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An eco-friendly procedure for one-pot synthesis of β-phosphonomalonates: micellar solution of sodium stearate catalyzes tandem Knoevenagel–phospha-Michael reaction of aldehydes, malonitrile, and phosphites in aqueous media

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ABSTRACT

A new, one-pot convenient method for the synthesis of a variety of β-phosphonomalonates by a tandem Knoevenagel–phospha-Michael reaction of phosphite esters with aryl/heteroaryl/alkyl aldehydes and malonitrile in an aqueous micellar solution of sodium stearate is described. This method offers several advantages, such as using a cheap and environmentally benign reaction media, low loadings of sodium stearate as catalyst and offers good yields.

1. Introduction

Phosphonates exhibit a wide range of notable biological properties, which expand their applications as enzyme inhibitors, metabolic probes,[1] peptide mimetics,[2] antibiotics, and pharmacologic agents[3] besides to their traditional roles as intermediates in organic synthesis.[4] Extensive efforts have been made to introduce convenient and efficient methods for the synthesis of phosphonates. Direct phosphorus–carbon bond formation represents one of the most versatile and powerful tools for the synthesis of phosphonates. Amongst the methods for P–C bond formation, phospha-Michael addition, that is, the addition of a phosphorous nucleophile to an electron-deficient alkene has evoked remarkable attention by organic chemists.[5] Synthesis of β-phosphonomalonates by this method are most commonly promoted by bases,[5a–f] Brønsted/Lewis acids,[5g–i] transition metals,[5j,k] radical initiators, such as AIBN[5l,m] or microwaves.[5n] Although these methods are valuable, they suffer from one or more of the following drawbacks, such as: low yields; high temperature; long reaction times; requiring a promoter, such as microwave; using toxic solvents or a large amount of catalyst and tedious work-up procedures. Therefore, the development of a new method to overcome these shortcomings still remains an ongoing challenge for the synthesis of these significant scaffolds.

Water is a desirable solvent for the reasons of cost, safety, and environmental impact.[6] In addition, reactions in aqueous media illustrate unique reactivities and selectivities that are not usually observed in organic media.[7] However, organic solvents are still used instead of water for mainly two reasons. First, most organic substrates are not soluble in water and as a result, water cannot function as a reaction medium. Second, many reactive substrates, reagents, and catalysts are sensitive toward water and are decomposed or deactivated in aqueous media. A possible way to improve the solubility of substrates is the use of surface active reagents that can form micelles[8] or vesicular structures in aqueous media. Micelles are dynamic clusters of surfactant molecules, which posses both hydrophilic and hydrophobic structures.[9] It is well established that in many cases, the rates and pathways of many chemical reactions can be altered by performing the reactions in micellar media instead of pure bulk solvents. Micelles can concentrate the reactants within a small volume, stabilize substrates, intermediates or products, and orient substrates so that ionization potential, oxidation–reduction properties, dissociation constants, physical properties, and reactivities are changed. Thus, they can alter the reaction rate, mechanism, regio- and stereo-selectivity of the reaction.[10] The use of micellar and vesicle-forming surfactants as catalysts is widespread and has been investigated in detail for different reactions in aqueous solutions.[11] However, from the

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viewpoints of practicability and applicability, the surfactant-aided organic reactions are still at their preliminary stages.[12]

As part of our ongoing program directed toward the development of new methods for the synthesis of phosphonate derivatives,[13] recently we have introduced $HClO_4/SiO_2$ and $H_3PMo_{12}O_{40}$ as efficient catalysts for the two-pot synthesis of β-phosphonomalonates by phospha-Michael addition of trialkyl phosphite to α,β-unsaturated malonates.[13j,k] Herein, we wish to report the use of micellar solution of sodium stearate in water as an efficient media for the one-pot synthesis of β-phosphonomalonates directly from aldehydes, malononitrile, and trialkyl phosphites via tandem Knoevenagel–phospha-Michael reaction.

2. Results and discussion

In our initial study, evaluation of different types of surfactants was carried out for the tandem Knoevenagel–phospha-Michael reaction of 4-methoxybenzaldehyde, malononitrile, and triethyl phosphite in aqueous media. The results of these studies are summarized in Table 1.

Table 1
Tandem Knoevenagel–phospha-Michael reaction of 4-methoxybenzaldehyde, malononitrile, and triethyl posphite under different conditions

Entry	Surfactant	Amount (CMC)	T (°C)	Time (h)	Yield[a] (%)
1	CTAB	1	80	10	70[b]
2	Triton X-100	1	80	7	60[b]
3	SDS	1	80	2	70[c]
4	Sodium stearate	1	80	2	75
5	Sodium stearate	5	80	1	85
6	Sodium stearate	15	80	1	84
7	Sodium stearate	25	80	1	85
8	Sodium stearate	5	60	1	65
9	Sodium stearate	5	40	1	50
10	Sodium stearate	5	rt	1	50
11	—	—	80	24	60[c]

[a] Isolated yield, conditions: aldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol).
[b] The yield of the product remained constant after 24 h.
[c] A mixture of by-products besides the desired product was formed.

As shown in Table 1, surfactants, such as cetyltrimethylammonium bromide (CTAB) as a cationic micelle and Triton X-100 as a neutral micelle at their critical micellar concentrations (CMC) in water produced the desired product in 70 and 60% yields, respectively (entries 1 and 2). A drastic rate enhancement was observed when the reaction was performed in a micellar solution of sodium dodecyl sulfate (SDS) (entry 3). The yield of the product increased by using sodium stearate (entry 4) as the result of increasing surfactivity by lengthening of sodium stearate hydrocarbon chain compared with SDS. The required amount of sodium stearate for this reaction was also evaluated. It was found that when increasing the amount of sodium stearate from 1 to 5, 15, and 25 CMCs, the yields increased from 70 to 85% (entries 5–7). Thus, using a micellar solution of sodium stearate with 5 CMC in water is sufficient to push this reaction forward. Larger amounts of the surfactant did not improve the yields. In order to optimize the reaction temperature, the reaction was carried out at different temperatures ranging from room temperature to 80 °C (entries 8–10). Within the tested temperatures, 80 °C was found to be the most suitable reaction temperature. Further studies showed that the presence of sodium stearate in this reaction is crucial, such that the similar reaction in the absence of sodium stearate led to the formation of the desired product in 60% yields besides a mixture of side products (entry 11).

After optimization of the reaction conditions, to delineate this approach, particularly in regard to library construction, this methodology was evaluated for the synthesis of different β-phosphonomalonates from various structurally diverse aldehydes. The results of this study are depicted in Table 2.

As shown in Table 2, differently substituted benzaldehydes with electron-donating and electron-withdrawing groups underwent successful Knoevenagel–phospha-Michael reaction with malononitrile and triethyl phosphite (entries 1–7). The catalyst was compatible with functional groups, such as Cl, Br, and O–Me. No competitive nucleophilic methyl ether cleavage was observed in the substrate possessing an aryl-O–Me group (entry 1), despite the strong nucleophilicity of phosphites. Acid-sensitive aldehydes, such as furan-2-carbaldehyde and pyridine-3-carbaldehyde underwent smooth reactions without any decomposition or polymerization under the present reaction conditions (entries 8 and 9). This method is also applicable for the synthesis of β-phosphonomalonates from the reaction of triethyl phosphite with aliphatic aldehydes and malononitrile (entries 10 and 11). The reaction of ketones with malononitrile and triethyl phosphite was also studied under the same reaction conditions. However, the results were not as positive as those presented above.

Furthermore, we have evaluated the generality of the presented method for the one-pot synthesis of β-phosphonomalonates from different in situ generated Michael acceptors and trialkyl phosphites (Table 3).

As is obvious from Table 3, the catalytic one-pot reaction of 4-chlorobenzaldehyde and malononitrile proceeded well with trialkyl phosphites, such as triethyl/trimethyl/tri-*iso*-propyl phosphite (entries 1–3). These results demonstrate that both the yields and the reaction times are relatively independent of the phosphorus compounds. In addition to malononitrile, some other in situ generated Michael acceptors were also examined to carry out the reaction with triethyl phosphite (entries 4–6). The results showed that the reaction involving ethyl cyano acetate worked well and the desired product was obtained in 73% yield. However, no product was produced when diethyl malonate or nitromethane were used in this one-pot reaction under the same conditions.

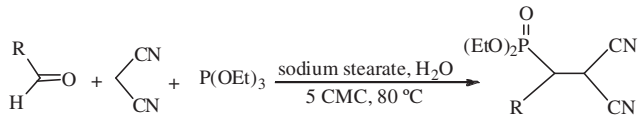
It should be noted that no competitive side reactions, such as the formation of α-hydroxyphosphonates were observed in these transformations. These observations prompted us to study the possibility of the formation of α-hydroxyphosphonate as an intermediate in these reactions. We have found that the treatment of 4-methoxybenzaldehyde with triethyl phosphite in micellar solution of sodium stearate in aqueous media at 80 °C did not produce any significant amount of the corresponding α-hydroxyphosphonate even after 24 h (IR, NMR, MS).

We have also studied the initial Knoevenagel reaction for the α,β-unsaturated malonate formation as the intermediate from the reaction of 4-methoxybenzaldehyde and malononitrile. The desired α,β-unsaturated malonate was isolated in 89% yield after 10 min in micellar solution of sodium stearate in aqueous media at 80 °C.

These observations delineate the tandem Knoevenagel–phospha-Michael reaction for the synthesis of β-phosphonomalonates in the micellar solution of sodium stearate. Thus, Knoevenagel reaction between the aldehydes and malononitrile produce an initial α,β-unsaturated malonate. Subsequent phospha-Michael addition of trialkyl phosphites then leads to the formation of the desired products. It is noteworthy to mention that reports on the synthesis of β-phosphonomalonates are mainly focused on the two-pot procedures and the report for the one-pot synthesis of these compounds directly from simple and readily available starting materials is rare in the literature.[5i]

The catalytic effect of micellar solution of sodium stearate in these reactions can be explained as follows: aldehyde, malononitrile, and trialkyl phosphite are hydrophobic molecules in aqueous media. In the micellar solution of sodium stearate, the hydrophobic moieties escape away from water molecules, which encircle the micelle core of sodium stearate and forced inside the hydrophobic

Table 2
Synthesis of different β-phosphonomalonates via tandem Knoevenagel–phospha-Michael reaction in solution of sodium stearate in water



R = aryl, heteroaryl, alkyl **1-11**

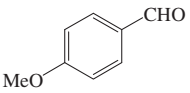
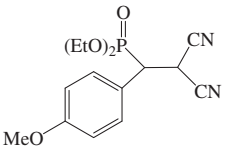
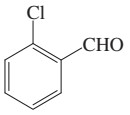
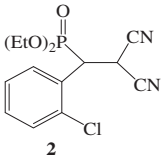
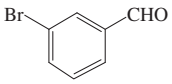
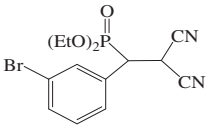
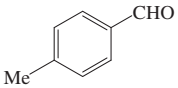
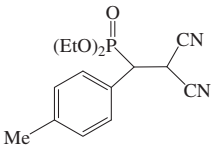
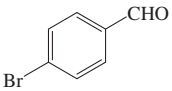
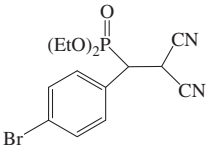
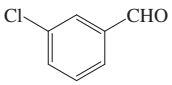
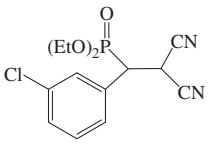
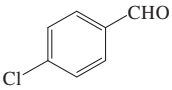
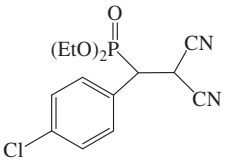
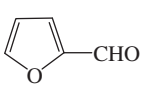
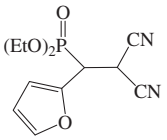
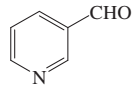
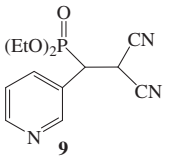
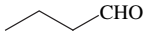
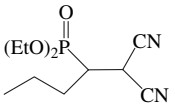
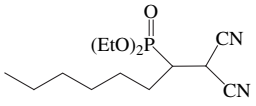
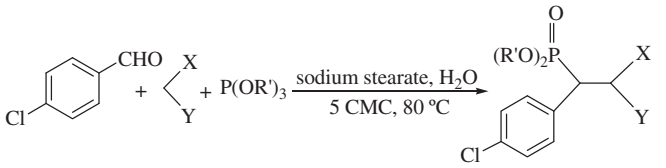
Entry[ref]	Aldehyde	Product	Time (h)	Yield[a] (%)
1[5f,14a]		 **1**	1	85
2[14c]		 **2**	2	85
3		 **3**	3	84
4[5f,14a]		 **4**	5.5	86
5		 **5**	3	82
6[5f]		 **6**	3	83
7[5f,14a]		 **7**	3	91
8[14a,b]		 **8**	2	80

Table 2 (*continued*)

Entry[ref]	Aldehyde	Product	Time (h)	Yield[a] (%)
9		 **9**	1	89
10		 **10**	2	85
11		 **11**	4	81

[a] Isolated yield, conditions: aldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol), 80 °C, aqueous solution of sodium stearate (4 mL, 5 CMC). All the products were characterized by spectroscopic methods and compared with the authentic spectra.[5f,14]

Table 3
One-pot synthesis of β-phosphonomalonates from different in situ generated Michael acceptors and trialkyl phosphites in micellar solution of sodium stearate in water



Entry[ref]	R×	X	Y	Time (h)	Yield[a] (%)
1[5f,5a,a]	Et	CN	CN	3	91
2[14a]	Me	CN	CN	1	82
3[15]	*i*-Pr	CN	CN	2	80
4[5f]	Et	CN	CO_2Et	1	73[b]
5	Et	CO_2Et	CO_2Et	24	0
6	Et	H	NO_2	24	0

[a] Isolated yield, 4-chlorobenzaldehyde (1 mmol), active methylene group (1 mmol), trialkyl phosphite (1 mmol), 80 °C, aqueous solution of sodium stearate (4 mL, 5 CMC). All the products were characterized by spectroscopic methods and compared with the authentic spectra.[5f,14a,15]
[b] dr=50:50, according to NMR.

core of the micelle droplets, where the reactions take place more easily. This explanation is schematically presented by Fig. 1.

In order to show the unique catalytic behavior of the micellar solution of sodium stearate in these reactions, we have performed the one-pot reaction of 4-methoxybenzaldehyde, malononitrile, and triethyl phosphite in the presence of a catalytic amount of $HClO_4$–SiO_2, metal oxides [e.g., TiO_2, CdO, CuO, Sb_2O_3, SnO_2, ZnO] and Brønsted acids [e.g., NH_2SO_3H and $H_3PMo_{12}O_{40}$] (Table 4). As is evident from Table 4, the micellar solution of sodium stearate is the most effective catalyst for this purpose leading to the formation of β-phosphonomalonate (**1**) in good yield.

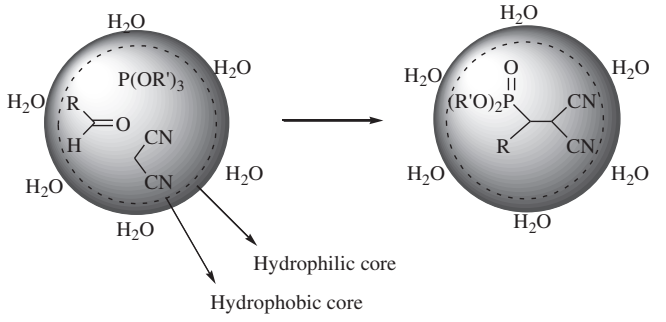


Fig. 1. The proposed pole of micellar sodium stearate droplets for the synthesis of different types of β-phosphonomalonates via Knoevenagel–phospha-Michael reaction.

Table 4
Comparison of the catalytic efficiency of micellar solution of sodium stearate with various catalysts

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Sodium stearate	1	85
2	$HClO_4$–SiO_2	24	28
3	TiO_2	24	10
4	CdO	24	25
5	CuO	24	20
6	Sb_2O_3	24	5
7	SnO_2	24	18
8	ZnO	24	15
9	NH_4SO_3H	24	5
10	$H_3PMo_{12}O_{40}$	24	0

[a] Isolated yield, conditions: catalyst (0.008 mmol), 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol), H_2O (4 mL), 80 °C.

3. Conclusions

In conclusion, we have successfully developed a simple one-pot protocol to generate phosphorus–carbon bonds via a tandem Knoevenagel–phospha-Michael reaction in aqueous micellar solution of sodium stearate. This simple procedure allows a series of β-phosphonomalonates to be synthesized from the reaction of aryl/heteroaryl/alkyl aldehydes, malononitrile, and trialkyl phosphites.

4. Experimental section

4.1. General

Chemicals were purchased from Merck and Fluka Chemical Companies. NMR spectra were recorded in parts per million in $CDCl_3$ on a Bruker Avance DPX-250 instrument using TMS as internal standard. Mass spectra were recorded on a Shimadzu GC–MS-QP5050A. Elemental analysis for C, H, and N were obtained using an Elementar, Vario EL III. The purification of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates.

4.2. Reaction procedures and spectral data

Aldehyde (1 mmol), malononitrile (1 mmol), and triethyl phosphite (1 mmol) was added to a micellar solution of sodium stearate (4 mL, 0.002 M) in water. The mixture was stirred for an appropriate time at 80 °C (Table 1). The solvent was evaporated under reduced pressure to give a crude product. Pure product was obtained by column chromatography eluted with *n*-hexane/EtOAc (1:1→1:2).

*4.2.1. [1-(4-Methoxy)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**1**).* Yield 0.27 g, 85%; yellow solid, mp 61 °C; R_f (50% *n*-hexane/EtOAc) 0.50; δ_H (400 MHz, $CDCl_3$) 1.17 (t, 3H, $^3J_{HH}$=7.2 Hz), 1.37 (t, 3H, $^3J_{HH}$=7.2 Hz), 3.57 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^2J_{HP}$=21.2 Hz), 3.84 (s, 3H), 4.00–4.24 (m, 4H), 4.51 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^3J_{HP}$=8.8 Hz), 6.97 (d, 2H, $^3J_{HH}$=8.8 Hz), 7.41–7.44 (m, 2H).

*4.2.2. [1-(2-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**2**).* Yield 0.28 g, 85%; yellow solid, mp 77 °C; R_f (50% *n*-hexane/EtOAc) 0.57; δ_H (400 MHz, $CDCl_3$) 1.11 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.36 (t, 3H, $^3J_{HH}$=7.0 Hz), 3.75–4.30 (m, 4H), 4.46 (dd, 1H, $^3J_{HH}$=8.2, $^1J_{HP}$=21.2 Hz), 4.61 (t, 1H, $^3J_{HH}$=8.5 Hz), 7.35 (d, 2H, $^3J_{HH}$=4 Hz), 7.47 (s, 1H), 7.75 (d, 1H, $^3J_{HH}$=5.3 Hz).

*4.2.3. [1-(3-Bromophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**3**).* Yield 0.31 g, 84%; white solid, mp 78–79 °C; [Found: C, 44.33; H, 4.12; N, 7.39. $C_{14}H_{16}BrN_2O_3P$ requires C, 45.30; H, 4.34; N, 7.55%]; R_f (50% *n*-hexane/EtOAc) 0.46; υ_{max} (KBr) 2242 (CN), 1003 (P=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14 (t, 3H, $^3J_{HH}$=7.2 Hz), 1.31 (t, 3H, $^3J_{HH}$=7.2 Hz), 3.65 (dd, 1H, $^3J_{HH}$=7.6 Hz, $^2J_{HP}$=21.6 Hz), 3.81–4.19 (m, 4H), 4.7 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^2J_{HP}$=9.2 Hz), 7.28 (t, 1H, $^3J_{HH}$=8.0 Hz), 7.44 (d, 1H, $^3J_{HH}$=7.2 Hz), 7.52 (d, 1H, $^3J_{HH}$=8.0 Hz), 7.62 (s, 1H); δ_C (100 MHz, $CDCl_3$) 16.1 (d, $^3J_{CP}$=5.0 Hz), 16.2 (d, $^3J_{CP}$=6.0 Hz), 25.3, 43.8 (d, $^1J_{CP}$=143.0 Hz), 63.6 (d, $^2J_{CP}$=7.0 Hz), 64.4 (d, $^2J_{CP}$=7.0 Hz), 111.3 (d, $^3J_{CP}$=12.1 Hz), 111.4 (d, $^3J_{CP}$=11.1 Hz), 123.1, 127.9 (d, $^3J_{CP}$=6.0 Hz), 130.8, 132.4 (d, $^2J_{CP}$=6.0 Hz), 132.6, 132.8 (d, $^3J_{CP}$=6.0 Hz); *m/z* (EI, 70 eV) 370 (22 M^+), 372 (22 M^++2), 207 (80), 209 (80), 138 (100%).

*4.2.4. [1-(4-Methyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**4**).* Yield 0.26 g, 86%; yellow solid, mp 97 °C; R_f (50% *n*-hexane/EtOAc) 0.44; δ_H (400 MHz, $CDCl_3$) 1.16 (t, 3H, $^3J_{HH}$=7.2 Hz), 1.38 (t, 3H, $^3J_{HH}$=7.2 Hz), 2.40 (s, 3H), 3.57 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^2J_{HP}$=21.2 Hz), 3.74–3.84 (m, 1H), 3.99–4.06 (m, 1H), 4.14–4.25 (m, 2H), 4.50 (dd, 1H, $^3J_{HH}$=8.4 Hz, $^3J_{HP}$=9.0 Hz), 7.25–7.29 (m, 2H), 7.37–7.39 (m, 2H).

*4.2.5. [1-(4-Bromophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**5**).* Yield 0.30 g, 82%; white solid, mp 102 °C; [Found: C, 44.46; H, 4.15; N, 7.39. $C_{14}H_{16}BrN_2O_3P$ requires C, 45.30; H, 4.34; N, 7.55%]; R_f (50% *n*-hexane/EtOAc) 0.44; υ_{max} (KBr); 2242 (CN), 1000 (P=O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.16 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.33 (t, 3H, $^3J_{HH}$=7.0 Hz), 3.58 (dd, 1H, $^3J_{HH}$=7.5 Hz, $^2J_{HP}$=21.5 Hz), 3.79–4.18 (m, 4H), 4.56 (t, 1H, $^3J_{HH}$=7.75 Hz), 7.36 (d, 2H, $^3J_{HH}$=8.25 Hz), 7.56 (d, 2H, $^3J_{HH}$=8.0 Hz); δ_C (62.9 MHz, $CDCl_3$) 16.1 (d, $^3J_{CP}$=4.4 Hz), 16.2 (d, $^3J_{CP}$=5.7 Hz), 25.4, 43.9 (d, $^1J_{CP}$=144.7 Hz), 63.6 (d, $^2J_{CP}$=7.5 Hz), 64.4 (d, $^2J_{CP}$=7.5 Hz), 111.0 (d, $^3J_{CP}$=11.9 Hz), 111.2 (d, $^3J_{CP}$=10.7 Hz), 123.9, 129.4, 131.0, 132.5; δ_P (101 MHz, $CDCl_3$) 19.27; *m/z* (EI, 70 eV) 370 (7 M^+), 372 (8 M^++2), 233 [12 M^+−P(O)(OEt)$_2$], 235 [12 (M^++2)−P(O)(OEt)$_2$], 207 (100), 209 (99), 138 (66%).

*4.2.6. [1-(3-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**6**).* Yield 0.27 g, 83%; yellow liquid; R_f (50% *n*-hexane/EtOAc) 0.56; δ_H (400 MHz, $CDCl_3$) 1.20 (t, 3H, $^3J_{HH}$=7.2 Hz), 1.38 (t, 3H, $^3J_{HH}$=7.2 Hz), 3.60 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^2J_{HP}$=21.2 Hz), 3.83–3.93 (m, 1H), 4.03–4.26 (m, 3H), 4.56 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^3J_{HP}$=9.2 Hz), 7.41–7.45 (m, 3H), 7.50 (s, 1H).

*4.2.7. [1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**7**).* Yield 0.30 g, 91%; yellow solid, mp 98 °C; R_f (50% *n*-hexane/EtOAc) 0.53; δ_H (250 MHz, $CDCl_3$) 1.16 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.33 (t, 3H, $^3J_{HH}$=7.0 Hz), 3.62 (dd, 1H, $^3J_{HH}$=7.5 Hz, $^2J_{HP}$=21.5 Hz), 3.82–4.19 (m, 4H), 4.55 (t, 1H, $^3J_{HH}$=7.7 Hz), 7.42 (s, 4H).

*4.2.8. [1-(Furan-2-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**8**).* Yield 0.23 g, 80%; dark yellow liquid; R_f (50% *n*-hexane/EtOAc) 0.42; δ_H (250 MHz, $CDCl_3$) 1.24–1.37 (m, 6H), 3.87 (dd, 1H, $^3J_{HH}$=6.5 Hz, $^2J_{HP}$=22.7 Hz), 3.98–4.23 (m, 4H), 4.51 (t, 1H, $^3J_{HH}$=8.7 Hz), 6.44 (s, 1H), 6.62 (s, 1H), 7.49 (s, 1H).

*4.2.9. [1-(Pyridin-3-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**9**).* Yield 0.26 g, 89%; dark orange liquid; [Found: C, 52.71; H, 5.32; N, 14.04. $C_{13}H_{16}N_3O_3P$ requires C, 53.24; H, 5.50; N, 14.33%]; R_f (50% *n*-hexane/EtOAc) 0.07; υ_{max} (KBr) 2236 (CN), 1011 (P=O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.18 (t, 3H, $^3J_{HH}$=6.8 Hz), 1.33 (t, 3H, $^3J_{HH}$=7.0 Hz), 3.65 (dd, 1H, $^3J_{HH}$=6.8 Hz, $^2J_{HP}$=21.6 Hz), 3.92–4.21 (m, 4H), 4.63 (t, 1H, $^3J_{HH}$=8.5 Hz), 7.39 (t, 1H, $^3J_{HH}$=6.5 Hz), 7.95 (d, 1H, $^3J_{HH}$=6.5 Hz), 8.67 (s, 2H); δ_C (62.9 MHz, $CDCl_3$) 16.1 (d, $^3J_{CP}$=5.0 Hz), 16.2 (d, $^3J_{CP}$=5.0 Hz), 25.3, 42.1 (d, $^1J_{CP}$=144.6 Hz), 63.8 (d, $^2J_{CP}$=7.0 Hz), 64.5 (d, $^2J_{CP}$=7.0 Hz), 110.8 (d, $^3J_{CP}$=10.7 Hz), 111.0 (d, $^3J_{CP}$=11.9 Hz), 124.0, 126.7, 136.5, 150.5, 150.8; δ_P (101 MHz, $CDCl_3$) 19.03; *m/z* (EI, 70 eV) 293 (10 M^+), 156 [100 M^+−P(O)(OEt)$_2$], 138 (92), 130 (25), 111 (98%).

*4.2.10. [1,1-Dicyanopentan-2-yl] phosphonic acid diethyl ester (**10**).* Yield 0.22 g, 85%; yellow liquid; [Found: C, 51.07; H, 7.12; N, 10.46. $C_{11}H_{19}N_2O_3P$ requires C, 51.16; H, 7.42; N, 10.85%]; R_f (50% *n*-hexane/EtOAc) 0.5; υ_{max} (KBr) 2240 (CN), 1011 (P=O) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.00 (t, 3H, $^3J_{HH}$=7.0 Hz), 1.37 (t, 6H, $^3J_{HH}$=7.0 Hz), 1.61 (q, 2H, $^3J_{HH}$=7.0 Hz), 1.73–2.10 (m, 2H), 2.29–2.34 (m, 1H), 4.16–4.25 (m, 4H), 4.29–4.35 (m, 1H); δ_C (62.9 MHz, $CDCl_3$) 13.73, 16.3 (d, $^3J_{CP}$=5.6 Hz), 20.7 (d, $^2J_{CP}$=7.6 Hz), 29.2, 37.8 (d, $^1J_{CP}$=144.9 Hz), 110.7 (d, $^3J_{CP}$=5.0 Hz), 112.2 (d, $^3J_{CP}$=17.0 Hz); *m/z* (EI, 70 eV) 259 (4 M^++1), 138 (100) 121 [20 M^+−P(O)(OEt)$_2$], 111 (72), 95 (6%).

*4.2.11. [1,1-Dicyanooctan-2-yl] phosphonic acid diethyl ester (**11**).* Yield 0.24 g, 81%; yellow liquid; [Found: C, 55.36; H, 8.03; N 9.20. $C_{14}H_{25}N_2O_3P$ requires C, 55.99; H, 8.39; N, 9.33%]; R_f (50% *n*-hexane/EtOAc) 0.6; υ_{max} (KBr) 2238 (CN), 1011 (P=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81 (t, 3H, $^3J_{HH}$=6.8 Hz), 1.23–1.25 (m, 6H), 1.29 (t, 6H, $^3J_{HH}$=7.2 Hz), 1.45–1.50 (m, 2H), 1.66–1.79 (m, 1H), 1.86–1.98 (m, 1H), 2.25–2.34 (m, 1H), 4.08–4.16 (m, 4H), 4.36 (dd, 1H, $^3J_{HP}$=13.2 Hz, $^3J_{HH}$=3.6 Hz); δ_C (62.9 MHz, $CDCl_3$) 13.9, 16.21 (d, $^3J_{CP}$=5.0 Hz), 22.3, 23.7, 27.1, 27.2 (d, $^3J_{CP}$=6.0 Hz), 28.8, 31.2, 37.7 (d, $^1J_{CP}$=143.0 Hz), 63.1 (d, $^2J_{CP}$=7.0 Hz), 111.1 (d, $^3J_{CP}$=3.0 Hz), 112.3 (d, $^3J_{CP}$=17.0 Hz); *m/z* (EI, 70 eV) 301 (1 M^++1), 163 [18 M^+−P(O)(OEt)$_2$], 138 (100), 111 (76), 81 (77%).

4.2.12. [1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid dimethyl ester. Yield 0.25 g, 82%; white solid, mp 118 °C; R_f (50% *n*-hexane/EtOAc) 0.31; δ_H (400 MHz, $CDCl_3$) 3.61–3.68 (m, 4H), 3.86 (d, 3H, $^3J_{HP}$=11.2 Hz), 4.51 (t, 1H, $^3J_{HH}$=8.0 Hz), 7.50 (s, 4H).

4.2.13. [1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid di-iso-propyl ester. Yield 0.28 g, 80%; yellow solid, mp 111 °C; R_f (50% *n*-hexane/EtOAc) 0.62; δ_H (400 MHz, $CDCl_3$) 1.00 (d, 3H, $^3J_{HH}$=6.4 Hz), 1.32 (d, 3H, $^3J_{HH}$=6.0 Hz), 1.39 (d, 6H, $^3J_{HH}$=6.0 Hz,), 3.51 (dd, 1H, $^3J_{HH}$=7.2 Hz, $^2J_{HP}$=21.6 Hz), 4.51–4.57 (m, 1H), 4.75–4.83 (m, 1H), 7.43–7.50 (m, 4H).

4.2.14. [1-(4-Chlorophenyl)-2-cyano-2-ethylcarboxylic acid ethyl ester] phosphonic acid diethyl ester. Yield 0.27 g, 73%; light yellow liquid; R_f (50% *n*-hexane/EtOAc) 0.46; δ_H (400 MHz, $CDCl_3$)

1.10–1.15 (m, 2H), 1.19–1.30 (m, 6H), 1.35 (t, 1H, $^3J_{HH}$=7.2 Hz), 3.74–3.85 (m, 1H), 3.96–4.21 (m, 6H), 4.27 (dd, 1H, $^3J_{HH}$=6.0 Hz, $^3J_{HP}$=8.4 Hz), 7.33–7.36 (m, 3H), 7.44–7.47 (m, 1H).

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References and notes

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