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The Synthesis and Regioselective Hydrolysis of Dialkyl 2-Phenylfuran (and 2-Phenyltetrahydrofuran) -3,4-dicarboxylates

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Abstract: Dialkyl 2-phenylfuran (and 2-phenyltetrahydrofuran)-3,4-dicarboxylates (**1**, **2**, **5**-**7**), which are potential precursors of the synthesis of furofuran and tetrahydrofurofuran lignans, can be selectively hydrolyzed to monoacid (**3**, **8**) by potassium hydroxide. The regioselective hydrolysis was affected significantly by the 2-phenyl group of the furan or tetrahydrofuran skeleton. The geometric structures of **3**, **8** and related compounds were elucidated and verified by NMR spectra.

Keywords: Regioselective hydrolysis, NMR spectra, dimethyl 2-phenylfuran-3,4-dicarboxylate.

In the previous paper[1], we reported regioselective hydrolysis of dimethyl 2-phenylfuran-3,4-dicarboxylate **1** to form 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid **3** which paved the way for the synthesis of natural tetrahydrofurofuran lignan[2,3]. The phenomenon of such regioselective hydrolysis was attributed to the steric effect of 2-phenyl group as well as the ring effect of furan skeleton. In this manuscript, we wish to understand more about the effects and the influence of bulkier 4-ester groups on the regioselective hydrolysis of the models of 2-phenylfuran and 2-phenyltetrahydrofuran skeletons.

The starting material dimethyl 2-phenyltetrahydrofuran-3,4-dicarboxylate **2** and dialkyl 2-phenylfuran-3,4-dicarboxylates **5-7** were prepared as shown in **Scheme 1**. Tetrahydrofuran diester **2** was synthesized from furan diester **1** by hydrogenation under 80 atm of hydrogen with palladium-charcoal (10 %, 0.05 eq.) as catalyst in methanol at 80°C for 6 hours (yield 77 %, m.p. 92-93°C). It was noted that the signal at unusually high field (3.19 ppm) in ^{1}H NMR was assigned as the methoxy group adjacent to the phenyl group, analyzing by the COSY and NOESY spectra. It was assumed that the ring current of aromatic group played an important role for the high field chemical shift. Furan diesters **5-7** were prepared as shown in **Scheme 1**[1,4]. Acid **3** was converted to acid chloride **4** by treatment with thionyl chloride in boiling dichloromethane and then reacted with ROH in the presence of triethyl amine to give **5-7**, respectively. The products were purified by column chromatography and the structures were verified by NMR spectra.

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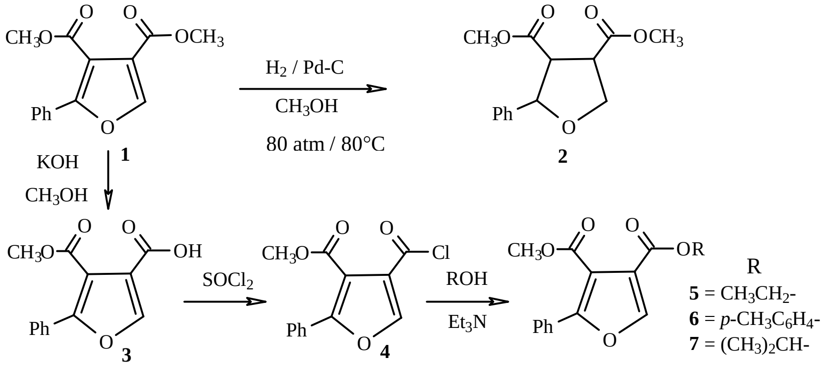
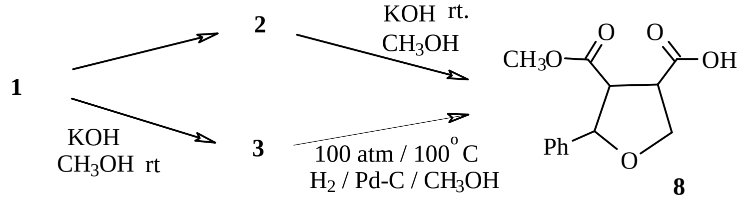
The hydrolysis experiments were carried out by treating the diesters **2**, **5-7** with potassium hydroxide (2.5 mol/L) and stirred for several hours at room temperature. The optimum amount of base for the reaction was 1.0 - 1.2 equivalents. For avoiding overhydrolysis to form diacid, the reactions were terminated while there still remained trace reactant in reaction system. The unreacted reactants were conveniently removed by ethyl ether extraction and the desired monoacids were obtained after acidifying the aqueous component with dilute hydrochloric acid.

Scheme 1



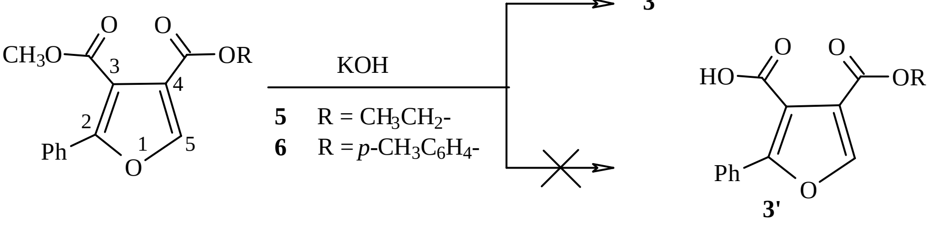
The selective hydrolysis of diester **2** to monoacid **8** was noted by comparison of the NMR spectra of **2** (3.69 and 3.19 ppm) and the product **8** (one singlet at 3.19 ppm). NOESY spectrum indicated that the 4-ester group was hydrolyzed because the protons of methoxy (3.19 ppm) exhibited a long range correlation with the carbon of phenyl (7.30 ppm) and hydrogen at 2-position of THF (5.27 ppm) and no correlation with the methylene group (4.00 and 4.63 ppm). Another support of the structure of **8** was obtained by conversion of furan diester **1** to **8** (**Scheme 2**). It was noted that after hydrogenation (100 atm hydrogen pressure and 100°C in methanol for 8 hours) of furan to tetrahydrofuran the chemical shift of methoxy group was significantly moved to high field (from 3.87 ppm of **2** to 3.19 ppm of **8**). Since the geometric structure of **2** was well established[1], the structure of **8** was further confirmed.

Scheme 2



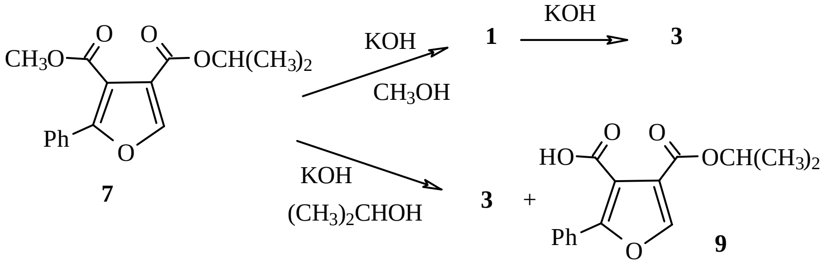
The above result suggested that the strain and resonance effect of furan skeleton were not decisive factors for the regioselective hydrolysis. In order to estimate the role of 2-phenyl and 4-alkyl groups, hydrolysis of diester **5-7** were studied. The hydrolysis of **5** and **6** with KOH were carried out in methanol and THF, respectively, due to solubility consideration. Monoacid **3** was the sole product for both reactions (**Scheme 3**). Though ethyl ester is bulkier and normally less reactive than methyl ester, the reaction of **5** showed that 4-ethyl ester rather than 3-methyl group was hydrolyzed. An even bulkier 4-methyphenyl ester group of **6** was also selectively hydrolyzed and no product of **3'** was detected.

Scheme 3



In the case of 4-*iso*-propyl ester (**Scheme 4**), **3** was the only hydrolyzed product also when reaction was preformed in methanol. Dimethyl ester **1** was noted as side-product and it was proposed that **7** was initially converted to **1**, in the excess methoxide/methanol environment, and then hydrolyzed selectively to **3**. When *iso*-propanol was used as solvent, mixtures of **3** and **9** were obtained with ratio around 2:1 (**Scheme 4**). The reaction was not regiospecific. The geometric configuration of **9** was verified by NOSEY spectra in which the *iso*-propyl hydrogen (1.32 and 5.42 ppm) exhibited a long range correlation with 5-THF hydrogen (8.16 ppm) and no correlation with 2-phenyl hydrogen (7.45-7.80 ppm). The formation of **9** was probably due to the bulky *iso*-propyl group and the less stable *iso*-propanoxy anion that decreased the selectivity of the reaction.

Scheme 4



In summary, it was found that dialkyl 2-phenyltetrahydrofuran-3,4-dicarboxylate **2** and 2-phenylfuran-3,4-dicarboxylates **1**,**5**,**6**,**7** were hydrolyzed predominately and regioselectively at 4-ester group. The strain and resonance effects of furan skeleton were not decisive factors for the selective hydrolysis. The steric hindrance of 2-phenyl group plays a remarkable and decisive role for regioselective but not regiospecific hydrolysis reaction.

References and Notes

1. S. S. Lin, J. H. Yu, J. M. Wang, B. Yang, X. L. Ye, *Chin. Chem. Lett.*, **2000**, *11*, 11.
2. W. M. Hearon, W. S. MacGregor, *Chem. Rev*., **1955**, 957.
3. A. Pelter, R. S. Ward, P. Collins, R. Venkateswarlu, *Chem. Soc. Rev.*, **1985**, 587.
4. W. W. Pei, J. Pei, H. Chen, Y. W. Li, X. L. Ye, *Scientianum Universitatis Pekinensis,* **1993**, *29*, 129.
5. NMR data of compound **2**: ^{1}H NMR (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR, in $CDCl_3$, δppm): 3.19 (s, 3H, OCH_3). 3.59 (m, 1H, 4-THF), 3.61 (s, 3H, OCH_3), 4.32 (t, 1H, J = 8.2 Hz, 5-THF), 4.66 (t, 1H, J = 8.2 Hz, 5-THF), 5.25 (d, 1H, J = 5.0 Hz, 2-THF), 7.30 (m, 5H, Ph); ^{13}C NMR: 47.69, 51.25, 52.08, 52.68, 68.52, 83.38, 125.80, 127.91, 128.02, 137.48, 170.52, 170.75. Compound **5**: ^{1}H NMR: 1.34 (t, 3H, J = 7.2 Hz, CH_3), 3.91 (s, 3H, OCH_3), 4.32 (q, 2H, J = 7.2 Hz, CH_2), 7.40 (m, 3H, Ph), 7.68 (m, 2H, Ph), 7.97 (s, 1H, furan-H). Compound **6**: ^{1}H NMR: 2.36 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.09 (d, 2H, J = 4.3 Hz, *p*-C_6H_4), 7.26 (d, 2H, J = 4.3 Hz, *p*-C_6H_4), 7.41 (m, 3H, Ph), 7.70 (m, 2H, Ph), 8.16 (s, 1H, furan-H). Compound **7**: ^{1}H NMR: 1.32 (d, 6H, J = 6.4 Hz, CH_3), 3.90 (s, 3H, OCH_3), 5.19 (m, 1H, CH), 7.39 (m, 3H, Ph), 7.69 (m, 2H, Ph), 7.95 (s, 1H, furan-H). Compound **8**: ^{1}H NMR: 3.19 (s, 3H, OCH_3), 3.73 (m, 1H, 3-THF), 3.77 (m, 1H, 4-THF), 4.00 (t, 1H, J = 8.6 Hz, 5-THF), 4.63 (t, 1H, J = 8.6 Hz, 5-THF), 5.27 (d, 1H, J = 7.8 Hz, 2-THF), 7.30 (m, 5H, Ph); ^{13}C NMR: 46.68. 51.65, 52.90, 70.10, 83.07, 126.22, 128.04, 128.11, 137.47, 171.02, 177.42. Compound **9**: ^{1}H NMR: 1.42 (d, 6H, J = 6.2 Hz, CH_3), 5.32 (m, 1H, CH), 7.45 (m, 3H, Ph), 7.80 (m, 2H, Ph), 8.16 (s, 1H, furan-H).

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