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UNUSUAL FRIEDEL-CRAFTS REACTIONS, IX.[1]
ONE-STEP ORTHO-ACYLATION OF PHENOLS WITH α,β-UNSATURATED ACYL CHLORIDES. SYNTHESIS OF 2'-HYDROXYCHALCONES AND SORBICILLIN ANALOGUES

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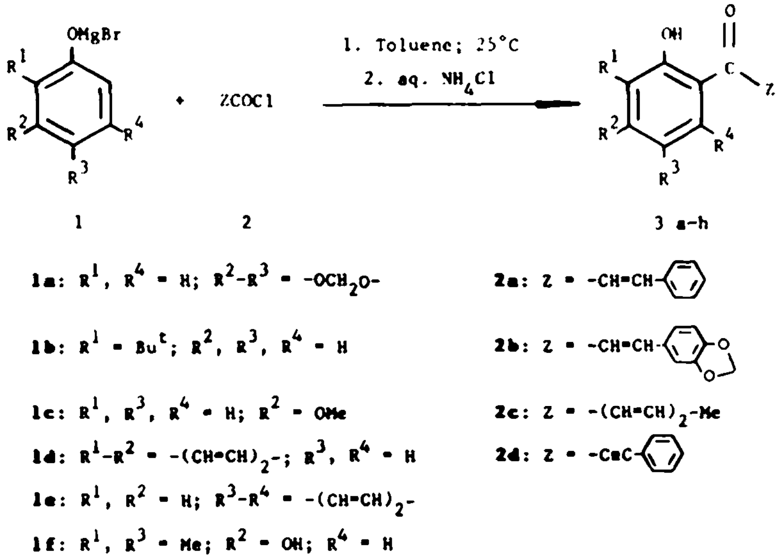
Abstract - The reaction of bromomagnesium phenolates **1** in toluene with α,β-unsaturated acyl chlorides **2** at room temperature provides a straightforward highly selective synthesis of α,β-unsaturated 2-hydroxyarylketones **3**. 2'-Hydroxychalcones, ortho-sorbylphenols including sorbicillin **3g**, and ortho-propiolylphenols were usefully synthesized by this way. This reaction provides a further example of the synthetic versatility of the chelation-controlled approach in the elaboration of phenol derivatives.

The acylation of phenols with acyl halides is a topic of continuing interest to organic chemists, offering a rich and fruitful area for study and synthetic application.[2]

Our previous experience with the chelation-controlled regiospecific electrophilic substitutions to metal phenolates[3] prompted us to reexamine the use of acyl chlorides as acylating agents, suggesting a simple and highly selective method to acylate phenols at the ortho-position under mild conditions. More specifically, this paper deals with the reaction of metal phenolates **1** with α,β-unsaturated acyl chlorides **2** providing a straightforward entry to α,β-unsaturated 2-hydroxyarylketones **3** including ortho-cinnamyl-, ortho-sorbyl-, and ortho-propiolylphenols, a class of important naturally occurring compounds and synthetic intermediates.[4,5]

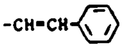
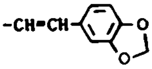
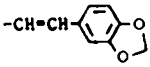
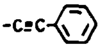


Scheme 1.

The most useful syntheses of these substances involve conventional Friedel-Crafts acylation,[2] Fries-type rearrangement of suitable aryl esters,[6] and cross-aldol condensation between ortho-hydroxyacetophenones and suitable aldehydes.[7] These procedures however suffer somewhat from disadvantages such as lack of selectivity, limited applicability, and multistep procedures. And such a limitation is an indication that the regiocontrol of the acylation process of phenol derivatives is still on open problem and that further synthetic studies are appropriate.

Our route starts from highly co-ordinating metal phenolates, in general bromomagnesium salts **1** and α,β-unsaturated acyl chlorides **2** working at ambient temperature in poorly donating media (Scheme 1). The α,β-unsaturated ortho-hydroxyarylketones **3a-h** listed in the Table were obtained by this way, free from para-acylated isomers, along with only a few percent yield (10-15%) of oxygen-acylated compounds.

Table. Synthesis of α,β-unsaturated 2-hydroxyarylketones **3a-h**.

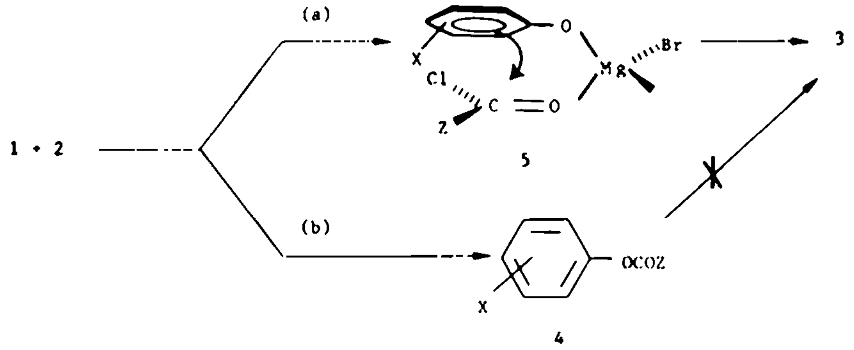
Entry	Starting compds	product	R^1	R^2	R^3	R^4	Z	Yield%	m.p./°C
1	**1a+2a**	**3a**	H	$-OCH_2O-$		H		70	117-119
2	**1b+2b**	**3b**	Bu^t	H	H	H		55	125-127
3	**1a+2b**	**3c**	H	$-OCH_2O-$		H		60	178-180
4	**1c+2c**	**3d**	H	OMe	H	H	$-(CH=CH)_2-Me$	70	106-108
5	**1a+2c**	**3e**	H	$-OCH_2O-$		H	$-(CH=CH)_2-Me$	78	158-160
6	**1e+2c**	**3f**	H	H	$-(CH=CH)-_2$		$-(CH=CH)_2-Me$	58	85-86
7	**1f+2c**	**3g**	Me	OH	Me	H	$-(CH=CH)_2-Me$	75	123-125[a]
8	**1a+2d**	**3h**	H	$-OCH_2O-$		H		89	125-127

[a] Lit.[8], m.p. 122-125°C.

Cinnamyl chlorides (entry 1-3) produced 2'-hydroxychalcones in 55-70% isolated yield, and sorbyl chloride (entry 4-7) gave rise to ortho-sorbylphenols (58-78% yield), including the Penicillium Chrysogenum metabolite sorbicillin **3g**. Similarly, phenylpropiolyl chloride (entry 8) yielded **3h** with nearly quantitative ortho-selectivity.

All the compounds in this study, whose purity was checked by HPLC and TLC techniques, were characterized by combined spectroscopic methods and, in particular, the absolute E,E-geometry of the hexadienoyl side-chain in **3g** was established by high field ^1H NMR spectroscopy, also in comparison with the reported structure[8] as well as simulation experiments.

The ortho-acylphenols produced in this reaction correspond to the expected products of a metal-template unusual Friedel-Crafts acylation. As demonstrated by IR and ^{13}C NMR measurements in recent works, acyl chlorides undergo adducts with Lewis acids in which the metal center co-ordinates the carboxy-group preferentially.[9] On the basis of these observations and foccusing previous studies on the chelation of aldehydic carbonyl-group with bromomagnesium phenolates,[10] we suggest the mechanistic path outlined in Scheme 2 for this ortho-specifically directed acylation.



Scheme 2

We emphasize that the basis of the remarkable ortho-selectivity is due to the initial interaction between the phenolic metal ion and the acyl chloride **2** leading to the oriented complex **5**. Electrophilic attack at the aromatic nucleous can then only occur at the proximate ortho-position (route a). On the other hand, nucleophilic displacement of **2** by means of phenolate anion produces esters **4** as side products (route b). We exclude instead a Fries-type ortho-specific rearrangement (**4** → **3**) mainly because the reaction of both aryl cinnamates (**4**, Z=-CH=CHAr) and aryl sorbates (**4**, Z=-$(CH=CH)_2$-Me) with a stoichiometric amount of bromomagnesium phenoxide under our reaction conditions resulted in complete recovery of unchanged starting esters.

In conclusion, the usefulness of the chelation-controlled approach in the ortho-specific substitution to phenols with electrophilic reagents is firmly established, and the present work represents a further example of the synthetic versatility.

EXPERIMENTAL

The instrumentation employed in UV, ^{1}H NMR, and ^{13}C NMR analyses as well as equipment description were given in the preceeding papers of this series.[11] 2,4-Dimethyl-3-hydroxyphenol (**1f**) was prepared by reduction of 2,4-dihydroxy-3-methylbenzaldehyde;[12] cinnamoyl chloride (**2a**), 3,4-methylenedioxycinnamoyl chloride (**2b**), sorbyl chloride (**2c**), and phenylpropiolyl chloride (2d) were prepared from the corresponding acids and thionyl chloride.

α,β-Unsaturated 2-hydroxyarylketones (**3**). General acylation procedure. To a solution of ethylmagnesium bromide (0.01 mol) in diethyl ether (25 mL) a solution of the selected phenol **1** (0.01 mol) in diethyl ether (25 mL) was added under stirring at room temperature. The ether was removed completely under vacuum and anhydrous toluene (50 mL) was added. To the resulting slurry, the appropriate acyl chloride **2** (0.01 mol) in toluene (15 mL) was added dropwise and the yellow-orange suspension was stirred at room temperature for 5 hr. The mixture was poured in aqueous ammonium chloride solution and then extracted with diethyl ether (3x50 mL). Drying (Na_2SO_4) and removal of the solvent gave a syrup from which 2-hydroxyarylketones **3** were obtained as follows: chalcones **3a–c** and propiolylphenol **3h**, by flash chromatography on silica gel by using hexane/ethyl acetate eluant mixture; sorbylphenols **3d–h** by 2N sodium hydroxyde extraction, acidification (1N HCl), ether extraction, drying (Na_2SO_4), removal of the solvent, and crystallization of the residue from benzene or hexane/benzene solvent mixtures. The following compounds were obtained by this procedure:

2'-Hydroxy-4'5'-methylenedioxychalcone (**3a**). Yellow crystals from benzene/hexane 1:1, yield 1.88 g (70%); m.p. 117-119°C (Found: C, 71.49; H, 4.69. Calc. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%); IR (KBr) 1638 cm^{-1} (C=O); UV λ_{max} 204, 228, 278, 331, and 390 nm (log ε 4.38, 4.05, 3.93, 4.20, and 3.96); MS m/z 268 (M^+, 30%), 191 (32%), 164 (100%), 136 (18%), 103 (44%), 77 (72%); ^{13}C NMR (DMSO) δ 98.2 (C-3'), 102.3 (O-CH_2-O), 107.4 (C-6'), 112.4 (C-1'), 121.3 (C-α), 128.8 and 129.2 (C-2, C-6, C-3, C-5), 130.7 (C-4), 134.6 (C-1), 140.6 (C-5'), 144.2 (C-β), 154.6 (C-4'), 163.0 (C-2'), 191.3 (C=O).

2'-Hydroxy-3'-tert-butyl-3,4-methylenedioxychalcone (**3b**). Yellow crystals from benzene, yield 1.78 g (55%); m.p. 125-127°C (Found: C, 74.26; H, 6.14. Calc. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22%); IR (KBr) 1638 cm^{-1} (C=O); UV λ_{max} 206, 266, and 375 nm (log ε 4.31, 4.01, and 4.33); MS m/z 324 (M^+, 53%), 209 (71%), 179 (53%), 175 (27%), 161 (72%), 148 (100%), 135 (51%); ^{13}C NMR (DMSO) δ 29.1 (Me_3C), 34.5 (Me_3C), 101.6 (O-CH_2-O), 101.7 (C-5), 108.4 (C-2), 118.1 (C-5'), 118.9 (C-6), 119.4 (C-1'), 126.5 (C-α), 128.8 (C-6'), 128.9 (C-1), 133.3 (C-4;), 137.4 (C-3'), 145.2 (C-β), 148.0 and 149.9 (C-4 and C-3), 162.3 (C-2'), 194.4 (C=O).

3,4,4',5'-bis-Methylenedioxy-2'-hydroxychalcone (**3c**). Orange crystals from benzene, yield 1.87 g (60%); m.p. 178-180°C (Found: C, 65.51; H, 3.68. Calc. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.87%); IR (KBr) 1630 cm^{-1} (C=O); UV λ_{max} 203, 237, 294, 340, and 395 nm (log ε 4.49, 4.03, 4.03, 4.01, and 3.83); Ms *m/z* 312 (M^+, 8%), 268 (5%), 191 (9%), 164 (42%), 148 (100%), 135 (14%), 77 (18%); ^{13}C NMR (DMSO) δ 98.1 (C-3'), 101.2 and 102.2 (O-CH_2-O), 107.3 (C-6), 126.5 (C-α), 129.2 (C-1), 140.5 (C-5'), 144.4 (C-β), 148.1 and 149.7 (C-4 and C-3), 154.3 (C-4'), 162.9 (C-2'), 191.3 (C=O).

5-Methoxy-2-sorbylphenol (**3d**). Orange crystals from hexane/benzene 1:1, yield 1.53 g (70%); m.p. 106-108°C (Found: C, 71.70; H, 6.29. Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%); IR (KBr) 1642 cm^{-1} (C=O); UV λ_{max} 207, 311, and 334 nm (log ε 4.30, 4.31, and 4.23); Ms *m/z* 218 (M^+, 69%), 203 (100%), 177 (62%), 161 (27%), 151 (81%), 124 (28%), 95 (57%); ^{13}C NMR (DMSO) δ 18.6 (C-ε), 38.6 (O-CH_3), 100.8 (C-6), 107.1 (C-4), 113.4 (C-2), 122.0 (C-α), 130.2 (C-γ), 131.8 (C-3), 141.6 (C-δ), 144.5 (C-β), 165.3 and 165.7 (C-1 and C-5), 191.7 (C=O).

4,5-Methylenedioxy-2-sorbylphenol (**3e**). Orange needles from benzene, yield 1.81 g (78%); m.p. 158-160°C (Found: C, 67.09; H, 5.26. Calc. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%); IR (KBr) 1650 cm^{-1} (C=O); UV λ_{max} 203, 239, 306, and 385 nm (log ε 4.28, 3.97, 4.25, and 3.98); Ms *m/z* 232 (M^+, 100%), 217 (63), 191 (34%), 175 (15%), 164 (98%), 136 (15%), 107 (22%); ^{13}C NMR (DMSO) δ 18.4 (C-ε), 97.9 (C-6), 101.9 (O-CH_2-O), 106.3 (C-3), 112.1 (C-2), 122.3 (C-α), 130.2 (C-γ), 140.1 (C-5), 141.1 (C-δ), 144.3 (C-β), 153.9 (C-5), 162.3 (C-1), 191.3 (C=O).

• *1-Sorbyl-2-hydroxynaphthalene* (**3f**). Orange crystals from benzene yield 1.38 g (58%); m.p. 85-86°C (Found: C, 80.58; H, 5.96. Calc. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92%); IR (KBr) 1620 cm^{-1} (C=O); UV λ_{max} 225, 282, and 370 nm (log ε 4.56, 4.36, and 3.65); Ms *m/z* 238 (M^+, 68%), 223 (66%), 197 (38%), 181 (48%), 170 (82%), 142 (38%), 115 (100%), 95 (28%); ^{13}C NMR δ 18.3 (C-ε), 118.4, 120.2, 123.5, 126.8, 127.9, 128.0, 130.0, 131.1, and 131.6 (aromatics), 122.2 (C-α), 130.3 (C-γ), 140.0 (C-δ), 144.2 (C-β), 153.4 (C-2), 191.8 (C=O).

4,6-Dimethyl-5-hydroxy-2-sorbylphenol (sorbicillin) (**3g**). Yellow microcrystals from benzene, yield 1.74 g (75%); m.p. 123-125°C (Found: C, 72.46; H, 7.09. Calc. for $C_{14}H_{16}O_3$: C, 72.36; H, 6.94%); IR (KBr) 1630 cm^{-1} (C=O); UV λ_{max} 204 and 323 nm (log ε 4.39 and 4.30); Ms *m/z* 232 (M^+, 48%), 217 (64) 191 (32%), 165 (45%), 136 (100%), 107 (25%), 95 (85%), 77 (48%); ^{13}C NMR (DMSO) δ 8.2 (Me-C6), 16.2 (Me-C4), 18.6 (C-ε), 110.5, 112.2, and 115.8 (C-2, C-4, and C-6), 122.2 (C-α), 128.7 (C-3), 130.4 (C-γ), 140.5 (C-δ), 143.6 (C-β), 166.6 and 161.9 (C-1 and C-5), 191.5 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.90 (d, 3H, J = 6.5 Hz, Me-ε), 2.16 and 2.23 (s, 3H each, Me-Ar), 5.45 (s, 1H, OH-5), 6.26 (qdd, 1H, J = 15.4, 6.5, 2.0 Hz, H-δ), 6.34 (ddd, 1H, J = 15.4, 11.0, 1.0 Hz, H-γ), 6.94 (d, 1H, J = 15.4 Hz, H-α), 7.46 (ddd, 1H, J = 15.4, 11.0, 2.0 Hz, H-β), 7.45 (s, 1H, H-3), 13.61 (s, 1H, OH-1).

1-(2'-Hydroxy-4',5'-methylenedioxyphenyl)-3-phenylpropynone (**3h**). Yellow crystals from benzene/hexane 2:1, yield 2.37 g (89%); m.p. 125-127°C (Found: C, 72.19; H, 3.85. Calc. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%); IR (KBr) 2190 (C=C), 1618 cm^{-1} (C=O); UV λ_{max} 218, 267, 299, 309, and 391 nm (log ε 4.25, 4.11, 4.14, 4.15, and 4.06); Ms *m/z* 266 (M^+, 83%), 164 (82%), 101 (67%), 77 (42%); ^{13}C NMR (DMSO) δ 85.4 (C-α), 95.0 (C-β), 98.0 (C-3'), 102.6 (O-CH_2-O), 107.8 (C-6'), 113.5 (C-1'), 119.0 (C-1), 128.9 (C-3 and C-5), 131.2 (C-4), 132.8 (C-2 and C-6), 140.9 (C-5'), 155.4 (C-4'), 162.1 (C-2'), 178.3 (C=O).

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