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An efficient procedure for multi-component synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester using $KF.Al_2O_3$

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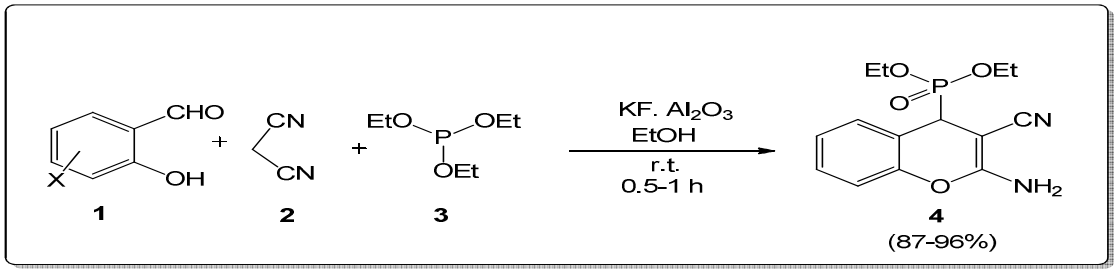
Abstract: Multi-component coupling of salicylaldehydes, malononitrile and triethyl phosphite has efficiently been carried out in a single step at room temperature using fluoride on alumina as a catalyst ($KF.Al_2O_3$) to furnish (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester in high yields.



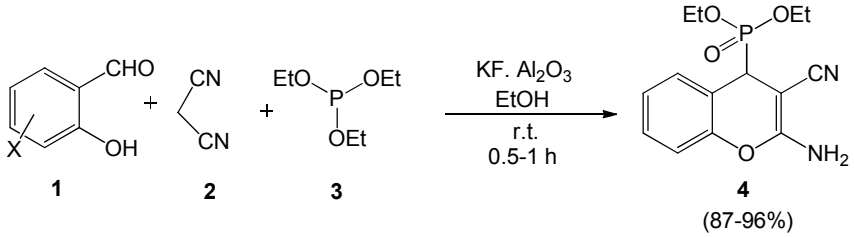
Keywords: Multi-component reaction, Triethyl phosphate, One-pot synthesis, Chromene, $KF.Al_2O_3$.

1. Introduction

Recently, synthetic chemists have focused their attention towards the transformations involving C-P bond formation.[1] In this endeavor Michaelis-Arbuzov,[2] Michaelis-Becker,[3] and phospha-Michael addition,[1] are most prominent because of the versatile chemistry of their products. Amongst these, the phospha-Michael addition, i.e. the addition of a phosphorus nucleophile to an acceptor-substituted alkene or alkyne represents one of the most versatile and powerful tools for the formation of a C-P bond since many different electrophiles and phosphorus nucleophiles can be combined with each other. This offers the possibility to access many diversely functionalized products. One of the important applications of the phospha-Michael addition is the synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester, which retains the basic skeleton of 2-amino chromene. This skeleton is an important structural motif in a series of natural products,[4,5] and can be converted into pyridine systems which relate to pharmacologically important calcium antagonists of the dihydropyridine [DHP] type.[6,7] Along with this, it accounts an important application in the field of drugs and pharmaceuticals as anti-coagulant, diuretic, anticancer, spasmolytic and anti-anaphylactin agent.[8-12] Also, it can be used as cognitive enhancer for the treatment of neurodegenerative disease including Alzheimer's disease, amyoprophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia, and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.[13] Besides biological significance, some 2-aminochromenes have been widely used as photoactive materials,[14] which led the scientific community to synthesize derivatives of 2-aminochromenes. Recently, the synthesis of novel derivatives of 2-aminochromenes, *viz* (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl esters, was carried out using $InCl_3$ as Lewis acid catalyst at ambient temperature,[15] as well as by Nageswar et al. using β-cyclodextrin at 60–70 ^{0}C.[16] Very recently, the similar method using potassium phosphate has also been reported.[17] Hence, an economical protocol with an easily available catalyst operable at room temperature for synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester is highly desired.

2. Results and Discussion

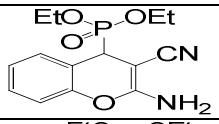
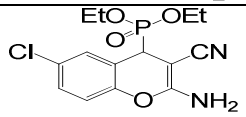
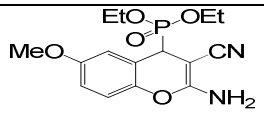
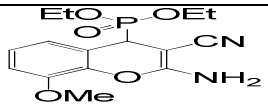
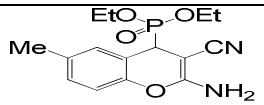
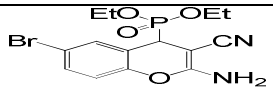
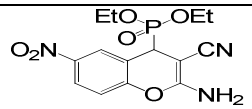
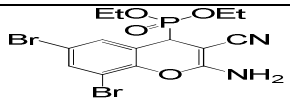
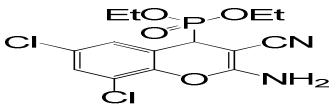
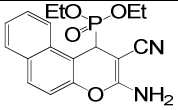
In continuation of our work,[18–20] on the development of useful synthetic methodologies, we have observed that the condensation of salicylaldehydes **(1)**, malononitrile **(2)** and triethyl phosphite **(3)** can efficiently be accomplished using a catalytic amount of potassium fluoride on alumina ($KF.Al_2O_3$) to produce the (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester **(4)** at room temperature (Scheme 1).



Scheme 1

A series of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester have been prepared from various substituted salicylaldehydes aforementioned procedure (Table 1). The salicylaldehydes containing both electron-donating and electron-withdrawing groups underwent the conversion smoothly. Different functionalities, such as chloro, bromo, methyl, methoxy, nitro and naphthyl remained unchanged. The conversion was complete with in 0.5-1 h and the corresponding phosphonic acid diethyl esters were formed in high yields (87-95%). The structures of the products were established from their spectral (IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and MS) data.

Table 1: Synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester using KF. Al_2O_3.

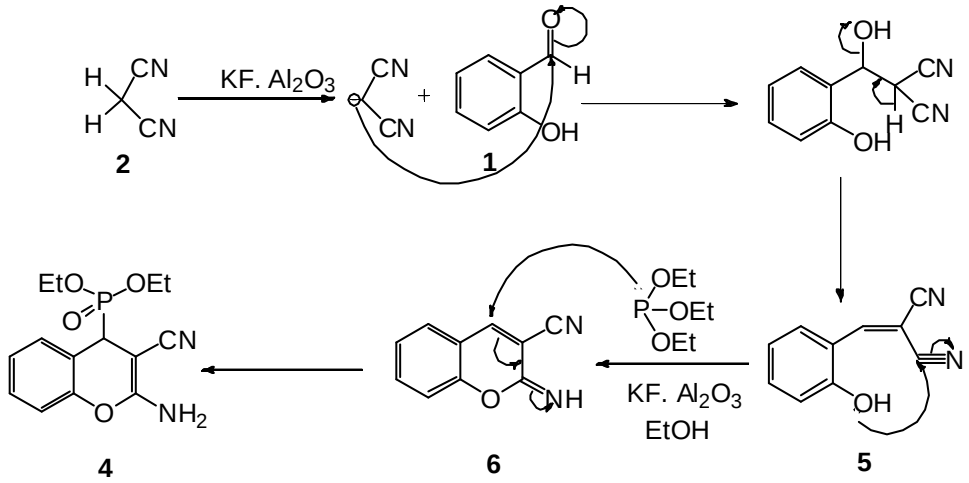
Entry	Product (4)	Time (min)	Yield (%)[a,b]
a		40	90
b		30	92
c		50	95
d		50	92
e		35	89
f		35	94
g		55	89
h		40	96
i		30	92
j		60	87

[a] The structures of the products were settled from their spectral (IR, ^{1}H -NMR, ^{13}C –NMR, ^{31}P–NMR and MS) values.

[b] Yields refer to pure, isolated products.

$KF.Al_2O_3$ has recently emerged as a valuable solid-phase catalyst for various organic transformations.[21,22] It possesses interesting catalytic activity. It can easily be handled and removed from the reaction mixture. It has been used here for the first time for the preparation of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester. In the absence of this catalyst the reaction did not proceed.

A plausible mechanism for the multicomponent synthesis of phosphonic acid diethyl ester using $KF.Al_2O_3$ in EtOH is depicted in Scheme2.



Scheme 2

3. Conclusion

In conclusion, we have improved the process of synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester using $KF.Al_2O_3$ at room temperature. The use of (i) inexpensive solid-phase catalyst, (ii) mild reaction conditions, (iii) impressive yields, and (iv) operational simplicity are the notable advantages of the present procedure. This methodology may find widespread uses in organic synthesis for preparation of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl esters.

4. Experimental Section

All reagents and solvents were purchased and used without further purification. Crude products were purified by column chromatography on silica gel of 60–120 mesh. ^{1}H-NMR spectra were recorded on a BrukerAC-400 spectrometer in DMSO-d_6 using tetramethylsilane as internal standard. LCMS Mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV.

General Procedure for the Synthesis of (2-amino-3-cyano-4H-chromen-4-yl) phosphonic acid diethyl esters: A mixture of salicylaldehyde (1 mmol), malononitrile (1 mmol), triethyl phosphite (1 mmol) and $KF.Al_2O_3$ (10 mol %) in ethanol (5 mL) was stirred at room temperature till the completion of reaction as monitored by TLC (Table 1). After completion, the mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, hexane-EtOAc) to obtain pure (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester. The spectral (IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR and MS) data of the products are given.

Spectral data of representative compounds:

Diethyl (2-amino-3-cyano-6-methoxy-4*H*-chromen-4-yl)phosphonate (4c): mp 172–174˚C; IR (KBr): 3342, 3160, 2979, 2191, 1658, 1499, 1232, 1040, 971 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, 3H, CH_3, *J* = 7.2 Hz), 1.21 (t, 3H, CH_3, *J* = 7.2 Hz), 3.73 (s, OCH_3), 3.95 (m, 4H, -CH_2), 4.05 (d, 1H, $^2J_{PH}$ = 18 Hz), 6.82 (t, 1H, *J* = 2.4 Hz), 6.86 (dt, 1H, *J* = 2.4, *J* = 9.2 Hz), 6.96 (d, 1H, *J* = 8.8 Hz), 7.07 (bs, 2H, -NH_2, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.1, 16.2, 34.1, 35.5, 46.9, 55.4, 62.1, 62.2, 114.0, 116.6, 118.6, 120.1, 143.8, 155.3, 162.8; ^{31}P-NMR (162 MHz, DMSO-d_6): δ 23.39; MS (70 eV, EI): *m/z* (%): 339 (M+1).

Diethyl (2-amino-6,8-dichloro-3-cyano-4H-chromen-4-yl)phosphonate (4i): mp 169–170˚C; IR (KBr): 3444, 3343, 2891, 2194, 1646, 1426, 1248, 1034, 864 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H, CH_3, *J* = 7.2 Hz), 1.18 (t, 3H, CH_3, *J* = 7.2 Hz), 3.98 (m, 4H, -CH_2), 4.25 (d, 1H, $^2J_{PH}$ = 18.8 Hz), 7.27 (t, 1H,

J = 2.4 Hz), 7.38 (bs, 2H, -NH_2, D_2O exchangeable), 7.64 (t, 1H, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.1, 33.9, 35.3, 47.3, 62.3, 62.5, 119.2, 121.2, 121.7, 127.7, 127.9, 128.5, 144.8, 161.8; ^{31}PNMR (162 MHz, DMSO-d_6): δ 22.47; MS (70 eV, EI): *m/z* (%): 377 (M+1).

5. Acknowledgment

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