# Selective Synthesis of Cyano-Functionalized 2-Aryl-4*H*-chromenes and 2-Amino-4*H*-chromene-3-carbonitriles by Catalyst-Tuned Reactions of 2-Hydroxychalcones with 2-Substituted Acetonitriles

Guodong Yin,* Houqiang Shi, Liqianyun Xu, Xianhong Wei, Qing Tao

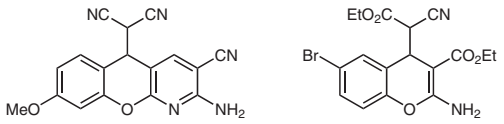
Hubei Key Laboratory of Pollutant Analysis and Reuse Technology, College of Chemistry and Environmental Engineering, Hubei Normal University, Huangshi 435002, P. R. of China
Fax +86(714)6515602; E-mail: gdyin@hbnu.edu.cn

*Received: 24.10.2012; Accepted after revision: 03.12.2012*

**Abstract:** A selective synthesis of 4*H*-chromenes by the reactions of 2-hydroxychalcone derivatives with acetonitriles substituted with electron-withdrawing groups is described. Under catalyst-free conditions, the reactions give cyano-functionalized 2-aryl-4*H*-chromenes, whereas in the presence of sodium bicarbonate, 2-amino-4*H*-chromene-3-carbonitriles are obtained in excellent yields.

**Key words:** heterocycles, nitriles, catalysis, chromenes

Chromenes are common structural motifs in a number of biologically active and natural compounds.[1] Among the various kinds of chromene systems, 4*H*-chromenes carrying dicyanomethyl or cyano(ethoxycarbonyl)methyl substituents at the 4-position are of particular interest. For example, the cyano-functionalized chromeno[2,3-*b*]pyridine **1** inhibits mitogen-activated protein kinase-activated protein kinase 2 (MK-2) and suppress the expression of tumor necrosis factor-α (TNF-α) in U937 cells.[2] The tumor antagonist HA14-1 **2** and related compounds exhibit binding activity to the surface pocket of cancer-implicated Bcl-2 protein and induce apoptosis or programmed cell death in follicular lymphoma B cells and leukemia HL-60 cells.[3]




**1** MK-2 inhibitor

**2** Bcl-2 protein inhibitor

**Figure 1** Examples of biologically active cyano-functionalized 4*H*-chromenes

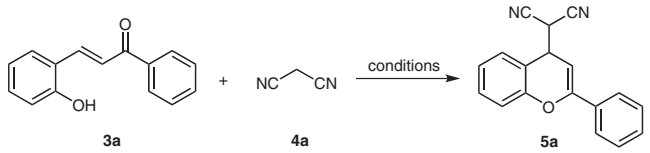
Acetonitrile derivatives carrying electron-withdrawing substituents, such as malononitrile, (phenylsulfonyl)acetonitrile, ethyl cyanoacetate, or methyl cyanoacetate are important building blocks in organic synthesis because of the presence of active methylene and cyano functional groups. Recently, such substituted acetonitriles have been widely used in the synthesis of 2-amino-4*H*-chromene scaffolds by means of sequential Knoevenagel condensation, Michael addition, and intramolecular cyclization reactions.[4–7] However, in most reported reactions, the cyano group is converted through intramolecular cyclization into an imine moiety that subsequently isomerizes to give an amino group. In a continuation of our efforts to develop new synthetic protocols for constructing heterocyclic frameworks,[8] we report an efficient reaction of 2-hydroxychalcones with substituted acetonitriles under catalyst-free conditions to give novel cyano-functionalized 2-aryl-4*H*-chromenes, and in the presence of a base to give 2-amino-4*H*-chromene-3-carbonitriles as the major products.

Initially, we examined the reaction of 2-hydroxychalcone (**3a**) with malononitrile (**4a**) to give (2-phenyl-4*H*-chromen-4-yl)malononitrile (**5a**) in various solvents under catalyst-free conditions. Our preliminary experiment showed that the reaction gave low yields of **5a** in methanol or ethanol (Table 1, entries 1 and 2), whereas the product was obtained in moderate-to-good yields (40–75%) in propan-1-ol, *tert*-butyl alcohol, tetrahydrofuran, acetonitrile, 1,2-dichloroethane, or benzene (entries 3–8). No reactions occurred in *N*,*N*-dimethylformamide (entry 9) or dimethyl sulfoxide (entry 10), even at 110 °C. However, to our delight, the reaction proceeded smoothly in refluxing toluene, giving the product **5a** in 85% yield after 8 h (entry 11). Extending the reaction time did not significantly improve the yield (entry 12), whereas decreasing the reaction temperature resulted in a low yield of **5a** (entry 13).

Having determined the optimal conditions (toluene, reflux, 8 h), we then examined the reactions of a variety of 2-hydroxychalcone derivatives with malononitrile to establish the scope of the transformation. The results are summarized in Table 2. We observed that substrates in which $R^1$ = H and $R^2$ was a phenyl ring optionally bearing an electron-donating (methoxy) or an electron-withdrawing substituent (chloro or fluoro) reacted smoothly to give the corresponding products **5b–d** in excellent yields (85–90%) (Table 2, entries 2–4). The corresponding hetaryl-group substituted substrates in which $R^2$ was a 2-furyl or 2-thienyl group were also suitable substrates for the reactions and gave the corresponding products **5e** and **5f** in 83% and 80% yield, respectively (entries 5 and 6). However, when $R^2$ was a methyl group, the expected product **5g** was not detected (entry 7). Substrates in which $R^1$ was a chloro group gave the corresponding products **5h** and **5i**

**SYNTHESIS** 2013, 45, 0334–0340
Advanced online publication: 03.01.2013
DOI: 10.1055/s-0032-1317945; Art ID: SS-2012-F0837-OP

**Table 1** Optimization of Reaction Conditions for the Synthesis of **5a**




**3a** **4a** **5a**

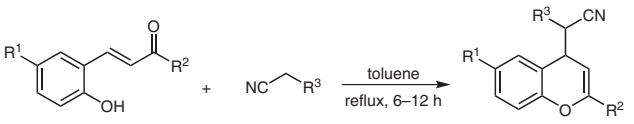
| Entry[a] | Solvent | Temp (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | MeOH | reflux | 12 | < 5 |
| 2 | EtOH | reflux | 12 | 10 |
| 3 | PrOH | reflux | 12 | 45 |
| 4 | *t*-BuOH | reflux | 12 | 75 |
| 5 | THF | reflux | 12 | 52 |
| 6 | MeCN | reflux | 12 | 69 |
| 7 | DCE | reflux | 12 | 40 |
| 8 | benzene | reflux | 12 | 74 |
| 9 | DMF | 110 | 8 | 0 |
| 10 | DMSO | 110 | 8 | 0 |
| 11 | PhMe | reflux | 8 | 85 |
| 12 | PhMe | 80 | 8 | 76 |
| 13 | PhMe | 50 | 8 | 40 |

[a] All reactions were performed with **3a** (0.5 mmol) and **4a** (0.5 mmol) in the appropriate solvent (3 mL).
[b] Isolated yield.

in 80% and 81% yield, respectively (entries 8 and 9). Because the phenylsulfonyl group is present in many biologically and pharmacologically active compounds,[9–11] we also examined the reactions of 2-(phenylsulfonyl)acetonitrile with 2-hydroxychalcones, and we obtained the corresponding products **5j–o** in 79–86% overall yields (entries 10–15). $^1$H NMR spectroscopy showed that these products consisted of mixtures of two diastereoisomers in an approximate molar ratio of 5:1. Similarly, treatment of ethyl cyanoacetate or methyl cyanoacetate with 2-hydroxychalcones gave the corresponding products **5p–r** in 82–85% yields (entries 16–18); the approximate molar ratios of the two diastereoisomers were 3:1 ($R^3 = CO_2Et$) or 2:1 ($R^3 = CO_2Me$), respectively.

From thermodynamic considerations and by comparison with data reported in the literature,[12,13] the structure of the major diastereoisomers of **5j–r** is likely to have an *erythro* configuration (Figure 2). The *erythro* configuration of **5o** was confirmed by X-ray crystallographic analysis (Figure 3).[14] It is important to note that single diastereoisomers of **5j–r** can be obtained by crystallization of the mixtures from hexane.

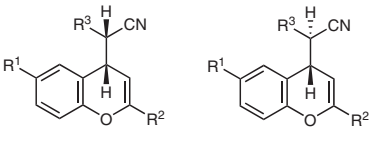
**Table 2** Synthesis of Novel Cyano-Functionalized 2-Aryl-4*H*-chromenes **5** under Catalyst-Free Conditions




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

| Entry[a] | $R_1$ | $R_2$ | $R_3$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | Ph | CN | **5a** | 85 |
| 2 | H | 4-$MeOC_6H_4$ | CN | **5b** | 88 |
| 3 | H | 4-$ClC_6H_4$ | CN | **5c** | 90 |
| 4 | H | 4-$FC_6H_4$ | CN | **5d** | 85 |
| 5 | H | 2-furyl | CN | **5e** | 83 |
| 6 | H | 2-thienyl | CN | **5f** | 80 |
| 7 | H | Me | CN | **5g** | –[c] |
| 8 | Cl | Ph | CN | **5h** | 80 |
| 9 | Cl | 4-$FC_6H_4$ | CN | **5i** | 81 |
| 10 | H | Ph | $SO_2Ph$ | **5j** | 82 (5:1) |
| 11 | H | 4-$MeOC_6H_4$ | $SO_2Ph$ | **5k** | 85 (5:1) |
| 12 | H | 4-$ClC_6H_4$ | $SO_2Ph$ | **5l** | 81 (5:1) |
| 13 | H | 4-$FC_6H_4$ | $SO_2Ph$ | **5m** | 79 (5:1) |
| 14 | H | 2-furyl | $SO_2Ph$ | **5n** | 85 (5:1) |
| 15 | H | 2-thienyl | $SO_2Ph$ | **5o** | 86 (5:1) |
| 16 | H | Ph | $CO_2Et$ | **5p** | 84 (3:1) |
| 17 | H | 4-$FC_6H_4$ | $CO_2Et$ | **5q** | 85 (3:1) |
| 18 | H | Ph | $CO_2Me$ | **5r** | 82 (2:1) |

[a] All reactions were performed with **3** (0.5 mmol) and **4** (0.5 mmol) in toluene (3 mL).
[b] Isolated yield; ratios of diastereoisomers (in parentheses) were calculated from $^1$H NMR analyses.
[c] None of the expected product was obtained.




(*S*,*R*)*-**5j–r** (*R*,*R*)*-**5j–r**
*erythro* *threo*

**Figure 2** Proposed configuration of *erythro*- and *threo*-diastereoisomers of **5j–r**

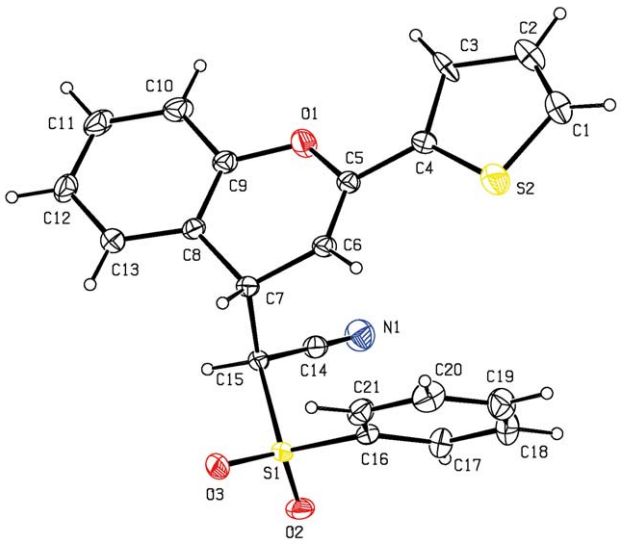
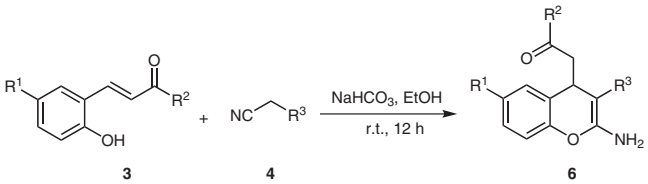



**Figure 3** X-ray structure of compound **5o**

It has been reported[4] that substituted acetonitriles can be used to synthesize 2-amino-4*H*-chromene-3-carbonitriles in the presence of a base. We therefore examined the reaction of 2-hydroxychalcone (**3a**) with malononitrile (**4a**) under similar conditions to those reported in the literature.[4a,11,15] By screening several bases (sodium carbonate, sodium bicarbonate, and triethylamine) and several solvents (toluene, acetonitrile, ethanol, and *N*,*N*-dimethylformamide), we found that the reaction in anhydrous ethanol for 12 hours at room temperature in the presence of sodium bicarbonate as the base gave 2-amino-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carbonitrile (**6a**)[15a] in 96% yield (Table 3, entry 1). Product **5a** was not formed under these conditions. Two representative substrates (2*E*)-1-(4-fluorophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one and (2*E*)-1-(2-furyl)-3-(2-hydroxyphenyl)prop-2-en-1-one gave the corresponding products **6d** and **6e** in 89% and 94% yield, respectively (entries 2 and 3). However, when 2-phenylsulfonyl acetonitrile was used, no reaction occurred, probably as a result of steric hindrance by the phenylsulfonyl group (entry 4).

A possible mechanism for these reactions was proposed, taking 2-hydroxychalcone (**3a**) as an example (Scheme 1). First, chalcone **3a** reacts with malononitrile (**4a**) through a Michael addition reaction to form intermediate **I** (step i).[16] This intermediate is converted into intermediate **II** by an intramolecular cyclization reaction (step ii).[17] The expected product **5a** is then obtained by elimination of water from intermediate **II** (step iii). In the presence of base, however, **I** can instead be easily converted into the anionic intermediate **III** (step iv). Because of the lower degree of steric hindrance, the anion attacks the carbon atom of the cyano group to form an imine, which isomerizes to form the 4-substituted 2-amino-4*H*-chromene-3-carbonitrile **6a** (step v).[4a,15a]

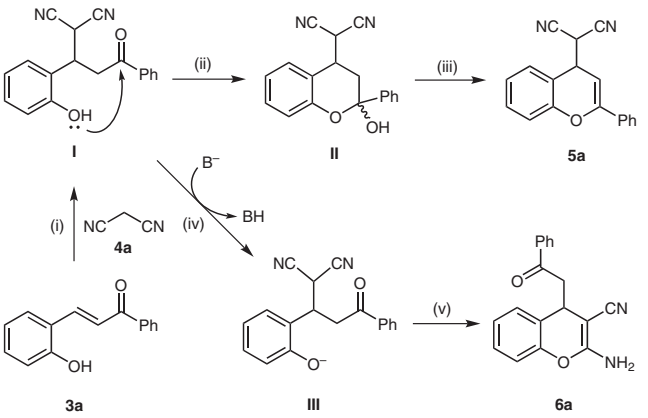
**Table 3** Synthesis of 2-Amino-4*H*-chromene-3-carbonitriles **6** in the Presence of Sodium Bicarbonate




3 4 6

| Entry[a] | $R^1$ | $R^2$ | $R^3$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | Ph | CN | **6a** | 96 |
| 2 | H | 4-$FC_6H_4$ | CN | **6d** | 89 |
| 3 | H | 2-furyl | CN | **6e** | 94 |
| 4 | H | Ph | $SO_2Ph$ | **6j** | –[c] |

[a] All reactions were performed with **3** (0.5 mmol), **4** (0.5 mmol), and $NaHCO_3$ (0.5 mmol) in EtOH (3 mL) at r.t.
[b] Isolated yield.
[c] No reaction occurred.




**Scheme 1** A possible mechanism for the reactions

In summary, we have developed a method for the selective synthesis of 4*H*-chromenes by the reaction of 2-hydroxychalcone derivatives with substituted acetonitriles. Under catalyst-free conditions, the reactions give the corresponding cyano-functionalized 2-aryl-4*H*-chromenes **5**, whereas in the presence of sodium bicarbonate, the corresponding 2-amino-4*H*-chromene-3-carbonitriles **6** are obtained in excellent yields at room temperature. Because the starting materials are easily accessible and the reactions give good yields, this new synthetic approach has potential applications in the synthesis of various functionalized 4*H*-chromenes, which are of considerable interest as potential biologically active compounds or pharmaceuticals.



All chemicals were obtained from commercial sources and used without further purification. All organic solvents were dried and freshly distilled before use. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AV 300-MHz spectrometers with $CDCl_3$ as the solvent. Chemical shifts are reported relative to TMS as internal standard. High-resolution mass spectra (ESI) were recorded on Bruker micrOTOF-QII. IR spectra were obtained as KBr pellet samples on a Nicolet 5700 FTIR spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh). The X-ray crystal structure determination for compound **5o** was performed on a Bruker SMART APEX CCD system.

**2-Aryl-4*H*-chromenes 5; General Procedure**

A mixture of chalcone **3** (0.5 mmol) and the appropriate substituted acetonitrile **4** (0.5 mmol) in anhyd toluene (3 mL) was refluxed until the chalcone disappeared (TLC; 6–12 h). The mixture was then cooled to r.t. and purified directly by column chromatography (silica gel, PE then PE–EtOAc) to give a yellow solid. Single diastereoisomers of **5j**–**r** were prepared by crystallization of the mixtures from hexane. Characterization data for **5j**–**r** are for the single diastereoisomers.

**(2-Phenyl-4*H*-chromen-4-yl)malononitrile (5a)**

Yellow solid; yield: 116 mg (85%); mp 116–117 °C.

IR (KBr): 759, 918, 1007, 1232, 1391, 1489, 1653, 2256, 2923 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.86 (d, *J* = 5.3 Hz, 1 H), 4.35–4.39 (m, 1 H), 5.67 (d, *J* = 5.1 Hz, 1 H), 7.17–7.25 (m, 2 H), 7.33–7.46 (m, 5 H), 7.74–7.77 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.4, 38.1, 92.1, 111.3, 111.6, 116.2, 117.7, 124.7, 125.3, 128.3, 128.5, 129.8, 130.2, 132.7, 151.9, 153.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{12}N_2NaO$: 295.0842; found: 295.0845.

**[2-(4-Methoxyphenyl)-4*H*-chromen-4-yl]malononitrile (5b)**

Yellow solid; yield: 133 mg (88%); mp 128–129 °C.

IR (KBr): 805, 1032, 1247, 1301, 1506, 1616, 1659, 2235, 2926 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.81 (d, *J* = 5.2 Hz, 1 H), 3.83 (s, 3 H), 4.32–4.35 (m, 1 H), 5.54 (d, *J* = 5.0 Hz, 1 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 7.16–7.25 (m, 2 H), 7.32–7.41 (m, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.4, 38.1, 55.4, 90.3, 111.4, 111.7, 113.9, 116.4, 117.6, 124.6, 125.2, 126.8, 128.3, 130.1, 152.0, 153.6, 160.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{14}N_2NaO_2$: 325.0947; found: 325.0953.

**[2-(4-Chlorophenyl)-4*H*-chromen-4-yl]malononitrile (5c)**

Yellow solid; yield: 138 mg (90%); mp 129–130 °C.

IR (KBr): 766, 1014, 1225, 1457, 1662, 2258, 2926 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.81 (d, *J* = 5.3 Hz, 1 H), 4.37–4.40 (m, 1 H), 5.66 (d, *J* = 5.1 Hz, 1 H), 7.19–7.26 (m, 2 H), 7.33–7.43 (m, 4 H), 7.70 (d, *J* = 8.6 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.4, 38.0, 92.3, 111.2, 111.5, 116.0, 117.7, 124.9, 126.6, 128.3, 128.8, 130.3, 131.1, 135.8, 151.8, 152.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{11}ClN_2NaO$: 329.0452; found: 329.0455.

**[2-(4-Fluorophenyl)-4*H*-chromen-4-yl]malononitrile (5d)**

Yellow solid; yield: 123 mg (85%); mp 125–126 °C.

IR (KBr): 919, 1010, 1108, 1229, 1395, 1614, 1657, 2259, 2937 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.87 (d, *J* = 5.2 Hz, 1 H), 4.36–4.40 (m, 1 H), 5.62 (d, *J* = 5.1 Hz, 1 H), 7.10–7.24 (m, 4 H), 7.34–7.41 (m, 2 H), 7.72–7.77 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.4, 38.0, 91.8 (d, $^5J_{C–F}$ = 1.6 Hz), 111.2, 111.5, 115.6 (d, $^2J_{C–F}$ = 21.8 Hz), 116.1, 117.7, 124.8, 127.3 (d, $^3J_{C–F}$ = 8.4 Hz), 128.3, 128.9 (d, $^4J_{C–F}$ = 3.3 Hz), 130.8, 151.8, 153.0, 163.7 (d, $^1J_{C–F}$ = 248.6 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{11}FN_2NaO$: 313.0748; found: 313.0751.

**[2-(2-Furyl)-4*H*-chromen-4-yl]malononitrile (5e)**

Yellow solid; yield: 109 mg (83%); mp 112–113 °C.

IR (KBr): 894, 1008, 1233, 1396, 1633, 1683, 2255, 2919 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.88 (d, *J* = 5.0 Hz, 1 H), 4.35–4.38 (m, 1 H), 5.69 (d, *J* = 5.1 Hz, 1 H), 6.49 (dd, $J_1$ = 3.4 Hz, $J_2$ = 1.8 Hz, 1 H), 6.77 (d, *J* = 3.4 Hz, 1 H), 7.17–7.22 (m, 2 H), 7.33–7.47 (m, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.3, 37.6, 90.6, 108.9, 111.3, 111.4, 111.5, 116.2, 117.7, 124.7, 128.3, 130.2, 143.5, 146.1, 147.0, 151.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{10}N_2NaO_2$: 285.0634; found: 285.0647.

**[2-(2-Thienyl)-4*H*-chromen-4-yl]malononitrile (5f)**

Yellow solid; yield: 110 mg (80%); mp 117–118 °C.

IR (KBr): 982, 1061, 1239, 1420, 1572, 1649, 2255, 2922, 3096 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.88 (d, *J* = 5.1 Hz, 1 H), 4.33–4.36 (m, 1 H), 5.69 (d, *J* = 5.1 Hz, 1 H), 7.08 (dd, $J_1$ = 4.7 Hz, $J_2$ = 3.6 Hz, 1 H), 7.18–7.23 (m, 2 H), 7.33–7.42 (m, 3 H), 7.48 (*J* = 3.6 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.3, 38.0, 91.0, 111.3, 111.5, 116.1, 117.7, 124.8, 125.6, 126.7, 127.6, 128.3, 130.3, 136.0, 149.4, 151.7.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{10}N_2NaOS$: 301.0406; found: 301.0421.

**(6-Chloro-2-phenyl-4*H*-chromen-4-yl)malononitrile (5h)**

Yellow solid; yield: 122 mg (80%); mp 123–124 °C.

IR (KBr): 917, 1012, 1091, 1275, 1338, 1668, 2252, 2922 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.88 (d, *J* = 5.0 Hz, 1 H), 4.33–4.36 (m, 1 H), 5.66 (d, *J* = 5.1 Hz, 1 H), 7.19 (*J* = 8.7 Hz, 1 H), 7.31–7.38 (m, 2 H), 7.43–7.46 (m, 3 H), 7.72–7.75 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.3, 37.9, 91.6, 110.9, 111.2, 117.6, 119.2, 125.3, 127.9, 128.6, 129.5, 130.0, 130.4, 132.3, 150.6, 153.8.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{11}ClN_2NaO$: 329.0452; found: 329.0458.

**[6-Chloro-2-(4-fluorophenyl)-4*H*-chromen-4-yl]malononitrile (5i)**

Yellow solid; yield: 131 mg (81%); mp 133–135 °C.

IR (KBr): 955, 1019, 1228, 1413, 1609, 1664, 2257, 2918 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.89 (d, *J* = 4.9 Hz, 1 H), 4.33–4.36 (m, 1 H), 5.60 (d, *J* = 5.0 Hz, 1 H), 7.10–7.19 (m, 3 H), 7.31–7.38 (m, 2 H), 7.70–7.75 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 32.4, 37.9, 91.3 (d, $^5J_{C–F}$ = 1.5 Hz), 110.9, 111.2, 115.7 (d, $^2J_{C–F}$ = 21.8 Hz), 117.5, 119.2, 127.4 (d, $^3J_{C–F}$ = 8.5 Hz), 127.9, 128.5 (d, $^4J_{C–F}$ = 3.3 Hz), 129.6, 130.5, 150.4, 153.0, 163.8 (d, $^1J_{C–F}$ = 248.9 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{10}ClFN_2NaO$: 347.0358; found: 347.0355.

**(2-Phenyl-4*H*-chromen-4-yl)(phenylsulfonyl)acetonitrile (5j)**
Yellow solid; yield: 159 mg (82%); mp 127–129 °C.

IR (KBr): 928, 1027, 1077, 1235, 1338, 1663, 2242, 2913 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.10 (d, *J* = 5.2 Hz, 1 H), 4.87–4.90 (m, 1 H), 5.69 (d, *J* = 5.0 Hz, 1 H), 7.13–7.41 (m, 7 H), 7.64–7.81 (m, 5 H), 8.09 (d, *J* = 7.9 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.8, 66.1, 93.3, 112.3, 117.2, 117.7, 124.5, 125.4, 127.8, 128.4, 129.3, 129.4, 129.6, 129.8, 133.3, 135.3, 136.8, 152.3, 152.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{17}NNaO_3S$: 410.0821; found: 410.0813.

**[2-(4-Methoxyphenyl)-4*H*-chromen-4-yl](phenylsulfonyl)acetonitrile (5k)**
Yellow solid; yield: 177 mg (85%); mp 143–145 °C.

IR (KBr): 936, 1027, 1252, 1452, 1607, 1663, 2233, 2918, 3014 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 4.10 (s, 1 H), 4.85 (s, 1 H), 5.56 (d, *J* = 4.8 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 7.11–7.31 (m, 4 H), 7.60–7.79 (m, 5 H), 8.07 (d, *J* = 7.3 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.8, 55.3, 66.1, 91.5, 112.4, 113.7, 117.3, 117.6, 124.4, 125.9, 126.8, 127.8, 129.3, 129.5, 129.8, 135.3, 136.8, 152.2, 152.3, 160.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{19}NNaO_4S$: 440.0927; found: 440.0931.

**[2-(4-Chlorophenyl)-4*H*-chromen-4-yl](phenylsulfonyl)acetonitrile (5l)**
Yellow solid; yield: 171 mg (81%); mp 139–140 °C.

IR (KBr): 816, 1083, 1232, 1327, 1636, 2242, 2940 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.09 (d, *J* = 2.5 Hz, 1 H), 4.87–4.89 (m, 1 H), 5.71 (d, *J* = 5.0 Hz, 1 H), 7.13–7.31 (m, 4 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.62–7.79 (m, 5 H), 8.08 (d, *J* = 8.7 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.7, 66.0, 93.8, 112.3, 117.0, 117.7, 124.7, 126.7, 127.8, 128.6, 129.3, 129.6, 129.8, 131.8, 135.3, 135.4, 136.8, 151.5, 152.1.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{16}ClNNaO_3S$: 444.0432; found: 444.0436.

**[2-(4-Fluorophenyl)-4*H*-chromen-4-yl](phenylsulfonyl)acetonitrile (5m)**
Yellow solid; yield: 160 mg (79%), mp 138–139 °C.

IR (KBr): 820, 1027, 1231, 1336, 1634, 2264, 2942 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.08 (d, *J* = 2.5 Hz, 1 H), 4.87–4.90 (m, 1 H), 5.67 (d, *J* = 5.0 Hz, 1 H), 7.10–7.32 (m, 6 H), 7.66–7.80 (m, 5 H), 8.09 (d, *J* = 9.0 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.7, 66.0, 93.1, 112.3, 115.3 (d, $^2J_{C-F}$ = 21.7 Hz), 117.1, 117.7, 124.6, 127.4 (d, $^3J_{C-F}$ = 8.3 Hz), 127.9, 129.3, 129.5 (d, $^4J_{C-F}$ = 3.3 Hz), 129.6, 129.8, 135.3, 136.8, 151.7, 152.2, 163.4 (d, $^1J_{C-F}$ = 247.6 Hz).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{16}FNNaO_3S$: 428.0727; found: 428.0741.

**[2-(2-Furyl)-4*H*-chromen-4-yl](phenylsulfonyl)acetonitrile (5n)**
Yellow solid; yield: 160 mg (85%); mp 136–137 °C.

IR (KBr): 915, 1014, 2884, 1234, 1396, 1628, 1674, 2239 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.12 (d, *J* = 2.4 Hz, 1 H), 4.83–4.86 (m, 1 H), 5.73 (d, *J* = 5.0 Hz, 1 H), 6.45 (dd, $J_1$ = 3.2 Hz, $J_2$ = 1.8 Hz, 1 H), 6.69 (d, *J* = 3.4 Hz, 1 H), 7.10–7.32 (m, 4 H), 7.44 (s, 1 H), 7.63–7.79 (m, 3 H), 8.07 (d, *J* = 7.8 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.2, 66.0, 91.9, 108.2, 111.3, 112.3, 117.2, 117.6, 124.6, 127.9, 129.3, 129.6, 129.8, 135.3, 136.7, 143.2, 145.0, 147.5, 151.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{15}NNaO_4S$: 400.0614; found: 400.0619.

**(Phenylsulfonyl)[2-(2-thienyl)-4*H*-chromen-4-yl]acetonitrile (5o)**
Yellow solid; yield: 169 mg (86%); mp 148–150 °C.

IR (KBr): 845, 1075, 1234, 1323, 1655, 2237, 2892 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.12 (d, *J* = 2.4 Hz, 1 H), 4.80–4.83 (m, 1 H), 5.55 (d, *J* = 5.1 Hz, 1 H), 7.02–7.14 (m, 4 H), 7.25–7.38 (m, 3 H), 7.64–7.69 (m, 2 H), 7.78 (t, *J* = 7.6 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 34.7, 66.0, 92.2, 112.3, 117.1, 117.6, 124.7, 125.1, 126.2, 127.4, 127.8, 129.4, 129.6, 129.8 (2C), 135.4, 136.6, 148.2, 152.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{15}NNaO_3S_2$: 416.0386; found: 416.0399.

Crystal structure: $C_{21}H_{15}NO_3S_2$, triclinic, space group *P*1, *a* = 7.727(4), *b* = 10.194(5), *c* = 12.377(6) Å, α = 91.253(5)°, β = 107.610(5)°, γ = 96.044(5)°, *U* = 922.6(7) $Å^3$, *T* = 296(2) K, *Z* = 12, $D_C$ = 1.227 $mg·m^{-3}$, λ = 0.71073 Å, *F*(000)408, crystal size 0.20 × 0.20 × 0.15 $mm^3$. Absorption coefficient: 0.310 $mm^{-1}$, reflections collected: 5155, independent reflections: 3200 [$R_{(int)}$ = 0.0118], refinement by full-matrix least-squares on $F^2$, data/restraints/parameters 32001/1/224, goodness-of-fit on $F^2$ = 1.031, final *R* indices [*I*>2s(*I*)] *R*1 = 0.0549, *wR*2 = 0.1614, *R* indices (all data) *R*1 = 0.0645, *wR*2 = 0.1716, largest diff. peak and hole 0.692 and –0.806 $e·Å^{-3}$.

**Ethyl Cyano(2-phenyl-4*H*-chromen-4-yl)acetate (5p)**
Yellow solid; yield: 134 mg (84%), mp 102–104 °C.

IR (KBr): 918, 1046, 1228, 1387, 1656, 1736, 2256, 2908, 2979 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H), 3.72 (d, *J* = 5.2 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.42–4.45 (m, 1 H), 5.59 (d, *J* = 5.2 Hz, 1 H), 7.10–7.43 (m, 7 H), 7.70 (d, *J* = 7.9 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.8, 37.1, 46.5, 62.9, 94.5, 115.4, 117.2, 118.2, 124.1, 125.1, 128.3, 128.4, 129.2, 129.3, 133.3, 152.2, 152.4, 164.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{17}NNaO_3$: 342.1101; found: 342.1106.

**Ethyl Cyano[2-(4-fluorophenyl)-4*H*-chromen-4-yl]acetate (5q)**
Yellow solid; yield: 143 mg (85%); mp 87–88 °C.

IR (KBr): 835, 1038, 1234, 1394, 1636, 1736, 2252, 2914, 2987 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H), 3.72 (d, *J* = 5.1 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.41–4.45 (m, 1 H), 5.53 (d, *J* = 5.1 Hz, 1 H), 7.07–7.36 (m, 6 H), 7.67–7.72 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.8, 37.1, 46.5, 62.9, 94.3 (d, $^5J_{C-F}$ = 1.6 Hz), 115.3, 115.6 (d, $^2J_{C-F}$ = 21.7 Hz), 117.1, 118.1, 124.2, 127.1 (d, $^3J_{C-F}$ = 8.4 Hz), 128.3, 129.3, 129.5, (d, $^4J_{C-F}$ = 3.5 Hz), 151.6, 152.1, 163.4 (d, $^1J_{C-F}$ = 248.9 Hz), 164.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{16}FNNaO_3$: 360.1006; found: 360.1005.

**Methyl Cyano(2-phenyl-4*H*-chromen-4-yl)acetate (5r)**
Yellow solid; yield: 125 mg (82%); mp 106–108 °C.

IR (KBr): 922, 1050, 1229, 1392, 1654, 1744, 2253, 2915, 2954 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.72 (d, *J* = 5.2 Hz, 1 H), 3.77 (s, 3 H), 4.41–4.45 (m, 1 H), 5.57 (d, *J* = 5.2 Hz, 1 H), 7.13–7.42 (m, 7 H), 7.70–7.73 (m, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 37.1, 46.5, 53.5, 94.6, 115.2, 117.2, 118.1, 124.1, 125.1, 128.3, 128.4, 129.2, 129.3, 133.3, 152.2, 152.6, 165.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{15}NNaO_3$: 328.0944; found: 328.0940.

**2-Amino-4*H*-chromene-3-carbonitriles 6; General Procedure**
A mixture of chalcone **3** (0.5 mmol), acetonitrile **4** (0.5 mmol), and $NaHCO_3$ (42 mg, 0.5 mmol) in anhyd EtOH (3 mL) was stirred at r.t. until the chalcone disappeared (TLC, 12 h). The solvent was then removed under reduced pressure. The mixture was poured into $H_2O$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over ($MgSO_4$), filtered, and concentrated to give a residue that was purified by column chromatography (silica gel, PE–EtOAc) to give a yellow solid.

**2-Amino-4-(2-oxo-2-phenylethyl)-4*H*-chromene-3-carbonitrile (6a)[15a]**
Yellow solid; yield: 139 mg (96%); mp 129–131 °C.

IR (KBr): 759, 1050, 1274, 1405, 1648, 2181, 3199, 3442 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.88 (d, *J* = 5.7 Hz, 2 H), 4.33 (t, *J* = 5.7 Hz, 1 H), 4.71 (s, 2 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 7.16–7.26 (m, 2 H), 7.40–7.56 (m, 3 H), 7.90 (d, *J* = 7.5 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 30.6, 47.3, 58.5, 116.3, 120.0, 123.3, 125.0, 128.0, 128.1, 128.3, 128.6, 133.2, 136.7, 149.2, 160.9, 197.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{14}N_2NaO_2$, 313.0947; found: 313.0950.

**2-Amino-4-[2-(4-fluorophenyl)-2-oxoethyl]-4*H*-chromene-3-carbonitrile (6d)**
Yellow solid; yield: 137 mg (89%); mp 101–102 °C.

IR (KBr): 836, 1051, 1229, 1412, 1602, 1648, 2183, 2927, 3440 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.36 (d, *J* = 5.7 Hz, 2 H), 4.32 (t, *J* = 5.7 Hz, 1 H), 4.71 (s, 2 H), 7.03–7.22 (m, 5 H), 7.90–7.95 (m, 2 H), 7.97 (d, *J* = 8.1 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 30.6, 47.2, 58.4, 115.8 (d, $^2J_{C-F}$ = 21.8 Hz), 116.3, 120.0, 123.2, 125.0, 128.1, 128.2, 130.7 (d, $^3J_{C-F}$ = 9.3 Hz), 133.2 (d, $^4J_{C-F}$ = 3.0 Hz), 149.2, 160.9, 163.8 (d, $^1J_{C-F}$ = 253.6 Hz), 195.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{13}FN_2NaO_2$: 331.0853; found: 331.0851.

**2-Amino-4-[2-(2-furyl)-2-oxoethyl]-4*H*-chromene-3-carbonitrile (6e)**
Yellow solid; yield: 132 mg (94%); mp 125–127 °C.

IR (KBr): 972, 1052, 1228, 1462, 1651, 2187, 2925, 3441 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.23 (d, *J* = 5.7 Hz, 2 H), 4.27 (t, *J* = 5.9 Hz, 1 H), 4.81 (s, 2 H), 6.50 (dd, $J_1$ = 3.6 Hz, $J_2$ = 1.7 Hz, 1 H), 6.94–7.07 (m, 2 H), 7.14–7.27 (m, 3 H), 7.54–7.56 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 30.8, 47.1, 58.0, 112.3, 116.2, 117.5, 119.9, 122.9, 124.9, 128.1, 128.3, 146.6, 149.1, 152.6, 160.9, 186.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}NaN_2O_3$: 303.0740; found: 303.0736.

## Acknowledgment

We gratefully acknowledge support received from the National Natural Science Foundation of China (Grant 21102042).

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

## References

(1) (a) Patil, S. A.; Wang, J.; Li, X. C. S.; Chen, J. J.; Jones, T. S.; Hosni-Ahmed, A.; Patil, R.; Seibel, W. L.; Li, W.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4458. (b) Khoshneviszadeh, M.; Edraki, N.; Miri, R.; Foroumadi, A.; Hemmateenejad, B. *Chem. Biol. Drug Des.* **2012**, *79*, 442.
(2) Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587.
(3) (a) Skommer, J.; Wlodkowic, D.; Mättö, M.; Eray, M.; Pelkonen, J. *Leuk. Res.* **2006**, *30*, 322. (b) Wang, J. L.; Liu, D. X.; Zhang, Z. J.; Shan, S.; Han, X. B.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124.
(4) (a) Costa, M.; Areias, F.; Abrunhosa, L.; Venâncio, A.; Proença, F. *J. Org. Chem.* **2008**, *73*, 1954. (b) Proença, F.; Costa, M. *Green Chem.* **2008**, *10*, 995. (c) Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Belyakov, P. A.; Chizhov, A. O.; Nikishin, G. I. *Tetrahedron* **2010**, *66*, 4043. (d) Kumaravel, K.; Vasuki, G. *Green Chem.* **2009**, *11*, 1945. (e) Gyuris, M.; Madácsi, R.; Puskás, L. G.; Tóth, G. K.; Wölfling, J.; Kanizsai, I. *Eur. J. Org. Chem.* **2011**, 848. (f) Du, Z. Y.; Siau, W. Y.; Wang, J. *Tetrahedron Lett.* **2011**, *52*, 6137. (g) Gupta, A. K.; Kumari, K.; Singh, N.; Raghuvanshi, D. S.; Singh, K. N. *Tetrahedron Lett.* **2012**, *53*, 650.
(5) (a) Kolla, S. R.; Lee, Y. R. *Tetrahedron* **2012**, *68*, 226. (b) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3649. (c) Das, B.; Balasubramanyam, P.; Reddy, G. C.; Salvanna, N. *Helv. Chim. Acta* **2011**, *94*, 1347.
(6) (a) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 6785. (b) Chen, W. L.; Cai, Y. F.; Fu, X.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, *13*, 4910.
(7) Lakshmi, N. V.; Kiruthika, S. E.; Perumal, P. T. *Synlett* **2011**, 1389.
(8) (a) Yin, G. D.; Wang, Z. H.; Chen, A. H.; Gao, M.; Wu, A. X.; Pan, Y. J. *J. Org. Chem.* **2008**, *73*, 3377. (b) Yin, G. D.; Liu, Q.; Ma, J. R.; She, N. F. *Green Chem.* **2012**, *14*, 1796. (c) Gao, Q. H.; Zhu, Y. P.; Lian, M.; Liu, M. C.; Yuan, J. J.; Yin, G. D.; Wu, A. X. *J. Org. Chem.* **2012**, *77*, 9865. (d) Lian, M.; Li, Q.; Zhu, Y. P.; Yin, G. D.; Wu, A. X. *Tetrahedron* **2012**, *68*, 9598. (e) Yin, G. D.; Fan, L.; Ren, T. B.; Zheng, C. Y.; Tao, Q.; Wu, A. X.; She, N. F. *Org. Biomol. Chem.* **2012**, *12*, 8877.
(9) Heffernan, G. D.; Coghlan, R. D.; Manas, E. S.; McDevitt, R. E.; Li, Y.; Mahaney, P. E.; Robichaud, A. J.; Huselton, C.; Alfinito, P.; Bray, J. A.; Cosmi, S. A.; Johnston, G. H.; Kenney, T.; Koury, E.; Winneker, R. C.; Deecher, D. C.; Trybulski, E. J. *Bioorg. Med. Chem.* **2009**, *17*, 7802.
(10) Ivachtchenko, A. V.; Golovina, E. S.; Kadieva, M. G.; Koryakova, A. G.; Kovalenko, S. M.; Mitkin, O. D.; Okun, I. M.; Ravnyeyko, I. M.; Tkachenko, S. E.; Zaremba, O. V. *Bioorg. Med. Chem.* **2010**, *18*, 5282.
(11) Dias, T. A.; Proença, M. F. *Tetrahedron Lett.* **2012**, *53*, 5235.
(12) Curini, M.; Epifano, F.; Chimichi, S.; Montanari, F.; Nocchetti, M.; Rosati, O. *Tetrahedron Lett.* **2005**, *46*, 3497.
(13) Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Ilovaisky, A. I.; Feducovich, S. K.; Belyakov, P. A.; Nikishin, G. I. *Adv. Synth. Catal.* **2008**, *350*, 591.

(14) Crystallographic data for compound **5o** have been deposited with the accession number CCDC 901984, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

(15) (a) Xie, J. W.; Huang, X.; Fan, L. P.; Xu, D. C.; Li, X. S.; Su, H.; Wen, Y. H. *Adv. Synth. Catal.* **2009**, *351*, 3077. (b) Pattan, S. R.; Dighe, N. S.; Musmade, D. S.; Gaware, V. M.; Jadhav, S. G.; Khade, M. A.; Hiremath, S. N. *Asian J. Res. Chem.* **2010**, *3*, 126.

(16) Li, X. F.; Cun, L. F.; Lian, C. X.; Zhong, L.; Chen, Y. C.; Liao, J.; Zhu, J.; Deng, J. G. *Org. Biomol. Chem.* **2008**, *6*, 349.

(17) (a) Liu, Y. B.; Liu, X. H.; Wang, M.; He, P.; Lin, L. L.; Feng, X. M. *J. Org. Chem.* **2012**, *77*, 4136. (b) Sashidhara, K. V.; Kumar, A.; Agarwal, S.; Kumar, M.; Kumar, B.; Sridhar, B. *Adv. Synth. Catal.* **2012**, *354*, 1129. (c) Nagarathnam, D.; Cushman, M. *Tetrahedron* **1991**, *47*, 5071. (d) Verma, A. K.; Pratap, R. *Tetrahedron* **2012**, *68*, 8523.

