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Phosphine-catalyzed [3 + 2] and [3 + 3] Annulations of Azomethine Imines with Ethyl 2-Butynoate

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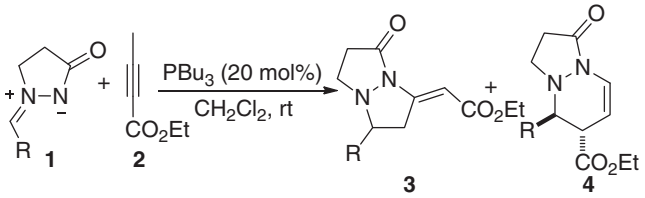
The phosphine-catalyzed [3 + 2] and [3 + 3] annulation reactions of azomethine imines and ethyl 2-butynoate were developed, providing 1,2-dinitrogen-containing heterocycles tetrahydropyrazolopyrazolones and tetrahydropyrazolopyridazinones in moderate to good yields.

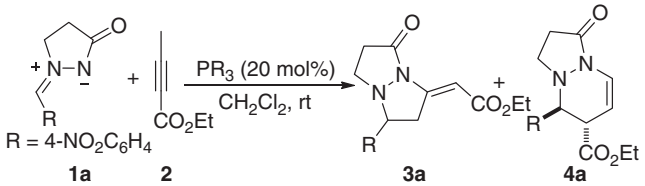
Over the last twenty years, nucleophilic phosphine catalysis has been successfully developed as one of the most powerful tools for convergent synthesis of a broad range of carbo- and heterocycles from simple starting materials.[1] Under the nucleophilic phosphine catalysis conditions, activated allenes have often been used as versatile synthons and exhibited diverse reactivity toward a variety of electrophilic partners including aldehydes, activated alkenes, imines, or aziridines, furnishing all kinds of formal cycloaddition reactions.[1] Most recently, we reported the first phosphine-catalyzed [3 + 2], [3 + 3], [4 + 3], and [3 + 2 + 3] annulation reactions of allenoates with azomethine imines, providing generally applicable routes toward dinitrogen-fused heterocycles, such as tetrahydropyrazolo-pyrazolone, -pyridazinone, -diazepinone, and -diazocinone,[2] which are key units in or building blocks of many pharmaceuticals, agrochemicals, biologically active compounds, and other useful chemicals.[3] Using phosphine as the catalyst, ethyl 2,3-butadienoate, served as a two- or three-carbon component to undergo the [3 + 2] or [3 + 3] annulation reactions with azomethine imine (1-(*p*-nitrobenzylidene)-3-oxopyrazolidin-1-ium-2-ide), giving tetrahydropyrazolo-pyrazolone and -pyridazinone.[2] It is known that ethyl 2-butynoate could undergo the same annulation processes as ethyl 2,3-butadienoate under the phosphine catalysis conditions.[4] As ethyl 2-butynoate is commercially available and very cheap, and tetrahydropyrazolo-pyrazolone and -pyridazinone are important biologically active compounds,[3] we attempted to investigating the cycloaddition reaction of various azomethine imines with ethyl 2-butynoate. Herein, we described the [3 + 2] and [3 + 3] cycloaddition of azomethine imines with ethyl 2-butynoate to furnish functionalized 1,2-dinitrogen-fused heterocycles (Scheme 1).

Initially, the annulation reactions of ethyl 2-butynoate (**2**) with 1-(*p*-nitrobenzylidene)-3-oxopyrazolidin-1-ium-2-ide (**1a**) were performed to screen the appropriate reaction conditions (Table 1). The azomethine imines have been extensively employed as efficient 1,3-dipoles in a variety of metal-catalyzed or organocatalytic cycloadditions[5] and can easily be prepared from the reaction of pyrazolidin-3-one with aldehydes.[2,5b–5d] In the presence of 20 mol % PBu_3, azomethine imine **1a** was treated with ethyl 2-butynoate (**2**) in dichloromethane at room temperature for 12 h to provide the tetrahydropyrazolopyrazolone **3a** as a single (*E*)-isomer and the tetrahydropyrazolopyridazinone **4a** as a single *trans* diastereoisomer in 49 and 34% yields, respectively (Table 1, Entry 1).[6] Considering that the efficiency of nucleophilic phosphine catalysis was often influenced by the nature of the tertiary-phosphine catalyst, several phosphines with different nucleophilicity had been screened for improving the yield and chemoselectivity (Entries 2–5). When phosphines PMe_3, $MePPh_2$, and Me_2PPh were utilized as catalysts, the [3 + 2] cycloaddition product **3a** was obtained as the major product in 34, 30, and 65% yield, respectively, and the [3 + 3] product **4a** was produced with 6, 3, and 14% yield, respectively (Entries 2, 3, and 4). Dimethylphenylphosphine achieved the best overall reaction efficiency, providing 65% yield of **3a** and 14% yield of **4a** (Entry 4). Methyldiphenylphosphine demonstrated the best chemoselectivity toward [3 + 2] product, affording 30% yield of **3a** and 3% yield of **4a** (Entry 3), however, its overall yield (33%) was somewhat bad. Hexamethylphosphorous triamide (HMPT) was quite sluggish, producing no product **3a**, and trace amount of product **4a** (Entry 5). In this



Scheme 1. The [3 + 2] and [3 + 3] annulation of azomethine imine **1** with ethyl 2-butynoate (**2**).

Table 1. Phosphine-catalyzed annulations of the azomethine imine **1a** with ethyl 2-butynoate (**2**)[a]



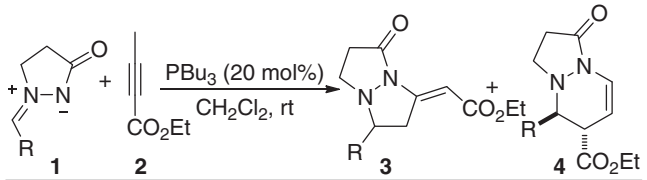
Entry	PR_3	Time/h	**3a** yield /%[b]	**4a** yield /%[b]
1	PBu_3	12	49	34
2	PMe_3	24	34	6
3	$MePPh_2$	72	30	3
4	Me_2PPh	24	65	14
5	HMPT	24	—	Trace

[a]1.2 equiv of ethyl 2-butynoate was used. [b]Isolated yield.

research, both tetrahydropyrazolopyrazolone **3** and the tetrahydropyrazolopyridazinone **4** were desired to be obtained in reasonable yield, therefore, tributylphosphine was chosen as the catalyst.

Using 20 mol % of tributylphosphine as the catalyst, the [3 + 2] and [3 + 3] annulation reactions of ethyl 2-butynoate (**2**) with a range of azomethine imines **1** were carried out in dichloromethane at room temperature within a given time period (Table 2). A variety of aromatic azomethine imines **1** underwent the [3 + 2] and [3 + 3] cycloaddition, providing the anticipated tetrahydropyrazolopyrazolone and tetrahydropyrazolopyridazinone products in moderate to good yields (Entries 1–11).[7]

Table 2. PBu_3-catalyzed [3 + 2] and [3 + 3] cycloadditions of azomethine imines **1** with ethyl 2-butynoate (**2**)[a]



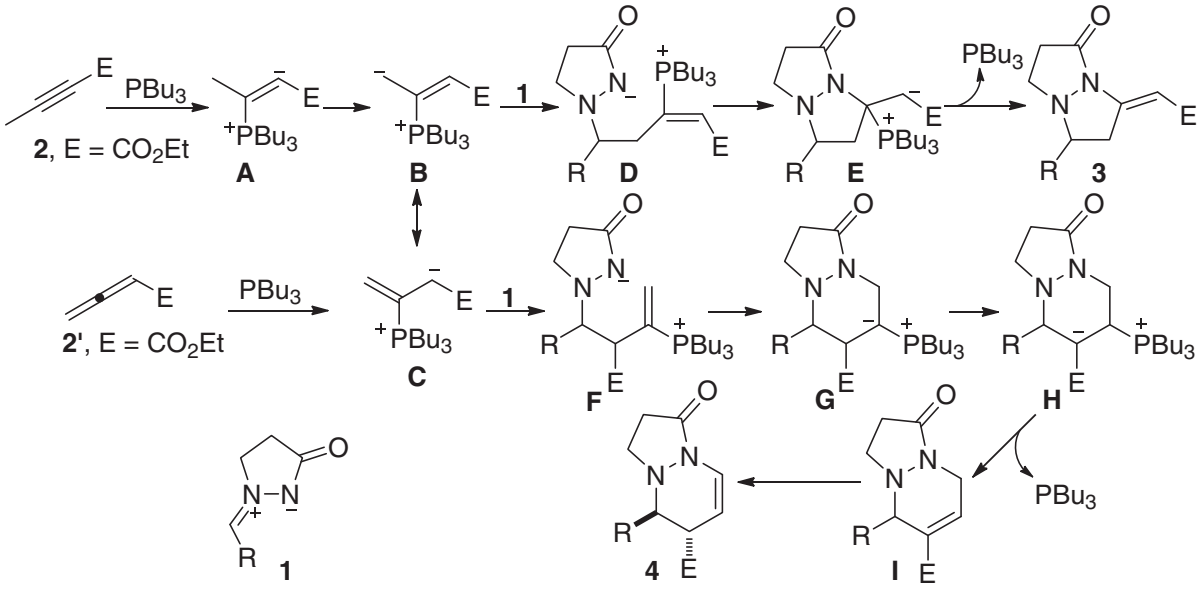
Entry	R	Time /h	Product	Yield /%[b]	**3**:**4**
1	C_6H_5 (**1b**)	36	**3b** + **4b**	44	82:18
2	4-MeC_6H_4 (**1c**)	72	**3c** + **4c**	60	90:10
3	4-*i*-PrC_6H_4 (**1d**)	72	**3d** + **4d**	51	97:3
4	4-FC_6H_4 (**1e**)	72	**3e** + **4e**	54	95:5
5	4-BrC_6H_4 (**1f**)	72	**3f** + **4f**	64	82:18
6	4-CNC_6H_4 (**1g**)	24	**3g** + **4g**	76	51:49
7	4-$CF_3C_6H_4$ (**1h**)	72	**3h** + **4h**	44	86:24
8	2-$NO_2C_6H_4$ (**1i**)	72	**3i** + **4i**	78	68:32
9	3-$NO_2C_6H_4$ (**1j**)	72	**3j** + **4j**	52	57:43
10	1-naphthyl (**1k**)	72	**3k** + **4k**	60	96:4
11	2-naphthyl (**1l**)	72	**3l** + **4l**	61	90:10
12	cyclohexyl (**1m**)	72	**3m**	27	100:0

[a]1.2 equiv of ethyl 2-butynoate was used. [b]Isolated yield.

A wide range of aryl groups with electron-donating and -withdrawing substituents on the benzene ring could be tolerated in the process. In general, the azomethine imines bearing strong electron-withdrawing groups such as nitro and cyano on the ortho- or para-position of the benzene ring afforded much higher yields of the corresponding cyclization products than the imines with phenyl and bearing electron-donating and weak electron-withdrawing groups on benzene did (Entry 1 in Table 1, Entries 6 and 8 in Table 2 versus Entries 1–5 in Table 2), but the chemoselectivities of the former toward [3 + 2] product were much lower than that of the latter (Entry 1 in Table 1, Entries 6 and 8 in Table 2 versus Entries 1–5 in Table 2). Interestingly, the azomethine imines bearing nitro on the meta-position were not very active to give a moderate yield of the cycloadduct (Entry 9). The phenomenon could be attributed to the weak electron-withdrawing effect of a nitro group at the meta-position of a benzene ring. The azomethine imines bearing 1-naphthyl (Entry 10) and 2-naphthyl (Entry 11) also underwent the cyclization reaction with 2-butynoate **2**, affording the corresponding pyrazolidinone derivatives in sound yields. Alkylimine could also carry out the annulation with ethyl 2-butynoate (**2**) to give only [3 + 2] product, albeit in low yield (Entry 12). In all reactions, the [3 + 2] annulation products were always obtained as the major product in a single (*E*)-isomer (Entries 1–12), and the [3 + 3] cycloadduct were obtained as the minor product in a single *trans* diastereoisomer.

The reaction of ethyl 2-pentynoate with azomethine imine **1a** has also been checked, unfortunately, no cycloaddition product could be isolated after the reaction was carried out in dichloromethane at room temperature for 72 h.

According to the reported mechanistic studies on nucleophilic phosphine-catalyzed reactions,[2] a plausible mechanism for the [3 + 2] and [3 + 3] cycloaddition of azomethine imines **1** with ethyl 2-butynoate (**2**) is proposed (Scheme 2). The addition of the Lewis-basic phosphine to the electrophilic β-carbon of ethyl 2-butynoate (**2**), results in the formation of a zwitterionic intermediate **A**. The conversion of vinyl anion **A** to β-phospho-



Scheme 2. Proposed mechanism for the [3 + 2] and [3 + 3] annulation of azomethine imines with ethyl 2-butynoate.

nium enoate **B** ↔ **C** should be thermodynamically favorable. In the case of using ethyl 2,3-butadienoate (**2′**), β-phosphonium enoate **B** and **C** can directly be generated by the addition of phosphine to the β-carbon of **2′**.[2] The γ-carbon anion of β-phosphonium enoate **B** attacks azomethine imine **1** leading to the formation of the amide **D**. Intramolecular conjugate addition of amide to the β-phosphonium enoate motif of intermediate **D** accomplishes the [3 + 2] cyclization to give β-phosphonium ester **E**, which undergoes a facile β-elimination to regenerate the catalyst and form the final tetrahydropyrazolopyrazolone products **3**, which are (*E*)-trisubstituted exocyclic alkylidenes. The distribution of the geometric isomers of [3 + 2] product would be thermodynamically controlled by the action of the phosphine.[2] Thus, the equilibrium between the intermediates **E** and the products **3** can support the exclusive formation of the more stable (*E*)-isomer **3**. Following another competing pathway, the α-carbon anion of zwitterion **C** attacks azomethine imine **1** to give the phosphonium amide **F**, which carries out the 6-*endo* cyclization to deliver the ylide **G**. The β-phosphonium ester **H** formed by proton transfer from **G** expels phosphine and provides the tetrahydropyrazolopyridazinone **I**, which isomerizes into [3 + 3] annulation product **4**.

In summary, we have developed phosphine-catalyzed [3 + 2] and [3 + 3] cycloaddition reactions of azomethine imines with ethyl 2-butynoate. Reactions are operationally simple and proceed smoothly under very mild reaction conditions, providing a broad range of tetrahydropyrazolo-pyrazolones and -pyridazinones in moderate to good yield.

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6 The structures of **3a** and **4a** have been established by NMR spectroscopy and X-ray crystallography. For the structures, also see ref. 2. Crystallographic data for **3a** and **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 804942 and 804945. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; fax: +44 1223 336033.

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