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One-pot synthesis of polyfunctionalized 4*H*-pyran derivatives bearing fluorochloro pyridyl moiety

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ABSTRACT

Polyfunctionalized 4*H*-pyran derivatives bearing fluorochloro pyridyl moiety were readily prepared in high yields via one-pot multicomponent reaction catalyzed by piperidine. This present protocol provides an efficient synthetic route to the target compounds with the characteristics of short reaction time, high yield, and easy separation of the products.

4*H*-Pyran is an important and common structural unit both in natural compounds and synthetic heterocyclic molecules.[1,2] In recent years, polyfunctionalized 4*H*-pyran and its derivatives are of great synthetic interest and have been widely recognized as versatile scaffolds with diverse biological activities.[3,4] These compounds showed wide pharmacological activities and some of them emerged as anti-coagulants, anti-anaphylactics, and anticancer agents.[5–7] In addition, they present a potential activity on the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.[8]

As part of our ongoing drug discovery program, in this Letter we introduced fluorochloro pyridyl moiety into a series of polyfunctionalized 4*H*-pyran derivatives. Use as a key starting material to synthesize quinolone antibiotics like enoxacin and tosufloxacin,[9,10] 2,6,-dichloro-5-fluoro pyridine has also attracted great attention in pesticide research. Some compounds showed good activity against *armyworm* and *culexmosquito* **1** and the structure with this multihalogen-containing pyridine fragment also presented pleased inhibitory activity against *sphaerotheca fuliginea* **2** (Fig. 1).[11,12] Employing this unique heterocyclic ring we hope would help to extend the activity profiles and improve the physicochemical properties of 4*H*-pyrans (Fig. 2).

The target-oriented synthetic method, retrosynthetic analysis, is an important approach to breakdown the aim compound into simple precursors.[13] By disconnecting the C–O bond in the designed molecule, synthon A was departed from fragment B which could easily be obtained from synthon C and synthon D (Fig. 3). Several issues proved our retrosynthetic plan,[14–19]and explorations

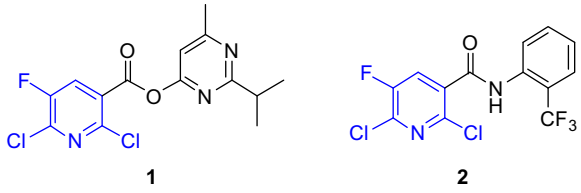

Figure 1. Structure with insecticidal activity bearing 2,6-dichloro-5-fluoro pyridine moiety.

were also conducted in combining the synthetic steps into one-pot synthesis.[20–23] Meanwhile, auxiliary techniques such as microwave, ultrasonic irradiation, and specific catalysts like ionic liquid and strong metal bases also were applied to shorten reaction time and increase yield.[5,8,24–27] Till now, very few literature had presented 4*H*-pyrans bearing heterocyclic rings like pyridine at position 6 and introduce the unique heterocycle, that is 2,6-dichloro-5-fluoro pyridine, might confer special physical and chemical properties to the compounds. In this Letter, while constructing the target structure from unit A, C, and D, we bring a protocol with the advantage of mild reaction condition, rapid conversion rate, high yield, and easy work up.

The catalyst played an important role in the formation of fully substituted 4*H*-pyrans. Initially, benzaldehyde **3**, malononitrile **4,** and ethyl 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate **5** were selected as representative substrates to investigate the reaction conditions. Without the catalyst, the reaction was conducted with a long reaction time. Then, we focused our attention on using various catalysts, which might help to reduce the reaction time and improve the yields of the target compounds. Lewis acid

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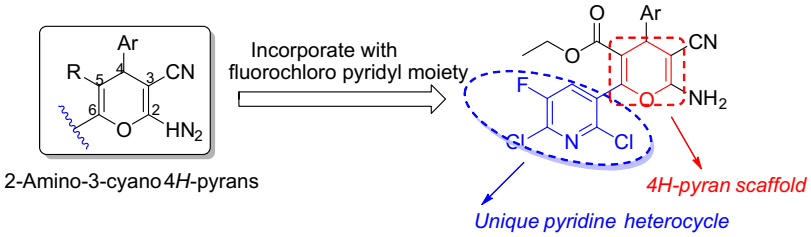


Figure 2. Design strategy of novel polyfunctionalized 4*H*-pyran derivatives.

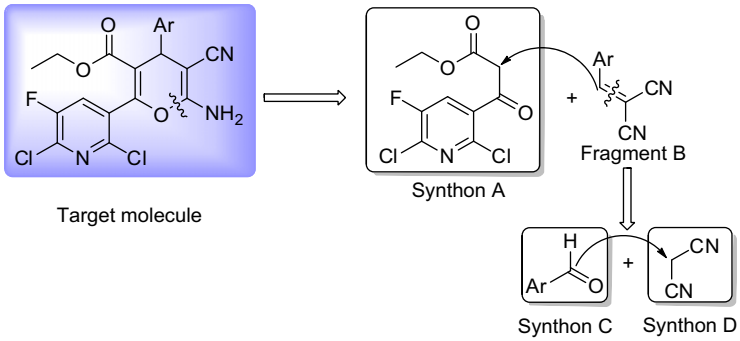
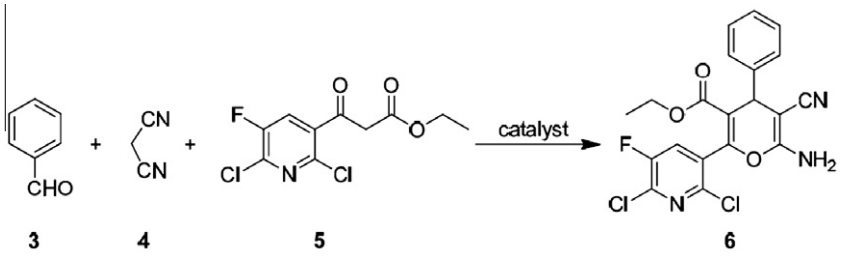


Figure 3. Retrosynthetic analysis of the target compounds.

Table 1
One-pot reaction of benzaldehyde, malononitrile and 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate using different catalysts[a]



3 **4** **5** **6**

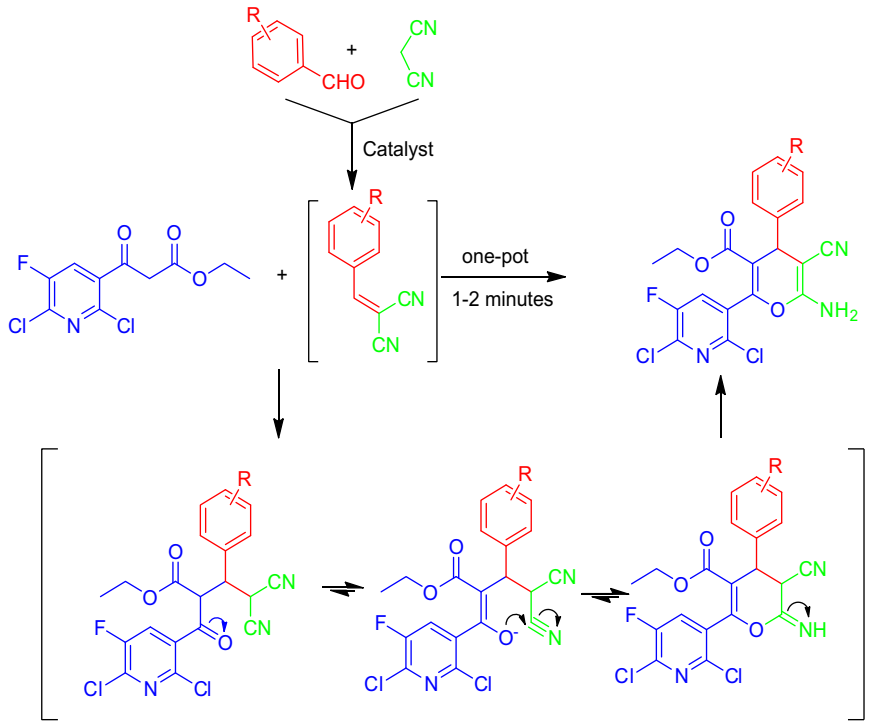
Entry	Catalyst[b]	Time (h)	Yield[c] (%)
1	$ZnCl_2$	24	52
2	$SnCl_2{\cdot}2H_2O$	24	Trace
3	None	10	71
4	TEA	1.5	84
5	Morphline	0.6	82
6	Piperidine	0.5	85

[a] Molar ratio of 3:4:5 = 1.2:1.2:1
[b] The amount of 10 mol % catalyst was used.
[c] Yields refer to isolated products.

$ZnCl_2$ and $SnCl_2{\cdot}2H_2O$ were employed[28] and the results demonstrated that they gave negative effects to the reaction, slowing down the rate and decreasing the yields (Table 1, entries 1 and 2). Subsequently, the organic bases were introduced into the reaction system. When morphline was applied to the reaction system, the reaction time was shortened and the yield was increased (Table 1, entry 5). Encouraged by this result, we tried different organic bases as listed in Table 1. Finally, piperidine showed a favorable catalytic activity to the reaction in terms of the reaction time as well as the yields.

The mechanism of this reaction was shown in Scheme 1.[5] Firstly, aryl aldehydes reacted with malononitrile and resulted in the formation of arylidenemalononitriles through Knoevenagel condensation in the presence of the catalyst at 35 °C. Secondly, 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate was added to the reaction system and the following Michael addition finished extremely rapid under reflux in ethanol in one to two minutes. The reaction accomplished complete conversion and the pure target compounds were obtained in considerably high yields without further purification.[29–31]

Various component molar ratios were applied to the reaction for optimization (Table 2). The results showed that the target compound was obtained in a relatively high yield with the ratio of **3**:**4**:**5** = 1.2:1.2:1 (Table 2, entry 2). Further increasing the ratio of benzaldehyde **3** and malononitrile **4** did not lead to an improvement of the yield (Table 2, entry 3), while the lowest yield was observed when the ratio of **3**:**4**:**5** = 1.1:1.1:1 (Table 2, entry 1). Moreover, the impact of the catalyst amount on the reaction rate and the conversion was also investigated. In the absence of the catalyst the reaction proceeded for a relatively long time in low yield.



Scheme 1. The reaction mechanism of the one-pot three components reaction.

Table 2
Optimization of the components ratio and amount of catalyst

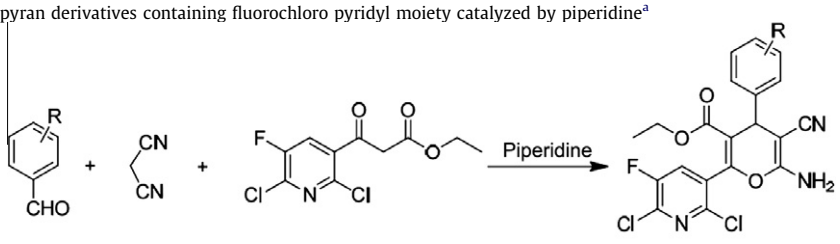
Entry	Catalyst amount (mol %)	Components molar ratio (3:4:5)	Time (h)	Yield[a] (%)
1	0	1.1:1.1:1	10	65
2	0	1.2:1.2:1	10	71
3	0	1.3:1.3:1	10	71
4	5	1.2:1.2:1	1.5	77
5	10	1.2:1.2:1	0.5	85
6	15	1.2:1.2:1	0.5	86

[a] Yields refer to isolated products (based on component **5**).

After optimization, it was found that 10 mol % piperidine was the appropriate amount to carry out the reaction smoothly. Further increasing of the catalyst amount did not help to improve the reaction time and the yield apparently, while decreasing the amount led to a lower yield and a longer reaction time. The optimized conditions and the results were illustrated in Table 2.

The optimal conditions for obtaining the target compounds involved the use of 10 mol % piperidine as the catalyst. To explore the overview of the one-pot transformation described above, different

Table 3
One-pot synthesis of different 4*H*-pyran derivatives containing fluorochloro pyridyl moiety catalyzed by piperidine[a]



3a-n **4** **5** **6a-n**

Entry	R	Product	Time (min)	Yield[b] (%)	Mp (°C)
1	3-CN	**6a**	20	92	203.1–204.1
2	4-NO_2	**6b**	50	82	129.8–131.4
3	H	**6c**	30	85	152.1–152.9
4	2-Cl-4-Br	**6d**	30	79	200.5–201.5
5	2,3-F_2	**6e**	20	87	181.8–182.9
6	2-F-4-Me	**6f**	80	85	190.4–191.1
7	4-Cl	**6g**	65	82	178.3–180.1
8	3-NO_2	**6h**	40	86	192.2–193.4
9	4-Me	**6i**	300	83	183.8–185.2
10	4-Cl-2-CF_3	**6j**	110	83	205.1–206.2
11	2,4-Cl_2	**6k**	25	90	185.4–186.9
12	4-CN	**6l**	45	81	148.9–150.6
13	3-Br	**6m**	30	85	155.7–157.0
14	4-F	**6n**	85	86	129.6–131.1

[a] All reactions were performed with substituted aldehyde (1.2 equiv), malononitrile (1.2 equiv), and 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate (1.0 equiv) catalyzed by piperidine (0.10 equiv).
[b] Yields refer to isolated products (based on compound **5**).

aryl aldehydes with electron-withdrawing groups or electron-donating ones were used as substrates. As shown in Table 3, under optimized reaction conditions, the target compounds were obtained in high yields. Notably, the electron-donating group and the electron-withdrawing group on the aryl ring had some impact on the reaction rates. Aryl aldehydes with electron-withdrawing groups took less time to complete the reactions. In conclusion, we introduced multihalogen-containing pyridine ring into a series of polyfunctionalized 4*H*-pyran derivatives under mild conditions. The reaction was completed in high yield via piperidine-catalyzed one-pot three components reaction of aryl aldehyde, malononitrile, and 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate. Our presented process represents the feasibility and diversity of incorporating various moieties with potential bioactivity into polyfunctionalized 4*H*-pyran derivatives, which would be a significant practice for the further synthesis of biologically active molecules.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.065.

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29. *Experimental*: All melting points (mp) were obtained with a Büchi Melting Point B540 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Coupling constants ^{n}J are reported in Hz. High-resolution electron mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (Silica Gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light. All chemicals or reagents were purchased from standard commercial supplies.
30. *General procedure for one-pot syntheses of* **6a**–**n**: To a solution of the appropriate aldehyde (1.2 mmol) in ethanol (15 mL), malononitrile (1.2 mmol) and piperidine (0.12 mmol) were added. The mixture was stirred for 0.5–1.5 h at 35 °C. After Knoevenagel condensation was finished, (monitored by TLC), 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate was added into the reaction mixture, and warmed to reflux for 1–2 min. The solvent was removed under reduced pressure. Then, the rude product was precipitated by adding 5 mL mixture solvent (PE/EA = 3:1). After filtration and drying, the pure compound was obtained.
31. *Typical data for a representative compound. Ethyl 6-amino-5-cyano-2-(2,6-dichloro-5-fluoropyridin-3-yl)-4-p-tolyl-4H-pyran-3-carboxylate* (**6i**): This compound was obtained as white solid following the above method, yield 83%, mp 183.8–185.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, d, J = 7.2 Hz, Py-H), 7.21 (2H, d, J = 8.0 Hz, Ph-H), 7.15 (2H, d, J = 8.0 Hz, Ph-H), 4.74 (2H, s, NH_2), 4.57 (1H, s, *CH*-Ph), 3.85–3.98 (2H, m, CH_2CH_3), 2.33 (3H, s, Ph-Me), 0.95 (3H, t, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.75, 159.88, 157.75, 154.92, 152.31, 149.12, 139.55, 138.66, 137.43, 130.932, 130.36, 129.55, 127.61, 118.34, 62.19, 61.37, 38.75, 21.01, 13.55. HRMS (EI^+): calcd for $C_{21}H_{16}N_3O_3F^{35}Cl_2$ (M^+), 447.0553; found, 447.0553; calcd for $C_{21}H_{16}N_3O_3F^{35}Cl^{37}Cl$ (M^+), 449.0523; found, 449.0540; calcd for $C_{21}H_{16}N_3O_3F^{37}Cl_2$ (M^+), 451.0494; found, 451.0518.