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Base-Catalyzed and Solvent-Dependent Cascade Reaction in the Regioselective Synthesis of Novel Fused Polycycles

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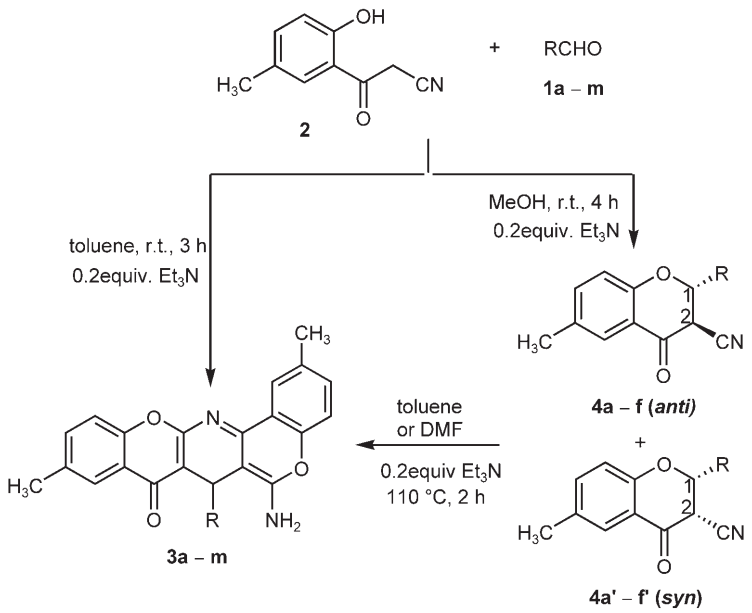
Abstract: A novel base-catalyzed cascade reaction induced by Knoevenegal condensation that can regioselectively generate cyanoflavanones and heavily fused polycycles with intensive fluorescence and high quantum yields is reported. The reaction is solvent-dependent, low-polarity solvents promote the formation of polycycles while high-polarity solvents favor the conversion to cyanoflavanones. A possible mechanism for such serial transformations is proposed.

Keywords: base-catalyzed reactions; cyanoflavanones; domino reactions; Knoevenegal condensation; polycycles; solvent effects

In recent years, there has been great interest in cascade reactions since they involve two or more bond-forming transformations from simple starting materials that take place under the same reaction conditions.[1] This results in an increased synthetic efficiency and ecologically and economically favorable synthesis of compounds with complicated or highly functionazlied chemical structures. Among them, the cascade reactions originating from the Knoevenagel condensation are useful approaches to the constructions of fused heterocycles, like Knoevenagel-hetero-Diels–Alder reactions,[2] Knoevenagel-hydrogenation-Robinson sequences,[3] Knoevenagel-electrocyclization[4] and Knoevenagel-epimerization[5] processes and so on. In order to develop a cascade reaction induced by a Knoevenagel condensation for obtaining some novel fused polycycles, herein we report the triethylamine-catalyzed sythesis of 6-amino-2,10-dimethyl-7-substituted-7*H*-5,13-dioxa-14-azabenzo[*a*] naphthacen-8-ones which exhibit intensive yellow fluorosence and excellent quatum yields. Although these compounds have highly complicated structures with five fused rings, they can be straightforwardly obtained in reasonable to good yields by the reaction of two easily available starting molecules, that is, α-cyano-*o*-hydroxyacetophenone and aldehydes. Moveover, the chemical outcome of the reaction involving the two substrates can be regioselectively controlled by convenient adjustment of the solvent polarity.

For example, when 4-methylbenzaldehyde (**1c**) and 3-(2-hydroxy-5-methylphenyl)-3-oxopropionitrile (**2**) are treated with 0.2 equivalents of triethylamine for 3 h in toluene or 10 h in CH_2Cl_2 at room temperature, polycyclic product **3c** is isolated in 78% or 76% yield, respectively (Scheme 1). However, when the same reaction is executed in MeOH or DMF for 4 h at room temperature, a mixture of the cyanoflavanones **4c/4c′** is generated in, respectively, 91% or 87% yield as the single product instead (Scheme 1). Apparently, the regioselective products of the reaction are solvent-dependent, the polycycle is favorably formed in low-polarity solvents and the cyanoflavanone is preferentially generated in high-polarity solvents. The cases for other tested aldehydes are analogous to that of **1c** when these cascade reactions are performed at room temperature in toluene under the catalysis of 0.2 equivalents of triethylamine (Scheme 1) and the results of the production of polycycles are listed in Table 1. It is notable that the corresponding cyanoflavanones are not detected in the process involving the formation of polycycles.

For all the selected aldehydes **1a–m**, the reactions to produce polycycles **3a–m** smoothly occur at room temperature and the isolation of products can be readily accomplished by simple filtration and washing rather than a prolonged chromatography method. Additionally, they display observable high bond-forming efficiency and atom economy, since six new bonds are simultaneously generated and only two molecules of water are eliminated in just a one-pot procedure. Both electronic and vicinal effects exist in these reactions. For example, it is difficult for *m*-nitrobenzaldehyde to accomplish the serial bond-forming process, the corresponding polycycle cannot be obtained.



Scheme 1.

Table 1. Triethylamine-catalyzed cascade synthesis of polycycles **3a–m** in toluene at room temperature.

Entry	Product	R	Yield [%][a]	Quantum yield [Φ_F][b]
1	**3a**	C_6H_5	72	0.823
2	**3b**	4-$CH_3OC_6H_4$	85	0.840
3	**3c**	4-$CH_3C_6H_4$	78	0.826
4	**3d**	4-FC_6H_4	58	0.826
5	**3e**	4-BrC_6H_4	71	0.836
6	**3f**	4-ClC_6H_4	68	0.836
7	**3g**	2-ClC_6H_4	47	0.845
8	**3h**	2-$C_2H_5OC_6H_4$	61	0.844
9	**3i**	4-$(CH_3)_2NC_6H_4$	79	0.874
10	**3j**	3,4-$OCH_2OC_6H_3$	80	0.846
11	**3k**	3-CH_3O-4-$C_2H_5OC_6H_3$	84	0.874
12	**3l**	2,4-$Cl_2C_6H_3$	49	0.861
13	**3m**	PhCH=CH	41	0.832

[a] Isolated yields referred to **2**.
[b] Using naphthacence ($\Phi_F = 0.6$, $\lambda_{ex} = 443$ nm) as a standard in THF.

Compounds **3a–m** are molecules with intensively yellow fluorescence and outstandingly high quantum yields in solutions. All the polycycles display analogous excitation and emission spectra, with their excitation wavelengths around 440 nm and emission peaks about 510 nm. A typical fluorescent excitation and emission spectrum of sample **3c** is displayed in Figure 1. The molecular structures of polycycles were determined by X-ray crystallography, as shown for the example **3b** (Figure 2).

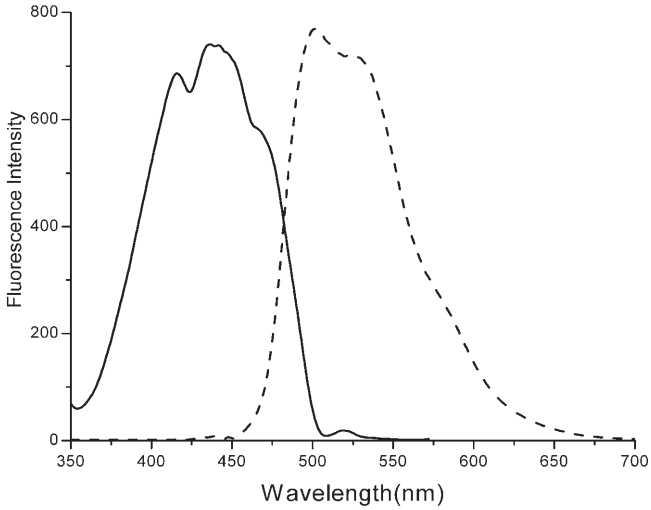


Figure 1. Fluorescence excitation (solid line) and emission (dotted line) spectra of **3c** in THF (2 μM) solution .

The flavanone structure is abundant in natual products that possess a broad array of biological activities.[6] Surprisingly, there has been no report in the literature about the preparation of 3-cyanoflavanones, herein we describe an effective and convenient approach to these compounds *via* a base-catalyzed cascade reaction of aldehyde and 3-(2-hydroxyl-5-methylphenyl)-3-oxopropionitrile (**2**) at room temperature in high-polarity solvents like methanol (Scheme 1) and the results are given in Table 2. It is found that cyanoflavanones can be obtained as the single products in good yields from the respective transformations of the screened aldehydes **1a–f**. Importantly, 3-

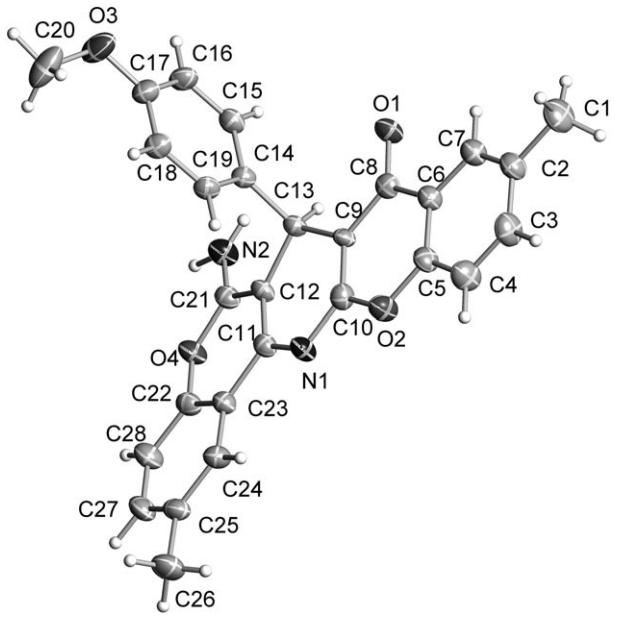


Figure 2. The molecular structure of structure of **3b**.

Table 2. Triethylamine-catalyzed preparation for the mixtures of **4a–f/4a′–f′** in methanol.

Entry	Product	R	Yield [%][a]	Ratio[b] of **4**	**4′**
1	**4a**	C_6H_5	86	88	12
2	**4b**	4-$CH_3OC_6H_4$	95	~100	–
3	**4c**	4-$CH_3C_6H_4$	91	92	8
4	**4d**	4-FC_6H_4	78	~100	–
5	**4e**	4-BrC_6H_4	83	72	28
6	**4f**	3-$O_2NC_6H_4$	74	72	28

[a] Isolated yield referred to **2**.
[b] Ratio determined on ^{1}H NMR.

nitrobenzaldehyde is also an efficient substrate to generate the corresponding cyanoflavanone in good yield (entry f). Unfortunately, these cyanoflavanones are mixtures containing two diastereomers which cannot be independently isolated by silica gel chromatography. The distribution of the two diastereomers in their mixture can be determined by ^{1}H NMR integrals, while *syn* and *anti* conformations are assigned from J_{H1-H2}. It is attractive that an outstanding stereoselectivity of *anti* addition is achieved in our reactions in the presence of a non-chiral catalyst like triethylamine. In a similar case, however, the highly stereoselective *anti* addition has to be accomplished with the aid of a complicated chiral base.[7]

It is interesting to find that the isolated cyano flavanones **4a–e/4a′–e′** can be converted to the corresponding polycycles **3a–e** under heating at 110 °C in either toluene or DMF under catalysis of 0.2 equivalents of

Table 3. Transformatons of **4a–e/4a′–e′** mixtures into **3a–e** on catalysis of Et_3N under heating.

Entry	Product[a]	R	Yield [%][b]	Yield [%][c]
1	**3a**	C_6H_5	83	80
2	**3b**	4-$CH_3C_6H_5$	86	82
3	**3c**	4-$CH_3OC_6H_5$	90	91
4	**3d**	4-FC_6H_5	72	74
5	**3e**	4-BrC_6H_5	87	82

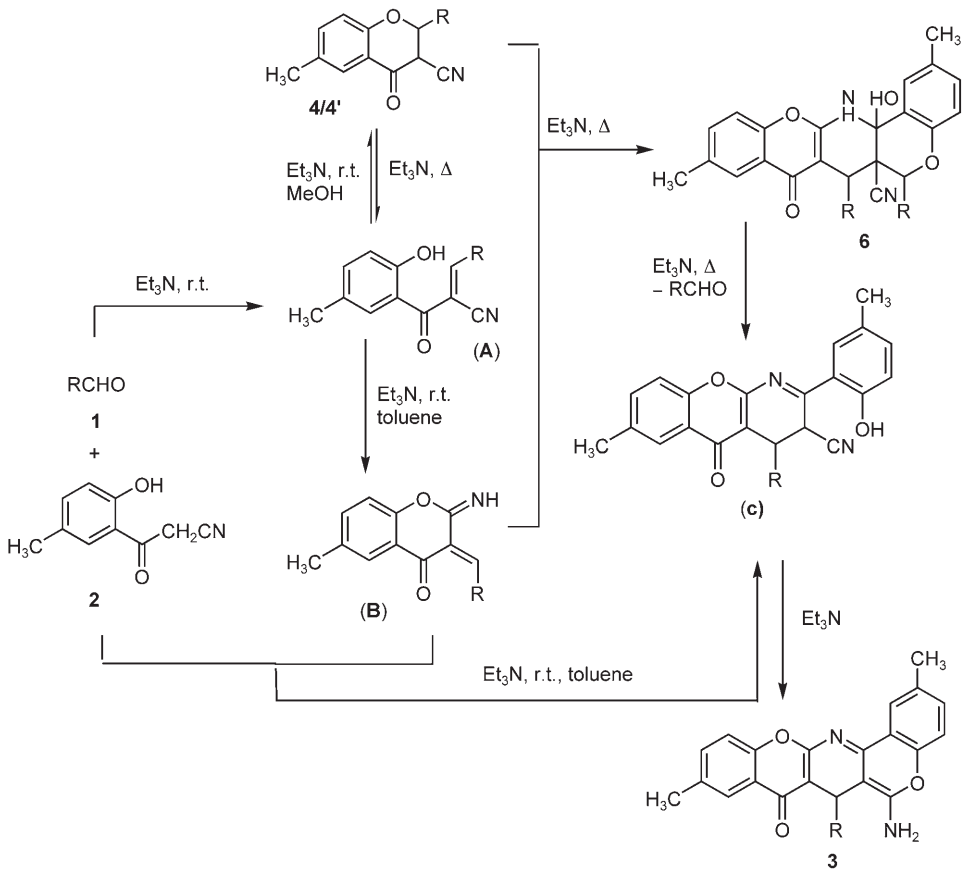
[a] Isolated yields referred to **4/4′**.
[b] Yields in toluene.
[c] Yields in DMF.

Et_3N (Scheme 1) and the results are listed in Table 3. Notably, 4**f/4f′** is unable to undergo such a conversion. When the transformation is executed for just 10 min and quenched by 0.1 N HCl aqueous solution, the intermediates **6b** and **6c** are obtained in 51% and 42% yields as white solids, and their structures are determined by various NMR experiments (^{1}H, ^{13}C, DEPT135°, H-D exchange in D_2O, HMBC and HMQC) and confirmed by IR and MS analysis. The separated intermediates **6b** and **6c** cannot be transformed to the polycycles

Compounds **3b** and **3c** are stable unless they are treated with triethylamine under heating. Also, the intermediates **6b** and **6c** are unable to be trapped in the reactions of aldehydes **1b** and **1c** with **2** in toluene at room temperature.

A possible mechanism is presented in Scheme 2. The intermediate **A** derived from a Knoevenagel condensation goes through either of the solvent-dependent routes to form cyanoflavanone in high-polarity solvents or the intermediate **B** in low-polarity solvents when **1** and **2** react at room temperature. Therefore, the further reaction will take place between **B** and unreacted **2** to provide the precursor **C** which subsequently undergoes an intramolecular nucleophilic addition followed by the final formation of polycycle **3**. It seems that the cyanoflavanone can be reversibly reverted back to **A** under heating, which is further converted to **B** at the increased temperature. Hence, the isolated **4/4′** can be transformed to **3** through a base-catalyzed elimination of aldehyde from the intermediate **6**.

In summary, we describe a novel Knoevenagel condensation-induced cascade reaction for the solvent-dependent synthesis of new compounds with nice polycylic structures. This cascade sequence exhibits a high bond-forming efficiency, stereoselectivity, regioselectivity as well as facile operation and good yields. Further research on the application of this protocol to develop new fluorescent materials and using cyanoflavanones as building blocks in the synthesis of natural products will be reported in due course.



Scheme 2.

Experimental Section

General Procedure for 6-Amino-2,10-dimethyl-7-substituted-7*H*-5,13-dioxa-14-azabenzo[*a*]naphthacen-8-ones 3

At room temperature, Et_3N (0.2 mmol) is added to a solution of 3-(2-hydroxy-5-methylphenyl)-3-oxopropionitrile (1 mmol) and aldehyde (1 mmol) in toluene (5 mL) and the resultant solution is stirred for 3 h. A yellow precipitate is gradually generated. After filtration, the solid is washed with some ether and ethyl acetate. The dried solid **3** is pure enough for spectral analysis.

6-Amino-2,10-dimethyl-7-(4-methylphenyl)-7*H*-5,13-dioxa-14-azabenzo[*a*]naphthacen-8-one (3c): Yield: 78%; yellow solid; mp 231–233 °C; FT-IR (KBr): ν = 3400, 1616, 1556, 1496, 1384, 1263, 813 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3H), 2.36 (s, 3H), 2.45 (s, 3H), 5.42 (s, 1H), 6.96 (d, J = 8.0 Hz, 2H), 7.30 (dd, J = 8.0, 14.4 Hz, 3H), 7.39–7.50 (m, 3H), 7.67 (s, 1H), 8.12 (s, 1H), 8.36 (bs, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.38, 20.47, 20.51, 34.16, 92.60, 101.18, 116.06, 117.19, 119.40, 123.28, 124.04, 124.69, 127.21, 128.38, 133.12, 133.36, 134.66, 135.22, 143.02, 149.30, 152.08, 156.69, 160.93, 164.22, 174.02; EI-MS (70 eV): *m/z* (%) = 434 (M^+, 88), 343($M^+-CH_3C_6H_4$, 100), 217 (14), 91 (7); anal. calcd. for $C_{28}H_{22}N_2O_3$: C 77.38, H 5.11, N, 6.45; found: C 77.45, H 5.13, N 6.38%.

6-Amino-2,10-dimethyl-7-(4-*N,N*-dimethylaminophenyl)-7*H*-5,13-dioxa-14-azabenzo[*a*]naphthacen-8-one (3i): Yield: 79%; yellow solid; mp 252–254 °C; FT-IR (KBr): ν = 3431, 1637, 1557, 1498, 1384, 1265, 814 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H), 2.43 (s, 3H), 2.73 (s, 6H), 5.30 (s, 1H), 6.50 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.36–7.46 (m, 3H), 7.65 (s, 1H), 8.10 (s, 1H), 8.24 (bs, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.88, 20.96, 34.02, 40.66, 93.62, 102.07, 112.53, 116.50, 117.65, 119.99, 123.85, 124.51, 125.15, 128.31, 133.43, 133.50, 133.65, 134.85, 135.07, 149.55, 149.76, 152.57, 156.83, 161.41, 164.55, 174.56; EI-MS (70eV): *m/z* (%) = 463 (M^+, 27), 343 [$M^+-(CH_3)_2NC_6H_4$, 100], 120 (39), 105 (51), 91 (51), 77 (76), 65 (23), 51 (27); anal. calcd. for $C_{29}H_{25}N_3O_3$: C 75.13, H 5.44, N 9.07; found: C 75.08, H 5.41, N 9.14%.

General Procedure for 6-Methyl-4-oxo-2-(4-aryl)-3,4-dihydro-2*H*-chromene-3-carbonitriles 4/4′

At room temperature, Et_3N (0.2 mmol) is added to the solution of 3-(2-hydroxy-5-methylphenyl)-3-oxopropanenitrile (1 mmol) and aldehyde (1.2 mmol) in methanol (5 mL), the resultant mixture is stirred for 4 h and then quenched by 0.1 N HCl aqueous solution. The solution is poured into water and extracted by EtOAc for two times. The combined organic layers are dried over anhydrous Na_2SO_4 and the solvent is removed under the reduced pressure. The residue is isolated on a silica gel column chromatography using petroleum/ethyl acetate (3:1) as the eluent to afford the mixture of **4/4′** in good yields.

6-Methyl-4-oxo-2-(4-methoxylphenyl)-3,4-dihydro-2*H*-chromene-3-carbonitrile (4b/4b′): Yield: 95%; white solid: FT-IR (KBr): $\nu = 3004$, 2889, 2261, 1702, 1615, 1488, 1293, 1248, 1130, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 3.82 (s, 3H), 4.14 (d, $J = 12.4$ Hz, 1H), 5.40 (d, $J = 12.0$ Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.45$, 47.40, 55.41, 80.62, 113.39, 114.50, 118.07, 118.39, 127.36, 127.41, 128.40, 132.48, 138.60, 158.94, 160.86, 182.94; EI-MS (70 eV): *m/z* (%) = 292 ($M^+ - 1$, 100), 278 (15), 159 (32), 134 (70), 107 (11), 77 (23); anal. calcd. for $C_{18}H_{15}NO_3$: C 73.69, H 5.16, N 4.78; found: C 73.55, H 5.11, N 4.83%.

6-Methyl-4-oxo-2-(4-fluorophenyl)-3,4-dihydro-2*H*-chromene-3-carbonitrile (4d): Yield: 78%; white solid; FT-IR (KBr): $\nu = 2259$, 1707, 1615, 1515, 1489, 1298, 845, 833 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H), 4.10 (d, $J = 12.4$ Hz, 1H), 5.45 (d, $J = 12.4$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 7.19 (t, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.56 (dd, $J = 5.6$, 8.0 Hz, 2H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.48$, 47.53, 80.17, 113.18, 116.48 (d, $^2J_{CF} = 21$ Hz), 118.02, 118.34, 127.43, 128.90 (d, $^3J_{CF} = 9$ Hz), 131.26, 132,78, 136.75, 158.69, 163.54 (d, $^1J_{CF} = 248$ Hz), 182.46; EI-MS (70 eV): *m/z* (%) = 280($M^+ - 1$, 94), 134 (100), 106 (46), 78 (38), 51 (18); anal. calcd. for $C_{17}H_{12}FNO_2$: C 72.57, H 4.30, N 4.98; found: C 72.51, H 4.33; N 4.95%.

Acknowledgements

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