

Synthesis of Cyclic Ethers from Diols in the Presence of Copper Catalysts

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Abstract—A number of cyclic ethers, namely tetrahydrofuran, 2,5-dimethyltetrahydrofuran, tetrahydropyran, 1,4-dioxane, oxepane, oxocane, and 1,4-oxathiane, have been synthesized in high yields by intramolecular dehydration of diols in the presence of copper-based catalysts.

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Cyclic ethers constitute an important class of oxygen-containing compounds. Among them, tetrahydrofuran and 1,4-dioxane are most widely used in practice. Tetrahydrofuran is a universal solvent for organic synthesis and manufacture of natural and synthetic resins. 1,4-Dioxane is used for degreasing of parts of electronic devices, in metal processing, cleaning of fabrics, in pharmaceutical industry and organic synthesis [1].

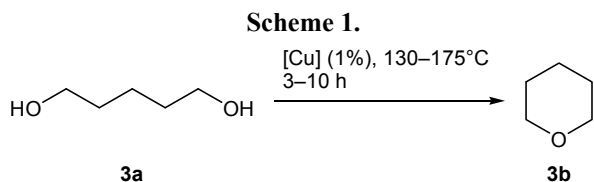
Tetrahydrofuran and 1,4-dioxane are produced on an industrial scale by cyclodehydration of butane-1,4-diol and diethylene glycol, respectively, in the presence of mineral acids (H₂SO₄, H₃PO₄), heteropolyacids, or zeolites [2]. 1,4-Dioxane was also synthesized by cyclodehydration of diethylene glycol in the presence of a number of catalysts such as SO₄²⁻-ZrO₂, H-ZSM5, Al³⁺-montmorillonite K10, Nafion-H, HMPT, and Al₂O₃, and SO₄²⁻-ZrO₂ turned out to be the most efficient [3]. Successful cyclodehydration of α,ω-diols to cyclic ethers was achieved using titanium, zirconium, and hafnium salts and complexes Cp_xMCl_{4-x} (Cp = cyclopentadienyl; M = Ti, Zr, Hf; x = 0–2). The best results were obtained with the use of TiCl₄ and ZrCl₄ which ensured, respectively, 98 and 96% yield of tetrahydrofuran (**1b**) from butane-1,4-

diol (**1a**). The yield of cyclic ethers decreased as the number of methylene units in the α,ω-diol increased. Anhydrous iron(III) chloride also catalyzed cyclodehydration of diols [4].

We have synthesized cyclic ethers such as tetrahydrofuran (**1b**), 1,4-dioxane (**2b**), tetrahydropyran (**3b**), 2,5-dimethyltetrahydrofuran (**4b**), 1,4-oxathiane (**5b**), oxepane (**7b**), and oxocane (**8b**) by cyclodehydration of diols **1a–9a** in the presence of copper catalysts. A number of copper compounds were tested as catalysts in the intramolecular dehydration of pentane-1,5-diol (**3a**) as model reaction: CuCl₂·2H₂O,

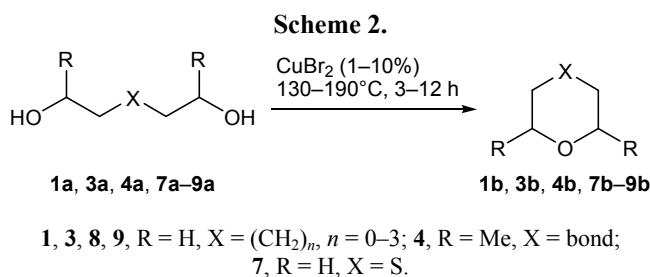
Table 1. Synthesis of tetrahydro-2H-pyran (**3b**) by cyclodehydration of pentane-1,5-diol (**3a**) in the presence of copper catalysts

Catalyst	Temperature, °C	Reaction time, h	Yield of 3b , %
–	175	3	0
CuBr ₂	130	10	0
CuBr ₂	150	10	40
CuBr ₂	175	3	99
CuCl ₂ ·2H ₂ O	175	3	86
CuI	175	3	0
CuBr	175	3	0
Cu(acac) ₂	175	3	0
Cu(OAc) ₂	175	3	0
Cu[C ₆ H ₄ (OH)CO ₂] ₂	175	3	10
Cu(PhCO ₂) ₂ ·2H ₂ O	175	3	5

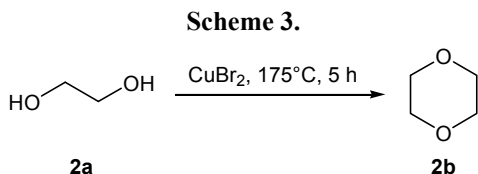


CuBr₂, CuBr, CuI, Cu(OAc)₂, Cu(acac)₂, copper(II) benzoate Cu(PhCO₂)₂·2H₂O, and copper(II) salicylate Cu[C₆H₄(OH)CO₂]₂. The best results were obtained using CuBr₂. The reactions were carried out for 3–10 h at 130–175°C, the catalyst [Cu]-to-substrate **3a** molar ratio being 1:100 (Scheme 1, Table 1). The highest yield of tetrahydropyran **3b** was attained at 175°C (3 h) and a CuBr₂–**3a** ratio of 1:100 (Table 1).

The reaction is general, and butane-1,4-diol (**1a**), pentane-1,5-diol (**3a**), hexane-2,5-diol (**4a**), diethylene glycol (**5a**), triethylene glycol (**6a**), 2,2'-sulfanedioldiethanol (**7a**), and hexane-1,6-diol (**8a**) were converted into the corresponding cyclic ethers **1b–4b**, **7b**, and **8b** in almost quantitative yield (99%). An exception was the reaction with heptane-1,7-diol (**9a**) which produced 65% of oxocane (**9b**) (Scheme 2, Table 2).



The reactions were carried out in an argon atmosphere. No cyclization was observed in the absence of a catalyst. The reaction with solid hexan-1,6-diol (**8a**) was carried out in tetrahydrofuran as solvent. Unlike di- and triethylene glycols **5a** and **6a**, ethylene glycol (**2a**) was converted to 1,4-dioxane (**2b**) as a result of intermolecular dehydration (Scheme 3).



The cyclodehydration of hexane-2,5-diol (**4a**) gave an equimolar mixture of *cis*- and *trans*-2,5-dimethyltetrahydrofurans **4b** whose structure was determined on the basis of one- (¹H, ¹³C) and two-dimensional NMR experiments (COSY, HSQC, HMBC). The structure of **1b–4b** and **7b–9b** was confirmed by NMR and mass spectra, as well as by comparing their characteristics with those of authentic samples and published data [5–7].

Thus, copper(II) bromide effectively catalyzes intramolecular dehydration of diols to the corresponding

Table 2. Synthesis of cyclic ethers from diols in the presence of CuBr₂^a

Diol	Time, h	Product (yield, %)	bp, °C
1a	3	 1b (99)	66 (65–67 [5])
2a	5	 2b (99)	101 (101 [5])
3a	3	 3b (99)	88 (88 [5])
4a	5	 4b (99) (<i>trans/cis</i> 1:1)	90–92 (91–92 [6])
5a	10	2b (99)	101 (101 [5])
6a	6	2b (99)	101 (101 [5])
7a	4	 7b , 99	71–72 (60 mm) (147 [7])
8a	12 ^b	 8b , 99	118–119 (118–119 [5])
9a	3 ^c	 9b , 65	58–59 (40 mm) (140–142 [5])

^a 175°C, CuBr₂–diol, 1:100.

^b 190°C, CuBr₂–**8a**, 10:100.

^c 190°C, CuBr₂–**9a**, 2:100.

cyclic ethers such as tetrahydrofuran, 1,4-dioxane, tetrahydropyran, 2,5-dimethyltetrahydrofuran, 1,4-oxathiane, oxepane, and oxocane.

EXPERIMENTAL

The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400.13 and 100.62 MHz, respectively, using CDCl₃ as solvent; the chemical shifts are given relative to tetramethylsilane.

The mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus instrument (SPB-5 capillary column, 30 m×0.25 mm; carrier gas helium; oven temperature programming from 40 to 300°C at a rate of 8 deg/min; injector temperature 280°C, ion source temperature 200°C; electron impact, 70 eV). Chromatographic analyses were obtained with Shimadzu GC-9A and GC-2014 gas chromatographs (2 m×3-mm column packed with 5% SE-30 on Chromaton N-AW-HMDS; oven temperature programming from 50 to 270°C at a rate of 8 deg/min; carrier gas helium, flow rate 47 mL/min). GC/MS analysis was also performed on a Shimadzu GCMS-QP2010 Ultra instrument (Supel-Q PLOT capillary column, 30 m×0.53 mm; oven temperature programming from 37 to 250°C at a rate of 10 deg/min; carrier gas helium, flow rate 3 mL/min; ion source temperature 200°C; electron impact, 70 eV).

Commercially available butane-1,4-diol, ethylene glycol, pentan-1,5-diol, hexane-2,5-diol, diethylene glycol, triethylene glycol, 2,2'-sulfanedioldiethanol, hexane-1,6-diol, and heptane-1,7-diol were used; liquid diols were distilled before use. The copper compounds CuCl₂·2H₂O, CuBr₂, CuBr, CuI, Cu(OAc)₂, Cu(acac)₂, copper(II) benzoate, and copper(II) salicylate were commercial reagents.

General procedure for the synthesis of cyclic ethers 1b–4b and 7b–9b. The reactions were carried out in a 12-mL glass ampule which was placed in a 17-mL stainless steel high-pressure microreactor. An ampule was charged under argon with 0.2–2 mmol (50–500 mg) of CuBr₂ and 20 mmol of the corresponding diol (1.8 g of **1a**, 1.24 g of **2a**, 2.08 g of **3a**, 2.36 g of **4a**, 2.12 g of **5a**, 3 g of **6a**, 2.44 g of **7a**, 2.36 g of **8a** in 1 mL of THF, or 2.64 g of **9a**). The ampule was sealed and placed in the reactor, and the reactor was tightly closed and heated for 3–12 h at 175–190°C with continuous stirring. The reactor was cooled to ~20°C, the ampule was opened, the mixture was neutralized with 10% aqueous sodium carbonate, and the organic phase was extracted with methylene chloride. The extract was filtered, the solvent was distilled off, and the residue was distilled under atmospheric or reduced pressure. For identification, samples of **1b–4b** and **7b–9b** obtained in 3–6 runs were combined.

Tetrahydrofuran (1b). Yield 1.42 g (99%), colorless liquid, bp 66°C [5]. ¹H NMR spectrum, δ, ppm: 1.84 br.s (4H, 3-H, 4-H), 3.73 br.s (4H, 2-H, 5-H). ¹³C NMR spectrum, δ_C, ppm: 25.60 (C³, C⁴), 67.96

(C², C⁵). Mass spectrum, *m/z* (*I*_{rel}, %): 72 (29) [*M*]⁺, 71 (27), 43 (22), 42 (100), 41 (52), 40 (13), 39 (25), 29 (22), 27 (33), 15 (10). Found, %: C 66.75; H 11.11. C₄H₈O. Calculated, %: C 66.63; H 11.18.

1,4-Dioxane (2b). Yield 1.74 g (99%), colorless liquid, bp 101°C [5]. ¹H NMR spectrum: δ 3.69 ppm, br.s (CH₂). ¹³C NMR spectrum: δ_C 66.97 ppm. Mass spectrum, *m/z* (*I*_{rel}, %): 88 (31) [*M*]⁺, 58 (24), 57 (6), 43 (11), 31 (17), 30 (13), 29 (37), 28 (100), 26 (9), 15 (16). Found, %: C 54.41; H 9.29. C₄H₈O₂. Calculated, %: C 54.53; H 9.15.

Tetrahydro-2H-pyran (3b). Yield 1.70 g (99%), colorless liquid, bp 88°C [5]. ¹H NMR spectrum, δ, ppm: 1.56 m (4H, 3-H, 5-H), 1.62 m (2H, 4-H), 3.64 t (4H, 2-H, 6-H, *J* = 5 Hz). ¹³C NMR spectrum, δ_C, ppm: 23.41 (C⁴), 26.55 (C³, C⁵), 68.65 (C², C⁶). Mass spectrum, *m/z* (*I*_{rel}, %): 86 (50) [*M*]⁺, 85 (57), 56 (59), 55 (23), 45 (56), 41 (100), 39 (29), 29 (51), 28 (59), 27 (501). Found, %: C 69.81; H 11.81. C₅H₁₀O. Calculated, %: C 69.72; H 11.70.

2,5-Dimethyltetrahydrofuran (4b). Yield 1.98 g (99%), colorless liquid, bp 90–92°C [6], a 1:1 mixture of *cis* and *trans* isomers. ¹H NMR spectrum, δ, ppm: *trans* isomer: 1.04 d (6H, CH₃, *J* = 6.5 Hz), 1.27 m and 1.86 m (2H each, 3-H, 4-H), 3.93 m (2H, 2-H, 5-H); *cis* isomer: 1.00 d (6H, CH₃, *J* = 6.5 Hz), 1.27 m and 1.77 m (2H each, 3-H, 4-H), 3.73 m (2H, 2-H, 5-H). ¹³C NMR spectrum, δ_C, ppm: *trans* isomer: 21.17 (CH₃), 32.86 (C³, C⁴), 75.04 (C², C⁵); *cis* isomer: 21.17 (CH₃), 33.99 (C³, C⁴), 74.17 (C², C⁵). Mass spectrum, *m/z* (*I*_{rel}, %): 100 (10) [*M*]⁺, 85 (74), 67 (20), 57 (23), 56 (100), 45 (25), 43 (60), 41 (75), 29 (25), 27 (17). Found, %: C 71.82; H 12.15. C₆H₁₂O. Calculated, %: C 71.95; H 12.08.

1,4-Oxathiane (7b). Yield 2.06 g (99%), colorless liquid, bp 71–72°C (60 mm); published data [7]: bp 147°C. ¹H NMR spectrum, δ, ppm: 2.62 t (4H, 3-H, 5-H, *J* = 5 Hz), 3.91 t (4H, 2-H, 6-H, *J* = 5 Hz). ¹³C NMR spectrum, δ_C, ppm: 27.07 (C², C⁶), 68.79 (C³, C⁵). Mass spectrum, *m/z* (*I*_{rel}, %): 104 (52) [*M*]⁺, 76 (7), 74 (18), 61 (45), 60 (11), 59 (10), 48 (7), 47 (11), 46 (100), 45 (25). Found, %: C 46.29; H 7.85. C₄H₈OS. Calculated, %: C 46.12; H 7.74.

Oxepane (8b). Yield 1.98 g (99%), yellowish liquid, bp 118–119°C [5]. ¹H NMR spectrum, δ, ppm: 1.35 br.s (4H, 4-H, 5-H), 1.57–1.62 m (4H, 3-H, 6-H), 3.39 t (4H, 2-H, 7-H, *J* = 6 Hz). ¹³C NMR spectrum, δ_C, ppm: 26.08 (C⁴, C⁵), 29.56 (C³, C⁶), 70.64 (C², C⁷). Mass spectrum, *m/z* (*I*_{rel}, %): 100 (26) [*M*]⁺, 82 (4), 70

(10), 69 (11), 68 (19), 67 (24), 55 (31), 43 (12), 42 (100), 41 (40). Found, %: C 71.86; H 11.93. C₆H₁₂O. Calculated, %: C 71.95; H 12.08.

Oxocane (9b). Yield 1.48 g (65%), yellowish liquid, bp 58–59°C (40 mm); published data [5]: bp 140–142°C. ¹H NMR spectrum, δ, ppm: 1.33 br.s (4H, 3-H, 7-H), 1.55 br.s (6H, 4-H, 5-H, 6-H), 3.38 t (4H, 2-H, 8-H, *J* = 6 Hz). ¹³C NMR spectrum, δ_C, ppm: 26.11 (C⁴, C⁶), 29.23 (C⁵), 29.64 (C³, C⁷), 70.91 (C², C⁸). Mass spectrum, *m/z* (*I*_{rel}, %): 114 (16) [*M*]⁺, 81 (12), 68 (32), 67 (21), 56 (42), 55 (21), 41 (45), 28 (100), 20 (43), 18 (37). Found, %: C 73.58; H 12.49. C₇H₁₄O. Calculated, %: C 73.63; H 12.36.

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