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PPh_3-Mediated [4 + 2]- and [4 + 1]-Annulations of Maleimides with Azoalkenes: Access to Fused Tetrahydropyridazine/Pyrrolidinedione and Spiro-dihydropyrazole/Pyrrolidinedione Derivatives

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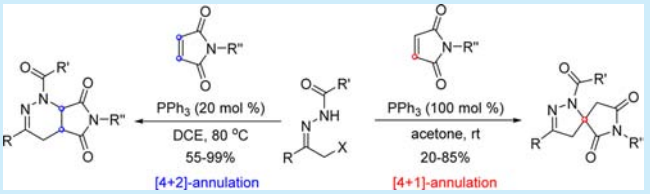
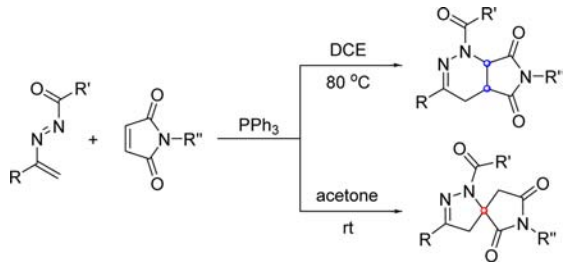
Supporting Information

ABSTRACT: Unprecedented PPh_3-mediated [4 + 2]- and [4 + 1]-annulation of maleimides with in situ formed azoalkenes have been successfully developed, affording fused tetrahydropyridazine/pyrrolidinedione and spiro-dihydropyrazole/pyrrolidinedione derivatives in good yields under mild reaction conditions. Maleimides serve as C2 synthons in the [4 + 2]-annulation using 1,2-dichloroethane as the solvent in the presence of 20 mol % of PPh_3. With a stoichiometric amount of PPh_3 in acetone, maleimides serve as C1 synthons, and the in situ formed phosphorus ylide is the key intermediate to realize this [4 + 1]-annulation.



Functionalized five- and six-membered carbo- and heterocycles containing fused or spiro frameworks are often found in a series of natural products and pharmacologically active molecules.[1] Thus, exploiting a valid strategy to construct diversified five- and six-membered carbo- and heterocycles is essential for organic synthesis. Phosphine-mediated/-catalyzed annulation reactions have been developed as an efficient method for preparing a variety of carbo- and heterocycles from readily available starting materials.[2] Recent years have witnessed the rapid growth of the phosphine catalysis,[3] which can account for a series of advantages, such as metal-free, atom-economy, and excellent regio- and stereoselectivity controls. These advantages make this methodology valuable from economic and environmental points of view. Phosphine-catalyzed [3 + 2]- and [4 + 2]-annulation reactions have been successfully exploited by Lu,[4] Kwon,[5] He,[6] and other groups[7] to construct functionalized carbo- and heterocycles. Most recently, Tong[8] and others[9] reported phosphine-catalyzed [4 + 1]-annulations to generate five-membered carbo- and heterocycles. Compared to the well-established phosphine-catalyzed [3 + 2]- and [4 + 2]-annulations, [4 + 1]-annulation as a valuable approach has been explored to a much lesser extent and therefore is still in highly demand. On the other hand, maleimides, as one of the privileged electron-deficient olefins, are usually used as C2 synthons in phosphine-mediated/-catalyzed [3 + 2]-annulations[10] to access various functionalized fused-pyrrolidinedione skeletons. However, maleimides are rarely employed as C1 synthons to participate in phosphine-mediated/catalyzed annulations.[11] In 2014, Shi and co-workers disclosed a novel phosphine-catalyzed [4 + 1]-annulation of maleimides with 4,4-dicyano-2-methylenebut-3-enoates to afford spirocycle products.[11a] Menawhile, He and co-workers reported an efficient phosphine-catalyzed [4 + 1]-annulation of maleimides with electron-deficient 1,3-dienes.[11b] Inspired by the above-mentioned investigations and our interest in the azoalkene chemistry,[12,13] herein, we communicated unprecedented PPh_3-mediated [4 + 2]- and [4 + 1]-annulations of maleimides with in situ formed azoalkenes, in which maleimides serve as C1 and C2 synthons, respectively (Scheme 1). In the latter process with the stoichiometric amount of PPh_3 and acetone as solvent, the in situ formed phosphorus ylide was the key intermediate to realize the [4 + 1]-annulations. The obtained fused- and spiro-pyrrolidinedione derivatives are of great value in organic and medicinal chemistry, considering that the

Scheme 1. PPh_3-Mediated [4 + 1]- and [4 + 2]-Annulation of Maleimide with Azoalkene for the Construction of Fused- and Spiro-heterocycles



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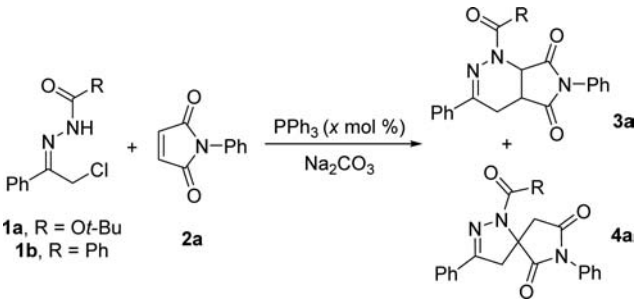
dihydropyrazole[14] and tetrahydropyridazine[15] moieties are widely existed in a plethora of pharmaceuticals and biologically active natural products. Both of the annulations share features such as exclusive regioselectivity, high yield, and broad substrate scope.

Initially, we began our research with the α-chloro *N*-Boc hydrazone **1a** as azoalkene precursor and *N*-phenylmaleimide **2** (Table 1). A reaction mixture of **1a** (0.3 mmol), **2a** (0.2 mmol),

Table 1. Initial Investigations on PPh_3-Mediated [4 + 2]-/[4 + 1]-Annulation of Hydrazone 1 with Maleimide 2a[a]



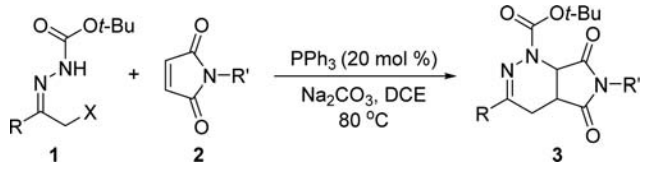
entry	1	PPh_3 (*x* mol %)	solvent	temp (°C)	time (h)	3/4[b]	yield[c] (%)
1	**1a**	20	CH_2Cl_2	20	48	>19:1	70
2	**1a**	20	CH_2Cl_2	40	48	>19:1	80
3	**1a**	20	DCE	60	24	>19:1	93
4	**1a**	20	DCE	80	12	>19:1	99
5	**1a**	10	DCE	80	24	>19:1	86
6	**1a**	20	acetone	20	48	10:1	48
7	**1a**	20	acetone	0	72	<1:19	43
8[d]	**1a**	100	acetone	20	12	1:6	60
9[d]	**1a**	100	acetone	0	24	<1:19	56
10[d]	**1b**	100	acetone	20	48	<1:19	77
11[d]	**1b**	100	EtOH	20	48	<1:19	73

[a]Unless otherwise noted, all reactions were carried out with 0.30 mmol of **1** and 0.20 mmol of **2a** in 2 mL of solvent. DCE = $ClCH_2CH_2Cl$. [b]The ratio was determined by crude ^1H NMR. [c]Isolated yield. [d]Premixing the stoichiometric amount of PPh_3 and **2a** before the hydrazone was added.

PPh_3 (20 mol %), and Na_2CO_3 (0.4 mmol) in CH_2Cl_2 was stirred at room temperature for 48 h, affording the fused-tetrahydropyridazine/pyrrolidinedione **3a** in 70% yield via a [4 + 2] reaction pathway[16] (Table 1, entry 1). The temperature effect was next examined, and the yield of the fused adduct **3a** was increased to 80% when the reaction temperature was improved to 40 °C (Table 1, entry 2). Up to 99% yield of **3a** can be achieved through switching the solvent from CH_2Cl_2 to $ClCH_2CH_2Cl$ (DCE) and improving the reaction temperature to 80 °C (Table 1, entries 3 and 4). Further investigation indicated that reducing the catalyst loading of PPh_3 to 10 mol % reduced the yield to 86% (Table 1, entry 5). When acetone was employed as the solvent at room temperature, the cycloadduct **3a** was contaminated with a small amount of byproduct (10:1 ratio) (Table 1, entry 6), which was determined to be spiro dihydropyrazole/pyrrolidinedione **4a** via [4 + 1]-annulation (vide infra) according to the NMR spectra and HRMS analysis. As the polar solvent, acetone is good for the formation of the key phosphorus ylide intermediate, which is the pivotal point in controlling the reaction for the [4 + 1] pathway. When the reaction temperature was lowered to 0 °C with an extended reaction time, [4 + 2]-annulation was suppressed and only [4 + 1]-annulation occurred smoothly to afford the spiro-**4a** in moderate yield (Table 1, entry 7). Premixing a stoichiometric amount of PPh_3 and *N*-phenylmaleimide **2** is beneficial to the conversion but is deteriorative to the chemoselectivity (Table 1, entry 8). Variation of the Boc group to a Bz group has a great influence on the reactivity and the chemoselectivity control, and spiro adduct **4a** was achieved in 77% yield as single adduct (Table 1, entries 9 and 10). EtOH could be used in this annulation, which also contributed to the formation of phosphorus ylide intermediate, delivering the spiro cycloadduct albeit in lower yield (Table 1, entry 11).

Using the optimized reaction conditions, the substrate scope of the PPh_3-catalyzed [4 + 2]-annulations was first explored. The representative results are shown in Table 2. All reactions

Table 2. Scope of PPh_3-Mediated [4 + 2]-Annulation of Various Hydrazones 1 with Maleimide 2[a]



entry	R	R′	3	yield[c] (%)
1	Ph	Ph	**3a**	99
2[b]	*p*-ClC_6H_4	Ph	**3b**	92
3[b]	*m*-ClC_6H_4	Ph	**3c**	97
4[b]	*p*-BrC_6H_4	Ph	**3d**	88
5[b]	*m*-BrC_6H_4	Ph	**3e**	82
6[b]	*o*-FC_6H_4	Ph	**3f**	80
7[b]	*m*-$MeOC_6H_4$	Ph	**3g**	83
8[b]	*p*-MeC_6H_4	Ph	**3h**	95
9[b]	*m*-MeC_6H_4	Ph	**3i**	72
10[b]	*o*-MeC_6H_4	Ph	**3j**	55
11[b]	2-naphthyl	Ph	**3k**	83
12[b]	Ph	Me	**3l**	60

[a]Unless otherwise noted, all reactions were carried out with 0.30 mmol of **1** and 0.20 mmol of **2** in 2 mL DCE. DCE = $ClCH_2CH_2Cl$. [b]α-Bromo *N*-benzoyl hydrazone was used. [c]Isolated yield.

proceeded well and afforded the fused pyrrolidinedione **3** in good to excellent yields. The electron-withdrawing (F, Cl, Br) substituents on the *para*-, *meta*-, and *ortho*-position of the aromatic ring of hydrazones have little effect on the reaction, affording **3b**–**f** in 80–97% yields (Table 2, entries 2–6). In addition, the electron-donating group on the aromatic ring could be tolerated and generated the fused products **3g**–**i** in good yield (Table 2, entries 7–9). *o*-Methyl-substituted **1j** worked well in this annulation, and the corresponding products **3j** was obtained in moderate yield (Table 2, entry 10). Notably, sterically bulky 2-naphthyl-substituted hydrazone **1k** was also a suitable substrate, giving the desired cycloadduct **3k** with 83% yield (Table 2, entry 11). However, alkyl-substituted hydrazone exhibited low reactivity in this transformation. *N*-Methylmaleimide **2b** is a viable reactant partner, and the annulation proceeded smoothly and provided the corresponding adduct **3l** in 60% yield (Table 2, entry 12).

We further investigated the substrate scope of the [4 + 1] annulations with respect to hydrazones under the optimized reaction conditions, and the results are summarized in Table 3. The different electronic properties of *ortho*-, *meta*-, and *para*-

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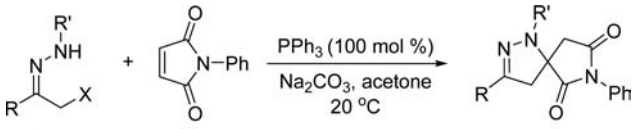
Table 3. Scope of PPh_3-Mediated [4 + 1]-Annulation of Various Hydrazone 1 with Maleimide 2[a,b]



1 2 4

entry	R	R′	4	yield[d] (%)
1	Ph	Bz	**4a**	77
2[c]	*p*-ClC_6H_4	Bz	**4b**	50
3[c]	*m*-ClC_6H_4	Bz	**4c**	85
4[c]	*o*-ClC_6H_4	Bz	**4d**	74
5[c]	*m*-BrC_6H_4	Bz	**4e**	73
6[c]	*o*-FC_6H_4	Bz	**4f**	80
7[c]	*m*-MeC_6H_4	Bz	**4g**	85
8[c]	2-furyl	Bz	**4h**	63
9	PhCH=CH	Bz	**4i**	56
10	$ClCH_2$	Bz	**4j**	20
11	Ph	CO_2Et	**4k**	68
12	Ph	Ts	**4l**	76

[a]Unless otherwise noted, all reactions were carried out with 0.20 mmol of **1** and 0.30 mmol of **2a** in 2 mL of acetone. [b]Premixing the stoichiometric amount of PPh_3 and **2a** before the hydrazone was added. [c]α-Bromo *N*-benzoyl hydrazone was used. [d]Isolated yield.

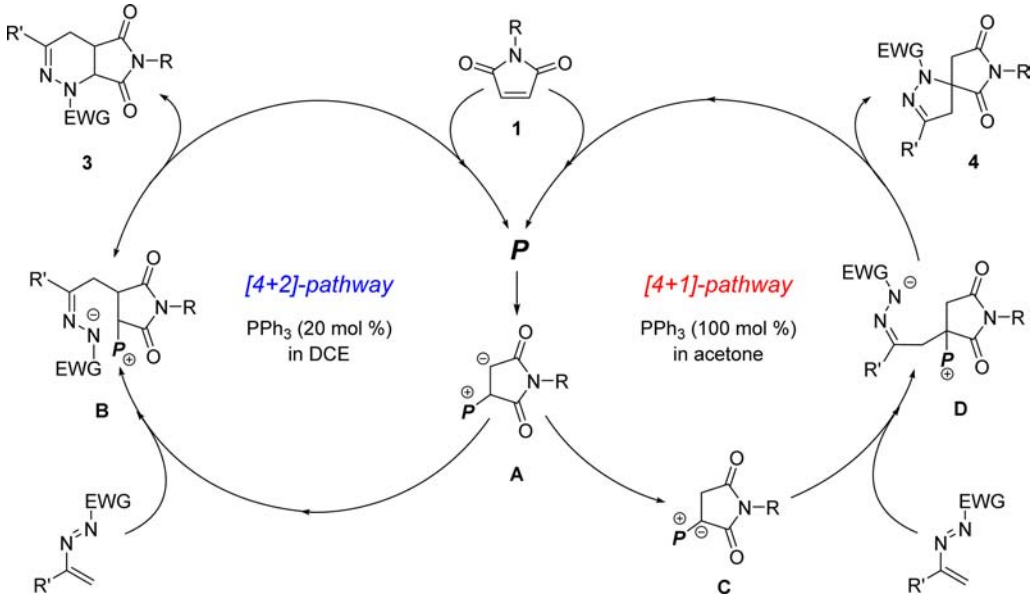
substituents on the aromatic ring of α-halo *N*-benzoyl hydrazones have little effect on the reactivity of this annulation, and the corresponding spiro-dihydropyrazole **4b–g** was achieved in the range of 50–85% yields (Table 3, entries 2–7). Furthermore, the challenging alkenyl-substituted cinnamyl and heteroaromatic hydrazone also proceeded well, giving rise to the spiro annulation product **4h,i** in moderate yield (Table 3, entries 8 and 9). However, alkyl-substituted hydrazone provided the desired annulation product **4j** in low yield (Table 3, entry 10). *N*-CO_2Et- and *N*-Ts-protected hydrazone could also be well tolerated in this PPh_3-mediated [4 + 1]-annulation (Table 3, entries 11 and 12).

A proposed mechanism was put forward to rationalize the PPh_3-mediated [4 + 2]- and [4 + 1]-annulations of maleimides and azoalkenes (Scheme 2). The initial nucleophilic attack of PPh_3 (***P***) to electron-deficient C=C bond in maleimide generates the zwitterionic intermediate **A**. In the lower polar solvent DCE, Michael addition of the negatively charged carbon in intermediate **A** with the in situ formed azoalkene generates zwitterionic species **B**, which subsequently undergoes a intramolecular cycloaddition reaction to furnish the fused product **3** and then regenerate PPh_3. Switching the less polar solvent to the more polar acetone along with a stoichiometric amount of PPh_3 promotes the annulation to undergo a different reaction pathway, probably because the initially generated zwitterionic intermediate **A** was efficiently converted into more stable phosphorus ylide **C**, which was believed to be promoted by acetone-aided proton transfer. Nucleophilic approach of the negatively charged carbon in ylide **C** to the azoalkene deliverers the zwitterionic species **D**. Subsequently, the negative-charged nitrogen atom attacks the phosphine-linked carbon via [4 + 1]-annulation to afford the spiro heterocyclic adduct **4**.

To further demonstrate the synthetic utility of this method, gram-scale [4 + 2]- and [4 + 1]-annulations of maleimides with hydrazone proceeded smoothly, delivering the fused- and spiro-adducts in good yields under standard reaction conditions (Scheme 3). Hydrogenation of **3a** with a catalytic amount of Pd/C led to the reduction of the C=N bond to afford **5** in good yield with high diastereoselectivity. Under acidic conditions, the *N*-Boc group of **3a** could be easily removed to provide **6** in high yield.

In conclusion, two novel PPh_3-mediated [4 + 2]- and [4 + 1]-annulations of maleimides with in situ formed azoalkenes have been developed, affording highly functionalized fused- and spiro-pyrrolidinedione derivatives in high yields in which maleimide served as C2 and C1 synthon, respectively. Further applications of those annulations in organic synthesis and elucidating the detailed mechanism are underway in our laboratory.

Scheme 2. Postulated Reaction Mechanism for PPh_3-Mediated [4 + 2]- and [4 + 1]-Annulations of Maleimides with in Situ Formed Azoalkenes



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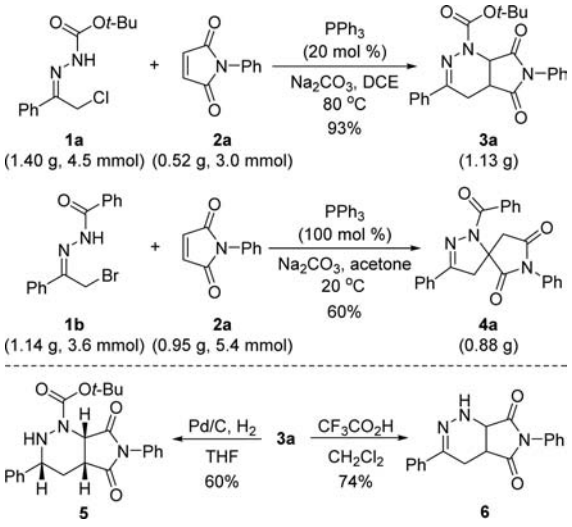
Scheme 3. Scale-up and Synthetic Transformations



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00215.

Experimental data and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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