http://dx.doi.org/10.5012/bkcs.2013.34.10.2953

A Versatile Synthesis of α-Keto (cyanomethylene)triphenylphosphorane Ylides from Alkyl Halides Utilizing a Noble Phenylsulfonyl Reagent

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Received May 22, 2013, Accepted July 12, 2013

A noble phenylsulfonyl reagent **8** having α-oxo (cyanomethylene)triphenylphosphorane ylide subunit readily condensed with various alkyl halides under basic conditions to afford β-alkyl-α-oxo-β-phenylsulfonyl (cyanomethylene)triphenylphosphorane ylides **9** in excellent yields. These sulfonyl ylides **9** were then reductively desulfonylated with Na(Hg)/Na_2HPO_4 in the presence of methanol to provide α-keto (cyanomethylene)-triphenylphosphorane ylides **2'** in good to excellent yields. Our new synthetic approach offers an expeditious access to various α-keto (cyanomethylene)triphenylphosphorane ylides from alkyl halides utilizing a new phenylsulfonyl reagent as the key reagent under mild reaction conditions in good overall yields.

Key Words : α-Keto amide/ester, α-Keto (cyanomethylene)triphenylphosphorane ylide, Alkylation, Desulfonylation, Sodium amalgam

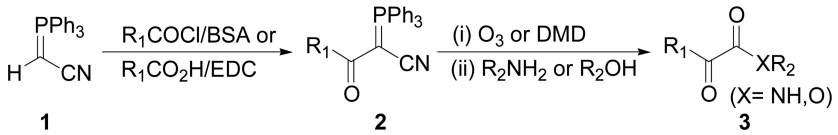
Introduction

The importance of α-keto amide/ester units from the chemical and medicinal points of view has well been documented in the literature,[1] and a number of synthetic approaches to these units have been developed.[2] Among the synthetic approaches reported, Wasseman's route based on phosphorane ylide chemistry appears to be the best approach to these units due to its mild reaction conditions and outstanding reaction convergence (Scheme 1).[3]

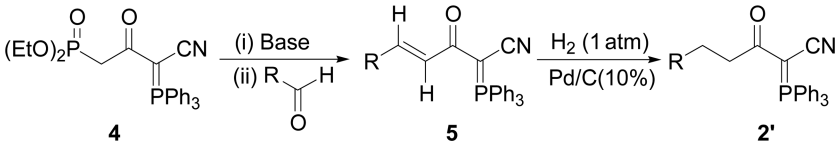
Therefore, this route has widely been utilized in the synthesis of numerous complicated bioactive compounds including peptides.[4] This route, however, has the limitation that α-keto (cyanomethylene)triphenylphosphorane ylides **2**, the key intermediates in Wasserman's route, can be prepared only from carboxylic acids or acyl chlorides.

In order to overcome this limitation and to expand the generality, we have developed new synthetic approaches to α-keto (cyanomethlene)triphenylphosphorane ylides (**5**, **2'**) from carbonyl compounds *via* Horner-Wadsworth-Emmons (HWE) reaction (Scheme 2),[5] and from alkyl bromides *via* alkylation-sulfoxide elimination protocol (Scheme 3).[6]

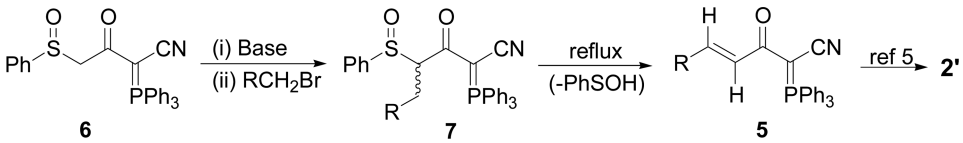
The sulfone-mediated methodologies in which sulfones are involved as activating groups and then removed after the required synthetic operations have well been exemplified in the literature.[7]



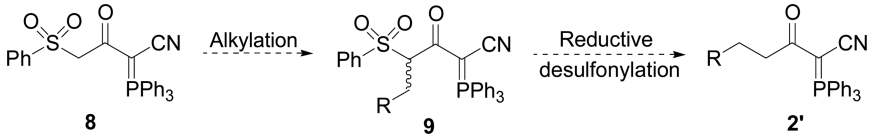
Scheme 1. Wasserman's synthetic route for α-keto amide/ester units.



Scheme 2. Synthetic approach to α-keto (cyanomethylene)triphenylphosphorane ylides (**5**, **2'**) from carbonyl compounds utilizing HWE reagent **4**.



Scheme 3. Synthetic approach to α-keto (cyanomethylene)triphenylphosphorane ylides (**5**, **2'**) from alkyl bromides utilizing phenylsulfinyl reagent **6**.



Scheme 4. A new approach to α-keto (cyanomethylene)triphenylphosphorane ylides **2'** from alkyl halides utilizing a new phenylsulfonyl reagent **8**.

In continuation of our effort to develop new synthetic approaches to α-keto (cyanomethylene)triphenylphosphorane ylides from readily available chemicals, we have devised a new synthetic approach based on the exciting sulfonechemistry as depicted in Scheme 4, and herein we wish to disclose our research results.

Results and Discussion

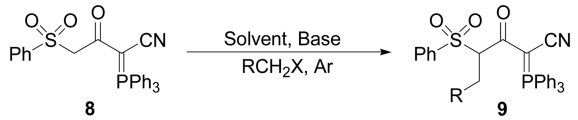
The study of new synthetic approach began with the attempted synthesis of the new phenylsulfonyl reagent **8**, which has been successfully prepared from the commercially available reagents, (phenylsulfonyl)acetic acid and (cyanomethylene)triphenylphosphorane, in the presence of EDC/DMAP in 86% yield according to the reported procedure.[3]

In order to obtain the basic information regarding the optimized reaction conditions for the alkylation reaction of **8**, compound **8** was reacted first with various bases and the resulting sulfonyl anion was attempted to be trapped with $PhCH_2X$ (X= Cl, Br) (Table 1).

Due to the very low solubility of **8** in THF, DMF and NaH were tested first as the solvent and the base, respectively. Although deprotonation of compound **8** with NaH appeared to proceed smoothly, alkylation of the resulting sulfonyl anion with benzyl chloride was found incomplete affording the alkylated ylide **9a** in 75% together with the recovered **8** in 12% yield (run 1). Benzyl bromide, however, was confirmed to be better than chloride counterpart with 88% yield of **9a** (run 2). This alkylated sulfonyl ylide **9a** was easily separated by flash column chromatography (SiO_2), and its structure was unambiguously corroborated by ^{1}H-NMR in which one *methine* proton appears at 5.22 ppm (dd) and two *methylene* protons of benzylic fragment appear at 3.15, 3.29 ppm (bt, dd). K_2CO_3 was then tested for **8** as the base, however, it required much excess of benzyl bromide (2.0 eq.) to complete the alkylation reaction (run 3, 4). We have also attempted DBU in DMF, and BuLi in THF as the base for the alkylation reaction (run 5, 6). These bases, however, could not bring the reaction to completion. Therefore, NaH and alkyl bromide were chosen as the standard base and the alkylating reagent, respectively, for the alkylation of **8** in DMF, and representative alkylation results are summarized in Table 1.

Under the standard conditions, 2-methylbenzyl bromide reacted smoothly with **8** to provide **9b** in 82% yield (run 7). The alkylation of **8** with octyl chloride under the standard conditions was determined to be almost ineffective (run 8). However, octyl bromide did provide much better yield of **9c** than chloride counterpart (run 9). Other simple alkyl bromide such as 3-phenylpropyl bromide gave the similar result as octyl bromide (run 10). Alkyl bromide substituted with alkenyl subunit gave rise to the alkylated ylide **9e** in 84% yield (run 11). Alkylation with heteroaromatic or heterocyclic subunit is of special interest due to the intrinsic bioactivities associated with these structural moieties.[8] Thiophene-derived alkyl bromide was smoothly coupled with **8** under the standard conditions to furnish the ylide **9f** in 83% yield (run 12). Alkyl bromides with heterocycle such as pyran or dioxane ring at β-position failed to complete the alkylation reaction (run 13, 15). However, iodo-analogues did afford the ylides **9g**, **9h** in 79% and 81% yield, respectively (run 14, 16). On the other hand, alkyl iodide having dioxane ring at α-position was confirmed to be almost unreactive with **8** under the standard conditions apparently

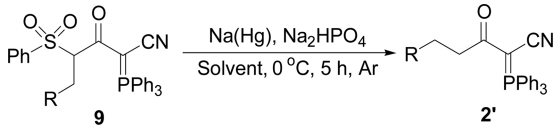
Table 1. Deprotonation of **8** with various bases and subsequent *in-situ* alkylation of the resulting sulfonyl anion with alkyl halides to provide **9**



Run	Solvent[a]	Base (eq.)[b]	RCH_2X (eq.)	**9** (%)[c]
1	DMF	NaH (1.3)	$PhCH_2Cl$ (1.3)	**9a** (75)[d]
2	DMF	NaH (1.3)	$PhCH_2Br$ (1.3)	**9a** (88)
3	DMF	K_2CO_3 (3.0)	$PhCH_2Br$ (1.3)	**9a** (47)[e]
4	DMF	K_2CO_3 (3.0)	$PhCH_2Br$ (2.0)	**9a** (86)
5	DMF	DBU (2.0)	$PhCH_2Br$ (1.3)	**9a** (36)[f]
6	THF	BuLi (1.1)	$PhCH_2Br$ (1.3)	**9a** (20)[g]
7	DMF	NaH (1.3)	2-Me$PhCH_2Br$ (1.3)	**9b** (82)
8	DMF	NaH (1.3)	$CH_3(CH_2)_6CH_2Cl$ (1.3)	**9c** (10)[h]
9	DMF	NaH (1.3)	$CH_3(CH_2)_6CH_2Br$ (1.3)	**9c** (85)
10	DMF	NaH (1.3)	$Ph(CH_2)_2CH_2Br$ (1.3)	**9d** (86)
11	DMF	NaH (1.3)	$PhCH{=}CHCH_2Br$ (1.3)	**9e** (84)
12	DMF	NaH (1.3)	2-ThiophenCH_2Br (1.3)	**9f** (83)
13	DMF	NaH (1.3)	YCH_2CH_2Br (1.3)[l]	**9g** (22)[i]
14	DMF	NaH (1.3)	YCH_2CH_2I (1.3)[l]	**9g** (79)
15	DMF	NaH (1.3)	ZCH_2CH_2Br (1.3)[m]	**9h** (36)[j]
16	DMF	NaH (1.3)	ZCH_2CH_2I (1.3)[m]	**9h** (81)
17	DMF	NaH (1.3)	ZCH_2I (1.3)[m]	**9i** (0)[k]

Reaction conditions & reagents: a: 1 mL of dry DMF or 15 mL of dry THF per 0.1 mmol of **8**; b: (i) NaH, rt, 20 min then 0 °C, 20 min, RCH_2X, 0 °C, 1 h then rt, 3 h; (ii) K_2CO_3, $PhCH_2Br$, rt, 24 h; (iii) DBU, $PhCH_2Br$, rt, 24 h; (iv) BuLi, −30 °C, 30 min, $PhCH_2Br$, −30 °C, 30 min then rt, 1 h; c: Isolated yield after flash column chromatography on SiO_2; d:12% of **8** was recovered; e: 36% of **8** was recovered; f: 45% of **8** was recovered; g: 70% of **8** was recovered; h: 78% of **8** was recovered; i: 65% of **8** was recovered; j: 53% of **8** was recovered; k: 95% of **8** was recovered; l: Y = (Tetrahydro-2*H*-pyran-2-yloxy); m: Z = (1,3-Dioxan-2-yl).

Table 2. Reductive desulfonylation of **9** to **2'** with Na(Hg)/ Na_2HPO_4 under mild conditions[a]



Run	9	R	Solventb	2' (%)[c]
1	**9a**	Ph-	DMF/MeOH	**2'a** (82)
2	**9b**	2-MePh-	DMF/MeOH	**2'b** (82)
3	**9c**	$Me(CH_2)_6$-	MeOH	**2'c** (88)
4	**9d**	$Ph(CH_2)_2$-	DMF/MeOH	**2'd** (86)
5	**9e**	PhCH=CH-	DMF/MeOH	**2'e** (85)
6	**9f**	2-thiophenyl-	DMF/MeOH	**2'f** (86)
7	**9g**	YCH_2-[d]	DMF/MeOH	**2'g** (85)
8	**9h**	ZCH_2-[e]	DMF/MeOH	**2'h** (80)

Reaction conditions & reagents: a: Na_2HPO_4 (4 eq.), Na(Hg) (4 eq.), 0 °C, 5 h, Ar; b: (i) (7 mL of DMF + 1 mL of MeOH) per 0.1 mmol of **9a-b**, **9d-e**, **9g-h**; (ii) 5 mL of MeOH per 0.1 mmol of **9c**; (iii) (10 mL of DMF + 1 mL of MeOH) per 0.1 mmol of **9f**; c: Isolated yield after flash column chromatography on SiO_2; d: Y = (Tetrahydro-2*H*-pyran-2-yloxy); e: Z = (1,3-Dioxan-2-yl).

due to the huge steric and/or electronic repulsion between the incoming sulfonyl anion nucleophile and the dioxane ring system (run 17).

With a variety of alkylated sulfonyl ylides **9** in hand, we next have to tackle the critical desulfonylation reaction of ylides **9**. For the reductive removal of the phenylsulfonyl moiety from ylides **9**, a number of reagents *e.g.*, Al(Hg),[9a] Na(Hg),[9b] Mg/MeOH,[9c] SmI_2,[9d] Zn/NH_4Cl,[9e] $Na_2S_2O_4$,[9f] and (n-Bu)$_3$SnH/AIBN[9g] have been tested for ylide **9a**. Among those reagents examined, Na(Hg) was confirmed to be the best in terms of the reaction progress and the desulfonylation yield (82%, **2'a**), and other desulfonylation results of ylides **9** using Na(Hg) are summarized in Table 2.

The desulfonylated ylide **2'a** was easily separated by flash column chromatography (SiO_2), and the structure of **2'a** was unambiguously confirmed by ^{1}H-NMR which shows two *methylene* protons at 2.99 and 3.05 ppm as two triplet peaks (J = 6.6 Hz, J = 6.6 Hz).

Under the same conditions as for **9a** (Na(Hg) (4 eq.), Na_2HPO_4 (4 eq.), 0 °C, 5 h, Ar), other phenylsulfonyl ylides (**9b**, **9d-9h**) were cleanly desulfonylated in a mixed solvent (DMF plus MeOH) to afford ylides (**2'b**, **2'd-2'h**), respectively, in the range of 80-86% yields. Phenylsulfonyl ylide **9c**, however, was completely desulfonylated in dry methanol only under the standard conditions due to the good solubility of **9c** in methanol.

Experimental Section

All reactions were carried out in an oven-dried glassware under an argon atmosphere. Melting points were determined on an electrothermal melting point apparatus and were uncorrected. FT IR 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 solvent, and chemical shifts (δ) are given in ppm downfield with respect to the solvent or tetramethylsilane as an internal standard. Mass spectra were measured with a Waters XEVO TQ-S in AP/CI mode. Flash column chromatography was carried out on silica gel (Merck, 230-400 mesh) and solvents were reported as v/v ratio mixture. (Phenylsulfonyl)acetic acid, (triphenylphosphoranylidene)acetonitrile,1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl (EDC), 4-dimethylaminopyridine (DMAP), NaH (60% in mineral oil), and Na(Hg) (5% Na) were purchased from Aldrich Chem. Co., and used directly as received. All alkyl bromides except 2-(bromomethyl)thiophene, dry DMF, and dry methanol were purchased from the commercial sources and used as received. Alkyl iodides were synthesized from their corresponding bromides *via* Finkelstein reaction (reflux with NaI (5.0 eq.) in dry acetone for 7 h under Ar).[10] The newly prepared cyanophosphorane ylides **9** were analyzed by IR, ^{1}H- & ^{13}C-NMR, and LRMS, and then utilized for the desulfonylation reaction without further analysis. The desulfonylated α-keto cyanophosphorane ylides (**2'a-2'd**) are known compounds and their physical and spectroscopic data (mp, IR, ^{1}H-NMR) are exactly matched with reported values.[5b] Compound **8** and other desulfonylated α-keto cyanophosphorane ylides (**2'e-2'h**) were fully characterized by their mp, IR, ^{1}H- & ^{13}C-NMR, LRMS, and CHN analysis.

Synthesis of 3-Oxo-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)butanenitrile (8). To a stirred, precooled (0 °C) solution of (phenylsulfonyl)acetic acid (1.42 g, 7.10 mmol) and (triphenylphosphoranylidene)acetonitrile (2.14 g, 1.0 eq.) in dry CH_2Cl_2 (30 mL) were added EDC (1.36 g, 1.0 eq.) and DMAP (86.7 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 by the addition of H_2O (20 mL), and the organic layer was separated. The aqueous layer was extracted further 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 on SiO_2 (CH_2Cl_2/EtOAc, 5/1) to provide **8** (2.95 g, 86%) as a white solid. mp 232-235 °C; IR (KBr) 2174, 1597, 1307, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.47 (s, 2H), 7.42-7.92 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.72, 53.96, 63.44, 63.52, 121.53, 122.46, 128.43, 128.83, 129.16, 129.29, 133.39, 133.43, 133.47, 133.62, 133.72, 139.84, 181.88, 181.93; MS (AP/CI) *m/z* 484 [M+H]$^+$; Anal. calcd for $C_{28}H_{22}NO_3PS$: C, 69.55; H, 4.59; N, 2.90, found: C, 69.38; H, 4.48; N, 2.97.

General Experimental Procedures for the Synthesis of Ylide 9 from 8. To a stirred solution of **8** (120.9 mg, 0.25 mmol) in dry DMF (3 mL) was added NaH (13.0 mg, 1.3 eq.), and the resulting mixture was stirred at rt for 20 min and then at 0 °C for 20 min under Ar. Alkyl halide (X = Cl, Br or I, 1.3 eq.) was added to this solution by syringe, and the reaction mixture was stirred at 0 °C for 1 h and then at rt for 3 h under Ar. The reaction mixture was combined with CH_2Cl_2 (20 mL) with stirring followed by water (10 mL). The lower organic layer was separated and the aqueous layer

was extracted further with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Residual DMF was distilled off *via* vacuum distillation to afford an-off white solid residue. The solid residue was purified by flash column chromatography on SiO_2 to provide **9** as a stable solid.

3-Oxo-5-phenyl-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)pentanenitrile (9a). (Method I) Benzyl chloride (37.4 μL, 1.3 eq.) was used as an alkyl halide, and the product **9a** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 75% yield along with the recovered starting material **8** (12%). A white solid; mp 263-265 ºC; IR (KBr) 2177, 1596, 1300, 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (bt, 1H, J = 12.7 Hz), 3.29 (dd, 1H, J_1 = 13.4 Hz, J_2 = 3.1 Hz), 5.22 (dd, 1H, J_1 = 12.7 Hz, J_2 = 3.1 Hz), 7.15-7.82 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.06, 53.87, 55.11, 70.88, 70.96, 120.94, 121.09, 121.45, 122.38, 126.72, 128.50, 128.61, 129.04, 129.17, 129.30, 129.48, 133.15, 133.18, 133.50, 133.58, 133.69, 136.31, 137.84, 184.37, 184.42; MS (AP/CI) *m/z* 574 [M+H]$^+$; Anal. calcd for $C_{35}H_{28}NO_3PS$: C, 73.28; H, 4.92; N, 2.44, found: C, 72.96; H, 4.97; N, 2.50. (Method II) Benzyl bromide (38.6 μL, 1.3 eq.) was used as an alkyl halide, and the product separated **9a** by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 88% yield is exactly same as that from benzyl chloride. (Method III) To a stirred solution of **8** (120.9 mg, 0.25 mmol) in dry DMF (3 mL) were added K_2CO_3 (103.7 mg, 3.0 eq.) and benzyl bromide (59.4 μL, 2.0 eq.), and the resulting mixture was stirred at rt for 24 h under Ar. The reaction mixture was combined with CH_2Cl_2 (20 mL) with stirring followed by water (10 mL). The lower organic layer was separated and the aqueous layer was extracted further with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Residual DMF was distilled off *via* vacuum distillation to afford an off-white solid residue, which was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) to furnish **9a** in 86% yield. The product separated **9a** is exactly same as that from benzyl chloride.

5-(2-Methylphenyl)-3-oxo-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)pentanenitrile (9b). 2-Methylbenzyl bromide (43.4 μL, 1.3 eq.) was used as an alkyl halide, and the product **9b** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 82% yield. A white solid; mp 224-225 ºC; IR (KBr) 2177, 1591, 1306, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3H), 3.19 (dd, 1H, J_1 = 13.4 Hz, J_2 = 2.9 Hz), 3.27 (bt, 1H, J = 12.4 Hz), 5.18 (dd, 1H, J_1 = 12.0 Hz, J_2 = 2.9 Hz), 7.03-7.91 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.16, 30.39, 53.69, 54.91, 69.71, 69.79, 121.00, 121.16, 121.45, 122.38, 125.74, 126.88, 128.72, 129.04, 129.17, 129.37, 130.17, 130.64, 133.18, 133.21, 133.53, 133.63, 133.74, 134.37, 136.90, 138.10, 184.35, 184.40; MS (AP/CI) *m/z* 588 [M+H]$^+$.

3-Oxo-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)dodecanenitrile (9c). (Method I) Octyl chloride (55.2 μL, 1.3 eq.) was used as an alkyl halide, and the product **9c** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 15/1) in 10% yield along with the recovered starting material **8** (78%). A white solid; mp 138-140 ºC; IR (KBr) 2178, 1592, 1306, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, J = 6.3 Hz), 1.15-1.39 (m, 12H), 1.77-1.99 (m, 2H), 4.81 (dd, 1H, J_1 = 11.0 Hz, J_2 = 3.2 Hz), 7.36-7.78 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.07, 22.60, 26.75, 27.51, 29.03, 29.18, 29.27, 31.77, 53.88, 55.11, 70.44, 70.51, 121.18, 121.33, 121.79, 122.72, 128.50, 129.11, 129.23, 129.41, 133.30, 133.34, 133.67, 133.77, 138.14, 185.85, 185.89; MS (AP/CI) *m/z* 596 [M+H]$^+$. (Method II) Octyl bromide (56.5 μL, 1.3 eq.) was used as an alkyl halide, and the product separated **9c** by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 15/1) in 85% is exactly same as that from octyl chloride.

3-Oxo-7-phenyl-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)heptanenitrile (9d). 1-Bromo-3-phenylpropane (49.4 μL, 1.3 eq.) was used as an alkyl halide, and the product **9d** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 15/1) in 86% yield. A white solid; mp 183-185 ºC; IR (KBr) 2177, 1593, 1306, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.73 (m, 2H), 1.82-2.09 (m, 2H), 2.47-2.68 (m, 2H), 4.86 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.9 Hz), 7.02-7.82 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.17, 28.72, 35.37, 53.99, 55.22, 70.09, 70.16, 121.11, 121.27, 121.58, 122.51, 125.77, 128.21, 128.25, 128.51, 129.06, 129.19, 129.30, 133.28, 133.31, 133.35, 133.57, 133.67, 138.01, 141.57, 185.53, 185.58; MS (AP/CI) *m/z* 602 [M+H]$^+$.

(6*E*)-3-Oxo-7-phenyl-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)hept-6-enenitrile (9e). Cinnamyl bromide (48.1 μL, 1.3 eq.) was used as an alkyl halide, and the product **9e** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 15/1) in 84% yield. A white solid; mp 230-232 ºC; IR (KBr) 2180, 1596, 1305, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72-2.90 (m, 2H), 5.01 (dd, 1H, J_1 = 10.5 Hz, J_2 = 4.2 Hz), 6.07-6.18 (m, 1H), 6.42 (d, 1H, J_1 = 15.6 Hz), 7.22-7.82 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.22, 53.59, 54.81, 69.43, 69.51, 121.47, 122.40, 123.68, 126.35, 127.51, 128.55, 128.57, 129.04, 129.16, 129.48, 133.21, 133.23, 133.49, 133.58, 133.69, 133.77, 136.84, 137.79, 184.73, 184.78; MS (AP/CI) *m/z* 600 [M+H]$^+$.

3-Oxo-2-(triphenyl-λ^5-phosphanylidene)-4-(phenylsulfonyl)-5-(thiophen-2-yl)pentanenitrile (9f). 2-(Bromomethyl)thiophene (57.5 mg, 1.3 eq.) was prepared according to the reported procedure,[11] and used directly for the alkylation reaction. The product **9f** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 83% yield. An off-white solid; mp 265-267 ºC; IR (KBr) 2177, 1595, 1308, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.38 (dd, 1H, J_1 = 14.3 Hz, J_2 = 3.7 Hz), 3.47 (dd, 1H, J_1 = 14.3 Hz, J_2 = 11.7 Hz), 5.20 (dd, 1H, J_1 = 11.7 Hz, J_2 = 3.7 Hz), 6.84 (d, 1H, J = 3.4 Hz), 6.95 (dd, 1H, J_1 = 5.0 Hz, J_2 = 3.4 Hz), 7.19 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.2 Hz), 7.37-7.82 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.56, 53.42,

54.27, 55.51, 70.92, 70.99, 121.01, 121.52, 122.46, 124.40, 126.41, 126.80, 128.74, 129.11, 129.25, 129.52, 133.25, 133.27, 133.70, 133.80, 137.75, 138.52, 184.07, 184.12; MS (AP/CI) *m/z* 580 $[M+H]^+$.

3-Oxo-4-(phenylsulfonyl)-6-(tetrahydro-2*H*-pyran-2-yloxy)-2-(triphenyl-λ^5-phos-phanylidene)hexanenitrile (9g). (Method I) 2-(2-Bromoethoxy)tetrahydro-2*H*-pyran (49.1 μL, 1.3 eq.) was used as an alkyl halide, and the product **9g** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 5/1) in 22% yield along with the recovered starting material **8** (65%). A white solid; mp 157-159 °C; IR (KBr) 2179, 1592, 1307, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.93 (m, 6H), 2.11-2.25 (m, 2H), 3.18-3.21 (m, 0.5H), 3.36-3.51 (m, 1.5H), 3.61-3.94 (m, 2H), 4.54 (t, 0.5H, *J* = 3.4 Hz), 4.60 (t, 0.5H, *J* = 3.4 Hz), 5.02-5.13 (m, 1H), 7.37-7.72 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.97, 19.12, 25.41, 25.48, 27.76, 28.16, 30.36, 30.45, 53.98, 54.06, 55.21, 55.29, 61.65, 62.03, 63.72, 64.00, 67.66, 67.71, 67.73, 67.79, 98.39, 98.97, 120.73, 120.78, 120.89, 120.93, 121.86, 122.79, 128.55, 129.14, 129.26, 129.42, 133.32, 133.35, 133.59, 133.70, 133.72, 133.80, 133.83, 138.10, 138.14, 185.20, 185.25, 185.33, 185.38; MS (AP/CI) *m/z* 612 $[M+H]^+$. (Method II) 2-(2-Iodoethoxy)tetrahydro-2*H*-pyran (83.2 mg, 1.3 eq.) was used as an alkyl halide, and the product separated **9g** by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 5/1) in 79% yield is exactly same as that from 2-(2-bromoethoxy)tetrahydro-2*H*-pyran.

6-(1,3-Dioxan-2-yl)-3-oxo-4-(phenylsulfonyl)-2-(triphenyl-λ^5-phosphanylidene)hexanenitrile (9h). (Method I) 2-(2-Bromoethyl)-1,3-dioxane (44.3 μL, 1.3 eq.) was used as an alkyl halide, and the product **9h** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 5/1) in 36% yield along with the recovered starting material **8** (53%), A white foam; mp 82-103 °C; IR (KBr) 2178, 1592, 1307, 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.34 (m, 1H), 1.50-1.72 (m, 2H), 1.91-2.12 (m, 3H), 3.61-3.79 (m, 2H), 3.95-4.18 (m, 2H), 4.52 (t, 1H, *J* = 4.9 Hz), 4.90-5.03 (m, 1H), 7.36-7.82 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.07, 25.69, 31.39, 54.05, 55.28, 66.74, 69.64, 69.72, 101.11, 121.03, 121.19, 121.86, 122.79, 128.50, 129.11, 129.24, 129.36, 133.25, 133.28, 133.71, 133.81, 138.23, 185.44, 185.49; MS (AP/CI) *m/z* 598 $[M+H]^+$. (Method II) 2-(2-Iodoethyl)-1,3-dioxane (78.7 mg, 1.3 eq.) was used as an alkyl halide, and the product separated **9h** by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 5/1) in 81% yield is exactly same as that from 2-(2-bromoethyl)-1,3-dioxane.

General Experimental Procedures for the Reductive Desulfonylation of 9 to 2' using Na(Hg)/Na_2HPO_4. To a stirred, precooled (0 °C) solution of ylide **9** (0.20 mmol) in a dry mixed solvent (16 mL, DMF/MeOH = 7/1) were added Na_2HPO_4 (114.0 mg, 4.0 eq.) and Na(Hg) (368.0 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 (10 mL). The upper organic layer was separated and the aqueous layer was extracted further with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Residual DMF was distilled off *via* vacuum distillation to provide an off-white solid residue. The solid residue was purified by flash column chromatography on silica gel to afford the pure compound **2'** as a stable solid. Dry methanol only (5 mL of MeOH per 0.1 mmol of **9c**) or a dry mixed solvent (10 mL of DMF plus 1 mL of MeOH per 0.1 mmol of **9f**) was utilized as the reaction medium, respectively.

3-Oxo-5-phenyl-2-(triphenyl-λ^5-phosphanylidene)pentanenitrile (2'a). The product **2'a** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 82% yield. A white solid; mp 170-172 °C (lit[5b] 172-174 °C); IR (KBr) 2172, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.99 (t, 2H, *J* = 6.6 Hz), 3.05 (t, 2H, *J* = 6.6 Hz), 7.15-7.32 (m, 5H), 7.42-7.68 (m, 15H).

5-(2-Methylphenyl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)pentanenitrile (2'b). The product **2'b** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 82% yield. A white solid; mp 163-165 °C (lit[5b] 161-162 °C); IR (KBr) 2170, 1579 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.98 (bs, 4H), 7.08-7.26 (m, 4H), 7.46-7.66 (m, 15H).

3-Oxo-2-(triphenyl-λ^5-phosphanylidene)dodecanenitrile (2'c). The product **2'c** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 88% yield. A white solid; mp 115-116 °C (lit[5b] 116-117 °C); IR (KBr) 2173, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.18-1.40 (m, 12H), 1.57-1.72 (m, 2H), 2.68 (t, 2H, *J* = 7.6 Hz), 7.47-7.67 (m, 15H).

3-Oxo-7-phenyl-2-(triphenyl-λ^5-phosphanylidene)heptanenitrile (2'd). The product **2'd** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 86% yield. A white solid; mp 124-126 °C (lit[5b] 126-128 °C); IR (KBr) 2169, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60-1.80 (m, 4H), 2.63 (t, 2H, *J* = 7.3 Hz), 2.73 (t, 2H, *J* = 7.3 Hz), 7.13-7.30 (m, 5H), 7.46-7.66 (m, 15H).

(6*E*)-3-Oxo-7-phenyl-2-(triphenyl-λ^5-phosphanylidene)-hept-6-enenitrile (2'e). The product **2'e** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 85% yield. A white solid; mp 154-156 °C; IR (KBr) 2175, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.59 (bq, 2H, *J* = 6.8 Hz), 2.89 (t, 2H, *J* = 7.1 Hz), 6.30 (dt, 1H, J_1 = 16.1 Hz, J_2 = 6.8 Hz), 6.46 (d, 1H, *J* = 16.1 Hz), 7.17-7.66 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.80, 38.64, 38.70, 48.11, 49.37, 122.71, 123.65, 126.07, 126.79, 128.39, 128.97, 129.10, 129.71, 130.46, 132.95, 132.97, 133.47, 133.57, 137.73, 196.06, 196.09; MS (AP/CI) *m/z* 460 $[M+H]^+$; Anal. calcd for $C_{31}H_{26}NOP$: C, 81.03; H, 5.70; N, 3.05, found: C, 81.21; H, 5.58; N, 3.37.

3-Oxo-5-(thiophen-2-yl)-2-(triphenyl-λ^5-phosphanylidene)pentanenitrile (2'f). The product **2'f** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 20/1) in 86% yield. An off-white solid; mp 151-153 °C; IR (KBr) 2174, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.10 (t, 2H, *J* = 6.8 Hz), 3.19 (t, 2H, *J* = 6.8 Hz), 6.87 (bd,

1H, J = 2.9 Hz), 6.94 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.4 Hz), 7.14 (dd, 1H, J_1 = 4.9 Hz, J_2 = 1.0 Hz), 7.45-7.68 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.18, 40.48, 40.55, 48.27, 49.52, 122.34, 122.50, 122.68, 123.00, 123.61, 124.53, 126.55, 129.01, 129.13, 132.98, 133.01, 133.49, 133.59, 144.34, 195.00, 195.03; MS (AP/CI) *m/z* 440 $[M+H]^+$; Anal. calcd for $C_{27}H_{22}NOPS$: C, 73.78; H, 5.05; N, 3.19, found: C, 73.60; H, 5.00; N, 3.27.

3-Oxo-6-(tetrahydro-2*H*-pyran-2-yloxy)-2-(triphenyl-λ^5-phosphanylidene)hexane-nitrile (2'g). The product **2'g** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 3/1) in 85% yield. An off-white solid; mp 127-129 °C; IR (KBr) 2171, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.75 (m, 5H), 1.77-1.89 (m, 1H), 1.91-2.02 (m, 2H), 2.80 (t, 2H, J = 7.6 Hz), 3.38-3.54 (m, 2H), 3.71-3.81 (m, 1H), 3.82-3.93 (m, 1H), 4.61 (t, 1H, J = 3.4 Hz), 7.47-7.67 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.38, 25.45, 25.50, 30.64, 36.10, 36.17, 47.63, 48.89, 61.97, 66.81, 98.50, 122.91, 123.84, 129.00, 129.12, 132.97, 133.00, 133.49, 133.58, 196.64, 196.67; MS (AP/CI) *m/z* 472 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}NO_3P$: C, 73.87; H, 6.41; N, 2.97, found: C, 73.73; H, 6.45; N, 2.96.

6-(1,3-Dioxan-2-yl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)hexanenitrile (2'h). The product **2'h** was separated by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 2/1) in 80% yield. An off-white solid; mp 142-144 °C; IR (KBr) 2177, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21-1.37 (m, 1H), 1.55-1.85 (m, 4H), 1.97-2.15 (m, 1H), 2.73 (t, 2H, J = 7.3 Hz), 3.75 (td, 2H, J_1 = 12.2 Hz, J_2 = 2.4 Hz), 4.09 (dd, 2H, J_1 = 10.7 Hz, J_2 = 4.9 Hz), 4.55 (t, 1H, J = 4.9 Hz), 7.46-7.69 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.93, 25.89, 34.53, 38.95, 39.02, 47.63, 66.86, 102.18, 122.62, 122.79, 123.00, 123.93, 129.04, 129.16, 132.99, 133.02, 133.56, 133.66, 196.84, 196.88; MS (AP/CI) *m/z* 458 $[M+H]^+$; Anal. calcd for $C_{28}H_{28}NO_3P$: C, 73.51; H, 6.17; N, 3.06, found: C, 73.62; H, 6.34; N, 3.23.

Conclusion

In summary, we have developed a new synthetic approach to α-keto (cyanomethylene)triphenylphosphorane ylides from alkyl halides utilizing a new sulfonyl reagent **8** as the key reagent. There are several advantages expected from this new approach, *e.g.*, (i) new sulfonyl reagent **8** is easy to prepare in good yield, and stable solid to handle at ambient temperature; (ii) the reaction conditions are mild, and overall yields are good to excellent; (iii) the reaction procedures are highly reproducible, and also provide direct access to β,γ-saturated, α-keto (cyanomethylene)triphenylphosphorane ylides from alkyl halides. Therefore, this new alkylation-desulfonylation protocol offers an expeditious approach to α-keto (cyanomethylene)triphenylphosphorane ylides from alkyl halides. We are currently trying to apply the same approach to the synthesis of α-keto alkoxycarbonyltriphenylphosphorane ylides,[12] triphenylphosphorane ylide precursors to tricarbonyl units, using a new sulfonyl reagent having alkoxycarbonylphosphorane subunit.

Acknowledgments. The authors gratefully acknowledge the financial support from Woosuk University as well as from the LINC program funded by Korean Ministry of Education, Science and Technology in 2013.

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