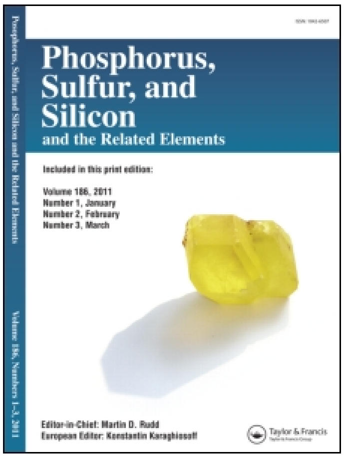

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The Behavior of 3,4,5-Trimethoxybenzylidenemalononitrile Towards Alkyl Phosphites

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THE BEHAVIOR OF 3,4,5-TRIMETHOXYBENZYLIDENEMALONONITRILE TOWARDS ALKYL PHOSPHITES

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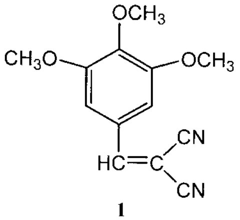
*3,4,5-Trimethoxybenzylidenemalononitrile **1** reacts with trialkyl phosphites **2a–c** in the absence of solvent to give the phosphonate derivatives **4a–c**. The dimeric compound **6** also was produced in the reaction with **2c**. The phosphonates **8a–c** were produced when compound **1** was allowed to react with dialkyl phosphites **3a–c** under the same experimental conditions. A mechanism is proposed to explain the formation of compounds **4** and **6**.*

Keywords: Dialkyl phosphites; malononitrile-3,4,5-trimethoxy bezylidene; phosphonates; trialkyl phosphites

Arylidenemalononitriles arereactive compounds and valuable synthetic intermediates in the preparation of a wide variety of organic compounds.[1] Some of these nitriles have potential biomedical and industrial applications.[2] as well as marked pesticidal activities.[3] They are used particularly as cytotoxic agents against tumors, riot control agents,[4] and chemical warfare agents.[2,5]

In view of these observations and in the line of the growing interest in the organophosphorus chemistry of arylidene malononitriles,[6–10]



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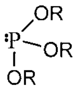
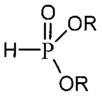


2a, R = CH_3
b, R = C_2H_5
c, R = $C_3H_{7\text{-}i}$



3 (R as in **2**)

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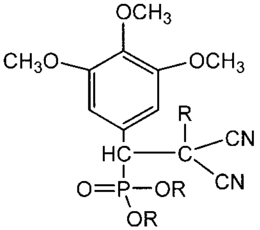
we have now investigated the behavior of 3,4,5-trimethoxybenzylidenemalono-nitrile **1** toward trialkyl phosphites **2** and dialkyl hydrogen phosphites **3**.

RESULTS AND DISCUSSION

We have found that compound **1** reacts with trimethyl phosphite **2a** and triethyl phosphite **2b** in absence of solvent at 90°C for 8–12 h to produce colorless crystalline compounds formulated as **4a,b** respectively. Structural elucidation for compound **4a**, taken as a representative example, was accomplished with the following evidences:

(a) elemental analyses and molecular weigh determination of compound **4a** corresponds to $C_{16}H_{21}N_2O_6P$;

(b) the MS of compound **4a** showed ion peaks at m/z = 368 [M^+], 20.52%, 289 [M^+—$CH_3C(CN)_2$]; 100% and 109 [$O = {}^+P(OCH_3)_2$]; 7.49%;



4a, R = CH_3
b, R = C_2H_5
c, R = $C_3H_{7\text{-}i}$

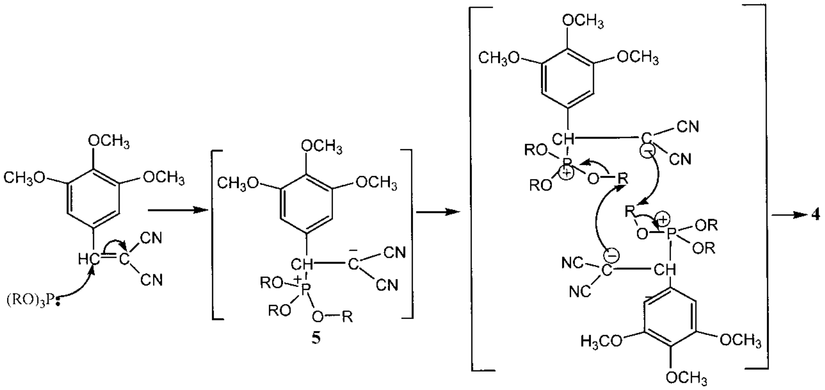
(c) the IR spectrum of **4a**, in KBr, revealed the presence of bands at 1250 cm^{-1} (P=O) and at 1030 cm^{-1} (P—O—CH_3);

(d) the ^{31}P NMR spectrum has a singlet at $\delta = 21.17$ ppm, which is consistent with the phosphonate structure;[11]

(e) the ^1H NMR spectrum showed a singlet at $\delta = 1.85$ due to the 3 protons of the C-methyl group, a doublet at $\delta = 3.1$ for the methine proton ($J_{HP} = 22$ Hz), two singlets at $\delta = 3.72, 3.80$ for the protons of three methoxyl groups attached to the ring, two doublets (each with $J_{HP} = 12$ Hz) for the two methoxyl groups attached to phosphorus at $\delta = 3.57$ and $\delta = 3.76$.

Apparently, the asymmetry of the molecule due to the presence of a stereocenter, would render the two methoxyl groups diastereotropic and hence anisochronous, resulting in the observed splitting pattern.[12–14] The aromatic protons (2H) appeared as a singlet at $\delta = 6.69$.

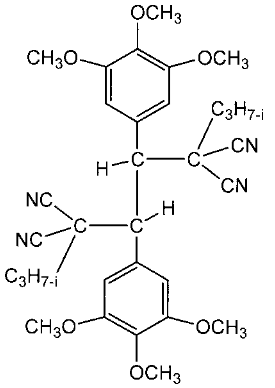
A possible explanation for the course of the reaction of trialkyl phosphites with compound **1** involves a nucleophilic attack by the phosphorus atom on the β-carbon atom of the exocyclic double bond, yielding the dipolar intermediate **5**. The latter would allow group translocation either intramolecularly or most probably intermolecularly to give **4** through the mutual nucleophilic attack by the carbanion of one molecule on the alkyl residue of the other.[15]



On the other hand, compound **1** reacted with triisopropyl phosphite **2c** to form a mixture of **4c** (70% yield) and the dimeric compound **6** (15% yield). These products were isolated and purified by column chromatography. The structure of phosphonate **4c** is based on compatible elemental analyses, molecular weight determination (MS), IR, and ^{1}H NMR spectra (cf. Experimental).

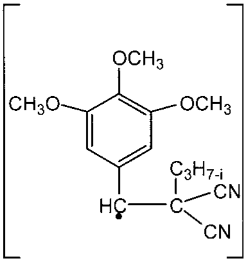
The dimeric structure **6** was established by different spectroscopic techniques as well as elemental analyses and molecular weight determination (MS) which correspond to $C_{32}H_{38}N_4O_6$. Moreover, its ^{1}H NMR spectrum showed a multiplet centered at $\delta = 1.3$, ppm due to the 12 protons of the CH_3 groups of the isopropyl moieties and a septet centered at $\delta = 4.65$ ppm for the two CH protons of the two isopropyl groups. Protons of the 6 methoxyl groups (18 H) appeared as 2 singlets at $\delta = 3.78$ and 3.81 ppm. A doublet ($J_{HH} = 22$ Hz) was centered at $\delta = 6.24$ ppm due to the two methine protons; indicating a *trans* configuration. The 4 aromatic protons appeared as two singlets at $\delta = 7.20$ ppm (2H) and $\delta = 6.67$ ppm (2 H).

The formation of compound **6** could be attributed to steric effects in compound **4c** due to the isopropyloxy groups attached to phosphorus in which the P-atom is forced to act partially as a good leaving group to



6

yield intermediate **7**. The latter radical species dimerizes to **6**. Formation of the dimeric product **6** through the trialkyl phosphite catalyzed reaction with compound **1** recalls the process of "tail to tail" dimerization observed with a number of methide derivatives.[16]



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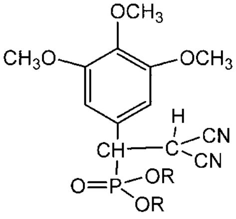
Treatment of compound **1** with dialkyl phosphites **3a–c** in absence of solvent at 90°C led to the formation of phosphonates **8a–c.** The structures of these compounds were verified by analytical and spectroscopic evidences (cf. Experimental).



8a, R = CH_3
b, R = C_2H_5
c, R = $C_3H_{7\text{-}i}$

EXPERIMENTAL

All melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in KBr discs, on a Jasco Fourier Transform Infrared Spectrophotometer Model FT/IR-3000E. The ^{1}H NMR spectra were measured on Joel JNM-EX 270 FTNMR system (National Research Centre) and chemical shifts are recorded in δ ppm relative to TMS. The ^{31}P NMR spectra were run on a Varian FT-80 Spectrometer (vs. 85% H_3PO_4). The MS spectra were performed at 70 eV on a Finnigan MAT SSQ 7000 spectrometer. The microanalyses were carried out at the Microanalytical Centre, Cairo University, Egypt. The microanalyses of the new compounds were in a good agreement with (C, H $\pm$ 0.1, N $\pm$ 0.05, P $\pm$ 0.05, S $\pm$ 0.05%). All solvents were purified and dried. The appropriate precautions in handling moisture-sensitive compounds were taken. Trialkyl phosphites were purified by treatment with sodium metal followed by fractional distillation. Dialkyl phosphites were freshly distilled.

Reaction of 3,4,5-Trimethoxybenzylidenemalononitrile 1 with Trimethyl Phosphite 2a

A mixture of nitrile **1** (5 mmol) and trimethyl phosphite (5 ml) was heated at 90°C for 10 h. After removal of excess trimethyl phosphite under reduced pressure, the residue was triturated several times with light petroleum. The solid product, thus formed, was crystallized from benzene to give [2,2-Dicyano-2-methyl-1-(3,4,5-trimethoxy-phenyl)-ethyl]-phosphonic acid dimethyl ester **4a** as colorless crystals in an 85% yield, m.p. 137–138°C.

Similarly, [2,2-Dicyano-1-(3,4,5-trimethoxy-phenyl)-butyl]-phosphonic acid diethyl ester **4b** was formed from the reaction of nitrile **1** with triethyl phosphite **2b** under the same experimental conditions described above.

Phosphonate **4b** [$C_{19}H_{27}N_2O_6P$; (62% yield)], was obtained from cyclohexane, as colorless crystals m.p. 132–133°C. IR (cm^{-1}): 1250 (P=O), 1030 (P—O—C_2H_5). ^{1}H NMR: $\delta = 0.85$ (t, 3H, C—$CH_2\mathbf{CH_3}$), $\delta = 1.02$ (q, 2H, C—$\mathbf{CH_2}CH_3$), $\delta = 1.05, 1.60$ (2t, 6H, (P—O—$CH_2\mathbf{CH_3})_2$), $\delta = 3.54$ (d, CH, $J_{HP} = 22$ Hz), $\delta = 6.70$ (s, 2H, aromatics). Ms: m/z = 410, 15.48%.

Reaction of Triisopropyl Phosphite (2c) with Compound 1

To nitrile **1** (5 mmol) was added triisopropyl phosphite (7 ml). The mixture was heated at 100°C for 16 h. Excess of the phosphite was removed in vacuo. The residual material was dissolved in methanol and evaporated to dryness in the presence of silica gel. The solid product was applied to a column previously charged with silica gel in petroleum ether. The column was eluted with petroleum ether containing increasing amounts of methylene chloride and then with ethyl alcohol.

Fractions up to 6:4 v/v gave pale yellow crystals of the [2,2-dicyano-3-methyl-1-(3,4,5-trimethoxy-phenyl)-butyl]-phosphonic acid diisopropyl ester **4c** [$C_{22}H_{33}N_2O_6P$; (70% yield)], m.p. 135-136°C, crystallized from absolute ethanol. IR (cm^{-1}): 1250 (P=O); 1010 (P—OC_3H_7). ^1H NMR: $\delta = 0.90$ ppm (d, $2CH_3$) of the isopropyl group; $\delta = 1.27$ ppm (m, 4 CH_3) of the isopropoxyl groups attached to phosphorus; $\delta = 3.28$ & 3.36 ppm (2d, CH) for the methine proton; $J_{HP} = 20$ Hz, $\delta = 4.47$ ppm (2H, octet) for the isopropoxyl CH protons, $\delta = 4.72$ ppm (1H, octet) for isopropyl proton; $\delta = 3.77$ and $\delta = 3.80$ (2s, 3 OCH_3) for the three methoxyl groups attached to the ring and $\delta = 6.66$ ppm (s, 2H, aromatic protons). MS: m/z 452 [M^+], 0.78%. Elution with ethyl alcohol afforded [2,5-Dicyano-2,5-dipropyl-3,4-bis-(3,4,5-trimethoxy-phenyl)-hexanedinitrile **6** as colorless crystals in a 15% yield, crystallized from ethanol, m.p. 189–190°C.

Reaction of Nitrile 1 with Dialkyl Phosphite 3a–c

A mixture of compound **1** (5 mmol) and dimethyl phosphite **3a** (5 ml) was heated at 90°C without solvent for (6–8 h) (TLC). After removal of the excess phosphite, in vacuo. The residue was triturated for three times with light petroleum ether, then crystallized from the appropriate solvent to give [2,2-Dicyano-1-(3,4,5-trimethoxy-phenyl)-ethyl]-phosphonic acid dimethyl ester **8a** as colorless crystals in an ($C_{15}H_{19}N_2O_6P$; 87% yield), from ethyl acetate, m.p. 118–120°C. IR (cm^{-1}): 1250 (P=O) and 1030 (P—O—CH_3). ^{31}P NMR: $\delta = 19.64$ ppm. ^1H NMR: $\delta = 3.51$ and 3.82 (2d, 1H) for the $(CN)_2$**CH**— proton; $\delta = 3.61$ and $\delta = 3.82$ (2d, 6H, 2**CH_3**) for the methoxyl groups attached to phosphorus; $\delta = 3.86$; $J_{HH} = 12$ Hz and $\delta = 3.87$ (2s, 9H) for the three methoxyl groups attached to the ring; $\delta = 4.49$ (d) and 4.52 ppm (2d, 1H) for the methine proton attached to phosphorus $J_{HP} = 22$ Hz and $\delta = 6.71$ (s, 2H, aromatic protons). MS: m/z 354 [M^+], 65.55%; 289 [M—$CH(CN)_2$], 100%; 245 [M—O = $P(OCH_3)_2$], 4.90%.

Similarly, the phosphonates **8b** and **8c** respectively, were, formed from the reaction of nitrile **1** with diethyl phosphite **3b** and diisopropyl phosphite **3c** under the same experimental conditions described above. [2,2-Dicyano-1-(3,4,5-trimethoxy-phenyl)-ethyl]-phosphonic acid diethyl ester **8b** was obtained as colorless crystals ($C_{17}H_{23}N_2O_6P$; 82% yield) from ethyl acetate, m.p. 108–110°C, IR (cm^{-1}): 1250

(P=O) and 1030 (P—OC_2H_5). ^{1}H NMR: $\delta = 1.07$ and $\delta = 1.26$ (2t, 2(O—CH_2**CH_3**); $\delta = 3.40$ and 3.50 (2d) for the methine proton, $\delta = 3.84$ and $\delta = 3.85$ (2s, 3 OCH_3) for the methoxyl groups attached to the ring; $\delta = 3.95$ and $\delta = 4.10$ (2q, 2(O—**CH_2**CH_3)) and $\delta = 6.65$ ppm (s, 2H, aromatic protons). MS: m/z 382 [M^+], 99.49%; 317 [M^+—CH$(CN)_2$]; 100%, 245 [M^+—O=P$(OC_2H_5)_2$], 11.33%. [2,2-Dicyano-1-(3,4,5-trimethoxy-phenyl)-ethyl]-phosphonic acid diiso-propyl ester **8c** was formed ($C_{19}H_{27}N_2O_6P$; 75% yield) as colorless crystals, mp. 114–116°C. IR (cm^{-1}): 1250 (P=O); 1010 (P—OC_3H_7). ^{1}H NMR: $\delta = 0.93$ (d, 3H); $\delta = 1.19$ (d, 3H) and $\delta = 1.27$ (d, 6H) for isopropoxyl methyl groups; $\delta = 3.74$ and $\delta = 3.86$ ppm (2s, 9H) for the three methoxyl protons attached to the ring; $\delta = 4.07$ and 4.10 (2d, 1H) for the $(CN)_2$**CH**— proton; $\delta = 4.46$ (octet, 2H) for the isopropoxyl —**CH** protons; $\delta = 5.50$ and 5.54 ppm (2d,1H) for the methine proton attached to phosphorus; $J_{HP} = 20$ Hz and $\delta = 6.86$ ppm (s, 2H, aromatic protons). MS: m/z 410 [M^+], 100%; 345[M^+—CH$(CN)_2$]; 47.20% and 245 [M^+—O=P$(OC_3H_7)_2$], 72.24%.

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