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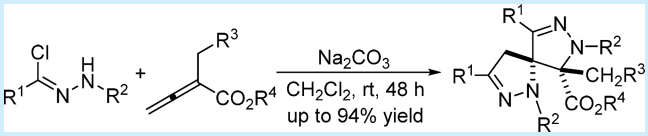
Synthesis of Spirobidihydropyrazole through Double 1,3-Dipolar Cycloaddition of Nitrilimines with Allenoates

Honglei Liu, Hao Jia, Bo Wang, Yumei Xiao, and Hongchao Guo*

Department of Applied Chemistry, China Agricultural University, Beijing 100193, P. R. China

Supporting Information

ABSTRACT: The double 1,3-dipolar cycloaddition of allenoates with nitrilimines has been achieved under mild reaction conditions, affording a variety of spirobidihydropyrazoles in moderate to excellent yields with excellent diastereoselectivities. The reaction diastereoselectively constructs double dihydropyrazole moieties and two chiral centers including a spiro carbon center.



Spirocyclic compounds having cyclic structures fused at a central carbon have received considerable attention because of their ubiquitous presence in natural products and their interesting conformational features.[1] Spiro heterocyclic compounds have been found to exhibit diversified biological activities and pharmacological and therapeutical properties.[2] Common approaches[3] (Figure 1) to spirocyclic compounds include (a) alkylation methods,[4] (b) transition-metal-based processes,[5] (c) radical cyclizations,[6] (d) ring closure of geminally substituted compounds,[7] (e) metathesis processes,[8] (f) Diels–Alder reactions,[9] (g) cycloaddition tactics,[10] rearrangement based processes,[11] ring-expansion and -contraction methods, cleavage of bridged ring systems, and so on to give spirocyclic compounds (Figure 1). Most strategies for construction of spiro structures are through constructing a new ring on an existing carbo- or heterocycle. Limited examples on the formation of two rings through a double-intramolecular 1,3-dipolar cycloaddition of diene in one pot for a spirocyclic compound have also been reported.[12] Although several cycloaddition reactions of allenoates with 1,3-dipoles have been achieved, only a carbon–carbon double bond was involved in these reactions.[13] As shown in method h of Figure 1, the double 1,3-dipolar cycloaddition involving both carbon–carbon double bonds of allenoates in one pot is obviously a great strategy for synthesis of spirocyclic compounds.

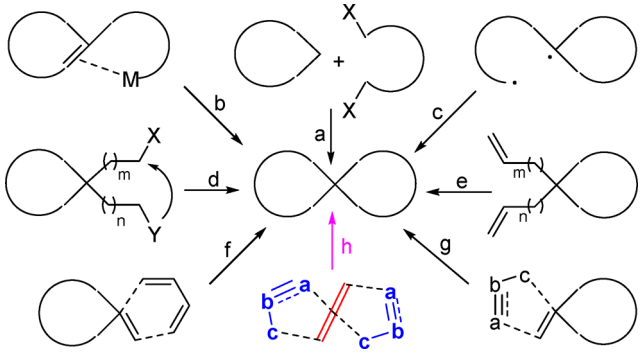
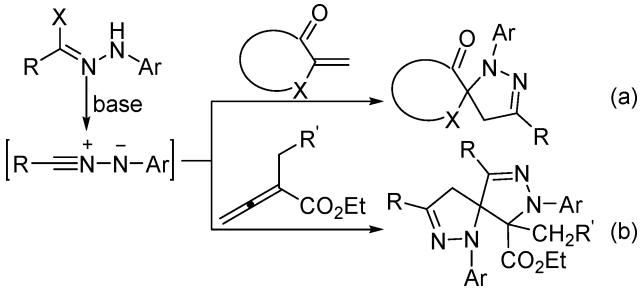


Figure 1. Methods for synthesis of spirocyclic compounds.

Due to the interesting biological activities of various spiro pyrazolines, their synthesis has attracted great attention. A number of methods have been developed for the synthesis of the functionalized spiropyrazolines.[14] In general, classical syntheses of the spiropyrazolines utilized protocols based on 1,3-dipolar cycloaddition[15−18] or condensation[19] as an essential step. A few examples of 1,3-dipoles applied in the synthesis of spiropyrazolines include nitrilimines,[15] diazoalkanes,[16] related diazo derivatives,[17] and diaziridines,[18] and the usual dipolarophile for this process is an alkene or alkyne. Nitrilimines that are generated in situ from the corresponding hydrazonyl halides in the presence of a base are important transient 1,3-dipolar species in organic synthesis and have been utilized as useful synthons of spiropyrazoline derivatives.[20] As shown in Scheme 1a, a typical synthesis of spiropyrazoline was accomplished via a 1,3-dipolar cycloaddition of nitrilimines with heterocyclic α,β-enone compounds possessing exocyclic double bonds (Scheme 1a).[20] Herein, we report a synthesis of spirobidihydropyrazoles through double 1,3-dipolar cycloaddition of nitrilimines with allenoates (Scheme 1b).

Scheme 1. Synthesis of Spiropyrazolines via 1,3-Dipolar Cycloaddition of Nitrilimines



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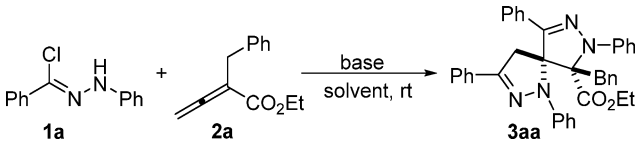
In our initial investigation, the reaction of nitrilimine precursor **1a** with allenoate **2a** was chosen as the model reaction. With the use of Et_3N as the base, the reaction was performed in dichloromethane at room temperature for 48 h to give the corresponding product spirobipyrazoline **3aa** in 82% yield (Table 1, entry 1). Then different bases were screened to

Table 1. Screening of the Reaction Conditions[a]



1a **2a** **3aa**

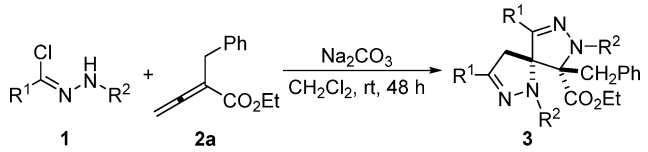
entry	base	solvent	yield[b,c] (%)
1	Et_3N	CH_2Cl_2	82
2	*i*-Pr_2NEt	CH_2Cl_2	67
3	*t*-BuOK	CH_2Cl_2	trace
4	NaOH	CH_2Cl_2	trace
5	KOH	CH_2Cl_2	trace
6	Cs_2CO_3	CH_2Cl_2	47
7	K_2CO_3	CH_2Cl_2	52
8	Na_2CO_3	CH_2Cl_2	91
9	Na_2CO_3	DCE	81
10	Na_2CO_3	$CHCl_3$	75
11	Na_2CO_3	AcOEt	43
12	Na_2CO_3	THF	85
13	Na_2CO_3	MeCN	88
14	Na_2CO_3	MeOH	trace
15	Na_2CO_3	toluene	trace
16	Na_2CO_3	DMF	trace

[a]Reactions of **1a** (0.22 mmol), **2a** (0.1 mmol) and base (0.22 mmol) were carried out in 1 mL of solvent at rt for 48 h. [b]Isolated yields. [c]Unless indicated otherwise, dr is >20:1, determined by ^1H NMR analysis of the crude product.

improve the yield (entries 2–8). Unfortunately, only a trace of product was observed with the use of *t*-BuOK, NaOH, or KOH as the base (entries 3–5). In comparison, the product **3aa** was obtained in moderate yields with the use of *i*-Pr_2NEt, Cs_2CO_3, or K_2CO_3 as the base (entries 2, 6, and 7). To our delight, the yield of the product **3aa** was increased to 91% with the use of Na_2CO_3 as the base (entry 8). The impact of the solvent was also examined. Compared with dichloromethane, 1,2-dichloroethane (DCE), chloroform, ethyl acetate, tetrahydrofuran (THF), and acetonitrile led to decreased yields (entries 9–13). Only a trace of product was observed when toluene, methanol, or *N*,*N*′-dimethylformamide (DMF) was used as the solvent (entries 14–16). The relative configuration of the cycloaddition product has been determined through X-ray crystallographic data of the product **3aa**.[21]

With the optimal reaction conditions in hand, we next explored the scope of the nitrilimine precursors. As shown in Table 2, the reaction could tolerate a wide scope of nitrilimines bearing different R^1 groups, giving products **3** in moderate to high yields with excellent diastereoselectivities (entries 1–18). Regardless of the electronic nature (electron-donating or electron-withdrawing) of the substituents on the benzene ring, the corresponding products **3aa**–**na** were obtained in good yields (62–91%) with excellent diastereoselectivities (entries 1–14). However, substrates bearing substituents at the 2-position of the aryl showed relative weak reactivities, leading to the corresponding products in a little lower yields (entries 2,

Table 2. Scope of Nitrilimine[a]



1 **2a** **3**

entry	R^1, R^2 in **1**	**3**	yield[b,c] (%)
1	Ph, Ph (**1a**)	**3aa**	91
2	2-FC_6H_4, Ph (**1b**)	**3ba**	63
3	3-FC_6H_4, Ph (**1c**)	**3ca**	85
4	4-FC_6H_4, Ph (**1d**)	**3da**	88
5	2-ClC_6H_4, Ph (**1e**)	**3ea**	72
6	3-ClC_6H_4, Ph (**1f**)	**3fa**	47
7	4-ClC_6H_4, Ph (**1g**)	**3ga**	84
8	2-BrC_6H_4, Ph (**1h**)	**3ha**	62
9	3-BrC_6H_4, Ph (**1i**)	**3ia**	86
10	4-BrC_6H_4, Ph (**1j**)	**3ja**	87
11	3-MeC_6H_4, Ph (**1k**)	**3ka**	73
12	4-MeC_6H_4, Ph (**1l**)	**3la**	81
13	3-$OMeC_6H_4$, Ph (**1m**)	**3ma**	65
14	4-$OMeC_6H_4$, Ph (**1n**)	**3na**	79
15	1-naphthyl, Ph (**1o**)	**3oa**	87
16	2-naphthyl, Ph (**1p**)	**3pa**	85
17	2-furanyl, Ph (**1q**)	**3qa**	67
18	*n*-Pr, Ph (**1r**)	**3ra**	64
19	Ph, 3-FC_6H_4 (**1s**)	**3sa**	65
20	Ph, 3-ClC_6H_4 (**1t**)	**3ta**	80
21	Ph, 3-BrC_6H_4 (**1u**)	**3ua**	72
22	Ph, 4-MeC_6H_4 (**1v**)	**3va**	35

[a]Reactions of **1** (0.22 mmol), **2a** (0.1 mmol), and Na_2CO_3 (0.22 mmol) were carried out in 1 mL of CH_2Cl_2 at rt for 48 h. [b]Isolated yields. [c]Unless indicated otherwise, dr is >20:1, determined by ^1H NMR analysis of the crude product.

5, and 8). The fused aromatic and heteroaromatic nitrilimines such as 1-naphthyl, 2-naphthyl, and 2-furanyl nitrilimine (**1o**–**q**) were also tolerated and yielded products (**3oa**–**qa**) in moderate to high yields (67–87%) with excellent diastereoselectivities (entries 15–17). Satisfactorily, the nitrilimine scope could be further expanded to the alkyl-substituted substrate **1r**, which delivered the product **3ra** in 64% yield (entry 18). In addition, different R^2-substituted nitrilimines also worked well to give the cycloadducts (entries 19–22).

Next, we carried out an investigation on allenoates **2** (Table 3). A series of α-substituted allenoates **2** bearing the electron-donating or electron-withdrawing substituents on the benzene ring could smoothly perform the reaction under mild conditions, affording the products **3** in good yields (76–94%) with excellent diastereoselectivities (entries 1–16). Generally, the position of the substituent on the benzene ring does not have a remarkable effect on the yields and diastereoselectivities (entries 1–16). A moderate 67% yield was obtained using the allenoate-containing dimethoxyl-substituted aryl as the substrate (entry 17). 2-Naphthyl-substituted allenoate is also a compatible substrate, giving the product **3as** in 75% yield (entry 18). The α-(ethoxycarbonylmethyl)allenoate **2t** performed the reaction to give the product **3at** in 58% yield. Varying the ester moiety of allenoates could be tolerated, and the corresponding products were isolated in moderate to high yields (entries 20–23).

To further demonstrate the practical utility of the synthetic method for spirocyclic compounds, the reaction of **2a** was

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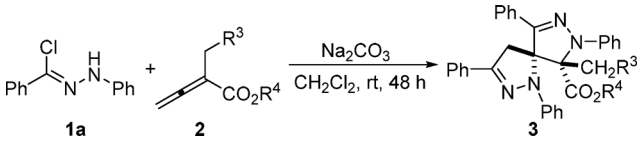
Table 3. Scope of Allenoate[a]



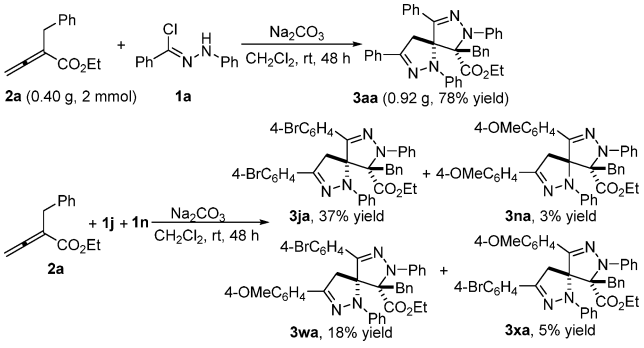
1a 2 3

entry	R^3, R^4 in **2**	**3**	yield[b,c] (%)
1	2-FC_6H_4, Et (**2b**)	**3ab**	83
2	3-FC_6H_4, Et (**2c**)	**3ac**	87
3	4-FC_6H_4, Et (**2d**)	**3ad**	92
4	2-ClC_6H_4, Et (**2e**)	**3ae**	83
5	3-ClC_6H_4, Et (**2f**)	**3af**	77
6	4-ClC_6H_4, Et (**2g**)	**3ag**	86
7	2-BrC_6H_4, Et (**2h**)	**3ah**	88
8	3-BrC_6H_4, Et (**2i**)	**3ai**	81
9	4-BrC_6H_4, Et (**2j**)	**3aj**	84
10	3-$CF_3C_6H_4$, Et (**2k**)	**3ak**	76
11	4-$CF_3C_6H_4$, Et (**2l**)	**3al**	82
12	2-MeC_6H_4, Et (**2m**)	**3am**	78
13	3-MeC_6H_4, Et (**2n**)	**3an**	80
14	4-MeC_6H_4, Et (**2o**)	**3ao**	94
15	4-*t*-BuC_6H_4, Et (**2p**)	**3ap**	86
16	3-$OMeC_6H_4$, Et (**2q**)	**3aq**	83
17	3,5-$OMe_2C_6H_3$, Et (**2r**)	**3ar**	67
18	2-naphthyl, Et (**2s**)	**3as**	75
19	CO_2Et, Et (**2t**)	**3at**	58
20	Ph, Me (**2u**)	**3au**	52
21	Ph, *t*-Bu (**2v**)	**3av**	85
22	Ph, Cy (**2w**)	**3aw**	56
23	Ph, Ph (**2x**)	**3ax**	64

[a]Reactions of **1a** (0.22 mmol), **2** (0.1 mmol), and Na_2CO_3 (0.22 mmol) were carried out in 1 mL of CH_2Cl_2 at rt for 48 h. [b]Isolated yields. [c]Unless indicated otherwise, dr is >20:1, determined by ^1H NMR analysis of the crude product.

performed on a gram scale, producing the desired product **3aa** in 78% yield (Scheme 2). Interestingly, when two different

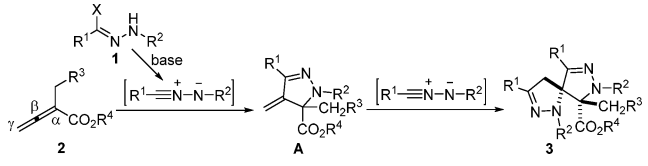
Scheme 2. Gram-Scale Synthesis and Cycloaddition of Two Different Nitrilimines with Allenoate in One Pot



nitrilimines **1j** and **1n** were used in the cycloaddition reaction with allenoate **2a** in one pot, besides the normal products **3ja** and **3na**, two cross products **3wa** and **3xa** could also be obtained. The yield of **3ja** is much higher than the yield of **3na**; thus, probably the nitrilimine with electron-withdrawing substituents is more reactive than that with electron-donating substituents on the benzene ring. The structure of the product **3wa** has been determined through X-ray crystallographic data.[21]

As shown in Scheme 3, a plausible mechanism was proposed. The nitrilimine generated in situ from the corresponding

Scheme 3. Proposed Mechanism



hydrazonyl halide **1** in the presence of a base reacts with the carbon−carbon double bond of allenoate **2** between the α- and β-carbon to give the intermediate dihydropyrazoline **A**, which could be observed on the ^1H NMR spectra of the reaction mixture (see the Supporting Information). Then the second nitrilimine performs the cycloaddition with the terminal olefin of the intermediate **A** to produce the product **3**.

In summary, we have developed the double 1,3-dipolar cycloaddition of allenoates with nitrilimines, affording a variety of spirobidihydropyrazoles in up to 94% yield with excellent diastereoselectivities. A wide range of allenoates and nitrilimines are compatible with the mild reaction conditions. This reaction provides an efficient method for synthesis of spirobidihydropyrazoline. The double 1,3-dipolar cycloaddition involving both carbon−carbon double bonds of allenoates in one pot is achieved for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01961.

Experimental procedure, characterization data, and NMR spectra (PDF)
X-ray data for compound **3aa** (CIF)
X-ray data for compound **3wa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hchguo@cau.edu.cn.

ORCID

Hongchao Guo: 0000-0002-7356-4283

Notes

The authors declare no competing financial interest.

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