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Nanosized zinc oxide as a catalyst for the rapid and green synthesis of β-phosphono malonates

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ABSTRACT

The design and development of a nano heterogeneous catalyst for the direct addition of P(O)–H bonds across various alkylidenes under solvent-free conditions is described. This is a mild, rapid, and efficient protocol to generate P–C bonds.

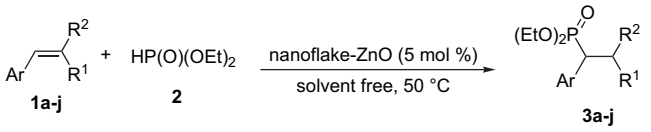
1. Introduction

Pioneering work on P–C bond formation was carried out by Arbusov in the early 20th century, culminating in the well-known Michaelis–Arbusov reaction.[1] In the following decades the chemistry of phosphonates developed relatively slowly because of the difficulty in formation of the C–P bond. Its renaissance came after 1959 with the discovery of naturally occurring aminophosphonic acids[2] and new biologically active phosphonates.[3]

Phosphonoacetic acid,[4] for example, has been shown to inhibit the replication of cytomegalovirus and herpes virus by interacting directly with the virus-induced DNA polymerase. Phosphonoformate[5] has shown activity in cell cultures against HTLV-III (the virus implicated in AIDS), and a derivative of β-phosphonomalonic acid[6] was used as an inhibitor of ras farnesyl protein transferase in studies directed toward the development of new antitumor agents. Amongst various methods to generate P–C bonds, the addition of P(O)–H bonds across alkenes[12] is one of the most utilized. There are three general approaches: (a) the phospha-Michael reaction of activated alkenes, most commonly promoted by alkaline metal alkoxides,[7,8] or the use of tetramethylguanidine (TMG),[9] Lewis acids,[10] microwaves,[11] or the use of bases;[12] (b) addition to unactivated olefins promoted by radical initiators such as AIBN;[13] (c) hydrophosphorylation of unactivated alkenes catalyzed by transition metals.[14]

The possibility of performing the addition of a phosphorus compound, containing a labile P–H bond, to double and triple bonds using a solid base was first shown by Koenig and coworkers,[15] who used an Al_2O_3/KOH system in the Pudovik reaction of various secondary phosphines and phosphites. In recent years, Enders and Tedeschi[12a] were also involved in the study of C–P bond formation using various metal oxides system as solid support catalysts. They showed that metal oxides can activate P(O)H groups so that deprotonation of the P–H bond occurs in the presence of a weaker base such as KOH.

Bearing this in mind, and during the course of our previous studies on ZnO as catalyst in many organic reactions,[16] herein, we decided to develop a new catalyst for conjugate addition of phosphorus nucleophile to α,β-unsaturated malonates (Scheme 1).



Scheme 1.

We first examined the effect of different metal oxides on the addition of diethyl phosphite (**2**) to malonate **1a**. The results are summarized in Table 1.

According to Table 1, the best results were obtained with ZnO. In all cases where the desired phosphonate **3a** was formed in poor yield, the unreacted starting materials remained unchanged (TLC). The presence of a catalyst appeared to be essential for the activation of the P–H bond toward deprotonation. No reaction could be observed when no catalyst was used (entry 7).

Recently, nanocrystalline inorganic oxides gained interest because of their different topical characteristics.[17–22] Nanocrystalline semiconducting II–IV metal oxides have been efficiently used as gas sensors and photocatalysts, whereas the catalytic properties of these materials are poorly explored.[23–25] Undoubtedly, one of the most important semiconductor materials is zinc oxide (ZnO). When used as catalyst, the activity of the nano ZnO material is expected to be enhanced with reference to the commercial compound, not only because of their increased surface area, but also because of the changes of surface properties such as surface defects.[26]

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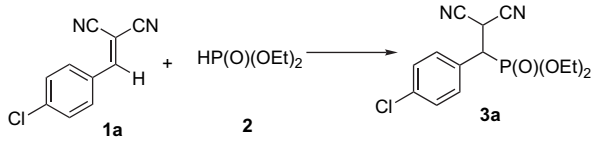
Table 1
Screening of different metal oxides for the Michael addition of diethyl phosphite (**2**) to 2-[(4-chlorophenyl) methylene]malononitrile (**1a**) to form the adduct **3a**[a]



Entry	Catalyst	Time (h)	Yield[b] (%)
1	ZnO	2	80
2	Fe_2O_3	18	20
3	Basic-Al_2O_3	18	30
4	CuO	18	67
5	MgO	18	Trace
6	TiO_2	18	Trace
7	No catalyst	24	0

[a] Conditions: all reactions were carried out at 50 °C under solvent-free conditions with 5 mol % of the catalyst.
[b] Isolated yields.

We have recently reported that nanosized ZnO was an effective catalyst for Knoevenagel and reduction reaction of double bond.[27] Therefore in continuation of our interest to develop environmentally benign protocols we report herein our results with nanosized ZnO that efficiently catalyzed the phospha-Michael addition.

In this study, we prepared nanosized ZnO catalyst and used it successfully in the synthesis of β-phopsphono malonates. The XRD pattern of the synthesized ZnO particles is shown in Figure 1. The nanoscopic nature of the crystalline ZnO particles is responsible for the broadness of XRD peaks. The peak broadening is used to estimate the average ZnO crystal grain size in terms of the Debey–Scherrer equation.[28] The average particle size of the ZnO sample thus estimated is in the range of 20–30 nm. The scanning electron micrograph (SEM) of the synthesized ZnO particles is shown in Figure 2. It can be seen that well defined and discrete ZnO nanoflake was formed. Similar particle sizes and shapes have been reported earlier for ZnO particles prepared by hydrolysis of $Zn(OAc)_2$ using urea under hydrothermal conditions.[29] However, unlike in the earlier case, individual small nanoparticles were not observed for the particles synthesized by this method. This is probably due to the difference in the procedure used for the preparation of these materials. Wu and co-workers have used 40 ml of the solution of $Zn(OAc)_2$ and urea using a Teflon-lines autoclave and heated in an electronic

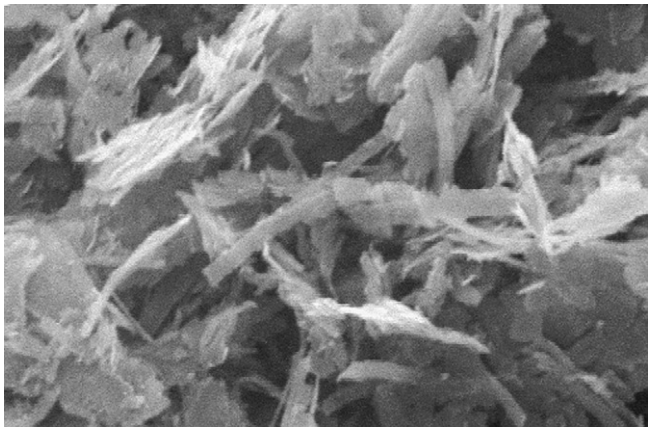


Figure 2. SEM of the synthesized nano-flake ZnO.

furnace at temperature 100 °C.[29] In the present study, the procedure is very simple and a large amount of $Zn(OAc)_2$ and urea was refluxed in a shorter time. Under the prevailing condition, it is likely that nanoflake ZnO was prepared in large scale.

Two kinds of ZnO crystals [commercial ZnO, CM-ZnO, and nanoflake prepared ZnO, NF-ZnO (20–30 nm)[29]] were screened in the reaction between diethyphosphite (**2**) and 2-[(4-chlorophenyl) methylene] malononitrile (**1a**) (Table 2). As shown in Table 2, NF-ZnO was found to be more effective than CM-ZnO in mediating the phospha-Michael addition under solvent-free conditions. In order to examine the solvent effect and in our quest for the deployment of

Table 2
Reaction between 2-[(4-chlorophenyl) methylene]malononitrile (**1a**) with diethyl phosphite (**2**) catalyzed by different crystallite of ZnO at 50 °C[a]

Entry	Catalyst	Solvent	Time (min)	Yield[b] (%)
1	CM-ZnO[d]	None	120	80
2	NF-ZnO[e]	None	30	98
3	NF-ZnO	CH_2Cl_2	180	43[c]
4	NF-ZnO	CH_3CN	180	40[c]
5	NF-ZnO	THF	180	40[c]
6	NF-ZnO	H_2O	180	0

[a] Conditions: (**1a**) (1.0 mmol), (**2**) (1.0 mmol), catalyst (5.0 mol %) were mixed at 50 °C.
[b] Isolated yields.
[c] The unreacted starting materials remained unchanged (TLC).
[d] 'CM-ZnO' means commercial ZnO.
[e] 'NF-ZnO' means nanoflake ZnO.

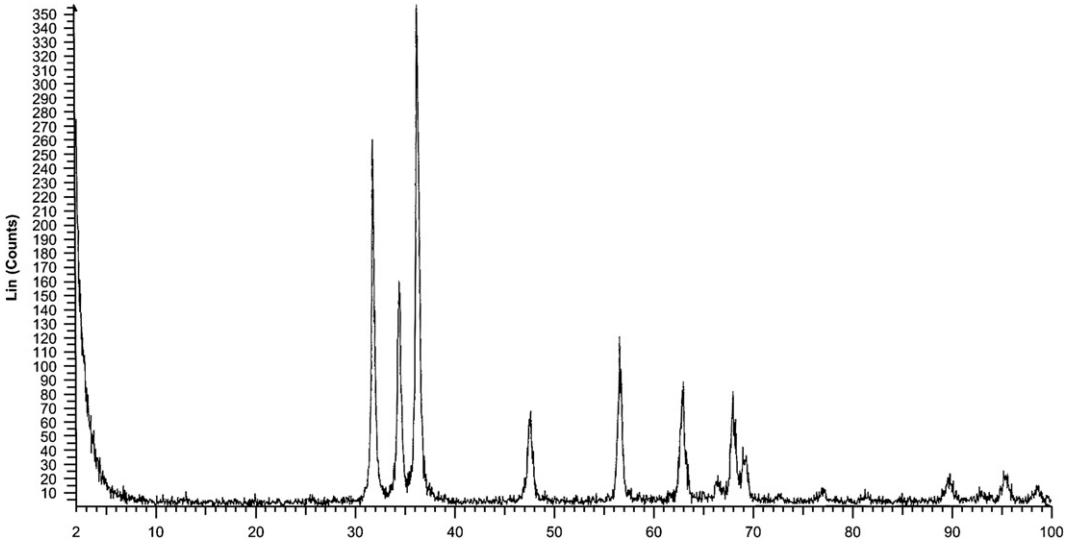
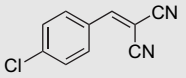
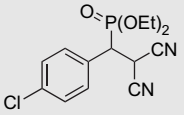
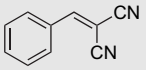
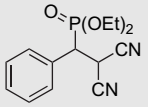
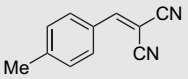
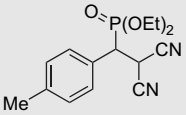
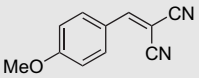
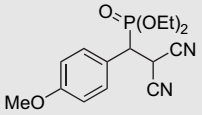
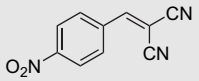
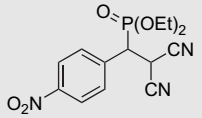
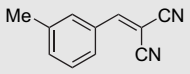
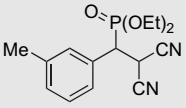
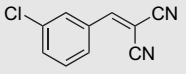
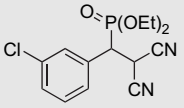
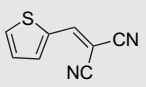
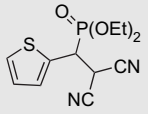
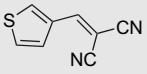
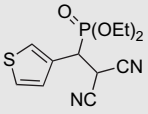
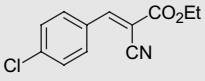
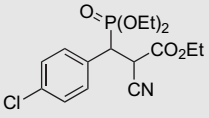


Figure 1. X-ray diffraction pattern of the synthesized nano-flake ZnO sample.

Table 3
Synthesis of β-phosphono malonates catalyzed by NF-ZnO at 50 °C in solvent-free condition

Entry	Substrate	Product		Type of catalyst	Time (h)	Yield[a] (%)
1			**3a**	CM-ZnO[b] NF-ZnO[c]	2 0.5	80 98
2			**3b**	CM-ZnO NF-ZnO	10 2.5	83 98
3			**3c**	CM-ZnO NF-ZnO	20 5	87 98
4			**3d**	CM-ZnO NF-ZnO	40 5	30 90
5			**3e**	CM-ZnO NF-ZnO	30 10	50 98
6			**3f**	CM-ZnO NF-ZnO	8 1	74 98
7			**3g**	CM-ZnO NF-ZnO	8.5 0.5	76 98
8			**3h**	CM-ZnO NF-ZnO	28 5	75 98
9			**3i**	CM-ZnO NF-ZnO	28 3.5	83 98
10			**3j**[d]	CM-ZnO NF-ZnO	28 7.5	50 98

[a] Isolated yields.
[b] 'CM-ZnO' means commercial ZnO.
[c] 'NF-ZnO' means nanoflake ZnO.
[d] Mixture of diastereoisomers, ratio is 50:50, and determined by ^{1}H NMR.

a benign reaction medium, the reaction was explored in CH_2Cl_2, CH_3CN, THF, and water. The reaction in solvents required relatively longer reaction times and afforded moderate yields of the product.

Subsequently, NF-ZnO with average diameters of 20–30 nm and CM-ZnO were employed in the synthesis of various β-phosphono malonates. As summarized in Table 3, NF-ZnO catalyzed this reaction to generate the corresponding β-phosphono malonates in high yields (mostly higher than 90%). The catalytic activity of the synthesized nanosized ZnO particles was compared with the commercially available ZnO catalyst. The reactions were carried out in solvent-free conditions for both catalysts at 50 °C.

In this study, the activity clearly indicates that the particle size in the nanoregime helps to expedite the reaction. This is in agreement with our recent report where an increase in the activity was observed in the case of nanoparticles as compared to the bulk ZnO catalyst.[27]

In the synthesis of β-phosphono malonates NF-ZnO can activate P(O)H groups so that deprotonation of the P–H bond occurs in the presence of Lewis basic sites (O^{2-}). Subsequently, a Lewis acid base interaction between the hard Zn^{2+} cation and one of the nitrile nitrogen atom of malonates was formed. Thus, the Lewis base (O^{2-}) of the catalyst activates P–H bond, and the Lewis acid moiety (Zn^{2+}) activates malonates.

To conclude, we have shown that nanoflake ZnO is a highly active catalyst for the synthesis of β-phosphono malonates in good yields. The title compounds are of chemical and medicinal interest. The advantages of this environmentally benign and safe protocol include a simple reaction set-up, does not require specialized equipment, mild reaction conditions, high product yields, short reaction times, and the limitation of solvents.

2. Experimental

2.1. Preparation of NF-ZnO

In a typical experiment for the synthesis of NF-ZnO, zinc acetate dehydrate (10 mmol) and $CO(NH_2)_2$ (0.2 mol) were dissolved in 200 mL deionized water at room temperature to form a transparent solution. Then the mixture was refluxed for 12 h. It was cooled by cold water to stop the reaction. The product was centrifuged and washed with deionized water and absolute ethanol, and dried at 80 °C for 8 h. The NF-ZnO was obtained by calcining the precursor in a furnace in air at 400 °C for 2 h.[29]

2.2. General procedure for synthesis of β-phosphono-malonates

Malonates (1 mmol) and diethylphosphonate (1 mmol) were added to NF-ZnO (5 mol %, 0.004 g) in a test tube. The mixture was stirred in an oil bath at 50 °C, and the progress of the reaction was monitored by TLC. After the reaction was complete, EtOAc was added to the reaction mixture and centrifuged to separate the catalyst. The organic solvent was removed under reduced pressure. After purification by chromatography on silica gel (solvent: *n*-hexane/ethyl acetate, 60:40) the product was obtained. The structure of the products was confirmed by ^{1}H NMR, IR and comparison with authentic samples obtained commercially or prepared by reported methods. Products, **3b**, **3h**, and **3j** are known and were characterized by ^{1}H NMR, IR, and mass spectral data, which were found to be identical with those described in Refs. 12b, 30, and 31, respectively.

*2.2.1. [1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**3a**)*

IR (neat) 2260, 2221 (CN), 1249 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.32–7.44 (s, 4H, Ar–*H*), 4.47 (dd, 1H, $^1J_{HH}$=7.5 Hz, $^2J_{HP}$=9.0 Hz, –C*H*(CN)$_2$), 4.05–4.14 (m, 4H, –OC*H*$_2$CH$_3$), 3.54 (dd, 1H, $^1J_{HH}$=7.5 Hz, $^2J_{HP}$=20.2 Hz, –C*H*P), 1.29 (t, 3H, J_{HH}=7.2 Hz, –OCH$_2$C*H*$_3$), 1.11 (t, 3H, J_{HH}=7.0 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.1 (d, $^3J_{CP}$=5.0 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=5.3 Hz, OCH$_2$*C*H$_3$), 25.4, 44.0 (d, J_{CP}=144.6 Hz, –*C*HP), 64.5 (d, $^2J_{CP}$=7.0 Hz, O*C*H$_2$CH$_3$), 63.6 (d, $^2J_{CP}$=7.1 Hz, O*C*H$_2$CH$_3$), 111.0, 111.2, 128.7, 129.6, 130.6, 138.2. Anal. Calcd for $C_{14}H_{16}ClN_2O_3P$: C, 51.47; H, 4.94. Found: C, 51.65; H, 4.99%.

*2.2.2. [1-(4-Methylphenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (**3c**)*

IR (neat) 2252, 2229 (CN), 1257 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.28 (d, 2H, *J*=7.1 Hz, Ar–*H*), 7.12 (d, 2H, *J*=7.1 Hz, Ar–*H*), 4.43 (dd, 1H, $^1J_{HH}$=7.8 Hz, $^2J_{HP}$=8.6 Hz, –C*H*(CN)$_2$), 3.68–4.13 (m, 4H, –OC*H*$_2$CH$_3$), 3.51 (dd, 1H, $^1J_{HH}$=7.8 Hz, $^2J_{HP}$=21.2 Hz, –C*H*P), 2.29 (s, 3H, –C*H*$_3$), 1.27 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$), 1.06 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.1 (d, $^3J_{CP}$=6.1 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=6.6 Hz, OCH$_2$*C*H$_3$), 21.1, 25.6, 44.37 (d, J_{CP}=144.8 Hz, *C*HP), 63.3 (d, $^2J_{CP}$=7.2 Hz, O*C*H$_2$CH$_3$), 64.2 (d, $^2J_{CP}$=7.0 Hz, O*C*H$_2$CH$_3$), 111.2, 111.4, 126.5, 129.0, 130.1, 140.0. Anal. Calcd for $C_{15}H_{19}N_2O_3P$: C, 58.82; H, 6.25. Found: C, 58.80; H, 6.20%.

*2.2.3. [1-(4-Methoxyphenyl)2,2-dicyanoethyl] phosphonic acid diethyl ester (**3d**)*

IR (neat) 2275, 2221 (CN), 1257 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.28 (d, 2H, *J*=7.1 Hz, Ar–*H*), 7.12 (d, 2H, *J*=7.1 Hz, Ar–*H*), 4.75 (m, 5H, C*H*(CN)$_2$ and –OC*H*$_2$CH$_3$), 3.79 (dd, 1H, $^1J_{HH}$=7.0 Hz, $^2J_{HP}$=22.1 Hz, –C*H*P), 3.71 (s, 3H, –OC*H*$_3$), 1.20 (t, 3H, *J*=7.0 Hz, –OCH$_2$C*H*$_3$), 0.96 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.2 (d, $^3J_{CP}$=6.6 Hz, OCH$_2$*C*H$_3$), 16.3 (d, $^3J_{CP}$=6.5 Hz, OCH$_2$*C*H$_3$), 35.8, 38.3, 54.8 (d, J_{CP}=144.2 Hz, *C*HP), 57.5 (d, $^2J_{CP}$=7.0 Hz, O*C*H$_2$CH$_3$), 58.8 (d, $^2J_{CP}$=7.3 Hz, O*C*H$_2$CH$_3$), 113.0, 113.2, 115.9, 122.6, 129.9, 172.5. Anal. Calcd for $C_{15}H_{19}N_2O_4P$: C, 55.90; H, 5.94. Found: C, 55.82; H, 5.91%.

*2.2.4. [1-(4-Nitrophenyl)2,2-dicyanoethyl] phosphonic acid diethyl ester (**3e**)*

IR (neat) 2255, 2204 (CN), 1255 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.68 (d, 2H, *J*=7.1 Hz, Ar–*H*), 7.22 (d, 2H, *J*=7.1 Hz, Ar–H), 4.62 (dd, 1H, $^1J_{HH}$=7.8 Hz, $^2J_{HP}$=9.2 Hz, –C*H*(CN)$_2$), 4.02–4.16 (m, 4H, –OC*H*$_2$CH$_3$), 3.77 (dd, 1H, $^1J_{HH}$=7.9 Hz, $^2J_{HP}$=21.6 Hz, –C*H*P), 1.32 (t, 3H, *J*=7.2 Hz, –OCH$_2$C*H*$_3$), 1.12 (t, 3H, *J*=7.0 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.1 (d, $^3J_{CP}$=6.6 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=6.6 Hz, OCH$_2$*C*H$_3$), 25.1, 44.0 (d, J_{CP}=144.2 Hz, *C*HP), 64.0 (d, $^2J_{CP}$=7.0 Hz, O*C*H$_2$CH$_3$), 64.6 (d, $^2J_{CP}$=7.1 Hz, O*C*H$_2$CH$_3$), 110.7, 111.1 123.8, 124.4, 130.5, 137.0. Anal. Calcd for $C_{14}H_{16}N_3O_5P$: C, 49.86; H, 4.78. Found: C, 49.81; H, 4.70%.

*2.2.5. [1-(3-Methylphenyl)2,2-dicyanoethyl] phosphonic acid diethyl ester (**3f**)*

IR (neat) 2298, 2254 (CN), 1257 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.12–7.31 (m, 4H, Ar–*H*), 4.51 (dd, 1H, $^1J_{HH}$=6.0 Hz, $^2J_{HP}$=9.0 Hz, –C*H*(CN)$_2$), 3.65–4.19 (m, 4H, –OC*H*$_2$CH$_3$), 3.53 (dd, 1H, $^1J_{HH}$=8.2 Hz, $^2J_{HP}$=22.4 Hz, –C*H*P), 2.29 (s, 3H, –C*H*$_3$), 1.24 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$), 1.03 (t, 3H, *J*=7.0 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.0 (d, $^3J_{CP}$=5.8 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=5.9 Hz, OCH$_2$*C*H$_3$), 21.3, 25.0, 44.5 (d, J_{CP}=143.9 Hz, *C*HP), 63.3 (d, $^2J_{CP}$=7.3 Hz, O*C*H$_2$CH$_3$), 64.2 (d, $^2J_{CP}$=7.1 Hz, O*C*H$_2$CH$_3$), 111.2, 111.5, 126.2, 129.2, 129.9, 130.1, 130.2, 139.2. Anal. Calcd for $C_{15}H_{19}N_2O_3P$: C, 58.82; H, 6.25. Found: C, 58.81; H, 6.22%.

*2.2.6. [1-(3-Chlorophenyl)2,2-dicyanoethyl] phosphonic acid diethyl ester (**3g**)*

IR (neat) 2260, 2227 (CN), 1259 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.24–7.44 (m, 4H, Ar–*H*), 4.62 (dd, 1H, $^1J_{HH}$=6.7 Hz, $^2J_{HP}$=8.4 Hz, –C*H*(CN)$_2$), 3.65–4.16 (m, 4H, –OC*H*$_2$CH$_3$), 3.58 (dd, 1H, $^1J_{HH}$=7.7 Hz, $^2J_{HP}$=22.0 Hz, –C*H*P), 1.29 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$), 1.1 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.0 (d, $^3J_{CP}$=6.1 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=5.5 Hz, OCH$_2$*C*H$_3$), 25.2, 43.9 (d, J_{CP}=143.9 Hz, *C*HP), 63.5 (d, $^2J_{CP}$=7.2 Hz, O*C*H$_2$CH$_3$), 64.3 (d, $^2J_{CP}$=7.0 Hz, O*C*H$_2$CH$_3$), 111.0, 111.3, 127.4, 129.6, 129.7, 130.6, 132.5, 135.0. Anal. Calcd for $C_{14}H_{16}ClN_2O_3P$: C, 51.47; H, 4.94. Found: C, 51.45; H, 4.90%.

*2.2.7. (2,2′-Dicyano-1-thiophene-3-ylethyl) phosphonic acid diethyl ester (**3i**)*

IR (neat) 2202 (CN), 1238 (P═O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.42 (s, 1H, Ar–*H*), 7.16 (d, 1H, *J*=2.7 Hz, Ar–*H*), 7.00 (d, 1H, *J*=2.7 Hz, Ar–*H*), 4.34 (dd, 1H, $^1J_{HH}$=7.4 Hz, $^2J_{HP}$=9.0 Hz, –C*H*(CN)$_2$), 3.76–3.94 (m, 4H, –OC*H*$_2$CH$_3$), 3.65 (dd, 1H, $^1J_{HH}$=6.4 Hz, $^2J_{HP}$=22.1 Hz, –C*H*P), 1.12 (t, 3H, *J*=7.0 Hz, –OCH$_2$C*H*$_3$), 0.91 (t, 3H, *J*=7.1 Hz, –OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.0 (d, $^3J_{CP}$=5.09 Hz, OCH$_2$*C*H$_3$), 16.2 (d, $^3J_{CP}$=5.1 Hz, OCH$_2$*C*H$_3$), 25.6, 39.8 (d, J_{CP}=146.3 Hz, *C*HP), 63.4 (d, $^2J_{CP}$=7.2 Hz, O*C*H$_2$CH$_3$), 64.2 (d, $^2J_{CP}$=6.9 Hz, O*C*H$_2$CH$_3$), 111.2, 111.6, 124.3, 126.1, 127.7, 128.4. Anal. Calcd for $C_{12}H_{15}N_2O_3PS$: C, 48.32; H, 5.07. Found: C, 48.40; H, 5.82%.

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