Chinese Journal of Chemistry, **2004**, *22*, 622—626 **Communication**

Dialdehyde in Heterocyclic Synthesis: Synthesis of Compounds Containing Two 4*H*-Benzopyran Building Blocks under Microwave Irradiation

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The syntheses of 4*H*-benzopyran derivatives were investigated using dialdehyde as a key starting material. The reaction proceeds under microwave irradiation in good yield (87%—95%) with short reaction time (5—8 min), therefore providing a rapid and efficient method of synthesizing a variety of compounds containing two 4*H*-benzopyran units.

Keywords 4*H*-benzopyran, dialdehyde, microwave irradiation

Introduction

Pyrans and fused pyrans are biologically interesting compounds with antibacterial activities,[1,2] antifungal activities,[3] antitumor activity[4] and hypotensive effect.[5] On the other hand, some pyran derivatives also have various biological properties like antiproliferation effect,[6] local anesthetic and antiarrhythmic activities,[7] antiallergic effect[8] and hypolipidemic activity.[9] The present study is part of our program aimed at developing new approaches for the synthesis of fused heterocyclic systems. Polyfuctionalised 4*H*-pyrans are the structural unit of a number of natural products[10] and are used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring. 4*H*-Pyran ring can be transformed to pyridine systems related to pharmacologically important calcium antagonists of the dihydropyridine (DHP) type.[11-13]

However, a majority of attention has so far been paid to the development of synthesis of compounds bearing only one 4*H*-benzopyran[14] and those cantaining two 4*H*-pyran units are seldom investigated. Forthermore, the synthesis of a variety of substituted condensed benzopyran derivatives was carried out by traditional heating with long time.[15] Recently, microwave irradiation has been widely used in the synthesis of heterocyclic compounds with good yields and short reaction time.[16] The efficiency of microwave irradiation (MWI) in promoting organic reactions and the success of its application in these heterocyclic synthesis prompted us to extend its application to the synthesis of bifunctional compounds containing two 4*H*-hydrobenzopyran units.

When a mixture of *p*-phenylenedialdehyde or *m*-phenylenedialdehyde **1** and active methylene compounds **2** (in a proper ratio) was radiated in a microwave oven using a small amount of glycol as energy transfer reagent (Scheme 1), the reactions were almost completed in 5—8 min. The reaction mixtures were then cooled and poured into cold water, filtered and washed with a small amount of ethanol. The crude products were purified by recrystallization from 95% ethanol or acetone to afford products with good yields (87%—95%). All the reactions were monitored by thin layer chromatography (TLC) and the experiments were replicated in order to ensure the reproductivity. The main results for the synthesis of these compounds are given in Table 1. It is seen that these reactions had the advantage of short reaction time, good yields, convenient workup procedures and being environmentally friendly. These new classes of compounds are new interesting leading compounds for biological activity evaluation. This work is in progress in our laboratories.

The structures of these new compounds are established on the basis of their spectroscopic and analytical data.

The IR and ^{1}H NMR data of all compounds are consistent with their assigned structures. And the elemental analyses of these compounds are in agreement with their structures. Furthermore, the structure of **8b** was established by an X-ray crystallographic analysis (Figure 1).

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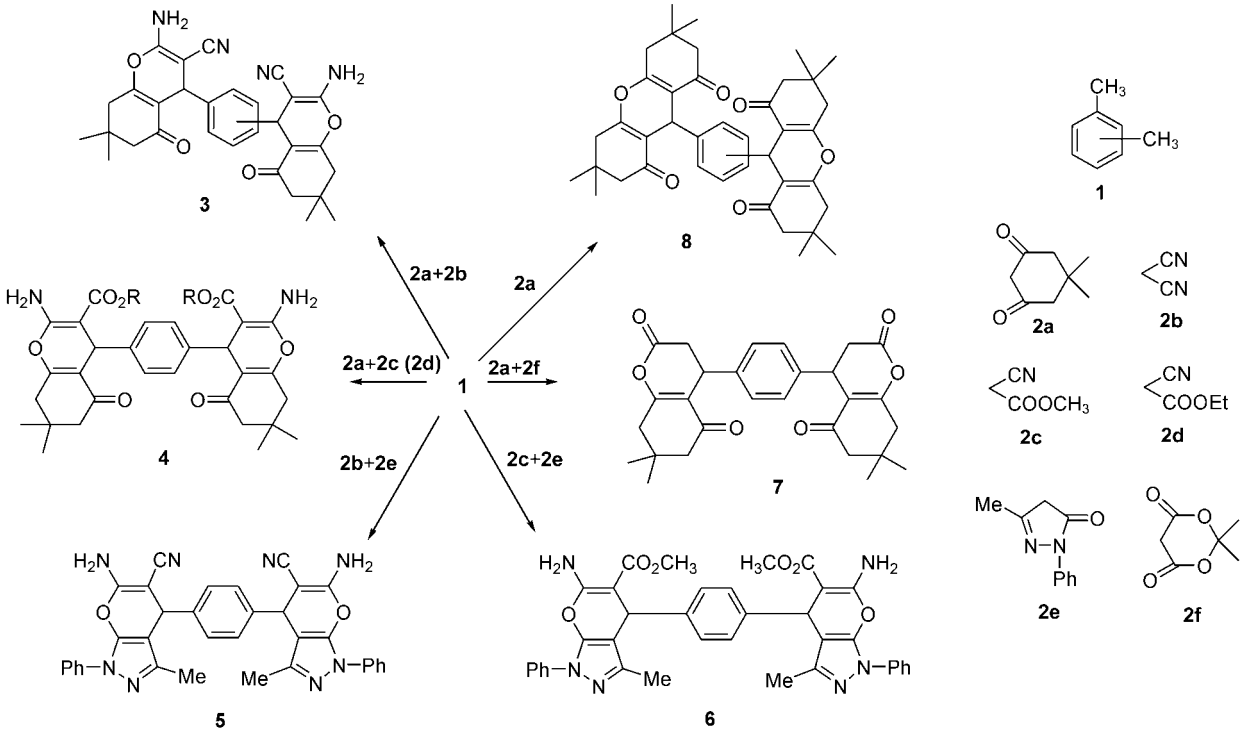
Scheme 1



The X-ray structure of compound **8b** shows that this molecule has two pyran groups. In the molecule, the pyran ring has a boat conformation. The two cyclohexenone rings lateral to the pyran rings have an envelope conformation.

In summary, in view of the utility of MWI and the pharmacological importance of the above-mentioned heterocyclic compounds, we have synthesized a series of new compounds containing two 4*H*-benzopyran units using MWI and have provided a facile, rapid, efficient and environmentally friendly method. These compounds may show interesting and unique properties.

Experimental

Melting points were determined in a capillary tube and were uncorrected. The ^{1}H NMR spectra were recorded on a DPX 400 MHz spectrometer with TMS as internal standard. The IR spectra were obtained with SE-1730 instrument as potassium bromide pellets. Elemental analyses was determined by using a Perkin-Elmer 240c elemental analysis instrument. X-ray data were collected using a Siemens P4 diffractometer. X-ray data were corrected by Lp factors and empirical absorption. The structure was solved by direct methods and expanded using Fourier techniques. Simenes (1994) SHELXTL (Version 5) program systems were used in the solution and refinement of the structure. The non-hydrogen atoms were refined aniso tropically, and hydrogen atoms were refined according to theoretical models. Microwave irradiation was carried out in a commercial microwave oven (2450 MHz) under atmospheric pressure.

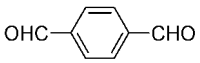
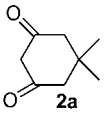
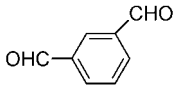
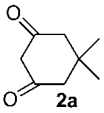
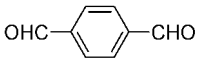
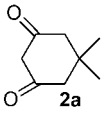
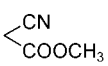
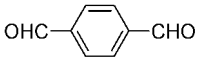
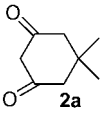
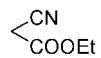
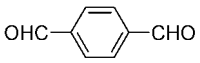
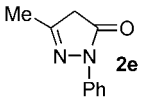
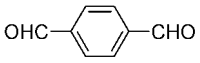
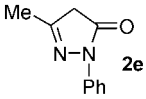
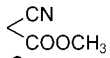
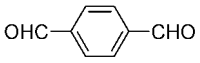
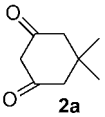
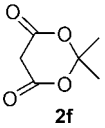
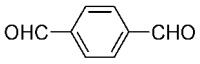
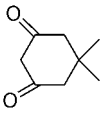
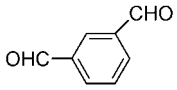
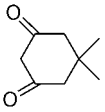
Typical procedure

The preparation of **3a**: A dry flask (25 mL) charged with *p*-phenylenedialdehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol)，malononitrile (2 mmol) and glycol (2 mL) was placed in a microwave oven. The flask was then connected with refluxing equipment. After being irradiated for 5 min, the reaction mixture was cooled and poured into cold water, then filtered and washed with ethanol (3 mL). The crude product was purified by recrystallization from 95% ethanol or acetone to afford products.

1,4-Bis(2-amino-3-cyano-5,6,7,8-tetrahydro-5-oxo-7,7-dimethyl-4*H*-benzo[*b*]pyran-4-yl)benzene (3a) Yield 92%; m.p. ＞300 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.98 (s, 6H, 2×CH_3), 1.03 (s, 6H, 2×CH_3), 2.14—2.56 (m, 8H, 4×CH_2), 4.13 (s, 2H, 2×CH), 6.95 (brs, 4H, 2×NH_2)，7.04 (s, 4H, ArH); IR (KBr) *v:* 3328, 3188, 2960, 2199, 1683, 1657, 1606, 1422, 1365, 1251, 1215, 1161, 1139, 1110, 1036, 974, 862, 794, 564 cm^{-1}. Anal. calcd for $C_{30}H_{30}N_4O_4$: C 70.57, H 5.92, N 10.97; found C 70.61, H 6.32, N 10.33.

1,3-Bis(2-amino-3-cyano-5,6,7,8-tetrahydro-5-oxo-7,7-dimethyl-benzo-[*b*]-pyran-4*H*-yl)benzene (3b) Yield 88%; m.p. ＞300 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.95 (s, 6H, 2×CH_3), 1.05 (s, 6H, 2×CH_3), 2.02—2.61 (m, 8H, 4×CH_2), 4.10 (s, 2H, 2×CH), 6.79 (brs, 4H, 2×NH_2)，6.92—7.02 (m, 4H, ArH); IR (KBr) *v*: 3396, 3302, 2960, 2938, 2189, 1681, 1658, 1606, 1373, 1337, 1250, 1217, 1163, 1143, 1088, 1055, 1037, 944, 885, 8578, 699, 620, 562 cm^{-1}. Anal. calcd for $C_{30}H_{30}N_4O_4$: C 70.57, H 5.92, N 10.97; found C 70.61, H 6.22, N 10.79.

Table 1 Synthesis of bifunctional benzopyran derivatives

Entry	Starting material 1	Starting material 2	Starting material ratio	Time/min	Yield/%
3a		 **2a** +  **2b**	1∶2∶2	5	92
3b		 **2a** +  **2b**	1∶2∶2	5	88
4a		 **2a** +  **2c**	1∶2∶2	6	87
4b		 **2a** +  **2d**	1∶2∶2	8	91
5		 **2e** +  **2b**	1∶2∶2	7	93
6		 **2e** +  **2c**	1∶2∶2	8	90
7		 **2a** +  **2f**	1∶2∶2	8	92
8a		 **2a**	1∶4	8	95
8b		 **2a**	1∶4	5	90

1,4-Bis(2-amino-3-methylcarboxylate-5,6,7,8-tetrahdro-5-oxo-7,7-dimethyl-4*H*-benzo[*b*]pyran-4-yl)benzene (4a) Yield 87%; m.p. 256—257 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.82 (6H, s, 2×CH_3), 1.02 (s, 6H, 2×CH_3), 2.02—2.55 (m, 8H, 4×CH_2), 3.47 (s, 6H, 2×CH_3), 4.44 (s, 2H, 2×CH), 6.93 (brs, 4H, 2×NH_2), 7.46 (s, 4H, ArH); IR (KBr) *v*: 3439, 3295, 2961, 1693, 1644, 1541, 1473, 1369, 1284, 1201, 1167, 1150, 1125, 1109, 1062, 1039, 976, 907, 859, 828, 806, 640, 570, 547 cm^{-1}. Anal. calcd for $C_{32}H_{36}N_2O_8$: C 66.65, H 6.29, N 4.86; found C 66.39, H 6.10, N 4.72.

1,4-Bis(2-amino-3-ethylcarboxylate-5,6,7,8-tetrahydro-5-oxo-7,7-dimethyl-4*H*-benzo[*b*]pyran-4-yl)-benzene (4b) Yield 91%; m.p. 260—261 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.82 (s, 6H, 2×CH_3), 1.00 (t, J= 7.08 Hz, 6H, 2 × CH_3), 1.02 (s, 6H, 2 × CH_3), 2.22—2.60 (m, 8H, 4×CH_2), 3.90 (q, J=7.14 Hz, 4H, 2×CH_2), 4.46 (s, 2H, 2×CH), 6.95 (brs, 4H, 2×NH_2), 7.50 (s, 4H, ArH); IR (KBr) *v*: 3491, 3385, 3309, 2959, 1688, 1664, 1525, 1493, 1369, 1289, 1200, 1165, 1149, 1124, 1089, 1037, 975, 916, 863, 832, 764, 638, 570, 544 cm^{-1}. Anal. calcd for $C_{34}H_{40}N_2O_8$: C 67.53, H 6.67, N 4.63; found C 67.42, H 6.62, N 4.39.

1,4-Bis(2-amino-3-cyano-4*H*-pyrazolo[4,5-*b*]pyran-4-yl)benzene (5) Yield 93%; m.p. >300 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 6H, 2×CH_3), 4.70 (s, 2H, 2×CH), 7.17 (brs, 4H, 2×NH_2); 7.46—7.71 (m, 14H, ArH); IR (KBr) *v*: 3200, 3064, 2885, 2285, 1601, 1556, 1449, 1460, 1315, 1208, 1181, 1113, 902, 825, 782, 752, 688, 672, 641, 602, 543, 495 cm^{-1}. Anal. calcd for $C_{34}H_{26}N_8O_2$: C 70.58, H 4.53, N 19.37; found C 70.77, H 4.72, N 19.62.

1,4-Bis(2-amino-3-ethylcarboxylate-4*H*-pyrazolo[4,5-*b*]pyran-4-yl)benzene (6) Yield

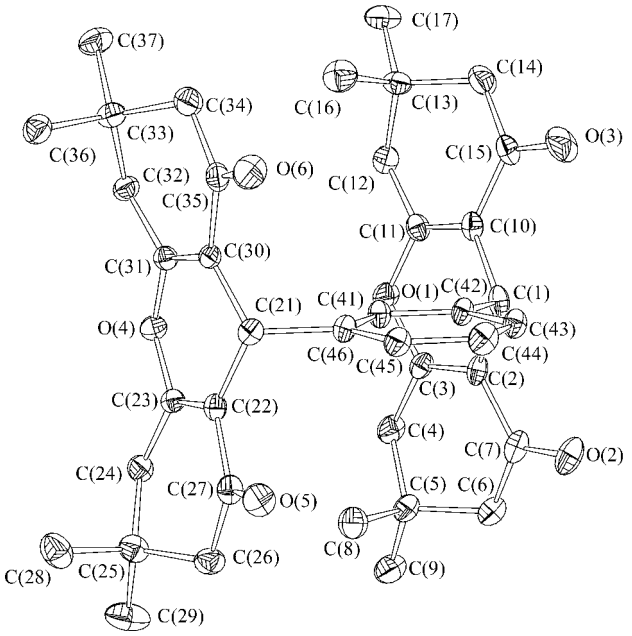


Figure 1 Molecular structure of **8b.**

90%; m.p. >300 ℃; ^{1}H NMR (DMSO-d_6) δ: 2.28 (s, 6H, 2×CH_3), 3.50 (s, 6H, 2×CH_3), 5.00 (s, 2H, 2×CH), 7.17—8.36 (m, 14H, ArH); 7.22 (brs, 4H, 2×NH_2); IR (KBr) *v*: 3365, 3062, 2921, 1729, 1597, 1578, 1500, 1456, 1415, 1372, 1265, 1186, 1125, 1072, 844, 814, 754, 691, 598, 502, 445 cm^{-1}. Anal. calcd for $C_{36}H_{32}N_6O_6$: C 67.07, H 5.00, N 13.04; found C 66.89, H 4.83, N 13.26.

1,4-Bis(7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin-4-yl)benzene (7) Yield 92%; m.p. > 300 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.81 (s, 6H, 2×CH_3), 0.99 (s, 6H, 2×CH_3), 2.02—2.88 (m, 12H, 6×CH_2), 4.46 (s, 2H, 2×CH), 6.97 (s, 4H, ArH); IR (KBr) *v*: 2960, 1782, 1652, 1507, 1468, 1423, 1370, 1311, 1296, 1259, 1236, 1208, 1187, 1162, 1111, 1038, 1016, 973, 960, 926, 860, 844, 819, 654, 619, 588, 551, 504, 422 cm^{-1}. Anal. calcd for $C_{28}H_{30}O_6$: C 72.71, H 6.54; found C 72.73, H 6.75.

1,4-Bis(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene-9-yl)benzene (8a) Yield 95%; m.p. 274—275 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.99 (s, 24H, 8×CH_3), 2.00—2.73 (m, 16H, 8×CH_2), 5.84 (s, 2H, 2×CH), 6.86 (s, 4H, ArH); IR (KBr) *v*: 2960, 2870, 1660, 1599, 1511, 1450, 1373, 1304, 1255, 1168, 1148, 1045, 851, 810, 733, 663, 592, 503 cm^{-1}. Anal. calcd for $C_{40}H_{46}O_6$: C 77.14, H 7.44; found C 77.26, H 7.25.

1,3-Bis(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7-hexahydroxanthene-9-yl)benzene (8b) Yield 91%; m.p. 252—253 ℃; ^{1}H NMR (DMSO-d_6) δ: 0.88 (s, 12H, 4×CH_3), 1.03 (s, 12H, 4×CH_3), 1.99—2.57 (m, 16H, 8×CH_2), 4.47 (s, 2H, 2×CH), 6.88—7.04 (m, 4H, ArH); IR (KBr) *v*: 2963, 2782, 1658, 1449, 1367, 1207, 1170, 1143, 1004, 813, 707, 679, 575, 493 cm^{-1}. Anal. calcd for $C_{40}H_{46}O_6$: C 77.14, H 7.44; found C 77.23, H 7.28.

X-ray structure determination of 8b

Colourless prisms, $C_{40}H_{46}O_6$, M_r=620.77, monoclinic, space group *P*2(1)/*c*, *a*=2.42576(7) nm, *b*=1.02677(5) nm, *c*=1.44606(6) nm, β=106.032(2)°, *V*=3.4616(2) nm^3, *Z*=4, D_{calc}=1.195 g•cm^{-3}, *F*(000)=1336, μ(Mo Kα)=0.079 mm^{-1}, crystal dimensions 0.40 mm×0.40 mm×0.14 mm. Intensity data were collected using a Siemens P4 diffractometer at 293(2) K, graphite monochromator Mo Kα radiation (λ=0.071073 nm), using the ω-2θ scan technique to a maximum 2θ of 44.0°. A total of 7772 reflections were collected with 4244 unique ones (R_{int}=0.0588), of with 2805 reflections were observed with $I>2\sigma(I)$. The final *R* and *wR* values were 0.0882 and 0.162, *s*=1.215, $(\Delta/\sigma)_{max}$=0.002. The maximum peak and minimum peak in the final difference map is 218 and −227 e•nm^{-3}. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-197032.

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