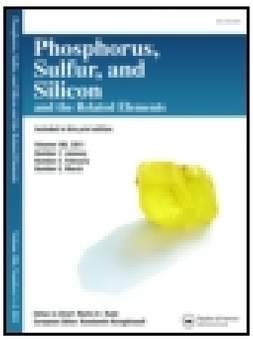

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Choline chloride based eutectic solvent for the efficient synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives via multicomponent reaction under mild conditions

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A shortened title of the article (running head): Chromenylphosphonates

Abstract

Synthesis of 2-amino-4*H*-chromen-4-ylphosphonate derivatives has been accomplished by the one-pot three-component reaction of salicylaldehyde, malononitrile / ethylcyanoacetate and dialkyl phosphites in the presence of reusable deep eutectic solvent (DES) under mild conditions. The advantages of this method are mild reaction conditions, simple work-up procedure, use of DES as a green solvent and an economical protocol for the preparation of important biologically active phosphorus-containing compounds.

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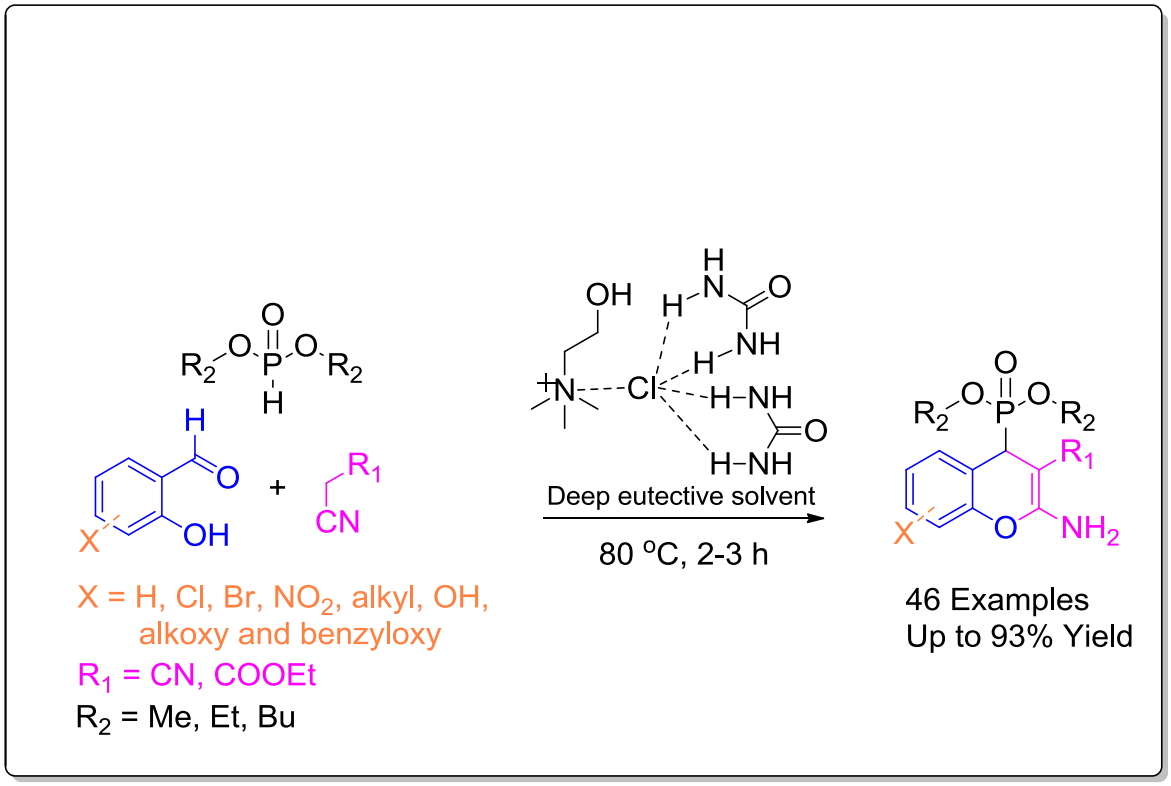
Graphical Abstract



Keywords: Multicomponent reaction; 2-amino-4*H*-chromen-4-ylphosphonate derivatives; deep eutectic solvent; one-pot synthesis; green chemistry

Introduction

Development of operationally simple and eco-friendly routes for the synthesis of organic and medicinal compounds having important biological properties are the most significant objectives in synthetic chemistry.[1] In this context, accomplishment of various transformations in a single operation is highly compatible with the goals of green chemistry. One-pot condensation reactions in which three or more component combine to form a new targeted product without isolation of any intermediate are known as multi-component reactions (MCRs).[2] They are highly attractive in terms of their ability to construct two or more C–C, C–heteroatom (C–P, C–O, C–N and C–S) bonds in a single step. MCRs with their inherent advantages such as short reaction times, high atom-economy and simple purification processes,[3] provide a unique way for optimizing chemical reactions. MCRs are involved in the recently introduced concept of fragment based drug-design[4,5] and diversity-oriented synthesis of heterocyclic entities with high selectivity.[6]

Phosphonates are an important class of organophosphorus compounds (OPCs). They have been the focus of research in organic chemistry because of their wide range of applications in material chemistry,[7] catalysis,[8] and medicinal chemistry.[9] There are various types of phosphonates, such as α-amino- and α-hydroxy-phosphonates and β- phosphonomalononitriles. All of these phosphonates are produced via P-C bond formation.[10] Phosphonates and their derivatives show diverse pharmacological activities, in addition to acting as enzyme inhibitors and metabolic probes,[11] peptide mimetics,[12] antibiotics and pharmacological agents.[13] Owing to the broad importance of these phosphorus compounds the researchers have focused their attention on them.[14] In this context, Michaelis-Arbuzov,[15] Pudovik,[16] and phospha-Michael

addition[14] are the most important reactions for the synthesis of OPCs. Amongst these, the phospha-Michael addition represents one of the most adaptable and powerful tools for C-P bond formation. 2-Amino-4*H*-chromen-4-ylphosphonates are formed through Knoevenagel condensation, Pinner cyclisation, and phospha-Michael reactions in a one-pot method. In addition, these compounds are analogues of 2-amino-4*H*-chromenes, and fused chromenes possess anti-tumour/cancer[17] and antiviral[18] activity and are used in biodegradable agrochemicals.[19] Some of the biologically active 2-amino-4*H*-chromenes shown in Figure 1.[20,21]

Recently synthesis of 2-amino-4*H*-chromen-4-ylphosphonates has attracted much attention.[22-34] Methods have been reported on the one-pot synthesis of 2-amino-4*H*-chromen-4-ylphosphonates promoted by DMAP,[22] imidazole,[23] SBA-IM/SO_3H,[24] LiOH,[25] tetramethylguanidine,[26] silica supported 2-hydroxyethylammonium acetate (HEAA),[27] diethylamine,[28] ethylenediamine diacetate,[29] I_2,[30] K_3PO_4,[31] poly(ethylene glycol) (PEG),[32] β-cyclodextrin,[33] and $InCl_3$.[34] However, most of these procedures are limited in scope because they suffer from relatively low product yields and require catalysts. Therefore the development of alternative solvents which are environmentally benign, cheap, inexpensive, easily preparable, and non-toxic is highly desirable.

The demand for “greener” solvents has lead to the emergence of Deep Eutectic Solvents (DES). DES are a sub-category of ionic liquids (ILs), first introduced in 2003 by Abbott and coworkers.[35] A notable feature of DES is their melting points, which are typically lower than the freezing points of their individual components. Thus, the majority of the DES stays in liquid form at room temperature. In general, the important components of DES include a hydrogen

bond acceptor (HBA) (e.g. quaternary ammonium or phosphonium salts) and hydrogen bond donor (HBD) (e.g. organic acids, amides, amino acids, polyols and sugars), that are bonded chemically via hydrogen bonds.[36,37] In addition, other attractive properties have been associated with DES, such as their lack of flammability, low volatility, thermal and chemical stability, tenability, wide polarity, negligible vapor pressure, high solvability, and affordability.[38] Although they are classified in several categories (according to the chemical nature of the HBA and HBD), the most frequently encountered DESs are prepared using the quaternary ammonium salt (ChCl), because of its biodegradability and low cost.[39] Another important point is a known component of vitamin B complex, its use for DES preparations has led to the anticipation of safe and sustainable mixtures. These interesting features of DESs have made them green solvents, which are increasingly popular for use in electrochemistry, material chemistry and organic synthesis.[40]

Result and discussion

In continuation of our ongoing research towards development of multicomponent reactions in novel and green reaction media,[41] we describe herein the dual role (as catalyst and solvent) of deep eutectic solvent based on urea and choline chloride for convenient synthesis of 2-amino-4*H*-chromen-4-ylphosphonates *via* the domino reaction of salicylaldehydes, malononitrile / ethylcyanoacetate and dialkyl phosphite (Scheme 1).

Deep eutectic solvent were prepared by a previously reported method[40c]. Choline chloride (1 mol) was allowed to react with urea, acids (oxalic acid, Mandelic acid) and inorganic salts ($ZnCl_2$, $FeCl_3$, $SnCl_2$) at 80-100 °C. The resulting DES was used directly in reactions without further purification. This method produced no byproducts; therefore there was no loss

during isolation of the solvent.

After preparation of DES, to optimize the reaction conditions, a model reaction involving salicylaldehyde (1 mmol), malononitrile (1 mmol) and diethyl phosphite (1 mmol) was carried out using different DES and the results are given in Table 1. The initial experiment was performed in the presence of DES (urea–ChCl) at room temperature for 5 h; no product was formed (entry 1). After that we increased the temperature to 40 °C; trace amounts of the product was observed. Next, the reaction was performed at higher temperatures (60 °C and 80 °C). The yield was higher at 80 °C than at 60°C. Hence, 80 °C was selected as the optimized reaction temperature. The corresponding product **4a** was formed as the only product and was isolated in 92 % yield (Table 1, entry 4).

To test the suitability of other DESs, the model reaction under optimized conditions was carried out in different DESs, such as oxalic acid–ChCl (Table 1, entry 5), glycerol–ChCl (Table 1, entry 6), mandelic acid–ChCl (Table 1, entry 7), $ZnCl_2$–ChCl (Table 1, entry 8), $FeCl_3$–ChCl (Table 1, entry 9), and $SnCl_2$–ChCl (Table 1, entry 10) at 80 °C for 2 h. The results presented in Table 1 demonstrate low activity of the other DESs. To test the model reaction with non choline based DES like fructose : urea at 80 °C for 5h, we obtained KC (Table 1, entry 9). Also model reaction performed at 80 °C for 5h in presence of choline chloride only trace amounts of the product were observed (Table 1, entry 9). Finally performing the model reaction at the same reaction conditions (80 °C) with $ZnCl_2$ and urea as solvent did not result in the formation of the product.

Under the optimized conditions, the reaction of salicylaldehyde with malononitrile and diethyl phosphite was then carried out. It furnished the product 2-amino-3-cyano-4*H*-chromen-4-

yl phosphonate (**4a**) in 92 % yield within 2 h (Table 2, entry 2). In order to establish the generality of this newly developed protocol, additional reactions of various substituted salicylaldehydes (**1**) with malononitrile (**2**) and dialkyl phosphites (**3**) such as methyl, ethyl, *n*-butyl phosphites were carried out in DES under optimized reaction conditions. The results are summarized in Table 2. Reactions of salicylaldehydes (**1**) having both electron-withdrawing and electron-donating groups such as chloro, bromo, nitro, methyl, *tert*-butyl, methoxy, ethoxy, hydroxy and benzyloxy groups at 80 °C for 2-3 h produced the corresponding chromeneyl phosphonates in 85-93 % yields (Table 2). With 2-naphthaldehyde, products **4z**, and **4ax** were also produced in 91 % and 90 % yield, respectively (Table 2, entries 26 and 27). The same reaction, when carried out with ethylcyanoacetate, resulted in the formation of the corresponding ethyl 2-amino-4-(diethoxyphosphoryl)-4*H*-chromene-3-carboxylate in good yields (Table 2). In these reactions the substituents of the salicylaldehyde do not have significant effect on the product yields. However, when we replaced malononitrile with ethylcyanoacetate there was a slight decrease in the product yields due to electronic factors. All the isolated products were fully characterized on the basis of analytical data and detailed spectral studies including ^{1}H and ^{13}C NMR as well as HRMS.

This reaction protocol was also successfully applied for the synthesis of bis-chromenylphosphonates for the first time. The synthesis of diethyl 7-((4-(ethoxyphosphono)-2-amino-3-cyano-4*H*-chromen-7-yl)methyl)-2-amino-3-cyano-4*H*-chromen-4-yl-4-phospho-nate (**4au**) from the multi-component reaction between 5,5'-methylene-bis-salicylaldehyde, malononitrile and diethyl phosphite was achieved following this protocol in 85 % yield (Scheme

2).

Although the detailed mechanism and the role of DES in the present work have not been confirmed yet, a possible mechanism is proposed in a manner similar to that described in the IL catalyzed reactions.[42] We assume that choline chloride and hydrogen-bonding donors of urea in DES are the main reason for the high catalytic activity.[42d,42e] DES activates the aldehyde functionality of salicylaldehyde (**1**) through hydrogen bonding to start the nucleophilic addition of malononitrile / ethylcyanoacetate (**2**), to provide a nucleophilic urea *via* capturing a proton of **2** (malononitrile / ethylcyanoacetate) to form corresponding carbanions. Activation of the starting aldehyde by hydrogen bonding increases the electrophilicity of the aldehyde and assists the formation of Knoevenagel condensations product (**5**) with malononitrile (Scheme 3). The resulting Knoevenagel condensation products undergo intramolecular Pinner reaction to form iminocoumarine (**6**). In the next step, imino-coumarin **6** takes part into a phospha-Michael addition reaction with diethylphosphite (**3**) giving rise to the desired functionalized amino-4*H*-chromen-4-yl phosphonate derivatives **4**.

The reusability of DES was further investigated using the reaction between salicylaldehydes (5 mmol), malononitrile (5 mmol) and diethyl phosphite (5 mmol) in DES (5 mL) under the optimized conditions (Table 3, entry 2). After completion of the reaction, water (15 mL) was added to the reaction medium to dissolve the DES. The chromeneyl phosphonate product was separated by simple filtration, washed with water, and purified by recrystallization from ethanol. The filtrate was evaporated under vacuum and recovered DES was used for the next cycle. Applying this procedure, DES could be reused up to four times without any significant loss of the initial catalytic activity (Table 3). We recorded ^{1}H NMR spectra of fresh

DES and recovered DES. It confirms that recovered DES was not decomposed after the reaction (see in SI).

Experimental

Material and methods

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies and used without further purification. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Jeol JNM ECP 600 or Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Standard abbreviations were used to denote signal multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and brs = broad signal) and the coupling constants are given in Hertz (Hz). Mass spectra were recorded with a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument and are uncorrected. The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR spectra for the products 4 (Figure S 1 – S 139).

Synthesis of diethyl 2-amino-3-cyano-4H-chromen-4-yl-4-phosphonate (4b)

A mixture of DES (1 mL), salicylaldehyde (1 mmol), malnonitrile (1 mmol), and diethyl phosphite (1 mmol) was stirred at 80 °C. Stirring was continued at 80 °C until reaction was complete. The reaction mixture was diluted with water (5 mL), whereupon the desired product was separated as a solid, that was isolated by filtration. Further purification was done by recrystallization from ethanol. The resulting compounds were characterized by melting point and ^{1}H and ^{13}C NMR spectra, which corresponded to those reported in the literature. Compounds **4a-4au** were also synthesized by adopting this procedure.

Ethyl 4-(ethoxyphosphono)-2-amino-4H-chromene-3-carboxylate (4d)

Viscous liquid; yield: 90 %; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35 – 7.33 (m, 1H), 7.22 – 7.19 (m, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.45 (brs, 2H), 4.38 (d, J = 19.5 Hz, 1H), 4.26 – 4.14 (m, 2H), 4.04 – 3.97 (m, 2H), 3.90 – 3.71 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.7, 161.9, 150.8, 129.6, 128.4, 124.6, 119.9, 116.0, 70.8, 62.8 (d, $^{2}J_{PC}$ = 7.6 Hz), 62.5 (d, $^{2}J_{PC}$ = 7.4 Hz), 59.8, 35.1 (d, $^{1}J_{PC}$ = 145.5 Hz), 16.5 (d, $^{3}J_{PC}$ = 6.1 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.7 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.4; HRMS (ESI, m/z): Calcd. for $C_{16}H_{22}NO_6P$ ($M+H^+$) 355.1185, Found: 355.1180.

Ethyl 4-(ethoxyphosphono)-2-amino-6-chloro-4H-chromene-3-carboxylate (4h)

Viscous liquid; yield: 87 %; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.3 Hz, 1H), 7.19 – 7.15 (m, 1H), 6.99– 6.88 (m, 1H), 6.46 (brs, 2H), 4.35 – 3.81 (m, 7H), 1.29 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.5, 161.8, 149.4, 129.5, 129.3, 128.4, 121.9, 117.3, 70.5, 62.9 (d, $^{2}J_{PC}$ = 7.4 Hz), 62.7 (d, $^{2}J_{PC}$ = 7.3 Hz), 59.9, 35.1 (d, $^{1}J_{PC}$ = 146.0 Hz), 16.5 (t, $^{3}J_{PC}$ = 5.8 Hz) 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.6; HRMS (ESI, m/z): Calcd. for $C_{16}H_{21}ClNO_6P$ ($M+H^+$) 389.0795, Found: 389.0792.

Ethyl 4-(ethoxyphosphono)-2-amino-6-nitro-4H-chromene-3-carboxylate (4l)

Solid; yield: 85 %; mp 145-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (t, J = 2.6 Hz, 1H), 8.19 – 8.14 (m, 1H), 7.13 (d, J = 9.0 Hz, 1H), 5.01 (brs, 2H), 4.33 (d, J = 19.9 Hz, 1H), 4.22

– 3.80 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 6.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.8, 168.5, 161.7, 149.4, 129.4, 129.3, 128.4, 121.9, 117.3, 62.9 (d, $^2J_{PC}$ = 7.6 Hz), 62.7 (d, $^2J_{PC}$ = 7.4 Hz), 59.9, 35.0 (d, $^1J_{PC}$ = 146.0 Hz), 16.5, 16.4, 14.6; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.5; HRMS (ESI, m/z): Calcd. for $C_{16}H_{21}N_2O_8P$ ($M+H^+$) 400.1036, Found: 400.1031.

Ethyl 4-(ethoxyphosphono)-2-amino-6-bromo-4H-chromene-3-carboxylate (4p)

Solid; yield: 88 %; mp 125-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (d, J = 1.7 Hz, 1H), 7.32 (dd, J = 8.6, 2.0 Hz, 1H), 6.86 (d, J = 8.6, 1H), 6.39 (brs, 2H), 4.33 (d, J = 19.9 Hz, 1H), 4.26 – 4.12 (m, 2H), 4.05 – 3.98 (m, 2H), 3.96 – 3.82 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.4, 161.6, 149.9, 132.2, 131.3, 122.5, 117.7, 116.9, 70.4, 62.9 (d, $^2J_{PC}$ = 7.7 Hz), 62.7 (d, $^2J_{PC}$ = 7.2 Hz), 60.0, 35.0 (d, $^1J_{PC}$ = 146.2 Hz), 16.5 (t, $^3J_{PC}$ = 6.1 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.6; HRMS (ESI, m/z): Calcd. for $C_{16}H_{22}NO_6P$ ($M+H^+$) 355.1185, Found: 355.1181.

Diethyl 2-amino-3-cyano-8-methoxy-4H-chromen-4-yl-4-phosphonate (4t)

Solid; yield 93 %; mp 168-171 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.08 (t, J = 8.0 Hz, 1H), 6.94 – 6.92 (m, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.93 (brs, 2H), 4.16 – 4.10 (m, 2H), 4.04 – 3.85 (m, 6H), 1.35 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.9, 147.7, 139.5, 124.9, 121.1, 119.6, 117.7, 111.6, 63.4 (d, $^2J_{PC}$ = 7.3 Hz), 63.1 (d, $^2J_{PC}$ = 7.2 Hz), 56.1, 51.7, 35.6 (d, $^1J_{PC}$ = 148.7 Hz), 16.5 (d, $^3J_{PC}$ = 5.7 Hz), 16.5 (d, $^3J_{PC}$ = 5.2 Hz); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.3; HRMS (ESI, m/z): Calcd. for $C_{15}H_{19}N_2O_5P$ ($M+H^+$)

338.1032, Found: 338.1029.

Dibutyl 2-amino-3-cyano-8-methoxy-4H-chromen-4-yl-4-phosphonate (4u)

Solid; yield: 92 %; mp 174-176 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.06– 7.03 (m, 1H), 6.91 – 6.86 (m, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.14 (brs, 2H), 4.10 – 3.81 (m, 8H), 1.48 – 1.15 (m, 8H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.9, 147.6, 139.5, 124.8, 121.0, 119.6, 117.8, 111.5, 67.0 (d, $^{2}J_{PC}$ = 7.7 Hz), 66.7 (d, $^{2}J_{PC}$ = 7.6 Hz), 56.1, 51.4, 35.6 (d, $^{1}J_{PC}$ = 148.3 Hz), 32.6 (d, $^{3}J_{PC}$ = 5.4 Hz), 32.5 (d, $^{3}J_{PC}$ = 6.2 Hz), 18.8, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.4; HRMS (ESI, m/z): Calcd. for $C_{19}H_{27}N_2O_5P$ ($M+H^+$) 394.1658, Found: 394.1654.

Ethyl 4-(ethoxyphosphono)-2-amino-8-methoxy-4H-chromene-3-carboxylate (4v)

Solid; yield: 89 %; mp 144-146 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.95 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.22 (brs, 2H), 4.32 (d, *J* = 19.5 Hz, 1H), 4.18 – 3.82 (m, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6, 162.0, 146.7, 140.5, 124.2, 121.1, 121.0, 112.5, 70.5, 62.8 (d, $^{2}J_{PC}$ = 7.4 Hz), 62.4 (d, $^{2}J_{PC}$ = 7.3 Hz), 59.9, 35.2 (d, $^{1}J_{PC}$ = 145.5 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.8 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.4 Hz), 14.8; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.7; HRMS (ESI, m/z): Calcd. for $C_{22}H_{33}N_2O_4P$ ($M+H^+$) 385.1290, Found: 385.1287.

Diethyl 2-amino-3-cyano-8-ethoxy-4H-chromen-4-yl-4-phosphonate (4w)

Solid; yield: 93 %; mp 181-183 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 8.0 Hz,

1H), 6.90 (dd, J = 6.4, 1.4 Hz, 1H), 6.83 (dt, J = 8.2, 1.6 Hz, 1H), 5.06 (brs, 2H), 4.14 – 3.91 (m, 6H), 3.87 (d, J = 17.8 Hz, 1H), 1.41 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.0, 147.0, 139.7, 124.8, 121.0, 119.7, 117.8, 112.9, 64.8, 63.3 (d, $^2J_{PC}$ = 7.6 Hz), 63.1 (d, $^2J_{PC}$ = 7.4 Hz), 51.8, 35.7 (d, $^1J_{PC}$ = 148.6 Hz), 16.5 (d, $^3J_{PC}$ = 5.8 Hz), 16.5 (d, $^3J_{PC}$ = 5.4 Hz), 14.8; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.3; HRMS (ESI, m/z): Calcd. for $C_{16}H_{21}N_2O_5P$ ($M+H^+$) 352.1188, Found: 352.1185.

Dibutyl 2-amino-3-cyano-8-ethoxy-4H-chromen-4-yl-4-phosphonate (4x)

Solid; yield: 91 %; mp 175-177 °C[14]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.02 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 5.09 (brs, 2H), 4.07 – 3.80 (m, 7H), 1.69 – 1.64 (m, 2H), 1.50 – 1.45 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H), 1.38 – 1.16 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.0, 147.0, 139.7, 124.7, 121.0, 119.7, 117.8, 112.8, 66.9 (d, $^2J_{PC}$ = 7.7 Hz), 66.7 (d, $^2J_{PC}$ = 7.4 Hz), 64.8, 51.6, 35.6 (d, $^1J_{PC}$ = 148.9 Hz), 32.6 (t, $^3J_{PC}$ = 5.3 Hz), 18.8, 14.8, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.4; HRMS (ESI, m/z): Calcd. for $C_{20}H_{29}N_2O_5P$ ($M+H^+$) 408.1814, Found: 408.1811.

Ethyl 4-(ethoxyphosphono)-2-amino-8-ethoxy-4H-chromene-3-carboxylate (4y)

Solid; yield: 90 %; mp 139-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.96 (t, J = 7.9 Hz, 1H), 6.88 – 6.86 (m, 1H), 6.77 – 6.76 (m, 1H), 4.33 (d, J = 19.5 Hz, 1H), 4.21 – 4.08 (m, 2H), 4.05 – 3.93 (m, 4H), 3.86 – 3.70 (m, 2H), 1.36 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6, 161.9, 146.6, 140.4, 124.1, 121.0, 120.9, 112.4, 70.4, 64.7, 62.7 (d, $^2J_{PC}$ = 7.4 Hz), 62.4 (d, $^2J_{PC}$ = 7.3

Hz), 59.6, 35.1 (d, $^{1}J_{PC}$ = 145.5 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.8 Hz), 16.3 (d, $^{3}J_{PC}$ = 5.4 Hz), 14.7, 14.5; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.4; HRMS (ESI, m/z): Calcd. for $C_{18}H_{26}NO_7P$ ($M+H^+$) 399.1447, Found: 399.1445.

Diethyl 3-amino-2-cyano-1H-benzo[f]chromen-1-yl-1-phosphonate (4z)

Solid, yield: 91 %; mp 218-220 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.59 (dd, *J* = 7.9, 6.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 5.11 (brs, 2H), 4.54 (d, *J* = 16.1 Hz, 1H), 4.05 – 3.74 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.7, 148.6, 131.4, 130.7, 129.9, 128.4, 127.1, 125.5, 124.2, 119.6, 116.7, 111.2, 63.3 (d, $^{2}J_{PC}$ = 7.6 Hz), 63.0 (d, $^{2}J_{PC}$ = 7.4 Hz), 51.8, 35.7 (d, $^{1}J_{PC}$ = 148.6 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.8 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.4 Hz); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.5; HRMS (ESI, m/z): Calcd. for $C_{18}H_{19}N_2O_4P$ ($M+H^+$) 358.1082, Found: 358.1078.

Dibutyl 3-amino-2-cyano-1H-benzo[f]chromen-1-yl-1-phosphonate (4aa)

Solid; yield: 90 %; mp 158-160 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.60 – 7.57 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 4.91 (brs, 2H), 4.54 (d, *J* = 16.2 Hz, 1H), 4.02 – 3.72 (m, 4H), 1.54 – 1.44 (m, 4H), 1.30 – 1.14 (m, 4H), 0.86 – 0.82 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.7, 148.6, 131.4, 130.6, 129.9, 128.4, 127.1, 125.5, 124.2, 119.6, 116.7, 111.2, 66.8 (d, $^{2}J_{PC}$ = 8.1 Hz), 66.6 (d, $^{2}J_{PC}$ = 7.9 Hz), 63.3, 32.9 (d, $^{1}J_{PC}$ = 144.8 Hz), 32.7 (d, $^{3}J_{PC}$ = 5.8 Hz), 32.5 (d, $^{3}J_{PC}$ = 5.9 Hz), 18.7, 13.6; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.8; HRMS (ESI, m/z): Calcd. for $C_{22}H_{27}N_2O_4P$ ($M+H^+$) 414.1708, Found:

414.1703.

Ethyl 1-(ethoxyphosphono)-3-amino-1H-benzo[f]chromene-2-carboxylate (4ab)

Solid; yield: 88 %; mp 142-144 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.59 (brs, 2H), 5.09 (d, J = 18.0 Hz, 1H), 4.30 – 4.21 (m, 2H), 3.97 – 3.76 (m, 4H), 1.35 (t, J = 7.1 Hz, 3H), 1.11 – 1.06 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.6, 162.3, 149.0, 131.1, 131.0, 129.1, 128.2, 126.7, 125.0, 124.4, 116.7, 113.8, 71.3, 62.7 (d, $^{2}J_{PC}$ = 7.7 Hz), 62.4 (d, $^{2}J_{PC}$ = 7.3 Hz), 59.8, 31.7 (d, $^{1}J_{PC}$ = 147.0 Hz), 16.4 (d, $^{3}J_{PC}$ = 2.2 Hz), 16.4 (d, $^{3}J_{PC}$ = 2.4 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.5; HRMS (ESI, m/z): Calcd. for $C_{20}H_{24}NO_6P$ ($M+Na^+$) 428.1239, Found: 428.1237.

Diethyl 2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl-4-phosphonate (4ac)

Solid; yield: 90 %; mp 168-170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (t, J = 2.3 Hz, 1H), 7.23 (t, J = 2.4 Hz, 1H), 5.08 (brs, 2H), 4.17 – 4.03 (m, 4H), 3.84 (d, J = 18.6 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.5, 144.8, 130.0, 129.6, 127.8, 122.8, 120.1, 118.7, 63.7 (d, $^{2}J_{PC}$ = 7.5 Hz), 63.5 (d, $^{2}J_{PC}$ = 7.3 Hz), 51.6, 35.8 (d, $^{1}J_{PC}$ = 149.1 Hz), 16.6, 16.5; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.0; HRMS (ESI, m/z): Calcd. for $C_{14}H_{15}Cl_2N_2O_4P$ ($M+H^+$) 376.0146, Found: 376.0146.

Dibutyl 2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl-4-phosphonate (4ad)

Solid; yield: 89 %; mp 115-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32 (d, J = 1.8 Hz,

1H), 7.22 (d, *J* = 1.7 Hz, 1H), 5.02 (s, 2H), 4.07 – 3.95 (m, 4H), 3.83 (d, *J* = 18.6 Hz, 1H), 1.68 – 1.52 (m, 4H), 1.42 – 1.27 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.3, 144.7, 129.9, 129.5, 127.9, 122.8, 120.1, 118.6, 67.2 (d, $^{2}J_{PC}$ = 7.8 Hz), 67.1 (d, $^{2}J_{PC}$ = 7.7 Hz), 51.8, 35.8 (d, $^{1}J_{PC}$ = 149.1 Hz), 32.6 (d, $^{3}J_{PC}$ = 5.5 Hz), 18.8, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.0; HRMS (ESI, m/z): Calcd. for $C_{18}H_{23}Cl_2N_2O_4P$ ($M+H^+$) 432.0772, Found: 432.0769.

Ethyl 4-(ethoxyphosphono)-2-amino-6,8-dichloro-4H-chromene-3-carboxylate (4ae)

Solid; yield: 87 %; mp 144-146°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 5.70 (brs, 2H), 4.46 – 3.85 (m, 7H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.4, 161.6, 149.9, 132.2, 131.3, 122.5, 117.7, 116.9, 70.4, 62.9 (d, $^{2}J_{PC}$ = 7.7 Hz), 62.7 (d, $^{2}J_{PC}$ = 7.2 Hz), 60.0, 35.0 (d, $^{1}J_{PC}$ = 146.2 Hz), 16.5 (t, $^{3}J_{PC}$ = 6.1 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.6; HRMS (ESI, m/z): Calcd. for $C_{16}H_{20}Cl_2NO_6P$ ($M+H^+$) 423.0405, Found: 423.0401.

Diethyl 2-amino-8-bromo-6-chloro-3-cyano-4H-chromen-4-yl-4-phosphonate (4af)

Solid; yield: 91 %; mp 200-203 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 2.3 Hz, 1H), 7.25 (t, *J* = 2.3 Hz, 1H), 5.20 (brs, 2H), 4.20 – 3.95 (m, 4H), 3.83 (d, *J* = 18.6 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.6, 145.8, 132.4, 130.3, 128.6, 120.0, 118.7, 111.2, 63.7 (d, $^{2}J_{PC}$ = 7.7 Hz), 63.5 (d, $^{2}J_{PC}$ = 7.5 Hz), 51.7, 36.0 (d, $^{1}J_{PC}$ = 149.2 Hz), 16.5, 16.4; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.0; HRMS (ESI, m/z): Calcd. for $C_{14}H_{15}BrClN_2O_4P$ ($M+H^+$) 419.9641, Found: 419.9637.

Dibutyl 2-amino-8-bromo-6-chloro-3-cyano-4H-chromen-4-yl-4-phosphonate (4ag)

Solid; yield: 89 %; mp 142-144 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48 (t, J = 2.3 Hz, 1H), 7.27 (t, J = 2.6 Hz, 1H), 4.93 (brs, 2H), 4.09 – 3.93 (m, 4H), 3.83 (d, J = 18.6 Hz, 1H), 1.69 – 1.64 (m, 2H), 1.56 – 1.27 (m, 6H), 0.93 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.5, 145.8, 132.3, 130.2, 128.6, 120.0, 118.7, 111.1, 67.2 (d, $^{2}J_{PC}$ = 7.8 Hz), 67.1 (d, $^{2}J_{PC}$ = 7.7 Hz), 51.6, 35.9 (d, $^{1}J_{PC}$ = 149.3 Hz), 32.6 (d, $^{3}J_{PC}$ = 5.9 Hz), 18.7, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.1; HRMS (ESI, m/z): Calcd. for $C_{18}H_{23}BrClN_2O_4P$ ($M+H^+$) 476.0267, Found: 476.0262.

Ethyl 4-(ethoxyphosphono)-2-amino-8-bromo-6-chloro-4H-chromene-3-carboxyla-te (4ah)

Solid; yield: 88 %; mp 141-143 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (d, 1.2 Hz, 1H), 7.26 (d, J = 1.2 Hz, 1H), 6.39 (brs, 2H), 4.32 (d, J = 20.0 Hz, 1H), 4.28 – 4.12 (m, 2H), 4.08 – 3.99 (m, 2H), 3.97 – 3.83 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.2, 161.3, 146.6, 131.6, 129.7, 128.6, 123.4, 110.6, 70.7, 63.0 (d, $^{2}J_{PC}$ = 7.6 Hz), 62.9 (d, $^{2}J_{PC}$ = 7.2 Hz), 60.1, 35.6 (d, $^{1}J_{PC}$ = 146.4 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.9 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.6 Hz), 14.6; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.9; HRMS (ESI, m/z): Calcd. for $C_{16}H_{20}BrClNO_6P$ ($M+H^+$) 466.9900, Found: 466.9895.

Diethyl 2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl-4-phosphonate (4ai)

Solid; yield: 90 %; mp 190-192 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63 (t, J = 1.8 Hz,

1H), 7.41 (t, *J* = 2.3 Hz, 1H), 5.13 (brs, 2H), 4.20 – 4.01 (m, 4H), 3.84 (d, *J* = 18.6 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.5, 146.3, 135.2, 131.5, 120.4, 118.7, 117.5, 111.5, 63.7 (d, $^{2}J_{PC}$ = 7.5 Hz), 63.5 (d, $^{2}J_{PC}$ = 7.3 Hz), 52.0, 35.9 (d, $^{1}J_{PC}$ = 149.1 Hz), 16.6, 16.5; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.0; HRMS (ESI, m/z): Calcd. for $C_{14}H_{15}Br_2N_2O_4P$ ($M+H^+$) 463.9136, Found: 463.9132.

Dibutyl 2-amino-6,8-dibromo-3-cyano-4H-chromen-4-yl-4-phosphonate (4aj)

Solid; yield: 89 %; mp 151-153 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.62 (t, *J* = 2.2 Hz, 1H), 7.41 (t, *J* = 2.4 Hz, 1H), 4.97 (brs, 2H), 4.07 – 3.93 (m, 4H), 3.83 (d, *J* = 18.6 Hz, 1H), 1.70 – 1.51 (m, 4H), 1.41 – 1.27 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.4, 146.2, 135.1, 131.4, 120.5, 118.6, 117.4, 111.4, 67.2 (d, $^{2}J_{PC}$ = 7.7 Hz), 67.1 (d, $^{2}J_{PC}$ = 7.6 Hz), 51.8, 35.8 (d, $^{1}J_{PC}$ = 149.3 Hz), 32.6, 32.5, 18.7, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.8; HRMS (ESI, m/z): Calcd. for $C_{18}H_{23}Br_2N_2O_4P$ ($M+H^+$) 519.9762, Found: 519.9758.

Ethyl 4-(ethoxyphosphono)-2-amino-6,8-dibromo-4H-chromene-3-carboxylate (4ak)

Solid; yield; 86 %; mp 146-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 2.1 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 6.26 (brs, 2H), 4.33 (d, *J* = 20.0 Hz, 1H), 4.26 – 3.85 (m, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 6.4 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.1, 161.2, 146.5, 131.6, 129.7, 128.5, 127.4, 123.3, 110.5, 63.0 (d, $^{2}J_{PC}$ = 7.6 Hz), 62.8 (d, $^{2}J_{PC}$ = 7.2 Hz), 60.1, 35.6 (d, $^{1}J_{PC}$ = 146.4 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.9 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.6 Hz), 14.6; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.9; HRMS (ESI, m/z): Calcd. for $C_{16}H_{20}Br_2NO_6P$

($M+H^+$) 510.9395, Found: 510.9390.

Diethyl 2-amino-6-bromo-3-cyano-8-methoxy-4H-chromen-4-yl-4-phosphonate (4al)

Solid; yield: 92 %; mp 173-174 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.05 (s, 1H), 6.96 (s, 1H), 5.06 (brs, 2H), 4.13 – 4.04 (m, 4H), 3.85 (s, 3H), 3.81 (d, J = 18.4 Hz, 1H), 1.34 (t, J = 6.5 Hz, 3H), 1.25 (t, J = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.0, 148.3, 138.8, 123.4, 119.5, 119.4, 117.0, 115.0, 63.5 (d, $^2J_{PC}$ = 7.4 Hz), 63.4 (d, $^2J_{PC}$ = 7.1 Hz), 56.4, 50.6, 35.4 (d, $^1J_{PC}$ = 149.3 Hz), 16.5 (dd, $^3J_{PC}$ = 5.0, 3.2 Hz); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.7; HRMS (ESI, m/z): Calcd. for $C_{15}H_{18}BrN_2O_5P$ ($M+H^+$) 416.0137, Found: 416.0136.

Dibutyl 2-amino-6-bromo-3-cyano-8-methoxy-4H-chromen-4-yl-4-phosphonate (4am)

Solid; yield: 90 %; mp 175-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.05 (d, J = 2.1 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 4.90 (brs, 2H), 4.06 – 3.79 (m, 8H), 1.68 – 1.23 (m, 8H), 0.92 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.0, 148.3, 138.8, 123.5, 123.4, 119.4, 117.0, 115.0, 67.2 (d, $^2J_{PC}$ = 7.8 Hz), 67.1 (d, $^2J_{PC}$ = 7.7 Hz), 56.4 51.8, 35.8 (d, $^1J_{PC}$ = 149.1 Hz), 32.6 (d, $^3J_{PC}$ = 5.5 Hz), 18.8, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 21.6; HRMS (ESI, m/z): Calcd. for C $C_{19}H_{26}BrN_2O_5P$ ($M+H^+$) 472.0763, Found: 472.0759.

Ethyl 4-(ethoxyphosphono)-2-amino-6-bromo-8-methoxy-4H-chromene-3-carboxylate (4an)

Solid; yield: 87 %; mp 137-140 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.08 (s, 1H), 6.95 (s, 1H), 6.46 (brs, 2H), 4.32 (d, J = 19.8 Hz, 1H), 4.28 – 3.90 (m, 6H), 3.85 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ =

168.5, 161.6, 148.1, 139.5, 123.7, 123.0, 116.5, 114.5, 70.5, 62.8 (d, $^{2}J_{PC}$ = 7.4 Hz), 62.7 (d, $^{2}J_{PC}$ = 7.1 Hz), 59.9, 56.4, 35.1 (d, $^{1}J_{PC}$ = 146.4 Hz), 16.6 (d, $^{3}J_{PC}$ = 5.7 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.7 Hz), 14.6; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.5; HRMS (ESI, m/z): Calcd. for $C_{17}H_{23}BrNO_7P$ ($M+Na^+$) 486.0293, Found: 486.0287.

Diethyl 6,8-di-tert-butyl-2-amino-3-cyano-4H-chromen-4-yl-4-phosphonate (4ao)

Solid; yield: 93 %; mp 190-192 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 2.3 Hz, 1H), 7.18 (t, *J* = 2.3 Hz, 1H), 4.78 (brs, 2H), 4.11 (p, *J* = 7.1 Hz, 2H), 4.00 – 3.89 (m, 2H), 3.87 (d, *J* = 17.8 Hz, 1H), 1.39 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 4H), 1.30 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.8, 147.1, 146.8, 136.7, 124.8, 123.7, 119.6, 116.5, 63.3 (d, $^{2}J_{PC}$ = 7.3 Hz), 62.8 (d, $^{2}J_{PC}$ = 7.3 Hz), 52.1, 36.3 (d, $^{1}J_{PC}$ = 148.7 Hz), 35.1, 34.7, 31.5, 30.4, 16.6 (d, $^{3}J_{PC}$ = 5.8 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.6 Hz); ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.6; HRMS (ESI, m/z): Calcd. for $C_{22}H_{33}N_2O_4P$ ($M+H^+$) 420.2178, Found: 420.2175.

Dibutyl 6,8-di-tert-butyl-2-amino-3-cyano-4H-chromen-4-yl-4-phosphonate (4ap)

Solid; yield: 91 %; mp 145-147 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 2.2 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 4.72 (brs, 2H), 4.12 – 3.78 (m, 5H), 1.68 – 1.14 (m, 26H), 0.91 (t, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.6, 147.1, 146.7, 136.6, 124.8, 123.6, 119.5, 116.5, 66.8 (d, $^{2}J_{PC}$ = 7.7 Hz), 66.5 (d, $^{2}J_{PC}$ = 7.7 Hz), 36.2 (d, $^{1}J_{PC}$ = 148.6 Hz), 35.0, 34.7, 32.7 (d, $^{3}J_{PC}$ = 5.8 Hz), 32.6 (d, $^{3}J_{PC}$ = 5.7 Hz), 31.5, 30.4, 18.8, 13.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 22.8; HRMS (ESI, m/z): Calcd. for $C_{26}H_{41}N_2O_4P$ ($M+H^+$) 476.2804, Found: 476.2801.

Ethyl 4-(ethoxyphosphono)-6,8-di-tert-butyl-2-amino-4H-chromene-3-carboxylate (4aq)

Solid; yield: 90 %; mp 214-216 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23 (d, J = 1.9 Hz, 1H), 7.21 (d, J = 1.7 Hz, 1H), 6.34 (brs, 2H), 4.37 (d, J = 19.5, 1H), 4.29 – 4.12 (m, 2H), 4.02 (m, 2H), 3.91 – 3.67 (m, 2H), 1.40 (s, 9H), 1.31 (m, 12H), 1.24 (t, J = 7.0 Hz, 4H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.4, 161.7, 147.5, 146.5, 140.5, 136.1, 124.8, 122.9, 119.8, 62.6 (d, $^{2}J_{PC}$ = 7.4 Hz), 62.3 (d, $^{2}J_{PC}$ = 7.2 Hz), 59.8, 35.8 (d, $^{1}J_{PC}$ = 145.3 Hz), 35.0, 34.7, 31.6, 30.4, 16.6 (d, $^{3}J_{PC}$ = 6.0 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.7 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.6; HRMS (ESI, m/z): Calcd. for $C_{24}H_{38}NO_6P$ ($M+H^+$) 467.2437, Found: 467.2435.

Ethyl 4-(ethoxyphosphono)-2-amino-7-hydroxy-4H-chromene-3-carboxylate (4ar)

Solid; yield: 87 %; mp 160-161 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.88 (brs, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.3 Hz, 1H), 6.38 (s, 1H), 4.32 (d, J = 17.6 Hz, 1H), 4.26 – 3.83 (m, 6H), 1.33 – 1.27 (m, 6H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.6, 161.9, 157.2, 150.8, 129.2, 111.2, 109.3, 102.3, 68.5, 61.6 (d, $^{2}J_{PC}$ = 7.3 Hz), 61.3 (d, $^{2}J_{PC}$ = 7.2 Hz), 58.5, 33.3 (d, $^{1}J_{PC}$ = 145.1 Hz), 15.9, 15.8 (d, $^{3}J_{PC}$ = 2.5 Hz) 14.1; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 23.6; HRMS (ESI, m/z): Calcd. for $C_{16}H_{22}NO_7P$ ($M+H^+$) 371.1134, Found: 371.1130.

Ethyl 4-(ethoxyphosphono)-2-amino-7-(benzyloxy)-4H-chromene-3-carboxylate (4as)

Solid; yield: 90 %; mp 133-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5H), 7.25 (d, J = 8.1 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.62 (s, 1H), 6.36 (brs, 2H), 5.04 (s, 2H), 4.33 (d, J = 18.2 Hz, 1H), 4.27 – 4.13 (m, 2H), 4.06 – 3.98 (m, 2H), 3.90 – 3.71 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H), 1.11 (t, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.8, 161.7, 159.0, 151.4, 136.6, 130.1, 128.7, 128.2, 127.6, 111.9, 111.5, 102.8, 71.3, 70.3, 62.8 (d, $^{2}J_{PC}$ = 7.4 Hz), 62.4 (d, $^{2}J_{CP}$ = 7.1 Hz), 59.8, 34.4 (d, $^{1}J_{PC}$ = 146.1 Hz), 16.5 (t, $^{3}J_{PC}$ = 5.7 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$): δ = 24.7; HRMS (ESI, m/z): Calcd. for $C_{23}H_{28}NO_7P$ ($M+Na^+$) 484.1501, Found: 484.1495.

Ethyl 4-(ethoxyphosphono)-7-(4-fluorobenzyloxy)-2-amino-4H-chromene-3-carboxylate (4at)

Solid; yield: 90 %; mp 112-115 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 – 7.38 (m, 2H), 7.26 (d, J = 8.5 Hz, 1H), 7.09 – 7.05 (m, 2H), 6.75 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 6.34 (brs, 2H), 5.00 (s, 2H), 4.33 (d, J = 18.3 Hz, 1H), 4.25– 4.10 (m, 2H), 4.04 – 4.01 (m, 2H), 3.88 – 3.72 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.8, 162.7 (d, $^{1}J_{CF}$ = 246.5 Hz), 161.7, 158.8, 151.5, 132.4, 130.2 (d, $^{4}J_{CF}$ = 3.9 Hz), 129.5 (d, $^{3}J_{CF}$ = 8.3 Hz), 115.7 (d, $^{2}J_{CF}$ = 21.6 Hz), 111.4, 102.8, 71.3, 69.7, 62.8 (d, $^{2}J_{PC}$ = 7.3 Hz), 62.4 (d, $^{2}J_{PC}$ = 7.0 Hz), 59.8, 34.9, 33.9, 34.4 (d, $^{1}J_{PC}$ = 146.0 Hz), 16.5 (t, $^{3}J_{PC}$ = 5.6 Hz), 14.7; ^{31}P NMR (243 MHz, , $CDCl_3$): δ = 24.7; HRMS (ESI, m/z): Calcd. for $C_{23}H_{27}FNO_7P$ ($M+H^+$) 479.1509, Found: 479.1504.

Diethyl 7-((4-(ethoxyphosphono)-2-amino-3-cyano-4H-chromen-7-yl)methyl)-2-amino-3-cyano-4H-chromen-4-yl-4-phosphonate (4au)

Solid; yield: 85 %; mp 198-200 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.10 (d, J = 8.3 Hz, 2H), 7.08 – 6.98 (m, 4H), 6.90 (s, 4H), 3.96 – 3.76 (m, 11H), 1.12-1.07 (m, 12H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 161.9, 147.7, 139.5, 124.9, 121.1, 119.6, 117.7, 111.6, 63.4 (d, $^{2}J_{PC}$ = 7.3 Hz), 63.1 (d, $^{2}J_{PC}$ = 7.2 Hz), 51.8, 46.4, 35.6 (d, $^{1}J_{PC}$ = 148.7 Hz), 16.5 (d, $^{3}J_{PC}$ = 5.7 Hz), 16.4 (d, $^{3}J_{PC}$ = 5.2 Hz); ^{31}P NMR (243 MHz, DMSO-d_6): δ = 22.1; HRMS (ESI, m/z): Calcd. for $C_{29}H_{34}N_4O_8P_2$ ($M+H^+$) 628.1852, Found: 628.1857.

Conclusion

We have developed an efficient, simple, and green protocol for the synthesis of 2-amino-4*H*-chromen-4-ylphosphonates in deep eutectic solvent based on urea and choline chloride. In this reaction medium, product separation is convenient and DES is reusable. Green solvent applicability to various substrates under mild reaction condition is the merit of this novel protocol.

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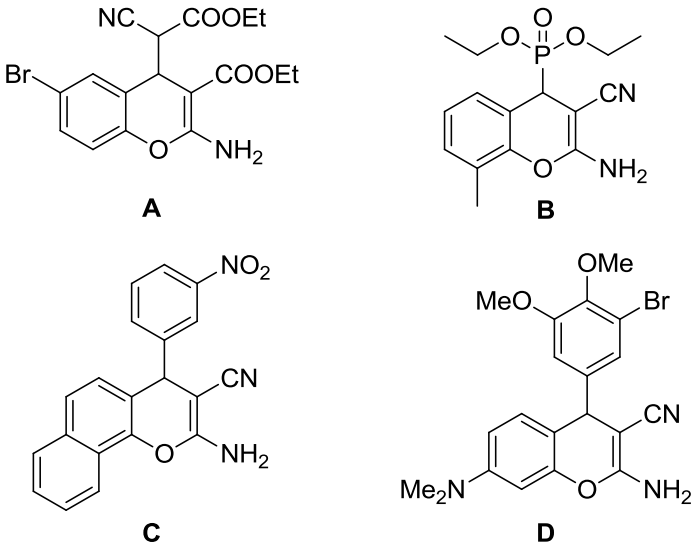
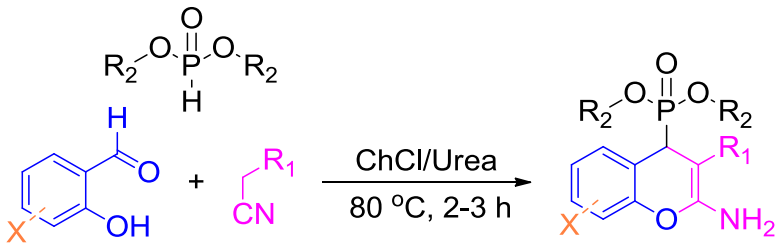
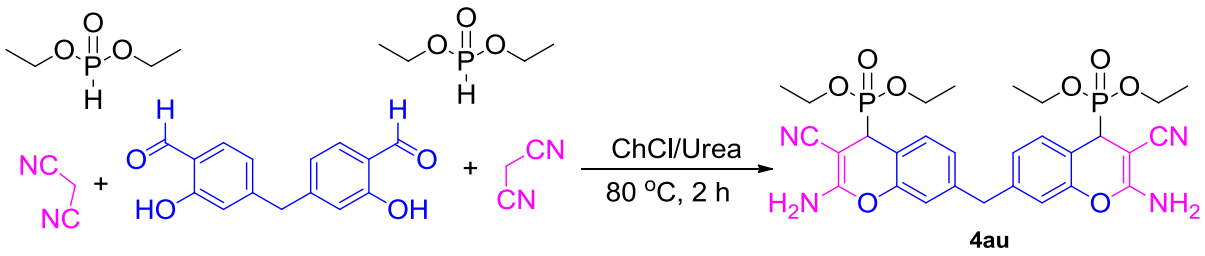


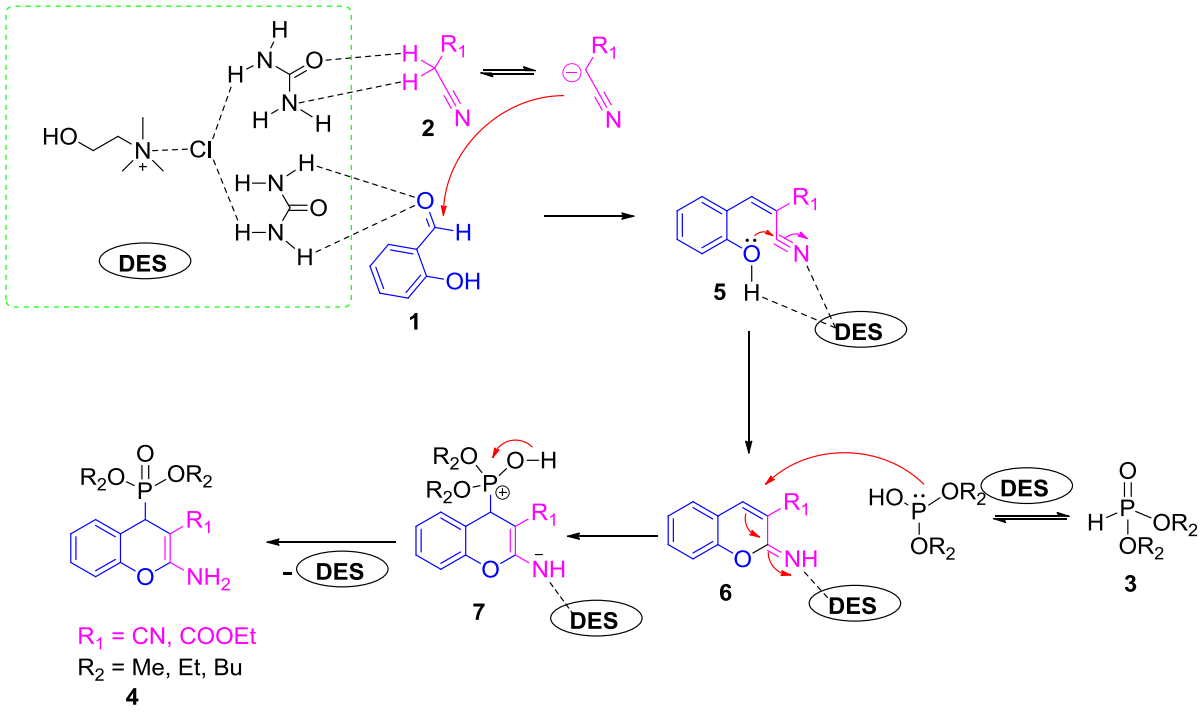
Figure 1 Structures of some biologically active 2-amino-4*H*-chromenes.



Scheme 1 Preparation of 2-amino-4*H*-chromen-4-yl phosphonate derivatives.

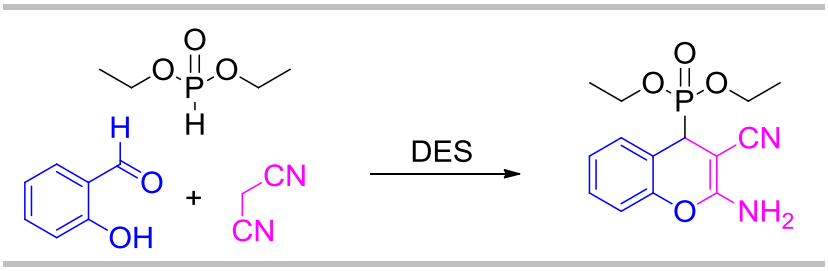


Scheme 2 Synthesis of bis-chromenylphosphonates



Scheme 3 Possible mechanism for the formation of chromenylphosphonates **4**.

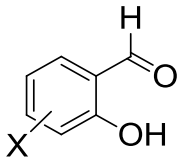
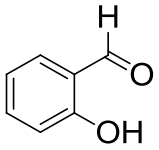
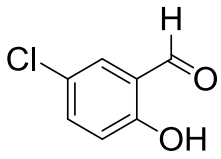
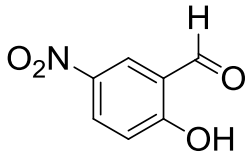
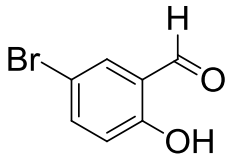
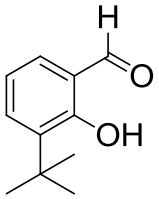
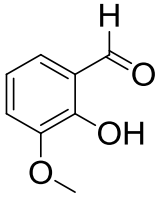
Table 1 Optimization of the reaction conditions.[a]

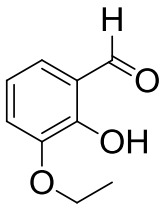
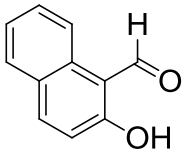
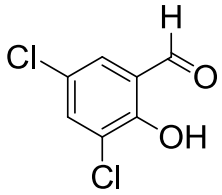
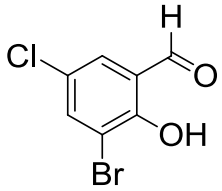
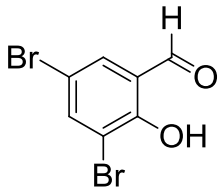
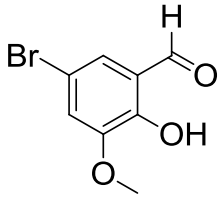
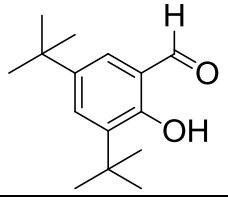
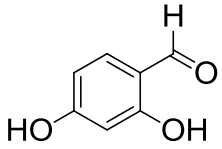


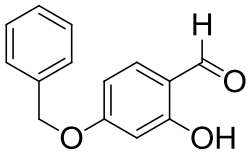
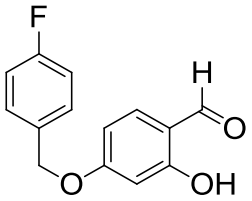
Entry	DES	Temp. (°C)	Yield (%)[b]
1	Urea–ChCl (2 : 1)	r.t.	-[c]
2	Urea–ChCl (2 : 1)	40	trace
3	Urea–ChCl (2 : 1)	60	40
4	Urea–ChCl (2 : 1)	80	92
5	Oxalic acid–ChCl (1 : 1)	80	70
6	Glycerol–ChCl (2 : 1)	80	87
7	Mandelic acid–ChCl	80	60
8	$ZnCl_2$–ChCl (2 : 1)	80	80
9	$FeCl_3$–ChCl (2 : 1)	80	75
10	$SnCl_2$–ChCl (2 : 1)	80	74
11	Fructose : Urea	80	13[d]
12	ChCl	80	traces[e]
13	ZnCl2	80	- [c]
14	Urea	80	- [c]

[a]Reaction conditions: salicylaldehyde (1 mmol), malononitrile (1 mmol), diethyl phosphite (1 mmol), DES (1.0 mL), 2 h. [b] Isolated yields. [c] No product was formed. [d] Knoevenagel condensation product (KC). [e] Along with product we observed mixture of products in TLC.

Table 2 One-pot synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives with dialkyl phosphites[a]

Entry		R_1	R_2	**4**	Time (hours)	Yield (%)[b]	Melting point (°C)
1		CN	Me	**4a**	2.1	91	154-156
2		CN	Et	**4b**	2.0	92	149-151
3		CN	Bu	**4c**	2.4	92	149-152
4		COOEt	Et	**4d**	2.7	90	viscous liquid
5		CN	Me	**4e**	2.3	90	165-167
6		CN	Et	**4f**	2.6	91	149-152
7		CN	Bu	**4g**	2.8	90	138-140
8		COOEt	Et	**4h**	3.0	87	Viscous liquid
9		CN	Me	**4i**	3.0	90	218-220
10		CN	Et	**4j**	2.8	91	222-224
11		CN	Bu	**4k**	2.8	90	149-151
12		COOEt	Et	**4l**	3.0	85	145-148
13		CN	Me	**4m**	2.6	90	161-162
14		CN	Et	**4n**	2.5	92	179-181
15		CN	Bu	**4o**	2.7	91	149-151
16		COOEt	Et	**4p**	2.9	88	125-127
17		CN	Me	**4q**	2.0	92	202-204
18		CN	Et	**4r**	2.1	92	236-238
19		CN	Bu	**4s**	2.3	91	178-180
20		CN	Et	**4t**	2.1	93	168-171
21		CN	Bu	**4u**	2.3	92	174-176
22		COOEt	Et	**4v**	2.6	89	144-146

23		CN	Et	**4w**	2.1	93	181-183
24		CN	Bu	**4x**	2.0	91	175-177
25		COOEt	Et	**4y**	2.3	90	139-141
26		CN	Et	**4z**	2.2	91	218-220
27		CN	Bu	**4aa**	2.2	90	158-160
28		COOEt	Et	**4ab**	2.5	88	142-144
29		CN	Et	**4ac**	2.5	90	168-170
30		CN	Bu	**4ad**	2.5	89	115-118
31		COOEt	Et	**4ae**	2.7	85	144-146
32		CN	Et	**4af**	2.7	91	200-203
33		CN	Bu	**4ag**	2.6	89	142-143
34		COOEt	Et	**4ah**	3.0	86	141-143
35		CN	Et	**4ai**	2.8	90	190-192
36		CN	Bu	**4aj**	2.8	89	151-153
37		COOEt	Et	**4ak**	3.0	84	146-148
38		CN	Et	**4al**	2.2	92	173-175
39		CN	Bu	**4am**	2.5	90	175-177
40		COOEt	Et	**4an**	2.8	87	137-140
41		CN	Et	**4ao**	2.0	93	190-192
42		CN	Bu	**4ap**	2.1	91	145-147
43		COOEt	Et	**4aq**	2.3	90	214-216
44		COOEt	Et	**4ar**	3.0	81	160-162

45		COOEt	Et	**4as**	2.6	90	133-136
46		COOEt	Et	**4at**	2.5	90	112-115

[a]Reaction conditions: Salicylaldehyde (1.0 mmol), malononitrile (1.0 mmol), dialkyl phosphites (1.0 mmol), DES (1 mL) at 80 °C. [b]Isolated yield.

Table 3 A study of the reusability of deep eutectic solvent[a]

Entry	Reaction cycle	Yield (%)[b]
1	First (fresh run)	92
2	Second cycle	90
3	Third cycle	87
4	Fourth cycle	84

[a]Reaction conditions: Salicylaldehydes (5 mmol), malononitrile (5 mmol), diethyl phosphite (5 mmol), DES (5.0 mL), 2 h, 80 °C). [b]Isolated yields.