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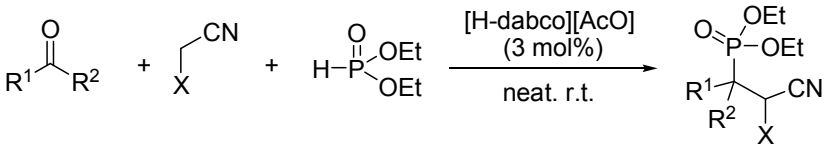
Graphical Abstract

A recyclable catalyst for one-pot synthesis of β-phosphonomalonates via tandem Knoevenagel–phospha-Michael reaction.



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A quaternary ammonium salt [H-dabco][AcO]: as a recyclable and highly efficient catalyst for the one-pot synthesis of β-phosphonomalonates

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Keywords

β-phosphonomalonates, multicomponent reactions, quaternary ammonium salts, recycling, green chemistry

Abstract

A simple, green and highly efficient approach for the one-pot three-component synthesis of β-phosphonomalonates has been developed. In the presence of the quaternary ammonium salt catalysts, the β-phosphonomalonates were obtained in excellent yields within short times via tandem Knoevenagel–phospha-Michael reaction. The reaction of aldehydes/ketones, active methylene compounds, and diethyl phosphite performed at room temperature under solvent-free conditions. No column purification is required and the products can be purified by simple crystallization. The catalysts can be easily recovered and reused several times without significant activity loss.

Introduction

The multi-component coupling reactions (MCRs), which enable the facile, automated and high throughput generation of small organic molecules, are a powerful synthetic tool to access complex structures from simple precursors via one-pot procedure.[1] MCRs are highly important reactions and have been widely used in pharmaceutical chemistry for the production of structural scaffolds and combinatorial libraries for drug discovery.[2]

The synthesis of phosphonates and their derivatives have attracted considerable attention over the last few years due to their wide range of applications in material chemistry,[3] catalysis[4] and medicinal chemistry as enzyme inhibitors,[5] peptide mimics,[6] antibiotics[7] and pharmacological agents.[8] As a result, various synthetic methods have been developed for the preparation of phosphonates. One of the most promising tools for the synthesis of β-phosphonomalonates involves the phosphorus–carbon (P–C) bond formation by phospha-Michael addition.[9] These methods are mainly focused on the two-pot procedures in which the α, β-unsaturated malonates should be prepared first in a separate step.[10] The reports for one-pot synthesis of β-phosphonomalonates via tandem Knoevenagel–phospha-Michael reaction are rare in the literature.[11] However, there are still a lot of disadvantages associated with these procedures, such as low yields, long reaction times, elevated temperature, special reaction conditions, using hazardous organic solvents or unrecyclable catalysts. Even though, nearly all the methods were based on the substrate of triethyl phosphite and few example employed diethyl phosphite,[11d, 11e] which fulfills the criteria of atom economy, as the phosphorous component in this transformation. Therefore, a simple and green procedure employing diethyl phosphite as the phosphorous component for one-pot synthesis of β-phosphonomalonates with an efficient and reusable catalyst remains a major challenge in synthetic organic chemistry.

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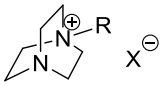
Ionic liquids (ILs) have attracted significant attention as ecofriendly media for many chemical and biochemical transformations due to their unique physicochemical properties, such as non-inflammability, negligible vapour pressure, reusability and high thermal stability.[12] The functional ILs have also been synthesized and utilized as recyclable catalysts for different reactions with good to excellent performance.[13-17] Recently, We have reported a series of ionic liquid catalysts based on the skeleton of 1,4-diazobicyclo [2.2.2] octane (DABCO) and they shown to be very effective catalysts for the Michael addition reaction[18] and Knoevenagel condensation.[19] Other kinds of functionalized ILs based on DABCO were also designed and invested in different reactions.[20] As our continuing interests in ionic liquid mediated organic reactions, here, we wish to disclose our study on using of the DABCO-base quaternary ammonium salts (QASs) as highly efficient catalysts for the multi-component one-pot synthesis of β-phosphonomalonates via tandem Knoevenagel–phospha-Michael reaction.

Results and discussion

The quaternary ammonium salts [H-dabco][AcO], [H-dabco]Cl, [C_4-dabco]Br and [C_8-dabco]Br were synthesized according to the literature.[14(a)]



[H-dabco][AcO], X = AcO, R = H
[H-dabco]Cl, X = Cl, R = H
[C_4-dabco]Br, X = Br, R = n-butyl
[C_8-dabco]Br, X = Br, R = n-octyl

Fig. **1**. Structures of the DABCO-base quaternary ammonium salts.

As can be seen from the results summarized in Table 1, the reaction of 4-methylbenzaldehyde (**1a**), malononitrile (**2a**) and diethyl phosphite (**3**) was performed in THF at room temperature with 10 mol% of DABCO-base QASs as the catalyst. All the catalysts tested exhibited good catalytic activity with the corresponding products obtained in good to excellent yields (Table 1, entries 1-4). The QAS catalyst [H-dabco][AcO] promoted the tandem Knoevenagel–phospha-Michael reaction for synthesis of β-phosphonomalonate **4a** with better yield under the same conditions (Table 1, entry 1 vs entries 2-4). The other QASs catalysts also gave good yields, but longer reaction times were needed (Table 1, entries 2-4). Catalyst [H-dabco][AcO] was used as the catalyst of choice and evaluated in different solvents. No better results were observed when the reaction performed in other solvent such as CH_2Cl_2, CH_3CN, Toluene or C_2H_5OH (Table 1, entries 5-8). It was found that, under neat conditions, the yield of the corresponding β-phosphonomalonate **4a** was obtained in 95% yield at room temperature within only 30 minutes (Table 1, entry 9). Without any solvents added, allowed the reactions to be performed in a very simple, cheap and green manner. After completion of the reaction, the crude products solidified when water was added, filtered and washed with cold water to remove the catalyst. The desired products could be purified by crystallization, and no chromatographic technique was used for product purification. This procedure avoids using large quantities of volatile organic solvents which is generally the main source of waste, and required less time for this transformation. Then we tried to reduce the amount of the catalyst [H-dabco][AcO], the product **4a** was formed in nearly the same yields within 30 minutes when 5 mol% and 3 mol% catalyst were used (Table 1, entries 10 and 11). When we reduced the amount of the catalyst to 1 mol%, β-phosphonomalonate **4a** could be also obtained in high yield in 2 hours (Table 1, entry 12). The loading of diethyl phosphite could be reduced to 1 eq, but

reaction time was changed to 4 hours (Table 1, entry 13). This reaction, performed under condition without any catalyst, led to the formation of product **4a** in a very low yield even after a long reaction time (Table 1, entry 14).

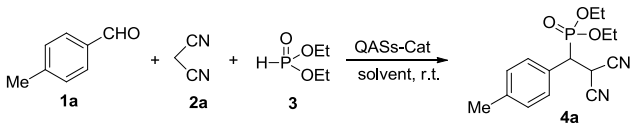


Table 1. One-pot reaction of benzaldehyde, malononitrile and diethyl phosphite under different conditions[a]

Entry	Cat. (mol %)	Solvent (mL)	T (h)	Yield[b] (%)
1	[H-dabco][AcO] (10)	THF (1)	2.5	95
2	[H-dabco]Cl (10)	THF (1)	6	87
3	[C_4-dabco]Br (10)	THF (1)	6	82
4	[C_8-dabco]Br (10)	THF (1)	6	80
5	[H-dabco][AcO] (10)	CH_2Cl_2 (1)	2	94
6	[H-dabco][AcO] (10)	CH_3CN (1)	2	90
7	[H-dabco][AcO] (10)	Toluene (1)	4	72
8	[H-dabco][AcO] (10)	C_2H_5OH (1)	6	51
9	[H-dabco][AcO] (10)	neat	0.5	95
10	[H-dabco][AcO] (5)	neat	0.5	94
11	[H-dabco][AcO] (3)	neat	0.5	95
12	[H-dabco][AcO] (1)	neat	2	94
13[c]	[H-dabco][AcO] (3)	neat	4	94
14	-	neat	24	<5

[a] Conditions: aromatic 4-methylbenzaldehyde (**1a**, 1 mmol), malononitrile (**2a**, 1 mmol), diethyl phosphite (**3**, 2 mmol), room temperature (25°C).

[b] Isolated yield.

[c] 1 mmol Diethyl phosphite was used.

To confirm the generality of the present method, next, the reactions of a variety of aldehydes (**1**) with active methylene compounds (**2**) and diethyl phosphite (**3**) were examined in the presence of catalyst [H-dabco][AcO] (3 mol%) under neat conditions at room temperature. The results are summarized in Table 2. The reactions of different substituted benzaldehydes containing electron withdrawing groups or donating groups with malononitrile and diethyl phosphite were converted to the corresponding β-phosphonomalonates in good to excellent yields (91–98%) within 15 to 100 minutes (Table 2, entries 1-18). Heteroaromatic aldehydes, such as thiophene-2-carbaldehyde (**1s**) was also effective substrates to execute the tandem Knoevenagel–phospha-Michael reaction in the presence of [H-dabco][AcO] (Table 2, entry 19). This catalytic system was successfully applied for the reaction of aliphatic ketone **1t** with malononitrile (**2a**) and diethyl phosphite (**3**) and produced the desired products **4t** in good yields (Table 2, entry 20). Ethyl cyanoacetate (**2b**), although the methylene group is less activated than malononitrile, was readily reacted with different substituted benzaldehydes (**1e**, **1f**, **1j**) and diethyl phosphite (**3**), and afforded the corresponding products (**4u**, **4v**, **4w**) in 90-97% yields (Table 2, entries 21-23).

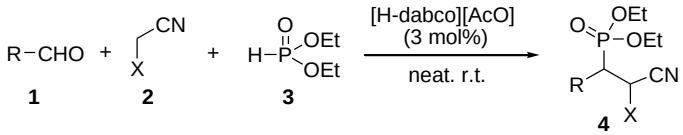


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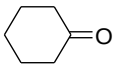
Table 2. One-pot synthesis of different β-phosphonomalonates catalyzed by [H-dabco][AcO][a]

Entry	R	X	Product	T (min)	Yield[b] (%)
1	4-MeC_6H_4	CN	**4a**	30	95
2	4-t-BuC_6H_4	CN	**4b**	35	93
3	C_6H_5	CN	**4c**	45	97
4	4-$MeOC_6H_4$	CN	**4d**	60	91
5	4-ClC_6H_4	CN	**4e**	25	95
6	3-ClC_6H_4	CN	**4f**	40	95
7	2-ClC_6H_4	CN	**4g**	15	96
8	4-FC_6H_4	CN	**4h**	20	93
9	3-FC_6H_4	CN	**4i**	30	98
10	4-$NO_2C_6H_4$	CN	**4j**	15	91
11	3-$NO_2C_6H_4$	CN	**4k**	20	95
12	4-BrC_6H_4	CN	**4l**	35	93
13	4-CNC_6H_4	CN	**4m**	35	97
14	3-Br-4-FC_6H_3	CN	**4n**	25	96
15	2,5-$(MeO)_2C_6H_3$	CN	**4o**	15	93
16	2,4-$Cl_2C_6H_3$	CN	**4p**	40	95
17	3,5-$Br_2C_6H_3$	CN	**4q**	40	97
18	naphthalen-1-yl	CN	**4r**	100	94
19	thiophen-2-yl	CN	**4s**	20	96
20		CN	**4t**	120	91
21[c]	4-ClC_6H_4	CO_2Et	**4u**	50	90
22[d]	3-ClC_6H_4	CO_2Et	**4v**	18	97
23[e]	4-$NO_2C_6H_4$	CO_2Et	**4w**	160	91

[a] Conditions: carbonyl compound (**1**, 1 mmol), active methylene compound (**2**, 1 mmol), diethyl phosphite (**3**, 2 mmol), room temperature (25°C), solvent-free conditions.

[b] Isolated yield.

[c e] d.r. = 2:1, according to NMR.

[d] d.r. = 3:2, according to NMR.

When diethyl phosphite (**3**) was replaced by triethyl phosphite (**5**) and reacted with aldehydes and malononitrile under the same reaction conditions, affording a mixture of products **4g** and **6** in a ratio of 2:1 (Scheme 1). Compound **6** is probably formed via a five-member ring transition state between $(EtO)_2P\text{-}O\text{-}CH_2CH_3$ and C=C bond, in which P and Et are inclined to add on the double bond simultaneously by a concerted process.

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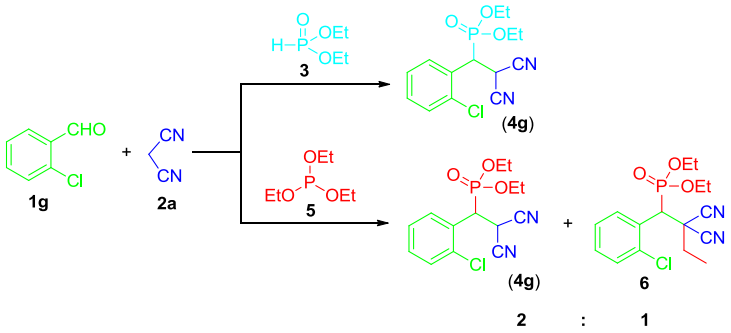


Scheme 1.

The reusability of the catalyst was also examined for the synthesis of β-phosphonomalonates **4a**. The catalyst could be recycled after removing the products and more diethyl phosphite. The reaction of 4-methylbenzaldehyde, malononitrile and diethyl phosphite gave the corresponding product **4a** in similar yields over six cycles (Fig. 2).

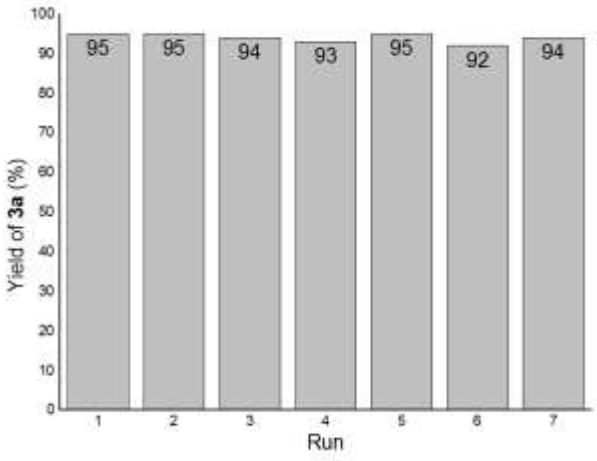
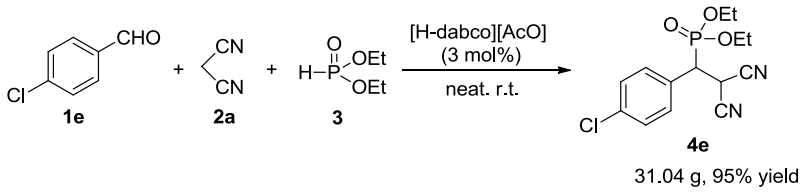


Fig. 2. Recycling of the catalyst [H-dabco][AcO] for the synthesis of β-phosphonomalonate **4a**.

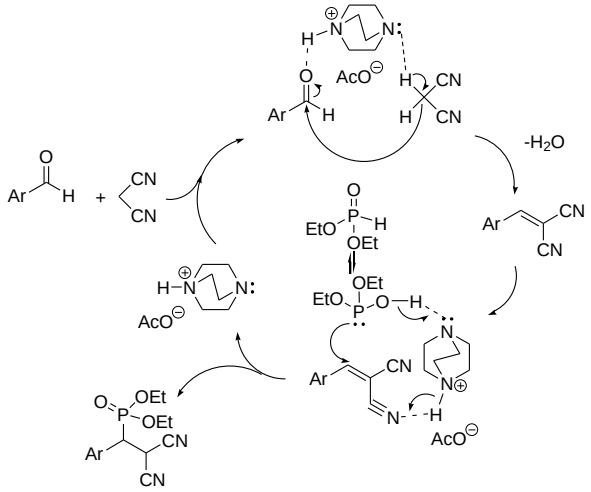
We have developed an improved process for one-pot synthesis of β-phosphonomalonates which offered several advantages over this procedure. This process performed at room temperature without any organic solvent, and the catalyst was a quaternary ammonium salt, which was easily recovered and could be reused more than six times. This is a simple and very mild reaction, which is readily amenable to large-scale synthesis. Using this procedure, we tried this reaction out on a 0.1-mol scale, and 31.04 g of **4e** was prepared in 95% yield. Therefore, this is an easy access to these β-phosphonomalonates on a large scale via tandem Knoevenagel–phospha-Michael reaction, using DABCO-base QASs as catalysts.



Scheme 2. Synthesis of β-phosphonomalonate **4e** on 0.1-mol scale.

A plausible mechanism for the formation of β-phosphonomalonates in the presence of [H-dabco][AcO] is shown in

Scheme 3. The process represents a typical tandem reaction by double-activation. In the initiation step of the catalytic cycle, double-activation of the carbonylgroup of aldehydes and malononitrile by the catalyst ([H-dabco][AcO]) occurred to formation of Knoevenagel product. After that, the catalyst may activate both the cyanogroup and diethyl phosphite, and take the H^+ from diethyl phosphite by the top N and give the H^+ attaching to bottom N to –CN. Then a tautomerzation via H [1, 3] shift takes place to produce target product.



Scheme 3. A plausible mechanism for [H-dabco][AcO] catalytic synthesis of β-phosphonomalonates.

In order to show the unique catalytic behavior of [H-dabco][AcO] in the reactions, other catalysts like L-proline, $FeCl_3$ and catalysts (3 mol%) from reported literatures, including sodium sterarate,[11(b)] ZnO[9(c)], $HClO_4$-SiO_2,[10(b)] NH_4SO_3H,[11(b)] I_2,[11(k)] and pyridine,[10(c)] were also employed in the one-pot reaction of benzaldehyde, malononitrile and diethyl phosphite. As shown in Table 3, [H-dabco][AcO] is the most effective catalyst for this tandem reaction, leading to the formation of β-phosphonomalonate **4c** in an excellent yield within very short time.

Table 3. Comparison of the catalytic activity of [H-dabco][AcO] with various reported catalysts for the synthesis of β-phosphonomalonate **4c**. [a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	[H-dabco][AcO]	0.75	95
2	L-proline	24	<5
3	$FeCl_3$	12	62
4	Sodium stearate	12	27
5	ZnO	12	51
6	$HClO_4$-SiO_2	12	43
7	NH_4SO_3H	6	78
8	I_2	12	19
9	Pyridine	6	59

[a] Conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), diethyl phosphite (2 mmol) and catalyst (3 mol%), room temperature (25°C), solvent-free conditions.

[b] Isolated yield.

Conclusion

In summary, it was demonstrated that the readily available, economic DABCO-base quaternary ammonium salts (QASs) could behave as recyclable and highly efficient catalysts for the multi-component one-pot synthesis of

β-phosphonomalonates via tandem Knoevenagel–phospha-Michael reaction. The reactions, performed under solvent-free conditions at room temperature, allowed a very simple, clean synthesis of β-phosphonomalonates with good to excellent yields in short times. The quaternary ammonium salts could be easily recovered and reused at least for seven times without activity loss. The desired products could be easily separated and purified without any requirement of column chromatographic purification. It is a simple route to large scale synthesis of β-phosphonomalonates.

Experimental

General procedure for the synthesis of β-phosphonomalonates (4)

A 10-mL round bottomed flask was charged with aldehyde (**1**, 1 mmol), active methylene compound (**2**, 1 mmol), diethyl phosphite (**3**, 2 mmol) and [H-dabco][AcO] (5.2mg, 0.03 mmol). The reaction mixture was stirred at room temperature under air. After completion of the reaction (monitored by TLC), cold water (5 mL) was added, the mixture was solidified in the round bottomed flask, filtered and washed with cold water to remove the catalyst and diethyl phosphite. The crude products were purified by the crystallization technique and no column purification was followed. The filtrate was extracted with ethyl acetate to remove diethyl phosphite, the quaternary ammonium salt [H-dabco][AcO] was left, more water were evaporated from the salt under vacuum, and reused in the next recycling run. The catalyst could be recovered and reused in the reaction for six times at least.

[1-(p-Tolyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4a)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (3H, t, J = 6.8 Hz), 1.34 (3H, t, J = 6.8 Hz), 2.35 (3H, s), 3.59 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.2 Hz), 3.72-3.82 (1H, m), 3.95-4.03 (1H, m), 4.09-4.18 (2H, m), 4.61 (1H, t, J = 8.8 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.36 (2H, d, J = 6.4 Hz).

[1-(4-(tert-Butyl)phenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4b)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09 (3H, t, J = 7.2 Hz), 1.31 (9H, s), 1.32 (3H, t, J = 7.2 Hz), 3.66 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.2 Hz), 3.73-3.83 (1H, m), 3.94-4.02 (1H, m), 4.10-4.20 (2H, m), 4.70 (1H, dd, J_1 = 8.0 Hz, J_2 = 8.8 Hz), 7.42 (4H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 15.95 (d, $^3J_{CP}$ = 5.7 Hz), 16.19 (d, $^3J_{CP}$ = 5.8 Hz), 25.53, 31.15, 34.61, 43.91 (d, J_{CP} = 143.4 Hz), 63.23 (d, $^2J_{CP}$ = 7.3 Hz), 64.15 (d, $^2J_{CP}$ = 7.0 Hz), 111.70, 126.20, 127.28, 129.05, 152.45. ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.73. Anal. Calcd. for $C_{18}H_{25}N_2O_3P$: C, 62.06; H, 7.23; N, 8.04. Found: C, 62.17; H, 7.15; N, 8.09.

[1-Phenyl-2,2-dicyanoethyl] phosphonic acid diethyl ester (4c)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.07 (3H, t, J = 7.2 Hz), 1.30 (3H, t, J = 6.8 Hz), 3.64 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.2 Hz), 3.70-3.78 (1H, m), 3.91-4.01 (1H, m), 4.08-4.17 (2H, m), 4.69 (1H, t, J = 8.4 Hz), 7.37-7.40 (3H, m), 7.45-7.47 (2H, m).

[1-(4-Methoxyphenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4d)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.14 (3H, t, J = 6.8 Hz), 1.34 (3H, t, J = 6.8 Hz), 3.60 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.2 Hz), 3.74-3.78 (1H, m), 3.81 (3H, m), 3.96-4.06 (1H, m), 4.11-4.20 (2H, m), 4.63 (1H, t, J = 8.4 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.41 (2H, d, J = 7.2 Hz).

[1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4e)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.13 (3H, t, J = 7.2 Hz), 1.31 (3H, t, J = 7.2 Hz), 3.64 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.6 Hz), 3.78-3.88 (1H, m), 3.96-4.06 (1H, m), 4.09-4.19 (2H, m), 4.68 (1H, t, J = 7.6 Hz), 7.38 (2H, d, J = 8.8 Hz), 7.43 (2H, d, J = 7.2 Hz).

[1-(3-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4f)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.16 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 6.8 Hz), 3.75 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.6 Hz), 3.83-3.93 (1H, m), 4.00-4.10 (1H, m), 4.14-4.23 (2H, m), 4.84 (1H, t, J = 7.6 Hz), 7.34-7.40 (2H, m), 7.42-7.45 (1H, m), 7.52 (1H, s).

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[1-(2-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4g)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.11 (3H, t, J = 7.2 Hz), 1.36 (3H, t, J = 6.8 Hz), 3.76-3.86 (1H, m), 3.96-4.03 (1H, m), 4.17-4.26 (2H, m), 4.50 (1H, dd, J_1 = 8.4 Hz, J_2 = 21.6 Hz), 4.86 (1H, t, J = 8.8 Hz), 7.32-7.39 (2H, m), 7.46-7.50 (1H, m), 7.79-7.82 (1H, m).

[1-(4-Fluorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4h)[11(j)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.15 (3H, t, J = 7.2 Hz), 1.34 (3H, t, J = 6.8 Hz), 3.70 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.2 Hz), 3.80-3.90 (1H, m), 3.98-4.06 (1H, m), 4.15-4.22 (2H, m), 4.73 (1H, t, J = 7.6 Hz), 7.13 (2H, t, J = 8.4 Hz), 7.52 (2H, t, J = 6.4 Hz).

[1-(3-Fluorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4i)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.16 (3H, t, J = 6.8 Hz), 1.33 (3H, t, J = 7.2 Hz), 3.73 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.6 Hz), 3.82-3.92 (1H, m), 4.00-4.10 (2H, m), 4.79 (1H, t, J = 8.8 Hz), 7.12 (1H, t, J = 8.4 Hz), 7.29 (2H, t, J = 8.0 Hz), 7.38-7.44 (1H, m). ^{13}C NMR (100MHz, $CDCl_3$): δ = 16.00 (d, $^3J_{CP}$ = 5.7 Hz), 16.12 (d, $^3J_{CP}$ = 5.9 Hz), 25.27, 43.83 (d, J_{CP} = 143.2 Hz), 63.64 (d, $^2J_{CP}$ = 7.3 Hz), 64.46 (d, $^2J_{CP}$ = 7.0 Hz), 111.42, 116.64, 125.27, 131.05, 132.85, 161.55, 162.78 (d, J_{CF} = 246.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.81. Anal. Calcd. for $C_{14}H_{16}FN_2O_3P$: C, 54.20; H, 5.20; N, 9.03. Found: C, 54.31; H, 5.16; N, 9.11.

[1-(4-Nitrophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4j)[9(c)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.22 (3H, t, J = 6.4 Hz), 1.37 (3H, t, J = 6.4 Hz), 3.88 (1H, dd, J_1 = 6.8 Hz, J_2 = 21.6 Hz), 3.94-4.00 (1H, m), 4.08 -4.14 (1H, m), 4.20-4.24 (2H, m), 4.81 (1H, t, J = 8.0 Hz), 7.76 (2H, d, J = 8.0 Hz), 7.73 (2H, d, J = 8.0 Hz).

[1-(3-Nitrophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4k)[11(j)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.23 (3H, t, J = 6.8 Hz), 1.37 (3H, t, J = 6.4 Hz), 3.90 (1H, dd, J_1 = 7.2 Hz, J_2 = 21.6 Hz), 3.98-4.04 (1H, m), 4.10 -4.18 (1H, m), 4.21-4.24 (2H, m), 4.84 (1H, t, J = 8.0 Hz), 7.68 (1H, t, J = 8.4 Hz), 7.93 (1H, d, J = 7.2 Hz), 8.31 (1H, d, J = 8.0 Hz), 8.43 (1H, s).

[1-(4-Bromophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4l)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.17 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 3.65 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.6 Hz), 3.81-3.91 (1H, m), 3.99-4.07 (1H, m), 4.12-4.21 (2H, m), 4.71 (1H, t, J = 8.4 Hz), 7.39 (2H, d, J = 7.2 Hz), 7.73 (2H, d, J = 8.4 Hz).

[1-(4-Cyanophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4m)[11(e)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.17 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 3.75 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.6 Hz), 3.85-3.95 (1H, m), 4.01-4.11 (1H, m), 4.11-4.22 (2H, m), 4.71 (1H, dd, J_1 = 7.6 Hz, J_2 = 8.8 Hz), 7.64 (2H, d, J = 6.8 Hz), 7.73 (2H, d, J = 8.0 Hz).

[1-(3-Bromo-4-fluorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4n)[11(j)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.21 (3H, t, J = 7.2 Hz), 1.36 (3H, t, J = 7.2 Hz), 3.68 (1H, dd, J_1 = 7.6 Hz, J_2 = 21.6 Hz), 3.91-3.98 (1H, m), 4.06-4.12 (1H, m), 4.16-4.25 (2H, m), 4.72 (1H, dd, J_1 = 7.6 Hz, J_2 = 9.2 Hz), 7.21 (1H, t, J = 8.4 Hz), 7.48-7.52 (1H, m), 7.74 (1H, d, J = 6.4 Hz).

[1-(2,5-Dimethoxyphenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4o)[11(i)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.15 (3H, t, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 3.82 (3H, s), 3.84-3.92 (1H, m), 3.98-4.07 (1H, m), 4.10-4.22 (1H, m), 4.35 (1H, dd, J_1 = 8.4 Hz, J_2 = 21.6 Hz), 4.76 (1H, t, J = 9.2 Hz), 6.90 (2H, s), 7.18 (1H, s).

[1-(2,4-Dichlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4p)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 3.77-3.87 (1H, m), 3.91-4.03 (1H, m), 4.11-4.20 (2H, m), 4.35 (1H, dd, J_1 = 8.0 Hz, J_2 = 22.0 Hz), 4.69 (1H, t, J = 8.0 Hz), 7.29 (1H, dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.45 (1H, t, J = 1.2 Hz), 7.69 (1H, dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ = 16.10 (d, $^3J_{CP}$ = 5.6 Hz), 16.22 (d, $^3J_{CP}$ = 5.8 Hz), 24.80, 38.94 (d, J_{CP} = 144.4 Hz), 63.87 (d, $^2J_{CP}$ = 7.0 Hz), 64.49

(d, $^2J_{CP}$ = 7.1 Hz), 111.02, 111.12, 127.33, 128.23, 130.18, 130.60, 135.92, 136.05. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.28. Anal. Calcd. for $C_{14}H_{15}Cl_2N_2O_3P$: C, 46.56; H, 4.19; N, 7.76. Found: C, 46.49; H, 4.13; N, 7.69.

[1-(3,5-Dibromophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4q)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.23 (3H, t, J = 6.8 Hz), 1.36 (3H, t, J = 6.8 Hz), 3.61 (1H, dd, J_1 = 8.0 Hz, J_2 = 21.6 Hz), 3.91-4.01 (1H, m), 4.06-4.14 (1H, m), 4.17-4.23 (1H, m), 4.69 (1H, t, J = 7.6 Hz), 7.60 (2H, s), 7.74 (1H, s). ^{13}C NMR (100MHz, $CDCl_3$): δ = 16.18 (d, $^3J_{CP}$ = 5.9 Hz), 16.26 (d, $^3J_{CP}$ = 6.0 Hz), 25.17, 43.54 (d, J_{CP} = 142.7 Hz), 63.95 (d, $^2J_{CP}$ = 7.2 Hz), 64.66 (d, $^2J_{CP}$ = 7.0 Hz), 111.04, 123.75, 131.14, 134.36, 135.32. ^{31}P NMR (162 MHz, $CDCl_3$): δ 17.98. Anal. Calcd. for $C_{14}H_{15}Br_2N_2O_3P$: C, 37.36; H, 3.36; N, 6.22. Found: C, 37.29; H, 3.31; N, 6.21.

[1-(Naphthalen-1-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4r)[11(j)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 0.80 (3H, t, J = 6.8 Hz), 1.33 (3H, t, J = 6.8 Hz), 3.34-3.44 (1H, m), 3.76-3.85 (1H, m), 4.08-4.26 (2H, m), 4.70 (1H, dd, J_1 = 9.2 Hz, J_2 = 21.6 Hz), 4.91 (1H, t, J = 8.8 Hz), 7.50-7.60 (3H, m), 7.88 (3H, d, J = 8.0 Hz), 8.04 (1H, d, J = 8.4 Hz).

[1-(Thiophen-2-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (4s)[11(e)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.23 (3H, t, J = 7.2 Hz), 1.34 (3H, t, J = 7.2 Hz), 3.95-4.01 (2H, m), 4.04-4.20 (3H, m), 4.68 (1H, d, J_1 = 4.8 Hz), 7.34-7.39 (2H, m).

[1-Cyclohexyl-2,2-dicyanoethyl] phosphonic acid diethyl ester (4t)[11(e)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.35 (6H, t, J = 7.2 Hz), 1.47 (4H, s), 1.73-1.81 (4H, m), 2.00-2.10 (2H, m), 4.09-4.29 (5H, m). ^{13}C NMR (100MHz, $CDCl_3$): δ = 16.29 (d, $^3J_{CP}$ = 5.5 Hz), 16.15 (d, $^3J_{CP}$ = 6.5 Hz), 24.47, 28.48, 28.77, 41.05 (d, J_{CP} = 145.3 Hz), 61.78 (d, $^2J_{CP}$ = 5.5 Hz), 63.33 (d, $^2J_{CP}$ = 7.3 Hz), 111.20.

[1-(4-Chlorophenyl)-2-cyano-2-ethylcarboxylic acid ethyl ester] phosphonic acid diethyl ester (4u)[11(h)]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.15-1.29 (6H, m), 1.30-1.38 (3H, m), 3.95-4.24 (7H, m), 4.37 (1H, dd, J_1 = 5.6 Hz, J_2 = 8.8 Hz), 7.74 (2H, d, J = 7.2 Hz), 8.25 (2H, d, J = 8.4 Hz).

[1-(3-Chlorophenyl)-2-cyano-2-ethylcarboxylic acid ethyl ester] phosphonic acid diethyl ester (4v)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.09-1.15 (3H, m), 1.18-1.36 (6H, m), 3.78-3.87 (1H, m), 4.00-4.22 (6H, m), 4.33 (1H, dd, J_1 = 1.5 Hz, J_2 = 2.1 Hz), 7.29-7.33 (2H, m), 7.42-7.48 (2H, m). ^{13}C NMR (100MHz, $CDCl_3$): δ = 13.69, 16.08 (d, $^3J_{CP}$ = 4.7 Hz), 16.13 (d, $^3J_{CP}$ = 4.4 Hz), 39.08, 43.01 (d, J_{CP} = 143.0 Hz), 63.31, 63.69 (d, $^2J_{CP}$ = 6.8 Hz), 63.73, 64.01 (d, $^2J_{CP}$ = 7.0 Hz), 114.52, 127.96, 128.77, 130.04, 133.58, 134.35, 163.97. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.18. Anal. Calcd. for $C_{16}H_{21}ClNO_5P$: C, 51.41; H, 5.66; N, 3.75. Found: C, 51.49; H, 5.73; N, 3.71.

[1-(4-Nitrophenyl)-2-cyano-2-ethylcarboxylic acid ethyl ester] phosphonic acid diethyl ester (4w)

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.07-1.56 (3H, m), 1.19-1.37 (6H, m), 3.77-3.87 (1H, m), 4.05-4.21 (6H, m), 4.31 (1H, dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz), 7.35 (2H, d, J = 8.0 Hz), 7.47 (2H, d, J = 6.8 Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ = 13.76, 16.06 (d, $^3J_{CP}$ = 5.9 Hz), 16.18 (d, $^3J_{CP}$ = 5.6 Hz), 39.16, 42.79 (d, J_{CP} = 143.5 Hz), 63.15 (d, $^2J_{CP}$ = 5.6 Hz), 63.37, 63.74 (d, $^2J_{CP}$ = 6.9 Hz), 114.52, 114.60, 128.99, 130.70, 131.17, 134.72, 164.19. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.47. Anal. Calcd. for $C_{16}H_{21}N_2O_7P$: C, 50.00; H, 5.51; N, 7.29. Found: C, 50.10; H, 5.58; N, 7.23.

[1-(2-Chlorophenyl)-2,2-dicyanobuthyl] phosphonic acid diethyl ester (6)[21]

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (3H, t, J = 7.2 Hz), 1.21-1.28 (6H, m), 1.91-2.00 (1H, m), 2.16-2.25 (1H, m), 3.82-3.92 (1H, m), 3.95-4.05 (1H, m), 4.08-4.17 (2H, m), 4.30 (1H, d, J = 23.2 Hz), 4.86 (1H, t, J = 8.8 Hz), 7.26-7.33 (2H, m), 7.41-7.43 (1H, m), 7.95 (1H, dt, J_1 = 2.4 Hz, J_2 = 7.2 Hz).

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