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Phosphine-catalyzed [3+2] cycloaddition reactions of substituted 2-alkynoates or 2,3-allenoates with electron-deficient olefins and imines

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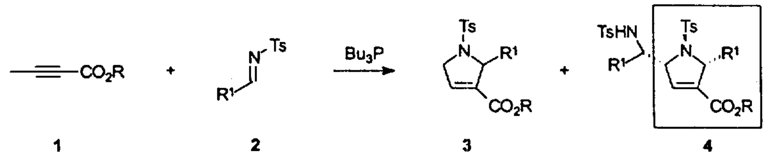
Abstract

In the presence of a catalytic amount of tributylphosphine, substituted 2-alkynoates or 2,3-allenoates reacted with electron-deficient olefins and imines at room temperature to afford the [3+2] cycloaddition products in moderate to good yields.

Key words: Tributylphosphine; [3+2] Cycloaddition; Cyclopentenes; Pyrrolines.

The widespread occurrence of cyclopentane and pyrrolidine rings in a large number of natural products and medicines makes it important to develop new methods for their synthesis [1,2]. Our recent discovery of the [3+2] cycloaddition reaction of an electron-deficient alkene or imine with a new three-carbon synthon, generated *in situ* from the reaction of 2,3-butadienoates or 2-butynoates using an appropriate phosphine as the catalyst [3] provides a convenient new method for the synthesis of cyclopentenes and pyrrolines [3]. However, owing to the fact that substituted 2-alkynoates can isomerize to 2,4-dienoates with catalysis by a phosphine [4,5], no work on the [3+2] cycloaddition reaction of substituted 2-alkynoates was reported [3,6]. Herein, we report preliminary results of tributylphosphine-catalyzed reactions of substituted 2-alkynoates or 2,3-allenoates with electron-deficient olefins and imines as an extension of the use of the three-carbon synthon.

Recently, in our studies on the tributylphosphine-catalyzed reaction of 2-butynoates **1** with *N*-tosylimines **2**, we obtained a small amount of the three-component adduct **4**, which was composed of one molecule of alkyne and two molecules of imine, besides the corresponding [3+2] cycloadduct **3** as the major product (eq 1) [6].



(1)

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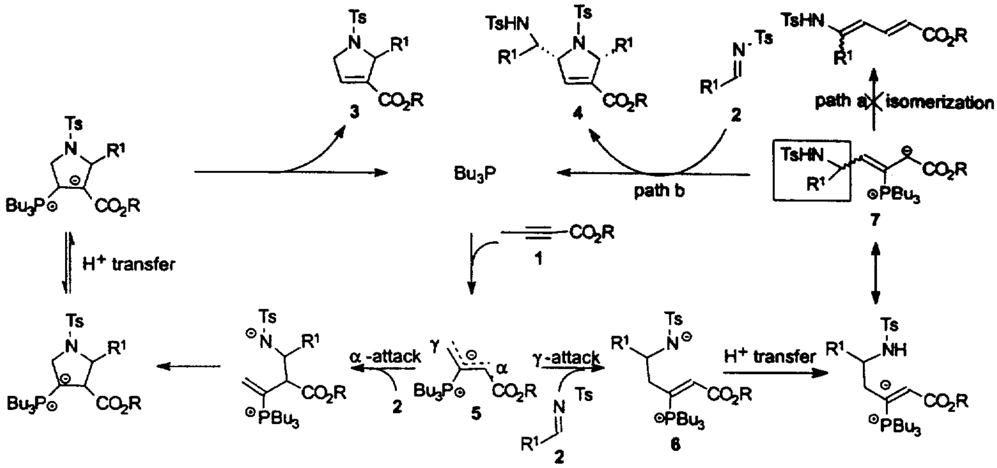
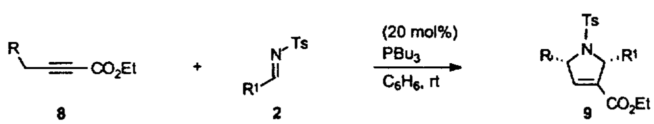
Scheme 1



It is interesting that 4 contains an identical ring skeleton to 3. Obviously, 4 cannot be formed from 3 and 2 by simple substitution on the ring under the reaction conditions. Thus, we proposed a mechanism as outlined in Scheme 1. Surprisingly, under our reaction conditions, the intermediate 7 having a substituent on the γ-carbon atom did not isomerize to dienoates (path a) [4] but further reacted with another molecule of the imine to afford the three-component adduct 4 (path b). It occurred to us that other substituted 2-alkynoates might also react with *N*-tosylimines to afford the normal [3+2] cycloaddition products.

Treatment of ethyl 2-heptynoate (**8a**) with *N*-tosyl benzaldimine (**2a**, R^1 = Ph) in the presence of a catalytic amount of tributylphosphine in dry benzene at room temperature gave the corresponding [3+2] cycloaddition product **9a** in 63% isolated yield (eq 2).[1] Similar conditions were applied to other 2-alkynoates and *N*-tosylimines, and the expected [3+2] cycloadducts were also obtained in moderate to good yields. The stereochemistry of 9 was determined by NMR spectra. The structure of **9a** was further determined by its COSY, NOESY and HMQC spectra. The success of these reactions expands the synthetic utility of the cycloaddition reaction.

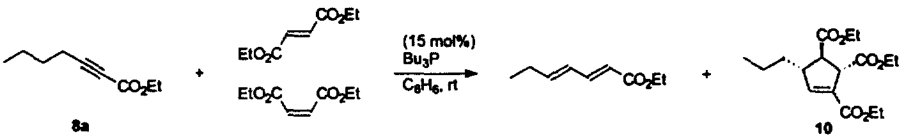

(2)

a) R = *n*-Pr, R^1 = Ph, 63% c) R = *n*-Pr, R^1 = 2-furyl, 33%
b) R = Et, R^1 = piperonyl, 65% d) R = $THPO(CH_2)_7$, R^1 = 1-naphthyl, 75%

The success of the cycloaddition of substituted 2-alkynoates with the electron-deficient imines led us to examine further the reaction of substituted 2-alkynoates with electron-deficient olefins. Stirring a mixture of

(1) All new compounds are fully characterized by spectral and HRMS analyses. Data for **9a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.35-7.24 (m, 5H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.76 (br s, 1H), 5.67 (br s, 1H), 4.65-4.60 (m, 1H), 4.08-3.94 (m, 2H), 2.38 (s, 3H), 2.04-1.98 (m, 1H), 1.76-1.69 (m, 1H), 1.50-1.43 (m, 2H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.25, 143.56, 140.15, 139.75, 135.56, 134.20, 129.63, 128.27, 128.09, 127.92, 127.59, 69.45, 67.41, 60.83, 39.08, 21.54, 19.41, 14.05, 13.92; IR (KBr) 1723, 1656, 1334, 1263, 1157, 1096 cm^{-1}; MS m/z 414 (M^++1, 50.67), 370 (M^+-C_3H_7, 100.00), 298 (M^++1-C_3H_7-CO_2Et, 89.38), 170 (M^+-C_3H_7-OEt-Ts, 32.19); HRMS calcd for $C_{20}H_{20}NO_4S$ (M^+-C_3H_7) 370.1113, found 370.1110.

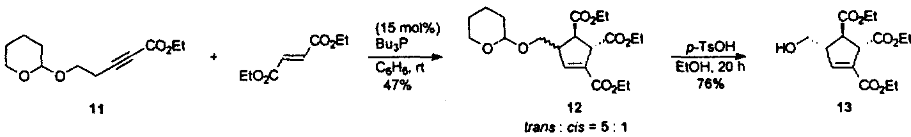
ethyl 2-heptynoate (**8a**) and diethyl fumarate in dry benzene with 15 mol% of tributylphosphine at room temperature gave **10** as the major product along with a small amount of ethyl 2,4-heptadienoate, a phosphine-catalyzed isomerization product of **8a** (eq 3) [2]. Here, both diethyl maleate and diethyl fumarate gave identical



(3)

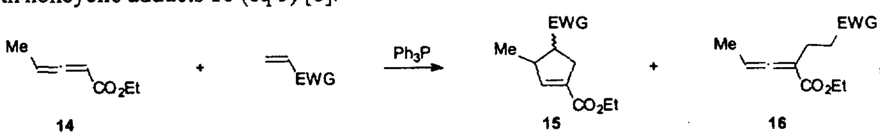
E	11%	73%
Z	16%	67%

results, possibly due to the rapid isomerization of diethyl maleate to diethyl fumarate in the presence of tributylphosphine [3a] or the non-synchronous nature of the mechanism. For the 2-alkynoate **11** possessing a functionalized group on 4-carbon atom, cycloaddition also occurred (eq 4). The relative stereochemistry of **10** and **13** was assigned based on the J value of the ring hydrogen atoms [7].



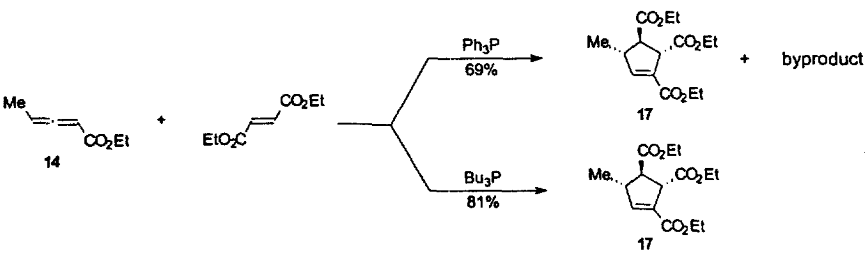
(4)

As the phosphine-catalyzed reaction of the 2-alkynoate is hypothesized to occur through an intermediate of the 2,3-dienoate [4], we further tried the phosphine-catalyzed reaction of substituted 2,3-allenoates with electron-deficient olefins. Stirring a mixture of ethyl 2,3-pentadienoate (**14**) and ethyl acrylate or vinyl phenyl sulfone in dry benzene with 10 mol% of triphenylphosphine at room temperature gave the cycloadducts **15** together with noncyclic adducts **16** (eq 5) [8].



(5)

EWG = CO_2Et	59%	64(*trans* : *cis* = 67 : 33)	:	36
= SO_2Ph	67%	59(*trans* : *cis* = 65 : 35)	:	41



(6)

(2) All new compounds are fully characterized by spectral and HRMS analyses. Data for **10**: oven temperature: 150-160 °C/1 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (t, *J* = 2.1 Hz, 1H), 4.22-4.12 (m, 6H), 4.01 (dt, *J* = 7.0, 2.0 Hz, 1H), 3.11-3.07 (m, 1H), 2.92 (t, *J* = 6.8 Hz, 1H), 1.58-1.50 (m, 2H), 1.48-1.32 (m, 2H), 1.28-1.22 (m, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.40, 173.31, 163.78, 147.21, 132.97, 61.18, 61.12, 60.66, 53.30, 53.02, 49.45, 36.72, 20.63, 14.21, 14.03; IR (KBr) 1736, 1642, 1249, 1186 cm^{-1}; MS m/z 327 (M^++1, 100.00), 281 (M^+-OEt), 253 (M^+-CO_2Et), 206; HRMS calcd for $C_{17}H_{26}O_6$ (M^+) 326.1730, found 326.1742.

For the triphenylphosphine-catalyzed reaction of **14** with diethyl fumarate, besides a small amount of uncharacterized byproduct, compound **17** was also produced (eq 6). The stereochemistry of **17** was determined by NMR spectra similarly [7]. However, when tributylphosphine was used instead of triphenylphosphine as the catalyst, the cycloadduct **17** was obtained in higher yield, implying that the phosphine may also play an important role in this reaction.

In conclusion, we have developed a new synthetic route to polysubstituted cyclopentenes and pyrrolines *via* the tributylphosphine-catalyzed cycloaddition reaction of substituted 2-alkynoates or 2,3-allenoates with electron-deficient olefins and imines. The present work further expands the synthetic scope of the cycloaddition.

Acknowledgement

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