



One-pot synthesis of novel spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]-dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives

D. Ashok*, D. Shrivani

Department of Chemistry, Osmania University, Hyderabad 500 007, India

ARTICLE INFO

Article history:

Received 29 July 2008

Revised 1 October 2008

Accepted 4 October 2008

Available online 8 October 2008

Keywords:

One-pot

Microwave irradiation

Resorcinol

Cyclic ketone

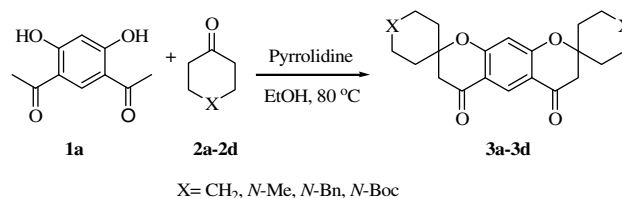
ABSTRACT

An efficient synthesis of novel spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives in high yields under microwave irradiation is described. The reaction was also studied under conventional heating conditions.

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1. Introduction

Flavanone and its derivatives exhibit a broad array of biological activities¹ such as anti-tumour, anti-inflammatory and anti-oxidant. Further flavanones have also been investigated as TNF- α inhibitors and as selective oestrogen receptor modulators.² Due to these potential applications, various approaches have been reported for the synthesis of flavanone derivatives.³ Although various synthetic routes are available, novel derivatives of flavanones, in particular, substituted spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives,⁴ are limited. The development of methodologies for new chemical entities is an important area of research, which aids in drug-discovery. Earlier, our research group reported different types of methods for the preparation of flavanone derivatives.^{4,5} In continuation of our interest, herein we describe the synthesis of novel spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives under microwave irradiation as well as conventional heating conditions (Scheme 1). In recent years, microwave-assisted organic synthesis (MAOS) has attracted the attention of synthetic chemists.⁶ The rate of a reaction is accelerated under microwave irradiation compared to conventional heating.

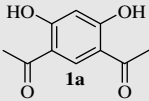
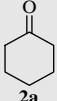
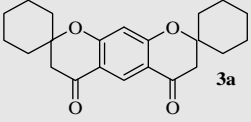
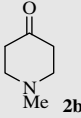
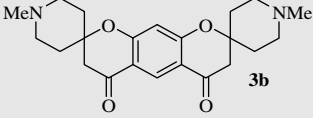
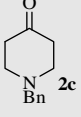
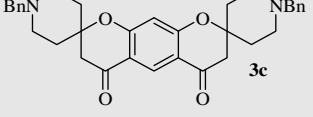
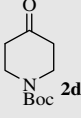
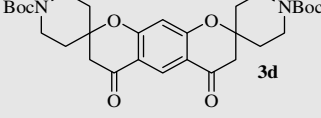
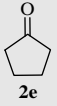
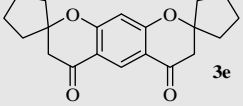
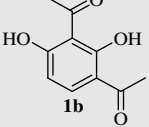
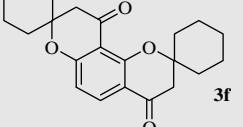
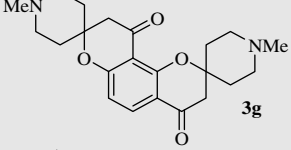
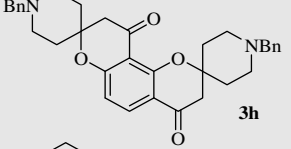
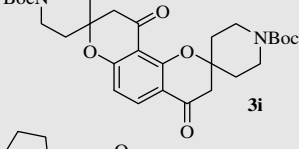
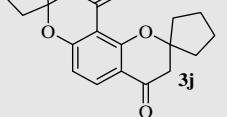


Scheme 1. Synthesis of spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives.

We chose diacetyl resorcinols and cyclic ketones as convenient starting materials to afford the spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione structures. Accordingly, in the first instance 4,6-diacetyl resorcinol (**1a**) and cyclohexanone (**2a**) were stirred together in the presence of pyrrolidine and subjected to microwave irradiation for 4 min and then poured into ice-cold water and filtered to afford the corresponding spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione derivative **3a**, in 95% yield. The same product was also obtained (90%) under conventional heating (80 °C) in ethanol for 10 h (Table 1, entry 1). To further investigate this result, various substituted cyclic ketones such as *N*-methyl, *N*-benzyl and *N*-tert(butoxycarbonyl) cyclohexanones, **2b–d** and cyclopentanone **2e** were treated with resorcinol **1a** under microwave irradiation in the presence of pyrrolidine to afford the corresponding spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione derivatives **3b–e** in good yields (entries 2–5).

* Corresponding author. Tel.: +91 9391024769; fax: +91 040 27664499.
E-mail address: ashokdou@gmail.com (D. Ashok).

Table 1One-pot synthesis of spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives

Entry	Substituted resorcinol	Ketone	Time		Product ^b	Yield ^c (%)	
			MW	(80 °C) ^a		MW	(80 °C) ^d
1			4 min	(10 h)		95	(90)
2	1a		5 min	(10 h)		93	(90)
3	1a		5 min	(10 h)		89	(84)
4	1a		5 min	(10 h)		90	(93)
5	1a		4 min	(10 h)		90	(85)
6		2a	5 min	(12 h)		92	(90)
7	1b	2b	6 min	(12 h)		95	(90)
8	1b	2c	6 min	(12 h)		90	(85)
9	1b	2d	6 min	(12 h)		92	(90)
10	1b	2e	5 min	(12 h)		95	(90)

^a Time for conventional heating (80 °C) reaction in ethanol.^b The products were characterized by ¹H NMR, mass and IR spectra.^c Isolated yields.^d Yield after conventional heating (80 °C) reaction in ethanol.

Next, the reaction of 2,6-diacetyl resorcinol **1b**, and cyclohexanone **2a** in the presence of pyrrolidine under microwave irradiation for 5 min gave the 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivative **3f**, in 92% yield (entry 6). To further explore substrate **1b**, cyclic ketones **2b–e** were reacted to give the corresponding products **3g–j** in very good yields (entries 7–10).

All these reactions were also run under conventional heating (80 °C) in ethanol, in order to compare the efficiency with microwave irradiation (Table 1, entries 1–10). All the obtained products were fully characterized by spectroscopic methods.⁷

In conclusion, an efficient synthesis of novel spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-

benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives under microwave irradiation conditions has been achieved. This new class of spiro 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-*b*:4,3-*b'*]dipyran-4,10-dione derivatives may find utility in medicinal chemistry.

2. Representative experimental procedures

2.1. Microwave heating

Pyrrolidine (0.08 mL) was added to a mixture of 4,6-diacetyl resorcinol (**1a**) (0.19 g, 1 mmol) and cyclohexanone (**2a**) (0.19 mL, 2 mmol), and the mixture was subjected to microwave irradiation for 4 min in a Multisynth series microwave system (Milestone). After cooling the reaction mixture to room temperature, it was poured into ice-cold water and the resulting precipitate was filtered to give the corresponding 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione derivative **3a**, in 95% yield.

2.2. Conventional heating

Pyrrolidine (0.08 mL) was added to a solution of 4,6-diacetyl resorcinol (**1a**) (0.19 g, 1 mmol) in ethanol (5 mL), and the mixture was refluxed for 5 min. Then, cyclohexanone (**2a**) (0.19 mL, 2 mmol) was added. The mixture was refluxed for 10 h and after cooling to room temperature, it was poured into ice-cold water. The resulting precipitate was filtered to afford the corresponding 2,3,7,8-tetrahydro-benzo[1,2-*b*:5,4-*b'*]dipyran-4,6-dione derivative **3a**, in 90% yield.

Acknowledgements

The authors are thankful to Dr. S. Chandrasekhar, Deputy Director, IICT, Hyderabad for fruitful discussions and to Professor K. Veera Reddy, Head, Department of Chemistry, Osmania University, Hyderabad for providing laboratory facilities. Thanks are also due to SERO-UGC, INDIA for financial assistance.

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- Characterization data for representative products (**3a**): Brown solid; mp 160–162 °C; ¹H NMR (200 MHz, CDCl₃): δ 8.4 (1H, s), 6.45 (1H, s), 2.65 (4H, s), 1.9–2.1 (4H, m), 1.3–1.8 (16H, m); ¹³C NMR (75 MHz, CDCl₃): δ 190.4, 165.0, 127.5, 115.6, 105.4, 81.1, 47.9, 34.9, 24.9, 21.3. IR (KBr): ν 1697, 1469, 1250 cm⁻¹; LC MS (*m/z*): 354. Anal. Calcd for C₂₂H₂₆O₄: C, 74.58; H, 7.3. Found: C, 74.39; H, 7.35. Compound (**3c**): White solid; mp 158–160 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.36 (1H, s), 7.24–7.32 (10H, m), 6.47 (1H, s), 3.56 (4H, s), 2.7 (4H, s), 2.62–2.68 (4H, m), 2.35–2.5 (4H, m), 1.99–2.03 (4H, m), 1.73–1.83 (4H, m); ¹³C NMR (75 MHz, CDCl₃): δ 189.3, 188.5, 165.7, 160.0, 154.5, 133.8, 114.8, 111.4, 110.4, 80.0, 48.8, 47.2, 38.9, 33.8. IR (KBr): ν 1693, 1427, 1245 cm⁻¹; LC MS (*m/z*): 536. Anal. Calcd for C₃₄H₃₆N₂O₄: C, 76.12; H, 6.72; N, 5.22. Found: C, 76.11; H, 6.78; N, 5.11. Compound (**3d**): Milky white solid; mp 190–192 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.45 (1H, s), 6.5 (1H, s), 3.75–3.95 (4H, m), 3.1–3.25 (4H, m), 2.73 (4H, s), 1.9–2.1 (4H, m), 1.55–1.7 (4H, m), 1.45 (18H, s); ¹³C NMR (75 MHz, CDCl₃): δ 189.4, 164.5, 154.6, 127.9, 115.9, 105.6, 79.9, 79.2, 47.7, 38.9, 34.1, 27.5. IR (KBr): ν 1684, 1472, 1250 cm⁻¹; LC MS (*m/z*): 556. Anal. Calcd for C₃₀H₄₀N₂O₈: C, 64.75; H, 7.19; N, 5.04. Found: C, 64.58; H, 7.26; N, 4.94. Compound (**3e**): Cream solid; mp 124–126 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.45 (1H, s), 6.35 (1H, s), 2.75 (4H, s), 2.04–2.16 (4H, m), 1.88–1.96 (4H, m), 1.64–1.82 (8H, m); ¹³C NMR (75 MHz, CDCl₃): δ 190.5, 165.47, 127.9, 115.8, 105.7, 90.9, 46.7, 37.5, 23.7. IR (KBr): ν 1695, 1484, 1255 cm⁻¹; LC MS (*m/z*): 326. Anal. Calcd for C₂₀H₂₂O₄: C, 73.62; H, 6.75. Found: C, 73.53; H, 6.81. Compound (**3f**): Cream solid; mp 130–132 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.92 (1H, d, *J* = 8.3 Hz), 6.53 (1H, d, *J* = 8.3 Hz), 2.66 (2H, s), 2.62 (2H, s), 1.22–2.18 (20H, m). IR (KBr): ν 1691, 1425, 1171 cm⁻¹; LC MS (*m/z*): 354. Anal. Calcd for C₂₂H₂₆O₄: C, 74.58; H, 7.3. Found: C, 74.55; H, 7.37. Compound (**3h**): Cream solid; mp 110–112 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.95 (1H, d, *J* = 10.7 Hz), 7.22–7.4 (10H, m), 6.66 (1H, d, *J* = 10.7 Hz), 3.52 (4H, s), 2.7 (4H, s), 2.60–2.69 (4H, m), 2.38–2.52 (4H, m), 2.00–2.12 (4H, m), 1.78–1.9 (4H, m). IR (KBr): ν 1703, 1427, 1180 cm⁻¹; LC MS (*m/z*): 536. Anal. Calcd for C₃₄H₃₆N₂O₄: C, 76.11; H, 6.78; N, 5.11. Found: C, 76.10; H, 6.76; N, 5.30. Compound (**3i**): Cream solid; mp 170–172 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.02 (1H, d, *J* = 10.5 Hz), 6.62 (1H, d, *J* = 10.5 Hz), 3.8–4.05 (4H, m), 3.15–3.30 (4H, m), 2.70 (4H, s), 1.98–2.1 (4H, m), 1.55–1.80 (4H, m), 1.45 (18H, s); ¹³C NMR (75 MHz, CDCl₃): δ 189.2, 188.4, 165.6, 160.0, 154.4, 133.7, 114.7, 111.4, 110.3, 80.0, 79.8, 79.4, 78.7, 48.7, 47.1, 38.8, 33.8, 29.5, 28.3, 28.2. IR (KBr): ν 1703, 1427, 1180 cm⁻¹; LC MS (*m/z*): 556. Anal. Calcd for C₃₀H₄₀N₂O₈: C, 64.75; H, 7.19; N, 5.04. Found: C, 64.70; H, 7.22; N, 4.96. Compound (**3j**): Cream solid; mp 106–108 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.9 (1H, d, *J* = 8.8 Hz), 6.5 (1H, d, *J* = 8.8 Hz), 2.8 (2H, s), 2.75 (2H, s), 1.1–2.2 (16H, m); ¹³C NMR (75 MHz, CDCl₃): δ 190.5, 189.5, 166.7, 161.5, 133.3, 130.7, 128.6, 111.2, 91.5, 90.4, 47.8, 45.6, 37.4, 37.3, 23.7, 23.5. IR (KBr): ν 1693, 1463, 1269 cm⁻¹; LC MS (*m/z*): 326. Anal. Calcd for C₂₀H₂₂O₄: C, 73.62; H, 6.75. Found: C, 73.50; H, 6.80.