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SYNTHESIS OF NATURAL ESTERS OF SUBSTITUTED CINNAMIC ACIDS

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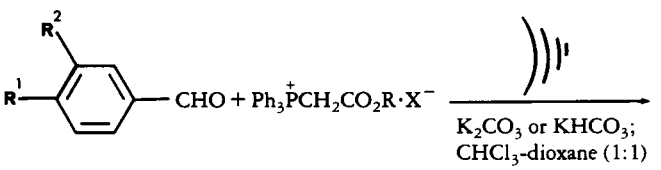
ABSTRACT.—Natural esters of substituted cinnamic acids, found in propolis and poplar buds, have been synthesized by the Wittig reaction from (carbalkoxymethyl)-triphenylphosphonium halides and unprotected phenolic aldehydes in solid-liquid heterogeneous medium under sonochemical conditions. The synthetic products confirm the previously described structures of the natural products and allow testing of their biological activities.

In the course of our investigations on the chemical composition of propolis (bee glue) and poplar buds (*Populus nigra, Populus italica*), we identified some new esters of caffeic and ferulic acids (1). It is known that esters of these acids possess versatile biological activities (2–7). Recently we showed that the antibacterial activity of propolis and poplar bud extracts is due mainly to the caffeates (8). We needed a convenient procedure for the preparation of caffeates and ferulates to confirm the structures of the novel compounds and to produce the larger amounts required for biological tests. Direct esterification, especially of caffeic acid, gives the corresponding esters in poor yields because of the high sensitivity of this acid toward oxidation (9). We attempted to use the Wittig reaction in solid-liquid heterogeneous medium (10,11), but it turned out to be unsuitable for caffeates.[1] Searching for milder reaction conditions, we decided to use ultrasound; until now, only the Wittig-Horner reaction has been carried out under sonochemical conditions (12). In this paper we report the results of the sonochemical reaction between (carbalkoxymethyl)-triphenylphosphonium halides and phenolic aldehydes in heterogeneous solid-liquid medium with K_2CO_3 or $KHCO_3$ as a base in order to obtain some natural hydroxycinnamic acid esters and confirm the structures of the previously isolated ones (1) (Scheme 1).

The presence of K_2CO_3 or $KHCO_3$ in the heterogeneous medium does not require protection of the hydroxyl groups of the aromatic aldehyde (10,13). Ultrasound reduces the reaction time, the sonochemical process taking place at room temperature. In MeOH we did not detect any aldehyde in the reaction mixture (by tlc) after 30 min, compared to 3 h in the case of the thermochemical reaction (60°). In this solvent, however, the sonochemical process, as well as the thermochemical one (11), was accompanied by transesterification. The solvent mixture $CHCl_3$-dioxane (1:1) was found to be the most suitable one. However, in this solvent mixture the sonochemical reaction required 2–8 h (under thermochemical conditions more than 24 h). The use of ultrasound for the conditions ultimately chosen reduces the reaction times. It improves the yield in the case of caffeates, preventing oxidation during prolonged heating. The stereochemical result of the reaction (*E*/*Z* ratio) remains unchanged relative to the thermal reaction.

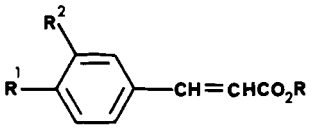


SCHEME 1

[1]V. Bankova, unpublished results.

The results obtained are summarized in Table 1. In most cases, the yields were over 70%, the main product being the desired *E* stereoisomer, as it is known from the literature for the Wittig reaction using (carbalkoxymethyl)-triphenylphosphonium salts (10–13). The product isomeric ratios were determined from ^{1}H-nmr evidence ($J^E_{\alpha,\beta}$ = 16 Hz, H^E_α-6,3 δ; $J^Z_{\alpha,\beta}$ = 12 Hz, H^Z_α-5,9 δ). In the presence of $KHCO_3$ we observed longer reaction times. Nevertheless, due to the lower basicity of the bicarbonate, the yields of caffeates were higher in this case, and $KHCO_3$ is the base of choice when caffeates are the reaction aim.

TABLE 1. Synthesis of Esters of Substituted Cinnamic Acids Under Sonochemical Conditions.



1–9

Compound	R	R^1	R^2	base	reaction time, h	yield %	ratio *E/Z*
1	$CH_2CH_2C(Me)=CH_2$	OH	OH	$KHCO_3$	4.5	80	90:10
2	$CH_2CH_2C(Me)=CH_2$	OH	OMe	$KHCO_3$	8	70	90:10
3	$CH_2C_6H_5$	OH	OH	K_2CO_3	3	52	90:10
				$KHCO_3$	4.5	70	90:10
4	$CH_2CH_2C_6H_5$	OH	OH	$KHCO_3$	5.5	71	90:10
5	$CH_2C_6H_5$	OH	OMe	K_2CO_3	2	84	80:20
				$KHCO_3$	4.5	81	80:20
6	$CH_2CH_2C_6H_5$	OH	OMe	$KHCO_3$	6.5	83	90:10
7	$CH_2C_6H_5$	OH	H	$KHCO_3$	6	60	90:10
8	$CH_2C_6H_5$	OMe	OH	K_2CO_3	2	75	80:20
9	$CH_2CH_2C(Me)=CH_2$	OMe	OH	K_2CO_3	4.5	70	80:20

Compounds **1** and **2** (*E* isomers) were recently found by us as novel natural compounds in poplar bud exudate (*P. nigra, P. italica*) and propolis (1), while Greenaway *et al.* (14) identified considerable amounts of isoferulate **9**, but not the ferulate **2** in *P. nigra* buds, by gc-ms. To the best of our knowledge this is the first synthesis of these compounds. Direct chromatographic comparison (tlc) as well as the comparison of spectral data proved that the natural product 3-methyl-3-butenyl caffeate (1) had the structure **1** (*E* isomer), and 3-methyl-3-butenyl ferulate had the structure **2** (*E* isomer), but not **9**. In our recent work (1) we indicated also the presence of compounds **3**, **4**, **5**, and **6** (*E* isomers) in poplar buds and propolis but failed to isolate them as individual compounds. Compounds **7** and **8** (*E* isomers) were recently identified by gc-ms as novel compounds in poplar buds and propolis of British origin (15).

EXPERIMENTAL

^{1}H-nmr spectra were recorded on a Tesla 60 MHz instrument for solutions in $CDCl_3$ or acetone-d_6 (for caffeates) with TMS as an internal standard. The mass spectra were recorded with a JEOL D-300 apparatus (eims, 70 eV). The uv spectra of EtOH solutions were measured with a Specord uv-vis spectrophotometer. The ir spectra of KBr pellets or $CHCl_3$ solutions were measured with a Specord ir spectrophotometer.

The starting halogenoacetates were synthesized from the corresponding alcohols and chloroacetic anhydride (for 3-methyl-3-butenyl alcohol) or chloroacetic acid (for benzyl and β-phenylethyl alcohol). The phosphonium salts were obtained from Ph_3P and the corresponding esters of chloroacetic acid using known procedures (16). (Carbobenzyloxymethyl)-triphenylphosphonium chloride is a known compound (17); the other two phosphonium salts are new compounds:

(Carboxymethyl)-triphenylphosphonium chloride, 3-methyl-3-butenyl ester: R = $CH_2CH_2C(Me)=CH_2$; mp 116–118°; ir (KBr pellet) cm^{-1} 1724, 1425, 1233, 1130, 1093, 987; ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.60 (3H, s), 2.15 (2H, t, J = 7 Hz), 4.12 (2H, t, J = 7 Hz), 4.53–4.90 (2H, m), 5.63 (2H, d, J_{HCP} = 14 Hz), 6.67–7.27 (15H, m).

(Carboxymethyl)-triphenylphosphonium chloride, β-phenylethyl ester: R = CH_2CH_2Ph; mp 148–151°; ir (KBr pellet) cm^{-1} 1720, 1412, 1217, 1089, 981; ^{1}H nmr (60 MHz, $CDCl_3$) δ 2.64 (2H, t, J = 7 Hz), 4.15 (2H, t, J = 7 Hz), 5.67 (2H, J_{HCP} = 14 Hz), 7.00–8.09 (20H, m).

GENERAL PROCEDURE.—A solution of 2.3 mmol (carbalkoxymethyl)-triphenylphosphonium halide in 4.5 ml $CHCl_3$ and a solution of 1.7 mmol aromatic aldehyde in 4.5 ml 1,4-dioxane were mixed and added to 0.4 g K_2CO_3 or 0.5 g $KHCO_3$ (Scheme 1). The reaction mixture was sonicated in an ultrasound bath Lechpan Type UM 0.5 at 25°. The reaction was monitored by tlc (Alufolien Kieselgel 60 F_{254} Merck, hexane/EtOAc or $CHCl_3$/EtOAc). When K_2CO_3 was used, after filtration the reaction mixture was washed successively with 5% HCl and H_2O, the organic phase was dried over Na_2SO_4, evaporated to dryness, and subjected to cc (silica, $CHCl_3$/EtOAc). When $KHCO_3$ was used, after filtration the reaction mixture was evaporated to dryness and subjected to cc (silica, $CHCl_3$/EtOAc). The stereoisomers (*E*/*Z*) were separated by preparative tlc (silica, hexane/EtOAc). All products were characterized by their uv, ir, ^{1}H-nmr, and mass spectra.

Compound **1**, *E* isomer: oil, uv (EtOH) nm 209, 221, 248, 302, 332; ir ($CHCl_3$) cm^{-1} 3550, 3312, 1695, 1632, 1605, 1558, 1442, 1267, 1212, 1168, 979, 893, 852; ^{1}H nmr (60 MHz, Me_2CO-d_6) δ 1.78 (3H, s), 2.40 (2H, t, J = 7.5 Hz), 4.31 (2H, t, J = 7.5 Hz), 4.78 (2H, m), 6.31 (1H, d, J = 16 Hz), 7.16–7.42 (3H, m), 7.60 (1H, d, J = 16 Hz); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 248 (22), 180 (100), 163 (80), 69 (53), 41 (70). Found ms 248.2780; calcd for $C_{14}H_{16}O_4$, 248.2786.

Compound **1**, *Z* isomer: oil, uv (EtOH) nm 218, 296, 320; ir ($CHCl_3$) cm^{-1} 3510, 3340, 1705, 1630, 1600, 1570, 1450, 1260, 1222, 1167, 985, 893; ^{1}H nmr (60 MHz, Me_2CO-d_6) δ 1.78 (3H, s), 2.41 (2H, t, J = 7,5 Hz), 4.33 (2H, t, J = 7,5 Hz), 5.81 (1H, d, J = 12 Hz), 7.18–7.42 (4H, m); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 248 (10), 180 (20), 163 (20), 69 (42), 41 (71).

Compound **2**, *E* isomer: oil; uv (EtOH) nm 217, 237, 302, 328; ir ($CHCl_3$), cm^{-1} 3540, 1707, 1635, 1607, 1590, 1514, 1448, 1272, 1232, 1160, 978, 890, 846; ^{1}H nmr (60 MHz, $CDCl_3$) δ 1.79 (3H, s), 2.41 (2H, t, J = 7 Hz), 3.91 (3H, s), 4.31 (2H, t, J = 7 Hz), 4.78 (2H, m), 6.32 (1H, d, J = 16 Hz), 6.89–7.09 (3H, m), 7.61 (1H, d, J = 16 Hz); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 262 (27), 194 (86), 177 (53), 69 (15), 41 (28). Found ms 262.3051, calcd for $C_{15}H_{18}O_4$, 262.3055.

Compound **2**, *Z* isomer: oil; uv (EtOH) nm 219, 243, 297, 322; ir ($CHCl_3$) cm^{-1} 3530, 1712, 1630, 1600, 1510, 1452, 1268, 1225, 1158, 977, 893; ^{1}H nmr (60 MHz, $CDCl_3$) δ 1.80 (3H, s), 2.40 (2H, t, J = 7 Hz), 4.30 (2H, t, J = 7 Hz), 4.76 (2H, m), 5.78 (1H, d, J = 12 Hz), 6.90–7.14 (4H, m); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 262 (18), 194 (67), 177 (40), 69 (23), 41 (100).

Compound **9**, *E* isomer: oil; uv (EtOH) nm 221, 245, 298, 330; ir ($CHCl_3$) cm^{-1} 3534, 1710, 1635, 1620, 1582, 1460, 1440, 1253, 1210, 1163, 990, 893, 853; ^{1}H nmr (60 MHz, $CDCl_3$) δ 1.80 (3H, s), 2.39 (2H, t, J = 7 Hz), 3.92 (3H, s), 4.32 (2H, t, J = 7 Hz), 4.79 (2H, m), 6.30 (1H, d, J = 16 Hz), 6.71–7.28 (3H, m), 7.62 (1H, d, J = 16 Hz); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 262 (100), 194 (76), 177 (90), 69 (17), 41 (21). Found ms 262.3053, calcd for $C_{15}H_{18}O_4$, 262.3055.

Compound **9**, *Z* isomer: oil; uv (EtOH) nm 218, 237, 293, 320; ir ($CHCl_3$) cm^{-1} 3540, 1698, 1632, 1620, 1580, 1460, 1445, 1272, 1220, 1167, 989, 556; ^{1}H nmr (60 MHz, $CDCl_3$) δ 1.79 (3H, s), 2.40 (2H, t, J = 7 Hz), 3.90 (3H, s), 4.34 (2H, t, J = 7 Hz), 4.78 (2H, m), 5.83 (1H, d, J = 12 Hz), 6.73–7.30 (4H, m); eims (70 eV) *m/z* (rel. int. %) $[M]^+$ 262 (28), 194 (100), 177 (75), 69 (38), 41 (76).

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