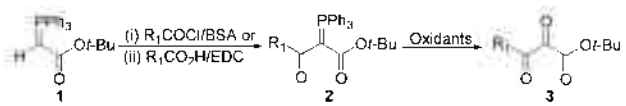
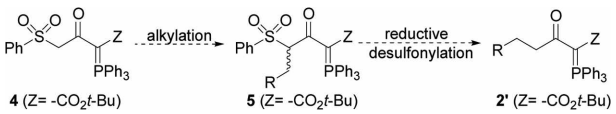
Due to the presence in many bioactive natural products such as FK-506,[1a] rapamycin,[1b] eurystatin,[1c] and cyclotryprostatin,[1d] and their usefulness in the synthesis of heterocyclic compounds,[2] the vicinal tricarbonyls have been attractive and challenging research topics for synthetic chemists.[3] Although Wasserman's synthetic approach to vicinal tricarbonyls has been extensively used in the synthesis of complex compounds,[2] it has a limitation that the phosphorane ylide **2**, the key precursors to vicinal tricarbonyls, should be prepared only from carboxylic acids or acid chlorides (*Scheme* 1).[4]

In previous studies[5] we have reported new approaches to **2** from carbonyl compounds using a new Horner-Wadsworth-Emmons reagent,[5a] and from alkyl halides using a new sulfinyl reagent[5b] to overcome the above-mentioned limitation.

In continuation of our study, we have recently developed a unique approach to α-keto cyanophosphorane ylides, the key precursors to α-keto amide/ester units in Wasserman's protocol, from alkyl halides using a novel phenylsulfonyl reagent.[6] As an extension of this chameleonic sulfone chemistry for the synthesis of phosphorene ylide precursors **2'** from chemicals other than carboxylic acids and acid chlorides, we herein wish to report a further method for forming **2'** from alkyl halides using a new phenylsulfonyl reagent **4** as the key reagent (*Scheme* 2).



***Scheme* 1.** Wasserman's synthetic route for vicinal tricarbonyls via phosphorane ylide precursors **2**.



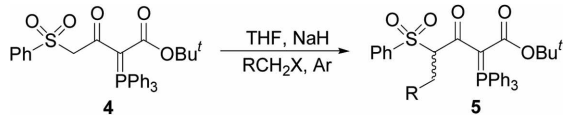
***Scheme* 2.** A new synthetic approach to phosphorane ylide precursors **2'** from alkyl halides utilizing a new phenylsulfonyl reagent **4**.

RESULTS AND DISCUSSION

The requisite new sulfonyl reagent **4** was successfully synthesized from phenylsulfonylacetic acid and phosphorane ylide **1** as a stable solid.[5b] Owing to good solubility of **4** in THF and good handling property of NaH as the base, THF and NaH were chosen for the alkylation of **4**, and the representative results are summarized in *Table* 1.

Although deprotonation of **4** with NaH proceeded smoothly, alkylation of the resulting anion with benzyl chloride was found almost inactive (Entry 1). Benzyl bromide, however, furnished benzylated sulfonyl ylide **5a** in 94% yield (Entry 2). This benzylated sulfonyl ylide **5a** was cleanly separated by flash chromatography, and its structure was unambiguously

***Table* 1.** Deprotonation of **4** with NaH/THF[a] and subsequent alkylation of the resulting sulfonyl anions with alkyl halides to provide **5**.[b]



Entry	Base	RCH_2X	Rxn time (h)	**5b** (%)[c]
1	NaH	$PhCH_2Cl$	24	NR[d]
2	NaH	$PhCH_2Br$	24	**5a** (94)
3	NaH	$CH_3(CH_2)_6CH_2Br$	52	**5b** (5)[e]
4	NaH	$CH_3(CH_2)_6CH_2I$	52	**5b** (84)
5	NaH	$Ph(CH_2)_2CH_2I$	12	**5c** (93)
6	NaH	$MeCH{=}CHCH_2Br$	24	**5d** (94)
7	NaH	2-(Bromomethyl)thiophene	33	**5e** (93)

Reaction conditions & reagents: a: 5 mL of dry THF per 0.1 mmol of **4** was used; b: NaH (1.3 eq), rt, 20 min then 0 °C, 20 min, RCH_2X (1.3 eq), 0 °C, 1 h, then rt for designated time (h); c: Isolated yield after flash chromatography on SiO_2; d: No reaction occurred; e: 87% of **4** was recovered.

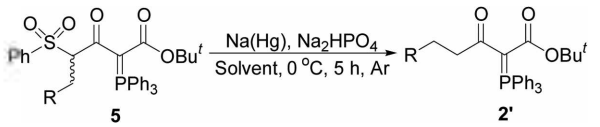
corroborated by ^{1}H-NMR spectrum in which one *methine* proton appears at 6.63 ppm (dd, 1H, J_1 = 12.2 Hz, J_2 = 3.4 Hz) and two *methylene* protons of benzyl subunit appear at 3.24 (bd) and 3.03 ppm (bt), respectively. Simple alkyl halide such as octyl bromide was found almost inactive towards **4**, however, octyl iodide provided much better yield (84%) of **5b** under standard conditions (Entry 3, 4). Similarly, 3-phenylpropyl iodide furnished **5c** in 93% yield (Entry 5). On the other hand, alkyl bromides with an alkenyl or a heteroaryl subunit such as thiophene were smoothly coupled with **4** under standard conditions to furnish sulfonyl ylides **5d** and **5e** in good yields (Entry 6-7).

We next attempted desulfonylation reaction of sulfonyl ylides **5**. Among the known reductive desulfonylation reagents[7] *e.g.*, Al(Hg), Na(Hg), Mg/MeOH, SmI_2, and Zn/NH_4Cl, Na(Hg) was determined to be the best reagent and desulfonylation results are summarized in *Table* 2.

Because of the low solubility of sulfonyl ylide **5a** in MeOH only, desulfonylation of **5a** was carried out in a mixed solvent (DMF + MeOH) with (Na(Hg)/Na_2HPO_4) at 0 °C for 5 h under an argon atmosphere. The desulfonylated ylide **2'a** was easily separated by flash chromatography, and the structure of **2'a** was clearly confirmed by ^{1}H-NMR spectrum which exhibited two *methylene* units at 2.91 ppm (*t*, 2H, J = 7.8 Hz) and 3.22 ppm (*t*, 2H, J = 7.8 Hz), respectively (Entry 1). However, sulfonyl ylides **5b-d** were efficiently desulfonylated in MeOH only under standard conditions to afford ylides **2'b-d** in 80–95% yields (Entry 2-4). Sulfonyl ylides **5e** necessitated a significant amount of DMF for its dissolution, however, desulfonylation reaction was smoothly taken place to produce ylide **2e** in 85% yield (Entry 5).

In summary, a new synthetic approach to phosphorane ylides **2'** has been developed from alkyl halides using a new sulfonyl reagent **4** as the key reagent. In view of the advantages of this new approach *e.g.*, easy preparation of **4** as a stable solid, mild conditions, wide scope of applicability, and good to excellent overall yields, this alkylation / desulfonylation protocol can be a method of choice for the synthesis of ylide precursors **2'**. We are currently applying this new approach to amino acid/peptide-derived halides, and the results will be reported in due course.

***Table* 2.** Reductive desulfonylation of **5** to **2'** with Na(Hg)/Na_2HPO_4.[a]



5 **2'**

Entry	**5**	R	Solvent[b]	**2'**(%)[c]
1	**5a**	Ph-	DMF/MeOH	**2'a** (71)
2	**5b**	$Me(CH_2)_6$-	MeOH	**2'b** (80)
3	**5c**	$Ph(CH_2)_2$-	MeOH	**2'c** (95)
4	**5d**	MeCH CH	MeOH	**2'd** (81)
5	**5e**	2-thiophenyl-	DMF/MeOH	**2'e** (85)

Reaction conditions & reagents: a: Na_2HPO_4 (4 eq), Na(Hg) (4 eq), 0 °C, 5 h, Ar; b: (i) (3 mL of DMF + 1 mL of MeOH) per 0.1 mmol of **5a**; (ii) 3 mL of MeOH per 0.1 mmol of **5b-d**; (iii) (10 mL of DMF + 1 mL of MeOH) per 0.1 mmol of **5e**; c: Isolated yield after flash chromatography on SiO_2.

EXPERIMENTAL

General

All reactions were carried out in an oven-dried glassware under Ar atmosphere. FTIR spectra were obtained on a Jasco FT-IR/410 using KBr. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Jeol JNM-EX400 FT NMR spectrometer using $CDCl_3$ as a solvent, and chemical shifts (δ) are given in ppm downfield with respect to TMS as an internal standard. Phenylsulfonylacetic acid, (*t*-butoxycarbonylmethylene)-triphenylphosphorane, 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide·HCl (EDC), 4-dimethylaminopyridine (DMAP), NaH (60% in mineral oil), alkyl bromides, and Na(Hg) (5% Na) were purchased from Aldrich Chem. Co., and used directly as received. Alkyl iodides were prepared from their corresponding bromides *via* Finkelstein reaction.[8] The sulfonyl ylides **5** except **5a** were analyzed only by mp, IR and ^{1}H- & ^{13}C-nmr spectra, and then subjected to the desulfonylation reaction without further analysis.

***t*-Butyl 3-Oxo-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)butanoate (4)**: To a stirred, precooled (0 °C) solution of phenylsulfonylacetic acid (0.600 g, 3.0 mmol) and (*t*-butoxycarbonylmethylene)triphenylphosphorane (1.139 g, 1.0 eq) in dry CH_2Cl_2 (20 mL) were added EDC (0.575 g, 1.0 eq) and DMAP (36.7 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 with 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 residue was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc − 5/1) to give **4** (1.123 g, 67%) as a white solid. mp 161–163 °C; IR (KBr) 688, 1072, 1160, 1306, 1341, 1601, 1662, 2969, 3058 cm^{-1}; ^{1}H NMR δ 1.02 (s, 9H), 4.95 (s, 2H), 7.22–7.78 (m, 20H); ^{13}C NMR δ 27.94, 63.24, 63.33, 73.21, 74.27, 79.51, 125.42, 126.35, 128.31, 128.40, 128.45, 128.59, 131.74, 131.76, 132.72, 133.17, 133.26, 140.60, 166.78, 166.90, 181.69, 181.76; Anal. calcd for $C_{32}H_{31}O_5PS$: C, 68.80; H, 5.59. found: C, 68.65; H, 5.63.

***Typical procedures for the alkylation of 4 to 5a*:** NaH

(10.4 mg, 1.3 eq) was added to a stirred solution of **4** (111.7 mg, 0.20 mmol) in dry THF (10 mL), and the resulting slurry was stirred at rt for 40 min under Ar. To this was added benzyl bromide (30.9 mL, 1.3 eq) by syringe, and the resulting mixture was stirred at rt for 24 h under Ar. The reaction mixture was quenched with CH_2Cl_2 (20 mL) and water (10 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 residue was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 10/1) to furnish **5a** (121.3 mg, 94%) as a white solid. mp 220–222 °C; IR (KBr) 1552, 1668 cm^{-1}; ^1H NMR δ 0.96 (s, 9H), 3.03 (bt, 1H, J = 12.8 Hz), 3.24 (bd, 1H, J = 11.2 Hz), 6.63 (dd, 1H, J_1 = 12.2 Hz, J_2 = 3.4 Hz), 7.15–7.56 (m, 25H); ^{13}C NMR δ 27.89, 33.15, 67.82, 67.90, 75.36, 76.42, 79.28, 125.46, 126.12, 126.39, 128.12, 128.13, 128.41, 128.54, 129.52, 129.66, 131.49, 131.52, 132.78, 133.06, 133.16, 137.35, 138.27, 166.26, 166.39, 183.79, 183.84; Anal. calcd for $C_{39}H_{37}O_5PS$: C, 72.20; H, 5.75. found: C, 71.86; H, 5.71.

Compound **5b**: A white solid, mp 48–49 °C; IR (KBr) 1556, 1663 cm^{-1}; ^1H NMR d 0.88 (s, 3H, J = 7.0 Hz), 1.07 (s, 9H), 1.14–1.40 (m , 12H), 1.67–1.83 (m, 2H), 7.30–7.55 (m, 14H), 6.10 (dd, 1H, J_1 = 10.6 Hz, J_2 = 3.9 Hz), 7.18–7.78 (m, 25H)); ^{13}C NMR δ 14.07, 22.63, 26.82, 27.53, 27.98, 29.11, 29.31, 29.45, 31.83, 67.78, 67.85, 75.30, 76.35, 79.42, 125.70, 126,63, 127.95, 128.45, 128.59, 129.53, 131.61, 131.63, 132.57, 133.13, 133.23, 138.38, 166.67, 166.79, 185.19, 185.24.

Compound **5c**: A white solid, mp 167–169 °C; IR (KBr) 1562, 1659 cm^{-1}; ^1H NMR δ 1.04 (s, 9H), 1.53–1.72 (m, 2H), 1.77–1.91 (m, 2H), 2.45–2.65 (m, 2H), 6.19 (dd, 1H, J_1 = 9.4 Hz, J_2 = 5.8 Hz), 7.05–7.75 (m, 25H)); ^{13}C NMR δ 27.32, 27.98, 28.92, 35.57, 67.49, 67.57, 75.34, 76.39, 79.50, 125.61, 126.55, 128.03, 128.18, 128.35, 128.49, 128.61, 129.52, 131.63, 131.66, 132.66, 133.12, 133.22, 138.32, 142.32, 166.70, 166.82, 185.01, 185.07.

Compound **5d**: A white solid, mp 178–179 °C; IR (KBr) 1552, 1660 cm^{-1}; ^1H NMR δ 1.07 (s, 9H), 1.67 (d, 3H, J = 5.8 Hz), 2.37–2.58 (m, 2H), 5.33–5.58 (m, 2H), 6.18 (dd, 1H, J_1 = 11.2 Hz, J_2 = 3.4 Hz), 7.16–7.78 (m, 20H); ^{13}C NMR δ 12.84, 18.01, 25.38, 27.98, 30.68, 67.07, 67.15, 75.33, 76.38, 79.42, 125.71, 126.31, 126.64, 127.71, 127.98, 128.12, 128.45, 128.58, 129.41, 129.55, 131.57, 131.60, 132.65, 133.13, 133.23, 138.24, 166.68, 166.81, 184.62, 184.66.

Compound **5e**: A yellow solid, mp 197–199 °C; IR (KBr) 1667, 1555 cm^{-1}; ^1H NMR δ 1.04 (s, 9H), 3.32 (d, 2H, J = 8.3 Hz), 6.58 (t, 1H, J = 8.3 Hz), 6.83 (dd, 1H, J_1 = 3.7 Hz, J_2 = 0.9 Hz), 6.92 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.7 Hz), 7.15 (dd, 1H, J_1 = 5.2 Hz, J_2 = 0.9 Hz), 7.22–7.63 (m, 20H); ^{13}C NMR δ 14.16, 21.00, 27.56, 27.96, 60.34, 67.90, 67.98, 75.68, 79.43, 123.77, 125.46, 126.13, 126.39, 126.50, 128.17, 128.45, 128.59, 129.63, 131.52, 131.55, 132.92, 133.09, 133.19, 137.97, 139.58, 166.37, 166.50, 183.26, 183.31.

Typical procedures for the reductive desulfonylation of 5a to 2'a: To a stirred, precooled (0 °C) solution of **5a** (129.7 mg, 0.20 mmol) in a mixed solvent (8 mL, DMF/MeOH = 3/1) were added Na_2HPO_4 (113.6 mg, 4.0 eq) and Na(Hg) (367.8 mg, 5%, 4.0 eq), and the reaction mixture was stirred at 0 °C for 5 h under Ar. EtOAc (20 mL) was added to the reaction mixture with vigorous stirring followed by H_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Residual DMF was removed under high vacuum to afford a solid residue, which was purified by flash chromatography (SiO_2, Hex/EtOAc = 2/1) to give **2'a** (72.6 mg, 71%) as a white solid. mp 156–158 °C (lit[5a] 160–162 °C); IR (KBr) 1552, 1663 cm^{-1}; ^1H NMR δ 1.03 (s, 9H), 2.91 (t, 2H, J = 7.8 Hz), 3.22 (t, 2H, J = 7.8 Hz), 7.10 –7.74 (m, 20H).

Compound **2'b**: A colorless liquid[5a]; IR (KBr) 1551, 1664 cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 7.1 Hz), 1.06 (s, 9H), 1.17–1.36 (m, 12H), 1.50–1.64 (m, 2H), 2.84 (t, 2H, J = 7.6 Hz), 7.37–7.77 (m, 15H).

Compound **2'c**: A white solid, mp 133–134 °C; IR (KBr) 1551, 1663 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 1.56–1.74 (m, 4H), 2.59 (t, 2H, J = 7.6 Hz), 2.90 (t, 2H, J = 7.1 Hz), 5.36–5.53 (m, 2H), 7.09–7.78 (m, 20H); ^{13}C NMR δ 25.59, 28.08, 31.41, 35.92, 39.57, 39.63, 70.68, 71.76, 78.33, 125.28, 126.83, 127.76, 128.01, 128.28, 128.37, 128.40, 131.24, 131.26, 131.88, 131.98, 132.08, 132.84, 132.93, 143.06, 167.15, 167.29, 197.39, 197.43; Anal. calcd for $C_{35}H_{37}O_3P$: C, 78.33; H, 6.95. found: C, 78.50; H, 7.66.

Compound **2'd**: A white solid; mp 153–154 °C; IR (KBr) 1549, 1654 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 1.61 (d, 3H, J = 4.9 Hz), 2.23–2.37 (m, 2H), 2.92 (t, 2H, J = 7.6 Hz), 5.36–5.53 (m, 2H), 7.37–7.79 (m, 15H); ^{13}C NMR δ 12.74, 17.92, 23.34, 28.11, 28.80, 39.69, 39.76, 70.55, 71.63, 78.33, 123.45, 124.25, 126.89, 127.81, 128.30, 128.42, 128.65, 131.24, 131.28, 131.51, 132.90, 132.99, 167.15, 167.28, 196.95, 196.98; Anal. calcd for $C_{30}H_{33}O_3P$: C, 76.25; H, 7.04. found: C, 76.49; H, 7.19.

Compound **2'e**: A white solid, mp 171–172 °C; IR (KBr) 1548, 1655 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 3.11 (t, 2H, J = 7.4 Hz), 3.28 (t, 2H, J = 7.4 Hz), 6.77 (dd, 1H, J_1 = 3.4 Hz, J_2 = 1.1 Hz), 6.87 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.4 Hz), 7.05

(dd, 1H, J_1 = 5.1 Hz, J_2 = 1.1 Hz), 7.36–7.75 (m, 15H); ^{13}C NMR δ 25.58, 28.13, 41.32, 41.39, 70.78, 71.86, 78.48, 122.48, 124.11, 126.41, 126.67, 127.60, 128.35, 128.48, 131.32, 131.34, 132.92, 133.02, 145.73, 167.15, 167.29, 195.38, 195.42; Anal. calcd for $C_{31}H_{31}O_3PS$: C, 72.35; H, 6.07. found: C, 71.88; H, 5.90.

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