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Highly Efficient Synthesis of Polysubstituted 2-Aminopyrroles via a Multicomponent Domino Reaction

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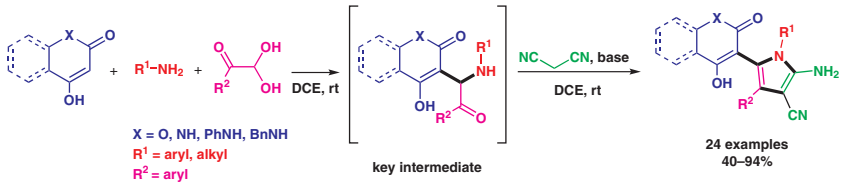

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Abstract A highly efficient approach to polysubstituted 2-aminopyrroles containing a coumarin derivative unit at the 5-position of the pyrrole ring was developed via a novel multicomponent domino reaction of glyoxal monohydrate derivatives, anilines, coumarin derivatives, and malononitrile. This transformation proceeded via an α-aminoketone as the key intermediate.

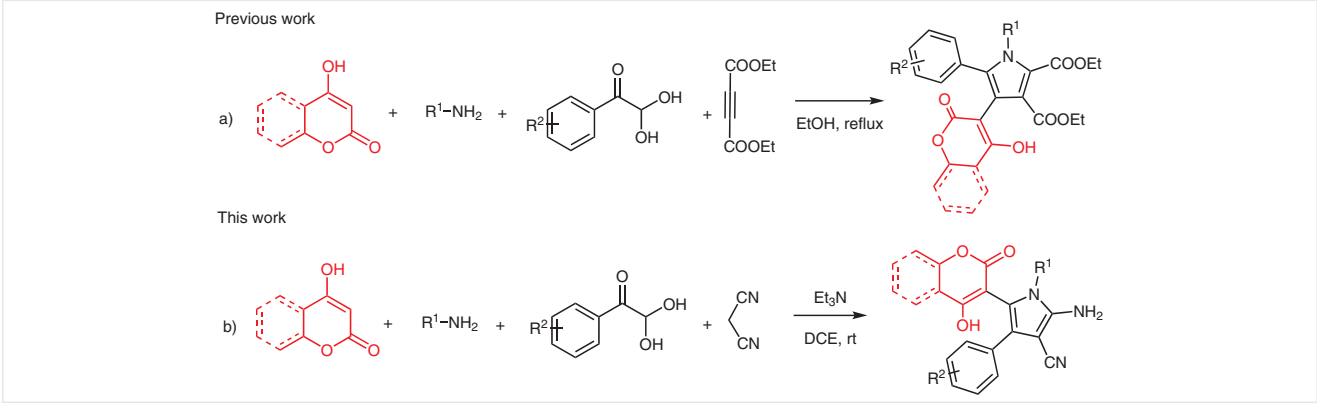
Key words 2-aminopyrroles, domino reaction, multicomponent reaction, coumarin derivatives, heterocycles

On the basis of the dominant skeleton, a rapid and efficient construction of compounds with structural diversity and high functionalization plays an important role in drug discovery.[1] The main goal of molecular diversity construction is to generate diverse small molecules efficiently for high-throughput screening (HTS).[2] One-pot multicomponent reactions (MCRs) were considered as one of the most promising approaches to synthesize a diverse range of functional molecules because it can shorten the reaction time, reduce the separation steps, improve the atom economy, as well as give a relatively higher total chemical yield and efficiency compared with multistep synthesis.[3] Over the past decade, there have been many new three- and four-component reaction methods developed,[4] and it is still meaningful to discover and develop new MCRs.

Diversified and highly functionalized 2-aminopyrrole ring systems are common structural units in many bioactive compounds.[5] They have also been applied as precursors of purine derivatives including pyrrolopyrimidines, pyrrolopyridines, and pyrrolotriazines.[6] Although the classic methods such as Knorr reaction, Paal–Knorr condensation, and Hantzsch reactions have been well established for the preparation of pyrroles,[7] the methods are not readily adaptable to synthesize 2-aminopyrroles. The common strategies to synthesize *N*-substituted 2-aminopyrroles are through the cyclization of α-aminoketones and acetonitrile derivatives,[8] or the reduction of 2-nitro pyrroles.[6c,9] However, these methods are not efficient enough for the synthesis of polysubstituted 2-aminpyrroles with complex motifs. In these regards, developing efficient and facile methods for the construction of highly functionalized 2-aminopyrroles are valuable.

Shi reported a four-component reaction for the synthesis of pyrroles with a coumarin motif at the 4-position in 2013 (Scheme 1, a).[10] We herein describe a facile synthesis of highly functionalized 2-aminopyrrole derivatives through a multicomponent strategy. Different from the previous work, coumarin analogues, which have a broad spectrum of biological activities, can be regioselectively introduced into the 5-position of the 2-aminopyrrole nucleus via our approach (Scheme 1, b).

At the beginning of this study, malononitrile and Et_3N were added into the model reaction after a mixture of *p*-methylphenylglyoxal monohydrate, 4-hydroxycoumarin, and isobutylamine (1:1:1) were stirred for 15 min in a variety of solvents. As showed in Table 1, the reaction proceeded smoothly in all selected solvents, and the results showed that DCE was the most favorable solvent for this reaction. X-ray diffraction revealed that the main product was **2a**. Next, various bases were screened for further optimizing the reaction, and Et_3N gave the best result among the selected bases with a yield of 79% (Table 1, entry 5). After screening different amounts of Et_3N, we found that one equivalent of Et_3N was the most suitable. The yield of **2a** decreased significantly when the model reaction was carried out at 0 °C and 60 °C, respectively. Besides, when the four starting materials were added together at the beginning, the yield of **2a** was decreased to 51% (Table 1, entry 13).

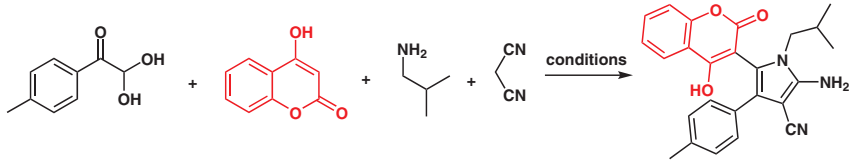


Scheme 1 Synthesis of pyrroles containing a 4-hydroxyl coumarin unit

The yield also decreased slightly in DCM instead of DCE when other condition parameters were the same. Finally, the optimal conditions were determined as using DCE as reaction solvent when one equivalent of Et_3N was added at room temperature.

With the optimized conditions in hand, we next examined the substrate scope of the MCR. First, the scope of amines was examined. Aliphatic primary amines such as isobutylamine (**2a**, Figure 1), *n*-amylamine (**2b**), benzylamine (**2d**), 3-phenylpropan-1-amine (**2e**), and cyclohexylmethanamine (**2f**) were well tolerated under the reaction conditions and afforded the desired products in satisfactory yields.

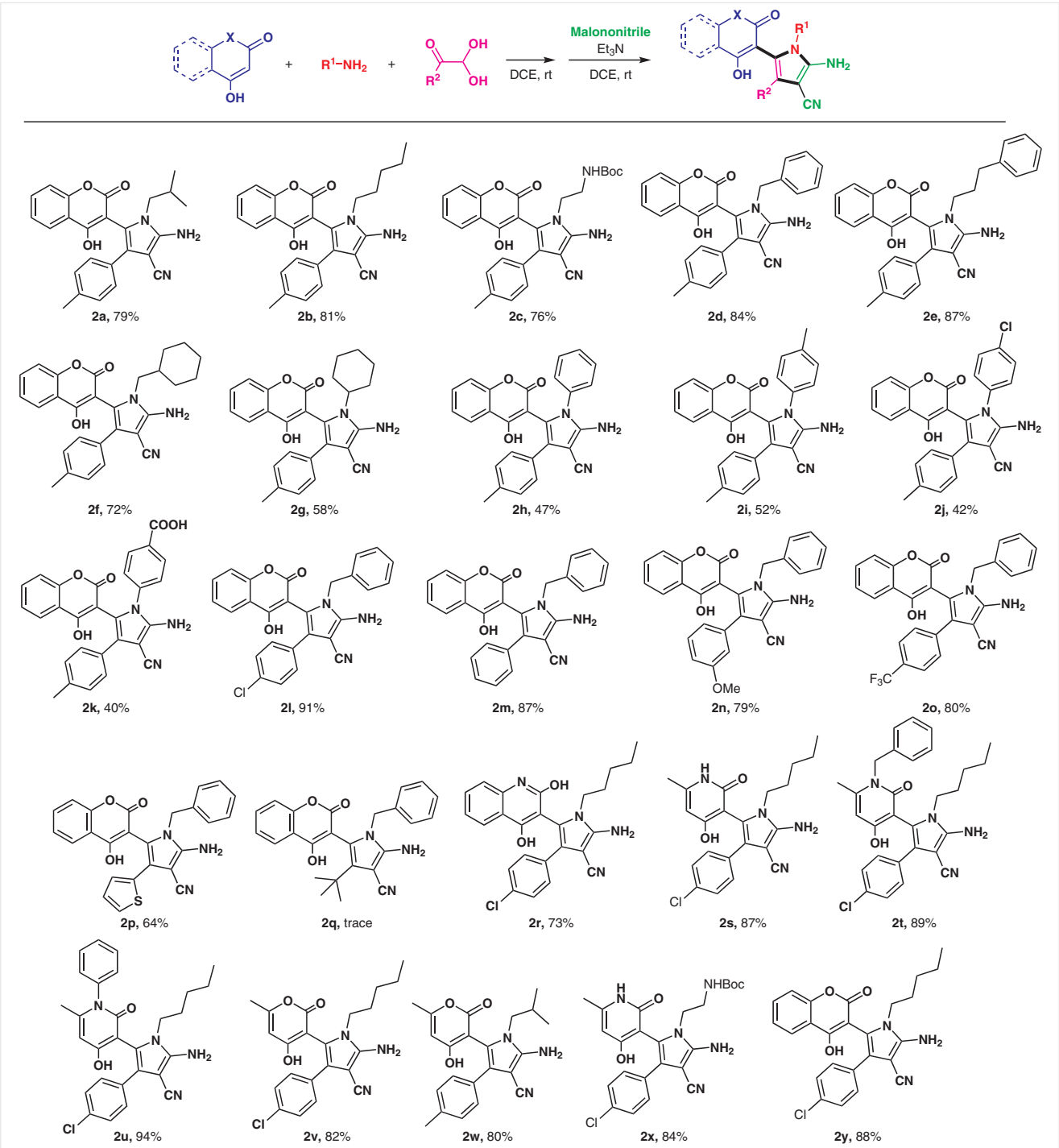
Table 1 Optimization of Reaction Conditions for the Multicomponent Reactions[a]



Entry	Solvents	Base (equiv)	Temp[b]	Yield (%)[c]
1	DMF	Et_3N (1)	rt	72
2	THF	Et_3N (1)	rt	66
3	MeCN	Et_3N (1)	rt	45
4	MeOH	Et_3N (1)	rt	65
5	DCE	Et_3N (1)	rt	79
6	DCE	K_2CO_3 (1)	rt	36
7	DCE	DIEA (1)	rt	74
8	DCE	DBU (1)	rt	64
9	DCE	Et_3N (0.5)	rt	58
10	DCE	Et_3N (1.5)	rt	78
11	DCE	Et_3N (1)	0 °C	14
12	DCE	Et_3N (1)	60 °C	31
13[d]	DCE	Et_3N (1)	rt	51
14	DCM	Et_3N (1)	rt	70

[a] Reaction conditions: *p*-methylphenylglyoxal monohydrate (0.5 mmol, 1.0 equiv), 4-hydroxycoumarin (0.5 mmol, 1.0 equiv), isobutylamine (0.5 mmol, 1.0 equiv), malononitrile (0.5 mmol, 1.0 equiv). Malononitrile and Et_3N were added into the reaction after phenylglyoxal monohydrate, 4-hydroxycoumarin, and isobutylamine were stirred for 15 min. Then the mixture was stirred for another 8 h under N_2.
[b] rt = 25 °C.
[c] Isolated yields are given.
[d] Malononitrile and Et_3N were added together with the other three starting materials at the beginning.

However, the yield decreased significantly when cyclohexanamine (**2g**) was applied under the same reaction conditions. To our delight, aliphatic diamines such as *tert*-butyl(2-aminoethyl)carbamate also performed well in this reaction (**2c** and **2x**). The arylamines led to a large decline in the reaction yields, and the yields of the corresponding



Scheme 2 The substrate scope of the multicomponent reaction.[a–c] [a]*Reagents and conditions*: glyoxal monohydrate derivative (0.5 mmol, 1.0 equiv), coumarin derivative (0.5 mmol, 1.0 equiv), amine (0.5 mmol, 1.0 equiv), malononitrile (0.5 mmol, 1.0 equiv). Malononitrile and Et_3N were added into the reaction after glyoxal monohydrate derivative, coumarin derivative, and amine were stirred for 15 min. Then the mixture was stirred for another 8 h under N_2. [b]Isolated yields are given.[c] rt = 25 °C.

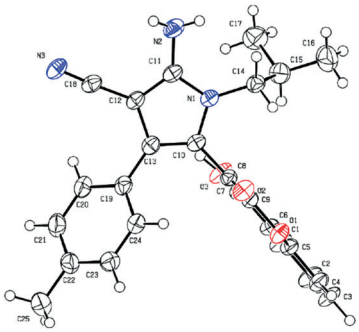


Figure 1 The X-ray crystallography of **2a**[11]

products were even lower when the aniline ring was bearing electron-withdrawing groups (**2h–k**). Phenylglyoxal derivatives with methoxyl, methyl, chloro, and trifluoromethyl on the benzene ring as well as (thiophen-2-yl)glyoxal monohydrate were all well tolerated under the reaction conditions (**2k–p**). It is regrettable that only trace amounts of the desired product were obtained when (*tert*-butyl)glyoxal monohydrate was employed in the reaction **(2q)**. At last, we examined the scope of coumarin derivatives. The results showed that this protocol was efficient with all the tested derivatives such as 4-hydroxycoumarin, 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxy-6-methyl-1-phenypyridin-2(1*H*)-one, 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one, as well as quinoline-2,4-diol, and in all these cases, the yields were up to 94%.

However, when malononitrile was replaced with ethyl cyanoacetate or cyanoacetamide, only traces of the desired products were observed. In all, the new found MCRs depicted in Scheme 2 show that various substituted 2-aminopyrroles can be designed and constructed via the control of the starting materials of glyoxal monohydrate derivatives, coumarin derivatives, and amines.

To gain insight into the reaction mechanism for the formation of **2**, control experiments were subsequently carried out (Scheme 3). A one-pot reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one, *p*-methylphenylglyoxal monohydrate, and isobutylamine provided **2w′** in 98% yield (Scheme 3, a). Compound **2w′** was then separated and characterized by NMR spectroscopy. Finally, the reaction of **2w′** and malononitrile using Et_3N as a base afforded the desired product **2w** in 88% yield (Scheme 3, b).

Based on the above results, a possible mechanism for this domino reaction is proposed in Scheme 4. There are two possible pathways to form α-aminoketone [**B**] as the key intermediate. In pathway a, the glyoxal monohydrate derivative first reacts with the coumarin derivative to form intermediate [**A**]. 1, 4-Michael addition of [**A**] and the amine provides key intermediate [**B**]. Afterwards, intermediate [**B**] is converted into intermediate [**C**] via an intermolecular nucleophilic attack. [**C**] then goes through a Knoevenagel condensation to furnish intermediate [**D**]. Finally, [**D**] tautomerizes to give the desired product **2**. The formation of [**B**] through pathway b cannot be ruled out. In pathway b, key intermediate [**B**] can be obtained by an electrophilic attack of imine [**A′**] that occurs at the 3-position of the coumarin derivative.

In conclusion, we have described a highly efficient and convenient one-pot synthesis of 2-aminopyrrole derivatives via a multicomponent reaction.[12] This domino reaction proceeds smoothly in moderate to good yields under mild reaction conditions and results in ubiquitous structures which contain a coumarin derivative unit at the 5-position of the 2-aminopyrrole ring.

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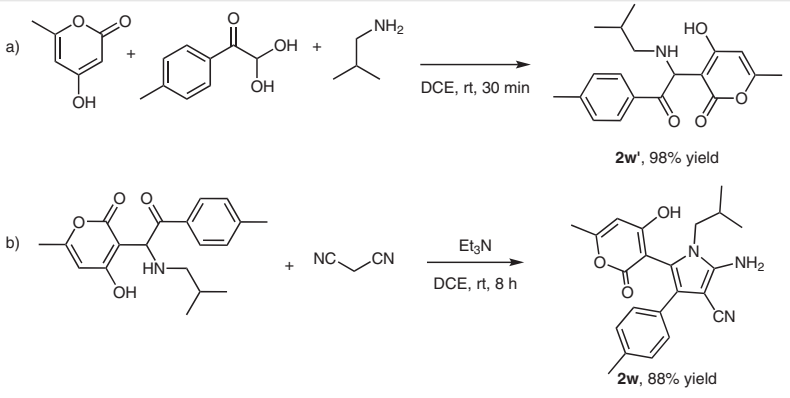
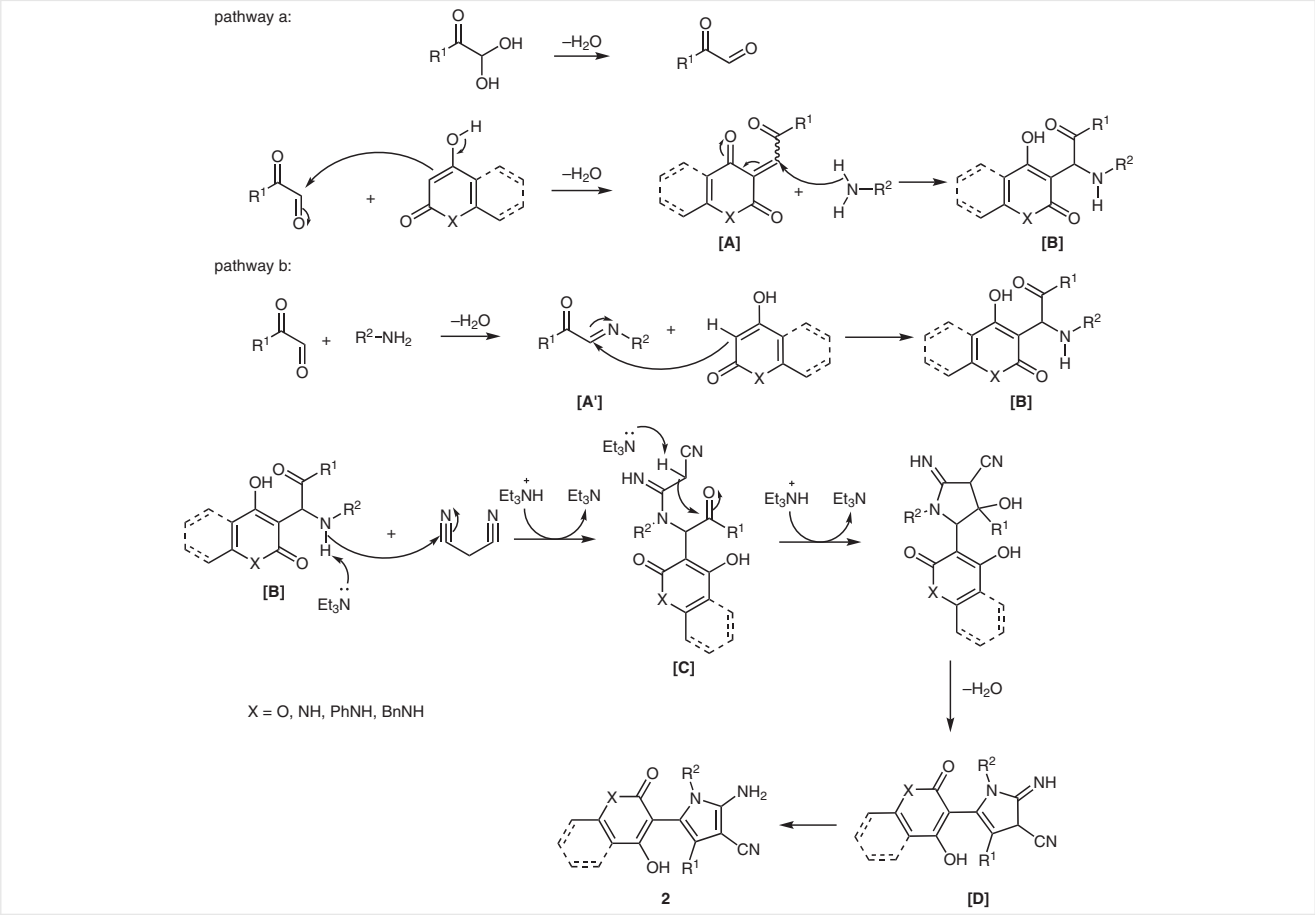


Scheme 3 Control reactions



Scheme 4 Possible mechanism of the "one-pot" multicomponent approach

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591907.

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(11) CCDC 1583386 contains the supplementary crystallographic data for **2a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(12) **General Procedure of 2a–y**

A mixture of glyoxal monohydrate derivative (0.5 mmol, 1.0 equiv), coumarin derivative (0.5 mmol, 1.0 equiv), and amine (0.5 mmol, 1.0 equiv) were stirred in DCE (3 mL) at rt for 15 min. Then, malononitrile (0.5 mmol, 1.0 equiv) and Et_3N (0.5 mmol, 1.0 equiv) were added to the mixture and the reaction was stirred for another 8 h under N_2. After the reaction was complete, the mixture was diluted with DCM (10 mL). The mixture was then washed with H_2O (5 mL). The organic extracts were collected and concentrated. Purification of the crude product was carried out by chromatography (silica gel, MeOH/DCM = 1:30) to afford **2a–y** as the desired products.

2-Amino-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1-isobutyl-4-(*p*-tolyl)-1*H*-pyrrole-3-carbonitrile (2a)

Pale yellow solid, 164 mg, 79% yield; mp 231.7–233.4 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.87 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.68–7.60 (m, 1 H), 7.39–7.31 (m, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 3.45 (qd, *J* = 14.8, 7.6 Hz, 2 H), 2.23 (s, 3 H), 1.91 (dt, *J* = 13.7, 7.0 Hz, 1 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 165.68, 163.96, 153.27, 149.26, 136.23, 132.97, 130.61, 128.50, 127.47, 124.99, 124.16, 123.86, 118.11, 116.20, 115.44, 111.76, 96.18, 72.19, 50.48, 28.70, 19.77, 18.93, 18.78. HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3O_3[M + H]^+$: 414.1812; found: 414.1812.