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Snail shell as a new natural and reusable catalyst for synthesis of 4H-Pyrans derivatives

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A simple, efficient and general method for the synthesis of 4H-pyrans is established through a multi component cyclocondensation of aromatic aldehydes, malononitrile and ethyl acetoacetate or acetyl acetone using snail shell as a natural catalyst. In this method the snail shell was used as green and reusable natural catalyst. Excellent yields, short reaction times and availability of the catalyst are the advantages of this method.

1. Introduction

Compared with classical methods, the heterogeneous catalysis solid-liquid has been shown to have desirable effects on reactions performance such as: good yields, short reaction times, easier work-up procedure, formation of pure products in milder conditions and waste minimization. In addition, introduction of clean procedures utilizing eco-friendly green catalysts has attracted great attention of workers.[1] Thus, development of a mild, inexpensive, and reusable catalyst for synthesis of organic compounds, still remains an attractive goal for researchers. 4H-Pyran derivatives occupy an important place in the realm of synthetic organic chemistry because of their biological and pharmacological properties as anticancer,[2] cytotoxic,[3] anti-HIV,[4-6] anti-inflammatory,[7] anti-malarial,[8-9] antimicrobial,[10] antihyperglycemic and antidyslipidemic.[11] In addition, these compounds are a common structural unit in a number of natural products.[12-14]

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Many of the methods for the synthesis of 4H-pyrans are reported in the literature.[15-21] Although, these methods have their own merits, they still have significant limitations like harsh reaction conditions, low yields, long times reactions and use of synthetic catalysts. These findings stimulated our interest to develop new simple, efficient and green process for the synthesis of these ring systems derivatives. In this article, we report a highly efficient route to the synthesis of 4H-pyran derivatives by cyclocondensation of aryl aldehydes, malononitrile, and ethyl acetoacetate or acetyl acetone using snail shell (SS) playing the role of ideal basic heterogeneous catalyst.

The snail shell has been utilized as natural source of calcium carbonate, as very effective coagulant in the treatment of waste water[22] and also as a source of calcium for the preparing nanocrystalline hydroxyapatite.[23] However, the use of snail shell, abundant in Morocco, as a catalyst in the synthesis of organic compounds, in particular 4H-pyrans derivatives, has not been reported.

2. Results and Discussion

General information for the catalyst

The waste of snail shells were collected, cleaned and dried in an oven at 100 °C during 24h. The shells obtained, without calcinations, are transformed by crushing into white soft powder. The latter has been characterized by X-ray diffraction, by scanning electron microscope and by measuring the specific surface.

The Analysis of the X-ray powder diffraction (Fig. 1) showed a well-crystallized phase. The presence of aragonite was confirmed by the characteristic 111, 221, and 202 reflections at 26.26°, 45.90° and 48.48° (2θ) (Joint Committee on Powder Diffraction International Centre for Diffraction Data (JCPDS : 76-0606). Further, it notes the absence of the characteristic reflections of calcium carbonate in the different allotropes calcite (JCPDS : 86-2334) and vaterite (JCPDS : 74-1867).[24]

The analysis by scanning electron microscopy (Fig. 2) shows that it crystallizes as irregular needles. The snail shell (aragonite) powder has an average specific surface of 3.15 m^2/g by measurements were carried out by the BET (Brunauer Emmett and Teller).

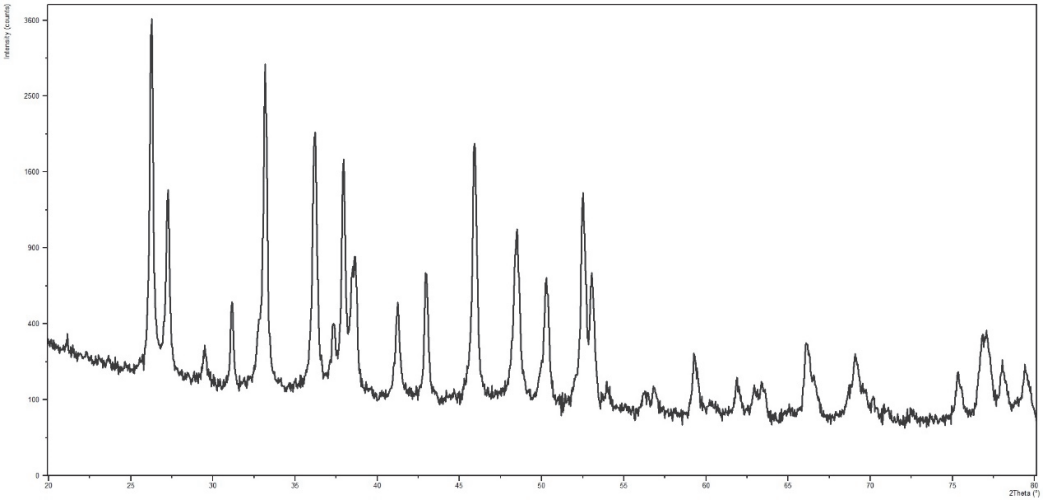


Fig. 1. XRD patterns of obtained powder of aragonite

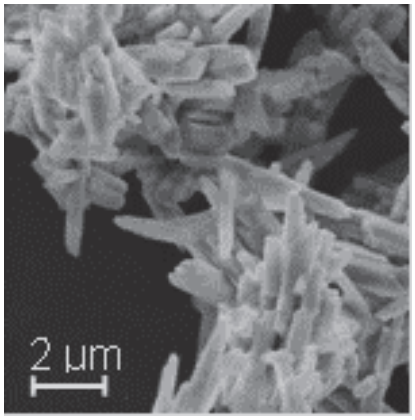
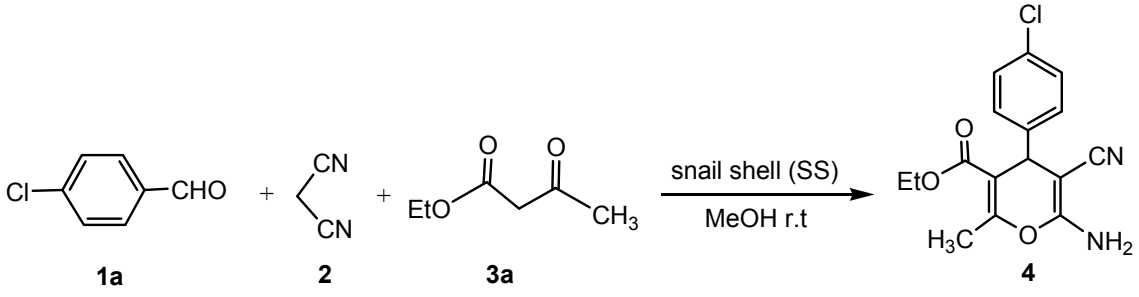


Fig. 2. Scanning electron microscopy of powder of snail shell (aragonite)

The catalytic activity of snail shell in synthesis of 4H-pyrans

Seeking good experimental conditions we run a one-pot synthesis of 4H-pyrans by the cyclocondensation of 4-chloro benzaldehyde (**1a**) malononitrile (**2**), and ethyl acetoacetate (**3a**) using snail shell (SS) catalysis. This reaction was considered as a model reaction (Scheme 1). When **1a** (2 mmol, 2 equiv), **2** (2 mmol, 2 equiv or 10 mmol, 10 equiv), and **3a** (2 mmol, 2 equiv or 10 mmol, 10 equiv) were mixed together in 3mL in methanol or ethanol at room temperature (or under reflux) without any catalyst, only a trace of the expected product was detected, even after 24 h. The catalytic effects of various bases were then studied (Table 1, entries 2-5). Among the different tested catalysts, snail shell showed the best activity (Table 1, entry 6).



Scheme 1. Model reaction for the synthesis of 4H-pyrans.

Table 1. Effect of the base used[a]

Entry	Base	Time (h)	Yield[b] (%)
1	-	24	-
2	KOH	2.5	75
3	Na_2CO_3	2.5	80
4	$CaCO_3$	2.5	81
5	NEt_3	2.5	70
6	Snail shell[c]	1	88 (94)[d]

[a]All reactions were performed in 2 mmol scale. The reactions were performed in 3 mL of methanol under reflux in the presence of 30 mol % of base. [b] Isolated yield of pur product. [c] The reaction was performed in 3 mL of methanol at room temperature in the presence of 0.15 g of catalyst. [d] Yield ( ) refer to those of pure isolated product when the reaction was performed in 3 mL of methanol under reflux in the presence of 0.15 g of catalyst.

An optimal catalyst loading had been define based on the results of model reactions which reveal that 0,15 g of catalyst per 2 mmol of aldehyde provided the best effects in terms of reaction time, economy of catalyst charge and purity of products. Higher amount of catalyst did not improve the rate considerably, what could be explain by fact that active sites of catalyst exist in a certain concentration more than that is required for the reactant molecules and hence the additional amount of snail shells does not increase the rate of the reaction.

As Table 2 indicates, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 0.15g of the catalyst in 3 mL of methanol; in these conditions, the corresponding 4H-pyran **4a** was obtained in 90% yield within 1h (Table 2, entries 4-5).

Table 2. Catalyst loading optimization study[a]

Entry	Amount of catalyst (g)	Time (min)	Yield (%)[b]
1	0.00	60	--
2	0.10	60	82
3	0.10	90	82
4	0.15 (without calcinations)	60	90
5	0.15 (calcined 900 °C for 2 h)	60	90
6	0.15 (without calcinations)	90	88
7	0.20	60	88
8	0.25	60	88
9	0.30	60	87
10	0.35	60	80
11	0.40	60	75

[a] 4-chlorobenzaldehyde **1a** (2 mmol), malononitrile **2** (2 mmol), and ethyl acetoacetate **3a** (2 mmol) were stirred in 3 mL of methanol in the presence of catalyst at room temperature .[b] Isolated yield of the pure product.

The model reaction was also examined in the presence of 0.15g of catalyst at room temperature in several solvents (3 mL). The use of butanol, isopropanol, AcOEt, THF and MeCN as solvent gave poor yields (Table 3, entries 2-6). Solvents like DMF and EtOH gave moderate yields (Table 3, entries 1, 7). The best conversion was observed when the reaction was performed in MeOH (Table 3, entry 8). Methanol proved to be the solvent of choice due to its safe nature and because it provided higher yields. The solvent free conditions gave average yields (Table 3, entry 9).

Table 3. Solvent screening for the model reaction[a]

Entry	Solvent	Time (min)[b]	Yield (%)[c]
1	EtOH	90	83
2	Butanol	90	65
3	Isopropanol	120	11
4	Ethyl acetate	60	19
5	THF	60	35
6	MeCN	60	44
7	DMF	60	70
8	MeOH	60	90
9	Solvent free	60	80

[a] 4-chlorobenzaldehyde **1a** (2 mmol), malononitrile **2** (2 mmol), and ethyl acetoacetate **3a** (2 mmol) were stirred in 3 mL solvent in the presence of 0.15g catalyst at room temperature. [b] Time reported in min monitored by TLC.
[c] Isolated yield of the pure product

The study of the influence of the volume of the solvent showed that 1 ml (Table 4, entry 1) of MeOH permitted to reach the best yield 92%. An increase in the volume up to 2 ml (Table 4, entry 2) slightly decreases the reaction yield (90 %), and this drops further to 84 % when a volume of 4 ml or 5 ml (Table 4, entries 4-5) is used. The large volume of the solvent reduces the concentration what explains the decreasing of the yields and the results were summarized in Table 4.

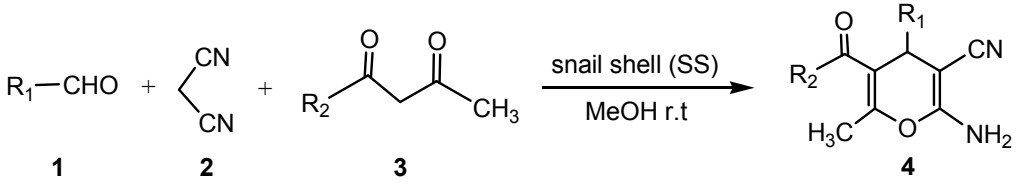
Table 4. Volume solvent optimization study for the model reaction[a]

Entry	Volume of methanol (mL)	Yield[b] (%)
1	1	92
2	2	90
3	3	90
4	4	84
5	5	84

[a] 4-chlorobenzaldehyde **1a** (2 mmol), malononitrile **2** (2 mmol), and ethyl acetoacetate **3a** (2 mmol) were stirred in methanol in the presence of 0.15g of catalyst at room temperature for 60 min.
[b] Isolated yield of the pure product.

Encouraged by the obtained results, we have investigated the scope and versatility of the process. Aromatic aldehydes substituted with either electron donating or electron-withdrawing groups reacted successfully with malononitrile and ethyl acetoacetate or acetylacetone and gave the products of 2-amino-3-cyano-4H-pyrans derivatives **4a-j** in high yields (Scheme 2). The results are listed in Table 5, which clearly indicate the generality of the reaction. Apparently, the nature of the substituent does not affect significantly the reaction time and yield for the employed reaction conditions.

The structures of compounds **4a-j** were confirmed by the comparison of melting points and spectral data with those reported in the literature.[25-26]



Scheme 2. Snail shell catalyzed one-pot three component synthesis of 4H-pyrans **4**.

Table 5. Synthesis of polyfunctionalized 4H-pyrans**.**

Product	R_1	R_2	Time [a] (min)	Yield[b] %
4a	4-ClC_6H_4	OEt	60	92
4b	4-$NO_2C_6H_4$	OEt	55	94
4c	4-$MeOC_6H_4$	OEt	40	92
4d	4-$MeOC_6H_4$	Me	35	92
4e	C_6H_5	OEt	45	90
4f	C_6H_5	Me	50	89
4g	4-MeC_6H_4	OEt	50	93
4h	4-MeC_6H_4	Me	45	89
4i	2,4-$(Cl)_2C_6H_3$	OEt	30	96
4j	2-ClC_6H_4	OEt	50	90

[a] Time reported in min monitored by TLC. [b] Yields refer to those of pure isolated product.

In our studies, the recycling of catalyst has also been investigated. At the end of the reaction, the catalyst could be recovered by simple filtration. The recycled catalyst could be washed with methanol and subjected to a second run of the reaction process. As shown in Table 6, the yields of reactions after using this catalyst five times show a slight reduction. It is likely that the snail shell can be recycled many more than five times.

Table 6. Yield (%) of product **4** versus the number of times the catalyst was reused.

Product	R_1	R_2	No. of recycling runs[a]				
			1	2	3	4	5
4a	4-ClC_6H_4	OEt	92	91	90	90	89
4b	4-$NO_2C_6H_4$	OEt	94	93	82	91	90
4d	4-$MeOC_6H_4$	Me	92	90	89	88	85
4e	C_6H_5	OEt	90	88	87	86	85

[a] Isolated yield of the pure product.

3. Conclusions

In conclusion, a simple and efficient method for the synthesis of 4H-pyran derivatives, catalyzed with snail shell, obtained from renewable source, is described. Compared with other procedures, this method has the advantage of being easy operation with short reaction times, mild and environmentally friendly reaction conditions, and good yields of the compounds. This work adds new snail shell catalyst to organic transformations and shows that snail shell could be an attractive alternative to the regular base catalysts.

4. Experimental

All the chemicals used were purchased from Sigma-Aldrich and were used as such. All products are known, and were identified by comparison of spectral and physical data with the literature. Melting points were taken on a KOFLER hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 300-MHz spectrometer in DMSO-d_6 using TMS as an internal reference (chemical shift in δ ppm). Mass spectra were recorded on a Thermo DSQII-Focus mass spectrometer. All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F_{254}).

Preparation of snail shell catalyst

The waste of snail shells were collected, cleaned and dried in an oven at 100◦C during 24h. The shells obtained, without calcinations, are transformed by crushing into white soft powder, which was denominated as SS.

General procedure for the synthesis of 4-substituted-2-amino-3-cyano-4H-pyrans 4

To a solution of aldehydes **1** (2 mmol), malononitrile **2** (2 mmol), and ethyl acetoacetate or acetyl acetone **3** (2 mmol) in the MeOH (1 mL), was added the snail shell (0.15 g). The progress of the reaction was monitored by thin layer chromatography using petroleum ether:ethyl acetate as solvent system. After filtration of the catalyst and cooling, the obtained solid was filtered and recrystallized in the ethanol, affording the corresponding pure 4H-pyran derivatives **4a-j**. The structures of compounds **4a-j** were confirmed by the comparison of melting points and spectral data with those reported in the literature.[25-26]

Spectral data for 4H-pyrans (Table 6) are as the followings:

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4a): White solid, mp. 171-172°C (lit.[26] 171-172°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.93 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.29 (s, 1H, CH), 6.93 (s, 2H, NH_2), 7.12 (d, *J* = 8.4 Hz, 2H, ArH), 7.25 (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.1, 18.6, 38.7, 57.3, 60.7, 107.2, 120.0, 128.8, 129.5, 131.8, 144.4, 157.4, 158.9, 165.7.

Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate (4b): White solid, mp. 175-176°C (lit.[26] 176-178°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.10 (t, *J* = 7.0 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.93 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.44 (s, 1H, CH), 7.05 (s, 2H, NH_2), 7.42 (d, *J* = 8.4 Hz, 2H, ArH), 8.17 (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.1, 18.7, 39.1, 56.6, 60.8, 106.4, 119.7, 124.2, 129.0, 146.8, 153.0, 158.4, 159.0, 165.5.

Ethyl 6-amino-5-cyano-4-(4-methoxy phenyl)-2-methyl-4H-pyran-3-carboxylate (4c): White solid, mp. 139-140°C (lit.[25] 136-138°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.12 (t, 3H, *J* = 7.2 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 4.10 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.41 (s, 1H, CH), 6.52 (s, 2H, NH_2), 6.80 (d, *J* = 8.2 Hz, 2H, ArH), 7.04 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.1, 18.2, 38.3, 57.3, 60.8, 62.1, 118.1, 120.3, 121.8, 128.9, 132.5, 145.2, 156.7, 157.8, 166.3.

5-acetyl-2-amino-6-methyl-4-(4-methoxyphenyl)-4H-pyran-3-carbonitrile (4d): White solid, mp. 157-158°C (lit.[25] 158-160°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.81 (s, 3H, $COCH_3$), 2.29 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.29 (s, 1H, CH), 6.92 (s, 2H, NH_2), 7.11 (d, *J* = 8.4 Hz, 2H, Ar), 7.24 (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 18.6, 29.3, 39.3, 56.3, 107.2, 120.0, 128.8, 129.5, 131.8, 144.4, 158.9, 196.7.

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**4e**): Yellow solid, mp. 193-195°C (lit.[25] 195-197°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.00 (t, *J* = 7.1 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.93 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.26 (s, 1H, CH), 6.89 (s, 2H, NH_2), 7.10-7.31 (m, 5H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.2, 18.6, 39.2, 57.7, 60.6, 107.7, 120.2, 127.3, 127.6, 128.9, 145.3, 157.1, 158.9, 165.9.

5-acetyl-2-amino-6-methyl-4-phenyl-4H-pyran3-carbonitrile (**4f**): White solid, mp. 158-159°C (lit.[25] 158-160°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.03 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.43 (s, 1H, CH), 6.83 (s, 2H, NH_2), 7.12-7.34 (m, 5H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 18.9, 30.2, 39.2, 58.2, 115.4, 120.2, 127.4, 127.6, 129.2, 145.0, 155.2, 158.2, 198.9.

Ethyl 6-amino-5-cyano-2-methyl-4-(4-methylphenyl)-4H-pyran-3-carboxylate (4g): White solid, mp. 177-178°C (lit.[25] 177-179°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 1.03 (t, *J* = 7.2 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.93 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.22 (s, 1H, CH), 6.85 (s, 2H, NH_2), 7.00 (d, *J* = 7.8 Hz, 2H, ArH), 7.09 (d, *J* = 7.2 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.2, 18.6, 21.1, 38.8, 57.8, 60.6, 107.9, 120.2, 127.5, 129.4, 136.4, 142.3, 156.7, 158.9, 165.9.

5-acetyl-2-amino-6-methyl-4-(4-methylphenyl)-4H-pyran-3-carbonitrile (**4h**): White solid, mp. 137-138°C (lit.[25] 138-140°C). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 2.03 (s, 3H, $COCH_3$), 2.24 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.25 (s, 1H, CH), 6.85 (s, 2H, NH_2), 7.41 (d, *J* = 8.1 Hz, 2H, ArH), 7.83 (d, *J* = 8.1 Hz, 2H, ArH); ^{13}C NMR (DMSO-d$_6$, 75 MHz) δ 14.2, 18.6, 21.9, 35.4, 60.6, 107.6, 114.8, 128.8, 129.1, 130.6, 131.1, 146.1, 160.9, 195.0.

Ethyl 6-amino-4-(2,4-dichlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4i): White solid, mp. 166-167°C (lit.[25] 166-168°C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.96 (t, J = 7.0 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.90 (q, J = 7.0 Hz, 2H, OCH_2), 4.82 (s, 1H, CH), 6.98 (s, 2H, NH_2), 7.21 (d, J = 8.2 Hz, 1H, ArH), 7.37 (d, J = 8.2 Hz, 1H, ArH), 7.52 (s, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.1, 18.6, 35.4, 56.0, 60.7, 105.9, 119.5, 128.4, 129.0, 131.6, 132.4, 133.3, 141.8, 158.7, 158.9, 165.5.

Ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (**4j**): Yellow solid, mp. 165-167°C (lit.[25] 167-169°C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.93 (t, J = 7.2 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.68 (q, J = 7.2 Hz, 2H, OCH_2), 4.85 (s, 1H, CH), 6.92 (s, 2H, NH_2), 7.16-7.38 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.1, 18.5, 35.7, 56.5, 60.6, 106.4, 119.6, 128.2, 128.8, 129.7, 130.2, 132.4, 142.5, 158.3, 158.9, 165.6.

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