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Ylidenenorbornadiene Carboxylates: Experimental Kinetic Analysis of a Nucleophile-Induced Fragmentation Reaction

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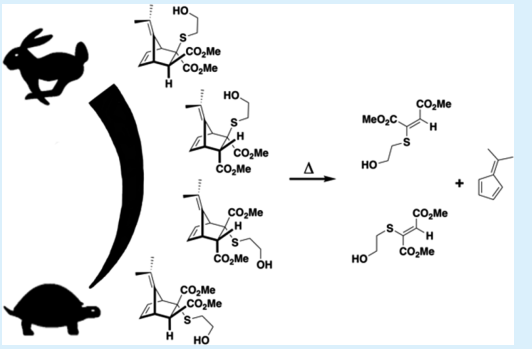
ABSTRACT: Ylidenenorbornadienes (YNDs), prepared by [4 + 2] cycloadditions between fulvenes and acetylene carboxylates, react with *beta*-mercaptoethanol to yield a mixture of four diastereomers. These four diastereomers fragment via a retro-[4 + 2] cycloaddition at differing rates. A simulated kinetics approach extrapolated the rate constants of the diastereomers from the observed rate data. YNDs display wide variability in rate of fragmentation, dependent on the stereoelectronics of the ylidene substituents. A substrate containing one carboxylic ester proved exceptionally stable to fragmentation.



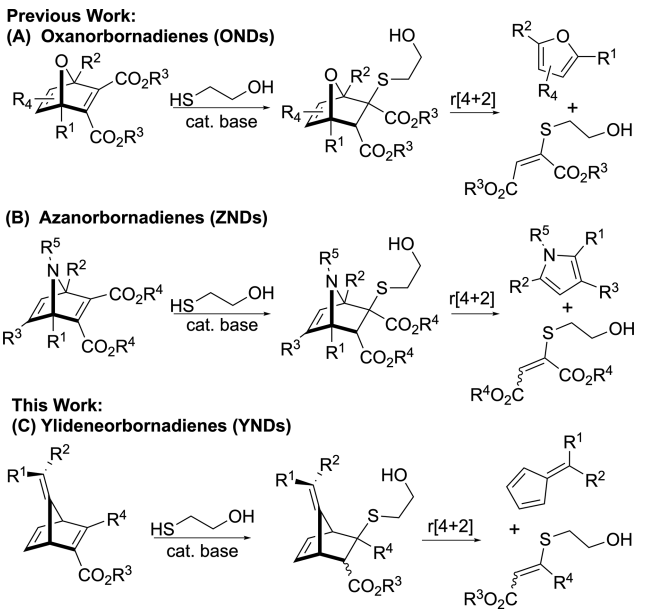
Functionalized molecules that fragment via retro-grade cycloadditions hold immense possibilities as dynamic covalent linkages. One commonly employed dynamic covalent system utilizes a furan diene and maleimide dienophile in a [4 + 2] cycloaddition reaction. This chemistry has been studied extensively, and the chemical reaction mechanisms are well understood.[1,2] Limitations for this reaction include fragmentation over a broad temperature range.[3−6] Fulvenes have previously displayed a wide array of cycloaddition reactivities,[7−15] and their use as dienes in place of furan has been shown to narrow this fragmentation temperature window.[16−19]

Previous work pioneered by the Finn group has recently highlighted [4 + 2] cycloadditions between furan or pyrrole dienes with acetylene dicarboxylate dienophiles, which are exergonic in the formation of oxa- and azanorbornadienes, ONDs[20−25] and ZNDs,[26] respectively (Scheme 1). These systems are then "switched on" by a nucleophile (thiol, amine, or phosphine) stimulus, and the fragmentation of the adduct is favored via a retro-[4 + 2] cycloaddition. To date, OND systems have shown potential in drug delivery,[27] degradable hydrogels,[21] and the synthesis of traditionally difficult to access small molecules.[23,28]

We envisioned a third nucleophile-induced fragmentation system with an ylidene atop the bridge of the norbornadiene motif. These systems could be prepared via a [4 + 2] cycloaddition of fulvenes and acetylene carboxylates to yield ylidenenorbornadienes (YNDs).

Following previously reported methodology,[11,29,30] a series of YNDs were prepared via [4 + 2] cycloadditions between fulvenes and acetylene dicarboxylates (Scheme 2). Synthetic

Scheme 1. Nucleophile-Induced Fragmentation Systems



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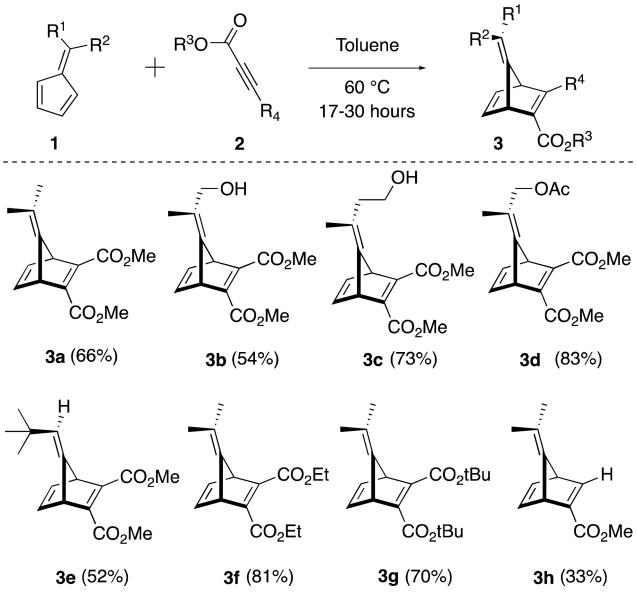
Scheme 2. YND Substrate Scope[a]



[a]Yields refer to isolated, purified products.

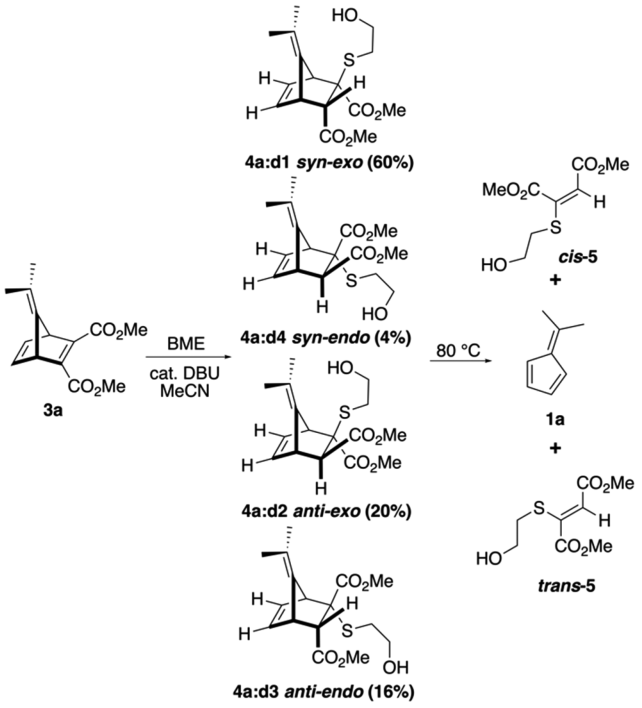
yields were fair to excellent with moderate heating in toluene under an air atmosphere. Notably, methyl propiolate reacts successfully with 6,6-dimethylfulvene to furnish **3h**. To date, there have been no reports of easily accessed ONDs from acetylene monocarboxylates, and in our hands, attempts to react an acetylene monocarboxylate with a furan ended in polymerization.

To test the thermal stability of YNDs, a crossover experiment was conducted. YND **3f** was heated in DMSO-d_6 for 30 min at each of the following temperatures, 60, 80, 100, and then 120 °C, in sequence with dimethylacetylene dicarboxylate (DMAD) (Scheme S3). No presence of YND **3a** was observed, indicating that even under elevated temperatures the [4 + 2] cycloaddition is not reversible. Based on the consistent observation of pyrrole, even with excess acetylene, Finn and co-workers suggest the reversibility of the cycloaddition of azanorbornadiene systems under similar conditions.[26] These two results indicate that YND systems exhibit a higher stability than ZNDs and would likely offer different fragmentation kinetics.

We then assessed the viability of YNDs as nucleophile-induced fragmenting systems. Model substrate **4a** was prepared via a conjugate addition with *beta*-mercaptoethanol (BME). However, unlike the OND and ZND systems with the BME nucleophile,[22,26] YND−BME adducts provided a complex mixture of four diastereomers **4a:d1−4** (Scheme 3). Presumably, this is because: (1) YNDs have increased steric hindrance at the top of the norbornadiene bridge, lessening the preference for an *exo*-face attack of the thiol nucleophile, and (2) YNDs lack a H-bond acceptor (O or N) that could potentially direct either the thiol nucleophile or the addition of the proton during the conjugate addition reaction. Reaction with BME and Et_3N as a catalytic base was sluggish and failed to reach completion within 24 h. However, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU)[31] yielded nearly quantitative amounts of YND−BME **4a** in less than 5 min.

The adduct mixture proved stable to chromatography, but the diastereomers could not be separated. After chromatographic isolation, the mixture of YND−BME adducts **4a:d1−4**

Scheme 3. YND−BME 4a:d1-4 Diastereomers[a]



[a]Diastereomer percentages were determined from ^{1}H NMR integrations in $CDCl_3$.

was then heated to 80 °C in DMSO-d_6 and analyzed for fragmentation kinetics via ^{1}H NMR. The plot of the integrated first-order rate law was not linear. The curvature appeared to be due to a difference in fragmentation rates of the diastereomers of YND−BME **4a**. To elucidate the degradation rates of the individual diastereomers, we applied kinetic simulations[32] extrapolating the observed rate data of the mixture in DMSO-d_6. For this approach to be successful we first needed to identify the diastereomeric ratio of YND−BME **4a**.

The ratio of diastereomers was determined by integrations of the alkene proton signals in the ^{1}H NMR spectrum in $CDCl_3$ (Figure S1). The structural assignment of diastereomers **4a:d1−4** was realized based on three factors: (1) the rapid disappearance of the ^{1}H NMR signal assigned to **4a:d2** in conjunction with the consequent appearance of the vinyl proton ^{1}H NMR signal of the thioether-fumarate *trans*-**5**; (2) the ratio of thioether-maleate:thioether-fumarate (*cis*-**5**:*trans*-**5**) isomers at the end of kinetic trials; and (3) the assumption that the major diastereomer **4a:d1**, present at 60%, is the syn-exo diastereomer since syn-exo isomers are the only isomers observed in the OND and ZND systems with BME nucleophiles.[22,26] (For a more thorough explanation of the ^{1}H NMR analysis, see the Supporting Information).

In DMSO-d_6, it was not possible to accurately follow the rate of fragmentation. During ^{1}H NMR kinetic experiments in DMSO-d_6, the peaks of **4a:d1**, **4a:d2**, and **4a:d3** overlap as one peak, and the peak of **4a:d4** overlaps with a product peak that appears quickly. To solve this issue, a genetic algorithm and the simplex method were used to iteratively determine the rate constants from limited concentration vs time data.[32] With the diastereomeric ratio measured from the distinguishable peaks in $CDCl_3$, kinetic simulations were performed in MATLAB to determine the rate constants for the retro-[4 + 2] cyclo-

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addition for **4a:d1−3** in DMSO-d_6. The error function used by the algorithm was defined as eq 1.

$$\epsilon(k_{d1}, k_{d2}, k_{d3}) = \sum (\ln(A_{exp}) - \ln(r_{d1}e^{-k_{d1}t} + r_{d2}e^{-k_{d2}t} + r_{d3}e^{-k_{d3}t}))^2 \quad (1)$$

The error function is the sum of the squared difference between the experimental concentrations, A_{exp}, and the computed concentrations based on the guessed rate constants, k_{d1}, k_{d2}, and k_{d3}, and the ratios for each diastereomer, r_{d1}, r_{d2}, and r_{d3}, at the same times, t. The minimum of the error function (Figure 1A) is where the simulated rate constants best

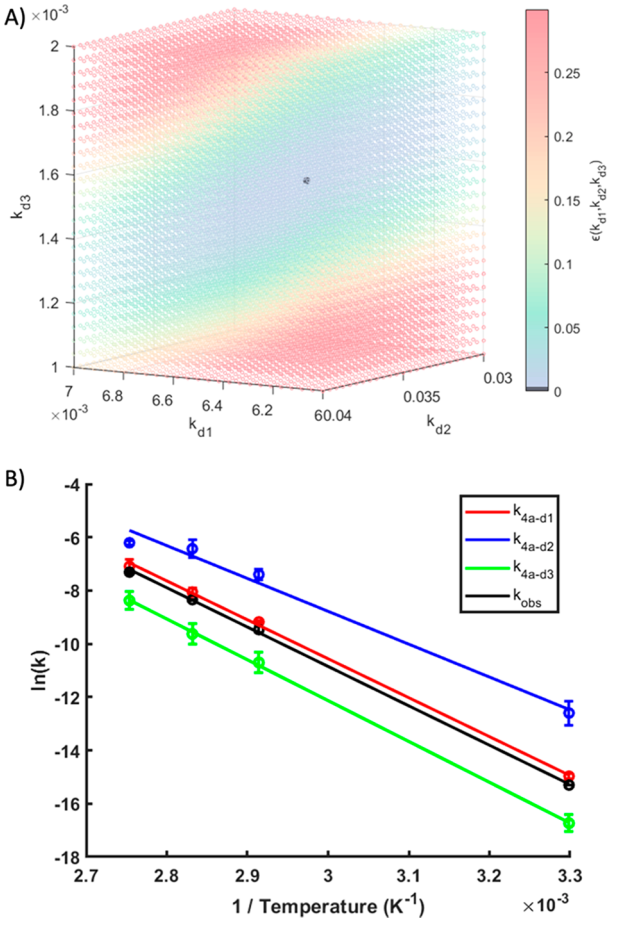
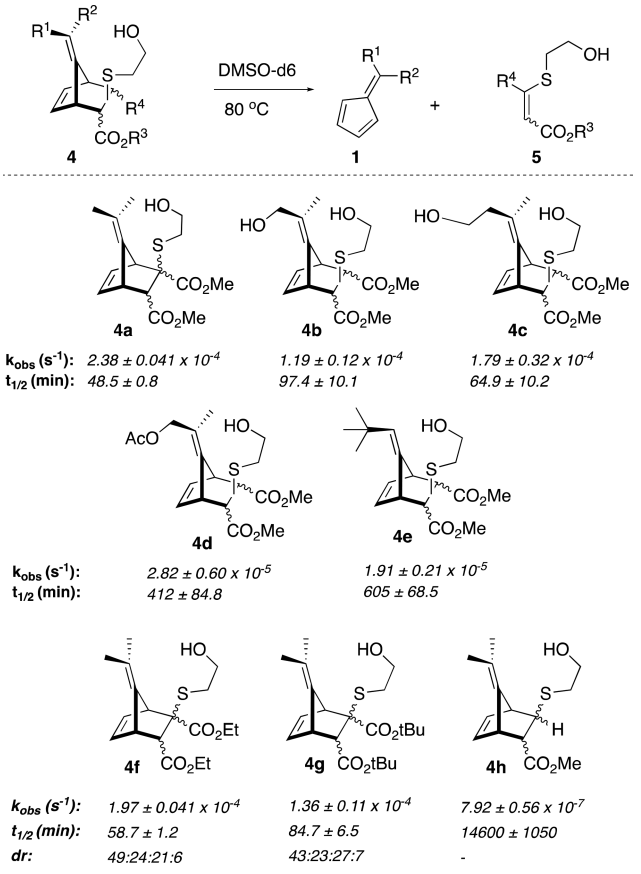


Figure 1. (A) Representative error function. (B) Arrhenius plots of observed kinetics and extrapolated kinetics of **4a:d1−3**.

fit the experimental data, and the best simulated rate constants from experimental data measured at multiple temperatures were used to construct an Arrhenius plot (Figure 1B). Using the Arrhenius parameters, $\Delta G^{\ddagger}_{d1}$ is 26.8 kcal/mol; $\Delta G^{\ddagger}_{d2}$ is 25.2 kcal/mol; and $\Delta G^{\ddagger}_{d3}$ is 27.9 kcal/mol.

Further substrate effects and functional group tolerance were first explored by the inclusion of an alcohol on the ylidene bridge (Scheme 4). YND−BME **4b** showed a 2-fold increase in half-life to 97.4 min, when compared to the model system YND−BME **4a** (48.5 min). Conversion of the alcohol to an acyl group (**4d**) increased the half-life nearly ten times to 412 min. This trend indicated that a decrease in the electron density in the ylidene bridge slows the fragmentation. As expected, moving the pendant alcohol one methylene unit

Scheme 4. YND−BME Substrate Scope Kinetics



further from the ylidene bridge (**4c**) reduced the degradation half-life to 64.9 min. The addition of an electron-rich *tert*-butyl group did not provide the projected increased degradation rate. Instead, YND−BME **4e** provided a longer half-life of 605 min. While YND−BMEs **4a−d** provide similar diastereomeric ratios, **4e** appeared to have a more even distribution of 8 diastereomers, and thus the decrease in degradation rate can be justified by a higher population of slower fragmenting diastereomers. It is likely that the oxygen atoms in the alcohol and acyl groups direct either the thiol nucleophile or the subsequent protonation step in the conjugate addition, therefore providing more diastereoselectivity. In the case of **4b**, this directing ability delivers a preference for primarily only one diastereomer. The integrated first-order rate plot for **4b** was nearly linear (Figure S6) compared to the model system **4a** which was not (Figure S4). Conversely, the increased steric bulk of the *tert*-butyl group further decreases the selectivity of the *exo*-face attack of the thiol nucleophile. This would limit the formation of the *exo*-diastereomers which proved to have faster degradation rates in the model system (**4a:d1** and **4a:d2**).

The effect of ester substitution can be seen in Scheme 4. The observed rate of degradation appears to decrease with the increased steric bulk of the ester substituent. Ethyl esters (**4f**) caused an increase in half-life by about 20% to 58.7 min versus the methyl esters (**4a**). Furthermore, the *tert*-butyl ester substrate (**4g**) saw a 75% increase in half-life to 84.7 min. This is contrary to the pattern observed in the OND systems, where the rate of degradation increases with ester substitution size.[22] The observed difference of this trend in YNDs versus ONDs is likely not due to a difference in reactivity but rather a change in

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Org. Lett. 2022, 24, 2793−2797

the diastereomeric ratios as the steric bulk of the ester substitution increases. While the percentage of the faster *d2* diastereomer does moderately increase in YND−BMEs **4f** (20% to 24%) and **4g** (20 to 23%), the more significant decrease in *d1*, 60% down to 49% (**4f**) and 43% (**4g**), and consequent increase in slower diastereomers *d3* and *d4* likely result in the overall observed rate decrease. The rate of degradation for YND-BME **4h** showed a remarkably long half-life of 14 600 min, due to the presence of only one electron-withdrawing ester functional group.

Our initial investigation into ylidenenorbornadienes has provided another viable nucleophile-induced fragmenting system similar to previously reported oxa- and azanorbornadiene systems. While YND−BME adducts provide mixtures of four diastereomers with differing rates, these rates were successfully extrapolated via a simulated kinetics method. In general, observed fragmentation rates are slower than both OND and ZND systems. The range of half-lives is vast and apparently tunable, spanning 48 min to 10 days at 80 °C. Thus, a continued exploration into the scope of this system will provide valuable insights for its potential as a dynamic covalent linkage.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00630.

Synthetic procedures, characterization data, kinetics data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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