Preparation of Cinnamate Esters from Styrenes

Mohammad Aslam,* Wayne F. Stansbury, Robert J. Reiter, and Donald R. Larkin†

Hoechst Celanese Corporation, Corporate Research and Technology, Corpus Christi Technical Center, 1901 Clarkwood Road, Corpus Christi, Texas 78409

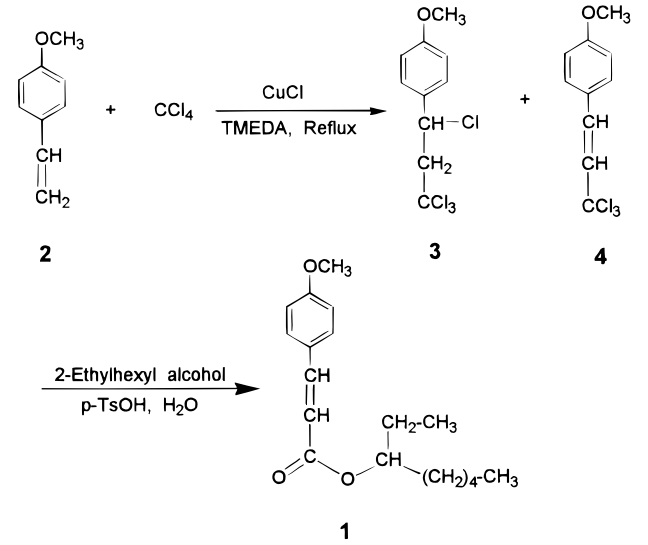
Received October 30, 1996

Introduction

Cinnamic acids and their derivatives are important in the flavors, perfumes, cosmetics, graphics, and pharmaceutical industries.[1,2] 2-Ethylhexyl 4-methoxycinnamate **(1)** is a UV absorbing sunscreen agent and is a common ingredient in most of the new sunscreen lotions and many other cosmetic formulations.[1] The Perkin reaction is one of the most common synthetic procedures to produce cinnamic acids. The reaction utilizes the corresponding aldehyde, acetic anhydride, and anhydrous sodium or potassium acetate.[3] Esterification of cinnamic acids with an alcohol affords the corresponding cinnamate esters. In our laboratories, Perkin condensation of anisaldehyde with acetic anhydride and potassium acetate afforded 4-methoxycinnamic acid **(4)** in minute to low yield. Similar findings have been reported elsewhere.[4] More recently, **1** has been synthesized by the homogeneous Pd-catalyzed coupling of 2-ethylhexyl acrylate (2-EHA) with *p*-chloroanisole,[5a] *p*-bromoanisole,[5b] *p*-iodoanisole[5c] or by the heterogeneous Pd/C-catalyzed coupling of *p*-haloanisoles.[6] A Pd-catalyzed coupling of 4-methoxybenzenediazonium tetrafluoroborate with 2-ethylhexyl acrylate using Li_2PdCl_4 and CuCl has also been reported.[7]

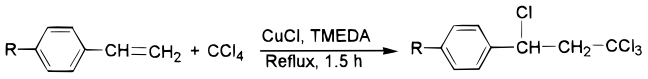
We have been evaluating new synthetic routes to **1** starting from substituted styrenes. A new, one-pot, two-step synthetic route to **1** has been developed starting with 4-methoxystyrene (**2**). In the first step, copper/diamine-catalyzed addition of CCl_4 to **2** gave a mixture of 1,1,1,3-tetrachloro-3-(4′-methoxyphenyl)propane **(3)** and 1,1,1,-trichloro-3-(4′-methoxyphenyl)-2-propene **(4)**. In the second step, reaction of a mixture **3** and **4** with 2-ethylhexyl alcohol and water afforded **1** (Scheme 1). These two steps can be combined, and the synthesis can be done in one pot without the isolation of intermediate coupling products. The addition of carbon tetrachloride to olefins has been investigated extensively.[8]

Scheme 1



2 **3** **4** **1**

Scheme 2



6: R = OAc
8: R = Cl
7: R = OAc
8: R = Cl

We have also evaluated the hydrolysis of a mixture of **3** and **4** to afford 4-methoxycinnamic acid (**5**). Since we wanted to minimize the number of steps and develop a one-step procedure for the synthesis of **1** from **2**, little attention was given to the synthesis of **5**.

Results and Discussion

2-Ethylhexyl 4-Methoxycinnamate. Copper chloride-catalyzed free radical addition of CCl_4 to **2** was investigated using copper(I) and copper(II) chlorides in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), and a few other amine ligands (see Table 1). The CuCl-catalyzed addition of CCl_4 in the presence of TMEDA proceeded with complete conversion in 2 h and afforded a mixture of **3** and **4** in ∼5:1 ratio. The overall yield in this reaction was calculated to be ∼86% (based on GC wt %) (Table 1, entry 1). The coupling reaction using TMPDA proceeded with 99% conversion and afforded a mixture of **3** and **4** in ∼95% yield (Table 1, entry 2). TMPDA reduced the formation of high molecular weight oligomers. Under similar conditions, *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine (TMBDA) and 2,2′-bipyridyl (2,2-Bipy) were not very effective as catalytic ligands for the coupling reaction, giving very low conversion (Table 1, entry 3 and 4). Use of pyridine as an amine ligand afforded a mixture of **3** and **4** in only 26% yield (Table 1, entry 5). We did not observe any reaction in the absence of an amine. We have also demonstrated that CuCl can be replaced with $CuCl_2$ in this reaction. $CuCl_2$ catalyzes this reaction as well as CuCl (Table 1, entry 6).

* To whom correspondence should be addressed. Tel.: (512) 242-4537, Fax: (512) 242-4626; E-Mail: MA@CORHCC1.HCC.COM.
†Deceased.

(1) Ringk, W. F. *Kirk Othmer Encyclopedia of Chemical Technology*, 3rd ed.; John Wiley and Sons: New York, 1981; Vol. 6; pp 143−149.
(2) Hajek, M..; Silhav, P. U. S. Patent, 4,806,681, 1989.
(3) Johnson, J. R. *The Perkin Reaction and Related Reactions* in *Organic Reactions*; Adams, R., Ed.; John Wiley and Sons, Inc.: New York, 1942, Vol. 1, p 218.
(4) Koepp, E.; Vogtle, F. *Synthesis* **1987**, 177.
(5) (a) Poetsch, E.; Meyer, V.; Heywang, U.; Christ, R.; Seubert, J. German Patent 4405830, 1995; *Chem. Abstr.* **1995**, *123*, 227816. (b) Kaufmann, D.; Hesse, C.; Himmler, T. European Patent 564919, 1993; *Chem. Abstr.* **1994**, *120*, 134050. (c) Caskey, D. C. U.S. Patent 4970332, 1990; *Chem. Abstr.* **1990**, *114*, 142883m.
(6) Gygax, P. World Patent 9405621, 1994; *Chem. Abstr.* **1994**, *120*, 322946.
(7) Elango, V. U. S. Patent 5300675, 1994; *Chem. Abstr.* **1994**, *120*, 322941.
(8) (a) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *J. Am. Chem. Soc.* **1947**, *69*, 1100. (b) Asscher, M.; Vofsi, D. *J. Chem. Soc.* **1963**, 1887. (c) Hajek, M.; Silhavy, P.; Malek, J. *Collect. Czech. Chem. Commun.* **1980**, *45*, 3502. (d) *Ibid.* 3488. (e) Adamek, F.; Hajek, M.; Janousek, Z. *Collect. Czech. Chem. Commun.* **1992**, *57*, 1291.

S0022-3263(96)02029-4 CCC: $14.00

Table 1. Copper−Diamine-Catalyzed Reaction of 4-Methoxystyrene (2) with Carbon Tetrachloride

entry	**2** (mol)	CCl_4 (mol)	Cu(I) Cl mol	diamine[a] (mol)	time (h)	conversion (%)	ratio (%)[b] **3**	ratio (%)[b] **4**	total (**3** + **4**) yield (%)
1	0.13	0.49	0.0045	TMEDA (0.014)	1.5	99.6	73	13	86
2	0.065	0.25	0.0045	TMPDA (0.014)	2.0	99.5	82	13	95
3	0.13	0.49	0.0045	TMBDA (0.014)	3.0	23.0	9	3	12
4	0.065	0.25	0.0023	2,2-Bipy(0.014)	5.5	11.0	1	1	2
5	0.05	0.16	0.008	pyridine(0.016)	6.0	54.0	19	7	26
6	0.065	0.25	0.0045[c]	TMPDA(0.014)	2.0	100.0	70	24	94

[a] TMEDA = *N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine; TMPDA = *N*,*N*,*N*′,*N*′-Tetramethyl-1,3-propanediamine; TMBDA = *N*,*N*,*N*′,*N*′-Tetramethyl-1,4-butanediamine, 2,2-bipypridyl. [b] Yields were calculated by GC using response factor analysis. [c] $CuCl_2$ was used in this reaction.

Reaction of a mixture of **3** and **4** with 2 equiv of 2-ethylhexyl alcohol (EHA) in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) afforded **1** in 60% yield. Purification via distillation afforded pure **1** in 57% yield. In another experiment, the hydrolysis and esterification of a mixture of **3** and **4** was repeated in the absence of *p*-TsOH. In this experiment, **1** was isolated in 61% yield. In a one-pot reaction avoiding isolation of intermediate coupling products **(3** and **4), 1** was isolated in 58% yield.

Attempted purification of a mixture containing **3** and **4,** via vacuum distillation at 130−200 °C, led to complete conversion of **3** to **4**, compound **4** being the only volatile product collected. The reaction of **4** with EHA in the presence of 1 equiv of water and catalytic amount of *p*-TsOH afforded **1** in 80% yield.

Hydrolysis of a mixture of **3** and **4** in acetic acid, in the presence of *p*-TsOH, proceeded with complete conversion and afforded 4-methoxycinnamic acid in only 15% yield.

1,1,1,3-Tetrachloro-3-(4′-acetoxyphenyl)propane (7). We have also evaluated copper/diamine-catalyzed addition of CCl_4 to 4-acetoxystyrene **(6)** in the presence of catalytic amount of TMEDA. The corresponding addition product, 1,1,1,3-tetrachloro-3-(4′-acetoxyphenyl)-propane **(7)**, was isolated in 93% yield. Surprisingly, formation of HCl elimination product, i.e., 1,1,1-trichloro-3-(4′-acetoxyphenyl)-2-propene was not observed in this reaction. The reaction of **7** with ethyl alcohol led to the formation of ethyl 4-hydroxycinnamate **(10)** along with some decomposition products. The acetate group of compound **7** underwent complete hydrolysis during this transformation.

1,1,1,3-Tetrachloro-3-(4′-chlorophenyl)propane (9). Copper−diamine-catalyzed reaction of 4-chlorostyrene **(8)** with CCl_4 as described above proceeded at a much slower rate as compared to **2** and **6**. The reaction went to completion in ∼7 h. Compound **9** failed to react with ethanol in the presence of a catalytic amount of *p*-TsOH, and after several hours at reflux, only starting material was recovered.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a 200 MHz and a 400 MHz spectrometer. The chemical shifts are reported on δ scale. The coupling constants are reported in hertz. IR spectra were recorded on a FT-IR spectrometer. GC analyses were done on gas chromatograph equipped with a 30 meter DB-1, 1.0 μm column with 0.32 i.d. GC/MS spectra were obtained on a benchtop instrument equipped with a mass selective detector. Mass spectra were obtained on a EI−CI spectrometer system. 4-Methoxystyrene, 4-acetoxystyrene, and 4-chlorostyrene were either purchased from Aldrich Chemical Co. or synthesized from the corresponding acetophenononones via hydrogenation and dehydration. 4-Methoxycinnamic acid was purchased from Aldrich Chemical Co.

2-Ethylhexyl 4-Methoxycinnamate (1) from 2. A solution of **2** (17.4 g, 0.13 mol), CCl_4 (75 g, 0.49 mol), Cu(I)Cl (0.9 g, 0.009 mol), and TMPDA (3.5 g, 0.027 mol) was stirred at reflux for 3.5 h. The reaction mixture was then filtered, washed with CCl_4, and concentrated *in vacuo* (∼5 mm Hg, 25 °C). The resulting amine-free mixture of **3** and **4** was then added to 2-ethyl-1-hexanol (33.8 g, 0.26 mol), water (2.3 g, 0.13 mol), and *p*-toluenesulfonic acid (0.26 g, 0.0013 mol) and stirred at 120 °C for 1 h. GC response factor analysis of a sample of the reaction mixture indicated an overall yield of 64%. Vacuum distillation afforded pure **1** (38.0 g, 62% yield); bp 160 °C at 0.05 mm of Hg; lit.[9] bp 185−195 °C at 1.0 mmHg. ^1H NMR δ: 7.64 (d, 1 H, J = 16 Hz), 7.19 (AA'BB' quartet, 4 H, aromatic), 6.32 (d, 1H, J = 16 Hz), 4.11 (d, 2 H), 3.83 (s, 3 H), 1.41−0.87 (m, 15 H); ^{13}C NMR δ: 167.6, 161.5, 144.2, 129.7, 127.4, 116.0, 114.4, 66.8, 55.3, 38.9, 30.4, 28.9, 23.8, 22.8, 13.8, 10.9 ppm. The product was identical to an authentic sample of **1** made via esterification of commercial 4-methoxycinnamic acid with 2-ethylhexanol.

1,1,1,-Trichloro-3-(4′-methoxyphenyl)-2-propene (4). A reaction mixture containing **3** (69.8 wt %) and **4** (23.7 wt %) was placed in a flask equipped with a simple distillation setup. The mixture was heated to 200 °C, and **4** was distilled, bp 130 °C at 0.5 mmHg. GC analysis of the distillate showed it to be 83 wt % pure. ^1H NMR δ: 7.15 (AA'BB' quartet, 4 H, aromatic), 6.37 (d, 1H, J = 10 Hz), 5.74 (d,1 H, J = 10 Hz), 3.82 (s, 3H); ^{13}C NMR δ: 160.2, 130.8, 129.7, 128.4, 123.9, 114.5, 58.3, 55.3 ppm; IR ν_{max}: 2833 (m), 1607 (vs), 1509 (vs), 1460 (s), 1252 (vs), 1030 (vs), 826 (vs) and 625 (vs) cm^{-1}. MS: (*m*/*z*, relative intensity) 250 (M^+, 12), 215 (100), 213 (42), 179 (55), 177 (22), 145 (20), 101 (15).

Synthesis of 1 from 4. A distilled sample of **4** (10 g, 0.04 mol), 2-ethyl-1-hexanol (10.4 g, 0.08 mol), water (0.7 g, 0.04 mol), and *p*-TsOH (0.076 g) were stirred at 120 °C for 50 min. GC response factor analysis of a sample of the reaction mixture indicated **1** was formed in 80% yield.

4-Methoxycinnamic Acid (5). A mixture of **3** and **4** (15:85) (5.0 g, ∼0.02 mol), acetic acid (25 mL), *p*-TsOH (0.035 g), and water (0.4 mL) was stirred at reflux for 1.5 h. The solvent was evaporated, the product dissolved in CH_2Cl_2 (150 mL), and **5** extracted with 10% KOH (2 × 100 mL). The aqueous layer was combined and acidified with dilute HCl. The precipitated solid was collected by filtration, washed with water, and dried to afford **5** as a white solid (0.52 g, 15% yield). Mp 169−173 °C, mixed melting point with an authentic sample (Aldrich) 173−176 °C.

1,1,1,3-Tetrachloro-3-(4′-acetoxyphenyl)propane (7). A solution of **6** (8.1 g, 0.05 mol), CCl_4 (25 g, 0.162 mol), CuCl (0.2 g, 0.002 mol), and TMEDA (0.46 g, 0.004 mol) was stirred at reflux for 1.5 h. The reaction mixture was extracted with CCl_4 and methylene chloride, filtered, and concentrated *in vacuo* to afford a green solid. GC analysis of this solid indicated that **7** had been formed with 99% selectivity, and the product was isolated in 93% yield. Recrystallization with CCl_4 afforded white crystals: mp 71 °C; ^1H NMR δ: 7.26 (q, 4 H, aromatic), 5.30 (t, 1 H), 3.55 (m, 2H), 2.30 (s, 3 H); ^{13}C NMR δ: 169.2, 150.9, 137.9, 128.5, 122.1, 96.1, 62.7, 57.5, 21.0 ppm; MS: (chemical ionization

(9) (a) Schudel, P.; Schwarzenbach, R.; Gozenbach, H. U.S. Patent, 4713473, 1987. (b) *The Merck Index*, 12th ed. Merck & Co., Inc.: Rahway, NJ, 1996; p 1163.

with CH_4) (*m*/*z*, relative intensity) 317 (MH^+, 18), 281 (28), 239 (55), 183 (100), 141 (69).

1,1,1,3-Tetrachloro-3-(4′-chlorophenyl)propane (9). A solution of **8** (6.95 g, 0.05 mol), CCl_4 (23 g, 0.15 mol), $CuCl_2$ (0.25 g, 0.0018 mol), and TMEDA (0.46 g, 0.0045 mol) was stirred at reflux for 6.5 h. The reaction mixture was cooled, extracted with CH_2Cl_2 (140 mL), filtered, and concentrated *in vacuo* to afford a green solid. The product was dissolved in CH_2Cl_2 and passed over a short silica gel column. The solvent was removed on the rotary evaporator to afford the product as a light yellow solid 9.02 g, 61.8% yield. Recrystallization of a small sample afforded a white crystalline solid, mp 38 °C. ^{1}H NMR δ: 7.3 (s, 4H, aromatic), 5.27 (t, 1H), 3.6 (m, 2H); ^{13}C NMR δ: 138.8, 134.8, 129.2, 128.9, 95.9, 62.6, 57.4 ppm. IR ν_{max}: 1480 (vs), 1100 (vs), 970 (vs), 740 (vs) and 700 (vs) cm^{-1}; MS: (*m*/*z*, relative intensity) 290 (4), 256 (1), 160 (100), 158 (65).

Reaction of (7) with 2-Ethyl Alcohol. A solution of **7** (32.2 g, 0.102 mol), ethyl alcohol (46 g, 2.17 mol), and *p*-TsOH monohydrate (0.2 g) was heated at reflux for 1.5 h. Unreacted ethyl alcohol was removed on the rotary evaporator to afford a thick brown oil. The product was dissolved in CH_2Cl_2 (150 mL) and washed with water (2 × 100 mL). The organic layer was separated, dried, and concentrated to afford a thick brown oil. The oil was dissolved in CH_2Cl_2 (25 mL) and passed over a short silica gel column. The column was eluted with CH_2Cl_2 (500 mL). Concentration of the organic layer afforded ethyl 4-hydroxycinnamate **(10)** as a thick yellow oil (7.83 g, 40% yield). The oil crystallized slowly (~95% pure by GC). A small sample was recrystallized with toluene/hexanes to afford white crystals, mp 81−82 °C; lit[10] mp 83 °C. ^{1}H NMR ($CDCl_3$) δ: 7.65 (d, 1 H, J = 16 Hz), 7.32 (s, 1 H, phenolic), 7.15 (AA'BB' quartet, 4 H, aromatic), 6.30 (d, 1H, J = 16 Hz), 4.28 (q, 2 H), 1.35 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ: 168.4, 158.5, 145.2, 130.0, 126.6, 116.0, 114.9, 60.8, 14.2 ppm. The NMR spectra of the product were identical to the NMR spectra of **10** reported in the literature.[11]

Acknowledgment. We thank Dr. B. Segmuller for valuable help with the NMR analysis and Dr. S. Huang for the mass spectral analysis.

JO962029K

(10) Freudenberg, K.; Gehrke, G. *Chem Ber*. **1951**, *84*, 443.
(11) Cernerud, M.; Reina, J. A.; Tegenfeldt, J.; Moberg, C. *Tetrahedron: Asym*. **1996**, *7*, 2863.