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One-pot synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives using β-cyclodextrin as reusable catalyst in water

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ABSTRACT

Various 2-amino-4*H*-chromen-4-yl phosphonate derivatives were synthesized in good yields by condensation of salicylaldehyde, malononitrile or ethylcyanoacetate, and triethyl phosphite using β-cyclodextrin as a reusable catalyst under neutral conditions, in water.

In the past, drug development has been done with iterative manipulation of individual structures with the aid of fundamental chemical reactions. Creation of combinatorial libraries of molecules containing different pharmacophoric components, which are responsible for varied biological activity, is presently required. In this regard, a large number of new and efficient synthetic strategies have been developed by synthetic chemists. Multi-component condensation (MCC) strategy is one such synthetic tool used by scientists all over the world to create new libraries of molecules with diverse biological activities.

Multi-component condensation (MCC) reactions are one-pot procedures in which two or more components react in a single operation to obtain a product, which incorporates all the reactants with elimination of simple molecules like water. These multi-component condensations which differ from multi-step processes are efficient strategies in the modern drug discovery and development.

Phosphonate is a 'bioisostere' of ester moiety and its analogues are found to possess widespread applications as enzyme inhibitors,[1] antibiotics, pharmacological agents,[2] and reaction intermediates in organic synthesis.[3] Numerous properties associated with this bioisostere in organic synthesis and bioorganic chemistry and their derivatization through formation of phosphorus–carbon linkage to form 2-amino-4*H*-chromen-4-yl phosphonate are not much explored.

2-Amino-4*H*-chromenes are important class of compounds found in many natural products[4] and are widely used as cosmetics, pigments,[5] and agrochemicals.[6] Some of these 2-amino-4*H*-chromene derivatives (Fig. 1) are Bcl-2 antagonists that are discovered through fluorescent polarization (FP) and have synergy with various anticancer therapies under diverse mechanism of action.[7] A few synthetic methodologies have been developed till now for the synthesis of 2-amino-4*H*-chromenes by using various catalysts and additives. Recently Perumal and co-workers reported indium(III) chloride as a lewis acid catalyst for the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl) phosphonic acid diethyl ester structural motif.[8] In continuation of our efforts toward the development of new synthetic protocols aided by supramolecular catalysis,[9] we report herein multi-condensation one-pot synthetic strategy involving salicylaldehyde, malononitrile or ethyl cyanoacetate, and triethyl phosphite leading to the formation of 2-amino-4*H*-chromen-4-yl phosphonate derivatives using β-cyclodextrin as a reusable catalyst. To the best of our knowledge this is the first report for the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl)

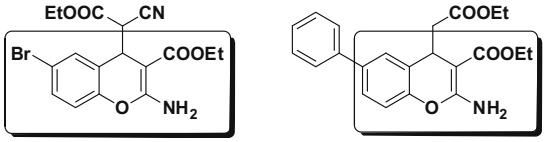

Figure 1. Structures of Bcl-2 protein antagonists.

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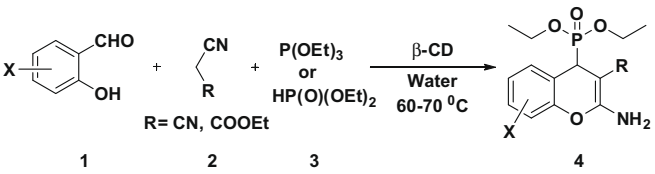


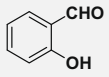
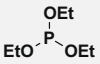
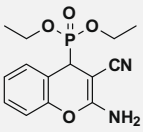
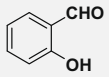
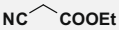
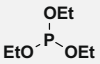
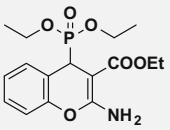
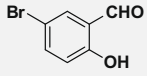
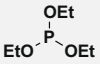
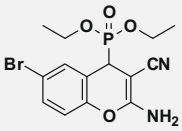
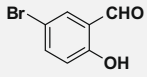
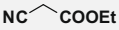
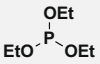
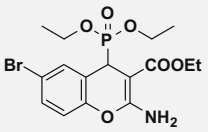
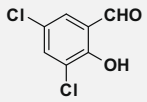
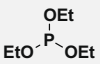
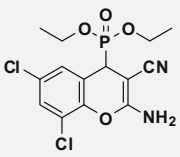
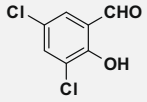
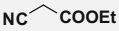
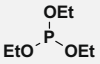
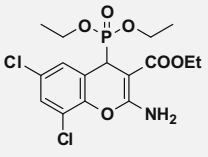
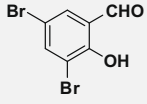
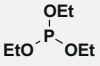
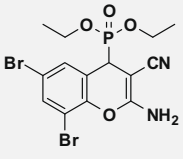
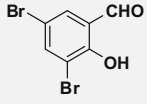
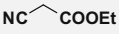
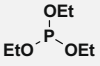
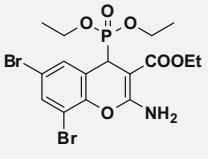
Scheme 1. Synthesis of 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate derivatives.

phosphonic acid diethyl ester structural motif, involving multicondensational approach using β-CD as a recyclable catalyst in water (Scheme 1).

Cyclodextrins and modified cyclodextrins have attracted much attention as aqueous-based hosts for inclusion complex phenomenon with a wide variety of guests. Inclusion complex formation occurs as a result of interaction between hydrophobic cavity of CD and hydrophobic portion of guest. These bind the substrates selectively and catalyze the chemical reactions by supramolecular catalysis involving reversible formation of host–guest complex with the substrate by non-covalent bonding as seen in the enzyme complexation process. These features of CDs attracted us to investigate reactions, under biomimetic conditions.

When we attempted the synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives in water under catalyst-free conditions, we were unsuccessful in getting the desired product. Then we realized the catalytic activity of the β-cyclodextrin to effect this multicomponent condensation by conducting a model reaction. Reacting salicylaldehyde, malononitrile and triethyl phosphite via formation of salicylaldehyde inclusion complex with β-CD at 60–70 °C in water gave corresponding diethyl 2-amino-3-cyano-4*H*-chromen-4-yl phosphonate in 88% yield.[10] The same reaction when carried out by replacing malononitrile with ethylcyanoacetate the corresponding ethyl 2-amino-4-(diethoxyphosphoryl)-4*H*-chromene-3-carboxylate resulted in good yields (Table 1).

Table 1
Synthesis of 2-amino-4*H*-chromen-4-yl phosphonate derivatives with triethyl phosphite[a]

Entry	Salicylaldehyde	**2**	Triethyl phosphite	Product	Time (h)	Yield[b] (%)
1					3.0	88
2					3.5	82
3					3.0	86
4					4.0	79
5					3.0	85
6					3.5	80
7					4.0	87
8					4.5	80