

Brønsted Acid-Promoted Intramolecular Carbocyclization of Alkynals Leading to Cyclic Enones

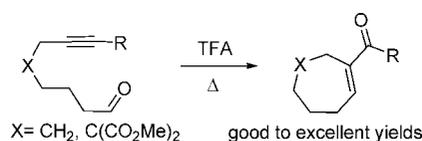
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ABSTRACT



TFA-promoted *exo* carbocyclizations of nonterminal 7-alkynals gave good to excellent yields of seven-membered cycloalkenones, a medium-sized functionalized ring present in natural products with relevant pharmacological properties. Nonterminal 5- and 6-alkynals also gave very good yields of the corresponding *exo* cyclopentenones and cyclohexenones. On the other hand, terminal 5-alkynals gave *endo* carbocyclizations to cyclohexenones. These carbocyclizations can be considered as tandem alkyne hydration/aldol condensation processes.

Transition-metal- and Lewis and Brønsted acid-catalyzed or promoted cyclizations involving alkynes and carbonyl groups have emerged as an important strategy for the assembly of functionalized carbocyclic compounds. Transition-metal-catalyzed cyclizations of alkynals to give a variety of cyclic structures have been described.¹ Brønsted and Lewis acid-catalyzed cyclizations of acetylenic ketones to afford conjugated cycloalkenones are well-known

processes.² More recently, Lewis acid-catalyzed cycloisomerizations of nonterminal alkynals and alkynones to *endo*- or *exocyclic* α,β -unsaturated cyclopentenones and cyclohexenones have been reported.^{3,4} We describe here the first cycloisomerization of nonterminal alkynals promoted by Brønsted acids (mainly trifluoroacetic acid) to give seven-membered *exo* cycloalkenones, an important core in several biologically important natural products,⁵ as well as new cycloisomerizations of alkynals to give *exo* and *endo* five- and six-membered cycloalkenones (Scheme 1 and Table 1).⁶

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(3) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493.

(4) (a) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259. Enynones: (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137. For related intermolecular cyclizations of alkynes and aldehydes, see: (c) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783.

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(6) For carbocyclization of ynamide-aldehyde substrates to five- and six-membered cycloalkenamides, see: (a) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231. (b) Formation of a seven-membered cycloalkenimide in low yield using a singular ynamide-aldehyde substrate has also been described. (c) For carbocyclization of terminal alkynals to cyclopentencarbaldehydes, see: Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025.

Scheme 1. Cycloisomerization of Nonterminal Alkynals in TFA

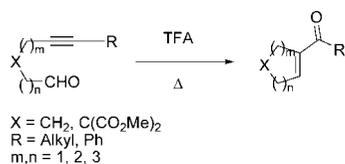


Table 1. Cycloisomerization of 5-Alkynal **1a** in Acidic Conditions

| entry | acid | temp (°C) | (%) |
|-----------------|----------------------------------|-----------|-----|
| 1 ^a | TFA | 90 | 90 |
| 2 ^a | TFA | 50 | 60 |
| 3 ^a | TFA | 25 | 15 |
| 4 ^b | TFA | 90 | — |
| 5 ^b | HBF ₄ | 25 | 55 |
| 6 ^b | TfOH | 25 | 49 |
| 7 ^a | AcOH | 90 | — |
| 8 ^b | TMSOTf | 25 | 30 |
| 9 ^b | TMSOTf | −78→25 | 35 |
| 10 ^b | InCl ₃ | 25 | 63 |
| 11 ^b | BF ₃ OEt ₂ | 25 | 60 |

^a 0.5 mmol of **1a** in 3 mL of acid. ^b 0.5 mmol of **1a** and 3 equiv of acid in 3 mL of DCE.

In the search for optimized conditions for the cycloisomerization of alkynals, we first examined the reaction of terminal 5-alkynal **1a** with the Brønsted and Lewis acids depicted in Table 1. Gratifyingly, heating a trifluoroacetic acid solution of **1a** (0.12 M) in a sealed tube at 90 °C for 1 h gave very smoothly the cyclohexenone **2a** in excellent yield (Table 1, entry 1). Lower yields and longer reaction times were found on using lower temperatures (entries 2 and 3). This is the first time that a new mode of *endo* cyclization of terminal 5-alkynals has been observed. Other Brønsted acids such as HBF₄ and TfOH also promote the reaction with only 3 equiv at rt, albeit in moderate yields (entries 5 and 6), but TFA (3 equiv) and the weaker AcOH led only to recovery of starting material (entries 4 and 7). The cyclization also occurs with Lewis acids: TMSOTf gave rapid evolution at rt to **2a** with a low yield (entries 8 and 9); InCl₃ or BF₃OEt₂ afforded quite good yields of **2a** (entries 10 and 11).

Under optimized conditions (Table 1, entry 1), other terminal 5-alkynals (mono- and disubstituted at C4, **1b** and **1c**) also cyclized to give quite good yields of the corresponding *endo* cyclohexenones **2b** and **2c** (Table 2, entries 2 and 3). Interestingly, when nonterminal 5-alkynals **1d–g** were subjected to acidic conditions, the corresponding *exo* cyclopentenones **3d–g** were obtained smoothly in quite good yields (Table 2, entries 4–7).⁷ Nitrogen-tethered alkynal **1d'**

Table 2. Cycloisomerization of 5-Alkynals **1a–h** and 6-Alkynals **4a–c** in TFA

| entry | alkynal | cycloalkenone | (%) ^a |
|-----------------|--|-------------------------|-----------------------------------|
| 1 | 1a | 2a | 90 |
| 2 | 1b | 2b | 70 |
| 3 | 1c | 2c | 65 |
| 4 | 1d X = C(CO ₂ Me) ₂ 1d' X = NTs | 3d 3d' | 3d , 82 3d' , 62 |
| 5 | 1e | 3e | 60 |
| 6 | 1f | 3f | 60 |
| 7 | 1g | 3g | 83 |
| 8 ^b | 1h | 3h | 90 |
| 9 ^c | 4a | 5a | 63 |
| 10 ^c | 4b | 5b | 67 |
| 11 ^c | 4c | 5c | 57 |

^a Conditions A: Heating a solution of 0.5 mmol of alkynal in 3 mL of TFA in a sealed tube at 90 °C for 1–2 h (conditions A). ^b Conditions B: Heating a solution of 0.5 mmol of alkynal and 20 equiv of TFA in 3 mL of DCE in a sealed tube at 90 °C for 1–2 h. ^c Conditions A but 5 h heating. E = CO₂Me.

also was cycloisomerized to the pyrroline derivative **3d'** in relatively good yield (entry 4).⁸

Even nonterminal alkynal **1h**, which does not have a favorable Thorpe–Ingold effect for cyclization,⁹ gave an

(7) Pyrroline **3d'** and *exo* cyclopentenone **3g** have been obtained by AgSbF₆-, HBF₄-, and BF₃·OEt₂-catalyzed cycloisomerization of **1d'** and **1g** in 58–81% yields. This and other cyclizations of nonterminal 5- and 6-alkynals are described in ref 3.

(8) Pyrroline **3d'** also was obtained by cycloisomerization of the precursor dimethyl acetal of aldehyde **1d'** in the same yield.

(9) Ingold, K. C.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, 1117. For a recent paper, see: Kaneti, J.; Kirby, A. J.; Koedjikov, A. H.; Pojarlieff, I. G. *Org. Biomol. Chem.* **2004**, *2*, 1098.

excellent yield of the *exo* cyclopentenone **3h** (Table 2, entry 8). Note also that nonterminal 6-alkynals **4a–c** gave the corresponding *exo* cyclohexenones **5a–c** in reasonably good yields (Table 2, entries 9–11).¹⁰

Gratifyingly, cycloisomerization of nonterminal 7-alkynals **9** occurred smoothly to give exclusively the new *exo* cycloheptenones **10** in good to excellent yields (Table 3).

Table 3. Cycloisomerization of Nonterminal 7-Alkynals **9**

| entry | alkynal | cycloheptenone | time | (%) ^a |
|-------|---------|----------------|-------|------------------|
| 1 | | | 3 h | 92 |
| 2 | | | 1.5 h | 74 |
| 3 | | | 3 h | 56 |
| 4 | | | 4 h | 74 |
| 5 | | | 2 h | 59 |
| 6 | | | 1.5 h | 77 ^b |

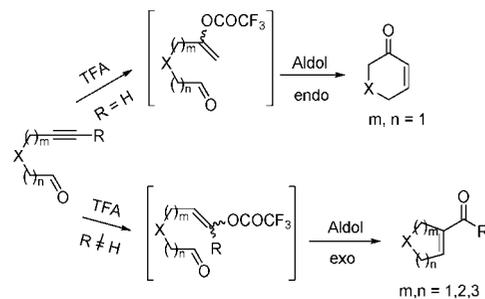
^a Conditions A. ^b Conditions B. X = C(CO₂Me)₂.

Thus, alkyl and aryl alkynals **9a–c** gave the corresponding cycloheptenones **10a–c** in good to excellent yields (Table 3, entries 1–3). The 4,4- and 3,3-disubstituted 7-alkynals **9d** and **9e** also cyclized to the corresponding *exo* cycloheptenones **10d** and **10e** in quite good yields (Table 3, entries 4 and 5). Even the parent hexadec-7-ynal **9f**, which lacks a favorable Thorpe–Ingold effect,⁹ cyclized smoothly to the cycloheptenone **10f** in very good yield (Table 3, entry 6).

A plausible cycloisomerization mechanism is shown in Scheme 2, although alternative oxete intermediates—as

(10) Unexpectedly, the corresponding terminal 6-alkynal **4d** gave a mixture of three cyclized products: cyclopentenal **6d** (27%), cyclopentenone **7d** (27%), and cyclohexenal **8d** (10%). See Supporting Information for details.

Scheme 2. Proposed Mechanism for the TFA-Promoted Carbocyclization of Alkynals



reported by Harding^{2a} and later by Krische³—cannot be ruled out. Addition of TFA to the terminal and nonterminal alkynes¹¹ could lead to the formation of vinyl trifluoroacetates **A** or **B**, respectively.¹² These intermediates can undergo aldol-type condensations to give the observed endo- or exocyclic enones, respectively.¹³ These products could be considered as being derived from a controlled tandem alkyne hydration/aldol condensation process.

In summary, we report here the efficient TFA-promoted *exo* carbocyclizations of nonterminal 5-, 6-, and 7-alkynals and *endo* carbocyclizations of terminal 5-alkynals to give cyclic enones in good to excellent yields. These carbocyclizations can be considered as tandem alkyne hydration/aldol condensation processes. Work is in progress aimed at highlighting further applications.

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Supporting Information Available: A typical experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) For Markovnikov and anti-Markovnikov hydration of alkynes, see: Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121.

(12) In careful cyclization experiments using CF₃COOD, evidence was found for some intermediates that contain vinyl groups (¹H NMR) and trifluoroacetate units (GCMS). See Supporting Information for details.

(13) Heating the 5,5-disubstituted 9-methyl-8-nonynal **11** in TFA gave the corresponding 8-oxodecanal **12** in 40% yield, indicating that only hydration of the alkyne (from the corresponding vinyl trifluoroacetate) occurred. See Supporting Information for details.