Triphenylphosphine Catalysed Facile Multicomponent Synthesis of 2-Amino-3-Cyano-6-Methyl-4-Aryl-4*H*-Pyrans

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ABSTRACT: *Triphenyl phosphine (PPh_3), an efficient and reusable catalyst, catalysed the synthesis of 2-amino-3-cyano-6-methyl-4-aryl-4H-pyran-5-ethylcarboxylate derivatives by one-pot condensation of aromatic aldehydes, malononitrile and ethyl acetoacetate in EtOH-H_2O (1:1) at reflux conditions. The results show that aromatic aldehydes containing electron-donating groups or electron-withdrawing groups could react smoothly to give the corresponding products in good to excellent yields. Given the increasing levels of interest in green chemistry, the recyclability and reusability of the catalyst have been evaluated. It was also found that triphenyl phosphine can be recycled at least four times without loss of activity. This method has the advantages of high yield, mild reaction conditions, environmentally benign methodology and short reaction time.*

KEYWORDS: *Malononitrile; Triphenyl phosphine; Pyrans; Multicomponent reaction; One-pot synthesis.*

INTRODUCTION

Multi-Component Reactions (MCRs) are effective tools for the synthesis of many complex molecules in an only reaction from easily available starting substrates without the difficult purification steps. MCRs comply with the principles of green chemistry in terms of economy of steps as well as many of the stringent criteria of an ideal organic synthesis. These reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity [1]. A one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of

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multicomponent reactions. Hence, the development of multicomponent reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest in modern organic synthesis [2-4].

Compounds containing 4*H*-pyran skeletons are of important classes of organic compounds on account of their interesting pharmacological and biological properties. Many of these compounds are known to have potential applications in the pharmaceutical field. They are widely used as antimicrobial [5], antiviral [6], mutagenicity [7], cancer therapy [8] and antitumor agents [9]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [10] which are structurally similar to biologically active 1,4-dihydropyridines. They are often used in cosmetics and pigments and utilize as potentially biodegradable agrochemical [11]. Therefore, the synthesis of such compounds has attracted strong interest.

Considering the broad spectrum of biological activities of 4*H*-pyrans, synthetic chemists have developed numerous protocols for their syntheses including two-step as well as one-pot three-component synthesis, catalyzed by Baker's yeast [12], MgO [13], sodium selenate [14], phenylboronic acid [15], L-proline [16] and ammonium alum [17]. Each of these reported methods has its own merits, with at least one of the limitation of the drastic condition, long reaction times, low yields, and effluent pollution. This has clearly indicated that there is still scope to develop an efficient and eco-sustainable method for the synthesis of 4*H*-pyrans. The 4*H*-pyrans were obtained by the three component condensation of ethyl acetoacetate, aldehydes with malononitrile using Ph_3P as a catalyst in aqueous ethanol.

In recent years PPh_3 has drawn much interest in different organic reactions due to its experimental simplicity [18,19]. We have also reported the application of PPh_3 for the synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles [20], 4,6-diphenyl-3,4-dihydro pyrimidine-2(1*H*)-thione [21]. In line with of our studies towards the development of new routes to the environmentally benign synthesis of biologically active molecules [22-26], in this manuscript, we wish to report the applicability of PPh_3 on the three-component reaction of aryl aldehydes, ethyl acetoacetate, and malononitrile for the synthesis of novel 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives in aqueous ethanol media at reflux condition (Scheme 1). This is a one-pot reaction, which is not only operationally simple but also consistently gives the corresponding products in good to excellent yields.

EXPERIMENTAL SECTION

Apparatus and analysis

Chemicals were purchased from Merck, Fluka, and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX- 500 Avance at ambient temperature, using TMS as an internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a varion-Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of perking Elmer 2400 CHN elemental analyzer flowchart.

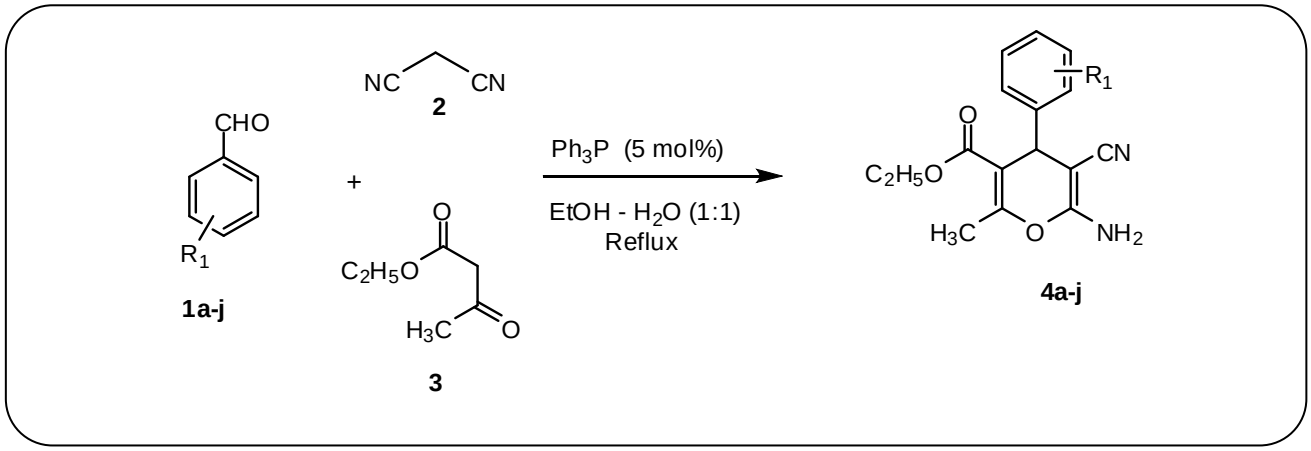
General procedure for synthesis of 2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran-5-ethylcaboxylate derivatives using PPh_3 (5 mol%) as catalyst

A mixture of ethyl acetoacetate (1 mmol), aldehydes (1 mmol), malononitrile (1 mmol) and catalyst PPh_3 (5 mol %), in 5 mL of EtOH-H_2O (1:1) were refluxed for appropriated time. After the TLC indicates the disappearance of starting materials, the reaction was cooled to room temperature, CH_2Cl_2 (20 mL) was added and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated under vacuum and the crude residue was purified by recrystallization. 2-Amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate was obtained as crystals. The recovered catalyst can be washed consequently with the diluted acid solution, water and then acetone. After drying, it can be reused without noticeable loss of reactivity. The products were identified by IR, ^{1}H NMR, ^{13}C NMR, mass, elemental analysis and melting points.

Spectral data for the synthesized compounds (4a-j)

*2-Amino-3- cyano-6- methyl-4- phenyl-4H-pyran-5-ethylcarboxylate (**4a**)*

IR (KBr, cm^{-1}): 3427, 3349, 3199, 2216, 1679, 1634, 1483, 1214, 788. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.09 (t, J = 7.2 Hz, 3H, CH_3CH_2), 2.19 (s, 3H, CH_3), 4.16 (q, J = 7.0 Hz, 2H, CH_3CH_2), 4.91 (s, 1H, CH), 5.07 (s, 2H, NH_2), 7.22-7.39 (m, 5H, Ar-H) ppm; ^{13}C NMR (125 MHz,



Scheme 1: Synthesis of various 2-amino-3-cyano-6-methyl-4-aryl-4H-pyran-5-ethylcarboxylate derivatives.

DMSO-d_6) *δ:* 15.3, 18.8, 40.4, 59.9, 106.3, 118.7, 125.7, 127.3, 129.5, 131.3, 144.2, 147.0, 159.2, 167.2 ppm; MS (ESI): *m/z* 285 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{16}N_2O_3$ (%): C, 67.60; H, 5.60; N, 9.86. Found: C, 67.53; H, 5.55; N, 9.86.

*2-Amino-3-cyano-6-methyl-4-(4-fluorophenyl)-4H-pyran-5-ethylcarboxylate (**4b**)*

IR (KBr, cm^{-1}): 3413, 3343, 3215, 2216, 1661, 1636, 1481, 1204, 780. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.13 (t, *J* = 7.2 Hz, 3H, CH_3CH_2), 2.17 (s, 3H, CH_3), 4.05 (q, *J* = 7.2 Hz, 2H, CH_3CH_2), 4.90 (s, 1H, CH), 5.22 (s, 2H, NH_2), 7.21 (d, *J*=7.2 Hz, 2H, Ar-H), 7.39 (d, *J*=7.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 15.0, 19.1, 39.7, 59.7, 105.7, 120.2, 125.0, 127.5, 129.0, 131.0, 144.7, 147.0, 159.3, 166.4 ppm; MS (ESI): *m/z* 303 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}FN_2O_3$ (%): C, 63.57; H, 4.96; N, 9.27. Found: C, 63.54; H, 4.91; N, 9.21.

*2-Amino-3-cyano-6-methyl-4-(3-hydroxyphenyl)-4H-pyran-5-ethylcarboxylate (**4c**)*

IR (KBr, cm^{-1}): 3435, 3342, 3214, 2204, 1674, 1646, 1496, 1206, 776. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.18 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 2.30 (s, 3H, CH_3), 4.13 (q, *J* = 7.3 Hz, 2H, CH_3CH_2), 4.93 (s, 1H, CH), 5.07 (s, 2H, NH_2), 7.10 (d, *J*=7.4 Hz, 2H, Ar-H), 7.42 (d, *J* = 7.4 Hz, 2H, Ar-H), 9.57 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 15.2, 20.2, 39.3, 59.7, 105.7, 119.3, 125.1, 127.4, 129.0, 131.0, 144.1, 147.4, 158.4, 167.0 ppm; MS (ESI): *m/z* 301 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{16}N_2O_4$ (%): C, 64.00; H, 5.33; N, 9.33. Found: C, 63.94; H, 5.32; N, 9.28.

*2-Amino-3-cyano-6-methyl-4- (3-nitrophenyl)-4H-pyran-5-ethylcarboxylate (**4d**)*

IR (KBr, cm^{-1}): 3402, 3336, 3204, 2215, 1683, 1639, 1481, 1223, 789. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.24 (t, *J* = 7.2 Hz, 3H, CH_3CH_2), 2.25 (s, 3H, CH_3), 4.12 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 4.88 (s, 1H, CH), 5.26 (s, 2H, NH_2), 7.14 (d, *J*=7.2 Hz, 2H, Ar-H), 7.41 (d, *J*=7.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 15.1, 19.5, 39.8, 59.7, 105.9, 119.5, 125.1, 127.5, 129.0, 131.0, 144.3, 146.6, 158.9, 166.6 ppm; MS (ESI): *m/z* 330 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}N_3O_5$ (%): C, 58.35; H, 4.56; N, 12.76. Found: C, 58.32; H, 4.54; N, 12.71.

*2-Amino-3-cyano-6-methyl-4-(4-chlorophenyl)-4H-pyran -5-ethylcarboxylate (**4e**)*

IR (KBr, cm^{-1}): 3437, 3337, 3213, 2213, 1673, 1645, 1475, 1207, 789. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.15 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 2.27 (s, 3H, CH_3), 4.07 (q, *J* = 7.2 Hz, 2H, CH_3CH_2), 4.89 (s, 1H, CH), 5.24 (s, 2H, NH_2), 7.07 (d, *J*=7.6 Hz, 2H, Ar-H), 7.31 (d, *J*=7.6 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 14.2, 19.6, 40.2, 59.8, 105.8, 119.4, 126.3, 127.6, 129.0, 131.0, 144.0, 146.2, 159.2, 167.5 ppm; MS (ESI): *m/z* 319 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}ClN_2O_3$ (%): C, 60.29; H, 4.71; N, 8.79. Found: C, 60.25; H, 4.66; N, 8.74.

*2-Amino-3-cyano-6-methyl-4- (4-nitrophenyl)-4H-pyran-5-ethylcarboxylate (**4f**)*

IR (KBr, cm^{-1}): 3424, 3336, 3216, 2224, 1675, 1640, 1481, 1211, 783. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.18 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 2.28 (s, 3H, CH_3),

4.18 (q, *J* = 7.2 Hz, 2H, CH_3CH_2), 4.84 (s, 1H, CH), 5.14 (s, 2H, NH_2), 7.04 (d, *J*=7.2 Hz, 2H, Ar-H), 7.38 (d, *J*=7.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 14.7, 19.6, 40.4, 60.4, 106.1, 119.7, 126.2, 127.2, 129.0, 131.0, 144.6, 147.1, 159.2, 167.4 ppm; MS (ESI): *m/z* 330 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}N_3O_5$ (%): C, 58.35; H, 4.56; N, 12.76. Found: C, 58.33; H, 4.55; N, 12.73.

*2-Amino-3-cyano-6-methyl-4- (4-N,N-dimethylaminophenyl)-4H-pyran-5-ethylcarboxylate (**4g**)*

(KBr, cm^{-1}): 3414, 3345, 3212, 2214, 1663, 1634, 1486, 1205, 786; ^{1}H-NMR (500 MHz, $CDCl_3$) *δ:* 1.24 (t, *J* = 7.2 Hz, 3H, CH_3CH_2), 2.64 (s, 6H, $N(CH_3)_2$), 2.32 (s, 3H, CH_3), 4.17 (q, *J* = 7.2 Hz, 2H, CH_3CH_2), 4.92 (s, 1H, CH), 5.13 (s, 2H, NH_2), 7.15 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.39 (d, *J* =7.2 Hz, 2H Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 15.1, 19.2, 39.8, 41.2, 57.4, 59.8, 105.8, 120.3, 125.2, 127.6, 128.3, 129.1, 131.1, 144.8, 147.1, 166.5 ppm; MS (ESI): *m/z* 328 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{21}N_3O_3$ (%): C, 66.05; H, 6.42; N, 12.84. Found: C, 66.03; H, 6.38; N, 12.81.

*2-Amino-3-cyano-6-methyl-4-(4-bromophenyl)- 4H-pyran-5-ethylcarboxylate (**4h**)*

IR (KBr, cm^{-1}): 3424, 3324, 3204, 2217, 1667, 1637, 1482, 1212, 791. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.17 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 2.21 (s, 3H, CH_3), 4.09 (q, *J* = 7.0 Hz, 2H, CH_3CH_2), 4.92 (s, 1H, CH), 5.16 (s, 2H, NH_2), 7.11 (d, *J*=7.4 Hz, 2H, Ar-H), 7.37 (d, *J*=7.4 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 14.6, 19.7, 39.5, 60.5, 105.4, 120.4, 125.4, 127.5, 128.2, 129.0, 131.0, 144.8, 146.9, 158.2, 167.6 ppm; MS (ESI): *m/z* 363.9 $(M+H)^+$. Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$ (%): C, 52.90; H, 4.13; N, 7.71. Found: C, 52.87; H, 4.08; N, 7.70.

*2-Amino-3-cyano-6-methyl-4- (4-methylphenyl)-4H-pyran-5-ethylcarboxylate (**4i**)*

IR (KBr, cm^{-1}): 3441, 3322, 3204, 2213, 1676, 1639, 1484, 1217, 783. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.16 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.19 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 4.97 (s, 1H, CH), 5.27 (s, 2H, NH_2), 7.11 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.36 (d, *J* = 7.4 Hz, 2H Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 15.3, 18.3, 19.9, 39.2, 59.6, 105.3, 120.0, 126.0, 127.6, 128.3, 129.0, 131.0, 144.9, 147.5, 159.1, 166.2 ppm; MS (ESI): *m/z* 299 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_3$ (%): C, 68.44; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.05; N, 9.34.

*2-Amino-3-cyano-6-methyl-4-(4-methoxyphenyl)-4H-pyran-5-ethylcarboxylate (**4j**)*

IR (KBr, cm^{-1}): 3439, 3324, 3203, 2215, 1675, 1634, 1489, 1221, 779. ^{1}H NMR (500 MHz, DMSO-d_6) *δ:* 1.22 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 2.30 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 4.15 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 4.91 (s, 1H, CH), 5.21 (s, 2H, NH_2), 7.16 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.31 (d, *J* = 7.4 Hz, 2H Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) *δ:* 15.3, 19.9, 39.2, 54.2, 59.6, 105.3, 120.0, 125.9, 127.1, 129.0, 131.0, 144.9, 147.5, 158.9, 166.2 ppm; MS (ESI): *m/z* 315 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_4$ (%): C, 64.97; H, 5.73; N, 8.92. Found: C, 64.93; H, 5.70; N, 8.89.

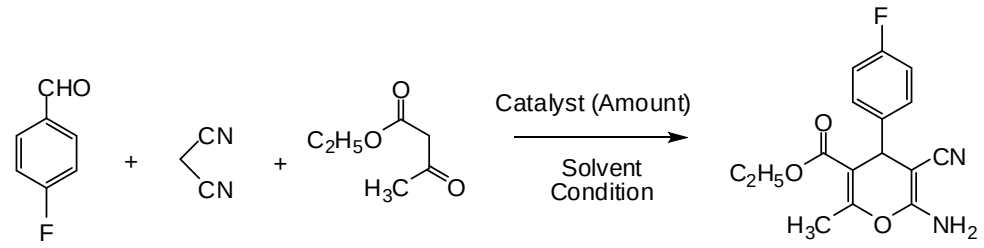
RESULTS AND DISCUSSION

In order to optimize the conditions, we studied the reaction of ethyl acetoacetate, 4-fluoro benzaldehyde with malononitrile and PPh_3 (5 mol%) as a simple model substrate in various conditions. The reaction was performed in various solvents, temperatures, the amount of catalyst and also with different catalysts as shown in Table 1. The results presented in Table 1 indicates that the use of 5 mol % of PPh_3 maintaining the yield at 95%, so this amount is sufficient to promote the reaction in EtOH-H_2O (1:1) under reflux condition (Table 1, Entry 7).

Green chemistry with its 12 principles would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible. One of the key areas of green chemistry is the replacement of hazardous solvents with environmentally benign ones or the elimination of solvents altogether [27]. By changing the methodologies of organic synthesis health and safety will be advanced in the small scale laboratory level but also will be extended to the industrial large scale production processes through the new techniques [28].

Encouraged by this successful three-component reaction, synthesis of diverse 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives 4a-j was undertaken. The aromatic aldehydes bearing electron-withdrawing and electron donating groups

Table 1: Optimization of reaction conditions for the synthesis of 2-amino-3-cyano-6-methyl-4-(4-fluorophenyl)-4H-pyran-5-ethylcarboxylate (4b)[a].



1b **2** **3** **4b**

Entry	Catalyst	Amount (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	Ph_3P	5	CH_3CN	Reflux	60	50
2	Ph_3P	5	H_2O	Reflux	60	72
3	Ph_3P	5	MeOH	Reflux	50	76
4	Ph_3P	5	EtOH	Reflux	50	73
5	Ph_3P	5	$CHCl_3$	Reflux	60	48
6	Ph_3P	5	Solvent-free	Reflux	40	29
7	**Ph_3P**	**5**	**EtOH-H_2O (1:1)**	**Reflux**	**30**	**95**
8	Ph_3P	5	EtOH-H_2O (1:1)	Rt	60	39
9	Ph_3P	5	EtOH-H_2O (1:1)	40	50	58
10	Ph_3P	5	EtOH-H_2O (1:1)	50	40	74
11	Ph_3P	5	EtOH-H_2O (1:1)	60	30	88
12	Ph_3P	0	EtOH-H_2O (1:1)	Reflux	60	0
13	Ph_3P	3	EtOH-H_2O (1:1)	Reflux	40	51
14	Ph_3P	10	EtOH-H_2O (1:1)	Reflux	30	95
15	$BiCl_3$	5	EtOH-H_2O (1:1)	Reflux	75	56
16	TBAB	5	EtOH-H_2O (1:1)	Reflux	60	76
17	LiCl	5	EtOH-H_2O (1:1)	Reflux	90	39
18	$ZnCl_2$	5	EtOH-H_2O (1:1)	Reflux	75	43

a) Reaction conditions: 4-fluorobenzaldehyde (1 mmol), malononitrile (1 mmol), and ethyl acetoacetate (1 mmol), solvent 5 mL.
b) Isolated yields

Table 2: Preparation of various 2-Amino-3-cyano-6-methyl-4-phenyl-4H-pyran-5-ethylcarboxylate derivatives.

Entry	R1	Product	Time (min)	Yield (%)[b]	Mp (°C)	
					Found	Reported
1	H	**4a**	40	93	194 – 195	195 – 196 [13]
2	4-F	**4b**	30	95	187 – 188	186 – 188 [23]
3	3-OH	**4c**	40	90	160 – 162	161 – 162 [13]
4	3-NO_2	**4d**	40	90	181 – 183	182 – 183 [13]
5	4-Cl	**4e**	30	92	170 – 172	172 – 174 [13]
6	4- NO_2	**4f**	30	91	183 – 185	182 – 184 [13]
7	4-$N(CH_3)_2$	**4g**	60	86	181– 183	180 – 182 [23]
8	4-Br	**4h**	30	93	173 – 175	172 – 174 [23]
9	4-CH_3	**4i**	50	88	178 – 179	177 – 179 [13]
10	4-OCH_3	**4j**	50	88	141 – 143	142 – 144 [13]

a) Reaction conditions: ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and malononitrile (1 mmol) in the presence of PPh3 (5 mol %) in EtOH-H2O (1:1) at reflux.
b) Isolated yield.

were found to be equally effective to produce 2-amino-4*H*-pyrans 4a-j in very good yields (Table 2).

Recyclability of catalysts is an important aspect of a reaction from an economical and environmental point of view, and has attracted much attention in recent years [29]. Thus the recovery and reusability of PPh_3 were investigated. After completion of the reaction, the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the PPh_3 was filtered off. The recycled catalyst has been examined in the next run. The PPh_3 catalyst could be reused four times without any loss of its activity and yields ranged from 95 to 90 %.

CONCLUSIONS

In conclusion, a simple, efficient and green protocol was demonstrated for the synthesis of 2-amino-3-cyano-6-methyl-4-phenyl-4*H*-pyran-5-ethylcarboxylate derivatives *via* one-pot multicomponent reactions in EtOH-H_2O (1:1) at reflux condition. General applicability, operational simplicity, mild reaction conditions, non-toxic and inexpensive catalyst were the advantages of the present procedure.

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