

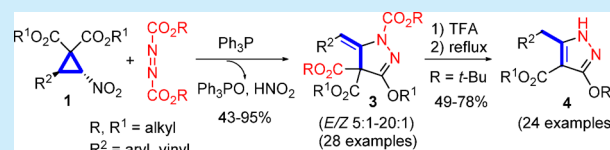
Divergent Reactivity of Nitrocyclopropanes with Huisgen Zwitterions and Facile Syntheses of 3-Alkoxy Pyrazolines and Pyrazoles

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S Supporting Information

ABSTRACT: A novel annulation reaction of *trans*-2-substituted-3-nitrocyclopropane-1,1-carboxylates with in situ generated Huisgen zwitterions is reported, providing facile synthesis of 3-alkoxy pyrazolines in good yields and high diastereoselectivities. This reaction unveils the divergent reactivity of the nitrocyclopropanes as a kind of versatile donor–acceptor cyclopropanes. It is also demonstrated that the prepared 3-alkoxy pyrazolines from di-*tert*-butyl azodicarboxylate can be readily transformed into the corresponding 3-alkoxy 1*H*-pyrazoles in moderate yields.



Pyrazoline and pyrazole are both privileged structural motifs frequently present in a large number of agrochemicals, pharmaceuticals, and other bioactive molecules.¹ Polysubstituted pyrazoles are also utilized as functional units in material science,² and as effective ligands in transition metal-catalyzed reactions.³ Among numerous bioactive pyrazolines and pyrazoles, it is noteworthy that a group of 3-oxy(oxo) analogues possess important and diverse properties including antipyretic, analgesic, fungicidal, and anti-inflammatory activities (Figure 1).^{4,5} Under

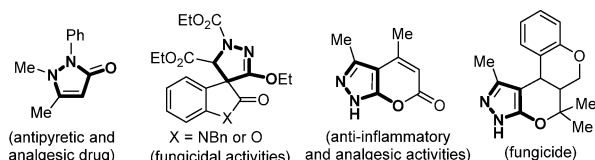


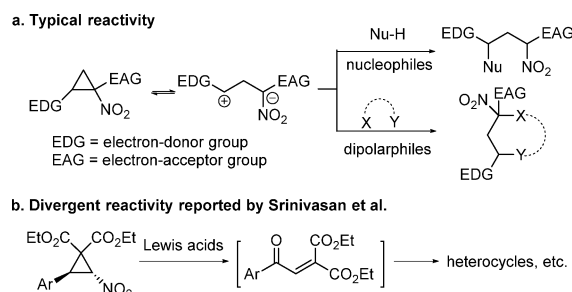
Figure 1. Bioactive 3-oxy(oxo) pyrazolines and pyrazoles.

this circumstance, the development of effective synthetic methods for pyrazolines and pyrazoles has therefore stimulated much interest from chemists.^{6–8} Traditional approaches such as the condensation of 1,3-dicarbonyl compounds with hydrazines and the [3 + 2] cycloaddition of 1,3-dipoles have proven to be effective;⁶ however, alternative and efficient synthetic strategies for structurally diverse pyrazolines and pyrazoles remain highly desirable. Over the past decade, great progress in this aspect has been witnessed.^{7,8}

Donor–acceptor (D–A) cyclopropanes have emerged as popular building blocks in the synthesis of a variety of carbocycles and heterocycles.⁹ Their versatility in organic synthesis may be attributed to the unique and diverse reactivity that is synergistically rendered by vicinal electron-donor and -acceptor substituents and inherent ring strain of the cyclopropane backbone as well. As a typical class of D–A cyclopropanes, nitrocyclopropanes have drawn considerable attention due to rich chemical transformations of nitro

functionality.^{10,11} Prior studies have shown that both the nature of substituents and substitution pattern significantly affect the reactivity of nitrocyclopropanes. Most of the studied nitrocyclopropanes have a common substitution pattern: adjacent to an electron-donor substituent, the nitro and another electron-acceptor group (usually an ester or carbonyl group) are geminally positioned at the cyclopropane backbone. This kind of nitrocyclopropanes exhibit typical reactivity of D–A cyclopropanes, engaging in ring-opening reactions, formal cyclo-additions, and rearrangements through a key 1,3-dipolar intermediate (Scheme 1a).^{11a–g} Other nitrocyclopropanes with

Scheme 1. Reactivity of Nitrocyclopropanes as D–A Cyclopropanes



different substitution patterns usually exhibit divergent and often unexpected reactivity.^{11h–m} For example, Srinivasan et al. found that, upon treatment of Lewis acids, *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates undergo ring-opening rearrangement and the Nef reaction to give aroylmethylidene malonates.¹¹ⁱ On the basis of this unique chemistry of nitrocyclopropanes, the same group has recently developed a couple of elegant synthetic methods for heterocycles (Scheme

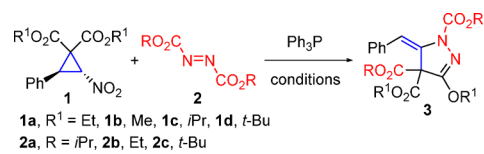
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1b).^{11i–l} It is thus anticipated that exploring the diverse reactivity of nitrocyclopropanes with different substitutions will further strengthen their utility in organic synthesis.

The Huisgen zwitterions are a class of classical and famous 1,3-dipolar intermediates, generally in situ formed from Ph_3P and dialkyl azodicarboxylates.¹² Recent renewed interest from chemists has disclosed that Huisgen zwitterions could readily undergo a series of annulation reactions with various electrophiles, affording unique and efficient approaches to aza-heterocycles.¹³ We are also interested in exploring new annulations of Huisgen zwitterions and have achieved some recent successes in the synthesis of complex aza-heterocycles.^{4b,14} As part of our continuous efforts, recently we investigated the possible reactions of nitrocyclopropanes with Huisgen zwitterions and found an unprecedented annulation reaction leading to facile syntheses of 3-alkoxy pyrazolines and pyrazoles. Herein we wish to communicate the relevant results.

Our investigation was commenced with the substrates *trans*-2-nitro-3-phenylcyclopropane-1,1-dicarboxylate **1a** and diisopropyl azodicarboxylate **2a** (Table 1). Under a N_2 atmosphere, a

Table 1. A Brief Survey on the Annulation Reaction between Nitrocyclopropanes **1 and Huisgen Zwitterions^a**



entry	1	2	molar ratio 1/2/ Ph_3P	solvent	time (h)	3 ^{b,c} (%)
1	1a	2a	1:1.5:1.5	THF	48	3a (40)
2	1a	2a	1:1.5:1.5	CH_2Cl_2	48	3a (45)
3	1a	2a	1:1.5:1.5	CHCl_3	48	3a (44)
4	1a	2a	1:1.5:1.5	CH_3CN	48	—
5	1a	2a	1:1.5:1.5	toluene	48	—
6	1a	2a	1:1.5:1.5	DMF	48	—
7	1a	2a	1:2.0:2.0	CH_2Cl_2	48	3a (58)
8	1a	2a	1:2.5:2.5	CH_2Cl_2	48	3a (68)
9	1a	2a	1:3.0:3.0	CH_2Cl_2	48	3a (67)
10	1a	2b	1:2.5:2.5	CH_2Cl_2	48	3b (43)
11	1a	2c	1:2.5:2.5	CH_2Cl_2	12	3c (70)
12	1b	2c	1:2.5:2.5	CH_2Cl_2	2	3d (88)
13	1c	2c	1:2.5:2.5	CH_2Cl_2	24	3e (56)
14	1d	2c	1:2.5:2.5	CH_2Cl_2	24	—

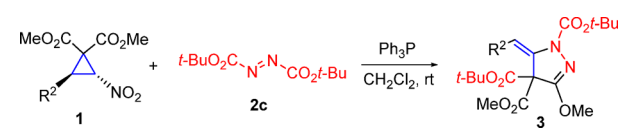
^aTypical conditions: under a N_2 atmosphere, to a mixture of **1** (0.3 mmol) and **2** (0.45–0.9 mmol) in a solvent (2.0 mL) was added PPh_3 (0.45–0.9 mmol); the mixture was then stirred at rt for a specified time. ^bIsolated yields. ^cIn all cases, the *E/Z* ratio > 20:1 as determined by ^1H NMR assay of the isolated products.

mixture of **1a** (0.3 mmol), **2a** (0.45 mmol), and PPh_3 (0.45 mmol) in THF (2.0 mL) was stirred at rt for 48 h. To our delight, a pyrazoline product **3a** was collected in 40% yield and high diastereoselectivity after column chromatographic isolation (Table 1, entry 1). This result unveiled a novel route to highly functionalized pyrazolines. To further improve the reaction efficiency, a brief survey of reaction conditions was conducted. Solvent screening indicated that CH_2Cl_2 and CHCl_3 provided better yields than THF (Table 1, entries 2 and 3); other common solvents such as CH_3CN , toluene, and DMF were found to be inappropriate for the reaction (Table 1, entries 4–6). With CH_2Cl_2 chosen as the solvent, increasing the loadings of both

azodicarboxylate **2a** and Ph_3P resulted in a substantial increase in the yield of **3a** (Table 1, entries 7–9), and the substrate molar ratio of 1:2.5:2.5 was preferred (Table 1, entry 8). Different azodicarboxylates **2** were then tested in the reactions with **1a**. Diethyl azodicarboxylate **2b** gave normal product **3b** in 43% yield while bulky di-*tert*-butyl azodicarboxylate **2c** delivered its corresponding product **3c** in 70% yield in a shortened reaction time (Table 1, entries 10 and 11). Nitrocyclopropanes **1** bearing different ester groups were further surveyed with azodicarboxylate **2c** used as a reactant. Dimethyl *trans*-2-nitro-3-phenylcyclopropane-1,1-dicarboxylate **1b** delivered product **3d** in 88% yield in 2 h (Table 1, entry 12). In contrast, nitrocyclopropanes **1c** and **1d** bearing bulky ester groups gave inferior results (Table 1, entries 13 and 14).

The scope of nitrocyclopropanes **1** was further explored (Table 2). A variety of 2-substituted-3-nitrocyclopropane-1,1-

Table 2. Scope of Nitrocyclopropanes **1^a**



entry	1 , R^2	time (h)	3 ^b (%)	<i>E/Z</i> ^c
1	1b , Ph	2	3d (88)	>20:1
2	1e , 4- FC_6H_4	1	3f (82)	>20:1
3	1f , 2- ClC_6H_4	1	3g (82)	>20:1
4	1g , 3- ClC_6H_4	1	3h (89)	>20:1
5	1h , 4- ClC_6H_4	1	3i (83)	>20:1
6	1i , 2,4- $\text{Cl}_2\text{C}_6\text{H}_3$	1	3j (81)	>20:1
7	1j , 2- BrC_6H_4	1	3k (91)	>20:1
8	1k , 3- BrC_6H_4	1	3l (95)	>20:1
9	1l , 4- BrC_6H_4	1	3m (93)	>20:1
10	1m , 2-Me C_6H_4	2	3n (84)	>20:1
11	1n , 3-Me C_6H_4	2	3o (85)	>20:1
12	1o , 4-Me C_6H_4	2	3p (91)	>20:1
13	1p , 2-OMe C_6H_4	2	3q (93)	>20:1
14	1q , 3-OMe C_6H_4	2	3r (92)	>20:1
15	1r , 3,4,5-(OMe) $_3\text{C}_6\text{H}_2$	2	3s (86)	>20:1
16	1s , 3- $\text{NO}_2\text{C}_6\text{H}_4$	1	3t (78)	>20:1
17	1t , 4- $\text{NO}_2\text{C}_6\text{H}_4$	1	3u (80)	5:1
18	1u , 4- $\text{CF}_3\text{C}_6\text{H}_4$	1	3v (83)	>20:1
19	1v , 1-naphthyl	1	3w (78)	>20:1
20	1w , 2-furyl	1	3x (65)	>20:1
21	1x , 2-thienyl	1	3y (62)	>20:1
22	1y , 3-pyridyl	2	3z (89)	>20:1
23	1z , <i>E</i> -styryl	2	3A (84)	>20:1
24	1A , <i>n</i> -hexyl	24	—	—
25 ^d	1j	1	3k (87)	>20:1

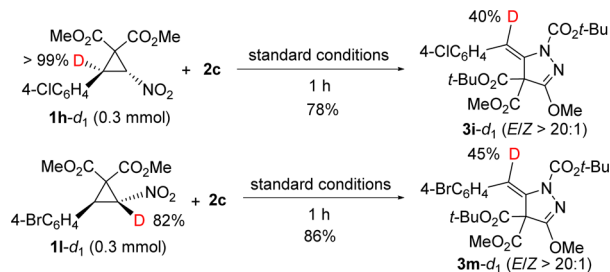
^aTypical conditions: Under a N_2 atmosphere, to a mixture of **1** (0.3 mmol) and **2c** (173 mg, 0.75 mmol) in CH_2Cl_2 (2.0 mL) was added PPh_3 (197 mg, 0.75 mmol), and the resulting mixture was then stirred at rt for a specified time. For details, see Supporting Information. ^bIsolated yields. ^cDetermined by ^1H NMR assay of the isolated product. ^dRun on a 3.0 mmol scale.

dicarboxylates **1** were evaluated in the reactions with azodicarboxylate **2c**. Under very mild conditions, a series of different aryl- or heteroaryl-substituted nitrocyclopropanes **1** smoothly gave their corresponding annulation products **3d,f–z** in moderate to excellent yields (Table 2, entries 1–22). A broad range of aryl substituents having different electronic and steric properties were well tolerated in the reaction. It is noteworthy

that all pyrazolines **3** were obtained as virtually single diastereomers with an *E*-configuration exocyclic alkene moiety except product **3u** in a modest 5:1 *E/Z* ratio (Table 2, entry 17). *E*-Styryl substituted nitrocyclopropane **1z** was also effective, furnishing product **3A** in 84% yield and high diastereoselectivity (Table 2, entry 23). However, aliphatic *n*-hexyl-substituted **1A** failed to yield the normal annulation product even though it was reacted for 24 h (Table 2, entry 24). A gram-scale synthesis of **3k** was also illustrated in 87% yield with 3.0 mmol of **1j** used (Table 2, entry 25).

To glean some mechanistic insights into this annulation reaction, we deliberately conducted the following experiments. Three control experiments were first run (for a schematic presentation, see Supporting Information). Under similar reaction conditions, nitrocyclopropane **1b** (0.3 mmol) was treated with Ph_3P (0.75 mmol) in the absence of azodicarboxylate **2c** for 24 h and no reaction was observed. This result clearly indicated that Ph_3P alone was not able to trigger any reactions of nitrocyclopropane **1b**. Also, two cyclopropanes dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1B** and dimethyl 2-methyl-2-nitro-3-phenylcyclopropane-1,1-dicarboxylate **1C** were found to be ineffective in the reactions with azodicarboxylate **2c** under the standard conditions (see Supporting Information). Two deuterium-labeling experiments were further performed (Scheme 2). Under the standard conditions,

Scheme 2. Deuterium-Labeling Experiments

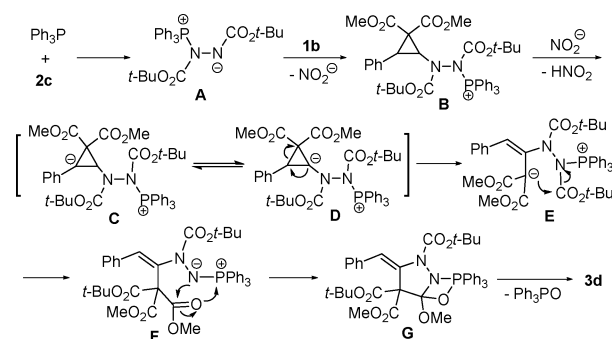


deuterated nitrocyclopropane **1h-d₁** (purity >99%) was reacted with azodicarboxylate **2c** and PPh_3 , affording a 78% yield of **3i-d₁** with 40% deuterium incorporation at the olefinic carbon. Under the same conditions, another deuterated nitrocyclopropane **1l-d₁** (purity 82%) also provided **3m-d₁** in 86% yield with 45% deuterium incorporation at the olefinic carbon (Scheme 2). These results implicated that proton exchanges occurred between 2- and 3-carbons of nitrocyclopropanes **1** in the annulation reaction.

Although a precise mechanism of this annulation reaction remains elusive, on the basis of the above mechanistic studies and previous reports,^{5c,15} a proposed mechanism for formation of pyrazolines **3** is exemplified in Scheme 3. Presumably the reaction sequence starts with the formation of Huisgen zwitterion **A**. Acting as a nucleophile, **A** engages in a substitution of nitrocyclopropane **1b** to give intermediate **B**.¹⁵ Upon deprotonation by the released nitrous anion,¹⁶ **B** yields interconvertible zwitterionic intermediates **C** and **D**, which undergo a ring-opening rearrangement to form intermediate **E**.^{17,18} Subsequently **E** undergoes a migration of the ester group from a N to C atom followed by an intramolecular aza-Wittig reaction to furnish the annulation product **3d** and byproduct Ph_3PO .¹⁹

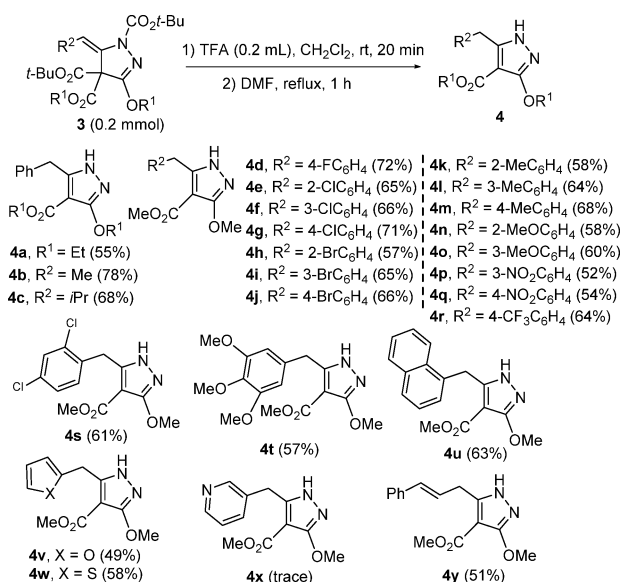
To expand its synthetic application of the annulation reaction, one-pot transformation of pyrazolines **3** into functionalized 1H-

Scheme 3. A Proposed Mechanism



pyrazoles **4** has been realized by taking full advantage of the vulnerability of the *tert*-butoxycarbonyl group to acids such as trifluoroacetic acid (TFA) (Scheme 4). In a typical procedure,

Scheme 4. Synthesis of Functionalized 1H-Pyrazoles 4



pyrazoline **3** (0.2 mmol) from azodicarboxylate **2c** was treated with trifluoroacetic acid (0.2 mL) in CH_2Cl_2 (2.0 mL) at rt for 20 min, and the solvent and volatile components were removed on a rotary evaporator. The residue was then dissolved in DMF (2.0 mL) and heated at reflux for 1 h, readily giving the corresponding functionalized 1H-pyrazole **4** in moderate yield after workup and isolation (Scheme 4). In pyrazolines **3**, ester groups other than *tert*-butoxycarbonyl remained intact in the reaction (Scheme 4, 4a–c). Other aryl-substituted pyrazolines **3** readily delivered their corresponding 1H-pyrazoles **4d–w** in acceptable yields except **3z** ($\text{R}^2 = 3$ -pyridyl) only yielded 1H-pyrazole **4x** in a trace amount. *E*-Styryl-substituted **3A** also smoothly delivered its product **4y** in 51% yield. Thus, the annulation reaction also provides a facile access to the functionalized 3-alkoxy 1H-pyrazoles.

In summary, we have successfully developed a novel annulation reaction of nitrocyclopropanes with in situ generated Huisgen zwitterions, leading to efficient synthesis of 3-alkoxy pyrazolines in good yields and high diastereoselectivities. This reaction represents a rare annulation reaction and accordingly reveals the new and divergent reactivity of nitrocyclopropanes as a kind of popular D–A cyclopropanes. Upon exposure toward the acid TFA, one-pot transformations of the prepared

pyrazolines from di-*tert*-butyl azodicarboxylate into corresponding 1*H*-pyrazoles have also been realized, providing a facile access to biologically important 3-alkoxy 1*H*-pyrazoles. Further expansion of the scope and applications in organic synthesis of this annulation reaction is currently underway in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b02415](https://doi.org/10.1021/acs.orglett.6b02415).

Experimental details, characterization data, NMR spectra for new compounds (PDF)

Crystallographic data for **3a** (CIF)

Crystallographic data for **4h** (CIF)

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Notes

The authors declare no competing financial interest.

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