Tetrahedron Vol 39, No 10, pp 1761 to 1764, 1983
Printed in Great Britain

0040-4020/83/101761-04$03.00/0

UNUSUAL FRIEDEL–CRAFTS REACTIONS—VI[1]

SYNTHESIS OF ETHYL 6-(2-HYDROXYPHENYL)-2-CARBETHOXY-4-HEXENOATES BY REACTION OF METAL PHENOLATES WITH DIETHYL 2-VINYLCYCLOPROPANE-1,1-DICARBOXYLATES

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(*Received in the UK 23 July* 1982)

Abstract—A mild synthesis of ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**4**) ($SnCl_4$-promoted *o*-specific alkylation of potassium phenolates **1** with diethyl vinylcyclopropane-1,1-dicarboxylates **2**) involves an oriented hexacoordinated substrate-reagent complex **3**, accounting for both *o*-specific attack on the phenol, and 1,7-homoconjugate addition to the vinylcyclopropane.

In recent years, the chemistry of electrophilic vinylcyclopropanes **2** has received great attention. When **2** are allowed to react with a number of nucleophiles such as malonate anion, amines and thiolates, a series of compounds is produced arising from 1,5- or 1,7-attack modes depending upon solvent, catalyst and reaction conditions.[2]

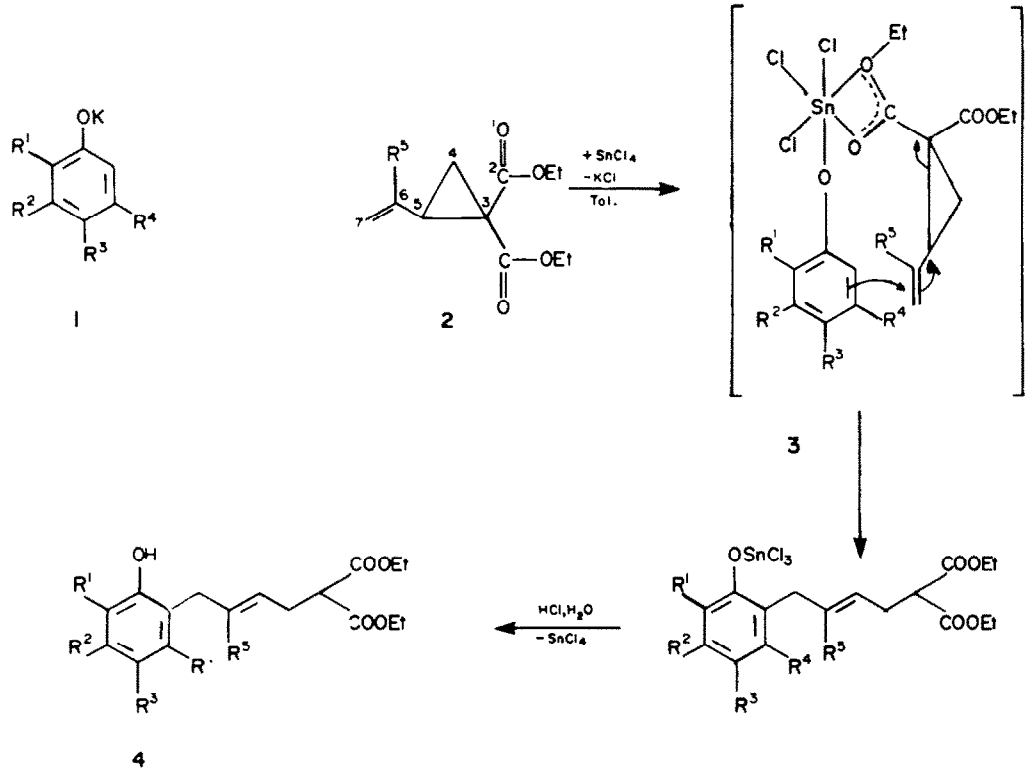
Although much interest has concentrated on anionic and carbanionic addition to these reagents,[3] there are only scant reports[4] dealing with the use of compounds **2** as C-alkylating agents in Friedel–Crafts type reactions.

Recently we have reported that under unusual Friedel–Crafts conditions, alkali and alkali earth phenoxides undergo electrophilic aromatic substitution with several reagents to give *o*-specific attack to the phenol ring.[5]

We show here that diethyl vinylcyclopropane-1,1-dicarboxylates (**2**) are valuable electrophiles in regio- and stereocontrolled alkylation of metal phenolates **1** leading to ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**4**) *via o*-specific attack on the phenol ring with exclusive 1,7-homoconjugate addition to vinylcyclopropane derivatives **2**.

Treatment of potassium phenoxides **1** with **2** in the presence of a stoichiometric amount of tin tetrachloride in toluene at 80° for 10 h, gave the ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**4**) in 25–50% isolated yields.

The reaction proceeds preferentially (> 85%) at



the *o*-position, entirely by 1,7-homoconjugated addition mechanism. Side products (ca 15%) are due to *p*-attack.

Representative compounds (**4a–j**) were prepared by this method employing a variety of potassium phenolates and vinyl cyclopropane 1,1-dicarboxylates. In all cases the regioisomer was shown to be that represented by general formula **4**.

For compound **4** two geometric isomers are possible. Values of the coupling constants for the olefinic protons (J = 15.0 Hz) and homonuclear Overhauser effect measurements proved their exclusive E configuration.

Synthetic data are summarized in Table 1. Significant spectroscopic data of all ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**4**) are collected in Table 2. The structure of all the foregoing products were especially supported by their ^{1}H NMR spectra. For derivatives **4** the proton spectra reveal two methylene signals at δ 2.6 (triplet) and δ 3.2 doublet in **4a–h** or singlet in **4i, j**), and one methine signal at δ 3.4 (triplet).

The potassium salt of phenol was the most efficient in this reaction giving moderate to good yield and high selectivity of compounds **4**. Lithium, sodium and magnesium salts as well as Lewis acids other than tin tetrachloride gave little or no alkylation products. Furthermore, electron-withdrawing substituents reduce the reactivity on the phenol and no reaction was observed with *p*-acetylphenol or nitrophenols.

As far as the reaction mechanism is concerned, at present it is not possible to provide a complete rationale for the results described herein. We would suggest, however, that an oriented complex such as **3**, in which the acid metal ion coordinates oxygen atoms of both reactants, plays a crucial directional role in the *o*-specific attack as well as in the 1,7-cyclopropane ring opening mode. The formation of **4** could proceed through the hexacoordinate adduct[6] **3** in which the vinyl group is placed in a proximity position favourable for *o*-specific process and facilitating the attack at the less hindered double bond terminal position. Evidence in support of this hypothesis comes from the observation that while main *o*-alkylated products only exist as one trans-diastereoisomer, *p*-alkylated by-products are a mixture of two isomers due to random 1,7- and 1,5-electrophilic attacks.

In conclusion we have shown here a facile metal-driven synthesis of ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates (**4**) *via* Lewis acid-promoted *o*-specific alkylation of potassium phenolates (**1**) with diethyl vinylcyclopropane-1,1-dicarboxylates (**2**). Compounds **4** are useful phenolic intermediates which can be, for example, smoothly and quantitatively converted into the corresponding 6-(2-hydroxyphenyl)-hexanoic acids by hydrogenation (C/Pd, H_2) and subsequent decarboxylation (a mixture of acetic and sulfuric acids, 9:1–v:v, at 80° for 5 h). Compounds **4** are also congeners of a variety of natural products, many of which display pronounced biological activity, as mycophenolic acid,[7] anacardic acids[8] and some components of the urushiol.[9]

EXPERIMENTAL

General. All chemicals were reagent grade and were used without further purification. IR spectra (film) were recorded on a Perkin–Elmer 298 spectrometer. UV spectra for solutions in 95% ethanol were measured using a Jasco-UVIDEC 505 spectrometer. ^{1}H NMR spectra were obtained with Varian EM-360 or XL-100 instruments. Chemical shifts are expressed in ppm with respect to internal TMS. Mass spectra were determined on a Varian MAT CH5 spectrometer using direct insertion probe (70 eV). TLC experiments were carried out on Merck silica gel GF_{254} plates using hexane/ethyl acetate mixtures as eluent.

Diethyl 2-vinylcyclopropane-1,1-dicarboxylates (**2**) were synthesized from 1,4-dibromo-2-butene and sodium diethylmalonate following the reported procedure.[10]

Ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoate (**4a**). *Typical procedure*

To a suspension of potassium phenolate (**1a**) [prepared *in situ* from phenol (0.94 g, 10 mmol) and potassium pellets (0.39 g, 10 mmol) in anhydrous toluene (50 ml)] a solution of tin(IV) chloride (2.60 g, 10 mmol) in toluene (10 ml) was added under stirring at room temperature. The slurry was heated under reflux with stirring for 15 min, while a stream of dry nitrogen was passed. The resulting yellow suspension was cooled to 80° and a solution of diethyl 2-vinylcyclopropane-1,1-dicarboxylate (2.12 g, 10 mmol) in toluene (10 ml) was added dropwise during 3 h, then the

Table 1. Preparation of ethyl 6-(2-hydroxyphenyl)-2-carbethoxy-4-hexenoates **4a–j**

Product	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]	n_D^{16}	Molecular formula (M.w.)[b]
4a	H	H	H	H	H	25 (85)	1.5098	$C_{17}H_{22}O_5$ (306.35)
4b	CH_3	H	H	H	H	33 (88)	1.5100	$C_{18}H_{24}O_5$ (320.37)
4c	H	H	CH_3	H	H	38 (90)	1.5095	$C_{18}H_{24}O_5$ (320.37)
4d	CH_3	H	CH_3	H	H	30 (91)	1.5100	$C_{19}H_{26}O_5$ (334.40)
4e	H	Cl	H	H	H	28 (80)[c]	1.5200	$C_{17}H_{21}ClO_5$ (340.84)
4f	H	H	OCH_3	H	H	42 (94)	1.5105	$C_{18}H_{24}O_6$ (336.27)
4g	H	H	$-(CH{=}CH)_2-$		H	50 (90)	1.5627	$C_{21}H_{24}O_5$ (356.40)
4h	H	$-OCH_2O-$		H	H	45 (90)	1.5200	$C_{18}H_{22}O_7$ (350.36)
4i	H	H	H	H	CH_3	29 (86)	1.5143	$C_{18}H_{24}O_5$ (320.37)
4j	H	H	CH_3	H	CH_3	32 (89)	1.5120	$C_{19}H_{26}O_5$ (334.40)

[a] Isolated yield based on total amount of starting phenol. Values in parenthesis refer to yields based upon unrecovered starting phenol, not optimized.

[b] Correct elemental analyses obtained for all prepared compounds.

[c] 5% of ethyl 6-(2-hydroxy-6-chlorophenyl)-2-carbethoxy-4-hexenoate also formed (by TLC analysis).

Table 2. Significant IR, UV, ^{1}H NMR and mass spectral data of compounds **4a–j**

Compound	IR (neat) ν [cm^{-1}]	UV (95% ethanol) λ_{max} [nm] (log ε)	^{1}H NMR ($CDCl_3$) δ [ppm]	Mass *m/e* (% relative abundance)
4a	3450,2985,1735, 1230,1030,755	213(3.91)*i*, 274(3.71)	1.24(6H,t,$OCH_2\underline{CH_3}$, J=7.5 Hz); 2.64(2H,t,$\underline{CH_2}CH$, J=7.5 Hz); 3.39(2H,d,$ArCH_2$, J=6.0 Hz); 3.44(1H, t,$CH_2\underline{CH}$, J=7.5 Hz); 4.20(4H,q,$\underline{OCH_2}CH_3$, J=7.5 Hz); 5.1-5.9(2H,m,CH=CH); 5.86(1H,s,OH); 6.7-7.3(4H, m,H_{arom})	306(4), 261(2), 243(5), 215(10), 172(15), 146(100), 133(22), 131(28)
4b	3460,2990,1740, 1272,1038,825	225(3.88), 275(3.76)	1.20(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.18(3H,s,$ArCH_3$); 2.57(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.13(2H,d,$ArCH_2$, J=6.0 Hz); 3.37(1H,t,$CH_2\underline{CH}$, J=7.0 Hz); 4.10(4H,q, $\underline{OCH_2}CH_3$, J=7.0 Hz); 5.2-5.9(2H,m,CH=CH); 5.85 (1H,s,OH); 6.4-7.0(3H,m,H_{arom})	320(6), 275(3), 229(6), 160(100), 145(34), 121(11)
4c	3470,2995,1740, 1270,1035,820	217(3.00)*i*, 280(3.56)	1.18(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.20(3H,s,$ArCH_3$); 2.59(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.27(2H,d,$ArCH_2$, J=6.0 Hz); 3.40(1H,t,$CH_2\underline{CH}$, J=7.0 Hz); 4.13(4H,q, $\underline{OCH_2}CH_3$, J=7.0 Hz); 5.2-5.9(2H,m,CH=CH); 6.36 (1H,s,OH); 6.5-7.0(3H,m,H_{arom})	320(8), 275(2), 257(4), 229(7), 160(100), 145(42), 121(19)
4d	3520,2990,1740, 1200,1035,862	218(3.98)*i*, 277(3.63)	1.15(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.15(6H,s,$ArCH_3$); 2.55(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.20(2H,d,$ArCH_2$, J=6.0 Hz); 3.32(1H,t,$CH_2\underline{CH}$, J=7.0 Hz); 4.06(4H, q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 4.73(1H,bs,OH); 5.2-5.9 (2H,m,CH=CH); 6.5-6.9(2H,m,H_{arom})	334(28), 243(9), 215(10), 174(100), 159(74), 135(31)
4e	3440,2995,1738, 1238,1045,865	218(3.97)*i*, 277(3.73)	1.22(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.61(2H,t,$\underline{CH_2}CH$, J=6.5 Hz); 3.25(2H,d,$ArCH_2$, J=5.0 Hz); 3.40(1H, t,$CH_2\underline{CH}$, J=6.5 Hz); 4.12(4H,q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 5.2-5.8(2H,m,CH=CH); 6.4-7.2(4H,m,H_{arom} and OH)	340(4), 295(4), 249(14), 221(8), 180(100), 145(71)
4f	3470,2990,1730, 1205,1040,865, 812	220(3.84)*sh*, 294(3.55)	1.20(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.56(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.26(2H,d,$ArCH_2$, J=5.0 Hz); 3.40(1H,t, $CH_2\underline{CH}$, J=7.0 Hz); 3.73(3H,s,OCH_3); 4.13(4H,q, $\underline{OCH_2}CH_3$, J=7.0 Hz); 4.8-5.9(2H,m,CH=CH); 6.2-6.7 (3H,m,H_{arom}); 6.76(1H,bs,OH)	336(25), 273(11), 244(21), 216(21), 176(100), 161(83), 137(51)
4g	3450,2990,1740, 1270,1035,820, 753	228(4.62), 268(3.88), 278(3.92), 290(3.80), 335(3.46)	1.10(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.68(2H,t,$\underline{CH_2}CH$, J=8.0 Hz); 3.23(2H,d,$ArCH_2$, J=7.5 Hz); 3.40 (1H, t,$CH_2\underline{CH}$, J=8.0 Hz); 4.05(4H,q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 4.9-5.8(2H,m,CH=CH); 6.63(1H,bs,OH); 6.9-8.1(6H, m,H_{arom})	356(27), 265(12), 237(5), 196(70), 173(100), 127(34)
4h	3460,2990,1740, 1180,1045,940, 865	236(3.66), 301(3.80)	1.22(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 2.60(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.18(2H,d,$ArCH_2$, J=5.0 Hz); 3.40(1H, t,$CH_2\underline{CH}$, J=7.0 Hz); 4.13(4H,q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 5.3-5.9(2H,m,CH=CH); 5.80(2H,s,$\underline{OCH_2O}$); 6.2-6.7 (2H,m,H_{arom}); 6.62(1H,bs,OH)	350(85), 259(20), 190(85), 173(100), 151(47), 147(68), 127(32)
4i	3440,2985,1735, 1218,1035,860, 825	226(3.98), 277(3.43), 284(3.38)	1.23(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 1.50(3H,s,CH_3C=C); 2.58(2H,t,$\underline{CH_2}CH$, J=7.0 Hz); 3.15(2H,s,$ArCH_2$); 3.35(1H,t,$CH_2\underline{CH}$, J=7.0 Hz); 4.10(4H,q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 5.10(1H,t,CH=C, J=7.0 Hz); 6.22(1H, bs, OH); 6.4-7.2(4H,m,H_{arom})	320(42), 229(5), 201(4), 173(13), 160(100), 145(80), 107(51)
4j	3460,2985,1735, 1265,1038,818	220(3.97)*i*, 286(3.39)	1.20(6H,t,$OCH_2\underline{CH_3}$, J=7.0 Hz); 1.60(3H,s,CH_3C=C); 2.20(3H,s,$ArCH_3$); 2.60(2H,t,$\underline{CH_2}CH$, J=7.5 Hz); 3.23(2H,s,$ArCH_2$); 3.33(1H,t,$\underline{CH_2}CH$, J=7.5 Hz); 4.10(4H,q,$\underline{OCH_2}CH_3$, J=7.0 Hz); 5.18(1H,t,CH=C, J=7.5 Hz); 5.88(1H,bs,OH); 6.6-7.1(3H,m,H_{arom})	334(16), 271(6), 174(69), 159(100), 121(36), 105(11)

resulting mixture was stirred at 80° for 10 h. After cooling to room temperature, the reaction mixture was quenched with an excess of an aqueous amonium chloride solution and extracted with diethyl ether (3 × 50 ml). After drying (Na_2SO_4) the ether was evaporated and **4a** was separated from the residue by chromatography on silica gel using hexane/ethyl acetate 85:15 (v:v): yield 0.766 g (25%; 85% based on unrecovered phenol); colourless liquid, n_D^{16} 1.5098.

Compounds **4b–j** in Table 1 were prepared in similar way.

Because of the great instability of compounds **4** under heating, bps are not reported here.

Acknowledgments—We are pleased to acknowledge support of this investigation by C.N.R., Italy (Progetto Finalizzato Chimica Fine e Secondaria).

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