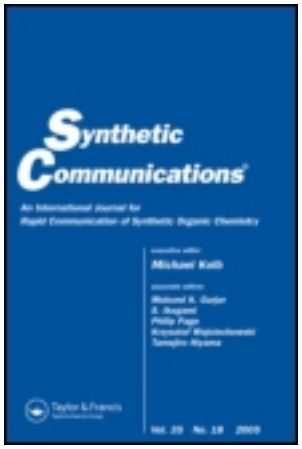

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One-Pot Synthesis of β-Phosphonomalonates Catalyzed by Molecular Iodine

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ONE-POT SYNTHESIS OF β-PHOSPHONOMALONATES CATALYZED BY MOLECULAR IODINE

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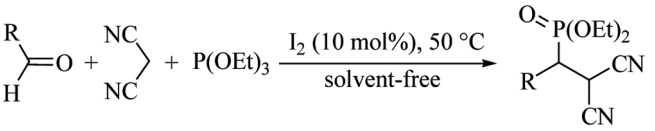
GRAPHICAL ABSTRACT



R = aryl, heteroaryl, alkyl **1-12**

Abstract *A one-pot procedure has been developed for the synthesis of* β*-phosphonomalonates via P-C bond formation through tandem Knoevenagel–phospha–Michael reaction catalyzed by iodine as a new, inexpensive, nonmetallic, and commercially available catalyst.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Iodine; malononitrile; phosphites; β-phosphonomalonates; tandem reaction

INTRODUCTION

Within organophosphorous compounds, the synthesis of phosphonates has evoked remarkable attention from organic chemists because of the biological activities and applications of phosphonates as enzyme inhibitors, metabolic probes,[1] peptide mimetics,[2] antibiotics, and pharmacologic agents.[3] The most versatile and powerful synthetic approach for the synthesis of phosphonates is direct phosphorus–carbon bond formation. Among the tools for P-C bond formation, phospha-Michael addition is known as the most important routes.[4] Synthesis of β-phosphonomalonates by this method is commonly promoted by Brønsted/Lewis acids,[4g,4h] transition metals,[4i,4j] bases,[4a–f] microwave radiation,[4m] and radical initiators.[4k,4l] Even though synthesis of β-phosphonomalonates could be proceeded by these methods, they suffer from one or more of the following drawbacks, such as long reaction time, drastic reaction conditions, and use of expensive catalyst. Sometimes, according to the nature of the catalyst, tedious workup is needed. Moreover,

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these methods proceed through a two-pot reaction in which P-C and C-C bond formations occurred in separate steps. On the other hand, a literature survey revealed that only a few papers have been published toward the one-pot synthesis of β-phosphonomalonates.[5,6] Therefore, a new, simple, and efficient protocol for the one-pot synthesis of such significant scaffolds is required.

Over the past few years, molecular iodine has emerged as a powerful catalyst for various organic transformations.[7] Utilizing iodine is interesting for organic chemists, because iodine is a mild Lewis acid, cheap, readily available, less toxic than alternatives, and moisture stable. Most of the reactions that are catalyzed by iodine are associated with mild conditions, greater stereo- and regioselectivities, short reaction times, and simplicity in their operation.

As part of our ongoing program on the development of new methods for the phosphonates synthesis via P-C bond formation,[8] recently we have reported iodine as an efficient nonmetallic catalyst for the synthesis of primary α-aminophosphonates.[9] Herein, we report iodine as a new catalyst for the synthesis of β-phosphonomalonates by one-pot reaction of aldehydes, trialkyl phosphites, and malononitrile.

RESULTS AND DISCUSSION

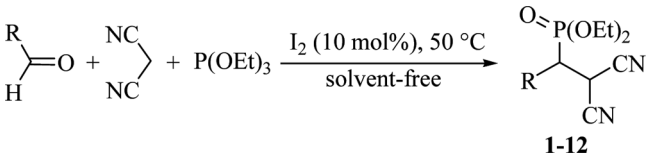
At first, the reactions of benzaldehyde, malononitrile, and triethyl phosphite in the presence of different amounts of iodine and at different temperatures were studied. The results of these studies are summarized in Table 1.

As depicted in Table 1, investigation of separate reactions in the presence of 5, 10, and 15 mol% of iodine under solvent-free conditions indicated that 10 mol% of this catalyst was the best amount for this transformation at room temperature (entry 2). The reason for the lower product yield in the presence of the greater amount of iodine might be ascribed to the production of a sticky mixture, which in turn led to decreased catalytic activity of iodine. Increase in reaction temperature (50 °C) using 10 mol% of iodine provided excellent product yield (entry 4). A similar reaction in the absence of any amount of catalyst produced the desired product in poor yield after a long reaction time at 50 °C (entry 5). Solvent screening (entries 6–9) showed that the reaction afforded maximum yield of the product under solvent-free conditions.

Table 1. Tandem Knoevenagel–phospha–Michael reaction of benzaldehyde, malononitrile, and triethyl posphite under different conditions

Entry	I_2 (mol%)	T (°C)	Solvent	Time (h)	Yield[a] (%)
1	5	rt	—	24	42
2	10	rt	—	24	65
3	15	rt	—	24	35
4	10	50	—	2	90
5	0	50	—	24	48
6	10	50	*n*-Hexane	6	71
7	10	50	CH_3CN	3	72
8	10	50	Toluene	4	63
9	10	50	CH_2Cl_2	4	71

[a]Isolated yield. Conditions: aldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol).



1-12

Scheme 1. One-pot synthesis of β-phosphonates catalyzed by iodine.

With these optimistic results in hand, the generality of the presented method was evaluated for the one-pot synthesis of β-phosphonomalonates. For this reason a range of various aldehydes were subjected to react with malononitrile and triethyl phosphite in the presence of 10 mol% of iodine at 50 °C under solvent-free conditions (Scheme 1, Table 2).

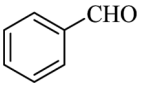
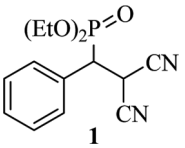
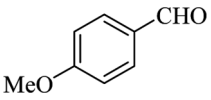
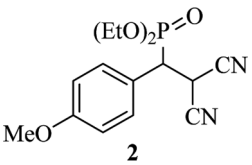
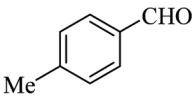
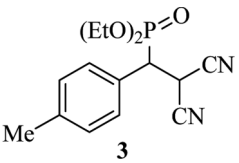
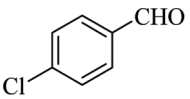
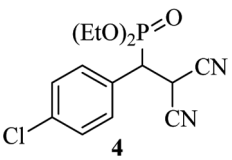
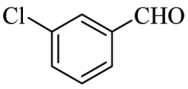
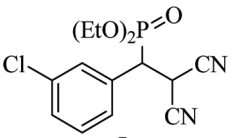
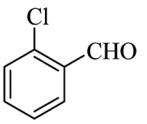
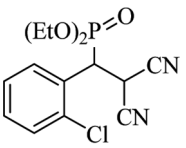
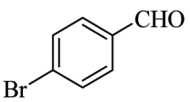
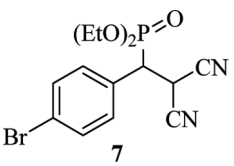
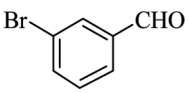
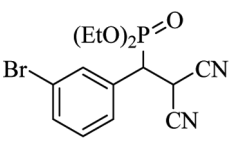
As shown in Table 2, different substituted benzaldehydes with electron-donating and electron-withdrawing groups underwent successful Knoevenagel–phospha–Michael reaction with malononitrile and triethyl phosphite to produce the desired products in good to excellent yields (entries 1–8). Furan-2-carbaldehyde and pyridin-3-carbaldehyde as acid-sensitive aldehydes underwent smooth reactions without any decomposition or polymerization under the present reaction conditions (entries 9 and 10). Aliphatic aldehydes such as butyraldehyde and heptanal reacted with malononitrile and triethyl phosphite to afford the corresponding products in good yields (entries 11 and 12). Synthesis of β-phosphonomalonates from the reactions of cinnamaldehyde and crotonaldehyde as unsaturated aldehydes with malononitrile and triethyl phosphite was also examined and no yields of the desired products were obtained even after 48 h. The reactions of some ketones including cyclohexanone, ethylmethyl ketone, and isatine were conducted under the present reaction conditions. These reactions resulted in the recovery of the starting materials with a trace amount of the corresponding products. It is worth noting that the phospha-Michael addition of triethyl phosphite to α,β-unsaturated malonates of cyclohexanone, ethylmethyl ketone, and isatine proceeded well in 1–3 h to afford the corresponding products (**13, 14, 15**) in 65, 76, and 83% yields, respectively.

Noticeably, possible side reactions leading to α-hydroxyphosphonates were not observed in all of these transformations. These observations encouraged us to examine the possibility of the formation of α-hydroxyphosphonate as an intermediate in these reactions. For this purpose, the reaction of 4-chlorobenzaldehyde and triethyl phosphite catalyzed by iodine at 50 °C was studied and we found that no amount of α-hydroxyphosphonate was not produced, even after 24 h.

Synthesis of β-phosphonomalonates through a one-pot reaction of aldehydes, malononitrile, and triethyl phosphite was proposed to involve in a tandem process. Aldehydes are activated by molecular iodine as a Lewis acid and undergo Knoevenagel condensation with malononitrile to produce α,β-unsaturated malonates. The resulting adducts are further activated by iodine to react with triethyl phosphite via a phospha-Michael addition reaction (Scheme 2).

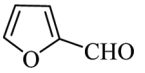
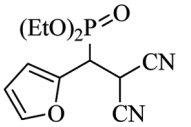
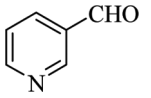
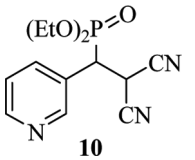
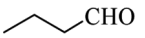
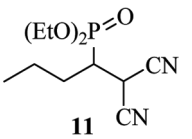
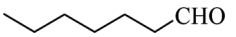
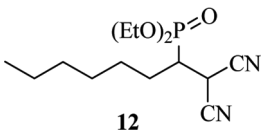
Occurrence of the initial Knoevenagel condensation reaction was confirmed by the isolation of α,β-unsaturated malonate in 89% yield from the reaction of 4-chlorobenzaldehyde and malononitrile as a model reaction catalyzed by iodine at 50 °C after 15 min.

Table 2. One-pot synthesis of different β-phosphonomalonates via tandem Knoevenagel–phospha–Michael reaction catalyzed by iodine

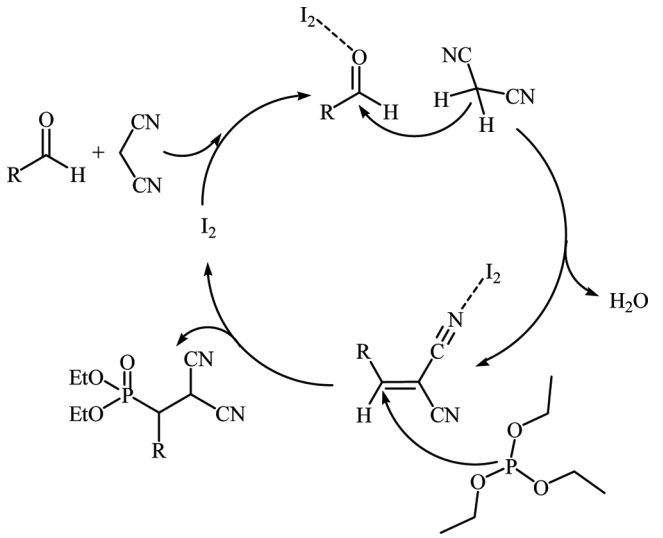
Entry[ref]	Aldehyde	Product	Time (h)	Yield[a] (%)
1[6]		 **1**	2	85
2[4f,6]		 **2**	3	91
3[4f,6]		 **3**	2	85
4[4f,6]		 **4**	2	90
5[4f]		 **5**	2.5	81
6[10]		 **6**	1	82
7		 **7**	2	95
8		 **8**	2	82

(*Continued*)

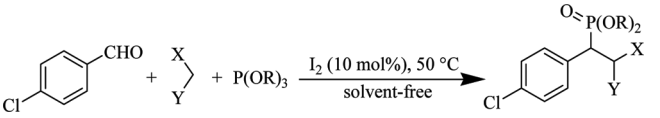
Table 2. Continued

Entry[ref]	Aldehyde	Product	Time (h)	Yield[a] (%)
9[11]		 **9**	1	81
10		 **10**	0.5	85
11		 **11**	1	82
12		 **12**	3	83

[a]Isolated yield. Conditions: aldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol), iodine (10 mol%), 50 °C, solent-free conditions. All the products were characterized by spectroscopic methods and compared with the authentic spectra.



Scheme 2. Suggested mechanism for one-pot reaction of aldehydes, malononitrile, and triethyl phosphite.



Scheme 3. Synthesis of *β*-phosphonates from in situ–generated Michael acceptors and trialkyl phosphites.

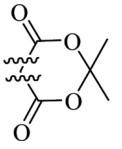
Further investigations were carried out to explore the applicability of iodine as a catalyst for the synthesis of β-phosphonomalonates from in situ–generated Michael acceptors and trialkyl phosphites (Scheme 3, Table 3).

As indicated in Table 3, the catalytic one-pot reaction of 4-chlorobenzaldehyde with malononitrile and trialkyl phosphites such as triethyl, trimethyl, and tri-*iso*-propyl phosphite worked well and the desired products were isolated in 95, 80, and 85% yields, respectively (entries 1–3). However, no products were not obtained when ethylcyanoacetate, diethyl malonate, nitromethane, ethylacetoacetate and Meldrum's acid were employed as Knoevenagel donors instead of malononitrile under the same reaction conditions (entries 4–8).

To show the unique catalytic behavior of iodine in the one-pot synthesis of β-phosphonomalonates, the reaction of benzaldehyde, malononitrile, and triethyl phosphite catalyzed by metal oxides such as CuO, Sb_2O_3, SnO_2, HgO, MgO, and CaO; Brønsted acids such as $HClO_4$–SiO_2 and $H_3PMo_{12}O_{40}$; and also sodium stearate was performed (Table 4). The summarized results in Table 4 illustrate that iodine is the most effective catalyst for this transformation (entry 1).

Successful application of iodine as a catalyst for the one-pot synthesis of β-phosphonomalonates via P-C bond formation encouraged us to study the applicability of this method for the synthesis of 4-substituted 2-amino-4H-chromenes with phosphonic acid diethyl ester by coupling reaction of salicylaldehyde, malononitrile/ethylcyanoacetate, and triethyl phosphite (Scheme 4, Table 5).

Table 3. One-pot synthesis of β-phosphonomalonates from the reaction of different in situ–generated Michael acceptors and trialkyl phosphites

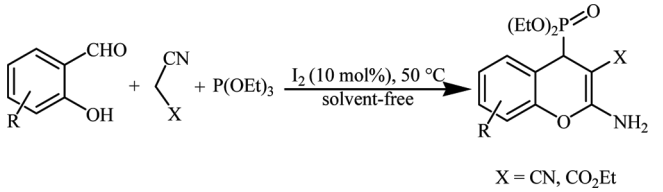
Entry[ref]	R	X	Y	Product	Time (h)	Yield[a] (%)
1	Et	CN	CN	**4**	2	90
2[12]	Me	CN	CN	**16**	24	81
3[13]	*iso*-Pr	CN	CN	**17**	2	85
4	Et	CN	CO_2Et	—	24	0
5	Et	CO_2Et	CO_2Et	—	24	0
6	Et	H	NO_2	—	24	0
7	Et	COMe	CO_2Et	—	24	0
8	Et			—	24	0

[a]Isolated yield. 4-Chlorobenzaldehyde (1 mmol), active methylene group (1 mmol), trialkyl phosphite (1 mmol), catalyst (10 mol %), 50 °C, solvent-free conditions. All the products were characterized by spectroscopic methods and compared with the authentic spectra.

Table 4. Comparison of the catalytic efficiency of iodine with various catalysts

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Iodine	2	85
2	CuO	24	37
3	Sb_2O_3	24	46
4	SnO_2	24	45
5	HgO	24	54
6	MgO	24	41
7	CaO	24	46
8	$HClO_4$–SiO_2	24	47
9	$H_3PMo_{12}O_{40}$	24	48
10	Sodium stearate	24	45

[a]Isolated yield. Conditions: catalyst (10 mol%), benzaldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite, 50 °C, solvent free.



Scheme 4. Synthesis of 4-substituted 2-amino-4H-chromenes with phosphonic acid diethyl esters catalyzed by iodine.

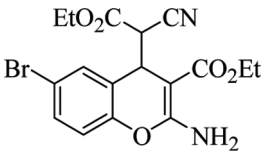
As shown in Table 5, coupling reaction of substituted salicylaldehydes bearing electron-withdrawing and electron-releasing groups with malononitrile and triethyl phosphite proceeded well to give the corresponding products in good to excellent yields (entries 1–4). The reaction of 3-methoxysalicylaldehyde and 3-ethoxysalicylaldehyde with ethylcyanoacetate and triethyl phosphite produced the desired products in 94 and 80% yields, respectively (entries 5 and 6).

It is worth mentioning that 4-substituted 2-amino-4H-chromenes were introduced as analogs of tumor antagonist HA 14-1 (Scheme 5).[16] HA 14-1 is a new class of small molecules that exhibits binding activity for the surface pocket of the

Table 5. Synthesis of 4-substituted 2-amino-4H-chromene with phosphonic acid diethyl ester in the presence of iodine

Entry[ref]	Aldehyde	Product	X	Time (h)	Yield[a] (%)
1[14]	5-Bromosalicylaldehyde	**18**	CN	4	79
2[15]	5-Chlorosalicylaldehyde	**19**	CN	3.5	81
3[14b]	3-Methoxysalicylaldehyde	**20**	CN	1	93
4	3-Ethoxysalicylaldehyde	**21**	CN	1	82
5[14b]	3-Methoxysalicylaldehyde	**22**	CO_2Et	2	94
6	3-Ethoxysalicylaldehyde	**23**	CO_2Et	2	80

[a]Isolated yield. Conditions: catalyst (10 mol%), salicylaldehyde (1 mmol), active methylene group (1 mmol), triethyl phosphite, 50 °C, solvent free.



Scheme 5. Tumor agonist HA 14-1.

cancer-implicated Bcl-2 protein and induces apoptosis or programmed cell death in follicular lymphoma B cells and leukemia HL-60 cells.[16]

EXPRIMENTAL

Typical Procedure for the Synthesis of [1-(4-Chlorophenyl)-2,2-dicyanoethyl]phosphonic Acid Diethyl Ester (4)

Iodine (0.005 g, 10 mol%) was added to a mixture of 4-chlorobenzaldehyde (0.141 g, 1 mmol), malononitrile (0.066 g, 1 mmol), and triethyl phosphite (0.166 g, 1 mmol). The reaction mixture was stirred at 50 °C for 2 h under solvent-free conditions. EtOH (10 mL) and $Na_2S_2O_3$ (≈0.3 g, in portion) were added to the cooled reaction mixture. The resulting mixture was stirred for an additional 10 min and filtered. The filtrated cake was washed with EtOH (10 mL), and the solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by chromatography eluted with *n*-hexane/EtOAc (1/1) and gave product **4** (0.294 g, 90%) as a yellow solid.

Data

Mp 98 °C; $R_f = 0.53$; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.16 (t, 3 H, $^3J_{HH} = 7.0$ Hz), 1.33 (t, 3 H, $^3J_{HH} = 7.0$ Hz), 3.62 (dd, 1 H, $^3J_{HH} = 7.5$ Hz, $^2J_{HP} = 21.5$ Hz), 3.82–4.19 (m, 4 H), 4.55 (t, 1 H, $^3J_{HH} = 7.7$ Hz), 7.42 (s, 4 H) ppm.

CONCLUSION

In conclusion, we have introduced a one-pot method for the successful synthesis of β-phosphonomalonates via P-C bond formation through tandem Knoevenagel–phospha–Michael reaction catalyzed by iodine as a new, inexpensive, nonmetallic, and commercially available catalyst. A variety of β-phosphonomalonates were synthesized by this simple method in good to excellent yields from the reaction of aldehydes (aromatic, heteroaromatic, and aliphatic), malononitrile, and trialkyl phosphites. Using this method, several 4-substituted 2-amino-4H-chromenes with phosphonic acid diethyl ester were also synthesized by coupling reaction of salicylaldehyde, malononitrile/ethylcyanoacetate, and triethyl phosphite in good to excellent yields.

SUPPORTING INFORMATION

Full experimental details, spectral data of the products, and ^{1}H NMR and ^{13}C NMR spectra of new compounds can be found via the Supplementary Content section of this article's Web page.

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