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PPh_3-catalyzed synthesis of multifunctional vinylesters from terminal alkynoates and aromatic aldehydes

Ling-Guo Meng[a], Kai Tang[a], Qing-Xiang Guo[a], Song Xue[a,b,*]

[a] Department of Chemistry, University of Science and Technology of China, Hefei 230026, PR China
[b] Department of Applied Chemistry, Tianjin University of Technology, Tianjin 300191, PR China

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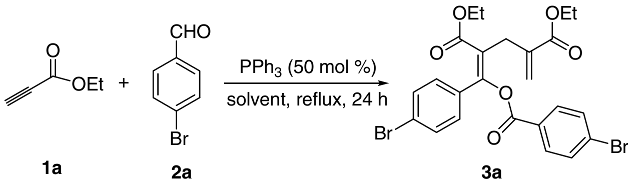
Abstract

A new four-component reaction involving two starting materials is described. The reaction of terminal alkynoates with aromatic aldehydes catalyzed by PPh_3 (50 mol %) in CH_2Cl_2 at reflux afforded multifunctional vinylesters in moderate yields. A plausible mechanism is proposed.

The formation of carbon–carbon bonds is of fundamental importance in organic synthesis.[1] One-pot multicomponent reactions (MCRs) constitute excellent manifolds to generate molecular complexity and have received considerable attention due to their high efficiency in the synthesis of organic building blocks from the easily available starting materials.[2] The electron-deficient alkynes are often used as nucleophile precursors for the formation of carbon–carbon bonds and recent studies on the chemistry of organocatalysts via conjugate addition of N- and P-nucleophiles have uncovered a number of interesting reactions.[3,4] In view of the general interest in the development of new reaction with defined chemoselectivity and atom economy,[5] we investigated the four-component reactions involving two starting materials.[6] The unexpected transformation resulted in multifunctional vinylesters from terminal alkynoates and aromatic aldehydes were observed in the presence of PPh_3 (50 mol %). It is noteworthy that vinylesters are important intermediates in organic synthesis.[7,8]

Our studies were initiated by the addition of 0.5 equiv of PPh_3 to a solution of 4-bromobenzaldehyde and ethyl propiolate (**1a**) under various reaction conditions, and the results are shown in Table 1. The reaction of 4-bromobenz-

Table 1
Reactions of ethyl propiolate with 4-bromobenzaldehyde catalyzed by PPh_3 (50 mol %)



Entry	**1a** (equiv)	**2a** (equiv)	Solvent	Yield[a] (%)
1	1.0	1.0	CH_2Cl_2	34
2	1.0	1.0	CH_2Cl_2	24[b]
3	1.0	1.0	CH_2Cl_2	Trace[c]
4	1.5	1.0	CH_2Cl_2	47
5	1.0	1.5	CH_2Cl_2	60
6	1.0	2.0	CH_2Cl_2	58
7	1.0	1.5	CH_2Cl_2	44[d]
8	1.0	1.5	THF	15
9	1.0	1.5	Benzene	45
10	1.0	1.5	MeCN	Trace
11	1.0	1.5	DMF	NR[e]

[a] Isolate yields.
[b] At rt.
[c] At 0 °C.
[d] 20 mol % PPh_3 was used.
[e] At 80 °C.

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[*] Corresponding author. Tel.: +86 022 23696705.
E-mail address: xuesong@ustc.edu.cn (S. Xue).

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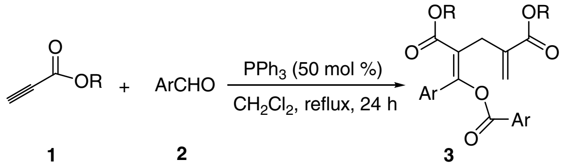
aldehyde with ethyl propiolate in the presence of PPh_3 (50 mol %) in CH_2Cl_2 at reflux for 24 h afforded a colorless oil in 34% yield, which was characterized as **3a**.

The yield decreased sharply when the reaction was stirred at 0 °C or room temperature. The ratio of propiolate and aromatic aldehyde has an effect on this reaction, and the desired product **3a** was obtained in 60% yield when 1.5 equiv of aldehyde was used and the yield of product was not improved with the further increasing of the amount of aldehyde. The yield of **3a** decreased to 44% when the amount of the catalyst PPh_3 decreased to 20 mol %. The choice of THF and benzene as solvent gave the desired product in 15% and 45% yields, respectively. PPh_3 as a catalyst was crucial for the course of this reaction. Only a trace amount of the product **3a** was detected by TLC when tributylphosphine, in place of PPh_3, was used. The use of other organic bases, such as 1,4-diazabicyclo[2,2,2]-octane (DABCO), 4-dimethylamino-pyridine (DMAP), Et_3N, and pyridine, did not give the desired products.

Under these optimized conditions,[9] various aldehydes were examined, and the representative results are summarized in Table 2. It was found that the reactions of aromatic aldehydes with ethyl propiolate afforded the corresponding products in moderate yields. Clearly, the substitutes on the aromatic aldehydes have an effect on the yields of the reactions. The substrate with an electron-withdrawing group on the aromatic ring gave better yield than that of an electron-donating group on the aromatic ring. For example, 4-nitrobenzaldehyde afforded the desired product **3f** as a white crystalline solid in 50% yield. The structure of the product was characterized, based on the spectra data and further confirmed unambiguously using single crystal X-ray analysis (Fig. 1).[10] However, 4-methoxybenzaldehyde gave no corresponding product under the same conditions. Subsequently, the aldehydes containing electron-withdrawing groups such as cyano and trifluoromethyl groups on their benzene ring were performed in the reaction, and the corresponding products produced in good yields. The benzyl propiolates, in place of ethyl propiolate, were also converted to the vinylesters in moderate yields. In many cases, the moderate yields obtained can be accounted for the formation of any other byproducts which cannot be isolated by column chromatography. It should be noted that no product was observed when aliphatic aldehyde was subjected to this reaction under the typical conditions.

Table 2
Reactions of terminal alkynoates with aromatic aldehydes catalyzed by PPh_3



Entry	R	Ar	Product	Yield[a] (%)
1	CH_3CH_2	4-BrC_6H_4	**3a**	60
2	CH_3CH_2	4-ClC_6H_4	**3b**	52
3	CH_3CH_2	4-FC_6H_4	**3c**	43
4	CH_3CH_2	C_6H_5	**3d**	33
5	CH_3CH_2	4-$CH_3C_6H_4$	**3e**	28
6	CH_3CH_2	4-$MeOC_6H_4$	NR[b]	—
7	CH_3CH_2	4-$NO_2C_6H_4$	**3f**	50
8	CH_3CH_2	4-CNC_6H_4	**3g**	56
9	CH_3CH_2	4-$CF_3C_6H_4$	**3h**	55
10	CH_3CH_2	3-CNC_6H_4	**3i**	65
11	CH_3CH_2	3-$NO_2C_6H_4$	**3j**	64
12	CH_3CH_2	3,4-$Cl_2C_6H_3$	**3k**	53
13	CH_3CH_2	3,5-$Br_2C_6H_3$	**3l**	66
14	CH_3CH_2	4-Me-3-$NO_2C_6H_3$	**3m**	56
15	$C_6H_5CH_2$	4-BrC_6H_4	**3n**	41
16	$C_6H_5CH_2$	4-$NO_2C_6H_4$	**3o**	47
17	4-$BrC_6H_4CH_2$	4-$NO_2C_6H_4$	**3p**	37

[a] Isolated yield.

[b] NR = no reaction.

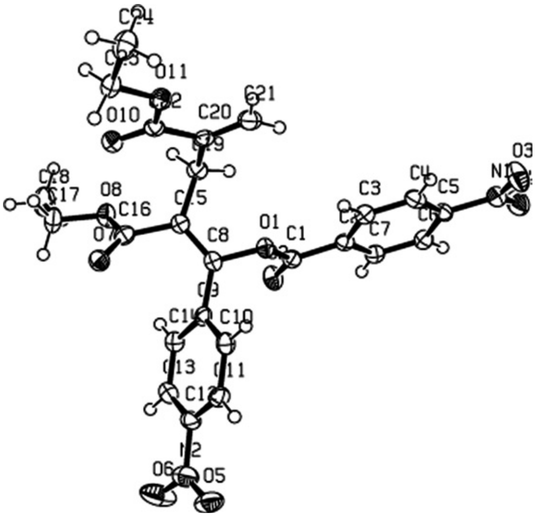
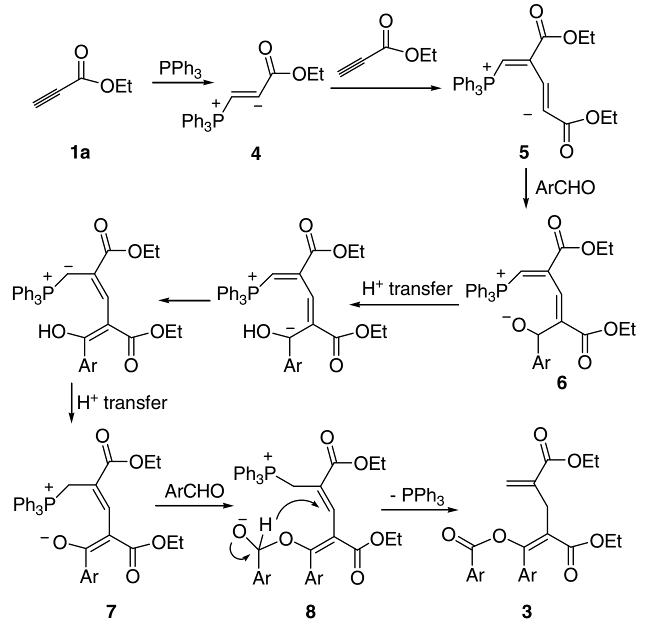


Fig. 1. X-ray crystal structure of **3f**.

Our mechanistic proposal for the reaction is as follows (Scheme 1). The reaction could be triggered by nucleophilic addition of a triphenylphosphine to the electron-deficient multiple bond to produce zwitterionic **4**. The intermediate **4** could undergo a Michael-type addition with another ethyl propiolate to generate **5**, which could add to aromatic aldehyde to form **6**, and subsequent generation of **7** through two consecutive proton-transfer steps. The intermediate **7** could add to secondary aromatic aldehyde to form **8**, which then could eliminate PPh_3 by an intramolecular Michael-type addition of hydride to give product **3**.

In summary, we have described the reaction of aromatic aldehydes with terminal alkynoates catalyzed by PPh_3 to give multifunctional vinylesters in moderate yields. The reaction should be represented by a four-component reaction involving two commercially available starting materials. The presented procedure leads to building blocks and potential intermediates of organic materials. This reaction will be useful in organic synthesis.



Scheme 1. Possible mechanism for the reaction of ethyl propiolate with aromatic aldehyde catalyzed by PPh_3.

Acknowledgments

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9. *General reaction procedure*: To a solution of terminal alkynoates (0.3 mmol) with aromatic aldehydes (0.45 mmol) in dry CH_2Cl_2 (3 mL) was added triphenylphosphine (40 mg, 0.15 mmol), and the resulting mixture was at reflux for 24 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (10:1 petroleum ether/EtOAc) to give the desired product. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm, 7.91 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 6.24 (s, 1H), 5.67 (s, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.46 (s, 2H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm, 167.2, 166.5, 163.2, 153.0, 137.1, 134.1, 132.2, 131.7, 131.4, 130.0, 129.5, 127.6, 126.0, 123.9, 123.0, 61.2, 61.0, 30.7, 14.2, 13.8. IR (neat) ν 1719, 1588 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{22}O_6{}^{79}Br^{81}Br$ (M^+): 565.9763; found: 565.9757. Compound **3f**: mp = 93–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm, 8.33 (d, $J = 8.7$ Hz, 2H), 8.25 (t, $J = 8.7$ Hz, 4H), 7.65 (d, $J = 8.7$ Hz, 2H), 6.26 (s, 1H), 5.69 (s, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.53 (s, 2H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm, 166.3, 166.3, 162.0, 151.3, 148.3, 141.1, 136.7, 133.6, 131.7, 131.4, 129.6, 126.4, 125.2, 124.0, 123.5, 61.6, 61.1, 30.8, 14.2, 13.7. IR (neat) ν 1717, 1601 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{22}N_2O_{10}$ (M^+): 498.1274; found: 498.1275.
10. X-ray data of **3f** has been deposited in CCDC as deposition number CCDC 674219. Empirical formula: $C_{24}H_{22}N_2O_{10}$; formula weight: 498.44; crystal color, habit: colorless, prismatic; crystal dimensions: $0.10 \times 0.04 \times 0.02$ mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: $a = 12.513(3)$ Å, $b = 8.2665(17)$ Å, $c = 23.483(5)$ Å, $\alpha = 90°$, $\beta = 105.11(3)°$, $\gamma = 90°$, $V = 2345.0(8)$ Å^3; space group: $P2(1)/n$; Z value = 4; $D_{calc} = 1.412$ g/cm^3; $F_{000} = 1040$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0499, 0.1203.