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Nucleophilic phosphine-catalyzed [3+2] cycloaddition of allenes with *N*-(thio)phosphoryl imines and acidic methanolysis of adducts *N*-(thio)phosphoryl 3-pyrrolines: a facile synthesis of free amine 3-pyrrolines

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Dedicated to Professor Chuchi Tang on the occasion of his 70th birthday

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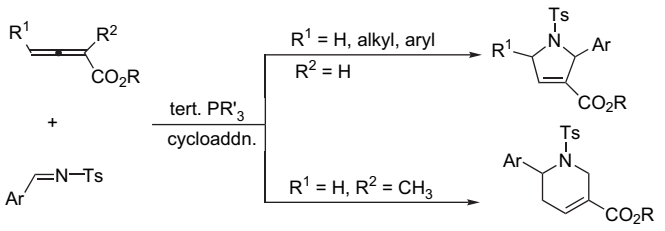
ABSTRACT

In this report, the dipolarophile imines with easily removable activating group *O*,*O*-diethyl(thio)-phosphoryl have been investigated in the nucleophilic phosphine-catalyzed [3+2] cycloaddition reaction of electron-deficient allenes. Under the catalysis of a tertiary phosphine, *N*-(thio)phosphorylimines readily undergo the [3+2] cycloaddition reaction with ethyl 2,3-butadienoate or ethyl 2,3-pentadienoate, affording the corresponding *N*-(thio)phosphoryl 3-pyrrolines in moderate to high yields with good diastereoselectivity. Removal of the (thio)phosphoryl group from the adducts has been successfully achieved via the acidic methanolysis of the P–N bond, giving the free amine 3-pyrrolines in fair to good yields without severe aromatization. Thus, a facile synthesis of *N*-unsubstituted 3-pyrrolines is established from the phosphine-catalyzed [3+2] cycloaddition reaction of allenes with imines.

1. Introduction

In recent years, the nucleophilic catalysis by tertiary phosphines has attracted much attention within the chemistry community. Many new phosphine-catalyzed reactions with highly synthetic potentials have been discovered.[1] The nucleophilic phosphine-catalyzed cycloaddition reactions of allenes with imines are the typical and important examples in this realm, which conveniently construct five- or six-membered *N*-heterocycles (Scheme 1). Due to the importance of such *N*-heterocyclic substructures in the biologically active substances, particularly pharmaceuticals,[2] those reactions have been extensively studied with regard to their synthetic potentials.[3] In those reactions, aryl substituted *N*-tosyl imines are most often used for their better reactivity, giving *N*-tosyl heterocycle products generally in high yields. Since tosyl group is not easy to be removed under mild conditions, in most cases products have been reported as *N*-tosylated ones.[3] Particularly, direct deprotection of the sulfonyl group from a fragile [3+2] cycloaddition adduct 3-pyrroline usually results in an aromatization of the pyrroline heterocycle, delivering the corresponding pyrrole product even if much easier-removed sulfonyl groups like nosyl and 2-trimethylsilylethanesulfonyl are used.[3b,c] This situation intrigued us exploring some effective and easy-deprotected activating groups for the substrate imine so that the synthetic values of the phosphine-catalyzed cycloaddition reactions of allenes with imines could be extended to those *N*-unsubstituted heterocycles.



Scheme 1. *N*-Heterocycles from tertiary phosphine-catalyzed cycloadditions of allenes with imines.

As part of our ongoing research efforts on nucleophilic phosphine-catalyzed carbon–carbon bond forming reactions,[4] we

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herein report the results on the [3+2] cycloaddition reaction of allenes with *N*-(thio)phosphoryl imines. The cycloaddition reaction, catalyzed by either Ph_3P or air-stable and highly nucleophilic PTA (1,3,5-triaza-7-phosphaadmantane), readily afforded the [3+2] cycloaddition products *N*-(thio)phosphoryl 3-pyrrolines **1** in fair to good yields. Also, the *N*-(thio)phosphoryl 3-pyrrolines **1** were successfully deprotected through a HCl-mediated acidic methanolysis, affording the corresponding free amine 3-pyrrolines **2** in moderate isolated yields. Thus, a facile synthesis for free amine 3-pyrrolines is established via the phosphine-catalyzed [3+2] cycloaddition reaction of allenes with *N*-(thio)phosphoryl imines.

2. Results and discussion

Most recently, *O*,*O*-diethylthiophosphoryl has been successfully used as an activating group for the imine substrate in the phosphine-catalyzed aza-Morita–Baylis–Hillman reaction in our laboratories.[5] Due to its better stability on storage than its oxo-analogue *N*-phosphoryl imine, *N*-thiophosphoryl imine was first chosen as the substrate in the phosphine-promoted [3+2] cycloaddition with activated allenes, although *N*-phosphoryl analogue has a similar reactivity in this reaction (vide infra).

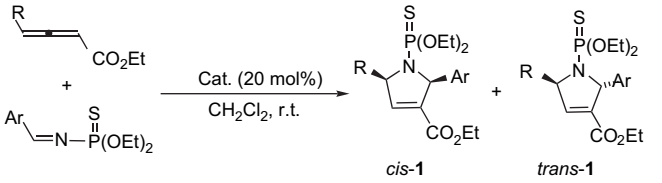
To date, nucleophilic phosphines are only found to be effective catalysts for the [3+2] cycloaddition of electron-deficient allenes with imines; nitrogen nucleophiles are ineffective in this reaction.[1a,b] The efficiency of the cycloaddition highly depends on the nucleophilicity of the employed catalyst phosphine and the reactivity of the allene; for a more reactive allene, e.g., 2,3-butadienoate, a relatively weaker nucleophile Ph_3P can readily mediate its cycloaddition with various imines, giving the adducts 3-pyrrolines in high yields;[3b] for a less reactive γ-substituted allenoate, a stronger nucleophilic catalyst like tributylphosphine is then required to secure the efficiency of its cycloaddition with imines.[3c]

In this study, two activated allenes, e.g., ethyl 2,3-butadienoate and ethyl 2,3-pentadienoate (γ-methyl allenoate), were selected to investigate their annulation with *N*-thiophosphoryl imines [Eqs. 1 and 2]. The initial survey of optimal reaction conditions was conducted on the [3+2] cycloadditions of *N*-(*O*,*O*-diethyl)thiophosphoryl phenylimine with both the allenes. It was found that methylene chloride delivered better product yields than other solvents (THF, ether, acetonitrile, benzene, toluene, and DMSO). The tertiary phosphine catalyst loading (20 mol %, compared to the substrate imine) was chosen because reduced loadings (5 mol % or 10 mol %) resulted in either substantially prolonged reaction time or much lower product yield.

Screening of the phosphine catalysts revealed that the nucleophilicity of the catalyst significantly affected its efficiency in the [3+2] cycloaddition of the allenes with *N*-thiophosphoryl imine. For the reactive ethyl 2,3-butadienoate, Ph_3P (20 mol %) delivered better results in the reaction of this allene with *N*-thiophosphoryl imine; in contrast, more nucleophilic phosphines such as Bu_3P, PTA, and $PhPMe_2$ caused severe side reactions, giving the normal cycloaddition product in lower yields. Thus, Ph_3P was chosen as the preferred catalyst for the allene ethyl 2,3-butadienoate. Under the catalysis of Ph_3P (20 mol %), various aromatic *N*-thiophosphoryl imines readily afforded the normal [3+2] cycloaddition adducts **1** in fair to good isolated yields (Table 1, entries 1–6). The substrate imines, bearing either electron-donating or electron-withdrawing groups in the benzene ring, both worked well in the cycloaddition.

For the relatively less reactive allene ethyl 2,3-pentadienoate, a more nucleophilic phosphine catalyst was expectedly needed in its cycloaddition with *N*-thiophosphoryl imine. Five selected

Table 1
Phosphine-catalyzed [3+2] cycloaddition reaction of allenes with *N*-thiophosphoryl imines[a]



cis-**1** *trans*-**1**

Entry	Ar	R	Reaction time (h)	Yield of **1**[b] (%)	Ratio of *cis*-**1**/*trans*-**1**[c]
1	C_6H_5	H	20	**1a**, 49	
2	*p*-$CH_3C_6H_4$	H	24	**1b**, 60	
3	*p*-$CH_3OC_6H_4$	H	40	**1c**, 62	
4	*p*-ClC_6H_4	H	7	**1d**, 68	
5	*o*-ClC_6H_4	H	8	**1e**, 41	
6	*p*-$NO_2C_6H_4$	H	6	**1f**, 76	
7	C_6H_5	CH_3	48	**1g**, 77	25:1
8	*p*-$CH_3C_6H_4$	CH_3	48	**1h**, 53	46:1
9	*p*-ClC_6H_4	CH_3	48	**1i**, 76	11:1
10	*o*-ClC_6H_4	CH_3	48	**1j**, 70	7:1
11	*p*-$NO_2C_6H_4$	CH_3	48	**1k**, 99	6:1

[a] For entries 1–6, the catalyst is PPh_3; for entries 7–11, PTA is used as the catalyst.
[b] Isolated yield based on the substrate imine.
[c] Determined by ^{31}P NMR.

phosphines (Ph_3P, Ph_2PMe, $PhPMe_2$, PTA, and Bu_3P) were screened in the model reaction with *N*-thiophosphoryl phenylimine under the same conditions (see Section 4, general procedure for ethyl 2,3-pentadienoate), and the result is shown as follows: isolated yield of the normal adduct/ratio of cis- and trans-isomers/catalyst: 0/Ph_3P; 57%/18:1/Ph_2PMe; 42%/11:1/$PhPMe_2$; 77%/25:1/PTA; 27%/5:1/PBu_3. This result clearly showed that the catalyst PTA was the best in terms of the product yield and diastereoselectivity. However, the catalysis of PBu_3 with the strongest nucleophilicity only produced the normal adduct in a low yield (27%) due to the complexity of the reaction. In our previous reports,[4,5] the air-stable phosphine PTA was found to be a convenient and versatile organocatalyst, with its nucleophilicity comparable to those of pure trialkylphosphines, in the phosphine-catalyzed Morita–Baylis–Hillman reaction and the [3+2] cycloaddition reaction of allenes with *N*-tosyl imines. Thus, in this study PTA was preferably chosen as a stronger nucleophilic phosphine catalyst. The experimental results (Table 1, entries 7–11) revealed that the annulation of ethyl 2,3-pentadienoate with *N*-thiophosphoryl imines smoothly proceeded under the catalysis

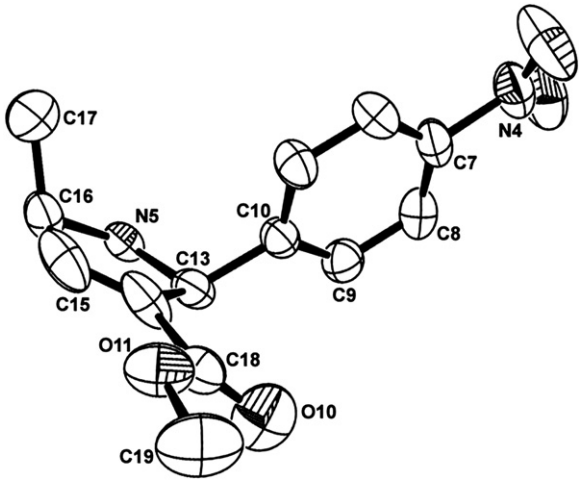


Figure 1. The crystal structure of **2k** picrate (for clarity, the picrate anion is omitted).