Iodine-Catalyzed Synthesis of Five-Membered Cyclic Ethers from 1,3-Diols under Solvent-Free Conditions

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Abstract: Intramolecular etherification of 1,3-diols was investigated using iodine as a catalyst under solvent-free conditions. The reaction proceeded to completion in a heterogeneous system. Five-membered cyclic ethers were obtained by intramolecular cyclization of 1,3-diols with dehydration. A propella ether (11-oxatricyclo[4.4.3.0^{1,6}]tridecane) was conveniently synthesized from a 1,3-diol (6-(2-hydroxyethyl)spiro[4.5]decan-6-ol) in 86% yield with carbon skeleton rearrangement under the following conditions: a temperature of 60°C, a molar ratio of 1,3-diol:iodine = 1:0.2, and a time period of 3 h. Bicyclic ethers were also obtained from the corresponding 1,3-diols, but spiro ethers were obtained in lower yield. Terpenic cyclic ethers were efficiently synthesized from the corresponding 1,3-diols, derived from (+)-camphor and (-)-fenchone. In the case of etherification with a mechanism of carbon skeleton rearrangement, the yield of the solvent-free reaction was as high as that of the corresponding reaction in solution. Etherification reactions with carbon skeleton rearrangement proceeded more smoothly than those with hydride shift.

Key words: iodine, solvent-free, 1,3-diol, etherification

1 INTRODUCTION

It is known that five-membered cyclic ethers are obtained by intramolecular cyclization of 1,3-diols in solution using strong acids, such as sulfuric acid, potassium hydrogen sulfate, and p-toluenesulfonic acid, as a catalyst¹⁻⁴. In addition, palladium compounds^{5,6}, triphenylphosphine⁷ and a seleniranium compound⁸ were also reported to be effective catalysts in the cyclic etherification of 1,3-diols. We previously reported efficient intramolecular etherification of 1,3-diols using iodine as a catalyst in solution⁹.

Recently, solvent-free reactions have been investigated from the viewpoint of "green chemistry". In particular, iodine has been studied as an efficient catalyst for various reactions under solvent-free conditions¹⁰⁻²². In this study, intramolecular etherification of 1,3-diols was investigated using iodine as a catalyst under solvent-free conditions.

2 EXPERIMENTAL

2.1 General

NMR spectra were obtained using a 400 or 300 MHz FT-NMR spectrometer (JEOL JNM-LA-400 or Bruker DPX-300) with an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110A and JEOL JMS-AX500.

2.2 Materials

2.2.1 1,3-Diols:

6-(2-hydroxyethyl)spiro[4.5]decan-6-ol (**1a**),
1-(2-hydroxyethyl)spiro[5.5]undecan-1-ol (**1b**),
3-(1-methylcyclopentyl)pentane-1,3-diol (**3a**),
3-(1-methylcyclohexyl)pentane-1,3-diol (**3b**),
3-cyclopentylbutane-1,3-diol (**5a**),
3-cyclohexylbutane-1,3-diol (**5b**),
1-(2-hydroxyethyl)-2-methylcyclohexanol (**7**),
2-(2-hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol

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(9), and

2-(2-hydroxyethyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11),

were prepared by reaction of the corresponding 3-hydroxy acid using lithium aluminum hydride as previously reported⁹.

2.3 Etherification

A typical procedure is as follows: in a reaction tube were placed 198 mg (1.0 mmol) of **1a** and 51 mg (0.2 mmol) of iodine, and the mixture was irradiated with ultrasound at room temperature for 6 h. 20 mL of a 5% aqueous solution of sodium thiosulfate (50 mL) was added to the reaction mixture in order to remove iodine, and the mixture was then extracted with 50 mL of diisopropyl ether three times. The organic layer was washed with 100 mL of water, dried with anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography eluted with hexane / ethyl acetate(10/1). A total of 155 mg (0.86 mmol; 86% yield) of 11-oxatricyclo[4.4.3.0^{1,6}]tridecane **2a** was obtained. The spectroscopic data of the products **2a**, **2b**, **4a**, **4b**, **6a**, **6b**, **10** and **12** were reported previously⁹.

The spectroscopic data of the product from **7** is as follows: 6-methyl-7-oxabicyclo[4.3.0]nonane (**8**)

¹H-NMR(δ , CDCl₃): 1.19(3H, s), 1.2-2.0(11H, m), 3.8(2H, m)

¹³C-NMR(δ , CDCl₃): 22.4, 22.8, 25.6, 6.3, 30.6, 34.1, 42.6, 64.4, 80.4

IR(neat, cm⁻¹): 1448

HRMS calcd for C₉H₁₆O : 140.1201 ; found *m/z* 140.1205

3 RESULTS AND DISCUSSION

The 1,3-diols used as starting materials were prepared by reduction of the corresponding 3-hydroxy acids, as reported previously⁹. The etherification reaction was performed as follows: the appropriate 1,3-diol and iodine were placed in the reaction tube and stirred or irradiated with ultrasound. After the reaction, an aqueous solution of sodium thiosulfate was added in order to remove the iodine, and the product was isolated. After purification, the spectroscopic data of the isolated product indicated the structure of the five-membered cyclic ether. The spectroscopic data of the product obtained from **1a** agreed with those of propella cyclic ether **2a**, which were reported previously⁹. Thus, propella cyclic ether **2a** was obtained from **1a** by dehydration and carbon skeleton rearrangement. Similarly, propella cyclic ether **2b** was obtained from **1b**. The results are summarized in Table 1.

The optimum conditions for the reaction of **1a** were investigated. The starting material and iodine (molar ratio = 1:0.1) were put into a reaction tube and stirred for 24 h. The reaction was attempted at room temperature (entry 1), but the yield was low, at 19%. When irradiation with ultrasound was carried out with a reaction time of 3 h (entry 2), the reaction proceeded further, with a yield of 48%. When the reaction temperature was raised to 60°C (entry 3), the yield of **2a** improved, reaching 63%. When the reaction time was extended to 6 h (entry 4), the yield was almost equal to that obtained with a reaction time of 3 h. However, when the reaction temperature was further raised to 80°C (entry 5), the yield decreased to 34%. Increasing the molar ratio of iodine to 1:0.2 (entry 6) resulted in an improved

Table 1 Intramolecular Cyclic Etherification of 1,3-Diols **1a,b**.

Entry	m	n	Material	I ₂ (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	2	1	1a	0.1	r.t.	24	19
2 ^a	2	1	1a	0.1	r.t.	3	48
3	2	1	1a	0.1	60	3	63
4	2	1	1a	0.1	60	6	58
5	2	1	1a	0.1	80	3	34
6	2	1	1a	0.2	60	3	86
7	2	2	1b	0.1	60	3	22

^a Irradiation with ultrasound was carried out.

yield (86%). Next, the reaction of **1b** was carried out under the reaction conditions shown in entry 3 (entry 7). The spectroscopic data of the product indicated the structure of propella cyclic ether **2b**, and the yield was 22%. Thus, iodine was shown to be an efficient catalyst in the solvent-free synthesis of propella cyclic ether **2a** from the corresponding 1,3-diol, as well as in solution.

A possible reaction mechanism is considered to be as follows: hydrogen iodide, which is initially formed by the interaction of iodine with the hydroxyl group, acts as an acidic catalyst to cause dehydration. An intermediate is formed by skeleton rearrangement, and subsequent nucleophilic attack of the oxygen atom to the carbocation results in the formation of the propella cyclic ether.

The reaction of 1,3-diol **3a** was also investigated using iodine as a catalyst under solvent-free conditions. The product was isolated and the structure was determined based on spectroscopic data as bicyclic ether **4a**. The results under various conditions are shown in Table 2. When the reaction was carried out under the optimum conditions for **1a** (temperature 60°C, time 3 h, molar ratio 1:0.2), the yield of **4a** was 51% (entry 1). However, the reaction time was extended to 6 h, the yield was improved to 62% (entry 2). On the other hand, the reaction temperature was raised to 80°C (entry 3) or lowered to room temperature (entry 4), the yield was reduced. The molar ratio of starting material to iodine was varied from 1:0.1 to 1:0.5 (entries 2, 5, and 6), but the most suitable ratio was found to be 1:0.2 (entry 2). The reaction of **3b** was then carried out under the most suitable conditions for the reaction of **3a**, and the resulting yield was 44% (entry 7), which was attributed to the formation of an unstable seven-membered

ring in the product.

The reaction of 1,3-diol **5a** gave a small amount of spiro ether **6a**. The results obtained under various conditions are summarized in Table 3. Similarly to the reactions of **1a** and **3a**, various reaction conditions (temperature, irradiation with ultrasound, molar ratio of starting material to iodine) were investigated, but the yields of spiro ether **6a** remained below 6%. In the reaction of **5b**, the yield was improved considerably: the value was 46%. This was attributed to the fact that the production of **5b** involves the formation of a stable six-membered ring. The reaction mechanism for the formation of the spiro ethers is considered to be as follows: hydrogen iodide acts as an acidic catalyst, and a carbocation is generated by dehydration; subsequent hydride shift and attack by the hydroxyl oxygen results in the formation of the spiro ether. The preferential formation of the spiro ether is attributed to the instability of the secondary cation as an intermediate. Thus, the reactions of 1,3-diols **5a** and **5b** gave the corresponding spiro ethers, but in low to moderate yield.

Bicyclic ether **8** was obtained from 1,3-diol **7**. The results obtained under various conditions are shown in Table 4. Similarly to the reactions of 1,3-diols **5**, the yields were low under various conditions. The reaction mechanism is considered to be dehydration, followed by hydride shift, and then formation of the ether ring. Thus, it was found that, in these etherification reactions, the reactions with carbon skeleton rearrangement (**1** and **3**) proceeded more smoothly than those with hydride shift (**5** and **7**).

This method was also used for the etherification of terpenic 1,3-diols **9** and **11** derived from (+)-camphor and (-)-fenchone, respectively. The reaction conditions for the

Table 2 Intramolecular Cyclic Etherification of 1,3-Diols **3a,b**.

Entry	n	Material	I ₂ (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	1	3a	0.2	60	3	51
2	1	3a	0.2	60	6	62
3	1	3a	0.2	r. t.	6	-
4	1	3a	0.2	80	6	29
5	1	3a	0.1	60	6	52
6	1	3a	0.5	60	6	42
7	2	3b	0.2	60	6	44

Table 3 Intramolecular Cyclic Etherification of 1,3-Diols **5a,b**.

Entry	n	Material	I ₂ (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	1	5a	0.1	r.t	3	-
2 ^a	1	5a	0.1	r.t.	3	3
3	1	5a	0.1	60	3	6
4	1	5a	0.2	60	3	5
5	1	5a	0.1	80	3	6
6	2	5b	0.1	r.t.	3	2
7	2	5b	0.1	60	6	46
8	2	5b	0.1	80	6	33

^a Irradiation with ultrasound was carried out. **Table 4** Intramolecular Cyclic Etherification of **7**.

Entry	I ₂ (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	0.1	r.t.	3	-
2 ^a	0.1	r.t.	3	9
3	0.1	60	3	10
4	0.1	60	6	9
5	0.2	60	3	7
6	0.1	80	3	-

^a Irradiation with ultrasound was carried out.

etherification of **9** were investigated and the results are summarized in **Table 5**. When the reaction of **9** was carried out at room temperature for 6 h with a 1:0.2 molar ratio of starting material to iodine, the yield of cyclic ether **10** was 65% (entry 1). Thus, 1,3-diol **9** possesses high reactivity. This result was unexpected because steric hindrance in **9**, which has bulky substituents, was greater than in the other 1,3-diols used. Under these conditions, irradiation with ultrasound was carried out (entry 2), but the yield was lower (40%; entry 2). With ultrasound irradiation, the reac-

tion time was shortened to 4 h (entry 3) and the yield was improved considerably to 89%. When the temperature was raised to 80°C for 1 h without ultrasound irradiation, the cyclic ether was not obtained (entry 4). Because **9** has high reactivity, the reaction was carried out over a shorter time of 10 min (entry 5). As a result, the yield was improved to 42%. When the molar ratio of starting material to iodine was changed to 1:0.1 (entry 6), the yield was further improved to 74%. Thus, the yield of **10** was high under mild conditions while the yield was low under harsh conditions.

Table 5 Intramolecular Cyclic Etherification of **9**.

Entry	I ₂ (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	0.2	r.t.	6 h	65
2 ^a	0.2	r.t.	6 h	40
3 ^a	0.2	r.t.	4 h	89
4	0.2	80	1 h	-
5	0.2	80	10 min	42
6	0.1	80	10 min	74

^a Irradiation with ultrasound was carried out. **Table 6** Intramolecular Cyclic Etherification of **11**.

Entry	I ₂ (eq.)	Temp (°C)	Time	Yield (%)
1 ^a	0.2	r.t.	6 h	76
2	0.1	80	10 min	78

^a Irradiation with ultrasound was carried out.

This was attributed to the decomposition of cyclic ether **10** by iodine. The reason **9**, which contains bulky substituents, shows such high reactivity is currently under investigation.

Based on the etherification of **9**, the reaction of 1,3-diol **11** was carried out. The results are shown in **Table 6**. When ultrasound was used at room temperature (entry 1), the yield of cyclic ether **12** was 76%. When 1,3-diol **11** was reacted at 80°C for 10 min using 1:0.1 iodine, the yield was 78%. Similarly to **9**, **11** showed high reactivity despite having bulky substituents.

A comparison of the method using sulfuric acid¹⁾, the reaction using iodine in solution⁹⁾, and the solvent-free

reaction is shown in **Table 7**. Cyclic ethers **10** and **12** were obtained in similar yields using all three methods. Thus, the solvent-free reaction using iodine is comparable in efficiency and utility with the reaction in solution.

In conclusion, the reaction of 1,3-diols using iodine as a catalyst under solvent-free conditions proceeds to give the corresponding five-membered cyclic ethers, and, in the case of those involving carbon skeleton rearrangement, the yields obtained by this method are as high as those obtained in the corresponding solution reactions. In this solvent-free etherification method, the reactions with carbon skeleton rearrangement proceed more smoothly than those with hydride shift.

Table 7 Comparison between Previous Reports and This Report.

Entry	Material	Product	Conditions	Yield (%)
1 ^a	9 (derived from (+)-camphor)	10	H ₂ SO ₄ (0.3eq) / H ₂ O	81
2 ^b	9 (derived from (+)-camphor)	10	I ₂ (0.2eq) / acetonitrile	91
3	9 (derived from (+)-camphor)	10	I ₂ (0.2eq) / solvent free	89 ^c
4 ^a	11 (derived from (-)-fenchone)	12	H ₂ SO ₄ (0.3eq) / H ₂ O	80
5 ^b	11 (derived from (-)-fenchone)	12	I ₂ (0.2eq) / acetonitrile	74
6	11 (derived from (-)-fenchone)	12	I ₂ (0.2eq) / solvent free	76 ^d

^a The results are quoted from ref. 1.^b The results are quoted from ref. 9.^c The results are quoted from entry 3 in **Table 5**.^d The results are quoted from entry 1 in **Table 6**.

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