1,3-Dipolar Cycloaddition with Diazo Groups: Noncovalent Interactions Overwhelm Strain

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S *Supporting Information*

ABSTRACT: Like azides, diazoacetamides undergo 1,3-dipolar cycloadditions with oxanorbornadienes (OND) in a reaction that is accelerated by the relief of strain in the transition state. The cycloaddition of a diazoacetamide with unstrained ethyl 4,4,4-trifluoro-2-butynoate is, however, 35-fold faster than with the analogous OND because of favorable interactions with the fluoro groups. Its rate constant ($k = 0.53$ M^{-1} s^{-1} in methanol) is comparable to those of strain-promoted azide–cyclooctyne cycloadditions.
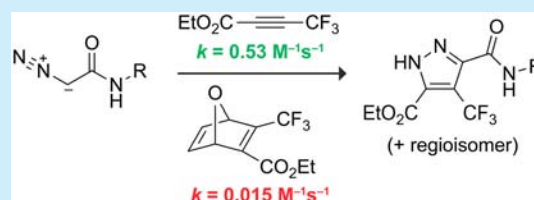
The Huisgen 1,3-dipolar cycloaddition dominates the landscape of reactions that are chemoselective in biological contexts.[1] Although the copper-catalyzed azide–alkyne cycloaddition (CuAAC)[2] and the strain-promoted azide–alkyne cycloaddition (SPAAC)[1a] fulfill many criteria of an ideal "click" reaction,[2] the desire for increased reactivity and selectivity in noncatalyzed reactions remains strong.[3]

Recently, we demonstrated the use of a stabilized diazo group as a chemical reporter.[1k,4,5] Despite significant conjugative stabilization, diazoacetamides are primed for rapid normal-electron-demand 1,3-dipolar cycloadditions and show reaction rates with strained alkynes that surpass those of azides.[6] Moreover, diazoacetamides endure cellular metabolism and provide chemoselectivity in the presence of terminal alkynes, a feature unobtainable with an azido moiety.[1k] Still, overlapping reactivity with azido groups does not allow for selective reactivity of diazo groups in an SPAAC. We have found, however, that removing strain and tuning the LUMOs of the dipolarophile can provide diazo-selective reactivity.[7] In addition, cycloaddition rates with α,β-unsaturated carbonyl compounds are increased by incorporating electron-withdrawing substituents.[8]

We sought to incorporate strain while retaining electronic tunability as a primary design feature. These attributes are enabled in the bicyclic oxanorbornadiene (OND) scaffold (Scheme 1). Electron-deficient ONDs are effective dipolarophiles in reactions with azides, displaying increased reactivity relative to their linear precursors.[9] This increase is a consequence of the relief of ring-strain in the transition state (TS), along with a lower LUMO energy of the bicyclic alkene compared to that of an alkynyl π-bond.[10] Their facile preparation from common starting materials and opportunity for alkenyl substitution make ONDs attractive in comparison to synthetically recalcitrant cyclooctynes. Moreover, the reactions of ONDs with nucleophilic species are rapid enough for numerous applications,[11] and diazo groups are more nucleophilic than are azido groups.[1j,6] Accordingly, we explored

Scheme 1. Pyrazole Product Obtained from the 1,3-Dipolar Cycloaddition of Diazoacetamide 1 with Alkyne 3 and Oxanorbornadiene 4[a]

3a,4a,5a: $R^1 = CO_2Et$, $R^2 = CF_3$
3b,4b,5b: $R^1 = R^2 = CO_2Me$
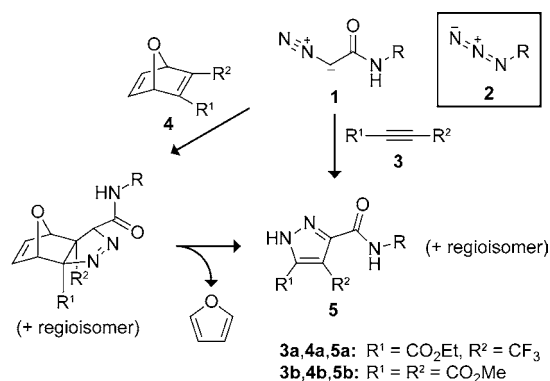
[a]Azide **2** reacts analogously to form a triazole.

the reactivity of ONDs shown previously to undergo 1,3-dipolar cycloadditions with azides.[9]

We found that, like azide **2**, diazoacetamide **1** (R = Bn) undergoes 1,3-dipolar cycloadditions with OND **4** followed by a retro-Diels–Alder reaction to eliminate furan (Scheme 1). The resulting pyrazole product is identical to that formed upon reaction with analogous alkyne **3**. Unlike with azides,[9] however, we found that diazoacetamide **1** (R = Bn) does not react with the unsubstituted alkenyl group of ONDs **4a** and **4b**.
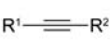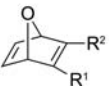
Cycloaddition reactions of an azido group with ONDs are known to be ~5-fold faster than are those with analogous alkynes.[9a] Accordingly, we determined rate constants for the cycloadditions of diazoacetamide **1** (R = Bn) with ONDs **4a** ($R^1 = CO_2Et$, $R^2 = CF_3$) and **4b** ($R^1 = R^2 = CO_2Me$) and

analogous alkynes **3a** and **3b** (Figure S1). We found the rate constants for the cycloaddition of diazoacetamide **1** (R = Bn) with ONDs **4a** and **4b** (Table 1) to be 10^2-fold faster than

Table 1. Rate Constants for the Cycloaddition of Diazoacetamide 1 (R = Bn) with Alkynes 3a and 3b and with ONDs 4a and 4b[a]

dipolarophile		R^1	R^2	k (10^{-2} M^{-1}s^{-1}) [a]
$R^1\text{---}R^2$	**3a**	CO_2Et	CF_3	53
	3b	CO_2Me	CO_2Me	0.46
	4a	CO_2Et	CF_3	1.5
	4b	CO_2Me	CO_2Me	1.1

[a]Values were determined in methanol with ^{1}H NMR or ultraviolet spectroscopy.

those of azides with ONDs.[9a] Moreover, the diazoacetamide−OND rate constants are comparable to those of known SPAACs.[3] The incorporation of strain into OND **4b** increases the rate constant by 2-fold relative to the reaction with alkyne **3b**, a slightly smaller effect than observed in the analogous reactions of azides.[9a]

The cycloadditions of diazoacetamide **1** with alkyne **3a** and analogous OND **4a** were dichotomous with those of azides.[9a] Rather than a modest increase in the reaction rate with an OND,[9a] we observed the reaction rate of diazoacetamide **1** with OND **4a** to be 1/35th that with alkyne **3a**. Moreover, the reaction rate of diazoacetamide **1** with alkyne **3a** is comparable to that of the fastest of reported SPAACs[1f,12] and approaches that of the diazoacetamide−DIBAC cycloaddition.[1k] This result was unexpected, as the lower LUMO of alkenes relative to alkynes and the strain imposed by the OND framework led us to anticipate the opposite trend in reactivity. Accordingly, we pursued a computational analysis to better understand the surprising reactivity of alkyne **3a**.

Calculated activation barriers for the cycloadditions of both alkynes and ONDs (Figure 1) correlate with their relative
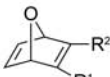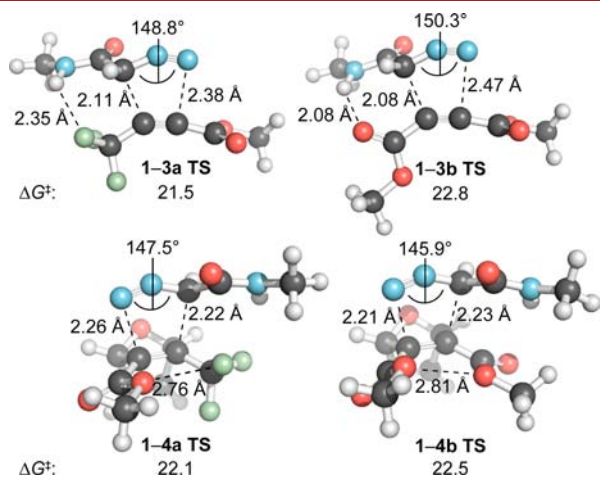

Figure 1. Optimized transition-state geometries for the cycloaddition of diazoacetamide **1** (R = Me) with alkynes **3a** and **3b** and with ONDs **4a** and **4b** as calculated at the M06-2X/6-31+G(2d,p) level of theory. Free energies (kcal/mol) include solvation corrections (MeOH) on gas-phase geometries with the IEFPCM model (radii = UFF).

reactivity (Table 1). The 1,3-dipolar cycloaddition should be the rate-determining step in the cycloadditions with ONDs (Figure S2). On the basis of $\Delta E^{\ddagger}$ values (Table 2), the origins of the increased reactivity of alkyne **3a** are not immediately apparent. Enthalpic contributions suggest that OND **4a** should react faster than alkyne **3a** (Table S1). FMO energies and the increased strain of bicyclic systems[13] relative to alkynes also predict a faster rate for the OND. To understand the increased reactivity of alkyne **3a**, we turned to the distortion/interaction analysis developed by Ess and Houk (Table 2).[14,15] In this approach, the overall reaction barrier can be understood as the sum of the free energy required to distort isolated reactants to transition state (TS) geometries and the free energy gained when these distorted reactants interact in the TS:[15a]

$$\Delta G^{\ddagger} = \Delta G_{dist}^{\ddagger} + \Delta G_{int}^{\ddagger} \qquad (1)$$

The origins of increased reactivity can be understood when free energies of distortion and interaction are taken into account (Table 2). The difference in total distortion free energy between the alkyne and OND TSs ($\Delta\Delta G_{dist}^{\ddagger} < 1$ kcal/mol for **1−3a TS** and **1−4a TS**) is much less than the difference in total distortion energy ($\Delta\Delta E_{dist}^{\ddagger} = 1.7$ kcal/mol for **1−3a TS** and **1−4a TS**; Figure S3), allowing interactions to dictate the observed reactivity ($\Delta\Delta G_{int}^{\ddagger} = 1.4$ kcal/mol versus $\Delta\Delta E_{int}^{\ddagger} = 0.2$ kcal/mol for **1−3a TS** and **1−4a TS**).

In agreement with FMO energies, the distortion energies of ONDs **4a** and **4b** are significantly lower than are those of alkynes **3a** and **3b**.[16] Interestingly, the distortion energy of fluorinated OND **4a** is much larger than that of bis-esterified OND **4b** (8.1 versus 6.4 kcal/mol). This increase appears to be due to a slightly smaller dihedral angle of the alkene in the starting geometry of **4b** along with increased steric crowding of electron-rich substituents in **4a** (Figure 1). The closest O···O distance decreases by 0.07 Å from the starting material to the TS geometry in **4b** (2.88 to 2.81 Å), whereas the closest O···F distance decreases by 0.12 Å in **4a** (2.88 to 2.76 Å).

In alkyne **3a**, which avoids deleterious steric interactions, fluorination facilitates bending, leading to decreased distortion energies.[1h] In addition, large interaction energies result from hyperconjugative assistance to the nascent bonds or hydrogen-bonding interactions (or both), depending on the regioisomer of the TS (Figure S4). Analogous effects of propargylic fluorination on alkyne bending and interaction energies have been reported previously during cycloadditions with azides[1h,j] and diazo compounds.[8]

Lowered distortion energies for diazoacetamide **1** in reactions with alkynes **3a** and **3b** (relative to reactions with ONDs **4a** and **4b**) and shorter incipient C−C bonds result in a highly asynchronous TS (Figure 1). The result is unidirectional charge transfer amplified by propargylic fluoro groups in the reaction of alkyne **3a**. The charge transfer creates a more polar TS and larger solvent effects (Table 2).[6,17] Only with alkyne **3a** is the free energy of activation lower in solution than in the gas phase (Figure S5), suggesting that fluorine induces a more favorable $\Delta S^{\ddagger}$ in polar media.

We have discovered an unexpectedly large effect of propargylic fluorination on 1,3-dipolar cycloadditions with diazoacetamides. These effects render the reaction with alkyne **3a** to be much faster than that with an OND having analogous substitution and comparable in rate to the fastest known SPAACs. Others have noted that strain relief is the most significant design principle for increasing the rate of azide−alkyne cycloadditions.[19] In particular, alkyne bending decreases

Table 2. Distortion/Interaction Analysis for the Cycloaddition of Diazoacetamide 1 (R = Me) with Alkynes 3a and 3b and with ONDs 4a and 4b[a]

dipolarophile		R^1	R^2	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{dist}$ dipolarophile	$\Delta G^{\ddagger}_{dist}$ dipole (1)	total	$\Delta G^{\ddagger}_{int}$	charge (e^-) on the dipole (1) in the TS[b] gas-phase	charge (e^-) on the dipole (1) in the TS[b] MeOH	charge (e^-) on the dipole (1) in the TS[b] Δ
R^1——R^2	3a	CO_2Me	CF_3	9.6	21.5	10.4	14.8	25.2	−3.6	0.25	0.28	0.3
	3b	CO_2Me	CO_2Me	9.8	22.8	12.7	13.1	25.8	−3.0	0.26	0.28	0.2
	4a	CO_2Me	CF_3	8.2	22.1	8.1	16.2	24.3	−2.2	0.24	0.25	0.1
	4b	CO_2Me	CO_2Me	7.8	22.5	6.4	17.7	24.1	−1.6	0.22	0.23	0.1

[a]Calculations were performed at the M06-2X/6-31+G(2d,p) level of theory. Energies (kcal/mol) include solvation corrections (MeOH) on gas-phase geometries with the IEFPCM model (radii = UFF). [b]Calculated with natural bond orbital (NBO) analysis.[18]

the HOMO−LUMO gap[1j], a scenario that is optimal for azido dipoles, which are substantially more ambiphilic than are diazo dipoles.[12b] In essence, strain provides the opportunity to increase the donor and acceptor properties of the alkyne π-bond simultaneously, leading to cycloadditions that can be more synchronous than those of linear alkynes.

In comparison to their azido congeners, diazo dipoles are much more nucleophilic.[6,7] Although strain relief can increase cycloaddition rates,[1k,4] a strong preference for electron-deficient dipolarophiles renders the diazo group much more sensitive to substituent effects, obviating strain relief as a sine qua non for rapid reaction.[20] This difference is advantageous in polar solvents (like water), where highly asynchronous TSs can lead to large rate enhancements. Accordingly, diazo groups are highly tunable moieties of broad potential utility in chemical biology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01938.

> Synthetic methods and analytical data along with additional computational data, Cartesian coordinates, energies, and imaginary frequencies (for TSs) (PDF)

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Notes

The authors declare no competing financial interest.

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