Three-component reaction between 4-hydroxycoumarin, ammonium thiocyanate and acid chlorides in the presence of *N*-methylimidazole under solvent-free conditions

Alireza Hassanabadi[a], Mohammad H. Mosslemin[b]* and Seyd Ehsan Tadayonfar[b]

[a]*Department of Chemistry, Islamic Azad University, Zahedan Branch, PO Box 98135-978, Zahedan, Iran*

[b]*Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran*

A novel method for oxazine ring formation is established using the reaction of ammonium thiocyanate and acid chlorides with 4-hydroxy coumarin in the presence of *N*-methylimidazole to afford oxazine derivatives in excellent yields.

Keywords: 4-hydroxy coumarin, acid chlorides, ammonium thiocyanate, oxazine

Oxazines constitute an important class of heterocycles, which have attracted considerable synthetic interest due to their wide range of biological activities.[1–5] Several oxazines exhibit diverse pharmacological properties, such as antagonism to progesterone receptor,[6] antitumor,[7] antiviral,[8,9] antithrombotic,[10] antimycobacterial,[11–13] anti-inflammatory,[3] antidiabetic and hypolipidaemic[14] effects. Further to these applications, they have also been reported as inhibitors of human leucocyte elastase[15] and serotonin reuptake.[16] This prompted us to establish a novel oxazine ring formation method to find promising bioactive oxazine compounds. We report an efficient synthesis of oxazines.

Results and discussion

Reaction of 4-hydroxycoumarin **1** and acid chlorides **2** with ammonium thiocyanate **3** in the presence of *N*-methylimidazole affords oxazine derivatives **4** in excellent yields (Scheme 1).

Structures of compounds **4a–f** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited nine proton resonances and 15 carbon resonances, in agreement with the proposed structure. The C=S group resonance in ^{13}C NMR spectra of **4a** appears at 194.02 ppm. The mass spectrum of **4a** displayed the molecular ion peak at m/z = 307. A tentative mechanism for this transformation is proposed in Scheme 2.

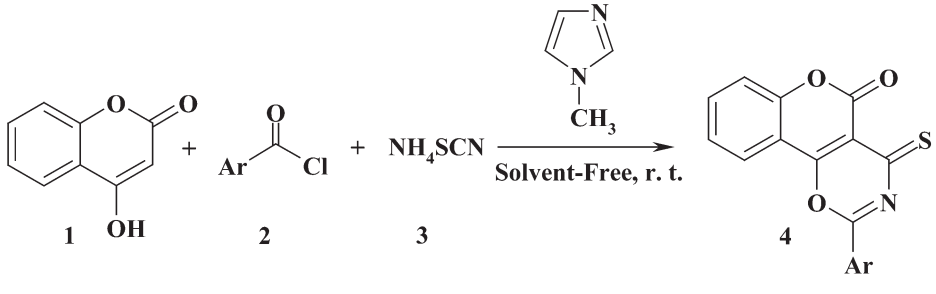
It is conceivable that the reaction starts with formation of aroyl thiocyanate **5**, followed by formation of the 1:1 adducts **6** and its subsequent protonation by 4-hydroxycoumarin to produce **7**. Then, the positively charged ion **7** is attacked by the anion of 4-hydroxycoumarin **8**. Intermediate **9** undergoes a cyclisation reaction and elimination of water to produce **4**.

In conclusion, the reaction of ammonium thiocyanate and acid chlorides with 4-hydroxy coumarin in the presence of N-methylimidazole led to oxazine derivatives in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions and the starting material can be used without any activation or modification.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at analytical laboratory of Islamic Azad University Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure:
Acid chloride (2 mmol) was added via a syringe to ammonium thiocyanate (0.15 g, 2 mmol) in a 50 mL flask at room temperature (r.t.). The reaction mixture was stirred in a water bath at about 90°C for 5 min. Then, 4-hydroxycoumarin (2 mmol) was added at this temperature. The reaction mixture was allowed to cool to room temperature. Finally, *N*-methylimidazole (0.032 g) (10 mol%) was added via

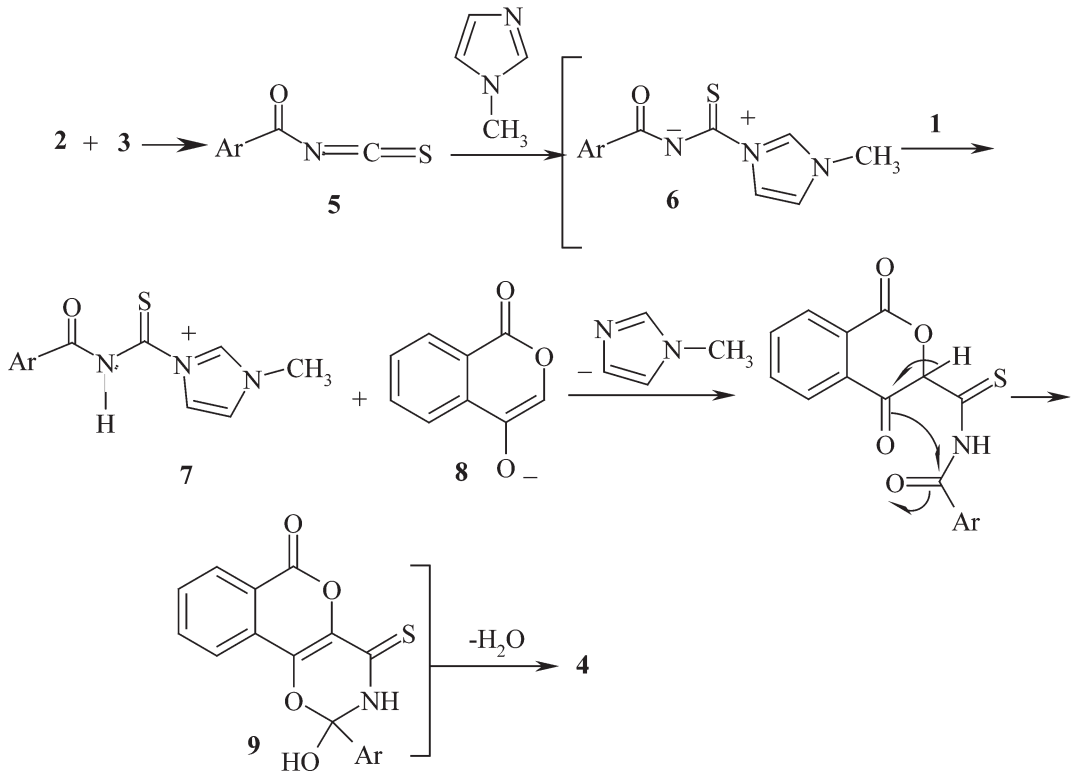


4	a	b	c	d	e	f
Ar	Ph	4-ClPh	4-BrPh	3-NO_2Ph	4-NO_2Ph	4-CH_3Ph
%Yield*	91	93	94	90	91	90

*Isolated yield

Scheme 1 Three-component reaction between 4-hydroxycoumarin, ammonium thiocyanate and acid chlorides in the presence of *N*-methylimidazole.

* Correspondent. E-mail: mhmosslemin@yahoo.com



Scheme 2 Suggested mechanism for formation of compound **4**.

syringe. The resulting mixture was stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, 15 mL distilled water was added over 5 min to the reaction mixture. The resulting precipitate was collected by filtration on a Buchner funnel and washed with 10 mL of cold diethyl ether to afford the pure title compounds.

3-(Phenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4a**): Yellow powder, m.p. 101–103 °C, IR (KBr) (ν_{max} cm^{-1}): 1699, 1604, 1558, 1448, 1383, 1266, 1211, 1087. Anal. Calcd for $C_{17}H_9NO_3S$: C, 66.44; H, 2.95; N, 4.56. Found: C, 66.62; H, 2.94; N, 4.70. MS (*m/z*, %): 307 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (1 H, t, $^3J_{HH}$ = 7 Hz, C*H* of C_6H_5), 7.34 (4 H, m, 4 C*H* of C_6H_5), 7.48 (1H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.63 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.77 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 8.14 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 105.82, 116.88, 117.45, 123.21, 124.89, 133.31, 154.32, 159.23 and 162.97 (carbons of coumarin moiety), 129.45, 130.83, 132.57 and 135.21 (carbons of C_6H_5), 161.83 (C=N), 194.02 (C=S) ppm.

3-(4-Chlorophenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4b**): Yellow powder, m.p. 148–150 °C, IR (KBr) (ν_{max} cm^{-1}): 1705, 1606, 1568, 1448, 1396, 1277, 1203, 1082. Anal. Calcd for $C_{17}H_8ClNO_3S$: C, 59.74; H, 2.36; N, 4.10. Found: C, 59.90; H, 2.55; N, 4.21. MS (*m/z*, %): 341 (10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.38 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.52 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4Cl), 7.60 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.67 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 8.15 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4Cl) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 106.10, 115.96, 117.64, 123.11, 124.94, 133.41, 154.09, 159.09, and 162.21 (carbons of coumarin moiety), 126.75, 129.92, 132.23 and 141.97 (carbons of C_6H_4Cl), 161.86 (C=N), 193.63 (C=S) ppm.

3-(4-Bromophenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4c**): Yellow powder, m.p. 156–158 °C, IR (KBr) (ν_{max} cm^{-1}): 1710, 1616, 1587, 1445, 1393, 1251, 1195, 1101. Anal. Calcd for $C_{17}H_8BrNO_3S$: C, 52.87; H, 2.09; N, 3.63. Found: C, 52.74; H, 2.03; N, 3.75. MS (*m/z*, %): 386 (3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.40 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.61 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.66 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.72 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4Br), 8.08 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4Br) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 106.18, 115.97, 117.67, 123.09, 124.92, 133.40, 154.12, 159.06 and 162.39 (carbons of coumarin moiety), 127.22, 130.74, 132.28, and 141.92 (carbons of C_6H_4Cl), 161.80 (C=N), 193.89 (C=S) ppm.

3-(3-Nitrophenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4d**): Yellow powder, m.p. 180–182 °C, IR (KBr) (ν_{max} cm^{-1}): 1713, 1629, 1533, 1441, 1382, 1253, 1211, 1109. Anal. Calcd for $C_{17}H_8N_2O_5S$: C, 57.95; H, 2.29; N, 7.95. Found: C, 58.02; H, 2.44; N, 7.83. MS (*m/z*, %): 352 (5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.41 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.63 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.67 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.81-8.57 (4H, m, 4CH of $C_6H_4NO_2$) ppm.^{13}C NMR (125.8 MHz, $CDCl_3$): δ 106.46, 115.64, 117.76, 125.09, 125.72, 133.64, 154.12, 158.79 and 161.58 (carbons of coumarin moiety), 122.98, 129.49, 130.14, 130.93, 136.39 and 149.02 (carbons of $C_6H_4NO_2$), 161.16 (C=N), 195.11 (C=S) ppm.

3-(4-Nitrophenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4e**): Yellow powder, m.p. 171–173 °C, IR (KBr) (ν_{max} cm^{-1}): 1708, 1654, 1588, 1495, 1390, 1251, 1229, 1118. Anal. Calcd for $C_{17}H_8N_2O_5S$: C, 57.95; H, 2.29; N, 7.95. Found: C, 58.02; H, 2.44; N, 7.83. MS (*m/z*, %): 352 (8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (2 H, m, 2 CH of coumarin moiety), 7.51 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$), 7.63 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 8.05 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 8.26 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 106.42, 116.98, 117.40, 124.31, 124.68, 133.23, 154.38, 158.92 and 162.06 (carbons of coumarin moiety), 123.57, 127.71, 133.07 and 149.49 (carbons of $C_6H_4NO_2$), 161.28 (C=N), 194.89 (C=S) ppm.

3-(4-Methylphenyl)1-thioxo-1H-4,9-dioxa-2-aza-phenanthren-10-one (**4f**): Yellow powder, m.p. 127–129 °C, IR (KBr) (ν_{max} cm^{-1}): 17012, 1672, 1593, 1484, 1395, 1262, 1217, 1170. Anal. Calcd for $C_{18}H_{11}NO_3S$: C, 67.28; H, 3.45; N, 4.36. Found: C, 67.45; H, 3.50; N, 4.51. MS (*m/z*, %): 321 (8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (3 H, s, CH_3), 7.35 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.41 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.52 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4CH3), 7.62 (1 H, t, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 7.69 (1 H, d, $^3J_{HH}$ = 8 Hz, C*H* of coumarin moiety), 8.24 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 CH of C_6H_4CH3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.9 (*C*H_3), 106.07, 116.95, 117.14, 124.31, 124.60, 133.17, 153.97, 158.77 and 162.25 (carbons of coumarine moiety), 126.6, 128.08, 130.02, 144.32 (carbons of C_6H_4CH3), 161.28 (C=N), 194.12 (C=S) ppm.

We gratefully acknowledge financial support from the Research Council of Islamic Azad University of Yazd and The Islamic Azad University of Zahedan of Iran.

Received 3 November 2010; accepted 16 November 2010
Paper 1000421 doi: 10.3184/174751911X556729
Published online: 21 January 2011

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