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Stereoselective Stobbe Condensation of Ethyl Methyl Diphenylmethylenesuccinate with Aromatic Aldehydes

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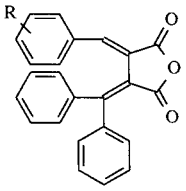
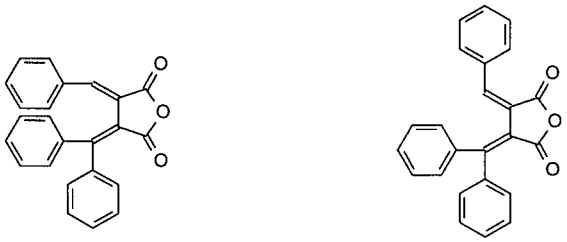
ABSTRACT



R = hydrogen, 4-methoxy, 4-methyl, 4-chloro, 4-nitro, 3,5-bis(trifluoromethyl), 2,4,6-trimethoxy.

The *E* configuration of benzylidene(diphenylmethylene)succinic anhydride (R = H), obtained by the Stobbe condensation of ethyl methyl diphenylmethylenesuccinate with benzaldehyde, was determined by single-crystal X-ray diffraction. Noncovalent π stacking interaction between two stacked phenyl groups is suggested as a stabilizing energy for the highly crowded molecule. The nature and the position of substituents (R) on the aromatic rings of substituted benzaldehydes showed no effect on the *E* stereoselectivity in the condensation.

In the course of our studies of noncovalent π stacking interaction between stacked phenyl groups,[1] we examined benzylidene(diphenylmethylene)succinic anhydride (**1**), a derivative of succinic anhydride. Some of these anhydride derivatives first discovered by Stobbe were known as thermally irreversible photochromic compounds (fulgides).[2] During the past few years, many research groups reported potential applications of new generations of fulgides.[3−5]



E and *Z* isomers of benzylidene(diphenylmethylene)succinic anhydride (**1**)

Compound **1** prepared by the Stobbe condensation of diethyl diphenylmethylenesuccinate (**2**) with benzaldehyde

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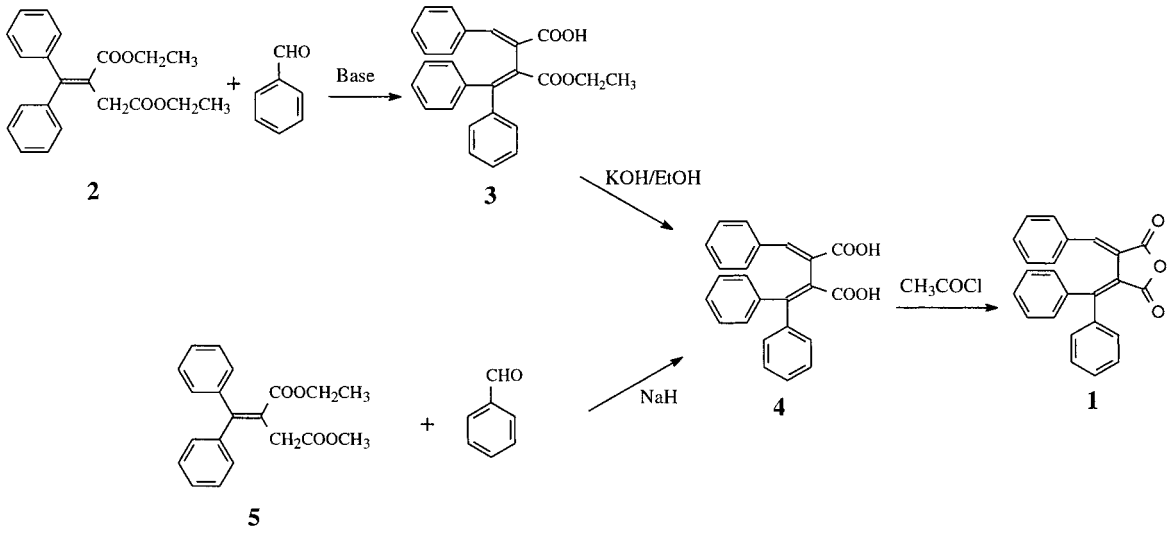
Scheme 1



was known (Scheme 1).[2] A literature survey has shown that the configuration of compound **1** was believed to be *Z* for many years, considering severe steric interaction existing in the *E* isomer. In 1972, Hart and Heller reported NMR data and assigned the *E* configuration of compound **1**, on the basis of deshielding of the olefinic proton and shielding of the aromatic protons in the *E* isomer.[6] However, the structure of compound **1** was not fully characterized. Moreover, it was uncertain whether the *E* stereoselectivity of this type of Stobbe condensation depended on the nature and the position of substituents on the aromatic ring of benzaldehyde.

To fully understand the stereoselectivity in the Stobbe condensation of diphenylmethylenesuccinate with aromatic aldehydes, we first decided to determine the configuration of compound **1** by way of single-crystal X-ray diffraction. Next, we planned to carry out similar condensations of diphenylmethylenesuccinate with substituted benzaldehydes containing different kinds of substituents at different positions on the aromatic rings, to investigate substituent effects on the stereoselectivity. Herein, we describe the results of our recent studies.

We chose ethyl methyl diphenylmethylenesuccinate (**5**)[2,7] instead of diethyl diphenylmethylenesuccinate (**2**) to prepare compound **1** and used sodium hydride as a base (Scheme 1). The diacid (**4**) was afforded directly from the Stobbe condensation, followed by an acidic workup. The second approach eliminated the base hydrolysis of the half ester (**3**) that was usually carried out at a high temperature, thus avoiding thermal isomerization during the process. Compound **1**, an orange powder, was afforded after dehydration of the diacid (**4**) using acetyl chloride.

Under the normal lab lights, the orange product (**1**) was stable in its solid form and in common organic solvents. At room temperature, the product was recrystallized from methanol to afford an orange crystal, which was analyzed by single-crystal X-ray diffraction. The *E* configuration of the product was determined (Figure 1).[8] The crystal structure

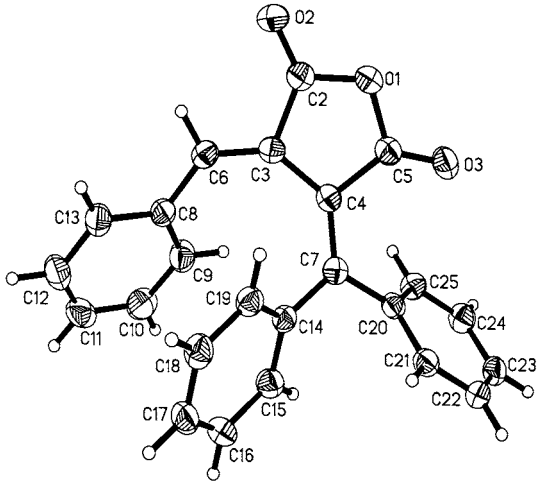


Figure 1. X-ray structure of compound **1** at 173 K (displacement ellipsoids shown at the 50% probability level).

reveals that the diene unit is highly twisted with a torsional angle (~25°).[9] The two phenyl groups connected to the same carbon (C7 in Figure 1) are not coplanar because of a large torsion angle (~42°). The phenyl group, which is closer to the carbonyl group (C_5 in Figure 1), is almost coplanar with the conjugated 1,3-butadiene unit. The other phenyl group nearly stacks onto the remaining phenyl group that gives the *E* configuration of the C=C bond. Also, the crystal-packing diagram (Figure 2) shows that the stacked phenyl groups tend to face each other in the crystal form.

(6) Hart, R. J.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1321−1324.

(7) Compound **5** was prepared by Stobbe condensation of benzophenone with diethyl succinate, followed by esterification using methanol and a catalytic amount of concentrated H_2SO_4.

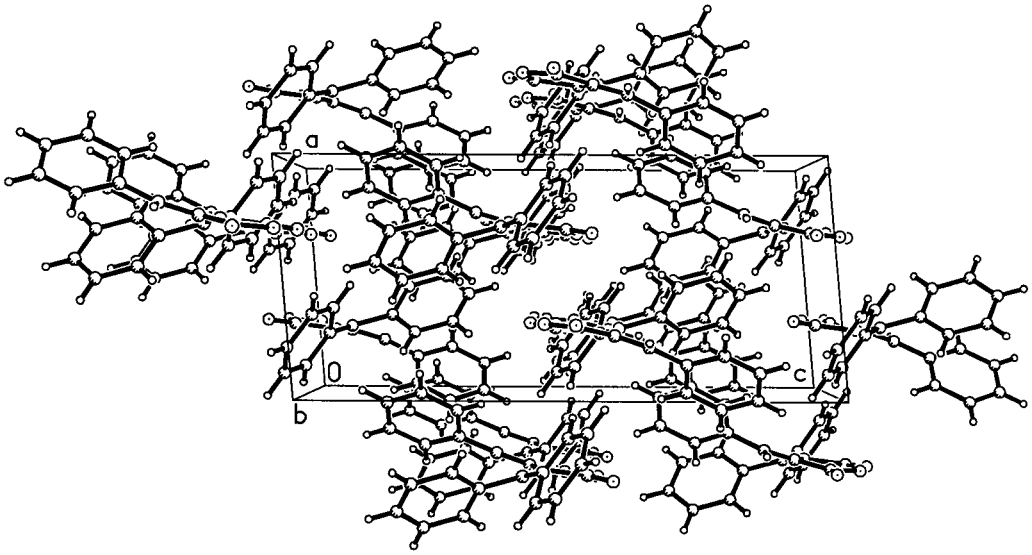


Figure 2. Crystal-packing diagram of compound **1**.

Although the formation of the *Z* configuration allowed compound **1** to maintain maximum conjugation across the 1,3-butadiene unit and to gain the stabilizing resonance energy, the experimental result indicated that the molecule preferred to form the highly crowded *E* configuration.

Noncovalent π stacking interactions play an important role in many areas of chemistry.[10] In organic chemistry, the effects of noncovalent π stacking interactions on photodimerization, photopolymerization,[11] and asymmetric synthesis[12] have been observed. Noncovalent π stacking interactions have been known to assemble various types of biological supramolecules, for example, DNA and RNA, and to provide the stabilizing energy for them.[13] Based on the stacking orientation and the distance of two phenyl groups (~3.26 Å) in compound **1**, a noncovalent π stacking interaction between the stacked phenyl groups is suggested as an important stabilizing energy for the crowded structure. The observed noncovalent interaction is an intramolecular force that occurs between two phenyl groups.

A closer examination of ^{1}H NMR of compound **1** revealed that the signals of 10 aromatic protons were more upfield-shifted than those of the five remaining protons. Because the formation of a $\pi-\pi$ complex caused electron shielding,[14] the upfield chemical shifts were assigned to the aromatic protons on the stacked phenyl rings. This method can also be applied to determine the configurations of some related anhydrides.

To examine the effects of different substituents on the stereoselectivity of the Stobbe condensation, diester **5** was condensed under the same reaction conditions with *p*-methoxybenzaldehyde, *p*-methylbenzaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde, respectively, to afford four dicarboxylic acids.[15] The anhydride products

(8) Data for compound **1**: $C_{24}H_{16}O_3$, monoclinic space group: $P2_1/c$; cell dimensions: $a = 8.1438(11)$ Å, $b = 11.5962(16)$ Å, $c = 18.591(3)$ Å, $\beta = 95.066(2)°$, $V = 1748.8(4)$ Å^3, $Z = 4$, $D_{calc} = 1.338$ Mg/m^3, $F(000) = 736$, $\mu = 0.088$ mm^{-1}. X-ray diffraction data were collected on an orange block crystal ($0.40 \times 0.20 \times 0.20$ mm^3) at 173(2) K using a Bruker SMART area diffractometer, λ (Mo Ka) = 0.71073 Å. Data integration was carried out with SAINT V6.1 (Bruker Analytical X-ray Systems, Madison, WI), corrections for absorption and decay were applied using SADABS. The structure was solved, by direct methods, and refined using the SHELXTL-Plus V5.10. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed with ideal positions and refined with isotropic thermal parameters related to the parent carbon atom. R1 = 0.0367 for 2732 data [I>2_(I)] and = 0.0418 for all 3093 data.

(9) Selected bond lengths: C(3)−C(4) = 1.4671(17); C(3)−C(6) = 1.3519(18); C(4)−C(7) = 1.3751(18); C(6)−C(8) = 1.4586(18); C(7)−C(14) = 1.4803(17); C(7)−C(20) = 1.4808(17) Å. Selected bond angles: C(6)−C(3)−C(4) = 137.02(12)°; C(7)−C(4)−C(3) = 132.07(11)°; C(3)−C(6)−C(8) = 131.31(12)°; C(4)−C(7)−C(14) = 122.78(11)°; C(4)−C(7)−C(20) = 121.37(11)°. Selected torsion angles: C(4)−C(3)−C(6)−C(8) = −4.6(2)°; C(3)−C(4)−C(7)−C(14) = −12.8(2)°; C(3)−C(4)−C(7)−C(20) = 168.14(12)°; C(6)−C(3)−C(4)−C(7) = −25.4(2)°.

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(14) Viel, S.; Mannina, L.; Segre, A. *Tetrahedron Lett.* **2002**, *43*, 2515−2519.

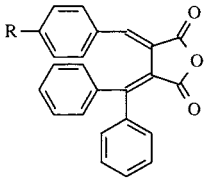
(15) **General Procedure.** With nitrogen flowing, aromatic aldehyde (1.4 mmol), the diester **5** (1.23 mmol), benzene (3.0 mL), and 60% sodium hydride in mineral oil (1.6 mmol) were added into a flame-dried flask (150 mL). The flow of nitrogen was stopped, and a drop of methanol was added carefully into the stirred mixture at room temperature to initiate the condensation. After the initial reaction had subsided, the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by slow addition of water (3.0 mL) and was acidified by addition of concentrated HCl. The resulting mixture was extracted with ethyl ether three times. The combined ethereal solutions were extracted with ammonia (1.0 N, 15 mL). The alkaline solution, cooled in an ice−water bath, was acidified using concentrated HCl. The precipitated oil was collected by ether extraction. The ethereal solution was washed with brine and dried over $MgSO_4$. Removal of ether in vacuo afforded the diacid as an oil. In dim red light, the diacid was dissolved in acetyl chloride (1.5−2.0 mL) and left at room temperature for 30 min. The extra acetyl chloride was removed in vacuo to give a residue, which was dissolved into a small amount of ethyl acetate (1.0−2.0 mL). The anhydride product was precipitated by addition of hexane.

Table 1. Yields, UV−Vis Absorption Maxima (nm) in Methanol, and Partial ^{1}H NMR Data (ppm, $CDCl_3$, 200 MHz) of the Products

aromatic aldehyde	yield (%)	λ_{max}	δ_1[a]	*o*-H[c]	*m*-H[c]	*o*-H[d]	*m*-H[d]	*p*-H[d]
benzaldehyde	**1** (70)	388, 297	7.63[b]			6.90	6.98	7.12
p-methoxybenzaldehyde	**6** (80)	412, 316	7.62	6.91	6.45	6.86	6.94	7.06
p-methylbenzaldehyde	**7** (53)	394, 304	7.61	6.85	6.74	6.91	6.91	6.99
p-chlorobenzaldehyde	**8** (59)	391, 299	7.55	6.96	6.86	6.91	6.91	7.06
p-nitrobenzaldehyde	**9** (53)	397, 304	7.57	7.11	7.80	6.93	6.93	7.00
3,5-bis(trifluoromethyl)-benzaldehyde	**10** (50)	384, 285	7.54	7.23		6.94	6.94	7.04
2,4,6-trimethoxybenzaldehyde	**11** (58)	428, 324	7.84		5.60	6.70	6.80	6.98

[a] Chemical shifts of the olefinic protons. [b] The chemical shift of the olefinic proton of the *Z* isomer is 6.85 ppm (ref 6). [c] Chemical shifts of the *ortho*/*meta* protons on the stacked and substituted phenyl rings. [d] Chemical shifts of the *ortho*/*meta*/*para* protons on the stacked and unsubstituted phenyl rings.

(**6**−**9**) were precipitated as orange solids immediately after dehydration.



R = -OCH_3 (**6**), -CH_3 (**7**), -Cl (**8**), -NO_2 (**9**)

The *E* configuration of these orange solids (**6**−**9**) was confirmed by their ^{1}H NMR and ^{13}C NMR spectra, MS, and UV−vis data and by comparing to those of compound **1** (Table 1). The upfield chemical shifts of the protons on the stacked and unsubstituted aromatic rings, as well as the downfield shifts of the olefinic protons, were observed. No other isomers were found from the above reactions.

Moreover, 3,5-bis(trifluoromethyl)benzaldehyde and 2,4,6-trimethoxybenzaldehyde were reacted with the ester (**5**), respectively, to afford compound **10** as an orange solid and compound **11** as a red solid. The *E* configuration of these two products was also confirmed by the spectral data (Table 1).

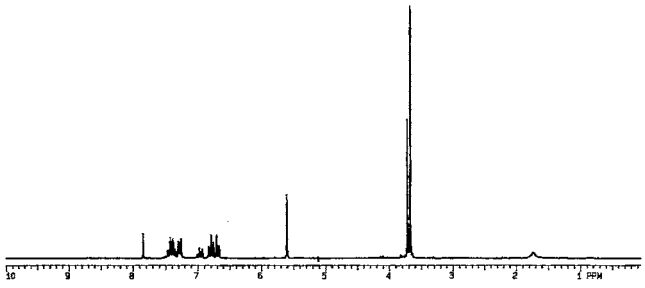
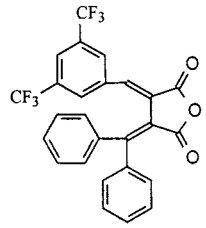


Figure 3. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of compound **11**.

The ^{1}H NMR spectrum (Figure 3) of compound **11** showed the signals of the aromatic protons of the stacked phenyl and 2,4,6-trimethoxyphenyl groups shifted upfield. The singlet at 5.60 ppm assigned for the *m*,*m*′-Hs on the 2,4,6-trimethoxyphenyl group indicated two equivalent protons, which was caused by fast rotation of the two stacking phenyl rings in solution at room temperature.[1] The preparation of six anhydrides (**6**−**11**) indicated that the number and the nature (electron-withdrawing or electron-donating) of substituents on the aromatic rings of substituted benzaldehydes have no effect on the *E* seteroselectivity of this type of the Stobbe condensation.[16]



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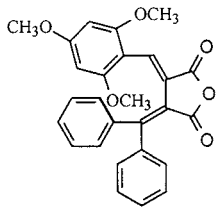

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In summary, we have determined the *E* configuration of the Stobbe condensation of compound **5** with the substituted benzaldehydes. The effort to study noncovalent π stacking interaction possibly existing in these anhydrides is currently ongoing in the author's lab.

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Supporting Information Available: Crystallographic data for compound **1** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The conclusion was also supported by our recent preparation of (*E*,*E*)-bis(2,4,6-trimethoxybenzylidene)succinic anhydride. Spectral data: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (s, 2H), 5.60 (s, 4H), 3.71 (s, 6H), 3.54 (s, 12H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 163.96, 158.36, 131.45, 121.53, 111.75, 107.80, 88.37, 55.16, 54.92; UV−vis λ_{max} = 560, 408 nm, in acetone; MS $(M+1)^+$, 457.