Alkylation Studies; Part II[1]: Bis-alkylation of Diethyl Cyanomethanephosphonate

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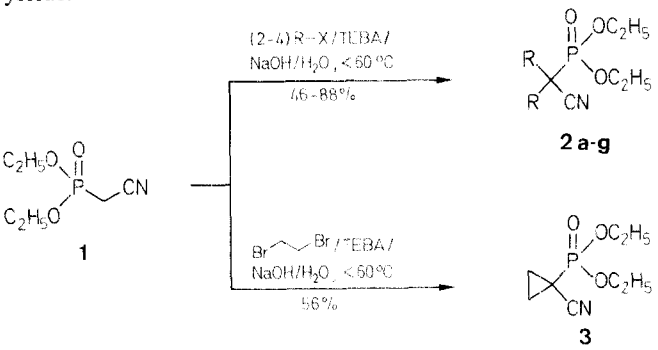
A convenient high-yield method for the geminal dialkylation of diethyl cyanomethanephosphonate with alkyl halides under ion-pair extraction conditions is described.

The monoalkylation of diethyl cyanomethanephosphonate **(1)** using the ion-pair extraction technique[3] has been described[2] and it has been shown[4,5] that cyanomethanephosphonic tetramethyldiamide can be monoalkylated under phase-transfer and under ion-pair extraction conditions. The synthesis of differently dialkylated cyanomethanephosphonic tetramethylamides has also been reported[4,5]. A patent[6] describes the synthesis of dibenzyl diethylcyanomethanephosphonate using DBU as a base. However, no other examples of bis-alkylation of diethylcyanomethanephosphonate **(1)** have thus far been reported.

We have already reported[1,7] that diethyl malonate can be cleanly bisalkylated under ion-pair extraction conditions. In order to define the scope and reactivity of phosphonate-activated methylene compounds, the bis-alkylation of diethyl cyanomethanephosphonate **(1)** was studied. Thus, it was found that compound **1** can be cleanly bis-alkylated by using primary, allylic, and benzylic halides under ion-pair extraction conditions. The reaction is complete in 1–3 hours and the usual work-up gives 46–88% yields of bis-alkylated phosphonates **2**. No attempt was made to optimize the yields.

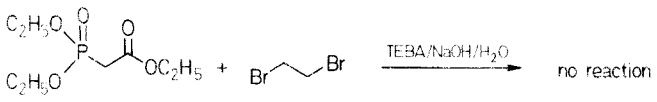


The reaction of diethyl cyanomethanephosphonate **(1)** with 1,2-dibromoethane gave diethyl 1-cyanocyclopropanephosphonate **(3)** in 56% yield. When cyclopropanation of **1** was attempted using a catalytic amount of TEBA (~ 5%) or without catalyst, no appreciable amount of **3** was formed. Contrary to the cyano derivative, triethylphosphonoacetate **(4)** could not be cyclopropanated under these conditions. The starting material was not recovered. The ester group presumably hydrolyzed before the alkylation step.

Table. Bis-alkylation of Diethyl Cyanomethanephosphonate (1)

Alkylating Agent R—X	Ratio 1 : R—X	Reaction Time [h]	Product	Yield [%]	b.p. [°C]/torr	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$) δ [ppm]
H_3C—I	1 : 4	3	**2a**	80	100/0.8	$C_8H_{16}NO_3P$ (205.2)	1.38 (t, 6H, $J_{H,H}$ = 7 Hz); 1.51 (d, 6H, $J_{P,CH}$ = 15 Hz); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz)
C_2H_5—I	1 : 3	1	**2b**	71	112/1.0	$C_{10}H_{20}NO_3P$ (233.2)	1.0–1.4 (2t, 12H); 1.6–2.05 (2m, 4H); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz)
H_2C=CH—CH_2—Br	1 : 3	1	**2c**	88	130–132/1.2	$C_{12}H_{20}NO_3P$ (257.3)	1.36 (t, 6H, $J_{H,H}$ = 7 Hz); 2.4–2.78 (d of d, 4H, $J_{H,H}$ = 7 Hz, $J_{P,CH}$ = 14 Hz); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz); 5.1–6.3 (m, 6H)
H_2C=C(CH_3)—CH_2—Cl	1 : 2.5	1	**2d**	72	121–125/0.8	$C_{14}H_{24}NO_3P$ (285.3)	1.36 (t, 6H, $J_{H,H}$ = 7 Hz); 1.92 (s, 6H); 2.5–2.7 (ABX, d, 2H, $J_{H,H}$ = 4 Hz, s, 2H, $J_{P,CH}$ = 14 Hz); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz); 5.98 (s, 4H)
$(CH_3)_2C$=CH—CH_2—Cl	1 : 2.5	1	**2e**	83	146–149/1.2	$C_{16}H_{28}NO_3P$ (313.4)	1.36 (t, 6H, $J_{H,H}$ = 7 Hz); 1.65 (s, 6H); 1.75 (s, 6H); 2.38–2.75 (2d, 4H, $J_{P,CH}$ = 14 Hz, $J_{H,H}$ = 7 Hz); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz); 5.30 (t, 2H, J = 7 Hz)
C_6H_5—CH_2—Cl	1 : 2	1	**2f**	46	208/0.8	$C_{20}H_{24}NO_3P$ (357.4)	1.25 (t, 6H, $J_{H,H}$ = 7 Hz); 2.9–3.25 (m, 4H); 4.00 (2q, 4H, $J_{H,H}$ = 7 Hz); 7.25 (br. s, 10H)
4-F—C_6H_4—CH_2—Cl	1 : 2	1	**2g**	70	198/0.8	$C_{20}H_{22}F_2NO_3P$ (393.4)	1.20 (t, 6H, $J_{H,H}$ = 7 Hz); 2.8–3.5 (m, 4H); 4.05 (2q, 4H, $J_{H,H}$ = 7 Hz); 6.8–7.2 (m, 8H)
Br—CH_2—CH_2—Br	1 : 2	1	**3**	56	100–104/0.6	$C_8H_{14}NO_3P$ (203.2)	1.40 (t, 6H, $J_{H,H}$ = 7 Hz); 1.60 (m, 4H); 4.25 (2q, 4H, $J_{H,H}$ = 7 Hz)

[a] The microanalyses were in good agreement with the calculated values: C ±0.25, H ±0.07, N ±0.15.



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Further reactions of diethyl 1-cyanocyclopropanephosphonate **(3)** toward nucleophilic ring opening are in progress.

Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. NMR spectra were recorded on Varian T-60.

Diethyl 4-Cyano-1,6-heptadiene-4-phosphonate (2c); Typical Procedure:

To a 12.5 normal solution (100 ml) of sodium hydroxide (prepared by dissolving 50 g sodium hydroxide in water and diluting to a total volume of 100 ml), benzyltriethylammonium chloride (TEBA; 22.75 g, 0.1 mol) is added with vigorous stirring. To this solution, a mixture of diethyl cyanomethanephosphonate (**1**; 17.7 g, 0.1 mol) and 3-bromopropene (36.3 g, 0.3 mol) is added. When the reaction temperature has reached ~ 60 °C, water-bath cooling is applied. The stirring is continued for 1 h, and the mixture is then diluted with water (100 ml) and extracted with ether (4 × 100 ml). The combined ether solution is washed with water (3 × 50 ml) and with saturated sodium chloride solution (50 ml), and dried with magnesium sulfate. The solvent is removed, and the residue distilled in vacuum; yield: 22.53 g (88%); b.p. 130–132 °C/1.3 torr.

$C_{12}H_{20}NO_3P$	calc.	C 56.02	H 7.84	N 5.44
(257.3)	found	56.27	7.89	5.39

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