The Synthesis of 4-Arylcarbonyl-3-methoxycarbonyl-2-phenylfurans by Friedel-Crafts Acylation Reactions

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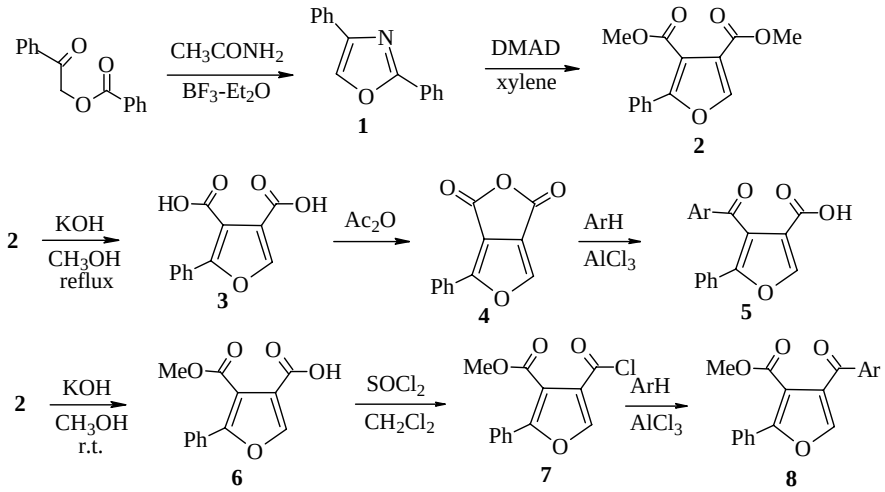
Abstract: Keto esters **8**, 4-arylcarbonyl-3-methoxycarbonyl-2-phenylfurans, potential precursors of the synthesis of furofuran lignans, were obtained from dimethyl 2-phenylfuran-3,4-dicarboxylate **2**. Diester **2** was selectively hydrolyzed to monoacid **6** followed by converting to its acid chloride **7**. Friedel-Crafts acylation reactions of **7** with aromatic compounds afforded keto esters **8**. The geometric structures of **8** and its precursors were elucidated and verified by NMR spectra.

Keywords: Friedel-Crafts acylation, selective mono hydrolysis, furofuran lignan.

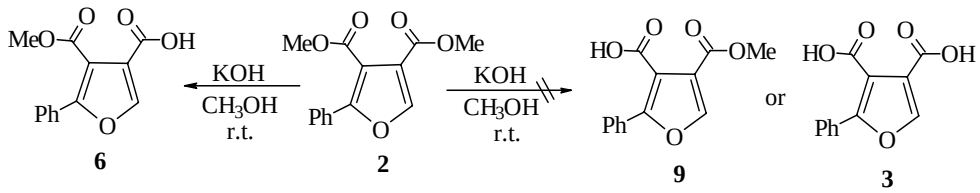
In a previous paper[1], we reported the Friedel-Crafts acylation reactions of 2-phenylfuran-3,4-dicarboxylic acid anhydride **4** with aromatic compounds to form 3-arylcarbonyl-2-phenylfuran-4-carboxylic acids **5**, in which aryl groups were introduced to the 3-position of the 2-phenylfuran skeleton. In this manuscript, we report a synthetic strategy to obtain 4-arylcarbonyl-3-methoxycarbonyl-2-phenylfuran **8** in which aryl group was introduced to the 4-position of the 2-phenylfuran skeleton (**Scheme 1**). **8** is a potential precursor for the synthesis of furofuran lignan[2,3] in the procedure designed by us.

Scheme 1.



This research work started from the studies of the mono hydrolysis reaction of dimethyl 2-phenylfuran-3,4-dicarboxylate **2** which was prepared[4,5] from the Diels-Alder reaction of 2,4-diphenyloxazole[6] **1** with DMAD (dimethylacetylene dicarboxylate). The treatment of diester **2** with potassium hydroxide in cold methanol gave monoacid **6** and the optimum amount of base for the reaction was determined to be 1.2 equivalents. To avoid overreaction for the formation of diacid **3**, the reaction was terminated while there still remained trace reactant in reaction system as was detected by TLC or NMR. The unreacted reactant **2** was conveniently removed by ethyl ether extraction and the desired monoacid **6** was obtained after acidifying the aqueous component with dilute HCl. The selective mono hydrolysis was noted by comparison of the NMR spectra of reactant diester **2** (two methoxy singlets at 3.92 and 3.85 ppm) and product acid **6** (one singlet at 3.87 ppm)[7]. A two dimensional NOESY spectrum was performed to determine which ester group was hydrolyzed and the result indicated that the 4-ester group, the one far away from the 2-phenyl group, was selectively hydrolyzed (**6** but not **9**, **Scheme 2**). As is illustrated in the NOESY spectrum of **6**, the methoxy group (3.87 ppm) exhibits a strong long range NOE interaction with the 2-phenyl group (7.48 ppm) and not with the 5-H furan hydrogen (8.26 ppm).

Scheme 2.

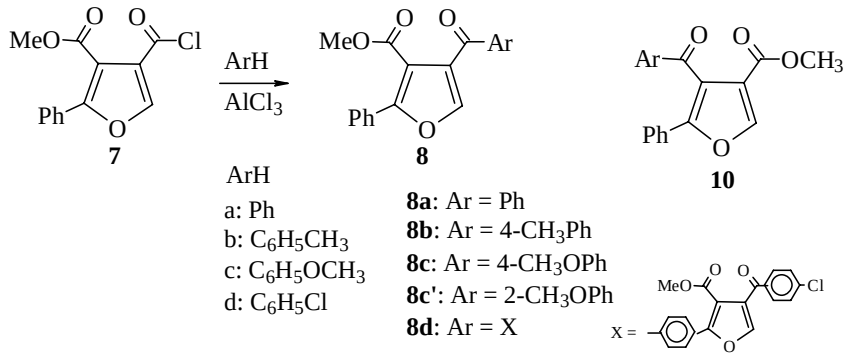


Monoacid **6** was converted to its acid chloride **7** by treatment with thionyl chloride in boiling dichloromethane for 10 hours. The reaction was clean and the crude product (90%) gave good NMR spectra of ^{1}H, ^{13}C, DEPT and NOESY. The NOESY spectrum

of **7** once again shows that the ester group is close to the 2-phenyl group and therefore is located at the 3-position.

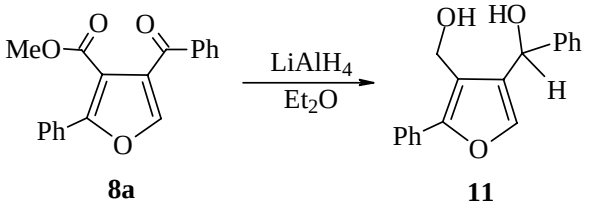
The target ketones **8** were synthesized by reaction of **7** with aromatic compounds and aluminum chloride by Friedel-Crafts acylation reactions. Ketones **8a** and **8b** were obtained in good yields (85% and 87%) for reactions of **7** with benzene and toluene (a mild electron-rich aromatic compound), respectively, in dichloromethane for 20 hours (**Scheme 3**). The reaction with methoxybenzene at room temperature gave a mixture of *para* and *ortho* substituted products (**8c** and **8c'**, ratio 2:1) as analysized by ^{1}H NMR, ^{13}C NMR and GC-Mass spectra. A lower reaction temperature (0 °C) did not improve much on the yield of **8c**. The reaction with chlorobenzene showed no reaction below 65 °C (in boiling CH_2Cl_2 or CH_3Cl for several days) and showed decomposition when reaction temperature was above 110 °C (in chlorobenzene). The reaction at 80 °C (in chlorobenzene) for three days gave a dimeric compound (**8d**, 65%) which was indicated by spectral data.

Scheme 3.



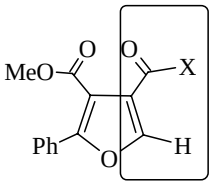
To further verify the structures of the target ketones obtained were **8** but not **10**, **8a** was reduced by $LiAlH_4$ in boiling ethyl ether to the corresponding alcohol **11** (83 %, m.p.131-2 °C) (**Scheme 4**). The HETCOR spectrum of **11** demonstrates a positive NOE interaction between the benzyl hydrogen (5.76 ppm) and the 5-C furan carbon (139.89 ppm, assigned by DEPT spectrum). This suggests that benzyl group is close to the 5-C furan carbon and therefore is consistent to the above assignment of the structure of ketone **8**.

Scheme 4.



In addition to the NOESY and HETCOR spectra described above, the significant changes of the chemical shifts of the 5-H furan proton of **2**, **6**, **7, 8** and **11** also supports that the aryl ketones are situated at the 4-positon of the 2-phenylfuran derivatives. The chemical shifts of 5-H furan proton are 7.97, 8.26, 8.22, 7.80. 7.15, and 6.96 for the compounds of diester **2**, monoacid **6**, acid chloride **7**, ketone **8a**, **8b** and alcohol **11**, respectively. The significant change of the chemical shifts of 5-H furan protons are consistent with the α,β-unsaturated system involving in the above compounds (**Figure 1**).

Figure 1.



		m.p.(°C)
X = OCH_3	**2**	71-3
OH	**6**	122-4
C l	**7**	---
Ph	**8a**	110-2
4-CH_3Ph	**8b**	113-4

References and Notes

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7. NMR data of **Compound 2**: ^{1}H NMR, δ 7.97 (1H, s), 7.15 (2H, m), 7.45 (3H, m), 3.92 (3H, s), 3.85 (3H, s). ^{13}C NMR, δ 164.83, 162.20, 154.06, 146.27, 146.23, 146.20, 129.42, 128.68, 126.37, 113.52, 52.69, 51.96. **Compound 6**: ^{1}H NMR, δ 8.26 (1H, s), 7.63 (2H, m), 7.48 (3H, m), 3.87 (3H, s). ^{13}C NMR, δ 167.09, 162.60, 160.21, 150.38, 130.31, 128.93, 128.73, 128.25, 120.30, 110.38, 53.08. DEPT, CH3 carbons: (1 peak) 53.08; CH2 carbons: none; CH carbons: (4 peaks) 150.38, 130.31, 128.73, 128.25. **Compound 7**: ^{1}H NMR, δ 8.22 (1H, s), 7.72 (2H, m), 7.45 (3H, m), 3.90 (3H, s). ^{13}C NMR, δ 163.49, 157.93, 156.25, 151.16, 130.18, 128.80, 127.89, 126.84, 124.55, 112.64, 52.91. **Compound 8a**: ^{1}H NMR, δ 7.89 (4H, m), 7.80 (1H, s), 7.62-7.44 (6H, m), 3.63 (3H, s). ^{13}C NMR, δ 188.73, 164.16, 156.04, 144.89, 138.02, 133.07, 129.78, 129.30, 129.03, 128.64, 128.55, 127.55, 127.41, 113.87, 52.10. **Compound 8b**: ^{1}H NMR, δ 7.88-7.76 (4H, m), 7.46 (3H, m), 7.32 (2H, m), 7.15 (1H, s), 2.44 (3H, s). ^{13}C NMR, δ 188.46, 164.22, 144.50, 144.00, 135.53, 129.76, 129.34, 129.30, 129.27, 128.83, 128.56, 127.72, 127.48, 126.43, 52.10, 21.70. DEPT, CH3 carbons: (2 peaks) 52.10, 21.70; CH2 carbons: none; CH carbons: (6 peaks) 144.50, 129.34, 129.27, 128.83, 128.56, 127.48. **Compound 8c**: ^{1}H NMR, δ 8.25-7.90 (2H, m), 7.60-7.25 (7H, m), 6.80 (1H, s), 3.83 (3H, s), 3.65 (3H, s). **Compound 8c'**: ^{1}H NMR, δ 8.25-7.90 (2H, m), 7.60-7.25 (7H, m), 6.90 (1H, s), 3.88 (3H, s), 3.71 (3H, s). **Compound 8d**: ^{1}H NMR, δ 8.25 (2H, d), 7.82 (2H, m), 7.61 (2H, m), 7.47 (9H, m), 4.00 (3H, s), 3.86 (3H, s). ^{13}C NMR, δ 167.30, 167.08, 150.63, 148.98, 130.39, 130.33, 129.33, 128.93, 128.51, 128.23, 128.04, 53.45, 53.16. **Compound 11**: ^{1}H NMR, δ 7.55 (2H, d), 7.37-7.17 (8H, m), 6.96 (1H, s), 5.76 (1H, s), 4.56 (2H, q). ^{13}C NMR, δ 152.44, 141.92, 139.89, 130.44, 130.11, 128.66, 128.47, 128.15,

127.84, 127.34, 126.84, 126.67, 126.26, 125.84, 119.10, 68.55, 55.37. DEPT, CH3 carbons: none; CH2 carbons: (1 peak) 55.37; CH carbons: (8 peaks) 139.89, 127.84, 127.34, 126.84, 126.67, 126.26, 125.84, 68.55.

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