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

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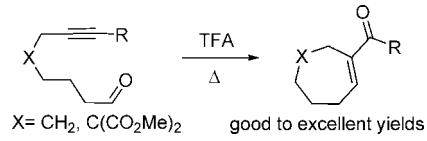
ABSTRACT



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]

(1) For Rh, see: (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (b) Tanaka, K.; Sasaki, K.; Takeishi, K.; Sugishima, K. *Chem. Commun.* **2005**, 4711. (c) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (d) Rhee, J. U.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 10674. For Ru, see: (e) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. (f) Varela, J. A.; González-Rodríguez, C.; Rubín, S. G.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9576. For Ni, see: (g) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. For Pd, see: (h) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (i) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (j) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406. (k) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1.

(2) (a) Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883, and references therein. (b) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345, and references therein. (c) Wempe, M. F.; Grunwell, J. R. *J. Org. Chem.* **1995**, *60*, 2714, and references therein.

(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.

(5) (a) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900. (b) Williams, M. J.; Deak, H. L.; Snapper, M. L. *J. Am. Chem. Soc.* **2007**, *129*, 486.

(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.

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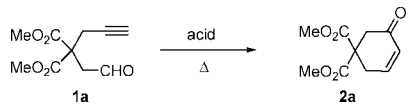
Scheme 1. Cycloisomerization of Nonterminal Alkynals in TFA

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_3OEt_2	25	60

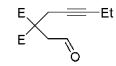
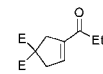
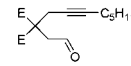
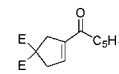
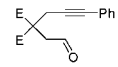
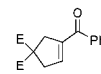
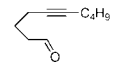
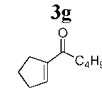
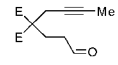
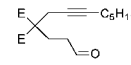
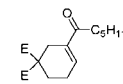
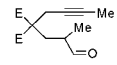
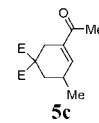
[a] 0.5 mmol of **1a** in 3 mL of acid. [b] 0.5 mmol of **1a** and 3 equiv of acid in 3 mL of DCE.

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 HBF_4 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); $InCl_3$ or BF_3OEt_2 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′** 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

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 = $C(CO_2Me)_2$ **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 = CO_2Me.

(7) Pyrroline **3d′** and *exo* cyclopentenone **3g** have been obtained by $AgSbF_6$-, HBF_4-, and BF_3·OEt_2-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.

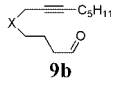
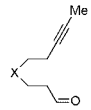
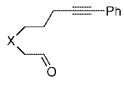
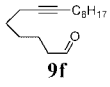
(8) Pyrroline **3d′** also was obtained by cycloisomerization of the precursor dimethyl acetal of aldehyde **1d′** in the same yield.

(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	 **9a**	 **10a**	3 h	92
2	 **9b**	 **10b**	1.5 h	74
3	 **9c**	 **10c**	3 h	56
4	 **9d**	 **10d**	4 h	74
5	 **9e**	 **10e**	2 h	59
6	 **9f**	 **10f**	1.5 h	77[b]

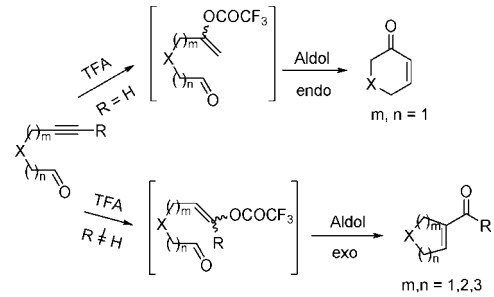
[a] Conditions A. [b] Conditions B. X = $C(CO_2Me)_2$.

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 Krische[3]—cannot be ruled out. Addition of TFA to the terminal and nonterminal alkynes[11] 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 CF_3COOD, evidence was found for some intermediates that contain vinyl groups (^{1}H 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.