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Electrochemically induced efficient, simple, non-catalytic synthesis of β-phosphonomalonates *via* multicomponent reaction

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Electrochemically induced efficient and economical method has been developed for synthesis of β-phosphono malononitriles *via* condensation of various aldehyde, malononitrile and phosphite esters at room temperature. The present protocol highlights cost efficient, one pot, easy work-up and environmentally benign process.

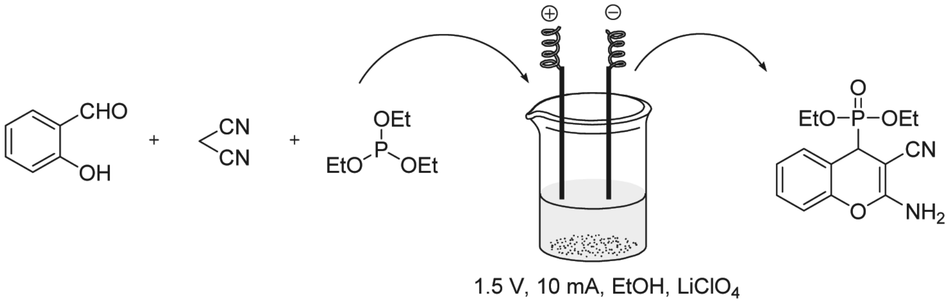
Keywords: Three component reaction, β-Phosphonomalonate, Malononitrile, Nucleophilic addition reaction, Electrochemically induced

Over the last decades, multicomponent reactions[1] become the most promising alternative approach for the synthesis of phosphorous-carbon bond. The strategy has significant advantages over classical stepwise approaches, as it proceeds with the formation of several bonds and the construction of molecule from simple precursors in a single synthetic step without isolation of intermediates, results in eco-friendly reaction with excellent yield. Electro-organic synthesis[2] is another powerful, versatile, and environmentally friendly protocol for synthesis of biologically and medicinally active compound. In recent years, electro synthetic, multicomponent reactions (EMCRs) have been used extensively to prepare biologically active compounds. As the particular method eliminates the hazardous chemicals, adverse reaction condition, minimise expensive catalyst and follow the green chemistry principle[3]. In an electrochemical reaction, electric current acts as an inexpensive and potentially renewable reagent to proceed the reaction. Extensive research on electro-organic synthesis, become revolutionized alternative technique for organic synthesis.

Phosphonate ester and their derivatives plays an important role in metabolic process, these molecules are easily derived by organophosphorus compounds (Scheme 1). In recent years, the phosphonates and their derivatives moiety has attracted chemist, to develop new reliable method due to their wide range of applications in medicinal chemistry, such as enzyme inhibitors[4], antibiotics[5], catalysis[6], pharmacological agents[7] and material chemistry[8].

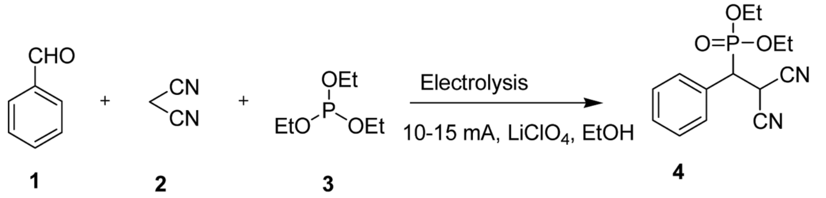
P-C bond formation is versatile and powerful way for the synthesis of phosphonates. Lithium hydroxide[9], triethylamine[10], Diethylamine[11], dibutylamine[12], imidazole[13], dimethyl-aminopyridine[14], ethylenediamine diacetate[15], potassium phosphate[16], magnesium oxide[17], indium chloride[18], iodine[19], PEG[20], β-cyclodextrin[21], iron oxide[22], ionic liquids[23,24], urea and choline chloride mixture[25], solvent-free reactions[26–29] are various catalyst and solvents used to synthesize β-phosphonomalonate derivative. These methods are valuable for the synthesis of β-phosphonomalonate, though most of the earlier methods take longer time, use hazardous reaction conditions, costly catalyst, generate toxic waste and involve tedious work-up. Hence, the development of new reliable and efficient method for formation of these compounds are still in demand.

During our research on the development of efficient methods for the synthesis of bioactive heterocycles[30], herein we have introduced electricity catalysed, green reagent for synthesis of β phosphonomalonates and 2-amino-3-cyno-4*H*-chromen-4-yl-phosphonate. We initiated our studies with three component reaction using benzaldehyde, malononitrile, and triethyl phosphite as



Scheme 1 — Synthesis of β-phosphonomalonate

Table 1 — Optimization of reaction conditions[a]



Entry	Solvent	Electrode	Potential(V)	Current (mA)	Time (h)	Electrolyte	Yield(%)[b]
1	MeOH	C ‖ Fe	1.5	10	8	$LiClO_4$	30
2	MeOH	C ‖ Fe	1.5	10	12	$LiClO_4$	45
3	CH_3CN	C ‖ Fe	1.5	10	12	$LiClO_4$	10
4	*n*-PrOH	C ‖ Fe	1.5	10	12	$LiClO_4$	40
5	EtOH	C ‖ Fe	1.5	10	12	$LiClO_4$	90
6	EtOH	C ‖ Fe	1.0	10	12	$LiClO_4$	68
7	EtOH	C ‖ Fe	1.7	10	12	$LiClO_4$	70
8	EtOH	C ‖ Fe	1.5	5	12	$LiClO_4$	80
9	EtOH	C ‖ Fe	1.5	20	12	$LiClO_4$	79
10	EtOH	C ‖ Fe	1.5	10	12	KBr	65
11	EtOH	C ‖ Fe	1.5	10	12	NaBr	66
12	EtOH	C ‖ Fe	1.5	10	12	Bu_4NClO_4	65
13	EtOH	C ‖ Fe	1.5	10	18	$LiClO_4$	90
14	EtOH	Pt ‖ Pt	1.5	10	12	$LiClO_4$	75
15	EtOH	C ‖ C	1.5	10	12	$LiClO_4$	70
16	EtOH	Pt ‖ C	1.5	10	12	$LiClO_4$	65

[a] Reaction condition: benzaldehyde **1a** (2.0 mmol), malononitrile **2** (2.2 mmol), and tri ethyl phosphite **3** (2.4 mmol), electrolyte (0.5 M), electrode cathode (5 cm^2), electrode anode (5 cm^2), solvents (30 mL) in a beaker, for 8-18 h, reaction was carried out at 35°C, progress of reaction mixture was monitored by TLC.

[b] Isolated yield of the product **4**.

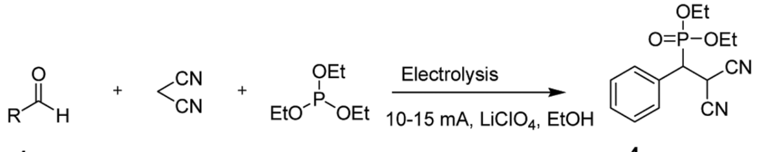
model substrate, using lithium perchlorate as electrolyte and ethanol as solvent.

The electrochemical synthesis was equipped in an undivided cell using graphite rod (5 cm^2) and iron rod (5 cm^2). Graphite rod acts as anode and iron rod acts as cathode at room temperature under constant current potential. The progress of the reaction was monitored by TLC using hexane/ethyl acetate mixture.

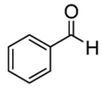
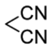
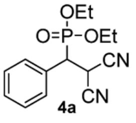
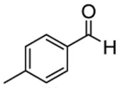
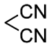
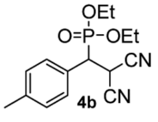
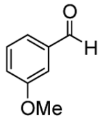
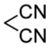
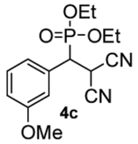
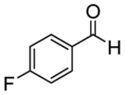
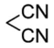
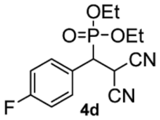
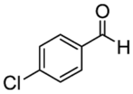
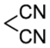
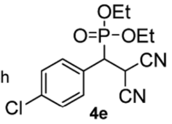
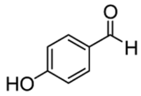
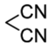
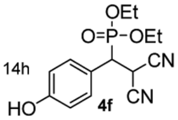
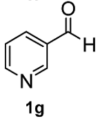
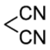
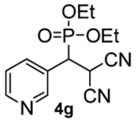
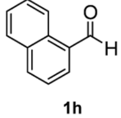
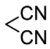
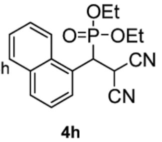
Our investigation commenced with the reaction of benzaldehyde (**1a**) and malononitrile (**2**) and triethyl phosphite (**3**) as the model starting materials to optimize the reaction. Reaction mixture was carried out with MeOH at potential 1.5V (Table 1 entry 1), small amount of product was formed with 30% yield, by increasing the reaction time yield of reaction increases 45% (Table 1 entry 2). Further reaction was tested with various other solvents such as CH_3CN, *i*PrOH, EtOH (Table 1 entries 1-5), the reaction was more facile and proceeded to give the highest yield 90% (Table 1 entry 5) when ethanol (20 mL) solvent was used. The solvent ethanol was adopted for further optimization. Change in potential decreases the yield (Table 1 entries 6-7). When the supplied current density was increased or reduced, the yield was slightly lowered (Table 1, entries 8-9). When the additive ($LiClO_4$, KBr, NaBr, Bu_4NClO_4) was changed, the yield was lowered (Table 1, entries 10, 11 and 12). We observed no change in the reaction yield when the reaction time was increased from 12 h to 18 h (Table 1 entry 13). Reaction was examined under different electrode combinations such as Pt II Pt, C II C, and Pt II C (Table 1, entries 14−16). We found that C II Fe electrode combination is best for this transformation.

Using these optimized conditions, we applied the present protocol to variety of substrates to elucidate the scope of the reaction (Table 2). We were pleased to find that reaction works with wide range of aromatic substituted aldehydes (Table 2, entries **1a-n**). The results are summarized in the Table 2 aromatic aldehydes having electron withdrawing substituents (Table 2, entries **1d-e**, **1i**, **1k-l**) gives β

Table 2 — Substrate scope for the preparation of β-phosphonomalonate

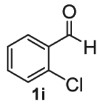
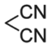
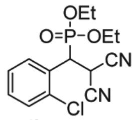
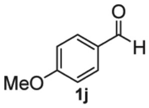
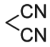
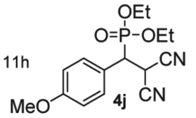
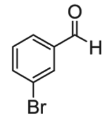
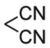
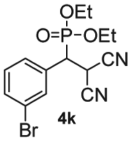
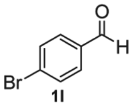
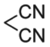
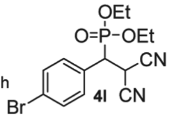
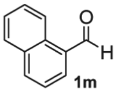
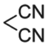
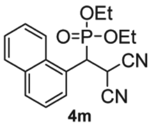
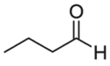
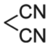
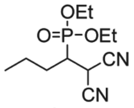


1a-n **2** **3** **4**

aldehyde	malononitrile	triethyl phosphite	time	product	yield(%)b
 **1a**		P(OEt)$_3$	12h	 **4a**	90%
 **1b**		P(OEt)$_3$	11h	 **4b**	89%
 **1c**		P(OEt)$_3$	14h	 **4c**	88%
 **1d**		P(OEt)$_3$	16h	 **4d**	85%
 **1e**		P(OEt)$_3$	15h	 **4e**	88%
 **1f**		P(OEt)$_3$	14h	 **4f**	90%
 **1g**		P(OEt)$_3$	16h	 **4g**	89%
 **1h**		P(OEt)$_3$	14h	 **4h**	88%

(*Contd.*)

Table 2 — Substrate scope for the preparation of β-phosphonomalonate

 1i		$P(OEt)_3$	16h	 4i	88%
 1j		$P(OEt)_3$	11h	 4j	90%
 1k		$P(OEt)_3$	14h	 4k	89%
 1l		$P(OEt)_3$	16h	 4l	89%
 1m		$P(OEt)_3$	14h	 4m	90%
 1n		$P(OEt)_3$	36h	 4n	76%

[a] For experimental procedure, see supporting information.

[b] Reaction condition: **1a-n** (2.0 mmol), malononitrile **2** (2.2 mmol), and triethyl phosphite **3** (2.4 mmol), $LiClO_4$ (0.5 M), iron cathode (5 cm^2), carbon anode (5 cm^2), EtOH (30 mL) in a beaker, for 8-18 h, reaction was carried out at 35°C.

phosphonomalonate in good to excellent yield. Aryl aldehyde with electron donating group on benzene ring (Table 2, entries **1b-c**, **1j**) produces 80 to 90% yields. Steric hindrance seemed to have few effects on the results (Table 2, entries **4h-**i). The reaction works well with polyaromatic and heteroaromatic groups to produce the desired products (Table 2, entries **1g-h**). Reaction is compatible with aliphatic aldehyde with slightly low yield (Table 2, entry **1n**)

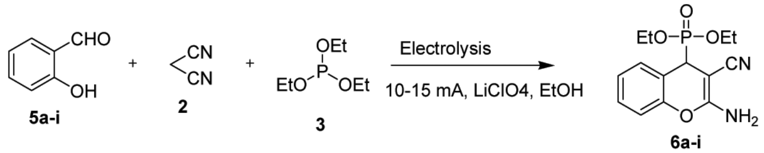
Aliphatic aldehyde takes longer time 36 h to complete the reaction, (Table 2, entry **1n**) with desired products in slightly less yield. This reaction provides reliable new synthetic route for synthesis of β phosphonomalonate.

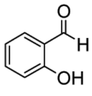
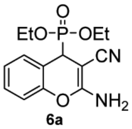
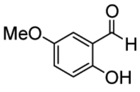
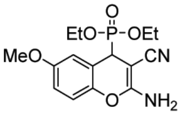
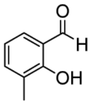
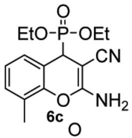
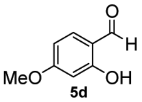
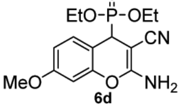
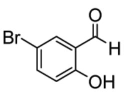
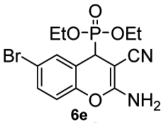
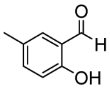
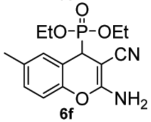
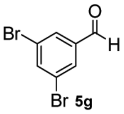
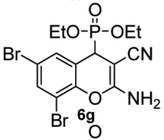
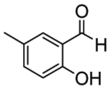
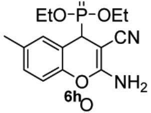
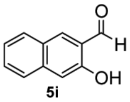
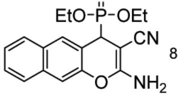
To expand and highlight the present methodology we replaced benzaldehyde by 2-hydroxy benzaldehyde, to proceed three component reaction of 2-hydroxy benzaldehyde, malononitrile (**2**) and triethyl phosphite (**3**) under electrolytic condition using lithium perchlorate as electrolyte in ethanol solvent at room temperature were carried out (Table 3) provides 2-amino-3-cyno-4*H*-chromen-4-yl-phosphonate. We found that reaction works with the substituted 2-hydroxybenzaldehyde to yield 2 amino-3-cyno-4*H*-chromen-4-yl-phosphonate. (Table 3, entries **1a-k**).

When aldehydes were replaced by ketones and reacted with malononitrile and triethyl phosphite under the same reaction conditions, the results were not as positive as those presented above and the corresponding products were obtained in traces under the above-mentioned conditions. It may be due to the low reactivity of ketones.

We propose that anion of malononitrile II act as intermediates, which are directly generated at the anode by reaction of malononitrile and *in situ* generation of ethoxide ion in ethanol solvent. Knoevenagel condensation of aldehyde with malononitrile anion takes place in the solution with the elimination of water and formation of the

Table 3 — Substrate scope for the preparation of 2-amino-3-cyno-4*H*-chromen-4-yl-phosphonate **6a-i**



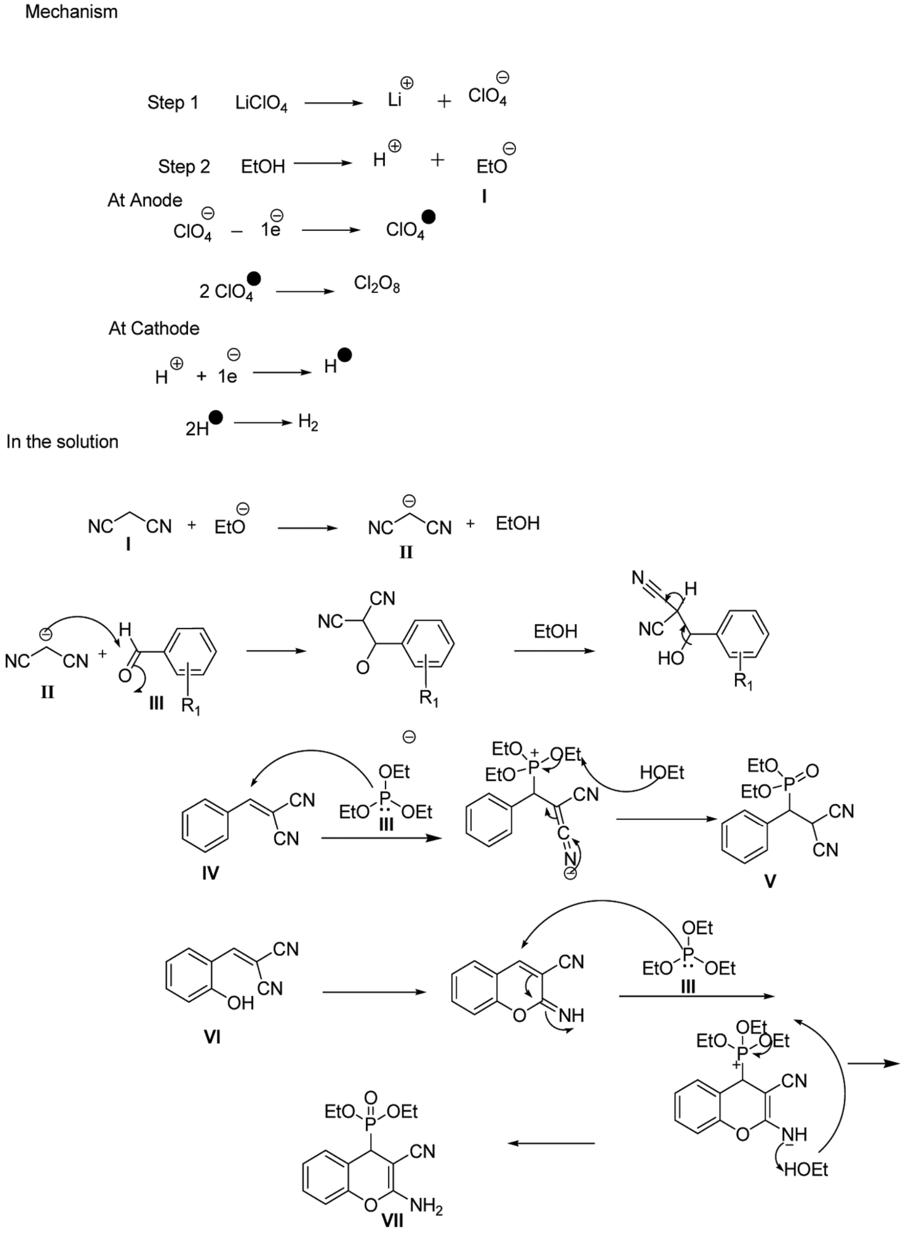
aldehyde	malononitrile	triethyl phosphite	time	product	yield(%)b
 **5a**		$P(OEt)_3$	16h	 **6a**	90%
 **5b**		$P(OEt)_3$	20h	 **6b**	89%
 **5c**		$P(OEt)_3$	24h	 **6c**	88%
 **5d**		$P(OEt)_3$	24h	 **6d**	85%
 **5e**		$P(OEt)_3$	24h	 **6e**	83%
 **5f**		$P(OEt)_3$	26h	 **6f**	86%
 **5g**		$P(OEt)_3$	25h	 **6g**	77%
 **5h**		$P(OEt)_3$	24h	 **6h**	88%
 **5i**		$P(OEt)_3$	28h	 **6i**	85%

[a] Reaction condition: **5a-i** (2.0 mmol), malononitrile **2** (2.2 mmol), and triethyl phosphite **3** (2.4 mmol), $LiClO_4$ (0.5 M), iron cathode (5 cm^2), carbon anode (5 cm^2), EtOH (30 mL) in a beaker, for 8-18 h, reaction was carried out at 35°C.

[b] Yields of isolated pure compounds **6a**

corresponding intermediate IV within 3 min with 95% yield, phospha-Michael addition of trialkyl phosphite to α,β-unsaturated malonates yield the desired product (Scheme 2).

In conclusion, we have demonstrated here simple, efficient, and environmentally friendly, electrochemical reaction protocol for the synthesis of β-phosphonomalonate and 2-amino-3-cyno-4*H*-chromen-4-yl-phosphonate. These reactions were conducted using inexpensive graphite and iron plate electrodes in a beaker open to air using $LiClO_4$ as the supporting electrolyte.



Scheme 2 — A plausible mechanism for the formation 3-indole

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgments

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