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MICROWAVE-ASSISTED SYNTHESIS AND CRYSTAL STRUCTURE OF NOVEL 2-DICHLOROMETHYL-1,3-DIOXOLANES

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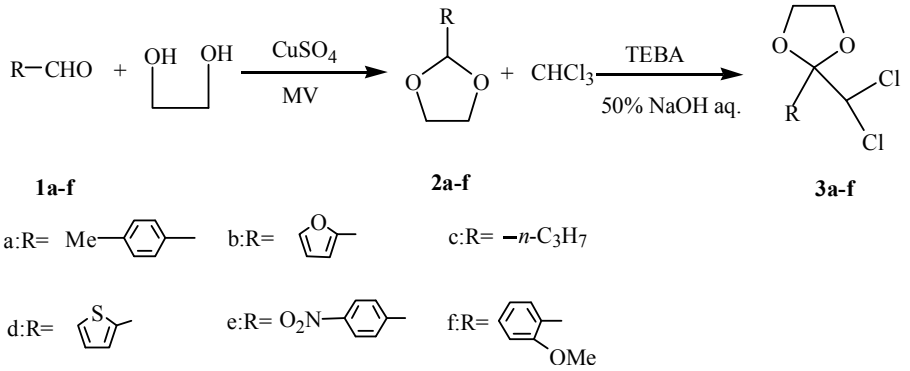
Abstract – An efficient synthesis of 2-dichloromethyl-1,3-dioxolane derivatives with microwave-assisted addition reaction was developed. The intermediate 1,3-dioxolanes **2** were obtained by exposing to microwave radiation with glycol at the present of anhydrous $CuSO_4$. A series of novel 2-dichloromethyl-1,3-dioxolane derivatives **3** were synthesized by carbenes insertion of dioxolanes **2** and chloroform with TEBA used as phase transfer catalyst. The structures of the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and elemental analysis. The configuration of **3f** was determined by X-ray crystallography.

A recent spur of interest in dioxolane derivatives acting as biological materials and intermediates in organic synthesis reflects a compelling need for convenient synthetic routes for them.[1] Depending on the structure of subsitiuents, they have been found to be of interest due to antifungal,[2] antibacterial,[3] antiallodynic,[4] anticonvulstant ones,[5] and so on. In particular, 2-dichloromethyl-1,3-dioxolane derivatives have been investigated for used as herbicide safeners which protect crops from the injury by herbicides.[6] Substituents changing at the dioxolane has showed significant safety activity,[7] which encouraged us to synthesize novel 2-dichloromethyl-1,3-dioxolane derivatives with better biological activity.

Several approaches had been developed to dioxolane derivatives with PTSA,[8] EPZG,[9] CdI_2,[10] choline chloride$\cdot$ $x$$ZnCl_2$ (x = 1-3),[11] trimethylsilylbromide[12] or $ZrO(OTf)_2$[13] used as catalysts. But most of these methods required harsh reaction conditions, expensive catalysts, or resulted in poor yields. Microwave-assisted organic synthesis, as one of the most convenient and efficient paths to obtain organic

compounds, could achieve fast, clean and high-yield transformation.[14] While, there were few reports on microwave-assisted synthesis of 2-dichloromethyl-1,3-dioxolanes. In this study we described the two-step synthesis of 2-dichloromethyl-1,3-dioxolane derivatives **3** by microwave-irradiated acetalization and insertion of dichlorocarbene into the α-C-H bond in corresponding dioxolanes **2** (**Scheme 1**).[15]



Scheme 1. Route for synthesis of 2-dichloromethyl-1,3-dioxolanes

The synthesis of compounds **2** was performed by the cyclization of aldehydes **1** with glycol in the presence of anhydrous $CuSO_4$ under microwave radiation (600W). The reaction conditions and physical data were summarized in **Table 1**. The reaction went smoothly under microwave radiation and afforded products **2** in moderate isolated yields 35.7-57.5%. The conjugation effect of aryl and carbonyl might lead the acetalization easier. The yield of **2c** was lower than others due to the substituent was alkyl on position 2. However, the yield of **2d** was the lowest, which was mainly caused by the instability of thiophene.

Table 1. Intermediate 1,3-dioxolanes 2a-f

Intermediate	Refluxing Temperature (°C)	Microwave-irradiated Time (min)	Yield (%)	Product Status
2a	105	24	57.5	colorless oil
2b	105	24	45.0	light yellow oil
2c	95	24	43.4	colorless oil
2d	90	50	35.7	light yellow oil
2e	100	60	50.6	light green solid
2f	100	60	54.2	colorless oil

The target compounds **3** were obtained by insertion of dichloromethyl in corresponding dioxolanes **2** with chloroform by stirring 24-28 h at 0-5 °C, TEBA used as the phase transfer catalyst. The process was monitored by thin-layer chromatography. Low temperature was employed for the reaction being exothermic. The structures of all the compounds **2** and **3** were supported by MS, IR, ^{1}H-NMR, ^{13}C-NMR spectral data and elemental analysis.

The IR spectra of compounds **3a-f** showed bands at 1007-1283 cm^{-1} due to C-O, which confirmed the formation of dioxolane. The ^{1}H-NMR spectra of **3a-f** exhibited a single signal in the range δ 5.51-6.11 for the proton of -CH-Cl_2. For the asymmetry of dioxolane with different substituents at position 2, the four hydrogen atoms of dioxolane splited at δ 4.24-4.37 and 3.94-4.14 ppm. In the ^{13}C-NMR spectra, the signals observed in the region of δ 74.58-76.63 ppm accounted for the carbon of -CH-Cl_2, and δ 66.68-67.45 ppm accounted for the two carbon of -O-CH_2-CH_2-O-. The elemental analysis of **3a-f** agreed with the molecular formulas of these compounds.

Finally, the single crystal of **3f** was obtained by dissolving it in ethanol and light petroleum, followed by slow evaporation. The X-ray data were collected on a Bruker AXS II CCD area-detector diffractometer with Mo-Kα graphite-monochromated radiation (λ = 0.71073 Å) at 293(2) K. The structure was solved by direct method using SHELXS-97, and refined by full matrix least squares on F^2, SHELXL-97.[16] The molecular structure and the packing view of **3f** were shown in **Figure 1** and **Figure 2**, respectively. The dioxolane was in an envelope conformation with the C atom forming the flap. The bond lengths and bond angles of the dioxolane were both normal (**Table 2**). In the crystal structure, molecules were linked by weak intermolecular C—H…O hydrogen bonds to form one-dimension chains (**Figure 2**), which stabilized the crystal structure. No significant π-π interactions were found in the crystal structure.

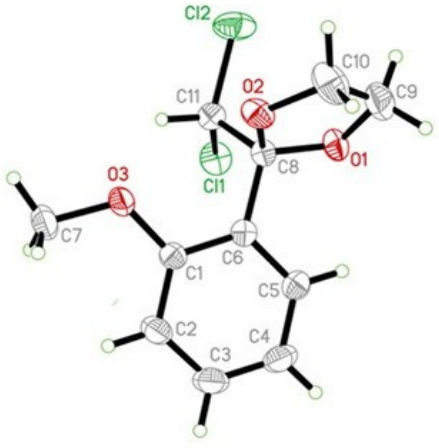


Figure 1. Molecular structure for compound **3f** at 30% probability level

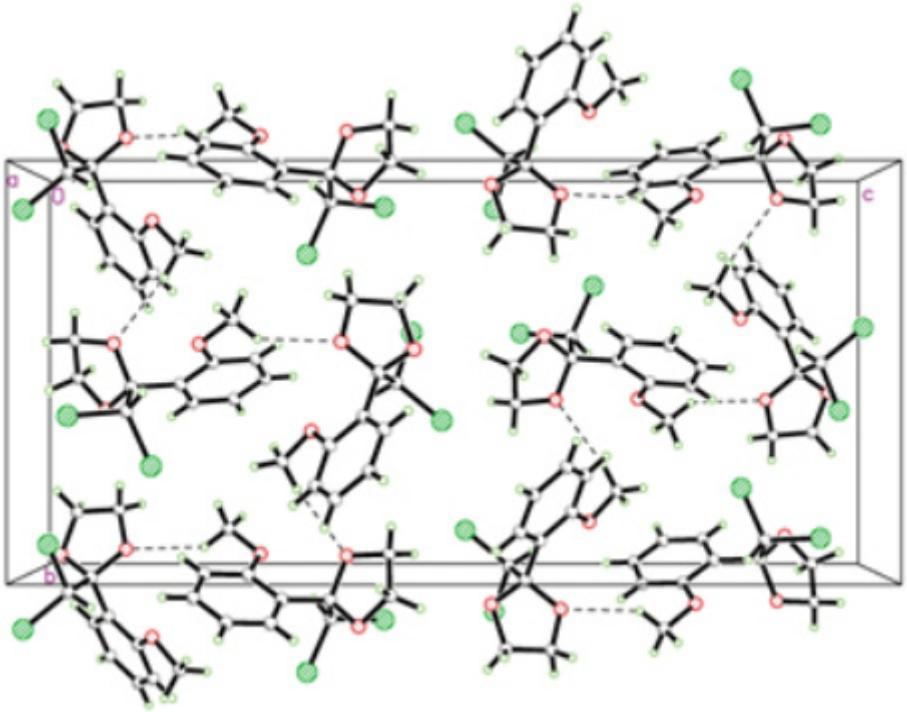


Figure 2. Packing view of the compound **3f**

Table 2. Selected bond lengths (Å) and angles (°) with their standard deviations relevant to **3f**

C1-O3	1.371(3)	C6-C8	1.523(3)
C7-O3	1.425(3)	C8-O1	1.407(3)
C8-O2	1.419(2)	C8-C11	1.541(3)
C9-O1	1.417(4)	C9-C10	1.461(5)
C10-O2	1.392(4)	C11-Cl1	1.772(2)
C11-Cl2	1.776(3)		
O3-C1-C2	123.1(2)	C1-C6-C8	121.67(19)
C5-C6-C8	120.1(2)	O1-C8-C6	110.68(19)
O1-C8-O2	107.83(18)	O1-C8- Cl1	109.47(18)
O2-C8-C6	109.85(16)	C6-C8-C11	111.76(18)
O2-C8-C11	107.11(18)	O2-C10-C9	107.6(2)
O1-C9-C10	106.3(3)	C8-C11-Cl2	110.80(17)
Cl1-C11-Cl2	109.25(12)	C8-C11-Cl1	110.73(16)
O3-C1-C6	116.5(2)		

EXPERIMENTAL

The IR spectra were taken on a KJ-IN-27G infrared spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANVE 300 MHz and 400 MHz, with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer. The melting points were determined on a Beijing Taike melting point apparatus(X-4) and are uncorrected. The automatic microwave synthesizer was XH-100B of Beijing Xianghu Company. All the reagents were of analytical reagents grade.

General procedure for the preparation of 2-substituted-1,3-dioxolanes (2a-f)

A mixture of aldehyde (**1**, 0.1 mol), glycol (0.15 mol), $CuSO_4$ (1.5 g) and cyclohexane (40 mL) was exposed to microwave radiation (600 W) for 24-60 min with refluxing and removing water. The reaction mixture was cooled and washed with water until the organic phase was colorless. The organic layer was extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude products. Compound **2d** and **2f** were purified on silica gel by column chromatography [*V* (EtOAc): *V* (light petroleum) = 1:30] and compound **2e** was crystallized with EtOAc and light petroleum until the light green crystal was obtained. The other crude products were separated under reduced pressure. The spectra data of the compounds **2a-f** were as follows:

2-*p*-Methylphenyl-1,3-dioxolane (2a). Yield 57.5%. Colorless oil, IR (KBr, cm^{-1}): *v* 2953-2885 (C-H), 1224-1022 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.20-7.40 (m, 4H, Ar-H), 5.81 (s, 1H, -CH-), 4.13-4.16 (m, 2H, -O-CH_2-), 4.04-4.07 (m, 2H, -CH_2-O-), 2.38 (s, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.09, 134.94, 129.07, 129.07, 126.41, 126.41, 103.83, 65.30, 65.30, 21.33. *Anal.* Calcd for $C_{10}H_{12}O_2$: C 73.13, H 7.37. Found: C 73.21, H 7.31.

2-(α-Furyl)-1,3-dioxolane (2b). Yield 45.0%. Light yellow oil, IR (KBr, cm^{-1}): *v* 3124-2892 (C-H), 1225-1014 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.44-7.45 (m, 1H, Ar-H), 6.46-6.48 (m, 1H, Ar-H), 6.37-6.38 (m, 1H, Ar-H), 5.95 (s, 1H, -CH-), 4.13-4.18 (m, 2H, -O-CH_2-), 4.02-4.05 (m, 2H, -CH_2-O-); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 151.03, 143.22, 110.17, 108.81, 97.75, 65.20, 65.20. *Anal.* Calcd for $C_7H_8O_3$: C 59.98, H 5.76. Found: C 59.90, H 5.85.

2-*n*-Propyl-1,3-dioxolane (2c). Yield 43.4%. Colorless oil, IR (KBr, cm^{-1}): *v* 2996-2770 (C-H), 1213-1023 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.84-4.88 (t, *J*=4.8 Hz, 1H, -CH-), 3.95-4.00 (m, 2H, -O-CH_2-), 3.85-3.88 (m, 2H, -CH_2-O-), 1.62-1.69 (m, 2H, C-CH_2-C-), 1.42-1.50 (m, 2H, -C-CH_2-C), 0.94-0.99 (t, *J*=7.3 Hz, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 104.54, 64.84, 64.84, 35.99, 17.48,

14.09. *Anal.* Calcd for $C_6H_{12}O_2$: C 62.02, H 10.42. Found: C 62.10, H 10.36.

2-(α-Thienyl)-1,3-dioxolane (2d). Yield 35.7%. Light yellow oil, IR (KBr, cm^{-1}): *v* 3106-2888 (C-H), 1212-1071 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.31-7.33 (m, 1H, Ar-H), 7.16-7.17 (d, *J*=3.2 Hz, 1H, Ar-H), 6.98-7.00 (m, 1H, Ar-H), 6.11 (s, 1H, -CH-), 4.10-4.16 (m, 2H, -O-CH_2-), 3.96-4.04 (m, 2H, -CH_2-O-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 141.73, 126.67, 126.37, 126.27, 100.26, 65.22, 65.22. *Anal.* Calcd for $C_7H_8O_2S$: C 53.84, H 5.17, S 20.49. Found: C 53.92, H 5.23, S 20.41.

2-*p*-Nitrophenyl-1,3-dioxolane (2e). Yield 50.6%. Light green solid, mp 91-93 °C. IR (KBr, cm^{-1}): *v* 3084-2895 (C-H), 1292-1080 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.24-8.26 (d, *J*=8.8 Hz, 2H, Ar-H), 7.66-7.68 (d, *J*=8.4 Hz, 2H, Ar-H), 5.91 (s, 1H, -CH-), 4.10-4.12 (m, 4H, -O-CH_2-CH_2-O); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 148.45, 144.98, 127.43, 127.43, 123.60, 123.60, 102.27, 65.50, 65.50. *Anal.* Calcd for $C_9H_9NO_4$: C 55.37, H 4.65, N 7.18. Found: C 55.42, H 4.71, N 7.09.

2-*o*-Methoxyphenyl-1,3-dioxolane (2f). Yield 54.2%. Colorless oil, IR (KBr, cm^{-1}): *v* 2952-2885, 1285-1027 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ 7.35-7.58 (m, 2H, Ar-H), 6.91-7.00 (m, 2H, Ar-H), 6.20 (s, 1H, -CH-), 4.12-4.17 (m, 2H, -O-CH_2-), 4.01-4.05 (m, 2H, -CH_2-O-), 3.87 (s, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 157.77, 130.32, 126.75, 125.92, 120.47, 110.77, 99.33, 65.31, 65.31, 55.64. *Anal.* Calcd for $C_{10}H_{12}O_3$: C 66.64, H 6.72. Found: C 66.58, H 6.79.

General procedure for the preparation of 2-dichloromethyl-1,3-dioxolanes (3a-f)

50% NaOH aq. was dropped into mixture of 0.05 mol dioxolane **2**, $CHCl_3$ (60 mL), anhydrous Na_2SO_4 (30 g), and TEBA (2 g) at 0 °C with vigorous stirring over a period of 24-28 h. Then 100 mL water and 100 mL Et_2O were added into the mixture. The aqueous layer was extracted with 50 mL Et_2O for five times. The organic layers were combined and washed with water until pH=7 and dried over anhydrous $MgSO_4$. The ether was removed by distillation. Compounds **3a-b** and **3d** were distilled under reduced pressure. The other crude products were purified on silica gel by column chromatography [*V* (EtOAc): *V* (light petroleum) = 1:30]. The physical and spectra data of the compounds **3a-f** were as follows:

2-Dichloromethyl-2-*p*-methylphenyl-1,3-dioxolane (3a). Yield 30.7%. White solid, mp 56-57 °C; IR (KBr, cm^{-1}): *v* 3016-2870 (C-H), 1226-1023 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.45-7.48 (m, 2H, Ar-H), 7.18-7.21 (m, 2H, Ar-H), 5.83-5.84 (s, 1H, -$CHCl_2$), 4.26-4.30 (m, 2H, -CH_2-O-), 3.97-4.01 (m, 2H, -O-CH_2-), 2.37 (s, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 139.15, 134.33, 128.75, 128.75, 127.00, 127.00, 109.15, 75.55, 66.68, 66.68, 21.31. *Anal.* Calcd for $C_{11}H_{12}Cl_2O_2$: C 53.65, H 4.92. Found: C 53.81, H 4.88.

2-Dichloromethyl-2-(-*α*-furyl)-1,3-dioxolane (3b). Yield 15.1%. White solid, mp 43-44 °C; IR (KBr, cm^{-1}): *v* 3014-2883 (C-H), 1283-1007 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34-7.51 (m, 3H, Ar-H), 5.52 (s, 1H, -$CHCl_2$), 4.26-4.32 (m, 2H, -CH_2-O-), 3.97-4.06 (m, 2H, -O-CH_2-); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.56, 142.41, 109.44, 107.21, 96.35, 75.81, 64.79, 64.79. *Anal.* Calcd for $C_8H_8Cl_2O_3$: C 43.25, H 3.63. Found: C 43.21, H 3.77.

2-Dichloromethyl-2-*n*-propyl-1,3-dioxolane (3c). Yield 39.5%. White solid, mp 85-86 °C, IR (KBr, cm^{-1}): *v* 2900-2830 (C-H), 1224-1039 (C-O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.63 (s, 1H, -$CHCl_2$), 4.20-4.24 (m, 2H, -O-CH_2-), 4.06-4.11 (m, 2H, -CH_2-O-), 1.92-1.98 (m, 2H, -CH_2-), 1.39-1.47 (m, 2H, -CH_2-), 0.93-0.98 (t, *J*=7.4 Hz, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 111.22, 75.04, 67.02, 67.02, 35.75, 16.07, 14.14. *Anal.* Calcd for $C_7H_{12}Cl_2O_2$: C 42.42, H 6.11. Found: C 42.48, H 6.05.

2-Dichloromethyl-2-(-*α*-thienyl)-1,3-dioxolane (3d). Yield 21.1%. White solid, mp 49-50 °C; IR (KBr, cm^{-1}): *v* 3113-2899 (C-H), 1278-1020 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36-7.38 (m, 1H, Ar-H), 7.25-7.28 (m, 1H, Ar-H), 7.03-7.06 (m, 1H, Ar-H), 5.89 (s, 1H, -$CHCl_2$), 4.28-4.35 (m, 2H, -CH_2-O-), 4.11-4.19 (m, 2H, O-CH_2-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 140.23, 127.30, 126.96, 126.87, 108.23, 74.97, 67.06, 67.06. *Anal.* Calcd for $C_8H_8Cl_2O_2S$: C 40.34, H 3.39, S 13.44. Found: C 40.48, H 3.41, S 13.29.

2-Dichloromethyl-2-*p*-nitrophenyl-1,3-dioxolane (3e). Yield 32.6%. White solid, mp 102-103 °C; IR (KBr, cm^{-1}) *v* 3119-2901, 1307-1049 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.24-8.27 (m, 2H, Ar-H), 7.82 (m, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 5.83 (s, 1H, -$CHCl_2$), 4.34-4.35 (m, 2H, -O-CH_2-), 4.02-4.03 (m, 2H, -CH_2-O-); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 148.54, 144.05, 128.56, 128.56, 123.10, 123.10, 108.59, 74.58, 66.97, 66.97. *Anal.* Calcd for $C_{10}H_9Cl_2NO_4$: C 43.32, H 3.27, N 5.06. Found: C 43.30, H 3.24, N 5.09.

2-Dichloromethyl-2-*o*-methoxyphenyl-1,3-dioxolane (3f). Yield 45.8%. White solid; mp 95-96 °C; IR (KBr, cm^{-1}): *v* 3028-2839 (C-H), 1282-1020 (C-O); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.62-7.64 (m, 2H, Ar-H), 6.95-7.00 (m, 2H, Ar-H), 6.67 (s, 1H, -$CHCl_2$), 4.36-4.37 (m, 2H, O-CH_2-), 4.08-4.09 (m, 2H, -CH_2-O-), 3.92 (s, 3H, -CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 156.63, 130.70, 128.14, 125.94, 120.57, 111.75, 109.50, 74.67, 66.98, 66.98, 55.95. *Anal.* Calcd for $C_{11}H_{12}Cl_2O_3$: C 50.38, H 4.62. Found: C 50.29, H 4.71.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structural analysis of **3f** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 892488). Copies may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; by quoting the publication citation and the deposit numbers. [Fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk]

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