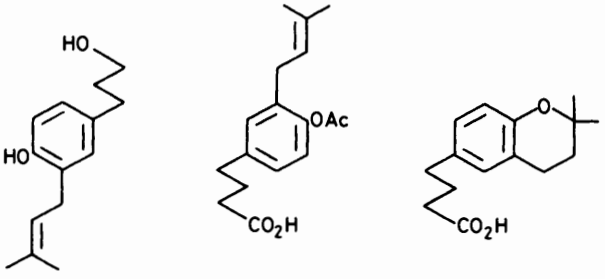
A Convenient Solvent-specific Synthesis of 4-[4-Acetoxy-3-(3-methylbut-2-enyl)phenyl]butyric Acid

By **Majekodunmi O. Fatope,*** Department of Chemistry, Bayero University, P. M. B. 3011, Kano, Nigeria
Joseph I. Okogun, Department of Chemistry, University of Ibadan, Ibadan, Nigeria

Three types of reaction, esterification, *C*-alkenylation, and *O*-alkenylation, have been observed between the di-anion (4) and 1-bromo-3-methylbut-2-ene (5) in different solvent systems. Our studies of the effect of the medium on the behaviour of the di-anion (4) towards electrophilic attack by the bromo-alkene (5) resulted in the synthesis of analogues (2) and (6d) of a known anti-sickling agent (3) in high yield. The regioselectivity of the alkenylation reactions is rationalised in terms of solvent polarity.

PREVIOUS WORK on the conversion of xanthoxylol [1] (1) to 4-[4-acetoxy-3-(3-methylbut-2-enyl)phenyl]butyric acid (2) had been reported by Enyenihi.[2] The desired product (2) was not obtained since intramolecular cyclization of compound (1) resulted, instead, in the formation of benzopyran; however the author was able to convert compound (1) into 4-(2,2-dimethylchroman-6-yl)butyric acid (3), a product which was later shown to possess anti-sickling [3,4] and anti-inflammatory [5] activity. The structural resemblance of the acetoxyphenylbutyric acid (2) to the salicylates, and its possible conversion into the chroman (3) *in vivo*, prompted us to attempt the synthesis of compounds (2) and (6d) by allowing the di-anion (4) to react with 1-bromo-3-methylbut-2-ene (5).

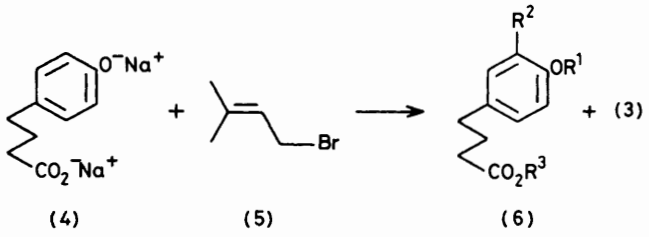


(1) (2) (3)

Usually, sodium salts of phenols undergo electrophilic attack by allyl halides to give both the *O*- and *C*-alkenylated derivatives [6] in proportions that vary with solvent polarity.

The extension of this reaction to the di-sodium salt of 4-*p*-hydroxyphenylbutyric acid provides an additional nucleophilic centre, the carboxylate anion, on which electrophilic attack by allyl halides could occur to give esters.[7] The results of our studies of the reaction in three aprotic solvents, which differed significantly in polarity, are shown in Table 1.

Treatment of 4-*p*-hydroxyphenylbutyric acid with sodium hydride in toluene gave the di-anion (4). Addition of 1-bromo-2-methylbut-2-ene to compound (4) in toluene at 35 °C, followed by acidification and work-up, gave the chroman (3) (20%) and the phenolic compound (6d) (52%), respectively. Following a similar procedure and using THF as solvent, compound (6d) was obtained in 18% yield. Reactions in HMPA were fast and complex, and gave a low yield of the *C*-alkenylated derivative (6d) at 35 °C. The relative increase in the proportions of *C*-alkenylated products as compared with *O*-alkenylated and ester derivatives from the di-anion (4)



(4) (5) (6)

a; $R^1 = R^3 = Me_2C{=}CHCH_2$; $R^2 = H$
b; $R^1 = R^2 = H$; $R^3 = Me_2C{=}CHCH_2$
c; $R^1 = Me_2C{=}CHCH_2$; $R^2 = R^3 = H$
d; $R^1 = R^3 = H$; $R^2 = Me_2C{=}CHCH_2$

when the solvent is changed from HMPA to THF to $PhCH_3$ (Table 2) parallels earlier studies of the effect of the solvent on ambident anion behaviour,[8] *i.e.* the use of a less polar aprotic solvent tends to promote *C*-alkylation. The differences in the distribution of alkenylated derivatives of the di-anion (4) in solvents that differ in polarity is of interest in relation to ambident anion behaviour and also for synthetic purposes.

TABLE 1

Reactions of 4-*p*-hydroxyphenylbutyric acid di-anion with 1-bromo-3-methylbut-2-ene (5)

Time (h)	Temp. (°C)	Solvent [a] (50ml)	Composition (mol%) [b] of recovered product (3)	(6a)	(6b)	(6c)	(6d)
4	35	HMPA	2	2.5	45	30.5	
72	35	THF			15	34	18
72	35	$PhCH_3$	20			1	52 [c]

[a] Hexamethylphosphoramide (HMPA); tetrahydrofuran (THF); toluene ($PhCH_3$). [b] Average of the major products after column chromatography. [c] Yield (accurate to ±5%), as observed from the average yield of (6d) in four repeated experiments.

The major problem in this synthesis, however, is the ready conversion of the phenolic compound (6d) into the chroman (3) at 25 °C on acidification. This presumably arises by protonation of the *gem*-dimethylallyl substituent of the phenol (6d) which cyclizes to

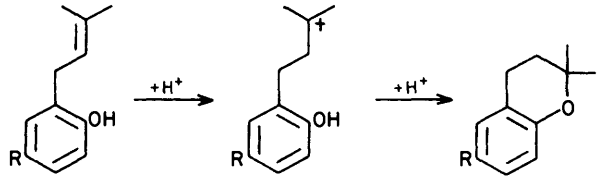
TABLE 2

Overall yield of ester, and *O*- and *C*-alkenylated products at 35 °C

Time (h)	Solvent	Ester (%)	*O*-Alkenylation (%)	*C*-Alkenylation (%)
4	HMPA	47.5 [a]	33	2 [b]
72	THF	15	34	18
72	$PhCH_3$		1	72 [b]

[a] Ester derivative of *O*-alkenylated product is included. [b] This includes cyclized *C*-alkenylated product (3).

compound (3). The use of low temperatures and 2M acetic acid greatly simplifies the work-up procedure and reduces the yield of the cyclization product (3).



(6d) (3)

R = $[CH_2]_3CO_2H$

EXPERIMENTAL

M.p.s were determined using a Reichert hot-stage apparatus. I.r. spectra were recorded on a Perkin-Elmer 137 spectrometer; n.m.r. spectra on a Varian T-60MHZ spectrometer for solutions in [^{2}H]chloroform using tetramethylsilane as internal standard; and mass spectra on a Hitachi Perkin-Elmer R.M.U. 6E spectrometer at 70 eV. T.l.c. was performed on silica gel 60 F_{254} (Merck) and column chromatography on silica gel 70—230 mesh (Merck). Elemental analyses were carried out by P. I. Mowete, Chemistry Department, University of Ibadan, Ibadan, Nigeria. Solvents were purified and dried by standard techniques.

Materials.—1-Bromo-3-methylbut-2-ene (5) was prepared according to literature methods [9] and purified by distillation from calcium hydride, b.p. 50—56 °C/45 mmHg. 4-*p*-Hydroxyphenylbutyric acid was prepared by Friedel-Crafts acylation [10] of anisole with succinic anhydride in the presence of aluminium chloride at 0—5 °C, using a mixture of 1,1,2,2-tetrachloroethane—nitrobenzene (4 : 1) as solvent. After work-up, the resulting 3-*p*-methoxybenzoylpropionic acid, m.p. 146—147 °C (from benzene–hexane) was reduced [11] to 4-*p*-methoxyphenylbutyric acid, m.p. 59—60 °C (lit.,[12] 59—60 °C) and demethylated [13] to 4-*p*-hydroxyphenylbutyric acid by refluxing with 47% hydriodic acid for 13 h. Throughout, ether refers to diethyl ether.

General Alkenylation Procedure.—A mechanically stirred mixture of 4-*p*-hydroxyphenylbutyric acid (4 g, 0.022 mol) and sodium hydride (60%; 2 g, 0.05 mol) in anhydrous solvent (50 ml) was heated at 60 °C for 2.5 h under nitrogen. After the mixture had been cooled to 35 °C, 1-bromo-3-methylbut-2-ene (4.5 g, 0.03 mol) was added to it from a syringe. The mixture was stirred and heated at this temperature for 72 h, after which it was poured into cold water (400 ml) and evaporated to dryness using a rotary evaporator. The semisolid obtained was dissolved in water and extracted with ether. The ether layer was evaporated and chromatographed on silica gel (hexane–ether as eluant) to give 3-methylbut-2-enyl 4-[*p*-(3-methylbut-2-enyloxy)-phenyl]butyrate (6a) $\nu_{max.}$ (liquid) 1 775 (C=O), 1 670 cm^{-1} (C=C); δ($CDCl_3$) 1.75 (6 H, s, *gem*-dimethyl), 1.69 (6 H, s, *gem*-dimethyl) 1.8—2.7 (6 H, m), 4.3 (2 H, d, *J* 7 Hz, CO_2-CH_2), 4.5 (2 H, d, *J* 7 Hz, CH_2OAr), 5.35 (1 H, t, CO_2CCH=), 5.5 (1 H, t, =CH·C·OAr), and 6.7—7.35 (4 H, m, ArH); *m/z* 316(M^+).

The aqueous layer was neutralized with cold 2M acetic acid and extracted with ether. The ether extract was washed (H_2O), dried (Na_2SO_4), evaporated, and chromatographed on silica gel. After a preliminary examination of the eluates by t.l.c., the following major products (in order of elution) were obtained.

(i) 3-Methylbut-2-enyl 4-(*p*-hydroxyphenyl)butyrate (6b) [hexane–ether (9 : 1) as eluant]; $\nu_{max.}$ (liquid) 3 410br (OH), 1 770 (C=O), and 1 670 cm^{-1} (C=C); δ($CDCl_3$) 1.7 (6 H, s, *gem*-dimethyl), 1.9—2.7 (6 H, m), 4.3 (2 H, d, *J* 7 Hz, CO_2-CH_2), 5.35 (1 H, t, CO_2·C·CH=), 6.7—7.3 (4 H, q, ArH), and 8.5br (1 H, exchanged with D_2O, ArOH); *m/z* 248 (M^+);

(ii) 4-[*p*-(3-Methylbut-2-enyloxy)phenyl]butyric acid (6c) [hexane–ether (4 : 1) as eluant], m.p. 45—48 °C [from light petroleum (boiling range 60—80 °C); $\nu_{max.}$ (Nujol) 1 690, 1 000, 835, and 810 cm^{-1}; δ($CDCl_3$) 1.70 (6 H, s, *gem*-dimethyl), 1.9—2.7 (6 H, m), 4.5 (2 H, d, *J* 7 Hz, CH_2OAr), 5.5 (1 H, t, CH=), 6.7—7.3 (4 H, q, ArH), and 9.4br (CO_2H); *m/z* 248 (M^+) 181, 180, 133, 120, and 107.

(iii) 4-[4-Hydroxy-3-(3-methylbut-2-enyl)phenyl]butyric acid (6d) [hexane–ether (3 : 2) as eluant]; $\nu_{max.}$ (liquid) 3 400br, 1 680, 1 670, and 815 cm^{-1}; δ($CDCl_3$) 1.78 (6 H, s, *gem*-dimethyl), 1.8—2.7 (6 H, m), 3.38 (2 H, d, *J* 7 Hz, CH_2Ar), 5.3 (1 H, t, CH=), 6.36br (2 H, exchanged with D_2O, OH and CO_2H), 6.7 (1 H, d, *J* 8 Hz, ArH), and 6.84 (2 H, m ArH) (Found: C, 72.5; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%); *m/z* 248 (M^+).

(iv) 4-(2,2-Dimethylchroman-6-yl)butyric acid (3) [hexane–ether (3 : 2) as eluant], m.p. 69—70 °C [identical with an authentic sample of compound (3) prepared from xanthoxylol[2]]; $\nu_{max.}$ (Nujol) 1 700 (CO_2H), 1 110 cm^{-1}; δ($CDCl_3$) 1.25 (6 H, s, CMe_2), 1.54—2.87 (10 H, m), 6.47—7.20 (3 H, m, ArH), and 9.9br (1 H, exchanged with D_2O); *m/z* 248 (M^+), 221, 203, 188, 163, 150, and 109.

4-[4-*Acetoxy*-3-(3-*methylbut*-2-*enyl*)*phenyl*]*butyric Acid* (2). —Mild acetylation [14] of the hydroxy-compound (6d) gave compound (2); $\nu_{max.}$ (liquid) 1 740 (acetate) and 1 690 cm^{-1} CO_2H; δ($CDCl_3$) 1.72 (6 H, s, *gem*-dimethyl), 1.8—2.8 (9 H, m, including a sharp acetate peak at 2.24), 3.2 (2 H, d, $ArCH_2$), 5.2 (1 H, t, $-CH$=), 7.0 (3 H, m, ArH), and 7.7br (1 H, exchanged with D_2O, CO_2H) (Found: C, 70.8; H, 7.75. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.64%); *m/z* 290 (M^+), 272, 248, 247, 215, 193, 175, and 145.

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