Notes

A New Method for the Preparation of 2-(*p*-Alkoxy)phenyl-3(2*H*)-dihydrofuranone Derivatives

Jae-Young Choi and Myoung-Seon Gong*

Department of Chemistry, Dankook University Cheonan, Chungnam 330-714, Korea
Received May 16, 1997

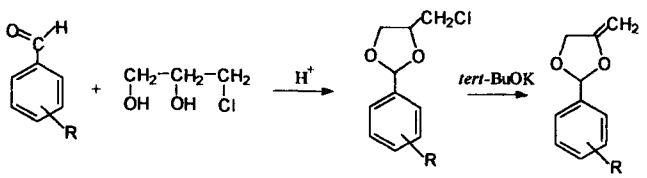
There are several preparative methods for the synthesis of the functionalized 3(2*H*)-dihydrofuranone ring system.[1] The synthesis of simple 2,5-disubstituted or 2,2,4,4-tetrasubstituted 3(2*H*)-dihydrofuranone is usually carried out by mercury catalyzed hydration of alkynic diols.[2] Also the Nazarov-type cyclization of α'-hydroxy-α,β-unsaturated carbonyl compound is one of the method for constructing certain type of furanone via acid catalyzed intermolecular 1,4-addition process.[3] Other method for generating 3(2*H*)-dihydrofuranone is based on Michael addition of anions derived from α-hydroxyesters to α,β-unsaturated carbonyl compound.[4] In spite of the usefulness of these methods in organic synthesis, the limited or particular chemical nature of reactants could be a major drawback for most of this type of organic reaction.

Appropriate exo-methylene or vinylic cyclic compound are the starting substances for the intramolecular cyclization reaction. For example, vinyloxirane,[5] 2,3-divinyloxirane[6,7] and 2-methylene-4-vinyl-1,3-dioxolane[8] were reported to give the corresponding dihydrofuran, oxepine and 2,3,6,7-tetrahydrooxepine-2-one, respectively.

4-Methylene-2-styryl-1,3-dioxolane was also reported to undergo intramolecular alkylation to form 2-styryl-3(2*H*)-dihydrofuranone during the polymerization by BF_3OEt_2.[9] In the course of studying 4-methylene-2-phenyl-1,3-dioxolane (4-MDO) derivatives with special alkyloxy substituent at phenyl group on 2-position, it was found that 2-[*p*-(2-methoxyethoxy)phenyl]-4-MDO (**4a**) would undergo ring-opening, followed by intramolecular cyclization to form 3(2*H*)-dihydrofuranone derivative.[10]

We applied this methodology to the synthesis of 3(2*H*)-dihydrofuranone derivatives. In this paper, we would like to report the cyclization pathway of some 4-MDO derivatives, which was a novel synthetic route to 3(2*H*)-dihydrofuranone from 2-(p-alkoxyphenyl)-4-methylene-1,3-dioxolane derivatives in the presence of boron trifluoride diethyl etherate as an acid catalyst.

Various 4-MDO derivatives, 2-(*p*-methoxyphenyl)-4-methylene-1,3-dioxolane (**1a**) 2-[*o*-(2-methoxyethoxy)phenyl]-4-MDO (**2a**), 2-[*m*-(2-methoxyethoxy)phenyl]-4-MDO (**3a**), 2-[*p*-(2-methoxyethoxy)phenyl]-4-MDO (**4a**), 2-[*p*-[2-(2-methoxyethoxy)ethoxy] phenyl]-4-MDO (**5a**) and 2-[*p*-(2-ethoxyethoxy)phenyl]-4-MDO (**6a**) were synthesized by acetalization of the corresponding *p*-substituted benzaldehyde with 3-chloro-1,2-propanediol, followed by dehydrochlorination with potassium *tert*-butoxide. The synthesis and spectral data of **1a**[11] and **4a**[10] were described in the literature previously reported. But the other 4-MDO derivatives designed in this experiment have been unknown compounds. The spectral data of **6a** as a representative 2-(*p*-alkoxy)phenyl]-4-MDO derivative were described in the experimental section. The 4-MDO derivatives were quite stable at room temperature but were very sensitive to acid moiety.



R : —OCH_3(*p*)(1), —$OCH_2CH_2OCH_3$(*o*)(2), —$OCH_2CH_2OCH_3$(*m*)(3), —$OCH_2CH_2OCH_3$(*p*)(4), —$OCH_2CH_2OCH_2CH_2OCH_3$(*p*)(5), —$OCH_2CH_2OCH_2CH_3$(*p*)(6)

Scheme 1.

Cyclization reactions were carried out in septum rubber capped glass with tube boron trifluoride diethyl etherate. The results and conditions of cyclization reaction are summarized in Table 1. Acid catalyzed reaction of **1a** proceeded *via* ring opening polymerization with rapid formation of poly(keto ether), **1d**. The *p*-methoxyphenyl substituent on the 2-position of 4-MDO certainly make ring-opening more favorable by forming stable resonance intermediate, **1c**, resulting in polymerization. On the other hand, the methoxyethoxy substituted compound, 2-[*p*-(2-methoxyethoxy)phenyl]-4-MDO (**4a**), underwent cyclization reaction to generate 2-[*p*-(2-methoxyethoxy)phenyl]-3(2*H*)-dihydrofuranone (**4g**). When **4a** was reacted with boron trifluoride diethyl etherate at −50 °C, the resulting rearrangement product, 3(2*H*)-dihydrofuranone was isolable by precipitation in cold *n*-haxane.

Another approach toward the isomerization reaction was examined by employing ethoxyethoxy or longer methoxyethoxyethoxy substituted analogues such as 2-[*p*-[2-(2-methoxyethoxy)ethoxy]phenyl]-4-MDO (**5a**) and 2-[*p*-(2-ethoxyethoxy)phenyl]-4-MDO (**6a**), respectively. When the MDO derivatives **5a** and **6a** were reacted with boron trifluoride diethyl etherate, 2-[*p*-[2-(2-methoxyethoxy)ethoxy]phenyl]-3(2*H*)-dihydrofuranone (**5g**) and 2-[*p*-(2-ethoxyethoxy)phenyl]-3(2*H*)-dihydrofuranone (**6g**) were formed quantitatively by acid catalyzed isomerization reaction. The selectivity between ring-

*Corresponding author.

Table I. Conditions and Results of Isomerization reaction of 2-(*p*-Alkoxyphenyl)-4-methylene-1,3-dioxolane Derivatives[a]

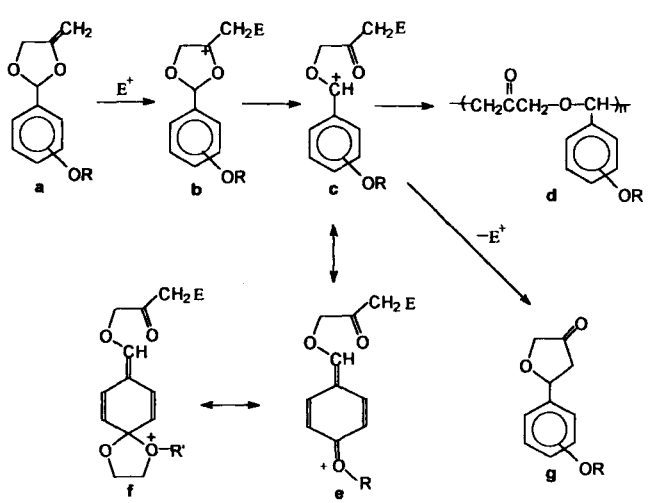
Monomer	Temp. (°C)	Yield[b] (%)	Mw[c] g/mol	Polymerization Content (%)[d]	Cyclization Content (%)[d]
1a	-50	85	4900	100	0
1a	25	84	4900	100	0
2a	-50	82	5900	40-50	50-60
3a	-50	90	9600	100	0
4a	-50	76	-	0	100
4a	25	80	-	5-10	90-95
5a	-50	69	-	0	100
6a	-50	69	-	0	100

[a] Boron trifluoride diethyl etherate (4 mol%) was used as a cationic catalyst. [b] Yields were measured gravimetrically. [c] Weight average molecular weight were taken with a Waters HPLC using three columns (μ-Styragel 10^2, 10^3 and 10^4 Å), calibrated with polystyrene standards in chloroform at 254 nm. [d] The content of ring-opened polymer and cyclization contents were determined gravimetrically.

opening polymerization and cyclization reaction was dependent upon the type of substituent at 2-position of 4-MDO ring. Although the precise mechanism for this rearrangement is not clear at the present time, a possible mechanism is shown in the following Scheme 2.

The reaction may be initiated through electrophile addition from BF_3OEt_2 itself or other cationic species to double bond of 4-MDO derivatives to give the corresponding cationic intermediate **b**. This intermediate may be then subject to isomerization, generating the more stable benzyl cation **c**, followed by other resonance forms **e** and **f**.

The release of ring strain of 1,3-dioxolane ring and the formation of relatively stable carbonyl group are strong driving forces for the ring-opening, and the extra resonance stabilization of ring-opened species is a contributing factor. Subsequently, the formed cationic intermediate may transformed to the product **4g**, **5g** and **6g** by ring-opening and cyclization of **4a**, **5a** and **6a**. This result can be interpreted in terms of the relative stabilities of initially formed cationic intermediate **b** which was easily rearranged to the more stable intermediate **c**. This intermediate was additionally stabilized by the resonance form e and f, thus cyclization took place exclusively to form 3(2*H*)-dihydrofuranone derivatives. Since the stability of these cationic intermediates increased, intramolecular isomerization reaction occured rather than polymerization.



Scheme 2.

It was of interest to compare the amount of ring opening polymerization and cyclization reaction, since the ortho compound **2a** could form ortho-type resonance structures **2e** and **2f**. At −50 °C this intramolecular process was found to compete with the polymerization and made the yield of the cyclization product relatively low. In the ^1H NMR spectrum of the polymerization mixture, the signal assignable to the methine proton on a benzyl carbon atom at 3.9 ppm was observed. Furthermore, two kinds of the signals assignable to the carbonyl carbon in ^{13}C NMR spectrum at 214 and 216 ppm was observed. In the IR spectrum, two splitted carbonyl stretching bands were shown. The stretching band at 1720 cm^{-1} is attributed to carbonyl of poly(keto ether) whereas the higher stretching band at 1752 cm^{-1} is attributable to that of dihydrofuranone. From these spectral data, compound **2a** underwent both ring opening polymerization and cyclization reaction to afford poly(keto ether) **2d** and 2-[*o*-(2-methoxyethoxy)phenyl]-3(2*H*)-dihydrofuranone (**2g**), respectively. Whenever the reaction mixture was distilled by Kugelrohr distillation apparatus, the cyclization product was separated in 50-60% yield.

An interesting extension of this work is achieved by the preparation of ortho- and meta-derivatives, because of differences of their ability in forming resonance stabilization. When **3a** was reacted for 12 h at −50 °C with 4 mol% of boron trifluoride diethyl etherate, a white powdery poly (keto ether), **3d** was isolated after precipitation. Interestingly, the chemical structure of this product was different from the one obtained from the similar monomer **4a**. The resonance forms, **3e** and **3f**, were not obtainable from the compound **3a**, which contributed a relatively lower resonance stabilization energy than para-isomer.

In conclusion, we have performed a novel reaction that the 4-MDO derivatives rearranges with BF_3OEt_2, which suggested a very convenient method for the preparation of 3(2*H*)-dihydrofuranone derivatives, and it was revealed that the content of the cyclization product and polymer was influenced by the substituent at 2-position of phenyl group at 2-position of the starting 4-MDO. Further work on the detailed mechanism of the cyclization is now in progress and will be presented in the furture.

Experimental

All chemicals were commercial products, which were further purified by standard methods before use. Methylene chloride was purified by distillation over sodium metal after drying with calcium hydride. *tert*-Butanol was purified by distillation over sodium metal. Dowex-50W (H+, strong cation exchange resin) was used as an acetalization catalyst. A cationic catalyst, boron trifluoride diethyl etherate

(Aldrich Chem. Co.) was used as recieved.

FT-IR spectra were recorded on with a Midac Model M-1200 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini 2000 spectrometer. ^{13}C NMR spectra were performed on a Bruker Am 300 spectrometer. Elemental analyses were obtained on a Yanaco MT-3 CHN-Analyzer. The mass spectrum was obtained on a HP 5989A mass spectrometer.

2-(p-Alkoxy)phenyl]-4-methylene-1,3-dioxolane (1a-6a). A solution of 50.0 mmol of 4-chloromethyl-2-(*p*-alkoxy)phenyl-1,3-dioxolane in 20 mL of *tert*-butanol was added slowly to the solution of 2.43 g (60.0 mmol) of potassium dissolved in 50 mL of *tert*-butanol at 20 °C under nitrogen atmosphere. After the addition was completed, the temperature was raised to 80 °C and the gentle refluxing was maintained for 24 h. The reaction mixture was cooled and *tert*-butanol was removed by evaporation. The crude product was dissolved in 100 mL of diethyl ether and washed with distilled water several times. After ethyl ether was evaporated, the resulting residue was vacuum distilled through a Vigreux column to give a colorless liquid.

The spectral data of **6a** as a representative 2-(*p*-alkoxy) phenyl]-4-MDO derivative were summarized as follows:

6a: yield 75%; bp 142 °C/ 0.1 torr.; FT-IR (KBr) 3052 (aromatic C-H), 2960-2850 (aliphatic C-H), 1682 (C=C), 1300-1100 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2-6.8 (2d, 4H, aromatic protons), 5.8 (s, 1H, acetal proton), 4.2-3.7 (m, 2d, $=CH_2$), 3.9-3.7 (m, 8H, $-OCH_2CH_2O-$, $-OCH_2C(=CH_2)O-$ and CH_3CH_2O-), 1.2 (t, 3H, CH_3-). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.07; H, 7.03.

Typical reaction of 2-(p-alkoxyphenyl)-4-MDO derivatives 1a-6a with BF_3·Et_2O. To a oven-dried septum rubber capped glass tube with a flush of dry nitrogen, a solution of **5a** (1 g, 5.5 mmol) in 4 mL of purified methylene chloride was injected. The tube was then cooled at − 50 °C and borontrifloride diethyl etherate solution was introduced. After the addition of catalyst, the tube was maintained at − 50 °C for 12h. The reaction mixture was quenched with excess triethylamine and poured into a large amount of cold n-hexane. The white precipitate was washed with distilled water and redissolved in methylene chloride and reprecipitated. The solid powdery product was dried at 50 °C for 12 h under vacuum.

Other 4-MDO derivatives **1a, 2a, 3a, 4a** and **6a** were reacted according to the similar procedures as described above.

1d: yield 90%; FT-IR 3055 (aromatic C-H), 2850 (aliphatic C-H), 1720 (C=O), 1245, 1125, 1062 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.4-7.4 (br, 4H, aromatic protons), 3.9 (m, 1H, -O-CH(Ph-)CH_2-), 3.7 (m, 2H, -CO-CH_2O-), 3.4 (s, 3H, CH_3O-), 2.5-2.3 (2d, 2H, -CO-CH_2-); Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.98; H, 6.21.

4g: yield 85%, mp 55 °C; FT-IR 3054 (aromatic C-H), 2830-2880 (aliphatic C-H), 1718 (C=O), 1250, 1125, 1060 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.4-7.2 (2d, 4H, aromatic protons), 4.9 (m, 1H, -O-CH(Ph-)CH_2-), 3.9-3.7 (m, 6H, $-OCH_2CH_2O-$ and -CO-CH_2O-), 3.3 (s, 3H, CH_3O-), 2.5 (2 d, 2H, -CO-CH_2-); ^{13}C NMR ($CDCl_3$) 214.0 (-CO-), 158.5, 131.9, 127.0, 114.4 (aromatic C's), 78.7 (-O-CH(Ph)-), 71.3, 70.6 ($-OCH_2CH_2O-$), 67.0 (-CO-CH_2-O-), 58.8 (OCH_3), 44.2 (-CH_2-CO-); MS (EI), m/e 237 (M^++1), 236 (M^+), 178, 120, 59, 44; Anal. Calcd for $C_{13}H_{16}O_4$: C, 68.10; H, 6.78. Found: C, 67.23; H, 6.62.

5g: yield 80%, mp 43 °C; FT-IR 3050 (aromatic C-H), 2820-2880 (aliphatic C-H), 1720 (C=O), 1250, 1120, 1060 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.4-7.2 (2d, 4H, aromatic protons), 4.8 (m, 1H, -O-CH(Ph-)CH_2-), 3.9-3.8 (m, 10H, $-OCH_2CH_2OCH_2CH_2-$ and -CO-CH_2O-), 3.4 (s, 3H, CH_3O-), 2.5 (2d, 2H, -CO-CH_2-); ^{13}C NMR ($CDCl_3$) 214.0 (-CO-), 158.7, 131.8, 127.2, 114.6 (aromatic C's), 79.0 (-O-CH (Ph)-), 71.6, 71.2, 70.5 ($-OCH_2CH_2OCH_2CH_2-$), 67.2 (-CO-CH_2-O-), 59.0 (OCH_3), 44.4 (-CH_2-CO-); MS (EI), m/e 281 (M^++1), 280 (M^+), 236, 178, 120, 91, 59, 31; Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.29; H, 7.14. Found: C, 64.01; H, 6.87.

Acknowledgment. This work has been supported by the Korea Science and Engineering Foundation (NL 03171, KOSEF 93-0300-10-01-3), 1995.

References

1. Semple, J. E.; Joulli, M. M. *Heterocycles* **1980**, *14*, 1825.
2. Bennett, G. B.; Houlihan, W. J.; Mason, R. B.; Engstrom, R. G. *J. Med. Chem.* **1976**, *19*, 709.
3. Nazarov, I. N.; Elizarova, A. N. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1948**, 107.
4. Moshfegh, A.; Fallab, S.; Erlenmeyer, H. *Helv. Chim. Acta,* **1957**, *40*, 1157.
5. Eberbach, W.; Burchardt, B. *Chem. Ber.* **1978**, *111*, 3665.
6. Braun, R. A. *J. Org. Chem.* **1963**, *28*, 1383.
7. Kim, B. G.; Park, Y. C.; Kim, C. B.; Gong, M. S. *Polymer (Korea)*, **1990**, *14*, 298.
8. Bailey, W. J.; Zhou, L. L. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, **1988**, *28*(1), 385.
9. Park, J.; Choi, W.; Kihara, N.; Endo, T. *J. Polym. Sci. Part A, Polym. Chem.* **1994**, *32*, 983.
10. Lee, S. J.; Park, J. K.; Gong, M. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 769.
11. Yoon, D. H.; Park, Y. C.; Kim, C. B., Yang, J. K.; Gong, M. S. *Polymer (Korea)*, **1990**, *14*, 82.