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Permalink
https://escholarship.org/uc/item/0w08290h

Journal
Journal of the American Chemical Society, 136(28)

ISSN
0002-7863

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Publication Date
2014-07-03

DOI
10.1021/ja502252t

Peer reviewed
Torquoselective Ring Opening of Fused Cyclobutenamides: Evidence for a cis,trans-Cyclooctadienone Intermediate

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Supporting Information

ABSTRACT: Electrocyclic ring opening of 4,6-fused cyclobutenamides 1 under thermal conditions leads to cis,trans-cyclooctadienones 2-E,E as transient intermediates, en route to 5,5-bicyclic products 3. Theoretical calculations predict that 4,5-fused cyclobutenamides should likewise undergo thermal ring opening, giving cis,trans-cycloheptadienones, but in this case conversion to 5,4-bicyclic products is thermodynamically disfavored, and these cyclobutenamides instead rearrange to vinyl cyclopentenones.

Small trans-cycloalkenes have unique reactivities and structural features, including inherent planar chirality, which have been the focus of many elegant experimental and seminal theoretical studies,1−6 and have recently attracted increasing interest relating to their applications in bioconjugate chemistry.7,8 Accommodating a trans olefin within a ring size of 7, 8, or 9 engenders significant ring strain, which may be alleviated if the ring contains heteroatoms such as N, O, or S but is exacerbated when the ring contains additional sp2-hybridized atoms.3−5 We report here the discovery of a new entry point into the chemistry of all-carbon trans-cycloalkenes, uncovered during our studies of cyclobutenamides 1 (Scheme 1).7−9 Under thermal conditions, 4,6-fused cyclobutenamides 1 undergo rearrangement to products whose structures are consistent with the intermediacy of the cyclooctadienone 2-E,E, containing one cis and one trans olefin, derived from cyclobutene ring opening. Small-ring trans-cycloalkenes are expected to be metastable intermediates that should undergo facile inter- or intramolecular transformations, and in the case of 2-E,E, this is manifested in a transannular cyclization leading to the 5,5-bicyclic product 3. This outcome is surprising as it is in direct contrast to previous studies of the related 4,6-fused cyclobutenamine 4 (Scheme 2), which showed no evidence for cycloalkadienone formation. Thermal rearrangement of 4 gave instead the dienes 6-cis and 6-trans.9,10 The sole difference is the amino group in 4 versus the amide in 1. Here we report our experimental and theoretical studies of the generation and fate of cis,trans-cyclooctadienones 2 from 4,6-fused cyclobutenamides 1 and the contrasting behavior of the corresponding 4,5-fused cyclobutenamides.

Our experiments on the thermal rearrangements of cyclobutenamides 1 are summarized in Table 1. When heated at 100−120 °C in toluene, 4,6-fused cyclobutenamides 1 rearranged to the synthetically useful pentalanes 3 in 45−62% yield. The choice of appropriate conditions was crucial: no reaction took place either in DMF or chloroform (entries 1 and 2), or in the presence of base or 4 Å molecular sieves (entries 4 and 5). Yields were slightly higher when the reaction was conducted at 120 °C than at 100 °C (e.g., entry 3 vs 6) and were higher when lower concentrations of cyclobutenamide were used (e.g., entries 7, 8, 10), but in no case could the reaction be driven to completion.

The scope and generality of this fascinating cascade are accentuated in Figure 1. Variation of substituents on the nitrogen atom and/or the β-carbon of the starting cyclo-

Scheme 1. Ring-Fused Cyclobutenamides as Potential Precursors to Small cis,trans-Cycloalkadienones

Scheme 2. Ficini’s Thermal Rearrangement of a Fused Cyclobutenamine10

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9802
dx.doi.org/10.1021/ja502252t J. Am. Chem. Soc. 2014, 136, 9802−9805

Received: March 4, 2014
Published: July 3, 2014
butenamides led to the pentalanes 3d (Table 1) and 3e−h (Figure 1). The initially formed hydroxypentalanes could undergo syn-dehydration to fulvenes, which may be isolated (3e′ and 3f′) or trapped by an intramolecular [4 + 2] cycloaddition onto a tethered alkene to give tetracycles (3g″ and 3h″). These last two examples reveal the synthetic potential of this rearrangement for the rapid assembly of structural complexity. It is also noteworthy that, in the case of 3e/3e′, only the Z exocyclic olefin was found.

Having uncovered this novel cascade reaction, we were intrigued by its mechanism and distinct contrast to Ficini’s observations on the 4,6-fused cyclobutenamides 4. We propose that the rearrangement of 1 to 3 follows the mechanism shown in Scheme 3. The details of the mechanism were established with the aid of density functional theory calculations, performed at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory (Figure 2). The 4π electrocyclic ring opening of 1 predictably favors the conrotatory mode in which the cyclohexanone alkyl group rotates outward and the carbonyl rotates inward (direction a) leading to 2-E,E. This intermediate lies 9.4 kcal/mol above 1. The computed torquoselectivity (ΔΔG°) is 9.8 kcal/mol.

The E,E isomer of 2 is not only kinetically favored but also the only isomer possessing an appropriate geometry for cyclization in the S,S mode to give 3 in 2-Z,Z, the carbonyl group and diene terminus are too far apart to form a bond. Ring closure of 2-E,E resembles a Nazarov cyclization (cf. resonance structure 2′-E,E, Scheme 3). Starting from the neutral cyclooctadienone, 5,5 ring closure leading to epoxide 7 has a very high barrier (ΔTS7, 47.5 kcal/mol), too high to be feasible at 100−120 °C. However, protonation of the carbonyl group (Figure 2 inset) lowers the energy of the Nazarov TS significantly, such that it lies only 6.2 kcal/mol above protonated 2-E,E.14,15 Based on this result, together with the lack of reaction in the presence of 4 Å molecular sieves (Table 1, entry 5), we propose that the cyclization step is catalyzed by adventitious water acting as an acid catalyst.15 Unfortunately, the yield of 3 could not be improved by deliberate addition of an acid catalyst; for example, addition of camphorsulfonic acid (CSA, 0.4 equiv) brought about severe decomposition.16

Table 1. Thermal Rearrangements of 4,6-Fused Cyclobutenamides 1

| Entry | EWG | R = solvent [conc (%)] | additive [equiv] | temp (°C) | time [h] | yield [%] | a | b |
|-------|-----|------------------------|-----------------|-----------|---------|---------|---|---|
| 1     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 2     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 3     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 4     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 5     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 6     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 7     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 8     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 9     | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|
| 10    | Ts  | Ts(CH2)2NMe2/0.10      | 4Å MS           | 47        | 100     | 100     | 100| 76|

All are isolated yields. Recovered starting 1. Mbs = para-methoxy-benzene-sulfonyl; Ns = para-nitro-benzene-sulfonyl. Complete recovery of 1.

The 4,5-fused cyclobutenamides 8 behaved differently from 1, instead echoing the behavior of 4 observed by Ficini (Scheme 2). As shown in Table 2, no products were identified that could be traced to the cis,trans-cycloheptadienone intermediate 9-E,E. Instead, 4,5-fused cyclobutenamides 8 rearranged to amido-dienes 12 as cis/trans mixtures. The
rearrangements involving the 4,5-fused series required much higher temperatures (195 °C) than those in the 4,6-fused series (100–120 °C).

The rearrangement of 8 to 12 is proposed to commence with formation of the conjugated cyclobutenone 11 (syn/anti), as previously observed by Ficini10c for 4 (Scheme 2). 4π electrocyclic ring opening of 11 gives 12. Each isomer of 11 undergoes ring opening with complete torquoselectivity, avoiding unfavorable inward rotation by the cyclopentanone alkyl group that would lead to a highly strained trans-cyclopentenone. Thus, 12-cis is derived from 11-anti and 12-trans from 11-syn.

Why does 8 rearrange to 12, rather than to 10? Theoretical calculations (Figure 3a) in fact predict that the cis,trans-cycloheptadienone 9-E,E, which would be the precursor of 10, can be accessed from 8 with a barrier of 33.1 kcal/mol (TS9). This value is only 0.8 kcal/mol higher than the barrier for formation of 2-E,E from 1. It is therefore likely that some 9-E,E is formed transiently during the course of the reaction at 195 °C. The transient formation of 9-E,E is not reflected in the final product distribution, however, because the transannular cyclization product 10 is higher in energy than the starting cyclobutenamide (ΔG = 10.4 kcal/mol).18 Given the thermodynamic driving force against the formation of 10, the cis,trans-cycloheptadienone 9-E,E reverts to 8 which rearranges by the alternative pathway shown in Figure 3b to 12. Conversion of 8 to the α,β-unsaturated intermediate 11 is likely to be acid catalyzed.19 Formation of 12-cis and 12-trans from 8 has ΔG ≈ −12 kcal/mol.

We have documented here the thermal rearrangements of 4,6-fused and 4,5-fused cyclobutenamides 1 and 8 and the discovery of contrasting mechanistic pathways. Theory predicts that 1 and 8 undergo electrocyclic ring opening to cis,trans-cyclooctadienone 2-E,E and cis,trans-cycloheptadienone 9-E,E, respectively. For 2-E,E, Nazarov-like ring closure leads to 5,5-bicyclic amido-dienes 3, but for 9-E,E, Nazarov cyclization is thermodynamically disfavored and an alternative rearrangement leads to monocyclic amido-dienes 12. The differing behavior between 1 and Ficini’s 4,6-fused cyclobutenamines 4 likely reflects the lower basicity of 1, which inhibits the isomerization to a conjugated cyclobutenamide (cf. 5) that would trigger rearrangement to monocyclic amido-dienes. Further synthetic and mechanistic studies and development of an asymmetric variant are underway.

### Table 2. Thermal Rearrangements of 4,5-Fused Cyclobutenamides 8

| entry | EWG | solvent (conc., M) | temp (°C) | time [h] | yield 12% cis trans | cis:trans |
|-------|-----|-------------------|-----------|----------|---------------------|----------|
| 1     | Mbs | toluene (0.025 M) | 140       | 32       | 12a: 9° 0           | 12:1     |
| 2     | Mbs | xylene (0.025 M)  | 195       | 36       | 12b: 46 16          | 12:1     |
| 3     | Mbs | xylene (0.025 M)  | 195       | 36       | 12: 51° 22          | 12:1     |
| 4     | Mbs | xylene (0.025 M)  | 195       | 36       | 12: 51° 22          | 12:1     |

*All are isolated yields. 12% recovered 8a. 16% recovered 8c.*

Figure 3. Free energy profiles for thermal rearrangements of 8 to (a) 10 and (b) 12 in toluene.

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### Notes

- The authors declare no competing financial interest.
ACKNOWLEDGMENTS

We thank the NIH (GM-66055 to R.P.H.), NSF (CHE-0548209 to K.N.H.), and Australian Research Council (FT120100632 to E.H.K.) for generous financial support, and the NCI NF (Australia) and University of Queensland Research Computing Centre for computer resources. R.C.J. thanks Oregon State University for a 2013–2014 Graduate Internationalization Grant.

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In contrast, H-bonding catalysis by a water molecule lowers the barrier of the Nazarov cyclization by only 5.8 kcal/mol.

(15) O-Protonation of cyclobutanolamide 1 (R = Me, X = SO2Ph) lowers the barrier for cyclobutene ring opening to 21.3 kcal/mol.

(16) When 1a was heated at 100 °C in the presence of 0.4 equiv of CSA, we obtained a complex mixture due to decomposition of 1a. However, we were able to identify from the mixture all four products including those corresponding [see 1] to Ficini’s observations.

(17) Amido-diienes 12-cis and 12-trans interconvert under the reaction conditions but do not fully equilibrate during the time scale of the synthetic experiments. The cis/trans ratios of 12 in Table 2 do not reflect thermodynamic control but are determined by the rates of isomerization of 8 to 11-syn and 11-anti, which are rate-determining under thermal conditions.

(18) It is noteworthy that, in the calculations on the 4,6 series (Figure 2), the final product 3 is only 1.6 kcal/mol lower in energy than the reactant 1. This likely explains our observation that these reactions could not be driven to completion in the laboratory.

(19) Isomerization of 8a–c to 11a–c (syn/anti) appears to be catalyzed by adventitious acid. In the presence of 0.4 equiv of CSA, amido-diienes 12a–c were obtained (85%–92% yield) after only 6 h, as compared with 36 h in the absence of CSA. Further discussion of the mechanism of conversion of 8 to 11 is provided in the Supporting Information.