3-Oxo-2-(triphenyl-λ^5-phosphanylidene)-4-(phenylsulfinyl)butanenitrile: An Efficient Reagent for α-Keto (Cyanomethylene)triphenylphosphoranes from Alkyl Bromides

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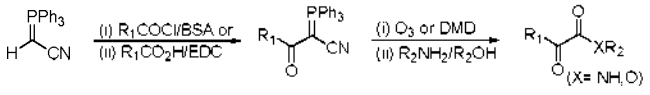
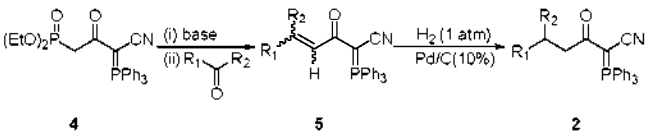
Due to the presence in biologically important natural products as the highly electrophilic structural unit[1] and incorporation into many clinically active synthetic peptides as the ketone pharmacophore in recent years,[2] α-keto amide/ester units have been active research topics for synthetic and medicinal chemists.[3] Wasserman *et al.* reported an elegant synthetic approach to these units utilizing cyanophosphorane ylide chemistry under very mild conditions in a convergent manner (Scheme 1).[4]

This approach has been successfully utilized for the synthesis of biologically active compounds.[5] however, there is a limitation that the key intermediates **2** can be prepared only from carboxylic acids and acid chlorides. In order to circumvent this problem and widen the scope, we recently reported a new synthetic route for α-keto cyanophosphoranes **2** from carbonyl compounds *via* Horner-Wadsworth-Emmons reaction (Scheme 2).[6]

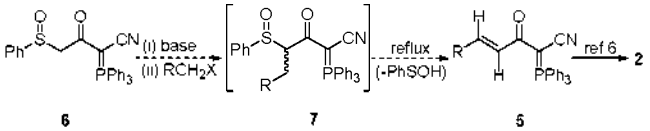
Although this route should be a valuable alternative approach to α-keto cyanophosphoranes, there is still a need to develop an additional new approach to α-keto cyanophosphoranes starting from halogen compounds since many halogen compounds could be easily prepared or commercially available in a variety of forms.



Scheme 1. Wasserman's approach to α-keto amide/ester units.



Scheme 2. Synthetic route for α-keto cyanophosphoranes **2** from carbonyl compounds utilizing HWE reagent **4**.



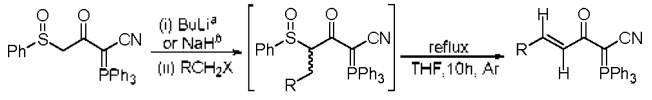
Scheme 3. A new synthetic approach to α-keto cyanophosphoranes **2** from alkyl halides utilizing a new sulfinyl reagent **6**.

It is well documented that the sulfoxide unit alpha to a carbonyl group are easily eliminated by pyrolysis to afford a double bond and sulfenic acid.[7] This interesting sulfoxide chemistry together with the easy availability of halogen compounds prompted us to devise a new synthetic approach to α-keto cyanophosphoranes *via* one pot alkylative-elimination procedure as described in Scheme 3, and herein we wish to report our preliminary results.

The requisite new sulfinyl reagent **6**[8] was prepared from phenylsulfinylacetic acid and cyanophosphorane **1** in the presence of EDC/DMAP in excellent yield,[4] and the representative results of our new approach using **6** as the key reagent are summarized in Table 1.

In optimization of the reaction conditions, BuLi[9] and alkyl

Table 1. Alkylation of **6** with alkyl halides and subsequent *in-situ* pyrolysis of **7** to **5** in THF under reflux conditions.



6 **7** **5**

Run	Base	eq	R	X	eq	**5** (Yield, %)[c,d]
1	BuLi	1.1	C_6H_5-	Cl	1.1	**5a** (5)[e]
2	BuLi	1.1	C_6H_5-	Br	1.1	**5a** (85)
3	BuLi	1.1	2-MeC_6H_4-	Br	1.1	**5b** (77)
4	BuLi	1.1	2-ClC_6H_4-	Br	1.1	**5c** (87)
5	BuLi	1.1	3-ClC_6H_4-	Br	1.1	**5d** (90)
6	BuLi	1.1	4-(*t*-Bu)C_6H_4-	Br	1.1	**5e** (77)
7	BuLi	1.1	CH_2=CH-	Br	1.1	**5f** (81)
8	BuLi	1.1	CH_3CH=CH-	Br	1.1	**5g** (80)
9	BuLi	1.1	C_6H_5CH=CH-	Br	1.1	**5h** (83)
10	BuLi	1.1	$CH_3(CH_2)_6$-	Br	1.1	**5i** (15)[f]
11	NaH	1.3	C_6H_5-	Br	1.3	**5a** (83)
12	NaH	1.3	4-(*t*-Bu)C_6H_4-	Br	1.3	**5e** (81)
13	NaH	1.3	CH_2=CH-	Br	1.3	**5f** (88)
14	NaH	1.3	CH_3CH=CH-	Br	1.3	**5g** (89)
15	NaH	1.3	C_6H_5CH=CH-	Br	1.3	**5h** (83)

[a]BuLi (1.1 eq), THF, -78 °C, 15 min, alkyl halide (1.1 eq), 30 min then rt, 1 h, Ar. [b]NaH (1.3 eq), THF, rt, 20 min, 0 °C, 20 min, alkyl halide (1.3 eq), 1 h then rt, 1 h, Ar. [c]Isolated yields after flash column chromatography on SiO_2. [d](*E*)-Stereochemistry was confirmed by coupling constant (*ca.* 15.0 ~ 15.6 Hz) between two vinylic protons. [e]Sulfinyl reagent **6** was recovered in 80%. [f]Sulfinyl reagent **6** was recovered in 61%.

halides (benzyl chloride & benzyl bromide) were tested first under the appropriate reaction conditions. Although complete enolization of sulfinyl reagent **6** was accomplished with a little excess of BuLi (1.1 eq) under mild conditions (−78 °C, 15 min), alkylation of the enolate formed with benzyl chloride was confirmed to be very sluggish and almost inactive (run 1). However, coupling of the same enolate with benzyl bromide (1.1 eq) under the same conditions proceeded smoothly to afford the alkylated intermediate **7a** (R = -Ph) (run 2). This alkylated intermediate **7a** (R = -Ph) was stable enough to be separated by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc (2/1)), and its structure was confirmed by ^{1}H-NMR in which one *methine* proton appears as two dd peaks (4.86, 4.70 ppm) and two *methylene* protons appear as two sets of two dd peaks (3.41, 3.30, 3.01, 2.85 ppm). Subsequent *in-situ* pyrolysis of **7a** under reflux conditions (THF, 10 h) took place cleanly to provide α-keto cyanophosphorane **5a**, and benzenesulfenic acid[10] known to be unstable. Under this standard conditions, various benzyl bromides reacted smoothly with **6** to afford the alkylated intermediates **7** which were then refluxed for 10 h affording the corresponding α-keto cyanophosphoranes **5** in good yields (run 3, 4, 5, 6). Allyl- and substituted allyl bromides were also effectively transformed into the corresponding α-keto cyanophosphoranes **5** in good yields (run 7, 8, 9). The alkylation of **6** with octyl bromide under the standard conditions, however, has been found to be sluggish and incomplete (run 10). We also tested 2° alkyl bromide ((1-bromoethyl)benzene)) for alkylation reaction, but the reaction was confirmed to be almost inactive.

We next turned our attention to NaH[9] as base, and also tested a variety of alkyl halides for alkylation reactions. The enolization of sulfinyl reagent **6** was accomplished with excess (1.3 eq) of NaH, and alkylations were successful with alkyl bromides (1.3 eq) as for the cases of BuLi (run 11 - 15). The reaction patterns and yields of alkylation using NaH as base were almost similar to those of BuLi.

The next hydrogenation of **5** to **2** could be worked out smoothly under the standard conditions (Pd-C (10%, 10 - 30 wt%), (THF/MeOH, 1/1), H_2 (1 atm)) as reported in our earlier result.[6]

In summary, we have developed another new synthetic approach to α-keto cyanophosphoranes starting from alkyl bromides utilizing a new sulfinyl reagent **6** as the key reagent. Considering several advantages expected from this new approach, *e.g.*, (i) easy preparation of sulfinyl reagent **6** in good yield (ii) sulfinyl reagent **6** is stable solid compound easy to handle (iii) the reaction conditions are mild, and the procedure itself is simple (iv) good to excellent overall yields, this one pot alkylative-elimination route renders another option for the synthesis of α-keto cyanophosphoranes, therefore, widen the scope of Wasserman's protocol. We are currently applying this new approach to heterocyclic/heteroaromatic halides, and trying to extend the same approach to the synthesis of α-keto alkoxycarbonylphosphoranes[12] utilizing the similar sulfinyl reagent having alkoxycarbonylphosphorane subunit.

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8. *Analytical data for compound* **6**: a white solid; mp 214 ~ 220 °C (dec.); IR (KBr) 3057, 2177, 1569, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.04 (d, 1 H, *J* = 13. 7 Hz), 4.35 (d, 1 H, *J* = 13. 7 Hz), 7.47-7.75 (m, 20 H); HRMS calcd for $C_{28}H_{22}NO_2PS$ 467.1109, found 467.1108; Anal. calcd for $C_{28}H_{22}NO_2PS$: C, 71.93; H, 4.74; N, 3.00; S, 6.86, found: C, 71.96; H, 4.80; N, 2.72; S, 6.48.
9. BuLi (2.5 M in THF) and NaH (60% in mineral oil) were purchased from Aldrich Chem. Co, and used directly without titration.
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11. *General procedure for* **5** *using BuLi*: To a stirred, precooled (−78 °C) solution of **6** (210.0 mg, 0.45 mmol) in dry THF (25 mL) was added BuLi (197.6 μL, 1.1 eq) by syringe and the resulting solution was stirred for 15 min at −78 °C under Ar. To this solution was added benzyl bromide (60.0 μL, 1.1 eq) by syringe, and the resulting solution was stirred for 30 min at −78 °C and then allowed warm to rt over 1 h under Ar. The mixture was heated to reflux for 10 h under Ar, and cooled to rt and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2 then CH_2Cl_2/Et_2O, 20/1) to afford **5a** (164.8 mg, 85%) as a pale-yellow solid: mp 232.5 ~ 233.5 °C (lit.[6] 232.0-234.0 °C); IR (KBr) 3055, 2172, 1636, 1550, 1438, 1346, 1237, 1179, 1109, 997, 979, 761, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.70 (m, 22 H).
General procedure for **5** *using NaH*: To a solution of **6** (210.0 mg, 0.45 mmol) in dry THF (25 mL) was added NaH (23.3 mg, 1.3 eq), and the resulting slurry was stirred at rt for 20 min, then cooled at 0 °C over 20 min under Ar. To this mixture was added benzyl bromide (70.9 μL, 1.3 eq) by syringe, and the resultant mixture was stirred at 0 °C for 1 h, then at rt for 1 h under Ar. The mixture was heated to reflux for 10 h under Ar, and cooled to rt and concentrated. Flash chromatography (SiO_2, CH_2Cl_2 then CH_2Cl_2/Et_2O, 20/1)) of the resultant residue afforded **5a** (161.0 mg, 83%) as a pale-yellow solid.
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