HETEROCYCLES, Vol. 55, No. 2, 2001, pp. 265 - 278, Received, 2nd October, 2000

REGIOSELECTIVE FRIEDEL-CRAFTS ACYLATION WITH UNSYMMETRICALLY SUBSTITUTED FURANDICARBOXYLIC ACID ANHYDRIDE AND FURAN ACID CHLORIDE: SYNTHESES OF 4-SUBSTITUTED 3-ARYLCARBONYL-2-PHENYLFURAN AND 3-SUBSTITUTED 4-ARYLCARBONYL-2-PHENYLFURAN

Shrong-Shi Lin, Xiao-Ping Nie, Jun-Hua Yu, and Xiu-Lin Ye *

Department of Chemistry, Peking University, Beijing, 100871, China

Abstract- Friedel-Crafts acylation of aromatic compounds with 2-phenylfuran-3,4-dicarboxylic acid anhydride (**4**) and 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid chloride (**6**) was studied. The reaction with **4**, unsymmetrically substituted cyclic anhydrides, afforded 2-phenyl-3-arylcarbonylfuran-4-carboxylic acids (**7**) in moderate to good yields. Possible mechanism for such regioselective ring opening was also proposed. No interchanged isomeric product was noted for acylation of aromatic compounds with ester acid chloride (**6**). The synthesis of the precursor of **6**, 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid (**5**), was achieved by regioselective hydrolysis from dimethyl 2-phenylfuran-3,4-dicarboxylate (**2**).

INTRODUCTION

Friedel-Crafts acylation reaction[1] is useful for introducing acyl group to aromatic compounds.[2] The yields of the reactions with cyclic anhydrides[1a,3] are usually good except for the unsymmetrically substituted ones probably due to regioselective ring opening process (Scheme 1). The parameters which decide the course of the Friedel-Crafts acylation still remain obscure.[1a,4] For reactions with substituted succinic acid anhydride[5] or glutaric acid anhydride,[6] the reactions take place at the less substituted carbonyl group when substituents are electron-donating. The reaction process is supposed to be electronically controlled. While for reactions with substituted maleic acid[7] or phthalic acid anhydride,[8] the more hindered carbonyl group acylates aromatic compounds and the reactions are supposed to be sterically controlled.

In the case of ester acid chlorides where the ester and carbonyl chloride groups are sufficiently close, interchange of the ester and carbonyl chloride groups may occur *via* cyclic intermediate formation[9] (Scheme 2). For unsymmetrical substituted compounds (R ≠ H, Scheme 2), the interchange of the ester and carbonyl chloride groups might lead to formation of isomeric products if Friedel-Crafts reactions were conducted.

Compounds containing furan moiety are common in many naturally occurring substances and they usually

Scheme 1.

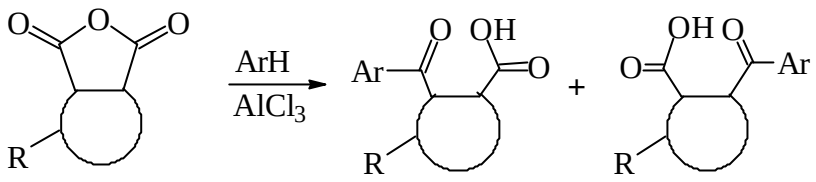
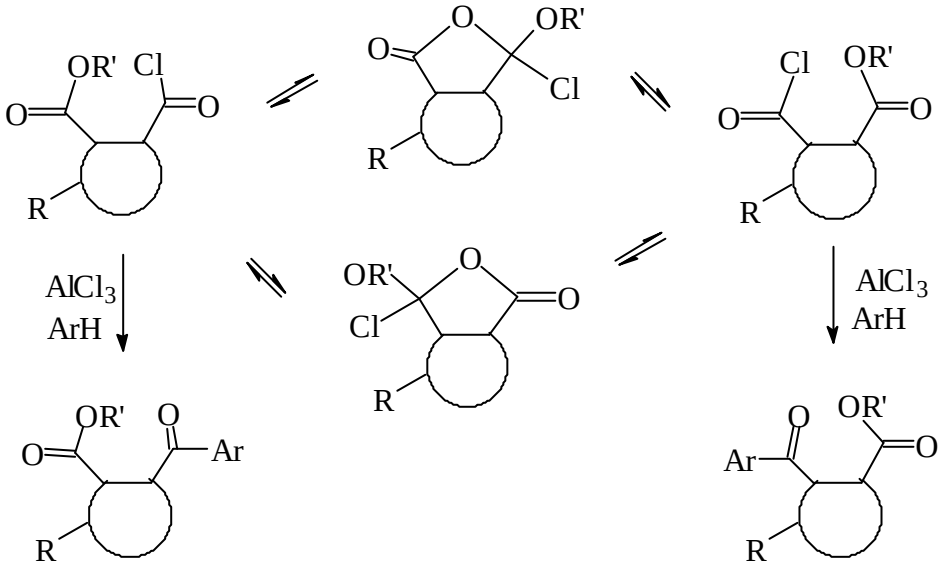


exhibit certain pharmacological activities.[10] Friedel-Crafts acylation with furan-3,4-dicarboxylic acid anhydrides or ester acid chlorides was scarcely studied.[3a,11] In this paper, we wish to report details of Friedel-Crafts acylation with 2-arylfuran-3,4-dicarboxylic acid anhydrides (**4**) and 3-methoxycarbonyl-2-arylfuran-4-carboxylic acid chlorides (**6**), both are unsymmtrically substituted compounds and are potential precursors of the syntheses of several natural furofuran lignans,[12,13] and discuss the factors that govern the regioselectivity in the ring opening process.

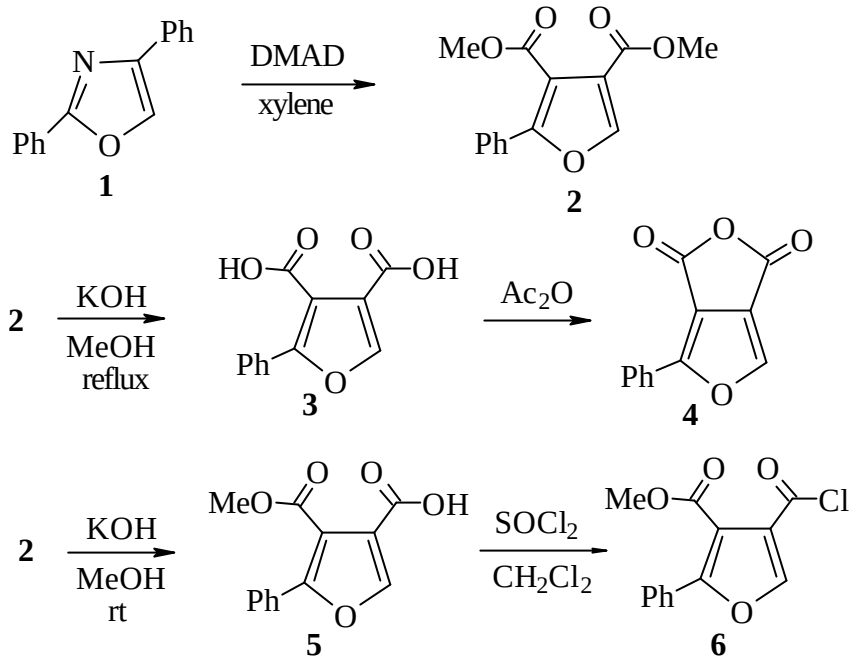
Scheme 2.



RESULTS AND DISCUSSION

Dimethyl 2-phenylfuran-3,4-dicarboxylate (**2**), prepared from the reaction of 2,4-diphenyloxazole (**1**)[14] with dimethyl acetylenedicarboxylate (DMAD), was chosen as the starting material for the syntheses of anhydride (**4**) and ester acid chloride (**6**) (Scheme 3). Diacid (**3**) was prepared by treating diester (**2**) with potassium hydroxide in boiling methanol. A subsequent dehydration of **3** with acetic anhydride afforded anhydride (**4**) in quantitative yield.

Scheme 3.



Friedel-Crafts acylation reactions of aromatic compounds with anhydride (**4**) and aluminum chloride as Lewis catalyst were performed and two possible keto acids (**7**) and (**8**) were expected (Scheme 4). However, the reactions of benzene, toluene and chlorobenzene afforded single products (**7**) in moderate to good yields. The reactions of methoxybenzene or 1,2-dimethoxybenzene gave, however, lower yields with most of the unreacted anhydride (**4**) being recovered in the form of diacid (**3**) (Table 1).

Scheme 4.

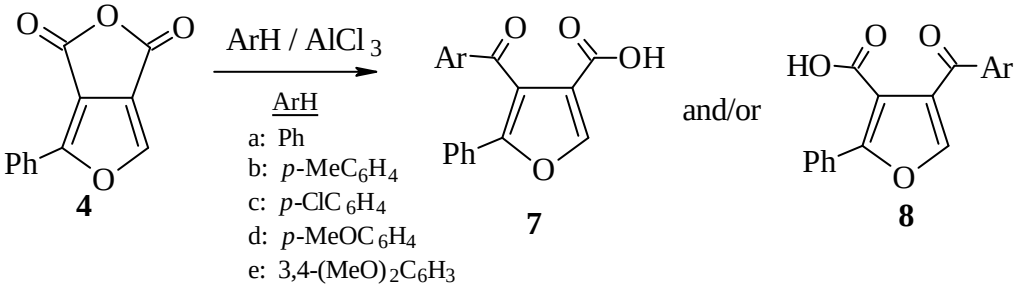


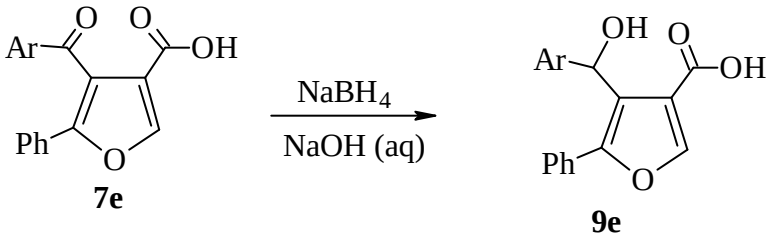
Table 1. Acylation of aromatic compounds with anhydride (**4**)

ArH	Temperature	Products	Yield (%)
benzene	rt.	**7a**	94
toluene	rt	**7b**	89
chlorobenzene	60 ^{o}C	**7c**	88

methoxybenzene	rt	**7d**	64
o-dimethoxybenzene	rt	**7e**	54

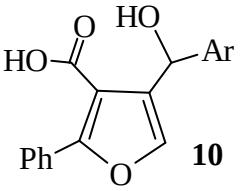
To identify the structure, keto acid (**7e**) was converted to the corresponding hydroxy acid (Scheme 5). The NOESY spectrum of the resulting hydroxy acid showed that the benzyl hydrogen (6.03 ppm) correlated to the *ortho* hydrogens (7.48 ppm) of the 2-phenyl and not to the furan 5-hydrogen (8.23 ppm). This result indicated that **9e** was the reduction product and therefore **7e** was the acylation product (Figure 1). Another MMR technique HMBC, which shows the long-range correlation between proton and vicinal carbon, also confirmed that **9e** was the hydroxy acid since the quaternary furan 5-carbon (152.58 ppm) correlated to the benzyl hydrogen (6.03 ppm, Figure 1) and therefore the furan 5-carbon and the benzyl hydrogen are on the same side.

Scheme 5.



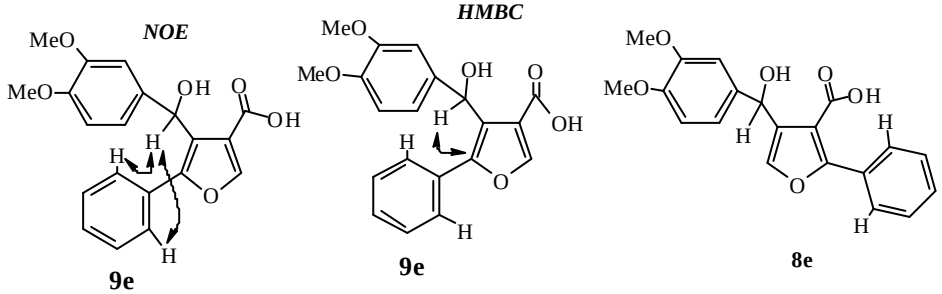
7e **9e**

Ar = 3,4-$(MeO)_2C_6H_3$-



10

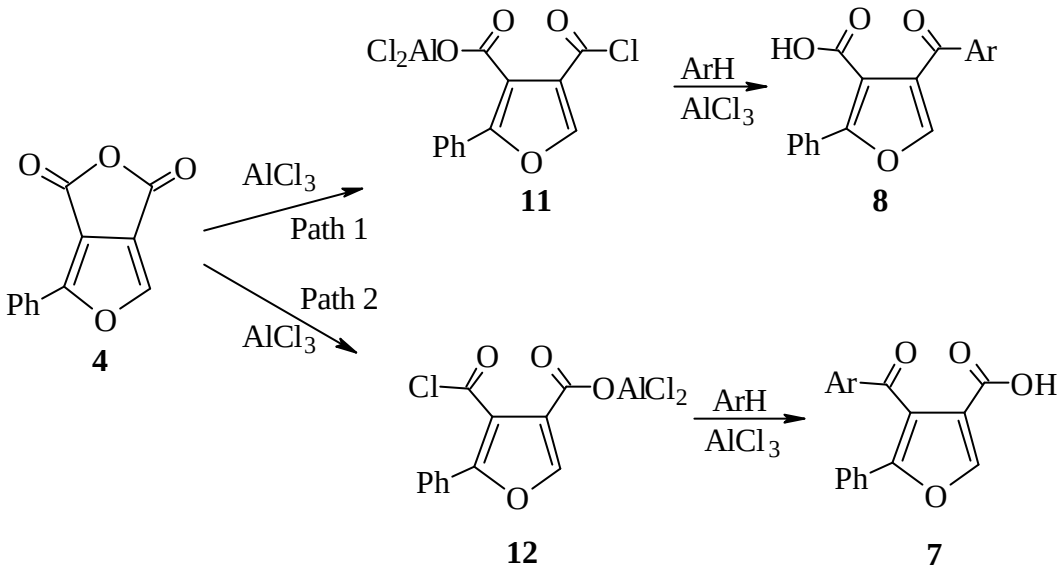
Figure 1.



The formation of the products (**7**) and (**8**) was rationalized[15] by pathway illustrated in Scheme 6. The

pathway 2 is favored by steric effect. Aluminum chloride might attack the carbonyl group far away from the phenyl group to avoid steric hindrance and form a non-acylating (CO_2AlCl_2) group. This resulted in formation of keto acid (**7**).

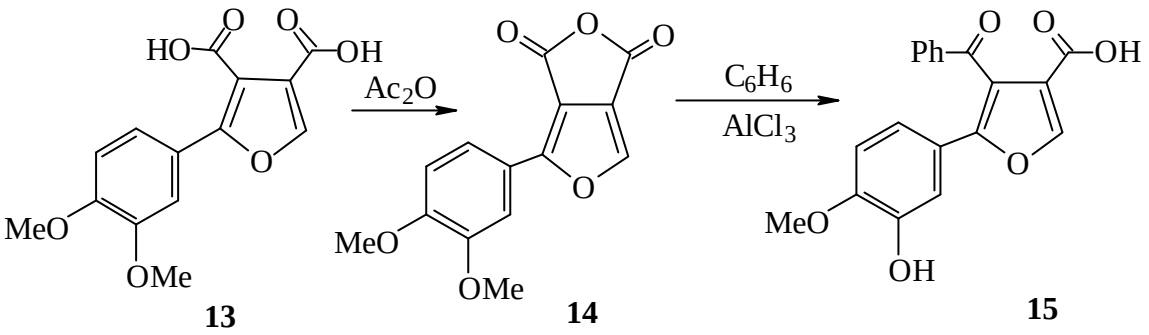
Scheme 6.



In order to verify the role of steric effect in determining the regioselectivity of the ring cleavage of anhydride, the 2-phenyl group of anhydride (**4**) was replaced by a bulkier 3,4-dimethoxyphenyl group. The results showed that acylations were retarded. The anhydrides (**14**) were inert, even under forced conditions, to toluene, chlorobenzene, methoxybenzene and 1,3-dimethoxybenzene except to the unsubstituted benzene. The reaction of benzene (stirred 2 days at 60 ^{o}C) afforded **15** (11 % yield, Scheme 7). The spectral data indicated that the 3' methoxy group was demethylated and the phenomenon was known earlier.[16] The structure of **15** was further confirmed by spectral analysis of the reduction product (**16**). The NOESY spectrum (Figure 2) showed that hydroxy acid (**16**) was the reduction product because the benzyl hydrogen (6.04 ppm) correlated to the *ortho*-hydrogens (7.00 and 7.07 ppm) of the 2-aryl group and not the furan 5-hydrogen (8.36 ppm). This fact once again illustrated that the more hindered keto acid (**15**) was obtained from the acylation reaction.

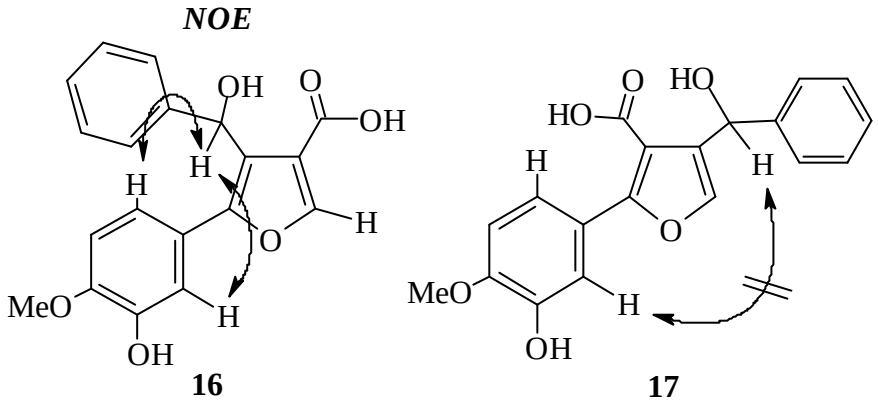
In summary, the Friedel-Crafts acylations with 2-phenylfuran cyclic anhydrides provide 2-phenyl-3-arylcarbonylfuran-4-carboxylic acids regioselectively with the arylcarbonyl group situated at the 3-position of the 2-phenylfuran ring.

Scheme 7.



13 **14** **15**

Figure 2.



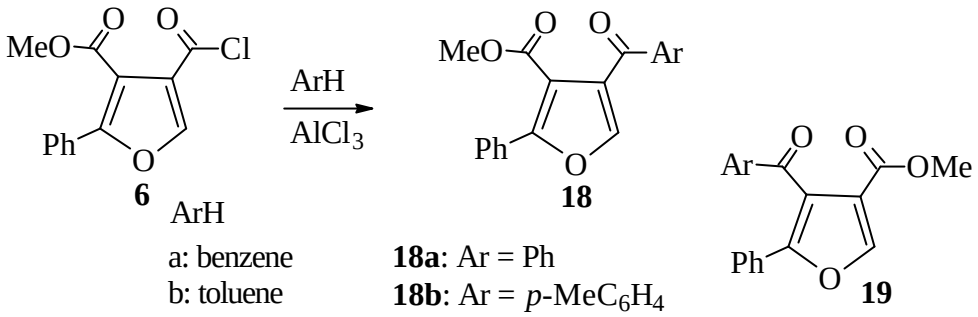
16 **17**

For the synthesis or 4-arylcarbony-3-methoxycarbonyl-2-phenylfuran (**18**), diester (**2**) was selectively hydrolyzed to monoacid (**5**) and then converted to the corresponding acid chloride (**6**) (Scheme 3). Subsequent Friedel-Crafts acylation of aromatic compounds with **6** afforded keto ester (**18**) with aromatic group introduced successfully to the 4-position of the 2-phenylfuran skeleton. It was noted that **18** was the sole product.

The selective hydrolysis, a key reaction of diester (**2**)[17] to monoacid (**5**)**,** was performed by treating **2** with 1.2 equivalents of potassium hydroxide in cold methanol. The selective mono hydrolysis was noted from NMR spectra while the two methoxy peaks of reactant (3.92 and 3.85 ppm) turned into single peak of product (3.87 ppm). The NOESY spectrum of **5** showed that the ester group (3.87 ppm) had long range interaction with 2-phenyl group (7.48 ppm) and not furan 5-hydrogen (8.26 ppm). This result suggested that the ester group locates at the 3-position instead of 4-position of the 2-phenylfuran skeleton. The NOESY spectrum of the subsequent reaction product of **6** once again illustrates that the ester group is close to the 2-phenyl group.

The reaction of benzene and toluene with **6** provided ketones (**18a**) and (**18b**), respectively, in satisfactory yields (85 % and 87 %) *via* Friedel-Crafts acylation (Scheme 8). The reaction of chlorobenzene showed no reaction below 65 °C (in boiling CH_2Cl_2 or CH_3Cl) and decomposed when reaction temperature was above 110 °C.

Scheme 8.

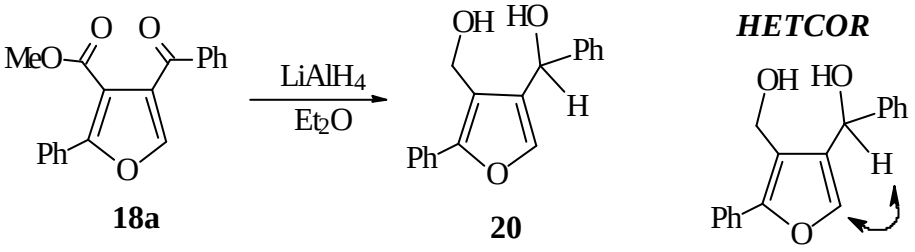


ArH
a: benzene
b: toluene

18a: Ar = Ph
18b: Ar = *p*-MeC_6H_4

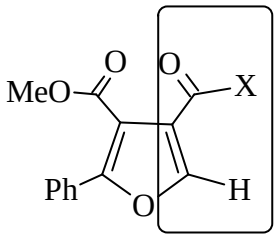
Compound (**18a**) was reduced to the corresponding alcohol (**20**) by treatment with $LiAlH_4$ (Scheme 9). The HETCOR spectrum of **20** demonstrated a positive NOE interaction between the benzyl hydrogen (5.76 ppm) and the furan 5-carbon (139.89 ppm, assigned by DEPT spectra). This result implied that **18** was the acylation product. The potential isomeric product (**19**), due to interchange of the ester and carbonyl chloride groups (Scheme 2)[9] in **6**, was not noted when Friedel-Crafts reactions were performed.

Scheme 9



In addition to the NOESY and HETCOR spectra described above, the significant change of chemical shifts of the furan 5-hydrogens also supports that the aryl ketones are situated at the 4-positon of the 2-phenylfuran derivatives. The chemical shifts of furan 5-hydrogens are 7.97, 8.26, 8.22, 7.80, 7.15 and 6.96 for the compounds (**2**, **5**, **6**, **18a**, **18b** and **20)**, respectively. The significant change of the chemical shifts of furan 5-hydrogens are consistent with the α,β-unsaturated system involving in the above compounds (Figure 3).

Figure 3.



X = OMe **2**
OH **5**
C l **6**
Ph **18a**
p-MeC_6H_4 **18b**

In conclusion, we demonstrated two pathways for introducing aromatic group to the 3 or 4 position of the 2-phenylfuran skeleton regioselectively to form carboxy ketones (**7**) and (**18**), respectively.

EXPERIMENTAL

Melting points were measured on a Yanaco MP-500 melting points apparatus and are uncorrected. IR spectra were recorded on Nicolet Magna 750 IR instrument. NMR spectra were determined on Bruker ARX 400 MHz or Varian Mercury 200 MHz spectrometers and the chemical shifts (ppm) were determined using tetramethylsilane as the internal reference. MS spectral data were obtained using either VG-ZAB-HS or GCQ GC/MS mass spectrometers.

Preparation of 2-phenylfuran-3,4-dicarboxylic acid (3).

A mixture of dimethyl 2-phenylfuran-3,4-dicarboxylate[17] (2.60 g, 0.01 mol) and potassium hydroxide (2.81 g, 0.05 mol) in water (20 mL) and methanol (10 mL) was heated under reflux for 2 h. The resulting mixture was acidified with concentrated HCl to form white precipitate. The product was recrystallized from methanol-water (1:1) to give corlorless needles (2.23 g, 96 %), mp 188-189 °C. Anal. Calcd for $C_{12}H_8O_5$: C, 62.07; H, 3.47. Found: C, 62.20; H, 3.73. υ_{max} / cm^{-1} 3500 (OH), 1690 (C=O), 1630, 1530; δ_H (400 MHz, CD_3COCD_3) 7.43-7.87 (5H, m, Ph–H), 8.38 (1H, s, Furan-H), 10.90 (2H, COOH); m/z (EI) 232 ($M^{+\cdot}$), 198 (M-CO_2, 100 %).

General procedure for the preparation of 7a-7e.

2-Phenylfuran-3,4-dicarboxylic acid (2.32 g, 0.01 mol) and acetic anhydride (15 mL) were refluxed for 2 h. The resulting solution was concentrated under vacuum and anhydride (**4**) was obtained quantitatively (2.14 g) as colorless needles, mp 194-196 ^oC; δ_H (200 MHz, $CDCl_3$) 7.52 (3H, m, Ph–H), 7.93 (1H, s, Furan-H), 8.15 (2H, m, Ph–H). The crude product (**4**) (2.14 g, 0.01 mol) was added to a stirred mixture of aromatic compounds (0.01 mol) and anhydrous $AlCl_3$ (3.00 g, 0.02 mol) in an appropriate solvent (50 mL). The resulting mixture was stirred at rt (at 60 ^oC for **7c**) for 24 h, cooled in ice bath and then acidified

with concentrated HCl. The solvents and excess aromatic compounds were removed by steam distillation and the crude product was purified by recrystallization from methanol-water.

2-Phenyl-3-benzoylfuran-4-carboxylic acid (7a). Benzene as solvent; corlorless needles, yield 94 %, mp 176-178 ^{o}C. Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.96; H, 4.14. Found: C, 73.56; H, 3.96. υ_{max} / cm^{-1} 3450 (OH), 3160, 2640, 1680 (C=O), 1600; δ_H (400 MHz, CD_3COCD_3) 7.36-7.94 (10H, m, Ar-H), 8.42 (1H, s, Furan-H), 11.10 (1H, br, COOH); m/z (EI) 292 ($M^{+\cdot}$, 100 %), 273 (M-H_3O), 248 (M-CO_2).

2-Phenyl-3-(4'-methylbenzoyl)furan-4-carboxylic acid (7b). Toluene as solvent; corlorless needles, yield 89 %, mp 184-185 ^{o}C. Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.68; H, 4.58. υ_{max} / cm^{-1} 3430 (OH), 2930, 2370, 1710 (C=O), 1670 (C=O), 1600; δ_H (400 MHz, CD_3OD) 2.36 (3H, s, CH_3), 4.70 (1H, br, COOH), 7.23-7.80 (9H, m, Ar-H), 7.96 (1H, s, Furan-H); m/z (EI) 306 ($M^{+\cdot}$, 100 %), 287 (M-H_3O), 262 (M-CO_2).

2-Phenyl-3-(4'-chlorobenzoyl)furan-4-carboxylic acid (7c). Chlorobenzene as solvent; corlorless needles, yield 88 %, mp 187-189 ^{o}C. Anal. Calcd for $C_{18}H_{11}O_4Cl$: C, 66.17; H, 3.39; Cl, 10.85. Found: C, 66.08; H, 3.23; Cl, 11.42. υ_{max} / cm^{-1} 3430 (OH), 3160, 2600, 1740 (C=O), 1590 (C=O), 1459; δ_H (400 MHz, $CDCl_3$) 7.47-7.56 (9H, m, Ph and ArH), 7.93 (1H, s, Furan-H), 12.57 (1H, br, COOH); m/z (EI) 326 ($M^{+\cdot}$, 100 %), 307 (M-H_3O).

2-Phenyl-3-(4'-methoxybenzoyl)furan-4-carboxylic acid (7d). 1,1,2,2-Tetrachloroethane as solvent; corlorless needles, yield 64 %, mp 196-198 ^{o}C. Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.37. Found: C, 70.62; H, 4.34. υ_{max} / cm^{-1} 3430 (OH), 2850, 2600, 1700 (C=O), 1660 (C=O), 1600; δ_H (400 MHz, DMSO-d_6) 3.81 (3H, s, Ph-OCH_3), 6.95-7.77 (9H, m, Ar-H), 7.82 (1H, s, Furan-H); m/z (EI) 322 ($M^{+\cdot}$, 100%).

2-Phenyl-3-(3',4'-dimethoxybenzoyl)furan-4-carboxylic acid (7e). 1,1,2,2-Tetrachloroethane as solvent; corlorless needles, yield 54 %, mp 209-210 ^{o}C. Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.58; H, 4.49. υ_{max} / cm^{-1} 3430 (OH), 3170, 2970, 1690 (C=O), 1650 (C=O), 1590; δ_H (400 MHz, CD_3COCD_3) 3.81 (6H, s, OCH_3), 6.89-7.53 (8H, m, Ar-H), 8.35 (1H, s, Furan-H), 10.90 (1H, br, COOH); ^{13}C NMR (CD_3COCD_3, ppm): δ 56.00, 56.04, 68.08, 111.47, 112.31, 119.18, 120.48, 123.36, 128.00, 129.66, 129.70, 130.64, 136.93, 149.66, 150.26, 150.70, 152.58, 166.48; m/z (EI) 352 ($M^{+\cdot}$,100%).

Preparation of 2-(3'-methoxy-4'-hydroxy)phenyl-3-benzoylfuran-4-carboxylic acid (15).

2-(3',4'-Dimethoxyphenyl)furan-3,4-dicarboxylic acid (**13**) was prepared from dimethyl 2-(3',4'-dimethoxyphenyl)furan-3,4-dicarboxylate[17] and aqueous potassium hydroxide using procedure similar to that for the preparation of **3**. The product was obtained as corlorless needles, yield 95 %, mp 241-242

°C. Anal. Calcd for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.47; H, 4.27. υ_{max} / cm^{-1} 3500 (OH), 2960, 1730 (C=O), 1630 (C=O), 1500; δ_H (400 MHz, DMSO-*d_6*) 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 7.06-7.32 (3H, m, Ph–H), 8.31 (1H, s, Furan-H); m/z (EI) 292 ($M^{+\cdot}$100 %), 271 (M-CH_3), 248 (M-CO_2). A mixture of **13** (0.29 g, 0.01 mol) and acetic anhydride (15 mL) was refluxed 2 h to give anhydride (**14)** quantitatively. To the mixture of **14** (0.27 g, 0.01 mol) and benzene (10 mL) was added anhydrous $AlCl_3$ (3.00 g, 0.02 mol) and the mixture was stirred at 60 °C for 2 days. After removal of solvents, the product was purified by recrystallization from methanol-water to give **15** (0.37 g, 11 %) as corlorless needles, mp 207- 208 °C. Anal. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 67.55; H, 4.03. υ_{max} / cm^{-1} 3360, 3070, 1690, 1670; δ_H (400 MHz, CD_3COCD_3) 3.82 (3H, s, OCH_3), 6.91-7.11 (3H, m, ArH), 7.47-7.95 (5H, m, Ph), 7.97 (1H, s, OH), 8.33 (1H, s, Furan-H), 11.18 (1H, br, COOH); m/z (EI) 338 ($M^{+\cdot}$,100 %), 261, 105, 77.

Preparation of 9 and 16.

Compounds (**9**) and (**16**) were prepared from the reduction of **7e** (0.33 g, 0.01 mol) and **15** (0.34 g, 0.01 mol), respectively, with sodium borohydride (0.45 g, 0.012 mol) in aqueous sodium hydroxide (0.5 N, 30 mL). The reaction mixture was refluxed 4 h and then treated with 6N HCl to pH < 3. The crude product was recrystallized from ethanol-water to afford colorless needles.

2-Phenylfuran-3-(3',4'-dimethoxyphenyl)carbinol-4-carboxylic acid (9). Yield 92 %, mp 157-158 °C. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.78; H, 5.12. Found: C, 67.89; H, 5.36. υ_{max} / cm^{-1} 3470 (OH), 3320, 3080, 3020, 1660 (C=O), 1520; δ_H (400 MHz, CD_3COCD_3) 3.87 (6H, s, OCH_3), 5.94 (1H, br, PhCHO*H*), 6.03 (1H, s, Ph-CH-O), 6.90-7.08 (3H, m, Ar-H), 7.37-7.48 (5H, m, Ph-H), 8.23 (1H, s, Furan-H), 11.82 (1H, br, COOH); δ_C (100 MHz, CD_3COCD_3) 56.01, 56.03, 68.08, 111.48, 112.31, 119.18, 120.48, 123.36, 128.00, 129.65, 129.70, 130.64, 136.93, 149.66, 150.26, 150.70, 152.58, 166.48; m/z (EI) 336 (M-H_2O, 100 %), 261, 105.

2-(3'-Methoxy-4'-hydroxy)phenylfuran-3-phenylcarbinol-4-carboxylic acid (16). Yield 93 %, mp 176-177 °C. Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.06; H, 4.74. Found: C, 67.21; H, 4.68. υ_{max} / cm^{-1} 3400 (OH), 3150, 3080, 2930, 1680 (C=O), 1510; δ_H (400 MHz, CD_3COCD_3) 3.87 (3H, s, Ph-OCH_3), 5.88 (1H, br, OH), 6.04 (1H, s, Ph-CH-O), 6.97-7.07 (3H, m, Ar-H), 7.24-7.38 (5H, m, Ph-H), 7.96 (1H, br, Ph-OH), 8.36 (1H, s, Furan-H), 11.20 (1H, br, COOH); m/z (EI) 340 ($M^{+\cdot}$), 322 (M-H_2O, 100 %).

Preparation of 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid (5).

Dimethyl 2-phenylfuran-3,4-dicarboxylate (**2**) (1.74 g, 6 mmol) in methanol (30 mL) was warmed to form a homogeneous solution and to the solution was added dropwise 2.4 mL of aqueous potassium

hydroxide (2.5 N, 6 mmol). The resulting light brown solution was stirred 15 h at rt and then methanol was removed by rotary evaporator. Water was added and the solution was extracted with ether to remove unreacted reactant. The aqueous layer was treated with 2N HCl to form white product with good purity (1.30 g, 88.2 %). Further purification was conducted by crystallization from 60 % methanol to yield white needles, mp 110.5-113.0 °C; m/z calcd for $C_{13}H_{10}O_5$: 246.0528, found: 246.0530; υ_{max} / cm^{-1} 3400-3200 (OH), 1740 (C=O), 1694 (C=O); δ_H (200 MHz, $CDCl_3$) 3.87 (3H, s, OMe), 7.48 (3H, m, Ar-H), 7.63 (2H, m, Ar-H), 8.26 (1H, s, Furan-H); δ_C (50 MHz, $CDCl_3$) 53.08 (OMe), 110.38, 120.30, 128.25, 128.73, 128.93, 130.31, 150.38, 160.21, 162.60 (CO), 167.09 (CO); DEPT: CH_3 carbons: (1 peak) 53.08; CH_2 carbons: none; CH carbons: (4 peaks) 128.25, 128.73, 130.31, 150.38.

Preparation of 3-methoxycarbonyl-2-phenylfuran-4-carboxylic acid chloride (6).

Thionyl chloride (3.43 g, 28.8 mmol) was added to a solution of monoacid (**5**) (5.10 g, 24 mmol) in methylene chloride (150 mL) under argon. The mixture was heated under reflux for 20 h and then evaporated by rotary evaporator to yield crude product as milky white gum (4.85 g, 76.4 %). The purity of the crude product was good as indicated in NMR and was applied directly to the next reactions. δ_H (200 MHz, $CDCl_3$) 3.90 (3H, s, OMe), 7.45 (3H, m, Ar-H), 7.72 (2H, m, Ar-H), 8.22 (1H, s, Furan-H); δ_C (50 MHz, $CDCl_3$) 52.91.(OMe), 112.64, 124.55, 126.84, 127.89, 128.80, 130.18, 151.16, 156.25, 157.93 (CO), 163.49 (CO).

General procedure for the syntheses of 3-methoxycarbonyl-4-arylcarbonyl-2-phenylfuran (18).

Anhydrous aluminum chloride (1.2 eq.) was added to a mixture of arene (10 mL), acyl chloride (1 eq.) and solvent under argon. The reaction was stirred for several hours with reaction time determined by TLC and temperature determined by the property of product and reactant. After the completion of reaction, the mixture was poured into 2.5 % sodium carbonate (3.6 eq.) and extracted with methylene chloride. The organic layer was washed with saturated sodium bicarbonate solution, brine. Removal of solvent afforded crude product. Further purification included trituration, column chromatography and recrystallization. Details for preparation of the individual acylation adducts are given below.

3-Methoxycarbonyl-4-phenylcarbonyl-2-phenylfuran (18a) was synthesized using the above general procedure from acyl chloride (**6**) (2.12 g, 8 mmol), 40 mL of dichloromethane, 10 mL of benzene and aluminum chloride (1.28 g, 9.6 mmol). The mixture was refluxed for 15 h and the removal of solvents furnished crude product as milky white gum. It was triturated with petroleum ether to give white solid with good purity. Recrystallization from ether / petroleum ether gave white needles (2.08 g, 85 %). mp 110-112 ^oC; m/z calcd for $C_{19}H_{14}O_4$: 306.0892, found: 306.0889; υ_{max} / cm^{-1} 3150 (C=C), 3100

(aromatic C-H), 1722 (C=O), 1655 (C=O), 1610 (C=C); δ_H (200 MHz, $CDCl_3$) 3.63 (3H, s, OMe), 7.62-7.44 (6H, m, Ar-H), 7.80 (1H, s, Furan-H), 7.89 (4H, m, Ar-H); δ_C (50 MHz, $CDCl_3$) 52.10 (OMe), 113.87, 127.41, 127.55, 128.55, 128.64, 129.03, 129.30, 129.78, 133.07, 138.02, 144.89, 156.04, 164.16 (CO), 188.73 (CO); m/z (EI) 306 ($M^{+\cdot}$, 100 %), 229 (M-C_6H_5), 201 (M-C_6H_5CO).

3-Methoxycarbonyl-4-(4'-methylphenyl)carbonyl-2-phenylfuran (18b) was synthesized using the above general procedure from acyl chloride (**6**) (0.27 g, 1 mmol), 10 mL of dichloromethane, 10 mL of toluene and $AlCl_3$ (0.16 g, 1.2 mmol). The mixture was stirred at rt for 15 h. The solution, after extraction, was concentrated from rotary evaporator and then treated with petroleum ether to induce solid formation (0.28 g, 87 %). The pure compound was isolated from silica gel column chromatography eluting from petroleum ether / ethyl acetate (3:1). mp 113-114 ^oC; m/z calcd for $C_{20}H_{16}O_4$: 320.1049, found: 320.1051; υ_{max} / cm^{-1} 3100 (aromatic C-H), 1722 (C=O), 1655 (C=O), 1610 (aromatic C=C); δ_H (200 MHz, $CDCl_3$) 2.44 (3H, s, OMe), 7.15 (1H, s, Furan-H), 7.32 (2H, m, Ar-H), 7.46 (3H, m, Ar-H), 7.88-7.76 (4H, m, Ar-H); δ_C (50 MHz, $CDCl_3$) 21.70 (ArMe), 52.10 (OMe), 126.43, 127.48, 127.72, 128.56, 128.83, 129.27, 129.30, 129.34, 129.76, 135.53, 144.00, 144.50, 164.22 (CO), 188.46 (CO); DEPT: CH_3 carbons: (2 peaks) 21.70, 52.10; CH_2 carbons none; CH carbons: (6 peaks) 127.48, 128.56, 128.83, 129.27, 129.34, 144.50; m/z (EI) 320 ($M^{+\cdot}$, 100 %), 289 (M-CH_3O), 229 (M-$C_6H_5CH_3$).

Preparation of 3-hydroxylmethyl-4-phenylcarbinol-2-phenylfuran (20).

Compound (**18a**) (3.67 g, 12 mmol) and $LiAlH_4$ (1.82 g, 48 mmol) in anhydrous ether (80 mL) was refluxed 20 h. The reaction was quenched with water and then neutralized with 2N HCl. The solid residue was filtered off and the filtrate was extracted with ether. The organic extract was dried over sodium sulfate and the removal of solvent afforded crude product. Purification was carried out by silica gel column chromatography (petroleum ether / ethyl acetate (3:1)) to give white solid (2.79 g, 83 %). mp 83 °C; m/z calcd for $C_{18}H_{16}O_3$: 280.1099, found: 280.1098; υ_{max} / cm^{-1} 3500-3200 (OH), 3050 (aromatic C-H), 1600 (aromatic C=C); δ_H (200 MHz, $CDCl_3$) 4.56 (2H, m, CH_2OH), 5.76 (1H, s, ArCH), 6.96 (1H, s, Furan-H), 7.37-7.17 (8H, m, Ar-H), 7.55 (2H, d, Ar-H, J=8.2 Hz); δ_C (50 MHz, $CDCl_3$) 55.37 (ArCHOH), 68.55 (CH_2OH), 119.10, 125.84, 126.26, 126.67, 126.84, 127.34, 127.84, 128.15, 128.47, 128.66, 130.11, 130.44, 139.89, 141.92, 152.44;. DEPT: CH_3 carbons: none; CH_2 carbons: (1 peak) 55.37; CH carbons: (8 peaks) 68.55, 125.84, 126.26, 126.67, 126.84, 127.34, 127.84, 139.89; m/z (EI) 280 ($M^{+\cdot}$), 262 (M-H_2O, 100 %), 203 (M-C_6H_5), 174 (M-C_6H_5CHO).

ACKNOWLEDGEMENTS

We thank the National Natural Science Foundation for the support of this research.

REFERENCES

1 For reviews see, (a) A. G. Peto, "*Friedel-Crafts and Related Reactions*", Vol. 3, ed. by G. A. Olah, Interscience, New York, 1964, Part 1, Chapter XXXIV; (b) G. A. Olah, "*Friedel-Crafts Chemistry*", John Wiley & Sons, New York, 1973.

2 G. Thomas, "*Recent Prog. Chem. Synth. Antibiot*", ed. by G. Lukacs and M. Ohno, Springer, Berlin, 1990, p. 467.

3 (a) D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, 1959, **24**, 497; (b) D. V. Nightingale and J. A. Gallagher, *J. Org. Chem.*, 1959, **24**, 501.

4 I. Hasumoto, K. Takatoshi, F. D. Badeu, T. Sawada, S. Makata, and M. Tashiro, *Res. Chem. Intermed.*, 1996, **22**, 855.

5 E. J. Eisenbraun, C. W. Hirman, J. M. Springer, J. W. Burnham, T. S. Chou, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.*, 1971, **36**, 2480.

6 R. K. Gautam, S. Kannan, and G. S. Saharia, *J. Indian Chem. Soc.*, 1982, **59**, 378.

7 R. E. Lutz, P. S. Bailey, C.-K. Dien, and J. W. Rinker, *J. Am Chem. Soc.*, 1953, **75**, 5039.

8 M. S. Newman, "*Steric Effects in Organic Chemistry*", ed. by M. S. Newman, John Wiley, New York, 1956.

9 B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 1952, 553.

10 M. V. Sargent and F. M. Dean "*Comprehensive Hetereocyclic Chemistry*", Vol. 4, ed. by A. R. Katritzky and C. W. Reese, Pergamon Press, Oxford, 1984, Part 3, p. 599.

11 M. Devys, M. Baraiers, and D. Parisot, *Heterocycles*, 1990, **31**, 1485.

12 (a) W. S. Johnson and M. W. Miller, *J. Am. Chem. Soc.*, 1950, **72**, 511; (b) W. M. Hearon and W. S. MacGregor, *Chem. Rev.*, 1955, **55**, 957.

13 For a recent review see R. S. Ward, "*Natural Product Reports*", 1997, **14**, 43.

14 C. Simion, F. D. Badea, I. Costea, D. Mihaiescu, M. Tashiro, and S. Matake, *Proc. Rom. Acad.* Series B, 1999, **1**, p.15-17.

15 (a) X. P. Nie, Z. Q. Wang, and X. L. Ye, *Chinese Chemical Letters*, 1997, **8**, 689; (b) W. W. Pei, S. H. Li, X. P. Nie, Y. W. Li, J. Pei, B. Z. Chen, and X. L. Ye, *Syntheisis*, 1998, 1298.

16 P. C. Mitter and H. G. Biswas, *J. Indian Chem. Soc.*, 1928, **5**, 769.

17 W. W. Pei, J. Pei, J. H. Chen, Y. W. Li, and X. L. Ye, *Acta Scientianum Universitatis Pekinensis*, 1993, **29**, 129.