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

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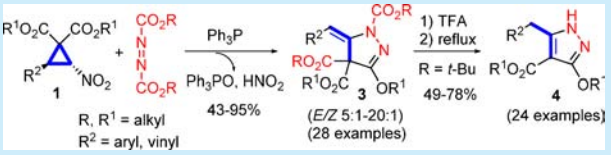
Supporting Information

**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

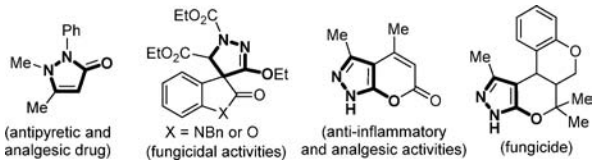
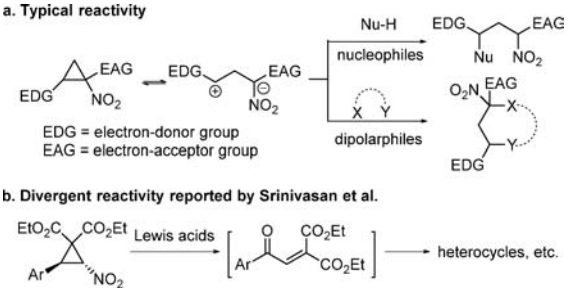



**Figure 1.** Bioactive 3-oxy(oxo) pyrazolines and pyrazoles.

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 cycloadditions, 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 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-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

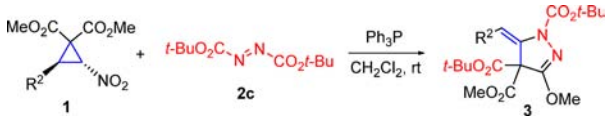
**Table 1. A Brief Survey on the Annulation Reaction between Nitrocyclopropanes 1 and Huisgen Zwitterions**[a]


**1a**, $R^1$ = Et, **1b**, Me, **1c**, *i*Pr, **1d**, *t*-Bu
**2a**, R = *i*Pr, **2b**, Et, **2c**, *t*-Bu

| 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 | – |

[a]Typical 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. [b]Isolated yields. [c]In all cases, the *E*/*Z* ratio > 20:1 as determined by $^1H$ NMR assay of the isolated products.

**Table 2. Scope of Nitrocyclopropanes 1**[a]




| entry | 1, $R^2$ | time (h) | 3[b] (%) | *E*/*Z*[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-$Cl_2C_6H_3$ | 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-$MeC_6H_4$ | 2 | **3n** (84) | >20:1 |
| 11 | **1n**, 3-$MeC_6H_4$ | 2 | **3o** (85) | >20:1 |
| 12 | **1o**, 4-$MeC_6H_4$ | 2 | **3p** (91) | >20:1 |
| 13 | **1p**, 2-$OMeC_6H_4$ | 2 | **3q** (93) | >20:1 |
| 14 | **1q**, 3-$OMeC_6H_4$ | 2 | **3r** (92) | >20:1 |
| 15 | **1r**, 3,4,5-$(OMe)_3C_6H_2$ | 2 | **3s** (86) | >20:1 |
| 16 | **1s**, 3-$NO_2C_6H_4$ | 1 | **3t** (78) | >20:1 |
| 17 | **1t**, 4-$NO_2C_6H_4$ | 1 | **3u** (80) | 5:1 |
| 18 | **1u**, 4-$CF_3C_6H_4$ | 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**, *E*-styryl | 2 | **3A** (84) | >20:1 |
| 24 | **1A**, *n*-hexyl | 24 | – | – |
| 25[d] | **1j** | 1 | **3k** (87) | >20:1 |

[a]Typical 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. [b]Isolated yields. [c]Determined by $^1H$ NMR assay of the isolated product. [d]Run on a 3.0 mmol scale.



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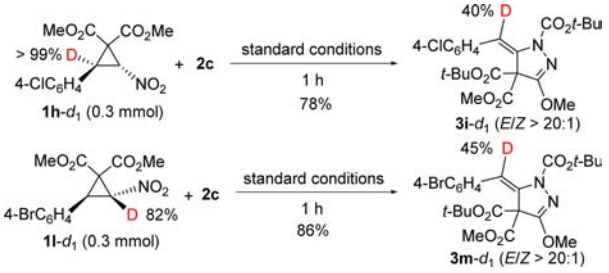
that all pyrazolines **3** were obtained as virtually single diastereomers with an *E*-configuration exocyclic alkene moiety except product **3u** in a modest 5:1 *E*/*Z* ratio (Table 2, entry 17). *E*-Styryl substituted nitrocyclopropane **1z** was also effective, furnishing product **3A** in 84% yield 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**

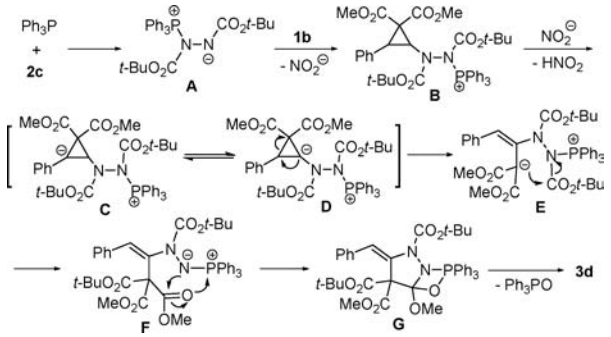



deuterated nitrocyclopropane **1h**-$d_1$ (purity >99%) was reacted with azodicarboxylate **2c** and $PPh_3$, affording a 78% yield of **3i**-$d_1$ with 40% deuterium incorporation at the olefinic carbon. Under the same conditions, another deuterated nitrocyclopropane **1l**-$d_1$ (purity 82%) also provided **3m**-$d_1$ 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]

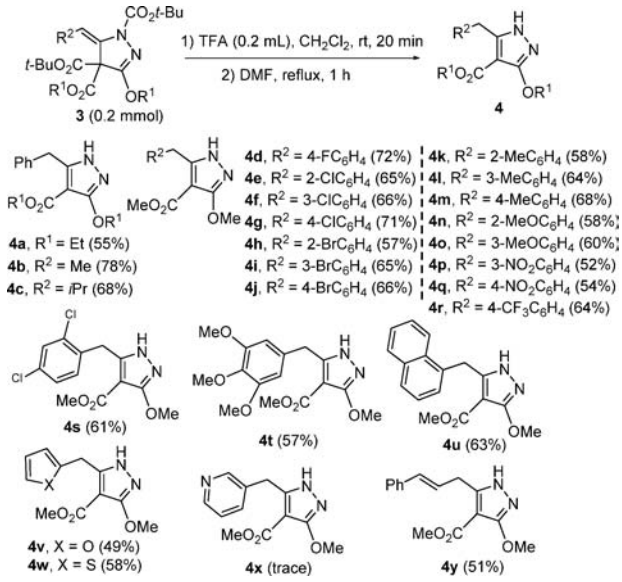
To expand its synthetic application of the annulation reaction, one-pot transformation of pyrazolines **3** into functionalized 1*H*-

**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 1*H*-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 1*H*-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 1*H*-pyrazoles **4d**−**w** in acceptable yields except **3z** ($R^2$ = 3-pyridyl) only yielded 1*H*-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 1*H*-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



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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.

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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