Tris(4-anisyl)phosphine as an Efficient and Practical Reagent for the Synthesis of (*E*)-2-Benzylidenesuccinates

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Condensation of maleic anhydride or dimethyl maleate with benzylaldehydes controlled by tris(4-anisyl)-phosphine to synthesize dimethyl (*E*)-2-benzylidenesuccinates has been systematically investigated. The protocol gives the product with high stereoselectivity in moderate to good yields under mild conditions. A plausible mechanism has been proposed.

Keywords condensation, tris(4-anisyl)phosphine, dimethyl (*E*)-2-benzylidenesuccinate, mechanism

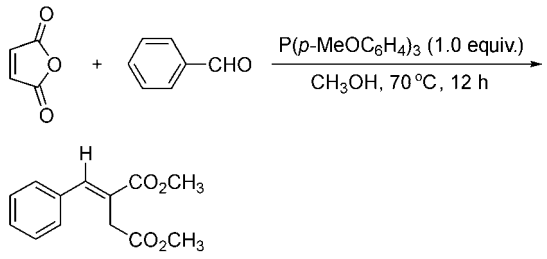
Introduction

In the area of synthetic organic chemistry tremendous progress has been made in the phosphine-involved reactions including Wittig reaction,[1] Wittig-Horner reaction,[2] and Horner-Wadsworth-Emmons reaction,[3] in the past decades, and some of these classic name reactions have become powerful synthetic tools for the construction of important synthons. Arylmethylidenesuccinates, one of the important synthons,[4] have been employed to synthesize 1,4-diphenylbutadiene derivatives,[5a] 2,3-butanediol,[4a] (*Z*)-methyl α-(acetoxy)acrylates and (*E*)-β-aryl itaconate derivatives.[4b] However, a considerable body of synthetic methods for arylmethylidenesuccinates has not been entirely satisfactory because of such drawbacks as low yields, strong bases, long reaction time, and expensive transition metal compounds.[6] Herein we wish to describe an efficient and practical method to synthesize (*E*)-2-benzylidenesuccinates via tris(4-anisyl)phosphine-involved highly selective succinylidenations of benzaldehydes with maleic anhydride or dimethyl maleate. The reaction does not require expensive reagents and special equipment, while the mild reaction conditions and the toleration of a range of functional groups are especially noteworthy.

Experimental

All the reactions were carried out in a round bottom flask equipped with a magnetic stir bar. Solvents and all reagents were used as received. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz and ^{13}C NMR spectra at 100 MHz, and the chemical shifts (δ) were referenced to TMS. GC-MS was obtained using electron ionization (EI). TLC was performed using commercially prepared 100—400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm. All other chemicals were purchased from Aldrich Chemicals.

Scheme 1



Typical procedure for the reaction of maleic anhydride with benzaldehyde

To a stirred mixture of maleic anhydride (98 mg, 1.0 mmol) and benzaldehyde (106 mg, 1.0 mmol), were added 2 mL of methanol and tris(4-anisyl)phosphine [$P(p\text{-}MeOC_6H_4)_3$] (352 mg, 1.0 mmol) successively. The mixture was stirred at 70 ℃ for 36 h in a round bottom flask. After cooling, the resulting mixture was then analyzed by GC-MS and subjected to isolation by PTLC (GF_{254}), eluted with a 10∶1 (*V*∶*V*) petroleum ether-ethyl acetate mixture to give compound **3a** (Table 1, Entry 1, Equation 1). The product was characterized with ^{1}H NMR spectra.

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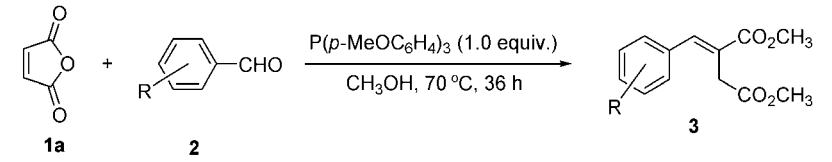
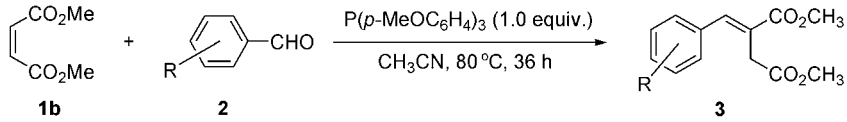
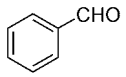
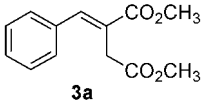
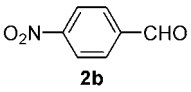
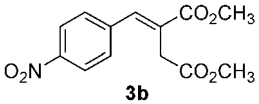
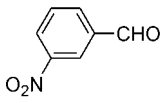
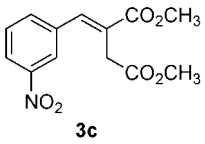
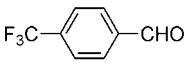
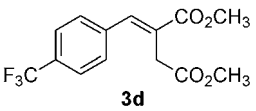
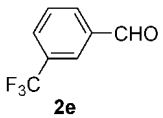
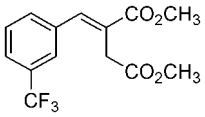
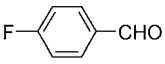
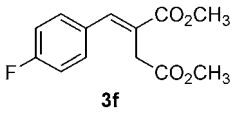
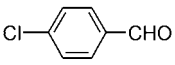
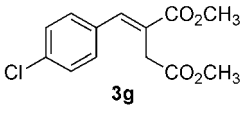
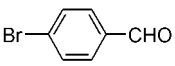
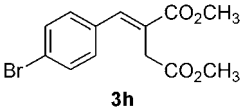
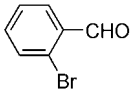
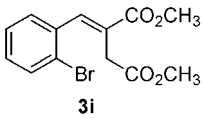
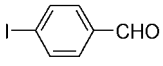
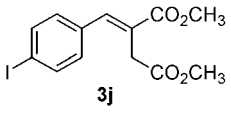
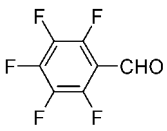
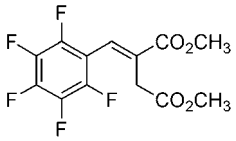
Table 1 Synthesis of (*E*)-2-benzylidenesuccinates using **1** and benzaldehydes **2**[a]





Entry	Benzaldehyde	Product	Eq. 1 yield[b]/%	Eq. 2 yield[c]/%
1	 **2a**	 **3a**	42	81
2	 **2b**	 **3b**	66	66
3	 **2c**	 **3c**	30	60
4	 **2d**	 **3d**	53	97
5	 **2e**	 **3e**	38	96
6	 **2f**	 **3f**	39	73
7	 **2g**	 **3g**	42	61
8	 **2h**	 **3h**	47	59
9	 **2i**	 **3i**	33	52
10	 **2j**	 **3j**	55	57

Continued

Entry	Benzaldehyde	Product	Eq. 1 yield[b]/%	Eq. 2 yield[c]/%
11	 **2k**	 **3k**	85	89

[a] All the reactions were carried out using 1 mmol of **1**, 1.0 mmol of **2**, and 1.0 equiv. of P(*p*-$MeOC_6H_4$)$_3$ in methanol (2.0 mL) at 70 ℃ (Eq. 1) and in acetonitrile (2.0 mL) at 80 ℃ (Eq. 2) for 36 h. [b] Isolated yield for Eq. 1. [c] Isolated yield for Eq. 2.

Typical procedure for the reaction of dimethyl maleate with benzaldehyde

To a stirred mixture of dimethyl maleate (72 mg, 0.5 mmol) and benzaldehyde (53 mg, 0.5 mmol), were added 2 mL of acetonitrile and tris(4-anisyl)phosphine [P(*p*-$MeOC_6H_4$)$_3$] (176 mg, 0.5 mmol) successively. The mixture was stirred at 80 ℃ for 36 h in a round bottom flask. After cooling, the resulting mixture was then analyzed by GC-MS and subjected to isolation by PTLC (GF_{254}), eluted with a 10∶1 (*V*∶*V*) petroleum ether-ethyl acetate mixture to give compound **3a** (Table 1, Entry 1, Equation 2).

Characterization data for products

(*E*)-Dimethyl 2-benzylidenesuccinate (Table 1, Entry 1)[7a] Yield: Eq. 1 42%, Eq. 2 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.88 (s, 1H), 7.24—7.39 (m, 5H), 3.80 (s, 3H), 3.70 (s, 3H), 3.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.6, 167.8, 142.1, 134.9, 129.0, 128.9, 128.6, 125.8, 52.2, 52.1, 33.4; MS (70 eV) *m/z* (%): 234 (M^+, 29), 174 (39), 115 (100), 91 (21).

(*E*)-Dimethyl 2-(4-nitrobenzylidene)succinate (Table 1, Entry 2)[7b] Yield: Eq. 1 66%, Eq. 2 66%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.24 (d, *J*=4 Hz, 2H), 7.89 (s, 1H), 7.49 (d, *J*=4 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.0, 197.0, 147.7, 141.4, 139.6, 129.7, 129.0, 123.9, 52.6, 52.4, 33.4; IR (KBr) *v*: 2958, 1657, 1497, 1437, 708 cm^{-1}; MS (70 eV) *m/z* (%): 279 (M^+, 5), 247 (100), 219 (40), 145 (86).

(*E*)-Dimethyl 2-(3-nitrobenzylidene)succinate (Table 1, Entry 3)[7c] Yield: Eq. 1 30%, Eq. 2 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.20 (d, *J*=2 Hz, 2H), 7.89 (s, 1H), 7.55—7.60 (m, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.0, 167.0, 147.5, 139.4, 136.5, 134.7, 129.8, 128.6, 123.7, 123.6, 52.6, 52.4, 33.4; MS (70 eV) *m/z* (%): 279 (M^+, 8), 247 (100), 173 (80), 145 (86).

(*E*)-Dimethyl 2-(4-trifluoromethyl)benzylidene)-succinate (Table 1, Entry 4)[7d] Yield: Eq. 1 53%, Eq. 2 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.87 (s, 1H), 7.62 (d, *J*=4 Hz, 2H), 7.42 (d, *J*=4 Hz, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 3.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.2, 167.2, 140.5, 138.5, 130.3, 129.1, 127.9, 125.5, 123.7, 52.4, 52.2, 33.3; MS (70 eV) *m/z* (%): 302 (M^+, 90), 270 (100), 183 (95), 115 (83).

(*E*)-Dimethyl 2-(3-trifluoromethyl)benzylidene)-succinate (Table 1, Entry 5) Yield: Eq. 1 38%, Eq. 2 96%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.88 (s, 1H), 7.59 (d, *J*=2 Hz, 2H), 7.51 (d, *J*=2 Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.2, 167.3, 140.4, 135.7, 132.0, 131.8, 131.6, 129.2, 127.3, 125.7, 123.7, 52.4, 52.3, 33.3; IR (KBr) *v*: 2958, 1666, 1452, 778, 701 cm^{-1}; MS (70 eV) *m/z* (%): 302 (M^+, 96), 270 (100), 242 (94), 189 (49). Anal. calcd for $C_{14}H_{13}F_3O_4$: C 55.63, H 4.34; found C 55.47, H 4.36.

(*E*)-Dimethyl 2-(4-fluorobenzylidene)succinate (Table 1, Entry 6)[7e] Yield: Eq. 1 39%, Eq. 2 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.85 (s, 1H), 7.11—7.27 (m, 4H), 3.80 (s, 3H), 3.70 (s, 3H), 3.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.6, 167.8, 142.3, 138.3, 134.8, 129.7, 128.5, 126.0, 52.2, 52.1, 33.4; MS (70 eV) *m/z* (%): 252 (M^+, 39), 220 (58), 192 (48), 133 (100).

(*E*)-Dimethyl 2-(4-chlorobenzylidene)succinate (Table 1, Entry 7)[7f] Yield: Eq. 1 42%, Eq. 2 61%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.82 (s, 1H), 7.35 (d, *J*=4 Hz, 2H), 7.25 (d, *J*=2 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.4, 167.5, 140.9, 135.0, 133.3, 130.3, 128.9, 126.4, 52.4, 52.3, 33.4; MS (70 eV) *m/z* (%): 268 (M^+, 58), 236 (70), 149 (85), 115 (100).

(*E*)-Dimethyl 2-(4-bromobenzylidene)succinate (Table 1, Entry 8)[7d] Yield: Eq. 1 47%, Eq. 2 59%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.79 (s, 1H), 7.49 (d, *J*=2 Hz, 2H), 7.19 (d, *J*=4 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.3, 167.5, 140.9, 133.7, 131.9, 130.5, 126.5, 123.2, 52.4, 52.2, 33.4; MS (70 eV) *m/z* (%): 312 (M^+, 43) , 280 (71), 253 (90), 194 (100).

(*E*)-Dimethyl 2-(2-bromobenzylidene)succinate (Table 1, Entry 9)[4b] Yield: Eq. 1 33%, Eq. 2 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.86 (s, 1H), 7.60 (d, *J*=4 Hz, 1H), 7.18—7.31 (m, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.4, 167.2, 141.4, 135.4, 132.8, 130.2, 129.9, 127.4, 123.9, 52.4, 52.3, 33.5; MS (70 eV) *m/z* (%): 312 (M^+, 40), 280 (74), 253 (84), 194 (100).

(*E*)-Dimethyl 2-(4-iodobenzylidene)succinate (Table 1, Entry 10) Yield: Eq. 1 55%, Eq. 2 57%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.78 (s, 1H), 7.71 (d, *J*=4 Hz, 2H), 7.05 (d, *J*=2 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.3, 167.5, 141.0, 137.8, 134.3, 130.6, 126.6, 35.1, 52.4, 52.3, 33.4; IR (KBr) *v*: 2957, 1659, 1500, 739, 699

cm^{-1}; MS (70 eV) *m/z* (%): 360 (M^+, 80), 300 (27), 262 (100). Anal. calcd for $C_{13}H_{13}IO_4$: C 43.35, H 3.64; found C 42.76, H 3.70.

(*E*)-Dimethyl 2-(pentafluorophenylmethylidene)-succinate (Table 1, Entry 11) Yield: Eq. 1 85%, Eq. 2 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.9, 166.0, 145.1, 142.7, 142.6, 139.0, 136.5, 133.7, 125.3, 109.6, 52.7, 52.2, 34.4; IR (KBr) *v*: 2958, 1657, 1497, 1437, 708 cm^{-1}; MS (70 eV) *m/z* (%): 324 (M^+, 30), 264 (50), 205 (100). Anal. calcd for $C_{13}H_9F_5O_4$: C 48.16, H 2.80; found C 48.38, H 2.81.

Results and discussion

Our studies were initiated by the reaction of 1.0 equiv. of PPh_3 to a solution of maleic anhydride, benzaldehyde and 2 mL of methanol at 70 ℃ for 12 h (Scheme 1, Entry 1 in Table 2), and the reaction resulted in dimethyl (*E*)-2-benzylidenesuccinate, which was determined via ^{1}H, ^{13}C NMR spectra and literature.[7]

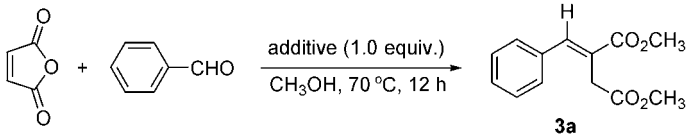
Encouraged by this result, we examined the reaction in detail under different conditions in an attempt to increase the yield. The representative results are summarized in Table 2. Among the additives examined in methanol, organic-phosphine compounds especially tris(4-anisyl)phosphine showed good activity for this reaction (Table 2, Entries 4—6), however organic- nitrogen compounds, such as pyridine (Py) and 1,4-diazabicyclo(2.2.2)octane (DABCO), showed no activity for the condensation (Table 2, Entries 2 and 3). When the reaction time was prolonged from 12 to 36 h (Table 2, Entries 6 and 8), the yield was increased from 48% to 70%, while when prolonged to 48 h, the yield was not raised further (Table 2, Entries 8 and 9). Besides, when the reaction was carried out at room temperature, it afforded **3a** in poor yield (Table 2, Entry 10).

With these optimized conditions in hand, we next explored the scope of the process by studying a wide variety of benzaldehydes as substrates. As outlined in Table 1 (Eq. 1), a wide range of benzaldehydes were condensed with maleic anhydride **1a** in moderate to good isolated yields with high stereoselectivity (Table 1, Entries 1—11). The reaction appeared quite sensitive with respect to the steric and electronic contribution of the substituent on the benzene ring of the benzaldehydes. As revealed in Entries 2—5, benzaldehydes with a *para*-electron-withdrawing group can be successfully employed in this reaction to produce the corresponding (*E*)-2-benzylidenesuccinate derivatives. For example, 2,3,4,5,6-pentafluorobenzaldehyde afforded dimethyl (*E*)-2-(pentafluorophenylmethylidene)succinate in 85% isolated yield (Table 1, Entry 11). While *meta*-electron-withdrawing-substituted (Table 1, Entries 3 and 5), *para*- or *ortho*-halogen-substituted benzylaldehydes were used (Table 1, Entries 6—10), the reaction gave relatively poor yields.

This protocol appeared to be well suitable for dimethyl maleate, and the results showed that the corresponding (*E*)-2-benzylidenesuccinates could be obtained in good to excellent isolated yields (Table 1, Eq. 2). It is interesting that the substituent groups on phenyl ring of benzaldehydes have little effect on the reaction stereo-selectivity, however dimethyl maleate proved to be a viable reaction partner in this protocol due to higher yields of the desired target compounds (Table 1, Entries 1—11).

The plausible mechanism for the formation of the

Table 2 Condition optimization for the synthesis of dimethyl (*E*)-2-benzylidenesuccinate[a]



1a **2a** **3a**

Entry	Additive (1.0 equiv.)	Temperature/℃	Time/h	Yield[b]/%
1	PPh_3	70	12	15
2	Py	70	12	none
3	DABCO	70	12	none
4	(n-Bu)$_3$P	70	12	23
5	Tribenzo[d][1,3]dioxol-5-ylphosphine	70	12	41
6	Tris(4-anisyl)phosphine	70	12	48
7	Tris(4-anisyl)phosphine	70	24	57
8	Tris(4-anisyl)phosphine	70	36	70
9	Tris(4-anisyl)phosphine	70	48	71
10	Tris(4-anisyl)phosphine	r.t.	36	trace

[a] Reaction conditions: maleic anhydride **1a** (0.25 mmol), benzaldehyde **2a** (0.25 mmol), methanol (2 mL); [b] GC yield.

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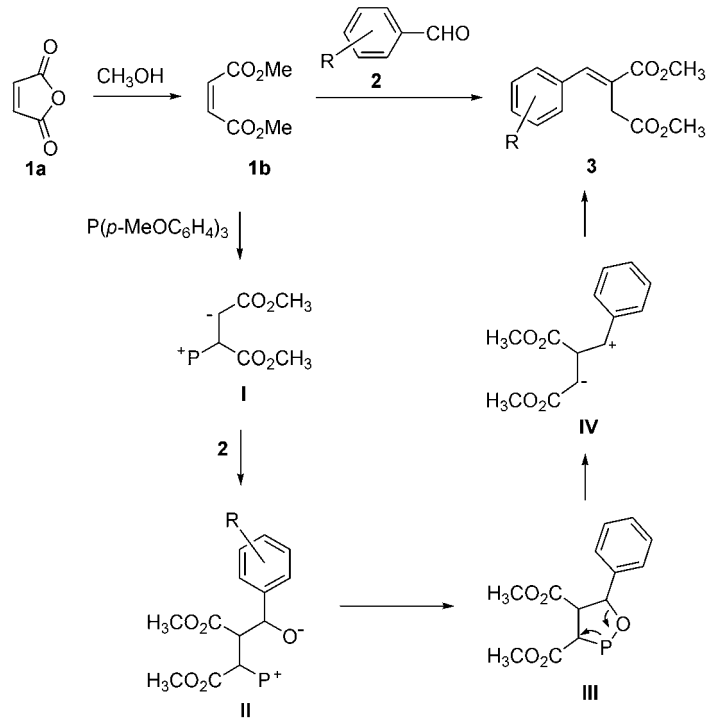
Scheme 2 Proposed route to synthesize (*E*)-2-benzylidenesuccinates



benzylidenesuccinate compounds was depicted in Scheme 2. The reaction could be triggered by nucleophilic addition of tris(4-anisyl)phosphine to the electron-deficient double bond to produce zwitterionic **I**, and then involved with nucleophilic attack of the carbanion of intermediate **I** on the carbon-oxygen double bond of benzaldehydes to form **II**, which is swiftly transformed to **III**. Subsequently, $(p\text{-MeOC}_6H_4)_3P{=}O$ was eliminated from the intermediate **III** to form another zwitterionic **IV**, which quickly resulted in the target compound **3** due to the intramolecular hydrogen transfer.

In summary, we have described the reaction of benzaldehydes with maleic anhydride or dimethyl maleate controlled by $P(p\text{-MeOC}_6H_4)_3$ to give (*E*)-2-benzylidenesuccinates with high stereoselectivity in moderate to good yields under mild conditions. To the best of our knowledge, this protocol opened up a direct way for the synthesis of (*E*)-2-benzylidensuccinates, which are very important potential organic intermediates in organic synthesis.

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