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Letter

Diversity-Oriented Synthesis of Spiropentadiene Pyrazolones and 1*H*-Oxepino[2,3-*c*]pyrazoles from Doubly Conjugated Pyrazolones via Intramolecular Wittig Reaction

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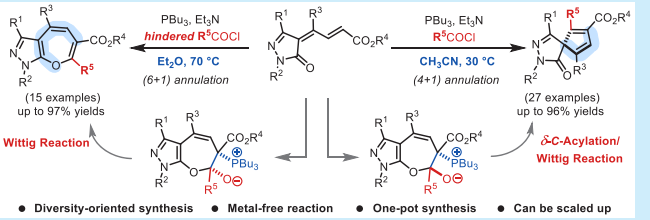
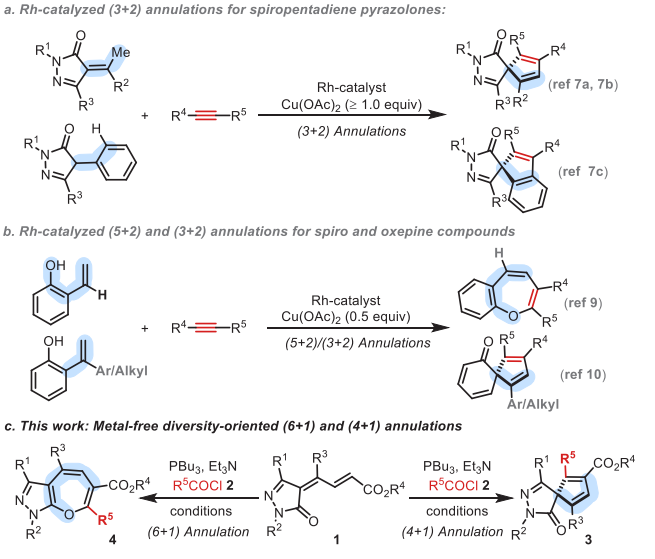
ABSTRACT: An efficient method for the diversity-oriented synthesis of spiropentadiene pyrazolones and 1*H*-oxepino[2,3-*c*]pyrazoles is reported. The methodology attributes *O*-acylation of phosphorus zwitterions which were formed by a tandem phospha-1,6-addition of PBu_3 to $\alpha,\beta,\gamma,\delta$-unsaturated pyrazolones, further generating betaine intermediates that preferentially resulted in the aforementioned cyclic products in a diversity-oriented manner. The mechanistic investigations revealed that formation of the betaines is the key step to provide the products via an intramolecular Wittig reaction or an unprecedented δ-*C*-acylation/cyclization/Wittig reaction.



Diversity-oriented synthesis is a potential approach to generate vast libraries of small molecules with structurally diversified skeletons, and it has attracted much attention to the synthetic community due to its efficiency toward the construction of valuable heterocycles in the area of drug discovery.[1] In recent years, the development of the Wittig reaction led to multifaceted applications toward the diversity-oriented synthesis of heteroarenes and heterocycles.[2] Remarkably, the activation of remote positions to access the spiro and fused compounds in a diversity-oriented manner is of foremost interest.

Pyrazolone is a privileged heterocycle scaffold extensively found in medicinally important compounds exhibiting a wide range of biological and pharmacological activities.[3] In particular, 4-spiro-5-pyrazolones act as promising pharmacophores,[4] and significant efforts have been focused on the synthesis of spiro six-membered rings over the last several years.[5] However, methods to prepare five-membered ring bearing spiro-pyrazolones were rarely explored.[6] Recently, You, Yao, and Waldmann independently developed Rh-catalyzed (3 + 2) annulation reactions to afford the spiropentadiene pyrazolones by employing pyrazolone derivatives and alkynes in the presence of $Cu(OAc)_2$ (Scheme 1a).[7] On the other hand, the oxepine core is also widely found in many molecules with pharmacological importance, but the methods to construct oxepine ring embedded heterocycles are scarcely reported.[8] In 2014, Gulías and co-workers disclosed Rh-catalyzed (5 + 2) annulation reaction for the synthesis of benzoxepines under the oxidative conditions.[9] This methodology further extended to generate the spiro compounds via (3 + 2) annulation, relying on the steric hindrance of the substrate (Scheme 1b).[10] Owing to the pharmacological importance of these highly appealing skeletons,

Scheme 1. Previous Methods and Our Strategy for Diversity-Oriented Synthesis



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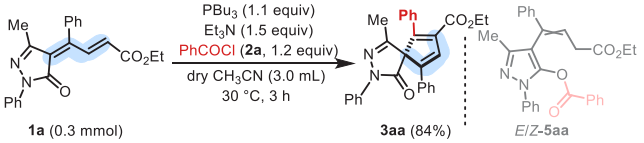
the development of an efficient method that could generate both of these privileged heterocycles in a diversity-oriented manner is highly desirable.

Our group has long been devoted toward the in situ generation of phosphorus zwitterions or phosphonium salts for their subsequent Wittig reaction.[11] In continuation of the legacy of our research, we were interested in the development of new methods for the diversity-oriented synthesis of privileged heterocycle scaffolds. In this context, we report a novel metal-free method for the efficient synthesis of spiropentadiene pyrazolones and 1*H*-oxepino[2,3-*c*]pyrazoles in a diversity-oriented manner (Scheme 1c). It is worthy to note that the method to construct the spiro compounds proceeds via an unprecedented *C*-acylation at the remote *δ*-position of the conjugated carbonyl compounds.

Our initial plan was to develop a new method for the synthesis of oxepines **4** through a tandem phospha-1,6-addition/*O*-acylation/Wittig reaction strategy. Accordingly, we examined the reaction of the readily accessible *α,β,γ,δ*-unsaturated pyrazolone **1a**, PBu_3, and PhCOCl (**2a**) in the presence of Et_3N at 30 °C. To our surprise, the spiropentadiene derivative **3aa** was found along with the dephosphorated compound *E*/*Z*-**5aa** (see the SI). In one instance, we realized that it would be the C−O bond cleavage of the betaine which formed an initial *δ*-*C*-acylated intermediate proceeding subsequent cyclization/Wittig reaction sequence to result in such a viable outcome. Surprised by the unprecedented *δ*-*C*-acylation/Wittig reaction sequence, we started our investigation to find the optimal reaction conditions. Upon screening of phosphines, different bases, solvents, and various other factors (see the SI for the detailed optimization), the optimal conditions were established as shown in Scheme 2.

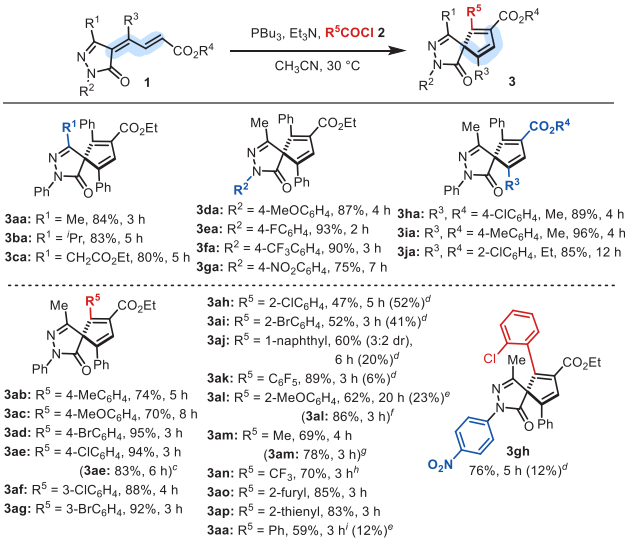
Scheme 2. Optimal Conditions for 3aa



Having established the optimal reaction conditions, the scope of the substrates was further investigated (Scheme 3). Substrates bearing R^1 as aliphatic groups **1a**−**1c** reacted well with **2a** to furnish the desired products **3aa**−**3ca** in up to 84% yields. Unfortunately, our efforts to prepare starting materials bearing R^1 as an aryl group were unsuccessful. Furthermore, we investigated the influence of R^2 and R^3 substituents. All of the substrates **1d**−**1j** furnished the spiro products **3da**−**3ja** in excellent yields, irrespective of the electronic and steric nature of the substituent.

Next, we tested the various acyl chlorides **2** under the optimal conditions to prepare a series of R^5-substituted spiro products **3**. In general, aroyl chlorides bearing *para*- and *meta*-substituents furnished the corresponding products **3ab**−**3ag** in good to high yields, regardless of the electronic nature. However, a significant steric influence was noticed when the *ortho*-substituted aroyl chlorides were tested in the reaction conditions. The sterically hindered acyl chlorides **2h** (R^5 = 2-ClC_6H_4) and **2i** (R^5 = 2-BrC_6H_4) have a pronounced effect on the selectivity of the reaction outcome to afford nearly 1:1 ratio of the corresponding spiro products **3ah**−**3ai** and oxepines **4ah**−**4ai**. We have also found a significant electronic effect besides the steric influence at

Scheme 3. Scope of the (4 + 1) Annulation Reaction for 3[a,b]

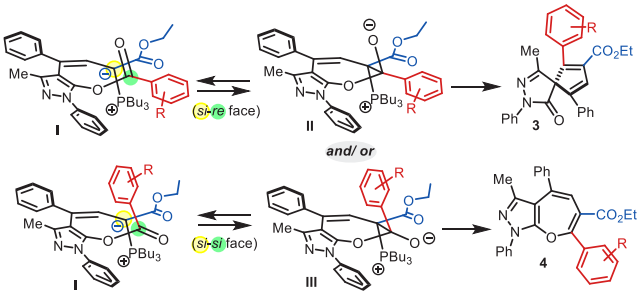


[a]The reactions were carried out with **1** (0.3 mmol), PBu_3 (1.1 equiv), Et_3N (1.5 equiv), and **2** (1.2 equiv) in dry CH_3CN (3.0 mL) under argon at 30 °C. [b]Isolated yield. [c]Gram scale of **1a** (3 mmol, 1.082 g). [d]The numbers in parentheses refer to the yields of **4**. [e]The numbers in parentheses refer to the NMR yield of the dephosphorated product **5**. [f]Reaction at 70 °C. [g]Acetic anhydride was used. [h]Trifluoroacetic anhydride was used. [i]Benzoic anhydride was used.

ortho-position. For example, **2l** (R^5 = 2-$OMeC_6H_4$) was less reactive with **1a** at 30 °C, but the corresponding product **3al** was obtained in 86% yield at 70 °C within 3 h. In addition, to examine the electronic effect in our protocol, a substrate bearing 4-$NO_2C_6H_4$ (**1g**) with **2h** was employed. To our delight, the corresponding products **3gh** and **4gh** were obtained in 76% and 12% yields, respectively. When the ratios of **3ah**/**4ah** (1:1) and **3gh**/**4gh** (7:1) are compared, it clearly indicates that the strong electron-withdrawing ability of NO_2 group enhances the *C*−*O* bond cleavage of betaine to result in a higher amount of the spiro product.

To understand the steric influence in the reaction, we have constructed the molecular models for the formation of possible betaine intermediates (Scheme 4 and the SI). The formation of

Scheme 4. Molecular Models for Betaine Intermediate Formation



the betaine **II** with pseudo-equatorial R^5 is more favorable than **III** with pseudo-axial R^5, which further undergoes the C−O bond cleavage to generate the spiro products **3**. Presumably, **I** with the less hindered R^5 gives the preferred intermediate **II**, leading exclusively to the spiro products **3**. When an *ortho*-substituted aroyl chloride, such as **2h** or **2i**, is subjected in the

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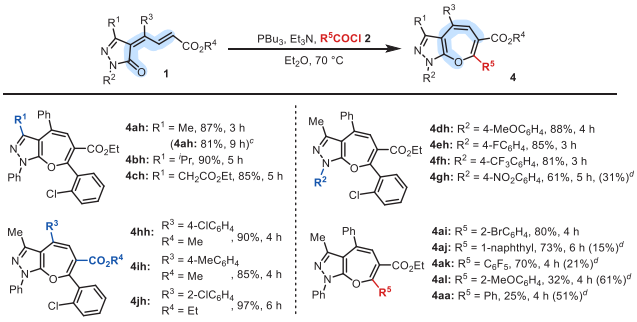
reaction with **1a**, it gives a more steric interaction of the *ortho*-substituted aryl and its surrounded bulky ethyl ester and PBu_3 groups of the betaine **II**. Therefore, it results in a lower difference of energy levels of the provided betaines **II** and **III**, giving rise to products **3** and **4** with lower selectivity. This interesting phenomenon opens up the possibility to achieve two different products in a diversity-oriented manner by the selection of acyl chlorides.

Inspired by the results from the *ortho*-substituted aroyl chlorides, we turned our attention to develop a method for the synthesis of oxepino[2,3-*c*]pyrazoles **4** which is our initial objective of *O*-acylation/Wittig reaction. To find the optimal conditions, other factors such as solvent, base, and temperature were evaluated (see the SI for the detailed optimization). It was delightful to find that the oxepino[2,3-*c*]pyrazole **4ah** was obtained in 87% yield exclusively when **1a** was treated with PBu_3 and **2h** in the presence of Et_3N in Et_2O at 70 °C in a sealed tube (Scheme 5). The formation of the dephosphorated compound

Scheme 5. Scope of the (6 + 1) Annulation Reaction for 4[a,b]



[a]The reactions were carried out with **1** (0.3 mmol), PBu_3 (1.1 equiv), Et_3N (1.5 equiv), **2** (1.2 equiv) in dry Et_2O (3.0 mL) at 70 °C in a sealed tube. [b]Isolated yield. [c]Gram scale of **1a** (3 mmol, 1.082 g). [d]The numbers in parentheses refer to the yields of **3**.

E/*Z*-**5** shows that the ylide **I** is not fully converted into the products **3**/**4** under ambient conditions in Et_2O. It clearly indicates that the temperature is critical for providing oxepines **4** in high yields.

With optimal conditions in hand, we further investigated the effect of different substitutions (R^1–R^4) of pyrazolone **1** with *o*-chloroaroyl chloride **2h** (Scheme 5). The reaction of substrates (**1b** and **1c**) bearing isopropyl and CH_2CO_2Et groups as R^1 with **2h** afforded the desired products **4bh** and **4ch** in excellent yields. Regardless of the electronic and steric nature of the substituent, substrates bearing different R^2 and R^3 groups, such as **1d**–**1j**, also furnished the corresponding products **4dh**–**4jh** in up to 97% yields. Similar phenomena in regard with the electronic effect on R^2 were also observed in the cases of **1g** and **2h**. Under our reaction conditions, the desired oxepine **4gh** and the spiro product **3gh** were afforded in 61% and 31% yields, respectively, whereas **1a** and **2h** gave only **4ah** in 87% yield.

Furthermore, various *ortho*-substituted aroyl chlorides were investigated in the reaction conditions with **1a**. The aroyl chloride **2i** (R^5 = 2-BrC_6H_4) afforded the desired oxepine **4ai** in 80% yield within 4 h. When 1-naphthyl and pentafluoroaryl acyl chlorides (**2j** and **2k**) were subjected to **1a**, a similar trend as that in Scheme 3 was observed but the selectivity was reversed in Et_2O. The corresponding oxepines **4aj** and **4ak** were obtained in 73% and 70% yields along with 15% and 21% yields of the spiro products **3aj** and **3ak**, respectively. It clearly indicates that the steric hindrance is enhanced by the hindered acyl chlorides that would drive the reaction toward the betaine **III** for the formation of oxepines **4** (Scheme 4). Interestingly, the *o*-OMe aroyl chloride **2l** provided the oxepine **4al** in only 32% yield along with the spiro product **3al** in 61% yield. Presumably, the OMe group is smaller in size when compared with other *o*-aryl substitutions, resulting in more amount of less hindered betaine **II**.[12] Although the role of the solvent is not clear, it could be understood that in addition to the solvent effect, the steric hindrance is crucial for the formation of the betaine **III** to result in the desired products in good yields. Furthermore, a gram-scale reaction of **1a** could be performed under the same conditions to afford **4ah** in 81% yield, albeit after longer reaction time.

In order to investigate the mechanism, we have performed several control experiments (see the SI). We found that solvent has a profound effect on the selective synthesis of spiro and oxepine compounds along with the steric hindrance from the acyl chloride. To find the intermediates, the reactions of phosphonium zwitterion **6a** with acyl chlorides **2a**/**2h** have been examined, and the progress of the reaction was monitored by ^{31}P NMR analysis.[13] The zwitterion peak at 36.7 ppm was converted into two peaks at 39.2/37.3 ppm in CH_3CN or 39.0/37.3 ppm in Et_2O with different ratios by using acyl chloride **2a** or **2h**, respectively (Figure 1). It could be understood that the zwitterion would generate the *O*-acylated intermediates **7** in *E* and *Z* forms which were further confirmed by the ESI-HRMS analysis.

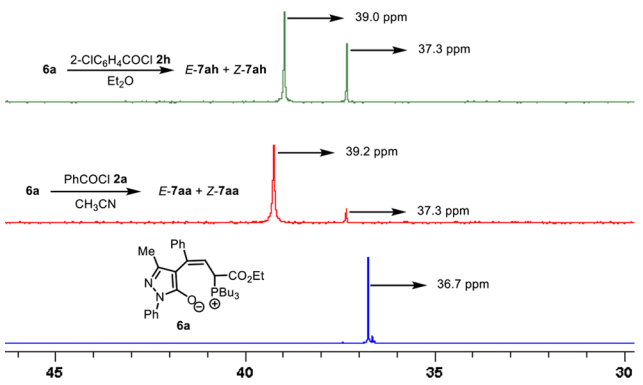
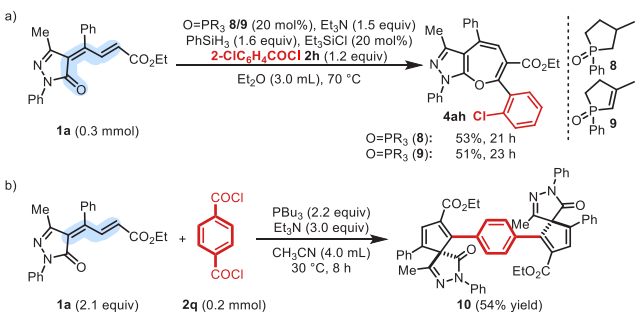


Figure 1. ^{31}P NMR analysis of intermediates **6a** and *E*/*Z*-**7aa**/**7ah**.

Furthermore, the effectiveness of our protocol was demonstrated by employing our reported catalytic Wittig reaction conditions with **1a** and **2h** in the presence of phosphine oxide **8** or **9** (Scheme 6a).[14,15] To our delight, the desired oxepine **4ah**

Scheme 6. Synthesis of 4ah and 10



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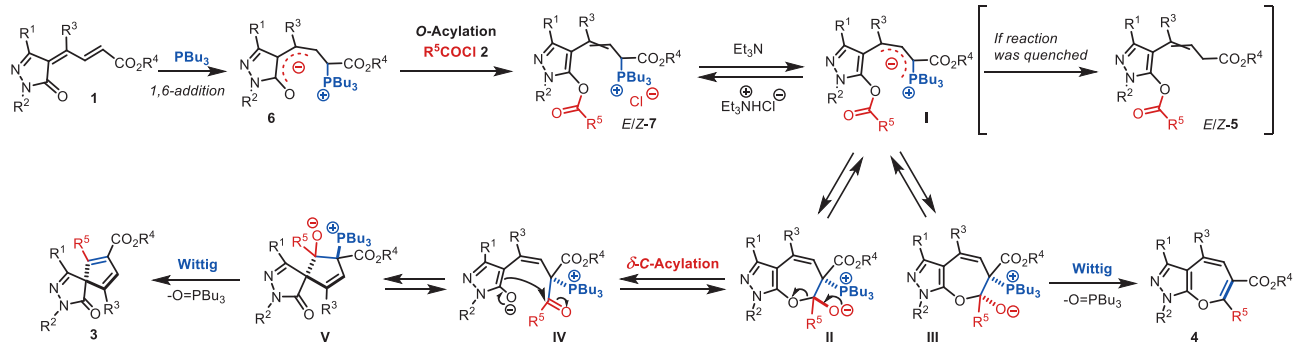
Scheme 7. Plausible Mechanism for 3 and 4



was obtained in up to 53% yields in both reactions. We also examined the reaction of terephthaloyl dichloride (**2q**) with **1a** under the standard conditions for synthesis of **3**. Interestingly, the product **10** bearing two spiro centers was afforded as a single diastereomer in 54% yield (Scheme 6b).

On the basis of the results and control experiments, a plausible mechanism is depicted in Scheme 7. The reaction is initiated by the phospha-1,6-addition of PBu_3 at the δ-position of **1** to generate the phosphorus zwitterion **6** that further undergoes *O*-acylation to result in the phosphonium salts *E*/*Z*-**7**. The deprotonation of *E*/*Z*-**7** by Et_3N furnishes ylide **I**, and further intramolecular cyclization of **I** provides the betaines **II** and/or **III**. The cleavage of the C−O bond of betaine **II** would facilitate the formation of the δ−acylated enolic intermediate **IV**, which upon subsequent cyclization and Wittig reaction leads to the spiro product **3** via an intermediate **V**. On the other hand, when the steric hindrance enhanced by the *ortho*-substituted aroyl chlorides, betaine **III** is selectively generated in Et_2O to further proceed the Wittig reaction, furnishing the oxepine **4**.

In summary, the efficient synthesis of spiropentadiene pyrazolones and oxepino[2,3-*c*]pyrazoles was demonstrated in a diversity-oriented manner. The reaction of $\alpha,\beta,\gamma,\delta$-unsaturated pyrazolones, PBu_3, and acyl chloride in the presence of Et_3N afforded the spiropentadiene pyrazolones in high yields via an unprecedented phospha-1,6-addition/*O*-acylation/δ-*C*-acylation/cyclization/Wittig reaction sequence. In addition, a series of oxepino[2,3-*c*]pyrazoles were prepared in good to high yields via tandem phospha-1,6-addition/*O*-acylation/Wittig reaction. Our investigations revealed that the nature of the solvent and the steric hindrance of acyl chlorides dominated the preferential formation of plausible betaines **II** or **III**, which plays a pivotal role to result in the spiro or fused product, respectively. Further investigations to employ this method for diversity-oriented synthesis of other cyclic compounds are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01552.

Optimization data, mechanistic studies, experimental procedures, characterization data, and spectra of all compounds (PDF)

Accession Codes

CCDC 1950758, 1972121, 1986342, 1995003, 1995844, and 1997280 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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