## CONCLUSIONS

Condensation of aryl bromides with styrenes in acetonitrile in the presence of nickel organometallic complex catalysts and metallic zinc occurs regio- and stereoselectively to give E-stilbenes.

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# PREPARATION OF SUBSTITUTED 3-HYDROXY-3-TRIFLUOROMETHYL-2(3H)BENZOFURANONES


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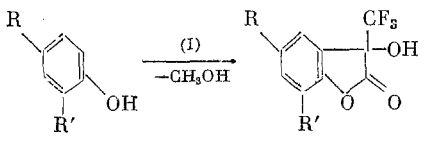
UDC 542.91:547.724


Trihydroxybenzenes, resorcinol, its simple mono- and diethers and other phenols containing electron donor substituents in meta positions undergo regioselective, uncatalyzed C-alkylation by polyfluorocarbonyl compounds in aprotic solvents. The position is governed by the ortho–para orientation of the substituents [1]. In this work we report the noncatalyzed, thermal reactions of phenols with $CF_3COCOOMe$ (I).

It has been shown that phenols in aprotic media (benzene, toluene, $MeNO_2$), not susceptible to mild C-alkylation, resemble alcohols [2] forming thermally unstable O-alkylation products with ketoester I. Conversion to C-alkylation products was quite rapid at 140-145°C and was accompanied by intramolecular condensation to give 3-hydroxy-3-trifluoromethyl-2(3H)-benzofuranones. Thus hydroquinone and catechol were heated (140-145°C, 6 h) with an equimolar amount of ketoester (I) in benzene to give 3,5-dihydroxy-3-trifluoromethyl-2(3H)benzo[b]furanone (II) and 3,7-dihydroxy-3-trifluoromethyl-2(3H)benzo[b]furanone (III) in 90 and 70% yields respectively.




R = OH, R′ = H (II), R = H, R′ = OH (III).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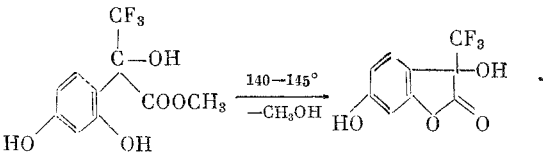
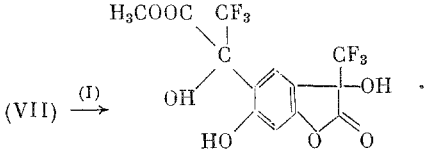
Under the same conditions p-, m-cresol and phenol gave 3-hydroxy-3-trifluoromethyl-5-methyl (IV), 3-hydroxy-3-trifluoromethyl-6-methyl (V), and 3-hydroxy-3-trifluoromethyl-2(3H)-benzo[b]furanone (VI) in 65-70% yields. Minor products of the above reactions were the o-C-alkylated phenols which were identified by lactonization to the corresponding benzofuranones. It therefore follows that the discussed reactions in aprotic solvents are realized principally in the position ortho to the OH group and formation of the final material is limited by the intramolecular condensation stage. In confirmation it has been shown that resorcinol and ketoester (I) readily formed the methyl ester of α-hydroxy-α-trifluoromethyl-2,5-dihydroxyphenylacetic acid (VII) which was heated at 140-145°C for 6 h in benzene to give 3,6-dihydroxy-3-trifluoromethyl-2(3H)benzo[b]furanone (VIII) in up to 60% yield.




(VII) (VIII)

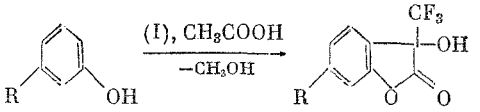
It has proved difficult to lactonize other previously obtained [1] products of the C-alkylation of phenols by ketoester (I). Only the reaction product with 3-hydroxyphenoxyacetic acid was relatively easily converted to 3-hydroxy-3-trifluoromethyl-6-carbomethoxy-2(3H) benzo[b]furanone (IX) in refluxing $MeNO_2$.

The reactions of ketoester (I) with phenols is strongly hindered by the presence of electron acceptor substituents in the aryl ring. Thus (VII) only reacts with (I) at 160°C, the principal reaction product being 3,6-dihydroxy-3-trifluoromethyl-5(α-hydroxy-α-carbomethoxytrifluoroethyl)-2(3H)benzo[b]furanone (X).




(X)

Some other features characterize the described reactions in AcOH solution. C-Alkylation of highly activated phenols is somewhat hindered, apparently because of the solvating effect of the medium. Thus resorcinol in AcOH at 50°C was not completely converted to ester (VII) even after 6 h and lactonization was practically absent. Only in refluxing AcOH was the furanone (VIII) formed after 2 h in 95% yield. Complete reaction of ketoester (I) occurred in refluxing AcOH with the highly activated m-methoxy- and m-ethoxyphenols and with m-acetamidophenol forming 3-hydroxy-3-trifluoromethyl-6-methoxy (XI), -6-ethoxy (XII), and -6-acetamido-2(3H)benzo[b]furanone (XIII) in 70-85% yields.




R = $CH_3O$ (XI); R = $C_2H_5O$ (XII); R = $CH_3C(O)NH$ (XIII).

Trihydroxybenzenes also underwent straightforward conversion to the benzofuranones upon treatment with (I) in refluxing AcOH. Under these conditions pyrogallol gave 3,6,7-trihydroxy-3-trifluoromethyl-2(3H)benzo[b]furanone (XIV).

Relatively low activity phenols also reacted with (I) in refluxing AcOH, m-cresol giving furanone (V) in 68% yield and 1- and 2-naphthol, the naphthofuranones (XV) and (XVI) in 92 and 83% yields respectively.

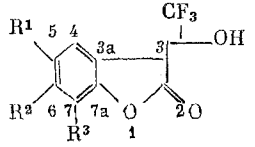
TABLE 1. Conditions for Formation, Yield, and Properties of (III)-(VI), (VIII), (IX), and (XI)-(XIV)

| Compound | Reaction time, h | | Yield, % | | Mp, °C (solvent) | $R_f$ (acetone: $CCl_4$) | Found/calculated, % | | | Empirical formula | Mass spectrum, $M^+$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | A | B | | | C | H | F | | |
| (III) | 6 | 6 | 64 | 70 | 143–145 † (heptane) | 0,45 (1 : 1) | 46,10 / 46,15 | 2,14 / 2,14 | 24,02 / 24,36 | $C_9H_5F_3O_4$ | 234 |
| (IV) | 6 | 6 | 63 | 65 | 93–95 (hexane) | 0,50 (1 : 3) | 51,92 / 51,72 | 3,01 / 3,02 | 24,80 / 24,57 | $C_{10}H_7F_3O_3$ | 232 |
| (V) | 6 | 6 | 65 | 68 | 50–52 (pentane) | 0,58 (1 : 3) | 51,52 / 51,72 | 3,38 / 3,02 | 24,31 / 24,57 | $C_{10}H_7F_3O_3$ | 232 |
| (VI) | 6 | 6 | 62 | 65 | 63–65 † (hexane) | 0,60 (1 : 3) | 49,24 / 49,54 | 2,32 / 2,29 | 26,12 / 26,15 | $C_9H_5F_3O_3$ | – |
| (VIII) | 6 | 2 | 60 | 95 | 135–137 (benzene) | 0,25 (1 : 3) | 46,34 / 46,15 | 2,31 / 2,14 | 24,02 / 24,36 | $C_9H_5F_3O_4$ | 234 |
| (IX) * | 6 | 2 | 75 | 85 | 152–155 ($MeNO_2$) | 0,30 (1 : 3) | 45,60 / 45,21 | 2,46 / 2,38 | 19,06 / 19,52 | $C_{11}H_7F_3O_6$ | – |
| (XI) | – | 3 | – | 85 | 68–70 (hexane) | 0,61 (1 : 3) | 48,56 / 48,39 | 2,70 / 2,82 | 22,90 / 22,98 | $C_{10}H_7F_3O_4$ | – |
| (XII) | – | 3 | – | 80 | – † | 0,50 (1 : 3) | 49,96 / 50,38 | 3,46 / 3,44 | 21,48 / 21,76 | $C_{11}H_9F_3O_4$ | – |
| (XIII) | – | 5 | – | 70 | 189–192 ($MeNO_2$) | 0,27 (1 : 1) | 48,36 / 48,00 | 2,92 / 2,91 | 20,60 / 20,73 | $C_{11}H_8F_3NO_4$ | – |
| (XIV) | 6 | 2 | 60 | 70 | 149–151 (benzene) | 0,37 (1 : 1) | 43,57 / 43,20 | 2,01 / 2,00 | 22,63 / 22,80 | $C_9H_5F_3O_5$ | – |

*Compound (IX) was obtained by refluxing in $MeNO_2$.

†Bp (1 mm Hg): 135-140 (III); 125-127 (VI); 122-125°C, $n_D^{20}$ 1.4870 (XII).

TABLE 2. NMR Spectra of (III)-(VI), (VIII), (IX), and (XI)-(XIV)



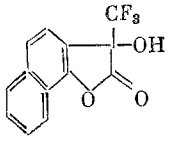

| Compound | R | $^{13}$C Chemical shifts (δ, ppm)* | | | | | | | | | $^{1}J_{C-F}$ | $^{2}J_{C-F}$ | $^{19}$F, ppm |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 3 | 3a | 4 | 5 | 6 | 7 | 7a | $CF_3$ | Hz | | |
| (III) | $R^1=R^2=H$; $R^3=OH$ | 168,15 | 73,96 | 122,59 | 119,26 | 124,78 | 115,31 | 140,55 | 140,40 | 121,69 | 283,00 | 32,50 | – |
| (IV) | $R^1=CH_3$; $R^2=R^3=H$ | 168,46 | 73,64 | 121,08 | 125,14 | 134,14 | 132,11 | 109,87 | 150,84 | 121,69 | 284,89 | 32,05 | 1,65 s |
| (V) | $R^1=R^3=H$; $R^2=CH_3$ | 168,49 | 73,61 | 118,23 | 124,81 | 124,58 | 142,93 | 110,64 | 153,02 | 121,71 | 284,89 | 32,08 | 1,74 s |
| (VI) | $R^1=R^2=R^3=H$ | 168,27 | 73,26 | 121,32 | 125,01 | 124,23 | 131,80 | 110,26 | 152,97 | 121,71 | 284,50 | 32,20 | 1,33 s |
| (VIII) | $R^1=R^3=H$; $R^2=OH$ | 170,75 | 75,46 | 113,52 | 127,96 | 113,29 | 162,35 | 99,83 | 156,23 | 123,83 | 283,00 | 32,45 | – |
| (IX) | $R^1=R^3=H$; $R^2=OCH_2COOH$ | 168,80 | 73,10 | 113,32 | 125,90 | 110,70 | 160,80 | 97,40 | 154,10 | 121,73 | 282,50 | 32,10 | 1,73 s |
| (XI) | $R^1=R^3=H$; $R^2=OCH_3$ | 170,68 | 75,21 | 114,58 | 127,84 | 112,21 | 164,52 | 98,52 | 156,32 | 123,85 | 283,50 | 33,50 | 1,80 s |
| (XII) | $R^1=R^3=H$; $R^2=OC_2H_5$ | 168,65 | 73,13 | 112,35 | 125,78 | 110,38 | 161,69 | 96,82 | 154,24 | 121,81 | 282,50 | 33,70 | – |
| (XIII) | $R^1=R^3=H$; $R^2=HNC(O)CH_3$ | 168,53 | 73,51 | 115,07 | 125,22 | 114,27 | 142,26 | 100,96 | 152,41 | 121,72 | 282,50 | 31,21 | 0,22 s |
| (XIV) | $R^1=H$; $R^2=R^3=OH$ | 168,59 | 73,87 | 112,71 | 115,55 | 110,84 | 148,53 | 128,89 | 140,23 | 121,81 | 282,50 | 32,18 | – |

*Compounds (IV), (V), and (XI)-(XIII) also showed signals corresponding to the R substituents.

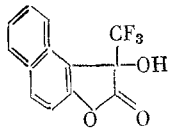
TABLE 3. PMR Spectra* of (III), (V), (VIII), (IX), (XI), and (XII)-(XIV)

| Compound | Chemical shifts (δ, ppm, J, Hz) | | | | |
|---|---|---|---|---|---|
| | 4 | 5 | 6 | 7 | OH |
| (III) | 7,10 dd (8,2) | 7,18 t (2,0) (7,0) | 7,06 br d | – | 10,40 br s<br>8,30 s |
| (V) | 7,45 d (8,0) | 7,13 d | – | 7,17 s | 8,28 s |
| (VIII) | 7,45 d (8,1) | 6,83 dd (2,0) | – | 6,77 d | 9,40 s<br>7,07 s |
| (IX) | 7,46 d (9,5) | 6,80 q (2,3) | – | 6,79 d | 6,35–5,45 br s |
| (XI) | 7,40 d (9,0) | 6,75 q (2,1) | – | 6,80 d | 5,58 s |
| (XII) | 7,42 d (8,5) | 6,82 q (2,4) | – | 6,95 d | 8,20 s |
| (XIII) | 7,48 d (8,5) | 7,30 dd (1,5) | – | 7,75 d | 10,30 s<br>8,35 s |
| (XIV) | 6,81 d (8,0) | 6,67 d | – | – | 10,20–9,90 br s<br>9,70–9,33 br s<br>8,08 br s |

*PMR spectra of (III), (V), (XII)-(XIV) recorded in DMSO-$d_6$ and (VIII), (IX), (XI), in acetone-$d_6$.




(XV)




(XVI)

The results show that reaction of (I) with phenols in AcOH occurs via regioselective o-C-alkylation. Differences in phenol reactivities were notably levelled with C-alkylation products became easier. Hence only highly activated phenols usefully gave rise to furanones. For low activity phenols these reactions were best initially carried out in aprotic solvents and lactonization completed in refluxing AcOH. In this way the benzofuranones (IV)-(VI) were prepared in yields ≥75%.

## EXPERIMENTAL

$^{13}C$, $^{1}H$, and $^{19}F$ NMR spectra were carried out on a Bruker WP-200 SY instrument at 50.31, 200.12, and 188.30 MHz respectively. Chemical shifts were determined relative to TMS ($^{1}H$, $^{13}C$, internal standard) or $CF_3COOH$ ($^{19}F$, external standard). Mass spectra were recorded on a Pye Unicam MS-30 instrument (70 eV). TLC was carried out on Silufol UV-254 plates (Kavalier Company, Ch.SSR) using $Me_2CO:CCl_4$ (1:1 and 1:3 ratio) as eluent and visualization by UV light.

3,5-Dihydroxy-3-trifluoromethyl-2(3H)benzo[b]furanone (II). a) A mixture of hydroquinone (1.1 g), (I) (1.6 g), and benzene (10 ml) were heated in a glass ampul for 6 h at 140-145°C, cooled, the solid product separated and recrystallized from benzene to give 2.39 g (90%) of (II) with mp 134-135°C and $R_f$ 0.30 (1:3). $^{13}C$ NMR spectrum (δ, ppm, acetone): 168.73 ($C^2$), 153.80 ($C^5$), 145.74 ($C^{7a}$), 121.81 ($C^{3a}$), 121.68 ($CF_3$), 118.14 ($C^7$) 111.44 ($C^4$), 111.03 ($C^6$), 74.01 ($C^3$). $^{19}F$ NMR spectrum (δ, ppm, acetone-d): 1.40 s ($CF_3$). Found: C 46.23; H 1.84; F 24.23%. $C_9H_5O_4F_3$. Calculated: C 46.15; H 2.14; F 24.36%.

Compounds (III)-(VI), (VIII), and (IX) were obtained similarly and the yields and physical data are given in Tables 1-3.

b) A mixture of hydroquinone (1.1 g), (I) (1.6 g), and glacial acetic acid (7 ml) were refluxed in the absence of moisture, evaporated in vacuo, and the residue recrystallized from benzene to give 2.53 g (95%) with mp 133-135°C, $R_f$ 0.30 (1:3).

Compounds (III)-(VI), (VIII), (IX), and (XI)-(XIV) were prepared in this way and their parameters are given in Tables 1-3.

3,6-Dihydro-3-trifluoromethyl-5(α-hydroxy-α-carbomethoxytrifluoroethyl)-2(3H)benzo[b]-furanone (X) was obtained from ester (VII) (2.66 g) and (I) (1.6 g) which were heated in a glass ampul with benzene (15 ml) at 160°C for 6 h to give 0.84 g (20%) with mp 193-195°C and $R_f$ 0.69 (1:3). PMR spectrum (δ, ppm, DMSO-$d_6$): 10.05-9.50 br.s, 8.25 br.s, 7.85 br.s (3H, 3 OH), 7.7. s (1H, $H^4$), 6.7 s (1H, $H^7$), 3.73 s (3H, $OCH_3$). $^{19}F$ NMR spectrum (δ, ppm, DMSO-$d_6$): −1.9 s and 0.7 s (1:1). Found: C 40.42; H 2.20; F 29.10%. $C_{13}H_8F_6O_7$. Calculated: C 40.00; H 2.05; F 29.23%.

3-Hydroxy-3-trifluoromethyl-2(3H)naphtho[2,1-b]furanone (XVI) was obtained from 2-naphthol (1.44 g), I (1.6 g) and AcOH (10 ml) by refluxing for 6 h to give 2.49 g (83%) with mp 133-135°C ($CCl_4$) and $R_f$ 0.60 (1:1). $^{13}C$ NMR spectrum (δ, ppm, acetone): 171.30 ($C^2$), 153.80 ($C^{9a}$), 135.35, 130.27, 129.40, 126.48, 124.38 ($C^4$-$C^8$), 132.32, 130.81 ($C^{3b}$, $C^{7a}$), 123.90 ($CF_3$, $J_{C-F}$ = 288.50 Hz), 115.38 ($C^{3a}$), 112.28 ($C^9$), 78.08 ($C^3$, $J_{C-F}$ = 30.51 Hz). PMR spectrum (δ, ppm, acetone-$d_6$): 8.25 br.d (1H, $H^4$, $J_{H-H^5}$ = 8.0 Hz), 8.20 d (1H, $H^8$, $J_{H-H^9}$ = 9.0 Hz), 8.05 br.d (1H, $H^7$, $J_{H-H^6}$ = 8.0 Hz), 7.70 m (1H, $H^6$, $J_{H-H^5}$ = 7.0, $J_{H-H^7}$ = 8.0, $J_{H-H^4}$ = 1.4 Hz), 7:55 m (1H, $H^5$, $J_{H-H_4}$ = 8.0, $J_{H-H^6}$ = 7.0, $J_{H-H^7}$ = 1.4 Hz), 7.51 d (1H, $H^9$, $J_{H-H^8}$ = 9.0 Hz), 7.43 s (1H, OH). $^{19}F$ NMR spectrum (δ, ppm, acetone-$d_6$): 0.92 s. Mass spectrum (m/z): 268 ($M^+$). Found: C 57.93; H 2.47; F 21.10%. $C_{13}H_6F_3O_3$. Calculated: C 58.21; H 2.64; F 21.27%.

3-Hydroxy-3-trifluoromethyl-2(3H)naphtho[1,2-b]furanone (XV) was obtained from 1-naphthol (1.44 g), (I) (1.6g), and AcOH (10 ml) by refluxing for 6 h to give 2.77 g (92%) with mp 132-134°C (benzene) and $R_f$ 0.60 (1:1). $^{13}C$ NMR spectrum (δ, ppm, acetone): 170.64 ($C^2$), 151.58 ($C^{9b}$), 136.76 ($C^{5a}$), 129.46 (2C), 128.59, 126.20, 121.89, 121.78 ($C^4$-$C^9$), 123.81 ($CF_3$, $J_{C-F}$ = 272.0 Hz), 120.19, 117.56 ($C^{3a}$, $C^{9a}$), 76.58 ($C^3$, $J_{C-F}$ = 30.75 Hz).

PMR spectrum (δ, ppm, acetone-$d_6$): 8.10 m, 7.75 m (4H, $H^6$-$H^9$), 7.96 d (1H, $H^5$, $J_{H-H^4}$ = 8.9 Hz), 7.68 qq (1H, $H^4$, $J_{H-H^5}$ = 8.8, $J_{H-F}$ = 0.8 Hz), 7.45 s (1H, OH). $^{19}F$ NMR spectrum (δ, ppm, acetone-$d_6$): 1.04 s. Found: C 57.99; H 2.28; F 20.72%. $C_{13}H_6F_3O_3$. Calculated: C 58.21; H 2.61; F 21.27%.

## CONCLUSIONS

When heated with methyl trifluoropyruvate in aprotic solvents and acetic acid above 120°C it was found that phenols (not containing electron acceptor ring substituents) regioselectively formed ortho-C-alkylation products which could be lactonized to 3-hydroxy-3-trifluoromethyl-2(3H)benzo[b]furanones.

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