A Convenient Synthesis of 3-Pyridinyl- and 3-Pyrimidinylcoumarins

Xuqing Zhang,* Zhihua Sui

Drug Discovery, Johnson & Johnson Pharmaceutical Research and Development, LLC, 665 Stockton Drive, Exton, PA 19341, USA
Fax +1(610)4588249; E-mail: xzhang5@prdus.jnj.com

Received 13 March 2006; revised 6 April 2006

Abstract: A mild and efficient synthesis of 3-pyridinyl- and 3-pyrimidinylcoumarins through one-pot tandem condensation–cyclization of various 2′-hydroxyacetophenones and pyridinyl- or pyrimidinylacetic acids is described.

Key words: coumarin, benzopyran, Perkin reaction, DCC coupling, SERM

In our recent medicinal chemistry efforts toward the discovery of selective estrogen receptor modulators (SERMs) for the prevention and treatment of osteoporosis and breast cancer, we developed an efficient and practical synthesis of a novel series of bis-benzopyrans.[1] As an extension of our continued interest in the benzopyran structures as SERMs, we were attracted to pursue the synthesis of 3-pyridinyl- and 3-pyrimidinylcoumarins **I** as the key intermediates to the benzopyran lead structures **II** (Figure 1). A significant number of synthetic methods to 3-phenylcoumarins have been documented in the literature, including the Perkin reaction,[2] the Knoevenagel reaction,[3] and the Pechmann reaction.[4] Recently, these efforts have been aided by progress in the transition metal-catalyzed annulation protocol.[5] However, very few synthetic methods to 3-heteroaryl group substituted coumarins are available, especially for 3-aromatic substitutions bearing basic functional groups.[6] This might be due to the major disadvantages of these classic methods: the use of stoichiometric amounts of strong acids and high temperature. Herein, we wish to report a convenient synthesis of 3-pyridinyl- and pyrimidinylcoumarins **I** through a one-pot tandem condensation–cyclization of the corresponding 2′-hydroxyacetophenones and pyridinyl- or pyrimidinylacetic acids under mild conditions and in good yields.

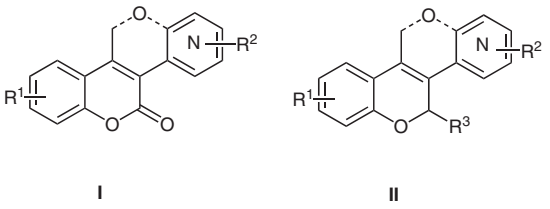
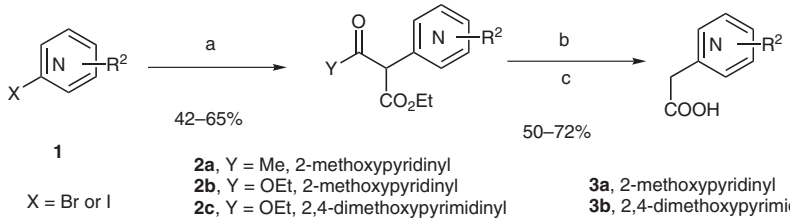


Figure 1 3-Pyridinyl- and 3-pyrimidinylcoumarins **I** and benzopyrans **II**

We first applied the standard coumarin synthesis procedures on the pyridinyl or pyrimidinyl substrates. The required precursors **2** and **3** were prepared by the method shown in Scheme 1. Nucleophilic aromatic substitutions[7] of halopyridines or halopyrimidines **1** by ethyl acetoacetate or diethyl malonate sodium salt catalyzed by CuBr afforded **2a**–**c**. Decarboxylations of **2b**,**c** were carried out through alkaline hydrolysis followed by acidic work-up to afford the phenyl acetic acids **3a**,**b**. However, Pechmann condensation between resorsinol or 3-methoxyphenol and β-keto ester **2a** in the presence of strong acids such as PPA or methanesulfonic acid failed to give any desired products. Perkin reaction of a mixture of 2-hydroxyacetophenones and pyridinyl- or pyrimidinylacetic acids **3** in the presence of triethylamine in refluxing acetic anhydride delivered only trace amounts of the desired coumarins.[8] This might be due to the basicity of the pyridinyl or pyrimidinyl substrates. In general, the substrates or the intermediates could not tolerate the harsh reaction conditions.

It is well known that the Perkin reaction, for the synthesis of 3-arylcoumarins, involves the condensation of 2-hydroxyphenylcarbonyl substrate with arylacetic acid in the presence of a coupling agent followed by a Dieckmann cyclization under catalysis by a base. Many attempts on improving the Perkin method have been described in the

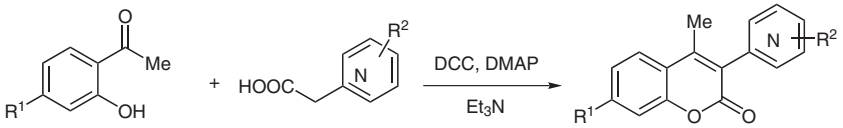


Scheme 1 *Reagents and conditions*: a) Ethyl acetoacetate or diethyl malonate, NaH, CuBr, 100 °C in dioxane overnight; b) aq 2 N NaOH, 2 h; c) 1 N HCl.

SYNTHESIS 2006, No. 15, pp 2568–2572
Advanced online publication: 04.07.2006
DOI: 10.1055/s-2006-942461; Art ID: M01406SS

literature.[9] We envisaged that condensation of 2-hydroxyacetophenones **4** and pyridinyl- or pyrimidinylacetic acids **3** required a mild coupling agent. *N*,*N*-Dicyclohexylcarbodiimide (DCC) is considered as powerful coupling agent that fits the criteria here. For this reason, we examined DCC coupling (DCC ~ 1.0 equiv, DMAP 0.1 equiv) process between **3** and **4**. To our satisfaction, we observed the coupling product in good yields with some Dieckmann cyclization adducts – the desired coumarins **5**. After preliminary investigation, we found that condensation–cyclization of various 2′-hydroxyacetophenones **4** and pyridinyl- or pyrimidinylacetic acids **3** to coumarins **5** could be achieved in one-pot tandem fashion by using DCC as coupling agent and Et_3N as base. The reaction was also successfully executed with various **3** and **4** to afford the corresponding coumarins **5** in moderate to good yields, as illustrated in Table 1. Unlike other Perkin modifications, the present method obviates the need to prepare unstable phenylacetic chloride or anhydride, eliminates strong acid/acid derivative as the condensing agent and avoids high reaction temperature. Thus, it appears to be an attractive approach toward 3-aryl substituted coumarins bearing basic groups.

Table 1 One-Pot Synthesis of Coumarins **5** via Condensation–Cyclization Process



4 **3** **5**

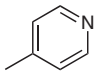
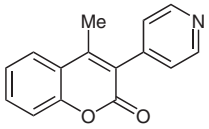
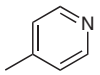
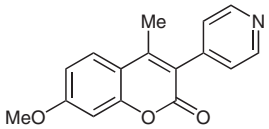
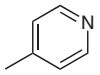
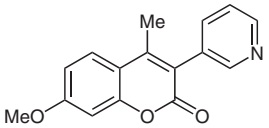
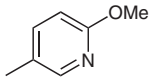
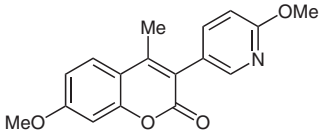
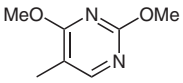
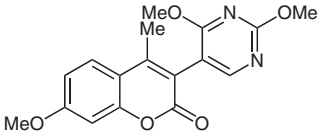
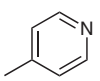
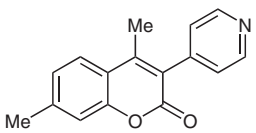
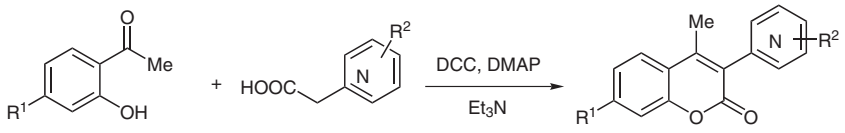
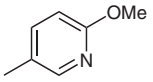
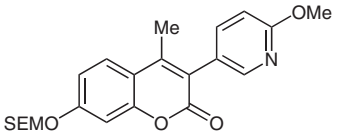
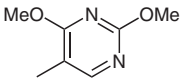
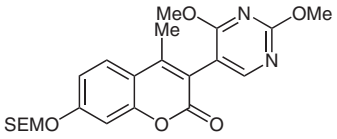
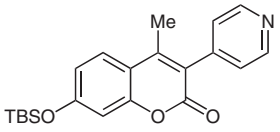
Entry	R^1		Product **5**[a]	Yield (%)[b]
1	H		 **5a**	75
2	OMe		 **5b**	58
3	OMe		 **5c**	71
4	OMe		 **5d**	68
5	OMe		 **5e**	65
6	Me		 **5f**	82

Table 1 One-Pot Synthesis of Coumarins **5** via Condensation–Cyclization Process (continued)



4 **3** **5**

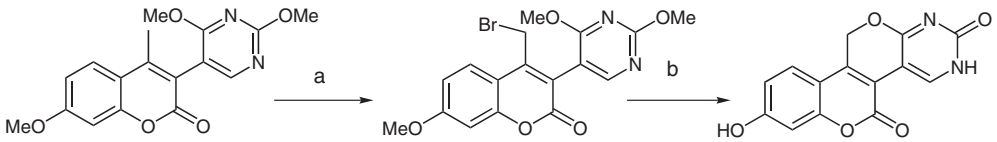
Entry	R^1		Product **5**[a]	Yield (%)[b]
7	OSEM		 **5g**	66
8	OSEM		 **5h**	65
9	OTBS		 **5i**	60

[a] Reagents and conditions: **3** (1.0–1.5 equiv), **4** (1.0 equiv), Et_3N (2.0–2.5 equiv), DCC (1.0 equiv), DMAP (0.1 equiv) in CH_2Cl_2, r.t. to reflux, 10 –20 h.
[b] Yield of isolated product.

Synthetic utility of this reaction has been shown by the synthesis of a key intermediate – tetracyclic coumarin **7** for SERM targets (Scheme 2). Anionic bromination of **5e** with LiHMDS and NBS in THF at –78 °C provided monobromide **6** in 81% yield. Demethylation of **6** was carried out by treatment with BBr_3 in 1,2-dichloroethane. In situ treatment of the corresponding tris-phenol intermediate with 10% K_2CO_3 in 1:1 methanol and acetone solution afforded the tetracyclic coumarin **7** in 51% yield.

In summary, we have developed an efficient one-pot synthesis of 3-pyridinyl and 3-pyrimidinyl coumarins **5** under mild conditions and in moderate to good yields. Further investigation on converting the coumarins **5** and **7** into typical SERMs structures **II** are under way in our laboratory and the biological data will be reported in due course.

Melting points were taken using a Thomas-Hoover MelTemp apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 MHz with $CDCl_3$ or DMSO-d_6 as solvent on a Bruker AVANCE 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. TLC was carried out using silica gel 60 (250 μM layer) plates with UV detection. Anhydrous Na_2SO_4 was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM Science silica gel 60 (230–400 mesh). Solvents from J. T. Baker or Aldrich and all other commercially available reagents were used without further purification. Microanalysis was done by Quantitative Technologies Inc., Whitehouse, NJ. Mass spectra were obtained on a Hewlett-Packard 5989A quadrupole mass spectrometer. HPLC analysis was carried on Agilent 1100 Series LC/MSD equipment. 3-Pyridylacetic acid, 4-pyridylacetic acid, 2′-hydroxy-4′methoxyacetophenone, 2′-hydroxy-4′-methylacetophenone and 2′,4′-dihydroxyacetophenone are available from Aldrich. 1-[4-(*tert*-



5e **6** **7**

Scheme 2 *Reagents and conditions*: a) LiHMDA for 20 min, NBS for 2 h, –78 °C, 81%; b) 1. BBr_3, $ClCH_2CH_2Cl$, r.t. to reflux for overnight, 2. 10% K_2CO_3, MeOH–acetone (1:1), 0 °C for 2 h, 51%.

Butyldimethylsilyloxy)-2-hydroxyphenyl]ethanone and 1-[2-hydroxy-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanone were prepared according to the literature.[10]

2-(6-Methoxypyridin-3-yl)malonic Acid Diethyl Ester (2b)

NaH (60%, 36.2 mmol, 1.45 g) was added to a solution of 5-bromo-2-methoxypyridine (16.5 mmol, 2.13 mL), CuBr (32.9 mmol, 4.72 g) and diethyl malonate (32.9 mmol, 5.0 mL) in 1,4-dioxane (20 mL) slowly at r.t. After the addition, the resulting mixture was heated to 100 °C and stirred overnight. The mixture was then passed through a pad of Celite to remove the brown solid. The filtrate was then concentrated in vacuo to afford a brown oil, which was then purified by silica gel column chromatography using hexanes–EtOAc (4:1–2:1 ratio) as eluent to afford the title compound **2b** as a light-yellow oil; yield: 2.87 g (65%).

^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 1 H), 7.74 (d, *J* = 8.5 Hz, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 4.55 (s, 1 H), 4.25 (m, 4 H), 3.95 (s, 3 H), 1.25 (m 6 H).

LC-CIMS (LC purity: 98%): *m*/*z* (%) = 268 ([M + 1]$^+$, 100).

2-(2,4-Dimethoxypyrimidin-5-yl)malonic Acid Diethyl Ester (2c)

Prepared following the procedure for **2b** using 5-iodo-2,4-dimethoxypyrimidine as the starting material.

Yield: 42%; light-yellow oil.

^{1}H NMR ($CDCl_3$): δ = 8.28 (s, 1 H), 4.32 (m, 4 H), 4.05 (s, 3 H), 4.01 (s, 3 H), 1.35 (m, 6 H).

LC-CIMS (LC purity: 98%): *m*/*z* (%) = 298 ([M + 1]$^+$, 100).

(6-Methoxypyridin-3-yl)acetic Acid (3a)

2-(6-Methoxypyridin-3-yl)malonic acid diethyl ester (**2b**; 5.6 g, 21.0 mmol) was dissolved in a solution of 2 N NaOH in THF–H_2O (1:1, 20 mL). The resulting mixture was refluxed for 2 h. The mixture was then adjusted to pH 1 with conc. HCl and stirred for another 1 h at r.t.. The solution was then adjusted to pH 13 with aq 1 N NaOH and extracted with Et_2O. The aqueous phase was acidified to pH 5 with 1 N HCl and extracted with EtOAc (3 ×). The combined organic phases were then washed with brine, dried (Na_2SO_4), filtered and concentrated to give the title compound as an off-white solid; yield: 2.45 g (72%); mp 110–113 °C.

^{1}H NMR ($CDCl_3$): δ = 12.5 (br, 1 H), 7.91 (s, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 3.83 (s, 3 H), 3.42 (s, 2 H).

LC-CIMS (LC purity: 98%): *m*/*z* (%) = 168 ([M + 1]$^+$, 100), 190 ([M + Na]$^+$, 26).

(2,4-Dimethoxypyrimidin-5-yl)acetic Acid (3b)

Prepared following the procedure for **3b** using 2-(2,4-dimethoxypyrimidin-5-yl)malonic acid diethyl ester (**2c**) as the starting material; yield: 50%; off-white solid; mp 101–103 °C.

^{1}H NMR ($CDCl_3$): δ = 10.3 (br s, 1 H), 8.15 (s, 1 H), 4.05 (s, 6 H), 3.48 (s, 2 H).

LC-CIMS (LC purity: 98%): *m*/*z* (%) = 199 ([M + 1]$^+$, 100), 221 ([M + Na]$^+$, 31).

One-Pot Synthesis of Coumarins 5; General Procedure

To a solution of acetophenone **4** (27 mmol) and AcOH (27 mmol) in CH_2Cl_2 (40 mL), was added Et_3N (68.0 mmol), DMAP (2.72 mmol) and CH_2Cl_2 (27 mmol) at r.t. The mixture was stirred overnight and then refluxed for 2 h. The resulting solution was concentrated in vacuo and dissolved in Et_2O (~ 200 mL). The solid was removed by filtration. The filtrate was then concentrated to give the crude material, which was then purified by silica gel chromatography using hexanes–EtOAc (3:1 to 1:1) as eluent to give **5** as white solids (Table 1).

4-Methyl-3-pyridin-4-yl-2*H*-chromen-2-one (5a)

Yield: 75%; white solid; mp 123–125 °C.

^{1}H NMR ($CDCl_3$): δ = 8.81 (d, *J* = 7.5 Hz, 2 H), 7.65 (m, 1 H), 7.55 (d, *J* = 7.5 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.26 (m, *J* = 6.5 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 2.32 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 238 ([M + 1]$^+$, 16), 260 ([M + Na]$^+$, 100).

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.88; H, 4.65; N, 5.85.

7-Methoxy-4-methyl-3-pyridin-4-yl-2*H*-chromen-2-one (5b)

Yield: 58%; white solid; mp 150–153 °C.

^{1}H NMR ($CDCl_3$): δ = 8.75 (s, 1 H), 7.58 (d, *J* = 6.8 Hz, 1 H), 7.25 (d, *J* = 4.3 Hz, 2 H), 6.90 (d, *J* = 6.8 Hz, 1 H), 6.82 (s, 1 H), 3.91 (s, 3 H), 2.30 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 268 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.79; H, 4.86; N, 5.18.

7-Methoxy-4-methyl-3-pyridin-3-yl-2*H*-chromen-2-one (5c)

Yield: 71%; white solid; mp 133–135 °C.

^{1}H NMR ($CDCl_3$): δ = 8.65 (s, 1 H), 8.60 (d, *J* = 6.5 Hz, 1 H), 7.62–7.49 (m, 3 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 6.15 (s, 1 H), 3.88 (s, 3 H), 2.48 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 268 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.86; H, 4.77; N, 5.23.

7-Methoxy-3-(6-methoxypyridin-3-yl)-4-methyl-2*H*-chromen-2-one (5d)

Yield: 68%; off-white solid; mp 155–157 °C.

^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 1 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 7.60 (d, *J* = 7.5 Hz, 1 H), 6.92 (d, *J* = 9.2 Hz, 1 H), 6.85 (d, *J* = 9.2 Hz, 1 H), 6.82 (s, 1 H), 4.01 (s, 3 H), 3.95 (s, 3 H), 2.32 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 298 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{17}H_{15}NO_4$·0.5EtOAc: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.97; H, 5.55; N, 4.23.

3-(2,4-Dimethoxypyrimidin-5-yl)-7-methoxy-4-methyl-2*H*-chromen-2-one (5e)

Yield: 65%; white solid; mp 161–163 °C.

^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 7.5 Hz, 1 H), 6.88 (s, 1 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 2.25 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 329 ([M + 1]$^+$, 25), 351 ([M + Na]$^+$, 100), 679 ([2 M + Na]$^+$, 16).

Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.10; H, 4.85; N, 8.46.

4,7-Dimethyl-3-pyridin-4-yl-2*H*-chromen-2-one (5f)

Yield: 82%; white solid; mp 120–122 °C.

^{1}H NMR ($CDCl_3$): δ = 8.72 (d, *J* = 6.1 Hz, 2 H), 7.52 (s, 1 H), 7.42 (d, *J* = 8.5 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 7.20 (d, *J* = 6.1 Hz, 2 H), 2.55 (s, 3 H), 2.34 (s, 3 H).

LC-CIMS: *m*/*z* (%) = 252, ([M + 1]$^+$, 100), 274 ([M + Na]$^+$, 35).

Anal. Calcd for $C_{16}H_{13}NO_2$·0.5EtOAc: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.08; H, 5.65; N, 4.62.

3-(6-Methoxypyridin-3-yl)-4-methyl-7-(2-trimethylsilylethoxymethoxy)-2*H*-chromen-2-one (5g)

Yield: 66%; off-white solid; mp 175–177 °C.

^{1}H NMR ($CDCl_3$): δ = 8.08 (s, 1 H), 7.58 (m, 2 H), 7.05 (m, 2 H), 6.82 (d, *J* = 6.5 Hz, 1 H), 5.28 (s, 2 H), 3.98 (s, 3 H), 3.76 (t, *J* = 6.5 Hz, 2 H), 2.40 (s, 3 H), 0.93 (t, *J* = 6.5 Hz, 2 H), 0.00 (s, 9 H).

LC-CIMS: *m*/*z* (%) = 414 ([M + 1]$^+$, 32), 436 ([M + Na]$^+$, 100).

Anal. Calcd for $C_{22}H_{27}NO_5Si·0.25H_2O$: C, 63.21; H, 6.63; N, 3.35. Found: C, 63.36; H, 6.75; N, 3.42.

3-(2,4-Dimethoxypyrimidin-5-yl)-4-methyl-7-(2-trimethylsilylethoxymethoxy)-2*H*-chromen-2-one (5h)

Yield: 65%; off-white solid; mp 180–182 °C.

^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1 H), 7.54 (d, *J* = 10.1 Hz, 1 H), 7.05 (s, 1 H), 7.00 (d, *J* = 10.1 Hz, 1 H), 5.28 (s, 2 H), 4.08 (s, 3 H), 4.01 (s, 3 H), 3.75 (t, *J* = 11.5 Hz, 2 H), 2.25 (s, 3 H), 0.98 (t, *J* = 11.5 Hz, 2 H), 0.02 (s, 9 H).

LC-CIMS: *m*/*z* (%) = 445 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{22}H_{28}N_2O_6Si$: C, 59.44; H, 6.35; N, 6.30. Found: C, 59.32; H, 6.26; N, 6.42.

7-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-pyridin-4-yl-2*H*-chromen-2-one (5i)

Yield: 60%; off-white solid; mp 165–167 °C.

^{1}H NMR ($CDCl_3$): δ = 8.68 (d, *J* = 5.8 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 1 H), 7.24 (d, *J* = 5.8 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 6.81 (s, 1 H), 2.23 (s, 3 H), 1.05 (s, 9 H), 0.28 (s, 6 H).

LC-CIMS: *m*/*z* (%) = 382 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{21}H_{25}NO_3Si·0.3MeOH$: C, 67.84; H, 7.00; N, 3.71. Found: C, 67.68; H, 6.94; N, 3.77.

4-Bromomethyl-3-(2,4-dimethoxypyrimidin-5-yl)-7-methoxy-2*H*-chromen-2-one (6)

To a solution of **5e** (210 mg, 0.64 mmol) in anhyd THF (5 mL) at –78 °C was added LiHMDS (1.0 M, 1.28 mmol, 1.28 mL) dropwise. The resulting reddish solution was stirred at –78 °C for 20 min. To this solution was added NBS (114 mg, 0.64 mmol) in THF (2 mL) slowly. The reaction was stirred for 2 h at –78 °C and then quenched with aq sat. $NaHCO_3$ and warmed to r.t. THF was removed in vacuo and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford a yellow solid. Purification by silica gel column chromatography using hexanes–EtOAc (4:1 to 2:1) afforded **6** as a white solid; yield: 210 mg (81%); white solid; mp 175–177 °C.

^{1}H NMR ($CDCl_3$): δ = 8.28 (s, 1 H), 7.68 (d, *J* = 7.5 Hz, 1 H), 6.95 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.85 (d, *J* = 1.5 Hz, 1 H), 4.35 (ABq, *J* = 12.5 Hz, 2 H), 4.08 (s, 3 H), 4.00 (s, 3 H), 3.95 (s, 3 H).

LC-CIMS (LC purity: 98%): *m*/*z* (%) = 407 ([M + 1]$^+$, 100), 409 ([M + 3]$^+$, 98).

2,8-Dihydroxy-11*H*-6,12-dioxa-1,3-diazachrysen-5-one (7)

To a solution of **6** (200 mg, 0.492 mmol) in $ClCH_2CH_2Cl$ (5 mL) at r.t., was added BBr_3 (1.0 N, 2.50 mmol, 2.5 mL). The resulting mixture was stirred at r.t. for 30 min and then refluxed overnight. The reaction was cooled to r.t. and the solvent was removed in vacuo. The residue was dissolved in 10% K_2CO_3 in MeOH–acetone (~1:1, 10 mL) at 0 °C, and stirred for another 2 h. The solvent was evaporated to dryness, the residue was dissolved in H_2O (15 mL) and then acidified with dilute HCl to about pH 4. The precipitated brown solid was isolated by filtration, washed with H_2O and dried to give **7**; yield: 71 mg (51%); pale-yellow solid; mp 195–198 °C.

^{1}H NMR (DMSO-d_6): δ = 11.6 (s, 1 H), 8.68 (s, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 6.80 (s, 1 H), 5.74 (s, 2 H).

LC-CIMS: *m*/*z* (%) = 285 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{14}H_8N_2O_5$: C, 59.16; H, 2.84; N, 9.86. Found: C, 58.86; H, 2.55; N, 9.75.

References

(1) (a) Kanojia, R. M.; Jain, N.; Xu, J.; Sui, Z. *Tetrahedron Lett.* **2004**, *45*, 5837. (b) Kanojia, R. M.; Jain, N.; Ng, R.; Sui, Z.; Xu, J. Patent WO 2003053977, **2003**; *Chem. Abstr.* **2003**, *139*, 85328.

(2) (a) Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 53. (b) Johnson, J. R. *Org. React.* **1942**, *1*, 210. (c) Vijayan, K. K. *Indian J. Heterocycl. Chem.* **1998**, *8*, 1. (d) Mahling, J. A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 467.

(3) (a) Kakehi, A.; Ito, S.; Suga, H.; Yasuraoka, K. *Heterocycles* **2001**, *54*, 185. (b) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1997**, *45*, 1715. (c) Bojilova, A.; Nikolova, R.; Ivanov, C.; Rodios, N. A.; Terzis, A.; Raptopoulou, C. P. *Tetrahedron* **1996**, *52*, 12597.

(4) (a) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1. (b) Baran-Marszak, M.; Massicot, J.; Molho, D. *Bull. Soc. Chim. Fr.* **1971**, 191. (c) Wang, L. M.; Xia, J. J.; Tian, H.; Qian, C. T.; Ma, Y. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2003**, *42*, 2097. (d) Bose, D. S.; Rudradas, A. P.; Babu, M. H. *Tetrahedron Lett.* **2002**, *43*, 9195.

(5) (a) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1286. (b) Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477. (c) Van T, N.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *108*, 6305. (e) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9432. (f) Catellani, M.; Chuisoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5919. (g) Catellani, M.; Chuisoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5923. (h) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516. (i) Park, K. H.; Jung, G. II; Chung, Y. K. *Synlett* **2004**, 2541.

(6) (a) Bhagwat, S. S.; McKie, J. A.; Khammungkhune, S. Patent WO 2001049673, **2001**; *Chem. Abstr.* **2001**, *135*, 92545. (b) Stein, B. M.; Anderson, D. W.; Gayo, L. M.; Sutherland, M. S.; Doubleday, M.; Shevlin, G. I.; Kois, A.; Khammungkhune, S.; Jalluri, R. K.; Bhagwat, S. S.; McKie, J. A. Patent WO 2000039120, **2000**; *Chem. Abstr.* **2000**, *133*, 73934. (c) Wolfbeis, O. S.; Marhold, H. *Chem. Ber.* **1985**, *118*, 3664. (d) Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4677.

(7) (a) Daisley, R. W.; Hanbali, J. R. *Synth. Commun.* **1981**, *11*, 743. (b) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.

(8) Moffett, R. B. *J. Med. Chem.* **1964**, *7*, 446.

(9) (a) Lokhande, P. D.; Ghiya, B. J. *J. Indian Chem. Soc.* **1989**, *66*, 314. (b) Rao, P. P.; Srimannarayana, G. *Synthesis* **1981**, 887. (c) Rao-Subha, A. V.; Sabitha, G. *Synth. Commun.* **1987**, *17*, 341. (d) Ming, Y.; Boykin, D. W. *Heterocycles* **1987**, *26*, 3229. (e) Gallastegui, D. J.; Lago, J. M.; Palomo, C. *J. Chem. Res., Synop.* **1984**, 17. (f) McKie, J. A.; Bhagwat, S. S.; Brady, H.; Doubleday, M.; Gayo, L.; Hickman, M.; Jalluri, R. K.; Khammungkhune, S.; Kois, A.; Mortensen, D.; Richard, N.; Sapienza, J.; Shevlin, G.; Stein, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3407.

(10) Romano, J. J.; Casillas, E. *Tetrahedron Lett.* **2005**, *46*, 2323.