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One-Pot, Three-Component Synthesis of Arylidenesuccinates and Related Compounds

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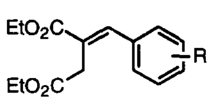
Abstract: *Aromatic and heteroaromatic aldehydes react with diethyl fumarate or diethyl maleate and tri-n-butylphosphine at room temperature to afford good yields of diethyl arylidenesuccinates. Unsaturated and saturated aldehydes afford cognate products.* © 1997 Elsevier Science Ltd.

For a recent project in the CNS area, we required a number of (arylmethyl)succinic acids, which were to be prepared as racemates by reducing the arylidenesuccinates (**1**), followed by hydrolysis. The Stobbe route to (**1**) from aldehydes and diethyl succinate requires strong bases and can give variable yields,[2] and hence the phosphorane (**2**)[3] or phosphonate (**3**)[4] are commonly employed, although reactions with (**2**) may require excess reagent and are subject to steric inhibition.[5] Reagents (**2**) and (**3**) require prior preparation; it should be noted that although maleimide reacts with triphenylphosphine at room temperature to give (**4**),[6] diethyl maleate is not similarly reactive. However, catalytic amounts of *trialkyl*phosphines isomerise maleate to fumarate,[7] presumably *via* addition-elimination.



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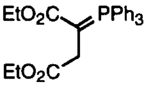

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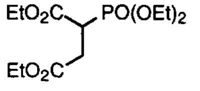

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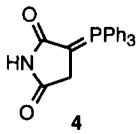

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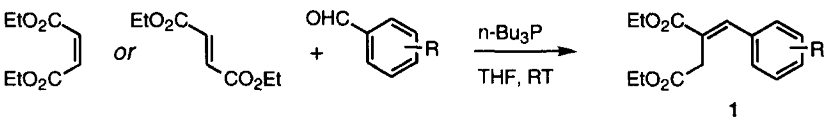
In this note we report that, as depicted in **Equation 1**, direct interaction of ArCHO and other aldehydes with diethyl maleate or fumarate and tri-*n*-butylphosphine in tetrahydrofuran at ambient temperatures gives good yields of the olefins (**1**). In contrast, reactions of aldehydes with acrylates or acrylonitrile afford 1-(1-hydroxyalkyl)-acrylates in a Baylis-Hillman process when catalysed by trialkylphosphines,[8] and modest yields of Wittig products at elevated temperatures when stoichiometric triphenylphosphine is present.[9]

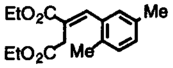
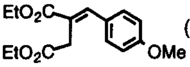
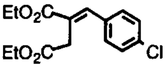
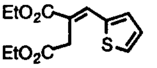


[eq. 1]

A typical experimental process follows; additional examples with different steric and electronic environments for the participating aldehyde are summarised in **Table 1**. Diethyl fumarate was used in these reactions; comparable yields were obtained using diethyl maleate.

Diethyl [3-(benzyloxy)benzylidene]succinate (**1**, R = 3-OCH_2Ph): Tri-*n*-butylphosphine (Aldrich, 95%; 14 mL; ~1.4 eq.) was added slowly by syringe to a stirred solution of diethyl fumarate (7.57 g; 0.044 mol) and 3-(benzyloxy)benzaldehyde (8.48 g; 0.04 mol) in dry THF (70 mL) at 20-25° under N_2, and stirring was continued for 20 h. The mixture was diluted with CH_2Cl_2 (300 mL) and stirred for 0.5 h. with the addition of H_2O (100 mL) containing 30% H_2O_2 (7.5 mL), to oxidise any remaining *n*-Bu_3P. The organic phase was washed with 1M $NaHCO_3$, dried ($MgSO_4$), and evaporated. TLC indicated that the residue contained product and tri-*n*-butylphosphine oxide, with a little starting aldehyde. Flash chromatography (silica; hexanes-CH_2Cl_2) gave the pure diester as a pale yellow oil (11.05 g; 75%).

Table 1: Reactions of Aromatic and Heteroaromatic Aldehydes According to Eq. 1

Aldehyde[1]	**Product**[2]	**Time**[3]	**Yield**[4]	δ (=C$\underline{H}$)[5]
2,5-dimethyl-benzaldehyde	 (5)	48	85	7.91
4-methoxy-benzaldehyde	 (6)	72	82	7.86
4-chloro-benzaldehyde	 (7)	24	75	7.83
Thiophene-2-carboxaldehyde	 (8)	72	71	8.00

Notes:
1. All reactants were used as received from the suppliers.
2. Typically, ~95:5 E:Z diester mixtures were obtained.
3. Reaction time (h) at RT for >95% consumption of aldehyde.
4. Refers to chromatographically purified, solvent-free product from reactions run on 10mmol or larger scale. All new compounds gave the correct molecular ions and microanalyses.
5. Olefinic proton of the major isomer, determined in $CDCl_3$.

Some preliminary experiments suggest both limitations and further potential for this process: Both *trans*-cinnamaldehyde and 3-phenylpropanal gave the expected olefins (24 h. reaction time; the isolated yields were 79% and 94%, respectively), whereas cyclohexanone was not reactive under these conditions. Benzaldehyde and *trans*-1,2-dicyanoethene gave a modest yield of $PhCH{=}C(CN)CH_2CN$ as an E/Z mixture.

In summary, we have developed a convenient, one-pot method for preparing arylidenesuccinate esters and related compounds utilising *in situ* generation of the novel phosphorane $EtO_2CC(=PBu_3)CH_2CO_2Et$ (**9**).[10] Other aspects of this process including intramolecular and solid phase variants are under investigation.

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References and Notes:

1. Participant in the SPRI Summer Intern Program.
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10. NMR experiments showed that (**9**) is the major component formed at equilibrium from Bu_3P and diethyl fumarate or maleate in $CDCl_3$ or THF-d_8. PMR of (**9**) in $CDCl_3$: $\delta = 0.95$ (m, 9H); 1.18 (t, 3H, J = 7Hz); 1.26 (t, 3H, J = 7Hz); 1.44 (m, 12H), 1.95 (m, 6H), 3.05 (d, 2H, J_{PCCH} = 15Hz) and 4.0-4.2 (m, 4H).

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