Iron-catalyzed, Microwave-Promoted One-Pot Synthesis of 9-substituted Xanthenes by the Cascade Benzylolation-Cyclization Process

Xiaobing Xu, Xiaolei Xu, Hongfeng Li, Xin Xie and Yanzhong Li*

Institute of Medicinal Chemistry, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai, 200062, P. R. China

Table of Contents	Pages
The characterization data of compounds 3a-n , 1a-f , 4a-b , 5a-b	S1-S7
References	S7
¹ H and ¹³ C NMR spectra of all new compounds	S8-S31

Experimental section

General Methods. All reactions were carried out using a CEM Explorer microwave synthesizer. DMF was distilled from magnesium sulfate anhydrous, dried overnight. ¹H and ¹³C NMR spectra were recorded at 400 MHz, in CDCl₃ (with 1% TMS) solutions. ¹H NMR spectra was recorded with CDCl₃ (δ = 7.25 ppm) or with tetramethylsilane (δ = 0.00 ppm) as internal reference; ¹³C NMR spectra was recorded with CDCl₃ (δ = 77.00 ppm) or C₆D₆ (δ = 128.02 ppm) as internal reference.

A typical procedure for the Fe-catalyzed formation of 9H-xanthene:

1-(2-bromophenyl)ethyl acetate (**1a**) (1.0 mmol), 4-methyl phenol (**2a**) (4.0 mmol) and FeCl₃ (0.05 mmol) was added orderly to a dried 10mL microwave reaction tube. The tube was sealed and irradiated on a CEM Explorer microwave synthesizer at 50°C for 10 min. After cooling to room temperature, DMF (4mL), Cs₂CO₃ (5.0 mmol) was added, it was stirred at room temperature for 10 min, then at 130°C for 10 min under microwave irradiation conditions. After cooling to room temperature, the mixture was quenched with water and extracted with Et₂O (3 x 15mL). The extract was washed with brine and dried over MgSO₄. The solvent was evaporated under vacuo and the residue was purified by chromatography on silica gel. A colorless oil of

product (151 mg, 72%) was obtained. **2,9-dimethyl-9H-xanthene (3a)**. ^1H NMR (CDCl_3 , Me_4Si) δ 1.51(d, $J = 8.0\text{Hz}$, 3H), 2.36(s, 3H), 4.06(q, $J = 8.0\text{Hz}$, 1H), 6.98-7.28(m, 7H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 20.68, 27.30, 33.21, 116.09, 116.34, 122.91, 126.12, 126.50, 127.37, 128.07, 128.32, 128.59, 132.36, 149.16, 151.46. HMRS calcd for $\text{C}_{15}\text{H}_{14}\text{O}$ 210.1045, found 210.1042.

2-methyl-9H-xanthene (3b). Isolated yield 50%, white solid, Mp 86-87°C. ^1H NMR (CDCl_3 , Me_4Si) δ 2.23(s, 3H), 3.93(s, 2H), 6.85-6.96(m, 5H), 7.07-7.18(m, 2H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 20.63, 27.88, 116.12, 116.40, 120.16, 120.56, 122.72, 127.54, 128.17, 128.90, 129.20, 132.26, 149.80, 152.11. HMRS calcd for $\text{C}_{14}\text{H}_{12}\text{O}$ 196.0888, found 196.0887.

9-ethyl-2-methyl-9H-xanthene (3c). Isolated yield 64%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 0.63(t, $J = 8.0\text{Hz}$, 3H), 1.64-1.68(m, 2H), 2.21(s, 3H), 3.80(t, $J = 8.0\text{Hz}$, 1H), 6.85-6.97(m, 5H), 7.06-7.10(m, 2H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 9.67, 20.71, 33.41, 39.99, 115.87, 116.14, 122.77, 124.81, 125.11, 127.32, 128.00, 128.63, 128.88, 132.24, 150.25, 152.52. HMRS calcd for $\text{C}_{16}\text{H}_{16}\text{O}$ 224.1201, found 224.1201.

2-methyl-9-phenyl-9H-xanthene (3d). Isolated yield 66%, white solid, Mp 142-143°C. ^1H NMR (CDCl_3 , Me_4Si) δ 2.11(s, 3H), 5.09(s, 1H), 6.74(s, 1H), 6.81-7.17(m, 11H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 20.66, 44.15, 116.25, 116.48, 122.99, 123.96, 124.45, 126.55, 127.76, 128.31, 125.58, 128.70, 129.69, 129.85, 132.50, 146.66, 148.96, 151.16. HMRS calcd for $\text{C}_{20}\text{H}_{16}\text{O}$ 272.1201, found 272.1205.

2,4,9-trimethyl-9H-xanthene (3e). Isolated yield 70%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 1.43(d, $J = 8.0\text{Hz}$, 3H), 2.26(s, 3H), 2.33(s, 3H), 3.98(q, $J = 8.0\text{Hz}$, 1H), 6.83-6.99(m, 2H), 7.01-7.08(m, 2H), 7.14-7.19(m, 2H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 15.81, 20.64, 27.33, 33.54, 116.44, 122.86, 125.23, 125.86, 126.03, 126.80, 127.24, 128.20, 129.54, 131.73, 147.43, 151.66. HMRS calcd for $\text{C}_{16}\text{H}_{16}\text{O}$ 224.1201, found 224.1200.

12-methyl-12*H*-benzo[*a*]xanthene (3f). Isolated yield 40%, colorless liquid. ¹H NMR (CDCl₃, Me₄Si) δ 1.51(d, *J* = 8.0Hz, 3H), 4.71(q, *J* = 8.0Hz, 1H), 7.03-7.49(m, 6H), 7.52-7.57(m, 1H), 7.70(d, *J* = 8.0Hz, 1H), 7.81(d, *J* = 8.0Hz, 1H), 8.03(d, *J* = 8.0Hz, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 26.00, 30.27, 116.29, 117.98, 118.41, 122.18, 123.54, 123.98, 126.59, 126.77, 127.43, 128.13, 128.50, 128.77, 130.78, 131.33, 148.99, 151.19. HMRS calcd for C₁₈H₁₄O 246.1045, found 246.1041.

2-chloro-9-methyl-9*H*-xanthene (3g). Isolated yield 77%, colorless liquid. ¹H NMR (CDCl₃, Me₄Si) δ 1.52(d, *J* = 8.0Hz, 3H), 4.07(q, *J* = 8.0Hz, 1H), 7.03-7.28(m, 7H); ¹³C NMR (CDCl₃, Me₄Si) δ 27.13, 33.10, 116.39, 117.77, 123.42, 125.62, 127.47, 127.66, 127.72, 128.00, 128.08, 128.26, 149.85, 150.93. HMRS calcd for C₁₄H₁₁ClO 230.0498, found 230.0504.

2-bromo-9-methyl-9*H*-xanthene (3h). Isolated yield 60%, colorless liquid. ¹H NMR (CDCl₃, Me₄Si) δ 1.35(d, *J* = 8.0Hz, 3H), 3.90(q, *J* = 8.0Hz, 1H), 6.80-7.22(m, 7H); ¹³C NMR (CDCl₃, Me₄Si) δ 27.18, 33.01, 115.14, 116.40, 118.20, 123.43, 125.65, 127.66, 128.26, 128.59, 130.37, 130.96, 150.36, 150.86. HMRS calcd for C₁₄H₁₁BrO 273.9993, found 273.9991.

2-chloro-9-phenyl-9*H*-xanthene (3i). Isolated yield 71%, white solid, Mp 144-145°C. ¹H NMR (CDCl₃, Me₄Si) δ 5.23(s, 1H), 7.03-7.34(m, 12H); ¹³C NMR (CDCl₃, Me₄Si) δ 44.28, 116.51, 117.93, 123.48, 123.63, 125.98, 126.91, 127.85, 127.97, 128.04, 128.32, 128.87, 129.28, 129.66, 145.69, 149.59, 150.67. HMRS calcd for C₁₉H₁₃ClO 292.0655, found 292.0661.

9-cyclohexyl-2-methyl-9*H*-xanthene (3j). Isolated yield 73%, white solid, Mp 74-75°C. ¹H NMR (CDCl₃, Me₄Si) δ 0.80-0.84(m, 3H), 0.86-0.99(m, 2H), 1.30-1.60(m, 6H), 2.24(s, 3H), 3.61(d, *J* = 4.0Hz, 1H), 6.87-7.13(m, 7H); ¹³C NMR (CDCl₃, Me₄Si) δ 20.78, 26.17, 26.44, 26.48, 29.26, 29.51, 45.91, 47.69, 115.73,

116.02, 122.53, 124.59, 124.78, 127.27, 127.93, 129.35, 129.62, 132.02, 151.00, 153.30. HMRS calcd for C₂₀H₂₂O 278.1671, found 278.1667.

2-chloro-9-cyclohexyl-9H-xanthene (3k). Isolated yield 40%, white solid, Mp 102-103°C. ¹H NMR (CDCl₃, Me₄Si) δ 0.79-0.91(m, 3H), 0.96-1.05(m, 2H), 1.30-1.60(m, 6H), 3.62(d, *J* = 4.0Hz, 1H), 6.92-7.16(m, 7H); ¹³C NMR (CDCl₃, Me₄Si) δ 26.09, 26.34, 26.38, 29.19, 29.36, 45.78, 47.65, 116.11, 117.41, 123.07, 123.96, 126.55, 127.36, 127.52, 127.59, 128.87, 129.31, 151.69, 152.79. HMRS calcd for C₁₉H₁₉ClO 298.1124, found 298.1125.

2-methyl-9-*p*-tolyl-9H-xanthene (3l). Isolated yield 75%, white solid, Mp 128-129°C. ¹H NMR (CDCl₃, Me₄Si) δ 2.17(s, 3H), 2.24(s, 3H), 5.12(s, 1H), 6.81-7.13(m, 11H); ¹³C NMR (CDCl₃, Me₄Si) δ 20.64, 20.95, 44.07, 116.20, 116.43, 122.95, 124.13, 124.64, 127.65, 128.13, 128.47, 129.37, 129.63, 129.80, 132.42, 136.05, 143.80, 148.95, 151.14. HMRS calcd for C₂₁H₁₈O 286.1358, found 286.1363.

2-chloro-9-*p*-tolyl-9H-xanthene (3m). Isolated yield 59%, white solid, Mp 122-123°C. ¹H NMR (CDCl₃, Me₄Si) δ 2.26(s, 3H), 5.11(s, 1H), 6.94-7.16(m, 11H); ¹³C NMR (CDCl₃, Me₄Si) δ 20.96, 43.86, 116.46, 117.88, 123.46, 123.84, 126.20, 127.82, 127.86, 127.95, 128.18, 129.25, 129.55, 129.63, 136.51, 142.84, 149.58, 150.67. HMRS calcd for C₂₀H₁₅ClO 306.0811, found 306.0810.

2-bromo-9-*p*-tolyl-9H-xanthene (3n). Isolated yield 38%, white solid, Mp 133-134°C. ¹H NMR (CDCl₃, Me₄Si) δ 2.25(s, 3H), 5.09(s, 1H), 6.92-7.24(m, 11H); ¹³C NMR (CDCl₃, Me₄Si) δ 20.96, 43.76, 115.27, 116.45, 118.30, 123.47, 123.87, 126.69, 127.94, 128.15, 129.54, 129.62, 130.74, 132.18, 136.48, 142.82, 150.07, 150.58. HMRS calcd for C₂₀H₁₅BrO 350.0306, found 350.0302.

The starting materials of benzylic compounds were synthesized according to the modified reported methods.^{1,2,3}

A typical procedure for the preparation of benzyl acetate¹

A solution of 1-(2-bromophenyl) ethanone (1.0 mmol) in THF/H₂O (V/V=30/1) was added NaBH₄ (0.5 mmol), the mixture was stirred at room temperature for 2h, after the reaction was completed, it was quenched with water and extracted with Et₂O (3×20mL). The combined extract was washed with brine and dried over MgSO₄. The solvent was evaporated under vacuo and the residue was dissolved in dichloromethane (5mL), after cooling to 0°C, pyridine (2.0 mmol) and acetyl chloride (2.0 mmol) was added orderly, stirred at 0°C for 1h. After the reaction was completed, it was quenched with water, extracted with ethyl acetate (3×20 mL), and dried over MgSO₄. The solvent was evaporated under vacuo and the residue was purified by chromatography on silica gel. A colorless oil (240mg, total yield of two steps: 99%) was obtained. **1-(2-bromophenyl)ethyl acetate (1a)**. ¹H NMR (CDCl₃, Me₄Si) δ 1.44(d, *J* = 8.0Hz, 3H), 2.02(s, 3H), 6.08(q, *J* = 8.0Hz, 1H), 7.02-7.08(m, 1H), 7.21-7.027(m, 1H), 7.37(d, *J* = 8.0Hz, 1H), 7.45(d, *J* = 8.0Hz, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 21.04, 21.08 71.38, 121.82, 126.66, 127.66, 128.99, 132.78, 141.16, 169.74. MS calcd for C₁₀H₁₁O₂⁺(M-Br) 163, found 163.

2-bromobenzyl acetate (1b). Isolated yield 99%, colorless liquid. ¹H NMR (CDCl₃, Me₄Si) δ 2.06(s, 3H), 5.12(s, 2H), 7.11-7.26(m, 2H), 7.33(d, *J* = 8.0Hz, 1H), 7.49(d, *J* = 8.0Hz, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 20.74, 65.66, 123.28, 127.37, 129.57, 129.71, 132.70, 135.11, 170.44. MS calcd for C₉H₉O₂⁺(M-Br) 149, found 149.

1-(2-bromophenyl)propyl acetate (1c). Isolated yield 70%, colorless liquid. ¹H NMR (CDCl₃, Me₄Si) δ 0.89(t, *J* = 8.0Hz, 3H), 1.77-1.82(m, 2H), 2.04(s, 3H), 5.98(t, *J* = 8.0Hz, 1H), 7.01-7.7.26(m, 2H), 7.31(d, *J* = 8.0Hz, 1H), 7.47(d, *J* = 8.0Hz, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 9.70, 21.04, 28.47, 75.88, 122.28, 127.15, 127.48, 128.92, 132.78, 140.26, 170.00. MS calcd for C₁₁H₁₃O₂⁺(M-Br) 177, found 177.

(2-bromophenyl)(phenyl)methyl acetate (1d). Isolated yield 75%, white solid. Mp

83-84°C. ^1H NMR (CDCl_3 , Me_4Si) δ 2.20(s, 3H), 7.19-7.44(m, 8H) 7.52(d, $J = 8.0\text{Hz}$, 1H), 7.61(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 21.08, 75.72, 123.05, 127.56, 128.09, 128.37, 128.44, 129.36, 133.02, 138.62, 139.35, 169.54. MS calcd for $\text{C}_{15}\text{H}_{13}\text{BrO}_2$ 304, found 304.

(2-bromophenyl)(cyclohexyl)methyl acetate (1e). Isolated yield 32%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 1.04-1.34(m, 6H), 1.53-1.70(m, 5H), 1.94(s, 3H), 5.84(d, $J = 8.0\text{Hz}$, 1H), 6.95-6.98(m, 1H), 7.13-7.7.20(m, 1H), 7.21(d, $J = 8.0\text{Hz}$, 1H), 7.39(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 20.65, 25.66, 25.89, 25.99, 27.75, 28.74, 42.47, 78.08, 122.89, 127.03, 127.82, 128.59, 132.42, 139.28, 169.58. MS calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2^+$ (M-Br) 231, found 231.

(2-bromophenyl)(p-tolyl)methyl acetate (1f). Isolated yield 81%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 2.13(s, 3H), 2.32(s, 3H), 7.12-7.15(m, 4H), 7.24-7.34(m, 3H), 7.47(d, $J = 8.0\text{Hz}$, 1H), 7.54(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 21.12, 75.12, 123.00, 127.52, 127.65, 128.24, 129.15, 129.27, 133.04, 135.67, 137.95, 139.51, 169.60. MS calcd for $\text{C}_{16}\text{H}_{15}\text{BrO}_2$ 318, found 318.

1-bromo-2-(1-bromoethyl)benzene (4a). Isolated yield 67%, light yellow liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 2.00(d, $J = 8.0\text{Hz}$, 3H), 5.58(q, $J = 8.0\text{Hz}$, 1H), 7.06-7.12(m, 1H), 7.26-7.33(m, 1H), 7.50(d, $J = 8.0\text{Hz}$, 1H), 7.62(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 25.97, 47.36, 122.96, 128.00, 128.17, 129.55, 132.91, 141.73.

1-bromo-2-(bromo(phenyl)methyl)benzene (4b). Isolated yield 49%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 6.69(s, 1H), 7.10-7.16(m, 1H), 7.22-7.37(m, 4H), 7.42-7.48(m, 2H), 7.54(d, $J = 8.0\text{Hz}$, 1H), 7.68(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 53.56, 122.99, 127.91, 128.13, 128.52, 128.55, 129.57, 131.53, 132.97, 139.87, 140.16.

1-(2-bromophenyl)ethyl ethyl carbonate (5a). Isolate yield 61%, light yellow liquid.

^1H NMR (CDCl_3 , Me_4Si) δ 1.29(t, $J = 8.0\text{Hz}$, 3H), 1.56(d, $J = 8.0\text{Hz}$, 3H), 4.17(q, $J = 8.0\text{Hz}$, 2H), 6.05(q, $J = 8.0\text{Hz}$, 1H), 7.11-7.17(m, 1H), 7.29-7.36(m, 1H), 7.47(d, $J = 8.0\text{Hz}$, 1H), 7.52(d, $J = 8.0\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 14.16, 21.26, 63.98, 74.98, 121.57, 126.51, 127.82, 129.16, 132.75, 140.88, 154.17.

(2-bromophenyl)(phenyl)methyl ethyl carbonate (5b). Isolated yield 80%, colorless liquid. ^1H NMR (CDCl_3 , Me_4Si) δ 1.29(t, $J = 8.0\text{Hz}$, 3H), 4.19(q, $J = 8.0\text{Hz}$, 2H), 7.05(s, 1H), 7.13-7.18(m, 1H), 7.27-7.37(m, 4H), 7.38-7.46(m, 2H), 7.50-7.58(m, 2H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 14.18, 64.32, 79.14, 122.84, 127.47, 127.70, 128.26, 128.28, 128.47, 129.51, 132.99, 138.16, 139.06, 154.21.

Reference:

1. (a) Hurski, A. L.; Sokolov, N. A.; Kulinkovich, O. G. *Tetrahedron*, **2009**, 65, 3518.
(b) Kapeller, D. C. ; Hammerschmidt, F. *Chem. Eur. J.* **2009**, 15, 5729.
2. Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner, F. S. *J. Med. Chem.* **2009**, 52, 1639.
3. Pothukanuri, S.; Pianowski, Z.; Winssinger, N. *Eur. J. Org. Chem.* **2008**, 3141.

3a

3a

3b

3b

3c

3c

3d

3d

3e

3e

3f

3f

3h

3h

3

3

3j

3j

1b

1b

1c

1c

1d

1d