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PPh_3-Catalyzed Domino Reaction: A Facile Method for the Synthesis of Chroman Derivatives

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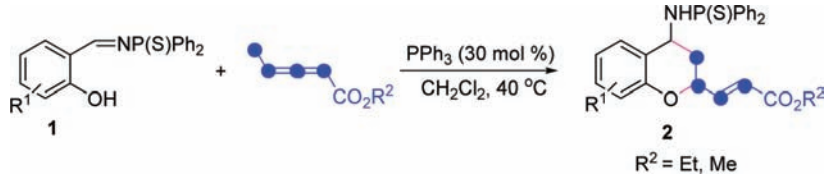
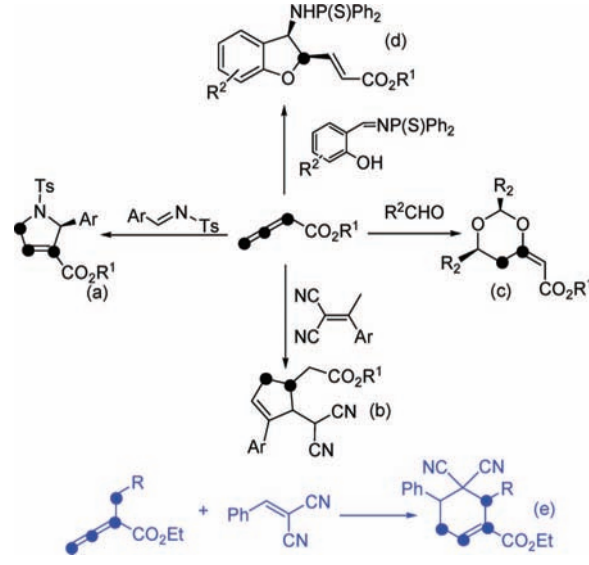
ABSTRACT



A novel domino reaction catalyzed by triphenylphosphine was developed for synthesis of the highly functionalized chroman derivatives. The first example that the γ-CH_3 of allenoate undergoes cyclization to form chroman derivates was reported.

A practical and efficient construction of highly functionalized and diversified molecules from simple starting materials is highly desirable and remains a great challenge. One of the ways to fulfill this goal is the development and use of domino processes, which consist of several bond-forming reactions and which allow the highly efficient synthesis of complex molecules starting from simple substrates.[1] Therefore, considerable efforts have been made to develop catalytic domino transformations by an organocatalyst. On the other hand, Lu's [3 + 2] cycloaddition reaction between allenoates and electron-deficient alkenes or imines which was catalyzed by tertiary phosphines has been widely studied.[2] In the formed five-membered carbocycles and heterocycles, three carbon atoms come from allenoate and two atoms from alkene or imine (Scheme 1, (a)). Recently, Lu and Kwon reported an unexpected phosphine-catalyzed annulation in which allenoate acted as the two-carbon unit (Scheme 1, (b) and (c)).[3]

Scheme 1. Various Pathways for Phosphine-Catalyzed Annulations



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Meanwhile, Kwon and co-workers expanded the scope of phosphine-catalyzed annulation in which allenoate acted as the four-carbon unit to give six-membered heterocycles (Scheme 1, (e)).[4] Very recently, we reported a bifunctional phosphine-catalyzed aza-Morita−Baylis−Hillman domino reaction between salicyl *N*-thiophosphinylimines and allenoates in which allenoate acted as the one-carbon unit (Scheme 1, (d)).[5] Among these phosphine-catalyzed annulations, ethyl 2,3-pentadienoate usually acts as substrate to react with electron-deficient alkenes or imines.[6] However, γ-CH_3 of the allenoate undergoing cyclization to form heterocycles has not been reported. Thus, it is of importance to continue the studies of ethyl 2,3-pentadienoate as synthons in the cycloaddition reaction.

Chroman derivatives are important classes of oxygenated heterocycles that have a broad and interesting range of biological activities.[7] Thus, various synthetic methods for the formation of these compounds have been reported. Among these methods, reactions of salicylaldehydes with various conjugated olefins such as α,β-unsaturated ketones,[8] acrylate derivatives,[9] and nitroalkenes[10] have been the most popular in recent years. DABCO,[9] potassium carbonate,[11] and DBU[12] are bases which are the most frequently used for these reactions. Recently, Shi has reported the reactions of allenic ester and ketones with salicyl *N*-tosylimines to give highly functionalized chromenes catalyzed by DABCO.[13] During our ongoing investigations on the domino reaction,[14] we found that reaction of salicyl *N*-thiophosphinylimine with allenic ester can give the chroman derivatives. Herein, we wish to report a PPh_3-catalyzed domino reaction that can efficiently produce various chroman derivatives.

In view of the intresting results we have already obtained,[5] studies were extended to ethyl 2,3-pentadienoate as substrate. The question arose if the reaction could still occur when ethyl 2,3-butadienoate is replaced with ethyl 2,3-pentadienoate. Thus, the reaction of salicyl *N*-thiophosphinylimines **1a** and ethyl 2,3- pentadienoate was first tested by using (2′-hydroxybiphenyl-2-yl)diethylphosphane (**LBBA**) as catalyst. The reaction gave a product **2a** in 53% yield. To our surprise, according to the NMR spectra, the product was not the product of dihydrobenzofuran which we originally reported since the methyl group disappeared in the product's ^{1}H NMR spectra. The structure and stereochemistry of the product were determined by NMR and HRMS spectrum. ^{1}H NMR and ^{13}C NMR spectral data of **2a** are partly summarized in Table 1. Considering the large coupling constants, the doublet of triplets centered at 1.82 ppm should be assigned to the axial proton of C2,[15] discharged by geminal proton (J = 13.6 Hz) and vicinal axial protons at C_1−H and C_3−H ($J_1 = J_2 = 10.4$ Hz). Thus, the substitutes on C1 and C3 adopt the *cis* configuration. In addition, the two olefinic protons resonate at 6.16 and 6.93 ppm as a doublet of doublets, respectively. The large coupling constant (J = 15.6 Hz) they share indicates that they are *trans* protons. In the ^{13}C NMR spectra of **2a**, the singlet at 36.56 ppm is due to C2, and further analysis of HSQC and DEPT 135° also supports such an assignment. Further confirmation of the product was derived from its HRMS analysis (see the Supporting Information).

Efforts were next directed toward the optimization of reaction conditions. We changed the catalyst to ^{n}Bu_3P, a stronger nucleophilic phosphine, no obvious improvement was made in yield (Table 2, entry 2). Surprisingly, although proven to be an ineffective catalyst for the

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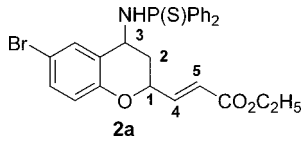
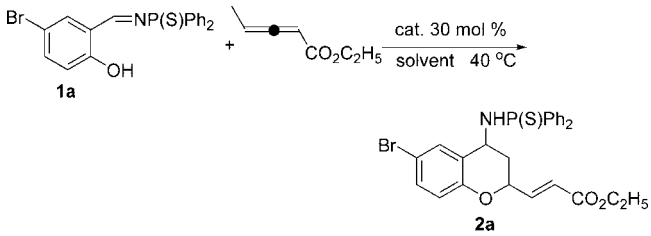
Table 1. ^{1}H and ^{13}C NMR Spectral Data of **2a**



2a

position	^{1}H NMR (400 MHz)	^{13}C NMR (100 MHz)
2	1.82 (td, J = 10.4, 10.4, 13.6 Hz, 1H) 1H)	36.56
2	2.60 (ddd, J = 2.4, 6.0, 13.6 Hz, 1H)	
1, 3	4.72−4.81 (m, 2H)	46.47, 73.70
5	6.14 (dd, J = 1.8, 15.6 Hz, 1H)	118.77
4	6.93 (dd, J = 3.2, 15.6 Hz, 1H)	121.49

Table 2. Screening Catalysts and Solvents for the Domino Reactions[a]



1a **2a**

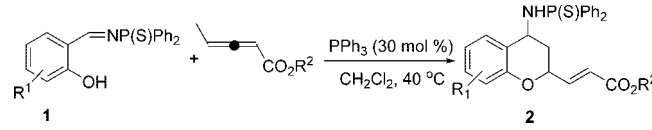
entry	catalyst	solvent	time (h)	yield (%)
1	LBBA	toluene	6	53
2	$^{n}Bu_3P$	toluene	6	46
3	PPh_3	toluene	6	68
4	DMAP	toluene	6	disordered
5	PPh_3	THF	12	0
6	PPh_3	Et_2O	12	0
7	PPh_3	CH_3CN	6	48
8	PPh_3	$^{t}BuOH$	6	56
9	PPh_3	$CHCl_3$	6	83
10	PPh_3	CH_2Cl_2	6	88
11[b]	PPh_3	CH_2Cl_2	12	trace
12[c]	PPh_3	CH_2Cl_2	4	80

[a] The reaction was carried out on a 0.5 mmol scale in solvent (2 mL). The ratio of the **1a**/allene is 1:3.0. [b] 20 mol % catalyst was used. [c] 50 mol % catalyst was used.

synthesis of *cis*-2,3-dihydrobenzofurans, PPh_3 serves as an effective one for this reaction and affords **2a** in good yield (Table 2, entry 3). When DMAP was used as the catalyst, however, the reaction was too complex to analyze (Table 2, entry 4). Therefore, we selected PPh_3 as the catalyst to optimize the reaction conditions further. No product could be isolated when THF (Table 2, entry 5) or Et_2O (Table 2, entry 6) was used as solvent. When CH_3CN (Table 2, entry 7) and $^{t}BuOH$ (Table 2, entry 8) were used, no improvement was made in yield. With $CHCl_3$ (Table 2, entry 9) and CH_2Cl_2 (Table 2, entry 10) as solvent, the reaction proceeded smoothly to produce **2a** in 83% and 88% yield, repectively. Therefore, CH_2Cl_2 is the best choice of solvent for this reaction. In addition, the catalyst amount was also examined as shown in Table 2. Using 20 mol % of PPh_3 as catalyst, merely trace amounts of **2a** were obtained (entry 11). When 50 mol % of PPh_3 was used as catalyst, the reaction rate was fast, while the yield of **2a** was slightly low (entry 12), due to the partial polymerization of allenoate.

With the optimal reaction conditions in hand, we next explored the scope of this domino reaction using ethyl 2,3-pentadienoate and a variety of salicyl *N*-thiophosphinylimines as substrates (Table 3). As shown in Table 3,

Table 3. Scope of the Domino Reactions in the Presence of PPh_3[a]



1 **2**

entry	R^1	R^2	time (h)	yield (%)	cis/trans
1	5-Br	C_2H_5	6	88 (**2a**)	13:1
2	5-CH_3	C_2H_5	4	90 (**2b**)	2:1
3[b]	5-CH_3O	C_2H_5	2	92 (**2c**)	3:1
4	5-Bu	C_2H_5	4	89 (**2d**)	>20:1
5	3-CH_3	C_2H_5	4	86 (**2e**)	>20:1
6[b]	3-Cl	C_2H_5	6	83 (**2f**)	>20:1
7	5-Cl	C_2H_5	6	86 (**2g**)	>20:1
8	H	C_2H_5	4	91 (**2h**)	11:1
9	5-Br	CH_3	6	82 (**2i**)	10:1
10	5-Cl	CH_3	6	85 (**2j**)	3:1
11	3-Cl	CH_3	6	78 (**2k**)	>20:1
12[b]	5-CH_3	CH_3	4	86 (**2l**)	2:1
13[b]	H	CH_3	4	83 (**2m**)	3:1
14	5-NO_2	C_2H_5	6	0 (**2n**)	

[a] The reaction was carried out in on a 0.5 mmol scale in solvent (2 mL). The ratio of the **1a**/allene is 1:3.0. [b] Cis and trans isomers were determined by ^{31}P NMR spectroscopic analysis.

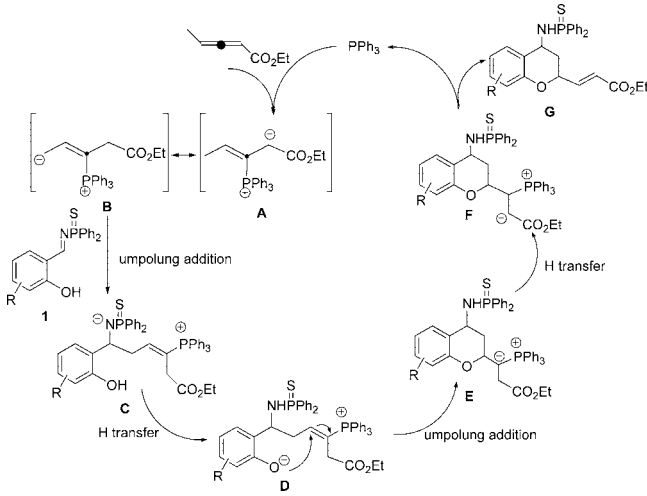
the corresponding adducts **2** were obtained in good to excellent yields. For imines with electron-donating groups on the phenyl rings (entries 2−5, 8, 12, and 13), the reaction was completed in a short time. In contrast, for imines with electron-withdrawing groups on the phenyl rings (entries 1, 6, 7, and 9−11), a prolonged reaction time was needed. The reason is that the electron-withdrawing groups decrease the nucleophilicity of the oxygen atom. For the imine bearing a strong electron-withdrawing group, such as the nitro group (entry 14), no reaction occurred. Similarly, methyl 2,3-pentadienoate can also react with various salicyl *N*-thiophosphinylimines under identical conditions to give the corresponding chroman derivatives. In addition, the chroman derivatives' cis/trans ratios were different. For the imine-bearing electron-withdrawing groups, the cis products predomi-

(15) Franklin, N. C. *Angew. Chem., Int. Ed.* **1965**, *4*, 774.

nated, with the exception of **2j**. For the imine-bearing electron-donating groups, however, the ratios of cis/trans were low (except **2d**, **2e**); the reason is not clear so far.

The detailed mechanism of these domino reactions has not been clarified. According to these experimental results and some related literature,[2c,s,4d,16] a plausible mechanism can be proposed (Scheme 2). The PPh_3 acts as a nucleophilic trigger and attacks the β carbon of the allenes to produce the intermediate **A**, which will transform to intermediate **B**

Scheme 2. Possible Mechanism for the Formation of **2**



via 1,4-proton transfer. The allylic carbanion **B** subsequently undergoes an umpolung addition with **1** to give the intermediate **C**, which will form intermediate **D** via proton transfer from the OH to the N anion. Finally, the intermediate **D** undergoes another umpolung addition of the oxygen anion to the β carbon of **D** to furnish product and regenerate PPh_3.

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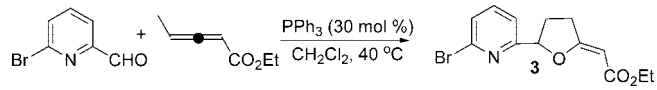
To the best of our knowledge, this is the first example where the γ-CH_3 of the allene was involved in the cyclization.

According to the proposed reaction mechanism, aldehyde should also undergo a similar reaction as salicyl *N*-thiophosphinylimine. To examine the feasibility, 6-bromopicolinaldehyde was subjected to the reaction with ethyl penta-2,3-dienodate under the standard conditions (Scheme 3). To our delight, the reaction could be completed within 10 h (Scheme 3) with substituted tetrahydrofuran obtained in 72% yield.

Scheme 3. Reaction of 6-Bromopicolinaldehyde with Ethyl Penta-2,3-dienodate



The structure and stereochemistry of the compound were determined by NMR and HRMS (see the Supporting Information).

In conclusion, we have developed a novel method to synthesize chroman derivatives through a PPh_3-catalyzed domino reaction sequence. More importantly, we discovered the first example that the γ-CH_3 of the allene undergoes the cyclization to form the chroman derivatives. Further investigation of the scope of the domino reaction and its application to the synthesis of biologically interesting molecules is underway, and the results will be reported in due course.

Acknowledgment. We thank the National Natural Science Foundation of China (20772061) and the Natural Science Foundation of Tianjin (05YFJMJC00600) for financial support.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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