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Altering the Cyclization Modes: Temperature-Dependent Intramolecular 7-*Endo-Dig* vs 6-*Endo-Dig* Electrophilic Ring Closures

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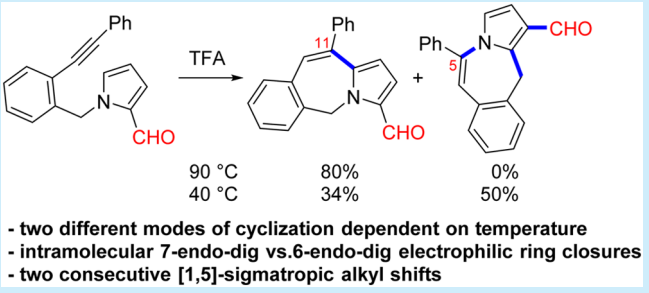
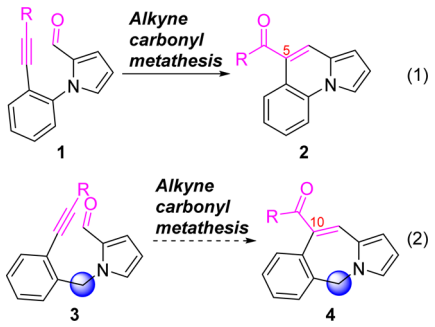
Supporting Information

ABSTRACT: In an attempt to construct 10-acyl-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepines via acid-catalyzed intramolecular alkyne carbonyl metathesis, two distinctive modes of cyclization were revealed to depend on the reaction temperatures. 5*H*-Benzo[*e*]pyrrolo[1,2-*a*]azepine-1-carbaldehydes with a substituent at the C11 position were obtained as major products at 90 °C as a result of intramolecular 7-*endo-dig* cyclization, while 6-*endo-dig* ring closure by electrophilic addition of nitrogen of the pyrrole to a vinyl cation generated under acidic medium followed by an unprecedented domino rearrangement process was observed at 40 °C in some cases, resulting in 5-aryl-11*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine-1-carbaldehydes along with the former products.



As part of our research interest in the synthesis of heterocycles with potential biological implications using intramolecular alkyne carbonyl metathesis (IACM),[1,2] we recently reported a regiospecific synthetic approach to 5-acylated pyrrolo[1,2-*a*]quinolines (**1** to **2**) (Scheme 1, eq 1).[3]

Scheme 1. IACM Approaches to N-Fused Heterocycles

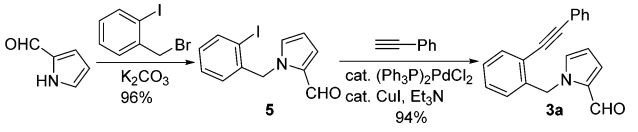


As an extension of this work, we envisioned that IACM of benzyl-substituted pyrrole-2-carbaldehyde (**3**) would give rise to 10-acyl-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepine, another N-fused heterocycle (**4**) (Scheme 1, eq 2). Compared with other azepine-containing chemical scaffolds, this tricyclic structure has been less explored as a pharmacophore in the area of medicinal chemistry.[4] In addition, only a small number of synthetic works toward this skeleton appeared in the literature.[5]

A lack of available synthetic methods as well as our continued research on nitrogen-fused heteroaromatics[6] led us to investigate our designed route to this chemical core structure through IACM. In this study, however, we observed the unexpected outcomes, which is the topic of this paper.

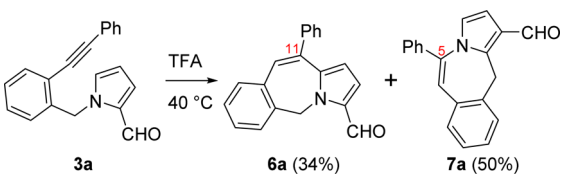
Preparation of the requisite substrate **3** for this study began with N-alkylation of pyrrole-2-carbaldeyde to afford **5** (Scheme 2). Sonogashira coupling of **5** with phenylacetylene gave **3a** in 94% yield.

Scheme 2. Synthesis of 3a



As shown in Scheme 3, treatment of **3a** in TFA at 40 °C produced two new compounds. Contrary to our expectation, NMR analysis indicated that they both had an aldehyde unit. No product from IACM was detected. It turned out that the

Scheme 3. TFA Reaction of 3a



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less polar compound was **6a**, a product resulting from intramolecular 7-*endo-dig*[7] electrophilic cyclization. The structure of the other one (**7a**, more polar than **6a**) was firmly established by X-ray crystallographic analysis (Figure 1).[8] Much to our surprise, it had a totally different connectivity from the starting material.

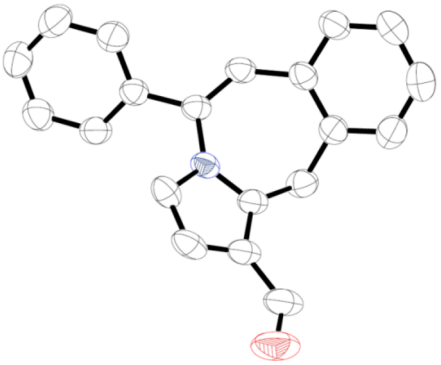
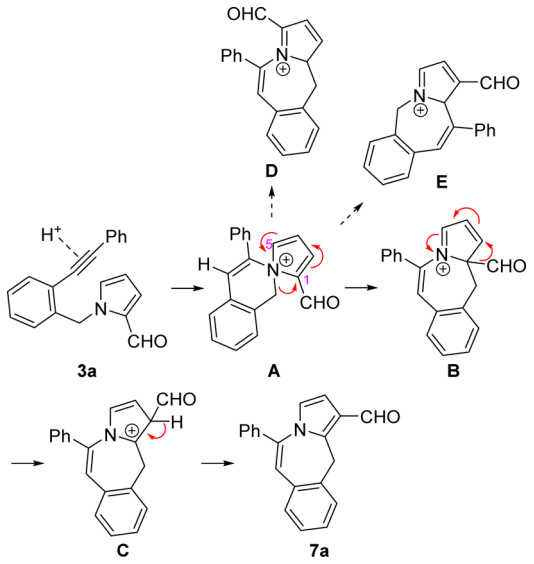


Figure 1. ORTEP diagram of **7a** with 50% ellipsoid probability.

The plausible mechanism for the formation of **7a** is proposed in Scheme 4. Intramolecular 6-*endo-dig* electrophilic attack of

Scheme 4. Proposed Mechanism for the Formation of 7a



nitrogen of the pyrrole ring to a vinyl cation generated under acidic conditions would occur to give the spirocyclic compound **A**, which then would undergo suprafacial [1,5]-sigmatropic alkyl shift[9] to afford **B**. Neither formal migration of the benzylic substituent to the C5 position of the pyrrole core nor [1,5]-vinyl group shift occurred to give the other isomers, **D** or **E**, which is ascribed to the resulting steric clash between the exocyclic phenyl substituent and the formyl moiety. Another [1,5]-sigmatropic migration of the formyl group at the ring juncture of **B** would lead to **C**. Final loss of proton to regain aromaticity would deliver **7a**. To the best of our knowledge, this type of domino sequence[10] has never been disclosed.

The populations of **6a** and **7a** were calculated as 33.5 and 66.5%, respectively, at the M06-2X/cc-pVTZ//M06-2X/6-31+G(d) level of theory in water, which are consistent with the observed values of 34 and 50% in TFA at 40 °C. The free-energy profile of the pathway of the formation of **7a**[11] at 40 °C is shown in Figure 2. The barriers ($\Delta G^{\ddagger}$) to transition states

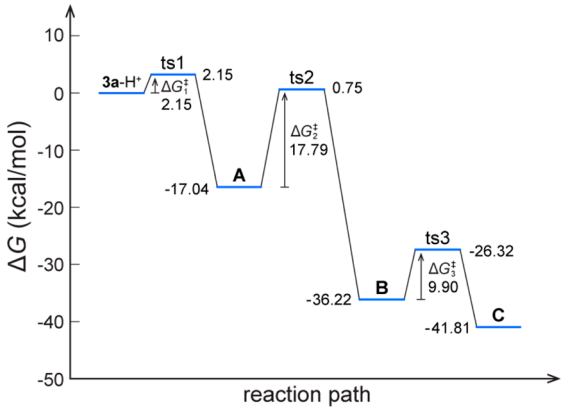


Figure 2. Gibbs free energy profile of the pathway of the formation of **7a**.

ts1, ts2, and ts3 were calculated as 2.15, 17.79, and 9.90 kcal/mol, respectively. This indicates that the first step of the intramolecular 6-*endo-dig* electrophilic attack of nitrogen of the pyrrole ring to a vinyl cation generated under acidic conditions seems to be much faster and that the second pathway of **A** undergoing a suprafacial [1,5]-sigmatropic alkyl shift to afford **B** is the rate-determining step of the reaction. In particular, the Gibbs free energy of the intermediate decreases in the order **A** → **B** → **C**, which may suggest that the formation of **7a** is thermodynamically favored.

Interestingly, this domino process initiated by intramolecular 6-*endo-dig* electrophilic cyclization did not take place at higher temperatures. Exposure of **3a** to TFA at 90 °C only provided **6a** in 80% yield.

To examine the effect of the R group on cyclization, several other alkyne-substituted substrates, **3b**–**i**,[12] were submitted to the same reaction conditions (Table 1). Subjection of **3b** to TFA at 40 °C yielded 75% of **6b** and 20% of **7b**, while **6b** was the only isolable product at 90 °C, indicating that 7-*endo-dig* ring formation was preferred at higher temperatures (entry 1). X-ray crystallographic analysis confirmed the molecular structure of **6b** (Figure 3).[13] When R was an electron-rich aromatic moiety, 7-*endo-dig* cyclization products **3c**–**f** were obtained as major products at 40 °C (entries 2–5). Surprisingly, exposure of the substrate having a cyclohexenyl group (**3f**) to TFA at 40 °C afforded the rearranged product as a major product (entry 6). The substrate containing a heterocycle such as thiophene (**3h**) was also treated with TFA to give 64% of **6h** (entry 7). Interestingly, when R was an electron-poor aromatic group, the domino process occurred as a major pathway to furnish **7i** in good yields irrespective of the reaction temperatures (entry 8).

To investigate the generality of this ring formation, indoles (**8** and **9**) and pyrroles (**10** and **11**) were also prepared and allowed to react with TFA (Scheme 5). A complex mixture of products was observed in cases of **8** and **9**, showing that indoles are not compatible under these conditions. Decomposition of **10** under TFA also revealed the importance of an electron-withdrawing group present in pyrrole rings. Exposure of **11a**,**b** having an ester or an acetyl unit to TFA at 40 °C afforded the corresponding products **12a**,**b** in good yields as a consequence

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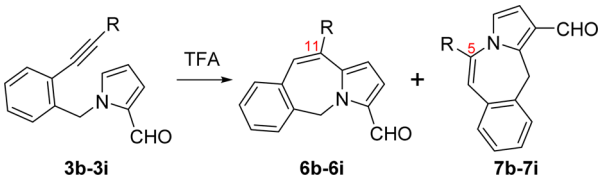
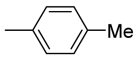
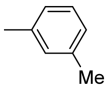
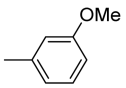
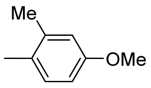
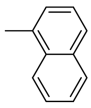
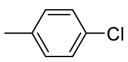
Table 1. Synthesis of 6 and 7



3b-3i 6b-6i 7b-7i

entry	R	temp	6 (yield)[b]	7 (yield)[b]
1	 3b	90 °C	**6b** (86 %)	**7b** (0 %)
		40 °C	**6b** (75%)	**7b** (20%)
2	 3c	40 °C	**6c** (50%)	**7c** (40%)
3	 3d	40 °C	**6d** (62%)	**7d** (28%)
4	 3e	40 °C	**6e** (89%)	**7e** (0%)
5	 3f	40 °C	**6f** (81%)	**7f** (0%)
6	 3g	40 °C	**6g** (30%)	**7g** (58%)
7	 3h	40 °C	**6h** (64%)	**7h** (28%)
8	 3i	90 °C	**6i** (16%)	**7i** (62%)
		40 °C	**6i** (10%)	**7i** (71%)

[a]A solution of **3** (0.1 mmol) in TFA (1 mL) was heated at 40 or 90 °C. [b]Isolated yield (%).

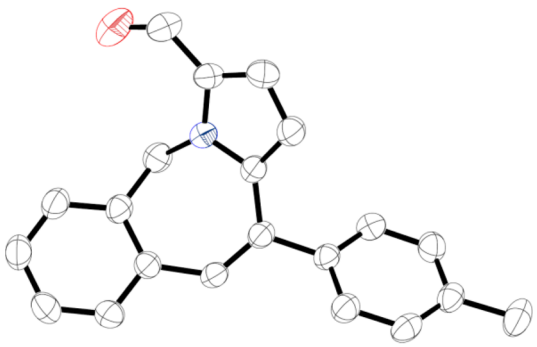
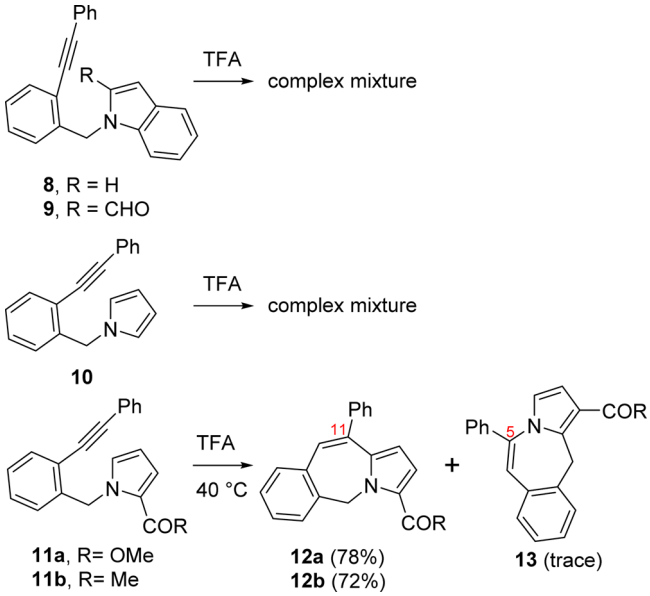


Figure 3. ORTEP diagram of **6b** with 50% ellipsoid probability.

Scheme 5. Reactions of 8−11



of intramolecular 7-*endo-dig* electrophilic ring closure, implying that formyl moiety is crucial for this unusual domino reaction.

In summary, we have observed temperature-dependent alteration of cyclization modes (intramolecular 7-*endo-dig* vs 6-*endo-dig* electrophilic ring cyclizations) in our effort to construct N-fused heterocycles. These studies enabled us to gain access to 11-(hetero)aryl- and 11-alkyl-5*H*-benzo[*e*]-pyrrolo[1,2-*a*]azepine-1-carbaldehydes via acid-catalyzed intramolecular 7-*endo-dig* cyclization reaction. At lower reaction temperatures, intramolecular 6-*endo-dig* electrophilic ring closure followed by two consecutive suprafacial [1,5]-sigmatropic alkyl shifts resulted in formation of 5-aryl-11*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine-1-carbaldehydes in variable yields depending on the substituent attached to the alkyne of the cyclization substrates. The plausible mechanism of this unprecedented domino bond-reorganization process was proposed, which is consistent with DFT calculations. Expansion of this work as well as evaluation of these scaffolds for medicinal use are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00472.

^{1}H and ^{13}C NMR spectra of synthesized compounds (PDF)

X-ray data for compound **6b** (CIF)

X-ray data for compound **7a** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) The free energy of each species was calculated at the M06-2X/cc-pVTZ//M06-2X/6-31+G(d) level of theory and the SMD M06-2X/6-31+G(d) level of theory at 40 °C in water. **3a**-H^+ is **3a** protonated at the alkyne carbon atom. See the Supporting Information for computational details.

(12) See the Supporting Information for details.

(13) CCDC 1515216 contains the supplementary crystallographic data for compound **6b**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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