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Rapid cycloaddition of a diazo group with an unstrained dipolarophile

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ABSTRACT

The cycloaddition of a diazoacetamide with ethyl 4,4,4-trifluorocrotonate proceeds with $k = 0.1\ M^{-1}\ s^{-1}$. This second-order rate constant rivals those of optimized strain-promoted azide–alkyne cycloadditions, even though the reaction does not release strain. The regioselectivity and a computational distortion/interaction analysis of the reaction energetics are consistent with the formation of an N—H···F—C hydrogen bond in the transition state and the electronic character of the trifluorocrotonate. Analogous reactions with an azidoacetamide dipole or with an acrylate or crotonate dipolarophile are much slower. These findings suggest a new strategy for the design of diazo-selective reagents for chemical biology.

Introduction

The diazo group has the potential to be a valuable addition to the armamentarium of chemical biology. A complement to azido groups, diazo groups have been employed in many biochemical applications, including reversible[1] and non-reversible protein alkylations,[2] nucleic acid conjugation,[3] and other bioconjugations.[4] Extant strategies to install pendant diazo groups[5] and to prepare them directly by deimidogenation of a parent azide[6] facilitate their use.

Mistakenly believed to be too reactive for physiological investigations, a diazo moiety stabilized by electronic delocalization can tolerate metabolism while retaining reactivity.[7] Nevertheless, the use and development of diazo compounds in chemical biology are constrained by a paucity of chemoselective reactions. Most confounding is the overlapping reactivity of the diazo group with that of the azido group in strain-promoted azide–alkyne cycloadditions (SPAACs).[7,8]

The need for reactions that are chemoselective in a biological context continues to grow.[9] Recently, we explored 1,3-dipolar cycloadditions of diazo compounds in the presence of azides.[10] Although we were able to achieve diazo group-specific conjugation in the absence of a catalyst (Scheme 1), the reaction rates were low—comparable to those obtained with early SPAAC reagents and exceeded by new SPAAC reagents.[8c,11] Hence, we sought a faster cycloaddition.

We were aware that fluoro groups can elicit favorable orbital interactions in cycloadditions[12] and other reactions.[13] Accordingly, we explored the utility of fluoro groups in a cycloaddition reaction with a diazo compound. We discovered that the reaction of a diazoacetamide with a fluorinated crotonate proceeds at an extraordinary rate. We used computations to provide insight into this rate acceleration. The results reveal a general strategy for the design of efficacious diazo-selective reagents for applications in chemical biology.

Results and discussion

In an initial screen of reactions, we dissolved *N*-benzyl-2-diazoacetamide (**1**) in 1:1 CH_3CN/H_2O and added ethyl 4,4,4-trifluorocrotonate (**2**) to the resulting solution (Scheme 2).[14] We found that the diazo compound was consumed rapidly, as monitored with thin-layer chromatography. The reaction product had the mass of the pyrazoline that would result from the dipolar cycloaddition reaction of the diazo group and the alkene. We monitored the reaction by ultraviolet spectroscopy, and found the observed rate constant to be $k = 0.105\ M^{-1}\ s^{-1}$. This rate constant is comparable to that of an azide with BARAC, which is the fastest known SPAAC reaction.[15]

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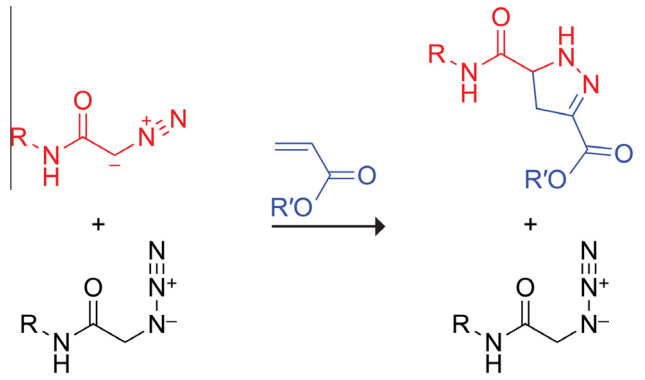


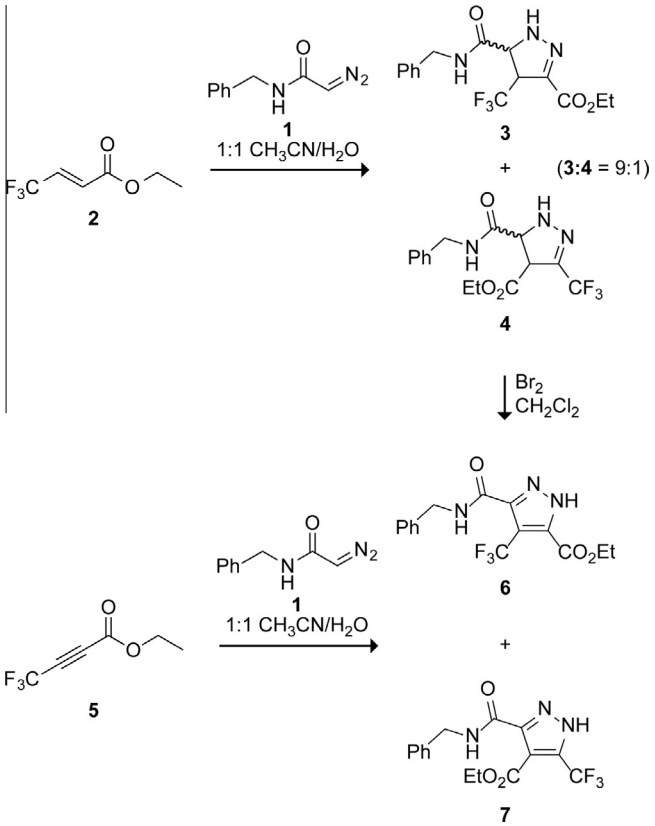
Scheme 1. Chemoselective cycloaddition of a diazoacetamide with an acrylate ester.

The putative pyrazoline product contained a mixture of isomers. We were able to purify the major product (**3**) and confirm its structure using ^{3}J coupling values from ^{1}H NMR spectroscopy as verified with heteronuclear multiple bond correlation (HMBC). Based on isolated yields, the cycloaddition occurred to produce **3** and **4** in a 9:1 ratio. This strong regiochemical preference for the *anti* orientation of the carbonyl groups is consistent with the π-acceptor ester group being a stronger electron-withdrawing substituent than is the σ-acceptor trifluoromethyl group and with the formation of an N—H···F—C hydrogen bond, as has been observed in other contexts.[16]

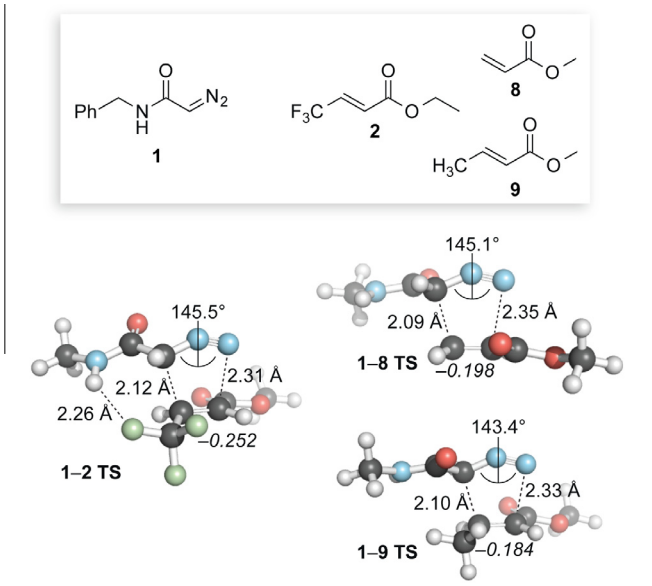
To verify the identity of products **3** and **4**, we sought to oxidize the enantiomeric mixture of pyrazolines to their aromatic pyrazole equivalents.[17] Attempts at oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were unsuccessful, but treatment with Br_2 produced the pyrazole product (Scheme 2). To confirm the assignment of pyrazolines **3** and **4**, the oxidation products were compared to those resulting directly from the reaction of diazoacetamide **1** with ethyl 4,4,4-trifluorobut-2-ynoate (**5**). The ^{1}H NMR and ^{13}C NMR spectra of **6** and **7** produced by the two routes were indistinguishable.

Next, we confirmed the importance of electronic acceleration provided by allylic fluorination by assessing the cycloaddition of diazoacetamide **1** with ethyl acrylate (**8**), which lacks the trifluoromethyl group, and methyl crotonate (**9**), which lacks the three fluoro groups. Previously, we reported that the reaction of **1** and **8** proceeds with a rate constant of $k = 1.6 \times 10^{-3}\ M^{-1}\ s^{-1}$ (Fig. 1), which is 10^{2}-fold less than that of trifluorocrotonate **2**.[10] Here, we found the rate constant for cycloaddition with crotonate **9** to be $k = 5.8 \times 10^{-7}\ M^{-1}\ s^{-1}$, which is 10^{5}-fold less than that for trifluorocrotonate **2**. Notably, the effect of allylic fluorination in this reaction is much larger than is the effect of propargylic fluorination on the cycloaddition of azides (~400-fold).[12d] Finally, when added to an equimolar mixture of diazoacetamide **1** and *N*-benzyl-2-azidoacetamide (**10**), excess trifluorocrotonate **2** reacted only with diazoacetamide **1**, demonstrating chemoselectivity.

We employed computational methods to investigate the origin of the increased reactivity of trifluorocrotonate **2**. Optimizations were performed with Gaussian 09 software[18] at the M06-2X level of theory[19] and the 6-31+G(2d,p) basis set. M06-2X has been shown to describe trends in reactivity accurately in other cycloadditions.[20] Optimizations were performed in the gas phase, and



Scheme 2. Rapid cycloaddition of a diazoacetamide with a 4,4,4-trifluorocronate ester, and product analysis.



	Alkene	k ($M^{-1}s^{-1}$)	$\Delta G^{‡}$	$\Delta E^{‡}$	ΔE_{dist} dipole	ΔE_{dist} alkene	ΔE_{int}
1–2 TS	Trifluorocrotonate **2**	1.05×10^{-1}	25.8	12.2	18.1	9.2	–15.1
1–8 TS	Acrylate **8**	1.6×10^{-3}	26.6	13.5	17.7	7.1	–11.4
1–9 TS	Crotonate **9**	5.8×10^{-7}	30.5	17.7	19.6	10.1	–12.4

Figure 1. Experimental rate constants and computational parameters of the transition state for cycloadditions of a diazoacetamide with a trifluorocrotonate (**1–2** TS), acrylate (**1–8** TS), and unfluorinated crotonate (**1–9** TS). Optimized geometries, activation energies, distortion/interaction energies, and NBO charges on the dipolarophile (*italics*) were calculated at the M06-2X/6-31+G(2d,p) level of theory. Energies (kcal/mol) include solvation corrections (water) on gas-phase geometries using IEFPCM model (radii = UFF). The methyl ester of trifluorocrotonate **2** was used to model the ethyl ester. Rate constants were measured in 1:1 CH_3CN/H_2O (**1** + **2**; **1** + **8**) or CH_3CN (**1** + **9**). Data for the cycloaddition of **1** and **8** were reported previously.[10]

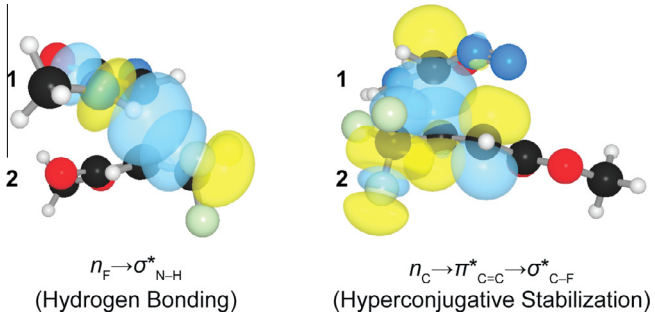


Figure 2. Orbital overlaps in the transition state for the reaction of diazoacetamide **1** and trifluorocrotonate **2** as calculated at the M06-2X/6-31+G(2d,p) level of theory on gas-phase optimized geometries using IEFPCM (water) solvation corrections. Depictions were generated with NBOView 1.1.

were followed by single-point solvation corrections. An IEFPCM dielectric continuum solvent model for water with UFF radii was employed. This model does not explicitly include non-electrostatic contributions and should be considered as a first approximation of solvation effects.[21] Frequency calculations were performed to confirm stationary points as minima or first-order saddle points (transition state, TS). All ΔE values include zero-point corrections.

Distortion/interaction analysis of the rapid cycloaddition of trifluorocrotonate **2** compared to that for methyl acrylate (**8**) and the unfluorinated crotonate (**9**) revealed the origin of the low barrier (Fig. 1).[22] Relative to the unfluorinated crotonate **9**, trifluorocrotonate **2** displays decreased distortion energies for both reacting partners, in addition to significantly larger interaction energies. The increased reactivity over acrylate **8**, however, stems not from a decreased distortion energy, as observed for typical cycloadditions of diazoacetamides,[10] but from a large increase in interaction energy (ΔE_{int}) that results from an N—H···F—C hydrogen bond formed between the diazoacetamide and a fluoro group of the trifluorocrotonate, along with hyperconjugative assistance to bond formation. Both hydrogen-bond formation[12d,23] and hyperconjugative assistance to bond formation have been asserted previously for cycloadditions with azides.[12e] A key attribute of these interactions is that they are weak or absent in the starting materials, even when the alkene is in the TS geometry, and do not manifest fully until the TS.

NBO analysis[24] (Fig. 2, Table 1) reveals a small increase (~4.0 kcal/mol) in key stereoelectronic interactions (e.g., $\pi_{C=C} \rightarrow \sigma^*_{C-F}$, $\pi_{C=C} \rightarrow \pi^*_{C=O}$) upon going from the starting material (SM) to the distorted alkene. Importantly, a large increase in these interactions is observed in the TS when the diazoacetamide is present. The difference arises because of assistance to bond formation (provided by the carbonyl and allylic C—F bonds[12d]) and the formation of a N—H···F—C hydrogen bond. The largest increase in NBO interaction energy of 15.2 kcal/mol upon proceeding from the SM to the TS (versus a 10.4 and 10.2 kcal/mol increase for acrylate **8** and unfluorinated crotonate **9**, respectively) is in gratifying agreement with the large ΔE_{int} = 15.1 kcal/mol predicted by the distortion analysis. Whereas electronic assistance to bond formation is a direct effect of a lower LUMO, the alternative strategy of employing a remote hydrogen-bonding interaction allows for increased reactivity without sacrificing intrinsic chemoselectivity.

Conclusions

In conclusion, we report on 'speed without strain'. The 1,3-dipolar cycloaddition between a stabilized diazo group and a fluorinated crotonate occurs at a reaction rate comparable to that of the fastest SPAAC reactions but requires no activation by strain. Through a computational distortion/interaction analysis, we conclude that the enhanced reactivity results from the development of strong interactions in the transition state, including an N—H···F—C hydrogen bond and hyperconjugation with allylic C—F bonds. Diazo compounds can complement azides as biological probes,[7] and the insights herein could inspire the de novo design of dipolarophiles tailored for rapid reaction with a diazo group.[25]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.020.

Table 1
Energies (kcal/mol) from the NBO analysis of stabilizing interactions in trifluorocrotonate **2**, acrylate **8**, and crotonate **9** in ground state and transition state geometries, and in the full transition state. Energies were calculated at the M06-2X/6-31+G(2d,p) on gas-phase optimized geometries using IEFPCM (water) solvation corrections

Alkene	Type of interaction	Interacting orbitals	SM	Distorted alkene (TS geometry)	TS	Δ(TS − SM)
Trifluorocrotonate **2**	Conjugative	$\pi_{C=C} \rightarrow \pi^*_{C=O}$	18.5	20.9	26.4	7.9
	Hyperconjugative	$\pi_{C=C} \rightarrow \sigma^*_{C-F}$ [a]	12.0	13.5	10.3	−1.7
	Hyperconjugative	$\pi^*_{C=C} \rightarrow \sigma^*_{C-F}$ [a]	<0.5	<0.5	7.1	7.1
	Hydrogen-bonding	$n_F \rightarrow \sigma^*_{N-H}$ [b]	—	—	2.9	2.9
		Σ	30.5	34.4	46.7	15.2
Acrylate **8**	Conjugative	$\pi_{C=C} \rightarrow \pi^*_{C=O}$	21.8	25.2	32.2	10.4
		Σ	21.8	25.2	32.2	10.4
Crotonate **9**	Conjugative	$\pi_{C=C} \rightarrow \pi^*_{C=O}$	24.8	28.4	35.3	10.5
	Hyperconjugative	$\pi_{C=C} \rightarrow \sigma^*_{C-H}$ [a]	4.9	3.4	2.5	−2.4
	Hyperconjugative	$\pi^*_{C=C} \rightarrow \sigma^*_{C-H}$ [a]	<0.5	<0.5	2.1	2.1
		Σ	29.7	31.8	39.9	10.2

[a] Value is the sum of the interactions of the alkene π-bond with each of the three allylic σ^* orbitals.
[b] Value is the sum of the interactions of two different lone pairs for a single fluoro group with the N—H σ^* at a distance of 2.26 Å (Fig. 1).

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