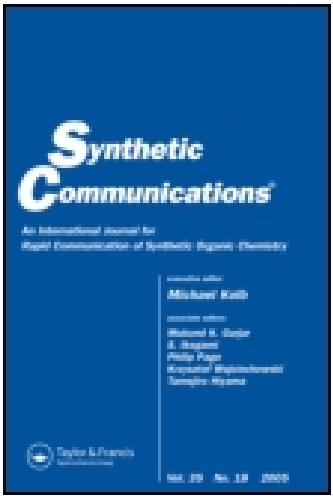

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of E- and Z-o-Methoxy-Substituted 2,3-Diphenyl Propenoic Acids and Its Methyl Esters

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Published online: 04 Dec 2007.

To cite this article: Károly Felföldi, Mária Sutyinszky, Nóra Nagy & István Pálinkó (2000) Synthesis of E- and Z-o-Methoxy-Substituted 2,3-Diphenyl Propenoic Acids and Its Methyl Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:9, 1543-1553, DOI: 10.1080/00397910008087187

To link to this article: http://dx.doi.org/10.1080/00397910008087187

SYNTHETIC COMMUNICATIONS, 30(9), 1543–1553 (2000)

SYNTHESIS OF *E*- AND *Z*-*o*-METHOXY-SUBSTITUTED 2,3-DIPHENYL PROPENOIC ACIDS AND ITS METHYL ESTERS

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Abstract: A series of stereoisomeric o-methoxy-substituted 2,3-diphenyl propenoic acids and their methyl esters have been synthesized. The *E* isomers were prepared by a modified Perkin condensation (substituted benzaldehyde, phenylacetic acid, Et_3N/acetic anhydride). The difficult to access *Z* isomers were obtained conveniently in good yields when the appropriate coumarin derivatives were allowed to react with KOH and CH_3I in DMSO.

Cinnamic acids and their derivatives, beside being compounds of biological importance[1] (they are the members of the shikimic acid metabolic pathway), offer the possibility of investigating hydrogen bonding interactions as well[2]. The acids, among them the α-phenylcinnamic acids, are capable of forming hydrogen bonded network in solution through dimerization and to a smaller extent trimerization (C=O...HO)[3,4]. This short-range order can be extended substantially in the solid-sate, where the dimers are kept together by (aromatic)C-H...O interactions[5].

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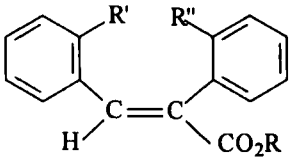
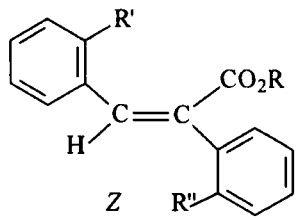
In continuation of studying the agglomeration behaviour of this family of molecules, we decided to introduce, on one hand, substituent(s) capable of further hydrogen bonds onto the phenyl ring(s) of 2,3-diphenyl propenoic acid, and, on the other hand, to eliminate the possibility of dimer and/or trimer formation, the methyl ester of the each acid was also prepared. For the molecules described in this work, see Scheme 1.



E



Z

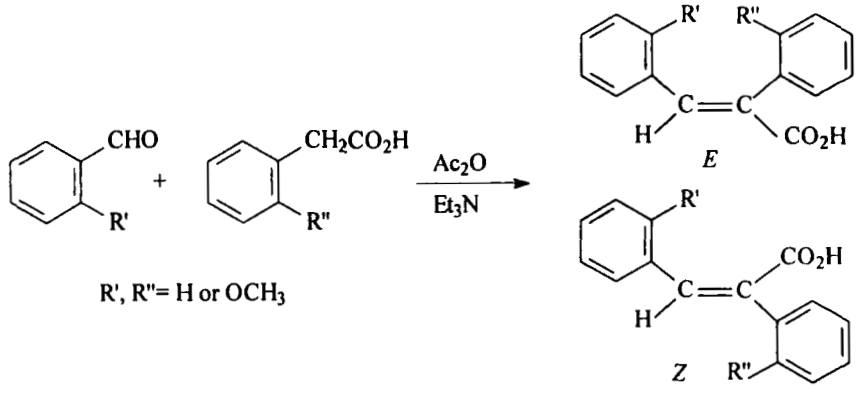
1a: R, R"= H, R'= OCH_3
1e: R= CH_3, R'= OCH_3, R"= H
3a: R, R'= H, R"= OCH_3
3e: R= CH_3, R'= H, R"= OCH_3
5a: R= H, R', R"= OCH_3
5e: R= CH_3, R', R"= OCH_3

2a: R, R"= H, R'= OCH_3
2e: R= CH_3, R'= OCH_3, R"= H
4a: R, R'= H, R"= OCH_3
4e: R= CH_3, R'=H, R"= OCH_3
6a: R= H, R', R"= OCH_3
6e: R= CH_3, R', R"= OCH_3

Scheme 1

Many of these model compounds have not been described in the chemical literature, yet. The known molecules are the stereoisomer pairs **1a**[6] and **2a**[7] and the ester **1e**[8]. Although the *E* isomers can be prepared in good yield without much difficulty, the *Z* isomers are not easily accessible[2]. Here, we also present a method, which provides the *Z* acids and esters in good yield.

The (modified) Perkin condensation of benzaldehyde and phenylacetic acid gives a mixture of 2,3-diphenylpropenoic acids (α-phenylcinnamic acids)[9]. The *E* isomer is overwhelming in the reaction, the quantity of the *Z* isomer rarely reaches 20 weight%. The actual ratio can be influenced by the solvent, the duration and temperature of the reaction[10]. If the pK_a values of the stereisomeric acids are substantially different the isomers can be separated easily by fractionated acidification[11]. This method may not work effectively with our compounds because their pK_a values are unknown. Moreover, even though condensation under Perkin conditions (Scheme 2) provided the *E* isomers in large quantities, yields for the *Z* isomer were poor (generally smaller than 4%).

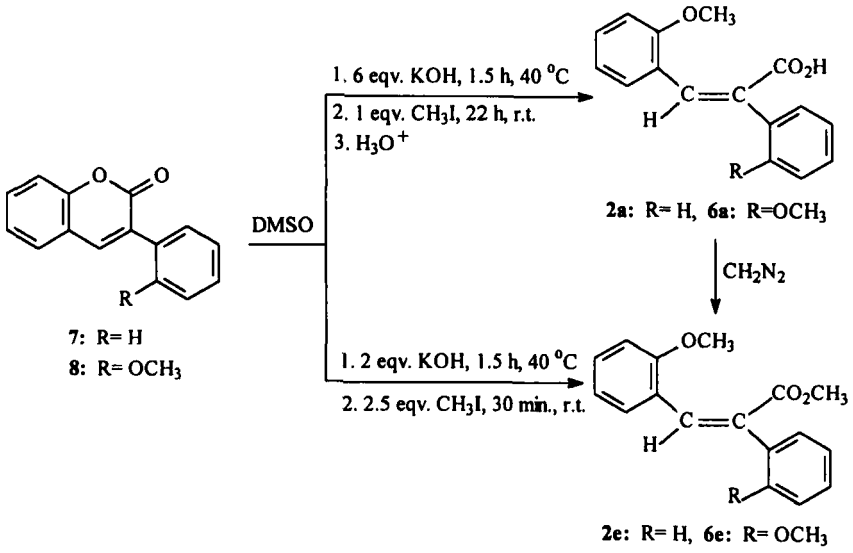


Scheme 2

For our agglomeration experiments, however, we needed larger quantities of the *Z* isomers molecules as well. Thus, a more efficient method was searched for.

First, a reaction, described for the preparation of *Z*-3-(o-methoxyphenyl)-2-phenyl propenoic acid from 3-phenylcoumarin with dimehyl sulfate in aqueous-basic medium, was tried[8]. Although 30 % yield was reported, in our hands, even after repeating it several times, it gave no more than 8% and even if the *Z* configuration was fixed in the reactant, some of the *E* isomer was always formed.

Another method[12], the reactions of various coumarins in DMSO with KOH and CH_3I have been reported to provide with *Z*-3-(o-methoxyphenyl) propenoic acids in good yield. An advantage of the reaction that applying an appropriate



Scheme 3

quantity of CH_3I results in the formation of methyl esters. After optimizing the conditions we were succesful in preparing the *Z* isomers of **2a** acid and **2e** ester and

6a acid **6e** ester in good yield from 3-phenylcoumarin (**7**) and 3-methoxycoumarin (**8**), respectively (Scheme 3).

The **2e** and **6e** methyl esters were synthesized with traditional CH_2N_2 method too from the **2a** and **6a** acids in 100% yield too.

The *E* isomers of **1a**, **3a** and **5a** were obtained from the mixture of the Perkin condensation by acidifying it with acetic acid (Scheme 2). Compound **4a** fell out on further acidification of the mother liquor of **3a**.

The **1e**, **3e**, **4e** and **5e** esters were prepared by Fischer esterification of the appropriate acids with long reflux and moderate yields.

Experimental

Compounds used throughout were Fluka products. Benzaldehyde, triethylamine and acetic anhydride were distilled before use.

The 3-phenylcoumarin (**7**) and the 3-(o-methoxyphenyl)coumarin (**8**) were prepared by literature methods[6,13].

Characterization data on the compounds prepared are summarized in Table 1. The purity of the compounds were checked by TLC (Fluka 60778 silica gel TLC cards, 5% or 10% ethanol in benzene eluents) and the GC/MS method (HP [Hewlett Packard] Model 5890 gas chromatograph equipped with a mass selective detector, HP 5997 Chemstation for data evaluation, 12-m long HP-1 capillary column, He carrier). The esters could be introduced directly, while the acids were

Table 1. Characterization data of the compounds

Comp.	Conf.	Method	Yield[a]/%	Mp[b]/°C	R_f	m/z[g]	IR/cm^{-1}	^{1}H NMR/ppm	^{13}C NMR/ppm[g]
1a	*E*	B	49	187-189[b]	0.44[c]	$M^{-\bullet}$=326(30), 311(14), 295(100) 194(20), 179(3), 165(23), 91(37), 73(64), 45(20)	3520 (OH mon.) 3300-2500 (OH ass.), 1746 (C=O mon.), 1690 (C=O ass.), 1625 (C=C)	3.9 (s, 3H), 6.6-7.3 (m, 9H), 8.3 (s, H), 12.6 (s, H [DMSO]),	55.5, 119.9, 123.5, 127.7, 128.4, 130.0, 130.6, 130.7, 131.3, 135.5, 137.4, 158.4, 173.1
2a	*Z*	C	69	130-132[c]	0.38[e]	$M^{-\bullet}$=326(30), 311(15), 295(100) 194(19), 179(3), 165(21), 91(36), 73(65), 45(20)	3522 (OH mon.) 3300-2500 (OH ass.), 1744 (C=O mon.), 1690 (C=O ass.), 1625 (C=C)	3.8 (s, 3H), 6.9-7.5 (m, 9H), 7.3 (s, H), 13.2 (s, H [DMSO])	55.2, 110.6, 120.5, 124.8, 127.3, 128.2, 128.5, 129.4, 130.1, 131.0, 134.0, 137.4, 157.2, 174.2
3a	*E*	A	38	147-148[d]	0.37[e]	$M^{-\bullet}$=326(63), 311(35), 295(8) 194(24), 179(28), 165(25), 91(51), 73(100), 45(24)	3520 (OH mon.) 3300-2500 (OH ass.), 1750 (C=O mon.), 1688 (C=O ass.), 1625 (C=C)	3.8 (s, 3H), 6.9-7.4 (m, 9H), 7.9 (s, H), 12.4 (s, H [DMSO])	55.7, 111.3, 121.0, 124.7, 128.2, 128.8, 129.3, 129.8, 130.1, 130.4, 130.8, 134.2, 142.3, 157.5, 172.7
4a	*Z*	A	3	179-180[d]	0.31[e]	$M^{-\bullet}$=326 (52), 311(31), 295(7) 194(22), 179(24), 165(24), 91(50), 73(100), 45(24)	3520 (OH mon.) 3300-2500 (OH ass.), 1750 (C=O mon.), 1690 (C=O ass.), 1623 (C=C)	3.8 (s, 3H), 7.3 (s, H), 6.9-7.4 (m, 9H), 13.1 (s, H [DMSO])	56.5, 77.7, 112.0, 121.9, 128.3, 128.8, 129.0, 129.5, 129.8, 130.1, 130.4, 131.6, 132.5, 138.0, 157.8, 174.1
5a	*E*	B	50	212-213[b]	0.31[e]	$M^{-\bullet}$=356(36), 341(14), 325(100) 209(13), 121(25), 91(25), 73(64), 45(16)	3520 (OH mon.) 3300-2500 (OH ass.), 1746 (C=O mon.), 1690 (C=O ass.), 1623 (C=C)	3.8 (s, 3H), 3.9 (s, 3H), 6.6-7.3 (m, 8H), 8.2 (s, H)	55.9, 56.9, 77.4, 78.0, 111.3, 111.9, 120.7, 121.6, 124.7, 126.0, 129.4, 130.1, 130.3, 131.8, 137.9, 156.0, 172.2
6a	*Z*	C	62	184-185[b]	0.30[e]	($M^{-\bullet}$)=356(30), 341(13), 325(100) 209(13), 121(26), 91(23), 73(65), 45(15)	3524 (OH mon.) 3300-2500 (OH ass.), 1742 (C=O mon.), 1690 (C=O ass.), 1627 (C=C)	3.7 (s, 3H), 3.8 (s, 3H), 7.1 (s, H), 6.9-7.4 (m, 8H)	55.4, 56.5, 77.4, 78.0, 111.3, 111.9, 121.0, 121.8, 125.7, 129.3, 130.6, 130.7, 131.2, 132.7, 134.0, 157.8, 173.2

1e	*E*	E	63	100.5-101.5[d]	0.81[f]	M^+=268(100), 237(92), 194(43), 165(57), 151(51), 121(7) 115(17), 91(67), 45(33), 15(41)	1717 (C=O), 1621 (C=C)	3.7 (s, 3H), 3.8 (s, 3H) 6.6-7.3 (m, 9H), 8.1 (s, H)	52.8, 56.2, 77.7, 111.0, 120.6, 127.9, 128.2, 129.0, 130.5, 130.9, 131.3, 133.1, 136.3, 136.8, 159.0, 169.1
2e	*Z*	D	78	71-72[a]	0.83[f]	M^+=268(100), 237(79), 194(41), 165(51), 151(49), 121(6), 115(15), 91(62), 45(31), 15(30)	1732 (C=O), 1620 (C=C, vw)	3.7 (s, 3H), 3.8 (s, 3H), 7.3 (s, H), 6.9-7.5 (m, 9H),	51.5, 56.1, 77.7, 111.3, 121.1, 125.9, 127.5, 128.7, 129.0, 129.2, 129.4, 130.4, 135.5, 138.2, 158.0, 170.7
3e	*E*	E	62	45-46[c]	0.77[f]	M^+=268(94), 237(9), 194(38), 165(45), 151(5), 121(100), 115(11), 91(76), 45(4), 15(30)	1719 (C=O), 1630 (C=C)	3.7 (s, 3H), 3.8 (s, 3H), 6.9-7.3 (m, 9H), 7.8 (s, H)	52.9, 56.4, 77.7, 112.0, 121.7, 126.1, 128.8, 129.5, 130.2, 130.4, 130.9, 131.6, 135.8, 141.1, 158.3, 169.2
4e	*Z*	E	52	74.5-76[d]	0.73[f]	M^+=268(99), 237(10), 194(40), 165(43), 151(5), 121(100), 115(10), 91(77), 45(4), 15(25)	1728 (C=O), 1625 (C=C, vw)	3.7 (s, 3H), 3.8 (s, 3H), 7.3 (s, H), 6.9-7.4 (m, 9H)	52.4, 56.5, 77.7, 111.9, 121.8, 128.9, 129.0, 129.3, 130.6, 130.8, 133.3, 136.1, 136.8, 157.8, 170.4
5e	*E*	E	48	118-119[e]	0.72[f]	M^+=298(100), 267(55), 181(17), 165(19), 152(28), 151(64), 131(20), 121(49), 91(51), 45(29), 15(47)	1718 (C=O), 1627 (C=C)	3.7 (s, 3H), 3.8 (s, 3H), 3.9 (s, 3 H), 6.6-7.3 (m, 8H), 8.1 (s, H)	52.7, 56.2, 56.3, 77.7, 77.8, 111.2, 111.9, 120.6, 121.5, 125.0, 126.5, 130.0, 130.5, 130.7, 131.7, 136.2, 158.8, 169.3
6e	*Z*	D	78	130-131[b]	0.65[f]	M^+=298(100), 267(54), 181(16), 165(16), 152(25), 151(60), 131(19), 121(45), 91(45), 45(26), 15(36)	1726 (C=O), 1624 (C=C, vw)	3.6 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 7.2 (s, H), 6.9-7.4 (m, 8H)	52.7, 55.9, 56.1, 77.7, 77.8, 111.1, 111.8, 120.8, 121.7, 126.1, 129.7, 130.3, 130.9, 132.1, 132.3, 133.2, 157.7, 170.5

a - isolated; crystallized from b - ethanol, c - benzene, d - methanol; e - 10%ethanol-benzene; f - 5%ethanol-benzene; g - the acids as trimethylsilylesters, the methyl esters as they are

transformed to trimethylsilyl esters and then measured[14]. Further characterization was made by IR (BIORAD FTS-65A/896 spectrometer equipped with a liquid nitrogen cooled MCT detector, 10^{-2} mol/dm^3 in CCl_4) and NMR (Bruker Avance 500 spectrometer, ^{1}H: 500 MHz, ^{13}C: 125.8 MHz, in $CDCl_3$) spectroscopies. All the compounds gave excellent microanalysis results.

Methods of preparation (based on specific compounds)

Method A (*E*- and *Z*-2-(o-methoxyphenyl)-3-phenyl propenoic acid (**3a**, **4a**))

A mixture of 100 g (0.6 mol) of o-methoxyphenyl acetic acid, 100 cm^3 (1 mol) of benzaldehyde, 65 cm^3 of triethylamine and 65 cm^3 of acetic anhydride were refluxed for 3 hours. The mixture was cooled and 300 cm^3 of benzene was added. Then the solution was extracted with 6x100 cm^3 of 10% NaOH solution. The aqueous solutions were unified and was extracted with 2x50 cm^3 of benzene, then, 150 cm^3 of acetic acid was added. The mixture was extracted with diethyl ether, the ethereal phase was washed with 2x100 cm^3 10% NaOH solution. Then the aqueous phase was diluted to 500 cm^3 (pH = 10) and fractionated acidification was performed by cc. HCl. The crude solid material melting in identical ranges were collected and recrystallized from methanol until constant melting range was reached.

Method B (*E*-3-(o-methoxyphenyl)-2-phenyl propenoic acid (**1a**))

A mixture of 25 g (0.183 mol) phenylacetic acid, 25 g (0.183 mol) of o-methoxybenzaldehyde, 20 cm^3 of triethylamine and 40 cm^3 of acetic anhydride was refluxed for 5 hours. The mixture was cooled and dissolved in 100 cm^3 of benzene.

The solution was extracted with 10% NaOH solution. The basic solution was acidified by acetic acid. The precipitate was filtered and recrystallized from ethanol until constant melting range was obtained.

Method C (*Z*-3-(o-methoxyphenyl)-2-phenyl propenoic acid (**2a**))

4.45 g (20 mmol) of 3-phenylcoumarin was dissolved in 40 cm^3 of abs. DMSO and 7.3 g (130 mmol) of powdered KOH was added. The mixture was stirred at 40 °C-on until all the coumarin was consumed (circa 75 min, followed by TLC). The mixture was cooled to room temperature and 1.6 cm^3 (26 mmol) of CH_3I was added. Stirring was continued for another 22 hours. The mixture was poured into 200 cm^3 of icy water and was acidified to pH = 1 by cc. HCl. The precipitate was then filtered, washed with water, dried and recrystallized from benzene until constant melting range was reached.

Method D (Methyl *Z*-3-(o-methoxyphenyl)-2-phenyl propenoate (**2e**))

4.45 g (20 mmol) of 3-phenylcoumarin was dissolved in 40 cm^3 of abs. DMSO and 2.4 g (43 mmol) of powdered KOH was added. The mixture was stirred at 40 °C-on until all the coumarin was consumed (circa 75 min, followed by TLC). The mixture was cooled to room temperature and 3.4 cm^3 (55 mmol) of CH_3I was added. Stirring was continued for another hour. The mixture was poured into 200 cm^3 of icy water. The precipitate was then filtered, washed with water, dried and recrystallized from methanol until constant melting range was reached.

Method E (Methyl *E*-2-(o-methoxyphenyl)-3-phenyl propenoate (**3e**))

12.7 g (50 mmol) *E*-2-(o-methoxyphenyl)-3-phenyl propenoic acid (**3a**) was

dissolved in 100 cm^3 of methanol. To the mixture 1 cm^3 of cc. H_2SO_4 was added and refluxed for 80 hours. The reaction was followed by TLC. The mixture was allowed to stand in the refrigerator overnight. The precipitate was filtered, dried and recrystallized from methanol until constant melting range was reached.

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Accepted 7/3/99