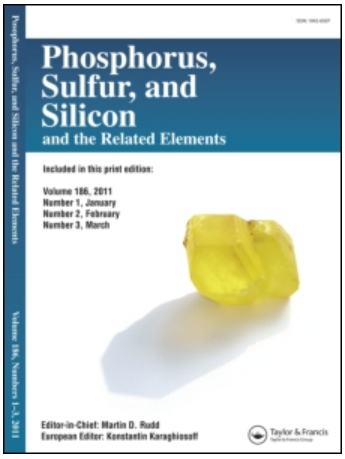

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An Efficient Approach to the Synthesis of Ethyl α-Cyanoalkyl β-Substituted Acrylates by the HWE Olefination of Ethyl 2-(Diethoxyphosphoryl) Cyanoalkanoates

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AN EFFICIENT APPROACH TO THE SYNTHESIS OF ETHYL α-CYANOALKYL β-SUBSTITUTED ACRYLATES BY THE HWE OLEFINATION OF ETHYL 2-(DIETHOXYPHOSPHORYL) CYANOALKANOATES

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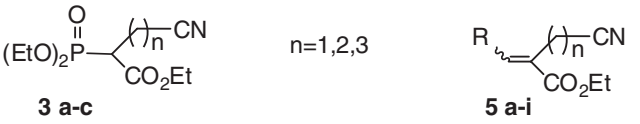
Ethyl α-cyanoalkyl β-substituted acrylates 5a–i were prepared in good yields on a synthetic scale by Horner–Wadsworth–Emmons olefination of the corresponding ethyl 2-(diethoxyphosphoryl) cyanoalkanoates 3a–c using different aldehydes and anhydrous potassium carbonate in dry THF at reflux.

Keywords Ethyl α-cyanoalkyl β-substituted acrylates; ethyl 2-(diethoxyphosphoryl) cyanoalkanoates; Horner–Wadsworth–Emmons reaction; triethyl phosphonoacetate

INTRODUCTION

α,β-Disubstituted acrylates containing various functional groups have found wide applications in organic synthesis.[1–3] Among many synthetic methods, Horner-Wadsworth–Emmons[4–7] and Baylis–Hillman[8,9] reactions are the most versatile tools in the preparation of these compounds. For example, ethyl α-(hydroxymethyl) acrylates[10] and ethyl α-(bromomethyl) acrylates[11] were prepared on a large scale and used as a precursor in organozinc chemistry. In continuation of our work on the synthesis of activated alkenes, we report in this article the results of the HWE olefination of ethyl 2-(diethoxyphosphoryl) cyanoalkanoates **3a–c** with aldehydes in which we have obtained a new series of ethyl α-cyano alkylacrylates **5a–i** in good yields (Scheme 1).



3 a-c **5 a-i**

Scheme 1

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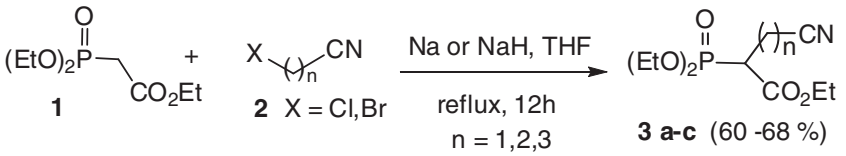
RESULTS AND DISCUSSION

Synthesis of Ethyl 2-(Diethoxyphosphoryl) Cyanoalkanoates 3a–c

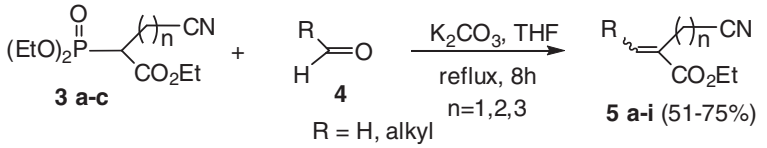
An efficient coupling between the anion of triethyl phosphonoacetate **1**[12] and commercially available bromo(chloro)alkanenitriles **2** in THF at reflux provided the di-functional phosphonates **3a–c** in good yields (60–68%) and excellent purity (^{31}P NMR) (Scheme 2, Table I). Similar phosphonates are very useful reagents in organic synthesis,[13,14] and they are becoming increasingly important in the field of pharmacology and drug design.[15–17]



Scheme 2

Synthesis of Ethyl α-Cyanoalkyl β-Substituted Acrylates 5a–i

Methylenation of phosphonates **3a–c** via the Horner–Wadsworth–Emmons reaction, using different aldehydes **4** and anhydrous solid potassium carbonate as a base, leads to the ethyl α-cyanoalkyl β-substituted acrylates **5a–i** in good yields (51–75%) and high purity with a large amount of ***E***-isomer (Scheme 3). It is clear that the reaction is limited by a steric factor imposed by the aldehydes. The *E/Z* ratio is known to be influenced by many factors, such as the nature of R group, the base, solvent, and temperature.[18] Interestingly, we found that diastereoselectivity (*E/Z* ratio) increases with the size of R groups in aldehydes. Yields and E/Z ratios are given in Table II.



Scheme 3

The reactions shown in Schemes 1 and 2 were conducted until TLC indicated that the starting materials had been completely converted. In order to find the best conditions for the synthesis of compounds **5a–i**, we examined the reaction under various conditions by changing the temperature, the base, and the solvent. It was found that the best yields were

Table I Physical data of phosphonates **3a–c**

Entry	n	Yield	Bp (°C)
3a	1	65	106/0.2 Torr
3b	2	60	143/0.1 Torr
3c	3	68	158/0.1 Torr

Table II Synthesis of ethyl α-cyanoalkyl β-substituted acrylates **5a–i**

Entry	n	R	(*E*/*Z*)*	Yield (%)
5a	1	H	—	72
5b	1	Me	63/37	64
5c	1	Et	70/30	62
5d	2	H	—	74
5e	2	Me	66/34	65
5f	2	^{i}Pr	78/22	62
5g	3	H	—	75
5h	3	Me	58/42	56
5i	3	^{i}Bu	81/19	51

*Determined by ^{1}H NMR spectral analysis.

obtained in heterogeneous solid–liquid medium using anhydrous solid potassium carbonate as a base under reflux of THF without phase transfer reagent. All isolated compounds **3** and **5** were purified by flash chromatography on silica gel (AcOEt:hexane, 1:4) or distilled under reduced pressure. They exhibited analytical and spectral data in agreement with the assigned structures.

CONCLUSION

In this work, we have described an efficient method for the synthesis of ethyl α-cyanoalkyl β-substituted acrylates **5a–i** from ethyl 2-(diethoxyphosphoryl) cyanoalkanoates **3a–c** via Horner–Wadsworth–Emmons reaction. This method represents a versatile and inexpensive approach to these compounds from easily available starting materials. The reactivity of phosphonates **3a–c** and β-substituted acrylates **5a–i** with nucleophilic reagents is under investigation.

EXPERIMENTAL

Apparatus

The IR spectra were recorded in chloroform on a Perkin-Elmer spectrophotometer Paragon 1000 PC. Mass spectra were recorded on a Hewlett-Packard 5989 instrument. ^{1}H, ^{13}C, and ^{31}P NMR were recorded in $CDCl_3$ solution on a Bruker AC 300 MHz for the proton, 75 MHz for ^{13}C, and 121 MHz for ^{31}P. Chemical shifts were in ppm using tetramethylsilane (TMS) as an internal standard for the ^{1}H and ^{13}C NMR and H_3PO_4 85% for ^{31}P NMR spectra as an external standard. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet doublet; dt, doublet triplet; m, multiplet.

Synthesis of Difunctional Phosphonates (3a–c)

In a 250 mL two-necked round-bottomed flask, fitted with a reflux condenser and 100 mL pressure-equalizing addition funnel, a suspension of sodium hydride (110 mmol) in anhydrous THF (100 mL) was cooled to 0°C in an ice bath. Triethyl phosphonoacetate

(100 mmol) diluted in dry THF (20 mL) was added dropwise under a nitrogen atmosphere. After complete addition, the mixture was stirred for 1 h at 0°C, then warmed to room temperature and stirred for 2 h. The mixture was heated to gentle reflux, chloroethanenitrile (130 mmol) was added neat, and the reaction was refluxed for further 12 h. It was cooled and quenched with a saturated aqueous NH_4Cl solution (30 mL), then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude oil was distilled under reduced pressure.

3-Cyano-2-(diethoxyphosphoryl)propanoic acid ethyl ester 3a. IR (cm^{-1}): $\nu_{CN} = 2148$, $\nu_{C=O} = 1735$. ^1H NMR: $\delta = 4.23$–4.08 (3q, 6H, $3OCH_2$), 2.96 (dt, $J = 16.8$, 7.7, 1H, CHP), 1.82 (dd, $J = 10.8$, 7.7, 2H, CH_2), 1.36–1.23 (3t, 9H, $3CH_3$). ^{13}C NMR: $\delta = 172.7$ (C=O), 95.8 (CN), 62.6 (OCH_2), 62.4 (OCH_2), 61.3 (OCH_2), 46.3 (d, $^1J_{PC} = 131.3$, CHP), 33.6 (d, $^2J_{PC} = 32.0$, CH_2–C–P), 16.1 (CH_3), 14.0 (CH_3), 13.9 (CH_3). ^{31}P NMR: $\delta = 22.0$. –MS (EI, 70 eV); *m/z* (%): 263 (M^+, 2), 218 (70), 190 (28), 162 (100), 148 (60), 29 (55).

4-Cyano-2-(diethoxyphosphoryl)butanoic acid ethyl ester 3b. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1740$. ^1H NMR: $\delta = 4.20$–4.05 (3q, 6H, $3OCH_2$), 2.95 (dt, $J = 16.6$, 7.6, 1H, CHP), 1.86 (m, 2H, CH_2), 1.55 (t, 2H, CH_2), 1.35–1.20 (3t, 9H, $3CH_3$). ^{13}C NMR: $\delta = 172.0$ (C=O), 95.5 (CN), 62.4 (OCH_2), 62.2 (OCH_2), 61.5 (OCH_2), 46.5 (d, $^1J_{PC} = 130.6$, CHP), 33.3 (d, $^2J_{PC} = 32.2$, CH_2–C–P), 25.4 (d, $^3J_{PC} = 16.5$, CH_2–CH_2–C–P), 16.0 (CH_3), 14.7 (CH_3), 14.3 (CH_3). ^{31}P NMR: $\delta = 22.2$. –MS (EI, 70 eV); *m/z* (%): 277 (M^+, 8), 232 (74), 204 (25), 176 (100), 73 (10), 29 (45).

5-Cyano-2-(diethoxyphosphoryl)pentanoic acid ethyl ester 3c. IR (cm^{-1}): $\nu_{CN} = 2153$, $\nu_{C=O} = 1735$. ^1H NMR: $\delta = 4.25$–4.02 (3q, 6H, $3OCH_2$), 2.92 (dt, $J = 16.5$, 7.7, 1H, CHP), 1.78 (m, 2H, CH_2), 1.32 (m, 2H, CH_2), 1.45 (t, 2H, CH_2), 1.32–1.25 (3t, 9H, $3CH_3$). ^{13}C NMR: $\delta = 172.3$ (C=O), 95.0 (CN), 62.5 (OCH_2), 62.2 (OCH_2), 61.6 (OCH_2), 46.2 (d, $^1J_{PC} = 131.0$, CHP), 33.5 (d, $^2J_{PC} = 32.0$, CH_2–C–P), 25.0 (d, $^3J_{PC} = 15.2$, CH_2–CH_2–C–P), 20.4 (CH_2), 16.3 (CH_3), 14.5 (CH_3), 14.2 (CH_3). ^{31}P NMR: $\delta = 22.5$. –MS (EI, 70 eV); *m/z* (%): 291 (M^+, 5), 244 (78), 218 (30), 190 (100), 73 (12), 29 (52).

Synthesis of Ethyl α-Cyanoalkyl β-Substituted Acrylates (5a–i)

In a 100 mL flask equipped with a reflux condenser protected by a calcium chloride drying tube, a mixture of phosphonate **3a** (40 mmol), anhydrous potassium carbonate (80 mmol), and paraformaldehyde (80 mmol) in dry THF (40 mL) was refluxed for 8 h. The reaction mixture was cooled and quenched with a saturated aqueous NaCl solution, then extracted with ether (4 × 40 mL). The combined organic layers were filtered through celite and evaporated in vacuum. The crude product was purified by chromatography on silica gel (AcOEt:hexane, 1:4).

2-Cyanomethyl propenoic acid ethyl ester 5a. Colorless liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1633$. ^1H NMR: $\delta = 6.17$ (s, 1H,=CH_2), 5.55 (s, 1H,=CH_2), 4.17 (q, $J = 7.2$, 2H, OCH_2–CH_3), 2.00 (s, 2H, CH_2–CN), 1.28 (t, $J = 7.2$, 3H, OCH_2–CH_3). ^{13}C NMR: $\delta = 173.0$ (C=O), 139.8 (C=C), 133.5 (C=C), 96.7 (CN), 60.2 (OCH_2), 30.1 (CH_2), 15.3 (CH_3). –MS (EI, 70 eV); *m/z* (%): 139 (M^+, 1), 94 (100), 66 (98), 38 (83), 29 (84).

2-Cyanomethyl but-2-enoic acid ethyl ester 5b. Pale yellow liquid. IR (cm^{-1}): $\nu_{CN} = 2153$, $\nu_{C=O} = 1740$, $\nu_{C=C} = 1630$. ^1H NMR: $\delta = 5.85$ (s, 1H,=CH), 4.10 (q, $J = 7.2$, 2H, OCH_2–CH_3), 1.95 (s, 2H, CH_2–CN), 1.42 (s, 3H, C=C–CH_3), 1.22

(t, $J = 7.2$, 3H, $OCH_2-C\underline{H_3}$). ^{13}C NMR: $\delta = 173.8$ (C=O), 137.6 (C=C), 134.4 (C=C), 98.2 (CN), 60.1 (OCH_2), 30.2 (CH_2), 16.5 (CH_3), 15.3 (CH_3). −MS (EI, 70 eV); *m/z* (%): 153 (M^+, 4), 108 (100), 80 (95), 52 (80), 29 (82).

2-Cyanomethyl pent-2-enoic acid ethyl ester 5c. Yellow liquid. IR (cm^{-1}): $\nu_{CN} = 2148$, $\nu_{C=O} = 1735$, $\nu_{C=C} = 1636$. ^1H NMR: $\delta = 5.92$ (s, 1H,=CH), 4.12 (q, $J = 7.2$, 2H, $OC\underline{H_2}-CH_3$), 1.95 (s, 2H, CH_2-CN), 1.72 (q, $J = 7.0$, 2H, $C\underline{H_2}-CH_3$), 1.03 (t, $J = 7.0$, 3H, $CH_2-C\underline{H_3}$), 1.12 (t, $J = 7.2$, 3H, $O\text{-}CH_2-C\underline{H_3}$). ^{13}C NMR: $\delta = 174.3$ (C=O), 137.4 (C=C), 134.0 (C=C), 98.5 (CN), 60.2 (OCH_2), 28.6 (CH_2), 26.4 (CH_2), 15.3 (CH_3), 14.7 (CH_3). −MS (EI, 70 eV); *m/z* (%): 167 (M^+, 2), 122 (100), 94 (96), 66 (78), 29 (80).

2-(2-Cyanoethyl)propenoic acid ethyl ester 5d. 83/0.3 Torr. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1633$. ^1H NMR: $\delta = 6.15$ (s, 1H,=CH_2), 5.52 (s, 1H,=CH_2), 4.16 (q, $J = 7.2$, 2H, $OC\underline{H_2}-CH_3$), 1.87 (t, 2H, CH_2-CN), 1.38 (t, 2H, $C{=}C-CH_2$), 1.28 (t, $J = 7.2$, 3H, $OCH_2-C\underline{H_3}$). ^{13}C NMR: $\delta = 173.0$ (C=O), 139.8 (C=C), 133.5 (C=C), 96.7 (CN), 60.2 (OCH_2), 30.1 (CH_2), 28.8 (CH_2), 15.3 (CH_3). −MS (EI, 70 eV); *m/z* (%): 153 (M^+, 2), 108 (100), 80 (98), 52 (76), 29 (80).

2-(2-Cyanoethyl)but-2-enoic acid ethyl ester 5e. Colorless liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1630$. ^1H NMR: $\delta = 5.85$ (s, 1H,=CH_2), 4.17 (q, $J = 7.2$, 2H, $OC\underline{H_2}-CH_3$), 1.92 (t, 2H, CH_2-CN), 1.45 (t, 2H, $C{=}C-CH_2$), 1.36 (s, 3H, $C{=}C-CH_3$), 1.28 (t, $J = 7.2$, 3H, $OCH_2-C\underline{H_3}$). ^{13}C NMR: $\delta = 173.0$ (C=O), 139.8 (C=C), 134.0 (C=C), 96.7 (CN), 60.2 (OCH_2), 32.6 (CH_2), 23.4 (CH_2), 16.0 (CH_3), 15.5 (CH_3). −MS (EI, 70 eV); *m/z* (%): 167 (M^+, 3), 122 (100), 94 (92), 66 (80), 29 (84).

2-(2-Cyanoethyl)-4-methylpent-2-enoic acid ethyl ester 5f. Colorless liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1630$. ^1H NMR: $\delta = 5.87$ (s, 1H,=CH_2), 4.15 (q, $J = 7.1$, 2H, $OC\underline{H_2}-CH_3$), 1.92 (m, 1H, CH), 1.84 (t, 2H, CH_2-CN), 1.50 (t, 2H, $C{=}C-CH_2$), 1.26 (t, $J = 7.1$, 3H, $OCH_2-C\underline{H_3}$), 1.05 (d, 6H, $2CH_3$). ^{13}C NMR: $\delta = 173.0$ (C=O), 139.8 (C=C), 134.0 (C=C), 96.7 (CN), 60.2 (OCH_2), 35.2 (CH), 33.3 (CH_2), 23.4 (CH_2), 16.0 (CH_3), 15.2 (CH_3), 14.8 (CH_3). −MS (EI, 70 eV); *m/z* (%): 195 (M^+, 3), 150 (100), 122 (93), 94 (80), 29 (78).

2-(3-Cyanopropyl)propenoic acid ethyl ester 5g. Pale yellow liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1633$. ^1H NMR: $\delta = 6.16$ (s, 1H,=CH_2), 5.52 (s, 1H,=CH_2), 4.14 (q, $J = 7.2$, 2H, $O\underline{CH_2}\text{-}CH_3$), 1.85 (t, 2H, CH_2-CN), 1.45 (t, 2H, $C{=}C-CH_2$), 1.28 (t, $J = 7.2$, 3H, $OCH_2\text{-}\underline{CH_3}$), 1.25 (m, 2H, $\text{-}CH_2\text{-}C\underline{H_2}\text{-}CH_2$). ^{13}C NMR: $\delta = 173.0$ (C=O), 96.7 (CN), 139.8 (C=C), 133.5 (C=C), 60.2 (OCH_2), 30.1 (CH_2), 28.8 (CH_2), 24.3 (CH_2), 15.2 (CH_3). −MS (EI, 70 eV); *m/z* (%): 167 (M^+, 1), 122 (100), 94 (95), 66 (77), 29 (83).

2-(3-Cyanopropyl)but-2-enoic acid ethyl ester 5h. Yellow liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1630$. ^1H NMR: $\delta = 5.85$ (s, 1H,=CH_2), 4.17 (q, $J = 7.2$, 2H, $O\underline{CH_2}\text{-}CH_3$), 1.92 (t, 2H, CH_2-CN), 1.24 (m, 2H, $\text{-}CH_2\text{-}C\underline{H_2}\text{-}CH_2$), 1.45 (t, 2H, $C{=}C-CH_2$), 1.28 (t, $J = 7.2$, 3H, $OCH_2\text{-}\underline{CH_3}$), 1.36 (s, 3H, CH_3). ^{13}C NMR: $\delta = 173.0$ (C=O), 96.7 (CN), 139.8 (C=C), 134.0 (C=C), 60.2 (OCH_2), 31.6 (CH_2), 28.8 (CH_2), 24.3 (CH_2), 16.0 (CH_3), 15.5 (CH_3). −MS (EI, 70 eV); *m/z* (%): 181 (M^+, 2), 136 (100), 108 (95), 80 (84), 29 (82).

2-(3-Cyanopropyl)-4-methylhex-2-enoic acid ethyl ester 5i. Yellow liquid. IR (cm^{-1}): $\nu_{CN} = 2150$, $\nu_{C=O} = 1733$, $\nu_{C=C} = 1630$. ^1H NMR: $\delta = 5.85$ (s, 1H,=CH_2), 4.16 (q, $J = 7.2$, 2H, $O\underline{CH_2}\text{-}CH_3$), 1.91 (t, 2H, CH_2-CN), 1.60 (m, 1H, CH), 1.43 (t, 2H, $C{=}C-CH_2$), 1.34 (m, 2H, $C{=}C-CH_2$), 1.28 (t, $J = 7.2$, 3H, $OCH_2-C\underline{H_3}$), 1.24 (m, 2H, $-CH_2-C\underline{H_2}-CH_2$), 1.02 (d, 6H, $2CH_3$). ^{13}C NMR: $\delta = 173.0$ (C=O), 96.7 (CN), 139.8

(C═C), 134.0 (C═C), 60.2 (OCH_2), 34.8 (CH), 32.0 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 24.3 (CH_2), 16.0 (CH_3), 15.3 (CH_3), 16.2 (CH_3). −MS (EI, 70 eV); *m/z* (%): 223 (M^+, 4), 178 (100), 150 (96), 122 (76), 29 (80).

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