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Inorganic base catalyzed synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonate derivatives via multi-component reaction under mild and efficient conditions

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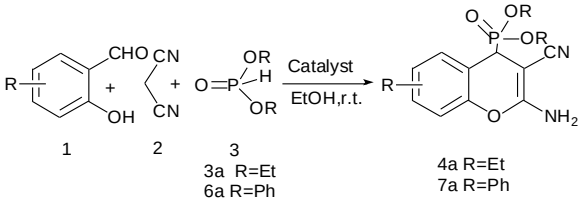
Various (2-amino-3-cyano-4H-chromen-4-yl) phosphonate derivatives were synthesized in good to excellent yields by condensation of diverse substituted salicylaldehyde, malononitrile and diethyl phosphite or diphenyl phosphite using anhydrous Lithium hydroxide as a catalyst under mild conditions.

Phosphorus-containing compounds have been the focus of research in organic chemistry. Many synthetic drugs and natural products extracted from the phosphorus atom-containing drugs and benzopyran phosphonate derivatives play important roles in the phosphorus-containing compounds[1]. Currently they have also been the focus of intensive studies due to their power use as enzyme inhibitors, metabolic probes, peptide mimetics, antibiotics, pharmacologic agents etc [2-6]. Owing to such a wide range of applications, development of efficient protocols for the synthesis of phosphonates, phosphonic acids and related compounds via C–P bond formation is enjoying growing interest[7-9]. It is worth mentioning that, apart from the Kabaschnik-Field[10], Michaelis-Beke[11] and Michaelis-Arbuzov[10] reaction, nucleophilic addition of phosphite across carbon-carbon double bond (phospha-Michael reaction[12]) is an ever green and widely used method in C–P bond formation.

Using relatively simple and readily available starting materials, MCR[13] (i.e., "one pot") means three or more substrates are added to a pot without isolation of intermediates and complex structure molecules can be directly obtained. MCR with simple operation, high resource utilization, high atom economy, high aggregation, high energy exploration and other features, can minimize chemical contamination, closer to the concept of ideal synthesis[14]. Since multi-component synthesis reaction can quickly form compounds[15] of structural diversity and complexity, easily establishing a large library of appropriate compounds, together with the characteristic that MCR in many research areas now have been widely used in organic chemistry, such as new drug development, total synthesis of high active natural products and so on, it has aroused widespread concern by chemist. Meanwhile it has become one of the frontiers in the field of organic chemistry today [16].

An extensive survey of the literature has revealed that a number of methods have been reported for the synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonates, some of which involve phospha-Michael addition catalyzed by diethylamine, ethylenediamine diacetate[17], K_3PO_4[18], PEG[19], β-cyclodextrin[4], $InCl_3$[20], silica-bonded 2-hydroxyethylammonium acetate (HEAA)[21] and tetramethyl guanidine (TMG)[22]. But there are rarely reports about phospha-Michael addition of lower active diphenyl phosphate to 2-imino-2H-chromene-3-carbonitrile. These methods show varying degrees of success as well as limitations, such as prolonged reaction time, low yields, requirement of excess reagent and catalyst, use of toxic solvent, and laborious work-up procedures. Hence, an economical protocol with an easy availability and low pollution basic catalyst operable at ambient temperature for synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonate derivatives are highly desired.

In the asymmetric reaction study, analytic conditions of raceme must be first set up. As a part of our research about asymmetric phospha-Michael addition, we would like to report a mild, cost-effective procedure for the one-pot multi-component synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonic acid diethyl ester and diphenyl ester (**4a, 7a**) by the condensation of salicyaldehyde (**1**), malononitrile (**2**) and triethyl phosphate (**3a**) or triphenyl phosphate (**6a**) adopting appropriate catalyst at ambient temperature in ethanol medium (Scheme 1).



Scheme 1 Multi-component synthesis of (2-amino-3- cyano-4H-chromen-4-yl) phosphonate derivatives

As phosphate ion has definite pollution on environment, we surmise if other inorganic base could be used as catalyst in this reaction. To verify this hypothesis, initally, a model reaction using **1a** (1mmol), **2** (1mmol) and **3a** (1mmol) was examined in the presence of inorganic bases catalysts in ethanol at ambient temperature (Table 1). With 20 mol % NaOH or KOH, the reaction did not proceed smoothly , only intermediate 2-imino-2H-chromene-3-carbonitrile was obtained (Table 1, entries 1, 2), but using of anhydrous Lithium hydroxide could catalyze the reaction and provide the target product in excellent yield (96%) (Table 1, entry 3).We examined several alternatives (Table 1, entries 4-7), Cs_2CO_3 and K_3PO_4 showed similar catalytic activity on reaction, the yield is respectively 87% and 85% under same conditions, while K_2CO_3 provided lower yield and no reaction occurred with CsF.

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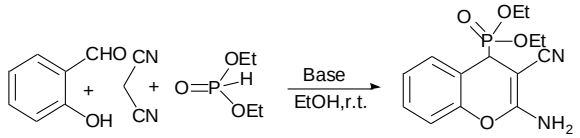
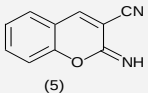
Table 1 . Effect of different catalysts on the yield of product **4a**[a]



1a 2 3a 4a

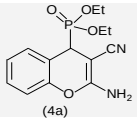
Entry	Inorganic bases	Catalyst（Mol%）	Yield (%)[b,c]
1	NaOH	20	76[c]
2	KOH	20	85[c]
3	LiOH	20	96[b]
4	K_2CO_3	20	63[b]
5	Cs_2CO_3	20	87[b]
6	C_SF	20	----
7	K_3PO_4	20	85[b]

[a]Reaction coditions: **1a**(1mmol), **2** (1mmol) with **3a** (1mmol) in ethanol using different catalysts (20%mol) at ambient temperature.
[b]intermediate 2-imino-2H-chromene-3-carbonitrile(**5**), Isolated yield.



(5)

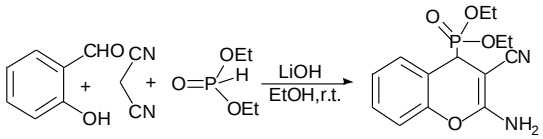
[c]diethyl 2-amino-3-cyano-4H-chromen-4-yl phosphonate(**4a**), Isolated yield.



(4a)

Effect of temperature on reaction was tested (Table 2). When temperature was below 30 ℃, reaction was slower, after 5h the reaction did not finish (Table 2, entries 1-3). When the temperature was above 30 ℃, inferior results were obtained (Table 2, entries 5-7). A survey of solvents resulted in conditions that provided excellent yield: the optimal result was obtained when the reaction was performed in ethanol at 30 ℃ for 20 minute (Table 2, entry4).

Table 2 . Effect of temperature on the yield of product 4a[a]



1a 2 3a 4a

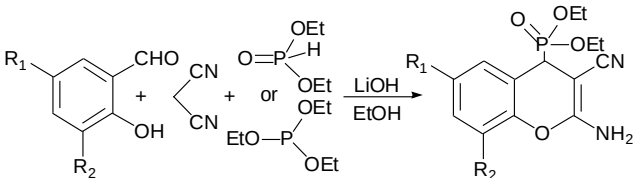
Entry	Temperature (℃)	Catalyst（Mol%）	Yield (%)[b]
1	0	20	12[b]
2	10	20	17[b]
3	20	20	38[b]
4	30	20	95[b]
5	35	20	88[b]
6	40	20	85[b]
7	50	20	73[b]

[a]Reaction coditions: **1a**(1mmol), **2** (1mmol) with **3a** (1mmol) in ethanol using LiOH (20%mol) at different temperature.
[b]diethyl 2-amino-3-cyano-4H-chromen-4-yl phosphonate(**4a**), Isolated yield.

With the optimal reaction condition in hand, we began to investigate the scope of this reaction with respect to various substituted salicylaldehydes **1**, **2** and **3a** or **6a** (Table 3, 4).

The results demonstrated that it's of good generality for salicylaldehydes with different substitutes. The reaction of malononitrile and triethyl phosphate or diethyl phosphite with salicylaldehydes substituted with electron-donating and electron-withdrawing groups proceeded well to give the desired products in 86-97% yields (Table 3, entries 2-8). The catalyst was compatible to functional groups such as -Cl, -Br, -OMe, -OEt and $-NO_2$. No competitive nucleophilic methyl/ethyl ether cleavage was observed for the substrates with possessed aryl-O-Me or aryl-O-Et groups (Table 3, entries 2, 3), despite of the strong nucleophilicity of phosphites.

Table 3 one-pot synthesis of the diethyl (2-amino-3-cyano-4H-chromen-4-yl) phosphonate compounds catalyzed by LiOH[a]

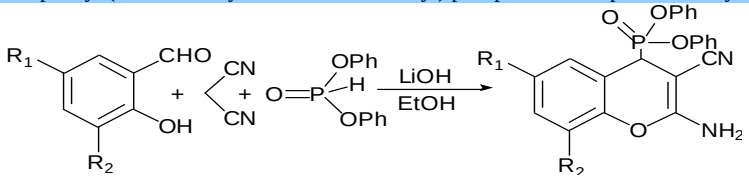


Entry	Salicylaldehyde	R_1	R_2	Malononitrile	Phosphate[c]	Time(min)	Product	Yield(%)[b]
1	**1a**	--	--	**2**	**3a** or **3b**	25	**4a**	94
2	**1b**	--	OEt			20	**4b**	96
3	**1c**	--	OMe			20	**4c**	96
4	**1d**	Me	--			20	**4d**	97
5	**1e**	Cl	--			30	**4e**	90
6	**1f**	Br	--			30	**4f**	91
7	**1g**	Br	Br			30	**4g**	89
8	**1h**	NO_2	--			40	**4h**	86

[a]Reaction coditions: **1**(**a-h**) (1mmol), **2** (1mmol) with **3a** or **3b** (1mmol) in ethanol using LiOH (20%mol) at ambient temperature.
[b]Isolated yield.
[c]**3a**----Triethylphosphite, **3b**----Diethylphosphite.

Despite nucleophilicity of triphenyl phosphate is weaker than that of triethyl phosphate, salicylaldehydes with different substituents reacted with malononitrile and triphenyl phosphate in the presence of anhydrous lithium hydroxide to produce the corresponding products in good to excellent yields for longer reaction time (Table 4, entries 1-7). It is noteworthy that no product was obtained when 5-nitro-salicylaldehyde was used as substrate (Table4,entry8).

Table 4 . one-pot synthesis of the diphenyl (2-amino-3-cyano-4H-chromen-4-yl) phosphonate compounds catalyzed by LiOH[a]



Entry	Salicylaldehyde	R_1	R_2	Malononitrile	Phosphate[c]	Time(min)	Product	Yield(%)[b]
1	**1a**	--	--	**2**	**6a**	25	**7a**	91
2	**1b**	--	OEt			20	**7b**	92
3	**1c**	--	OMe			20	**7c**	92
4	**1d**	Me	--			20	**7d**	93
5	**1e**	Cl	--			30	**7e**	90
6	**1f**	Br	--			30	**7f**	89
7	**1g**	Br	Br			30	**7g**	85
8	**1h**	NO_2	--			40	--	--[d]

[a]Reaction coditions: **1**(**a**-**h**) (1mmol), **2** (1mmol) with **6a** (1mmol) in ethanol using LiOH (20%mol) at ambient temperature.
[b]Isolated yield.
[c]**6a**----Diphenylphosphite
[d]The product is 2-imino-2H-chromene-3-carbonitrile(**5**).

In order to insight into the mechanism of this reaction, ^{1}HNMR spectra of different reaction time were recorded as follows. The ^{1}HNMR spectrum showed that characteristic hydrogen protons of three starting materials existed when they were mixed (Figure 1). After 5 minutes, peak of characteristic hydrogen protons of three starting materials became weak and peak of characteristic hydrogen proton of compound **5** at 4-position appeared at δ8.49 (Figure 2). After reaction completed, peak of characteristic hydrogen proton of compound **5** at 4-position completely disappeared and peak of characteristic hydrogen proton of compound at 4-position appeared at δ4.2-4.5(Figure 3).

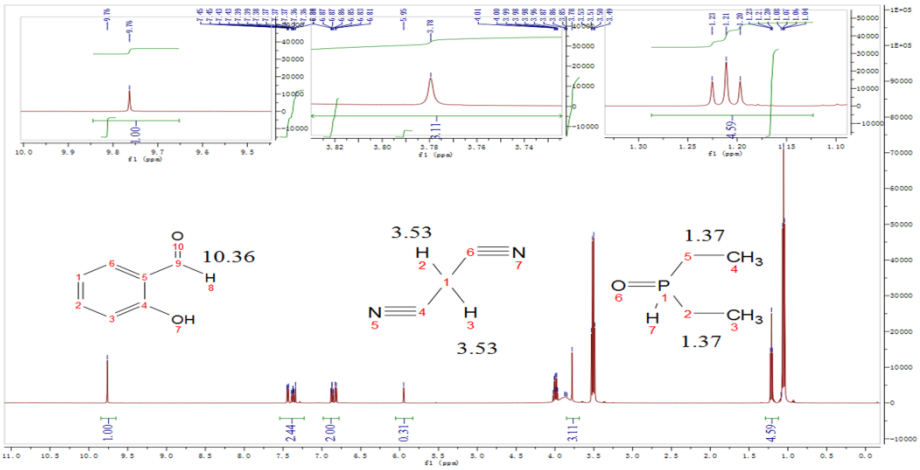


Figure 1. ^{1}H-NMR spectra of The reaction solution (sampled immediately after feeding)

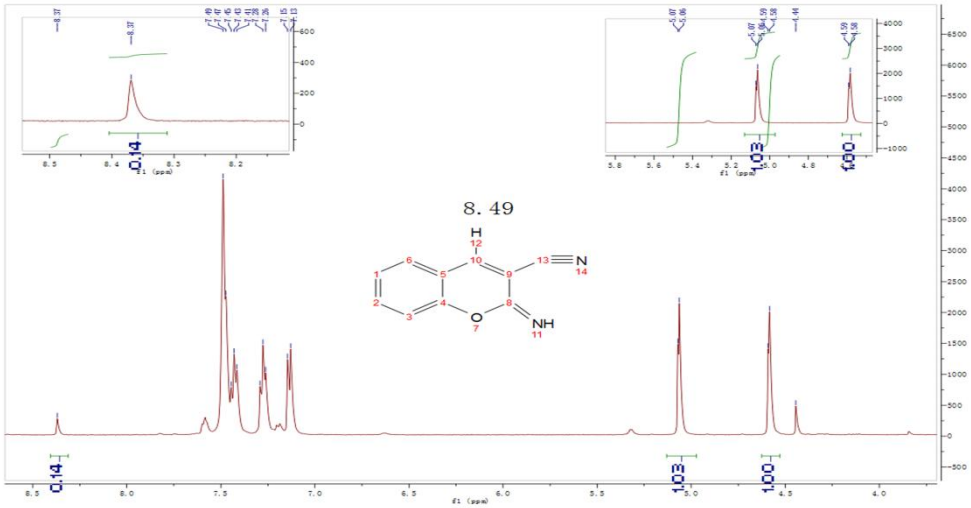


Figure 2. ^{1}H-NMR spectra of The reaction solution(5 minutes after feeding)

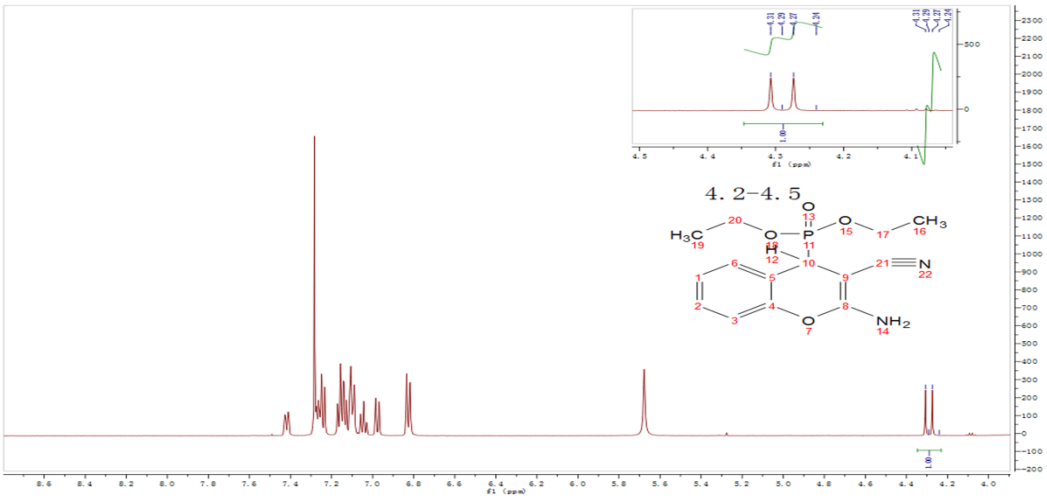


Figure 3. ^{1}H-NMR spectra of reaction solution (20 minutes after feeding)

The process represents a typical tandem reaction in which initial condensation of salicylaldehyde and malononitrile occurred to form the Knoevenagel product. The spontaneous cyclization as a result of nucleophilic attack of the hydroxyl group on the cyano group led to 2-imino-2H-chromene-3-carbonitrile which underwent nucleophilic attack by trialkyl phosphites or triaryl phosphites to produce the desired product **4a, 7a**. This mechanism is similar to that reported by Perumal[18].

In summary, we have developed a new, mild and highly efficient, one-pot reaction, which offers a simple method for the synthesis of new (2-amino-3-cyano-4H-Chromen-4-yl) phosphonic acid diethyl ester or diphenyl diester from salicylialdehyde, malononitrile and triethyl phosphite or triphenyl phosphite using lithium hydroxide as an inexpensive catalyst at ambient temperature. It compares favorably and represents a valid alternative to the existing methods. High yields along with simple reaction conditions, wide substrate scope as well as easy work-up procedure auger well for the application of the strategy for the synthesis of (2-amino-3-cyano-4H-Chromen-4-yl) phosphonic acid diethyl ester or diphenyl diester. Further effort will be directed at the study of asymmetric domino reaction of salicylaldehyde, malononitrile and triethyl phosphate or triphenyl phosphate and the results of these studies will be reported in due course.

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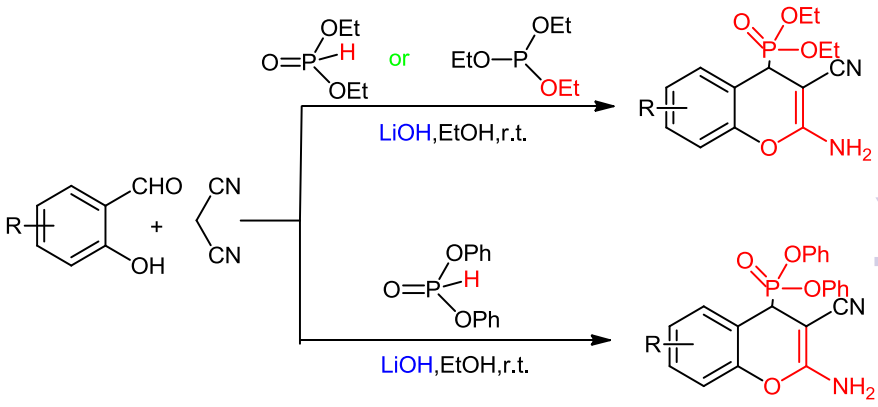
Graphical Abstracts

Inorganic base catalyzed synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonate derivatives via multi-component reaction under mild and efficient conditions	 Various (2-amino-3-cyano-4H-chromen-4-yl) phosphonate derivatives were synthesized in good to excellent yields by condensation of diverse substituted salicylaldehyde, malononitrile and diethyl phosphite or diphenyl phosphite using anhydrous Lithium hydroxide as a catalyst under mild conditions