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Indium(III)-Catalyzed Hydrative Cyclization of 1,7-Diynyl Ethers

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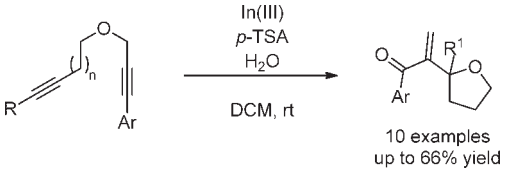
ABSTRACT



A new hydrative cyclization of 1,7- and 1,8-diynyl ethers is reported. Using catalytic InI_3 and *p*-TSA as a cocatalyst, several 2,2-disubstituted tetrahydrofurans with exocyclic enone appendages were prepared. Reaction optimization and scope, mechanistic insight, and further transformation to a *C*-nucleoside analog are presented.

The preparation of functionalized cyclic structures from simple acyclic precursors is of great value to the organic chemist, since many biologically active compounds contain carbo- and heterocyclic ring systems.[1] One class of substrates which has received attention is the nonconjugated 1,*n*-dialkynes.[2−9] There are several reports of these substrates being utilized in metal-catalyzed inter- and intramolecular [2 + 2 + 2] cyclizations with a third 2π component to produce six-membered rings.[3] We have reported the synthesis of fully substituted benzene rings[4a] and tetrahydronaphthyridines[4b,c] in this manner. Danheiser and co-workers have recently shown that without metal catalysis and in the presence of a dienophile, 1,6-diynes can undergo a tandem ene-[4 + 2] cycloaddition sequence to give cyclic systems bearing an exocyclic alkene.[5] Simple 1,6-diynyl systems have also been shown to cyclize in the absence of a third 2π partner using transition metal or Lewis acid catalyzed processes.[6] One recent example involves the hydrative cyclization of 1,6-diynes to cyclohexenones using Au(I) catalysis.[7,8]

We became interested in the reactivity of tethered 1,7-dialkynyl systems, which have received less attention in the literature,[9] with the hope that these substrates could produce synthetically useful seven-membered rings. Upon reaction of 1,7-diynyl ether **1a** with stoichiometric $InBr_3$ and *p*-TSA (0.5 equiv), an unexpected five-membered

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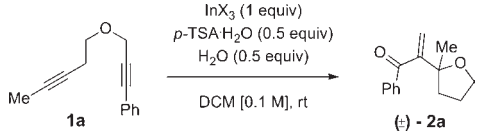
product, 2,2-disubstituted THF **2a**, was produced in a modest 37% yield (Table 1, entry 1). Substituted THF rings are present in several bioactive molecules,[10] and the potential for further transformations of the enone functionality appended to the THF ring intrigued us to pursue this chemistry. Furthermore, In(III) has shown potential as a π-Lewis acid,[11] and so additional screening with other counterions was performed to see if the yield of **2a** could be improved. Using InI_3 (entry 2), 53% of **2a** was isolated, while, with $In(OTf)_3$ (entry 3), lower reactivity was observed even after a prolonged reaction time. In the absence of a protic acid, the reaction proceeded more slowly and gave less product (entry 4). Any attempt to heat the reaction mixture resulted in a lower yield and greater amounts of decomposition (entry 5), and no reaction was observed in the absence of indium (entry 6). Attempts to perform the hydrative cyclization of **1a** with $MeAuPPh_3$[7] resulted only in uncyclized alkyne monohydration or ether cleavage products.[12]

Table 1. Initial Optimization Studies with In(III)

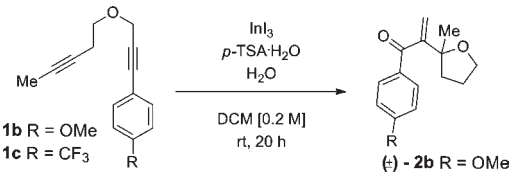


entry	X	time (h)	yield (%)[a]
1	Br	4	37
2	I	4	53
3	OTf	24	28
4[b]	I	22	38
5[c]	I	5	13[d]
6	N/A[e]	4	0

[a] Isolated yield. [b] H_2O (1.0 equiv), no *p*-TSA . [c] 40 °C. [d] Significant decomposition. [e] No metal used.

Two 1,7-diynes with substituents on the propargylic aryl ring were subjected to the reaction conditions to investigate the electronic effects on the cyclization (Table 2). Substrate **1b**, which has an electron-donating group on the aryl ring, underwent complete conversion within 1 h to yield small amounts of **2b** (9%, entry 1) as well as significant decomposition, while electron-deficient substrate **1c** produced no cyclized product (entry 2). Due to the high reactivity of electron-rich diyne **1b**, this substrate was chosen for additional optimization in an attempt to decrease the metal loading and determine the optimal amount of acid cocatalyst. By decreasing the amount of InI_3 from 1.0 to 0.5 equiv (entry 3), the yield of **2b** was increased 4-fold to 41%. When the catalyst loading was reduced to 0.2 equiv (entries 4–8), the reaction had 90% conversion of the starting dialkyne in 20 h, and the isolated yield could be increased to 49% by reducing the amount of *p*-TSA to 0.05 equiv (entry 7). Further reduction of the amount of metal to 0.1 equiv (entry 9) gave a comparable yield but required nearly 3 days to achieve useful conversion. In all trials, the modest yields were attributed to the recovery of small amounts of **1b** in addition to the formation of unidentified byproducts.

Table 2. Optimization of the Reaction Conditions



entry	substrate	InI_3 (equiv)	*p*-TSA (equiv)	H_2O (equiv)	product (% yield)[a]
1[b]	**1b**	1.0	0.5	0.5	**2b** (9)[c]
2	**1c**	1.0	0.5	0.5	N/A (0)
3	**1b**	0.5	0.25	0.75	**2b** (41)
4	**1b**	0.2	0.5	0.5	**2b** (15)
5	**1b**	0.2	0.2	0.8	**2b** (34)
6	**1b**	0.2	0.1	0.9	**2b** (38)
7	**1b**	0.2	0.05	0.95	**2b** (49)
8	**1b**	0.2	0.01	0.99	**2b** (14)
9[d]	**1b**	0.1	0.05	0.95	**2b** (46)

[a] Isolated yield. [b] 1 h reaction time. [c] Significant decomposition. [d] 70 h reaction time.

The scope of the hydrative cyclization with the optimized reaction conditions was investigated with a variety of dialkynes bearing electron-rich aryl rings, leading to the isolation of several 2,2-disubstituted THF derivatives (Table 3). A donating group in the *meta* position of the aryl ring resulted in significantly decreased levels of reactivity (entries 4 and 5), while addition of a second methoxy group in the *ortho* position gave many unidentified decomposition products with only 14% yield of the desired **2e** (entry 6). The 3,4,5-trimethoxy-bearing substrate **1h** gave the highest yield of cyclized product (61%, entry 9), with only a slightly increased yield (66%) obtained after an additional 24 h of reaction time (entry 10). An *n*-pentyl chain was also tolerated in place of the methyl terminus (entry 11), while terminal alkyne **1j** (entry 12) and diyne **1k**, with Me-capped internal alkynes (entry 13), were unreactive.

Upon lengthening of the homopropargylic side chain to a 1,8-diynyl ether, the hydrative cyclization also proceeded readily (Scheme 1). Although it was anticipated that the additional methylene unit would result in a six-membered ring, interestingly only the THF products were isolated. For methyl-terminated 1,8-diynyl ether **1l**, tetrahydrofuran **2l**, which has an angular ethyl group, was produced in 33% yield along with small amounts of other unidentified products. Furthermore, terminal 1,8-diynyl ether **1m** underwent cyclization, again providing access to **2h**, in 58% yield.

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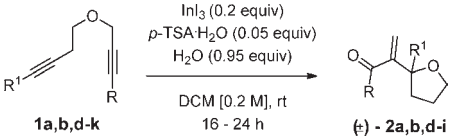
(12) See Supporting Information for experimental details.

Table 3. Scope of the Hydrative Cyclization[a]

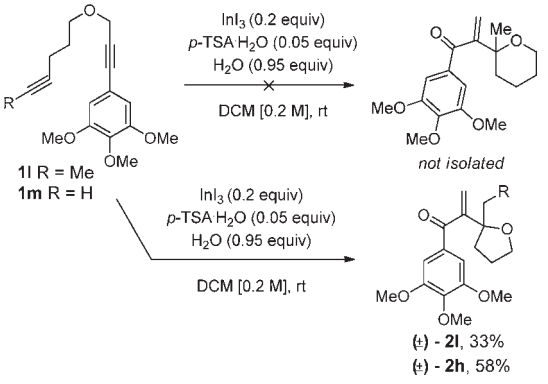


1a,b,d-k **(±) - 2a,b,d-i**

entry	substrate	R	R^1	product	yield (%)[b]
1[c]	**1a**	H	Me	**2a**	21
2[d]	**1a**	H	Me	**2a**	53
3	**1b**	4-OMe	Me	**2b**	49
4[c]	**1d**	3-OMe	Me	**2d**	16
5[d]	**1d**	3-OMe	Me	**2d**	28
6	**1e**	2,4-OMe	Me	**2e**	14[e]
7	**1f**	3,4-	Me	**2f**	56
8	**1g**	4-*t*Bu	Me	**2g**	50
9	**1h**	3,4,5-OMe	Me	**2h**	61
10[c]	**1h**	3,4,5-OMe	Me	**2h**	66
11	**1i**	3,4,5-OMe	nC_5H_{11}	**2i**	57
12	**1j**	H	Me	N/A	0
13	**1k**	Me	Me	N/A	0

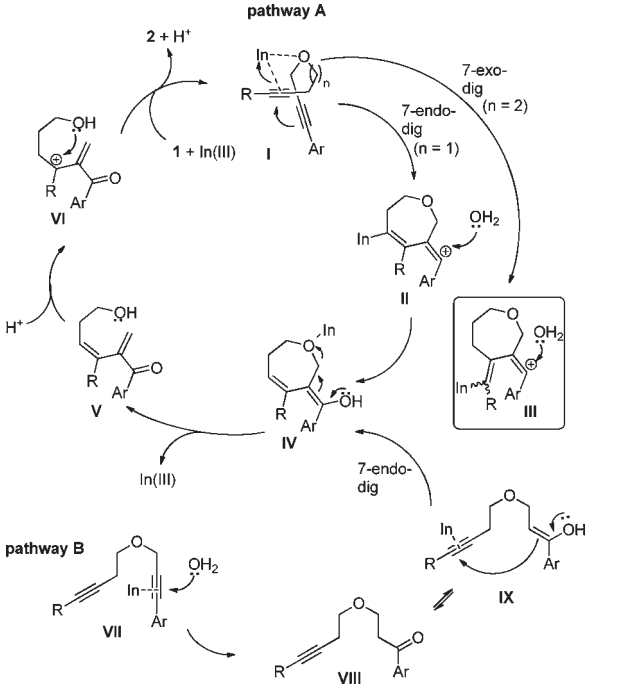
[a] See Supporting Information for specific reaction times. [b] Isolated yield. [c] 48 h reaction time. [d] InI_3 (1.0 equiv), *p*-TSA.H_2O (0.5 equiv) used. [e] Significant decomposition.

Scheme 1. Hydrative Cyclizations of 1,8-Diynyl Ethers



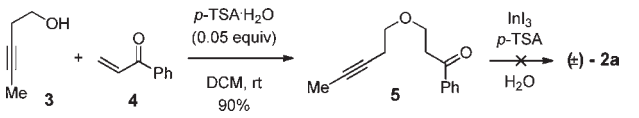
After observing the requirements necessary for successful cyclization, we envisioned two mechanistic possibilities (Scheme 2). The first (pathway A) begins with activation of the homopropargylic alkyne through an indium chelation[11c] with the ether oxygen, which promotes the initial 7-endo-dig cyclization with the required nucleophilic aryl alkyne. With the 1,8-diynes **1l** and **1m** ($n = 2$), initial 7-exo-dig closure would furnish vinyl carbocation **III** (*inset*). Subsequent trapping of **II** by water generates enol **IV**, which can undergo elimination to generate acyclic cross-conjugated dienone **V**. Protonation of **V** yields tertiary carbocation **VI**, and then ring closure gives the THF products **2**. After hydration, the 7-exo-dig-derived intermediate **III** can rejoin this pathway through either isomerization to an endocyclic alkene or protonation following the elimination to the enone. Alternatively, in pathway B, an In(III)-assisted hydration of the aryl-terminated alkyne gives hydrated alkyne **VIII**, which can react through the enol tautomer **IX** via an intramolecular 7-endo-dig closure onto the second alkyne. Zhang has shown that unactivated alkynes undergo hydrative cyclization using π-Lewis acidic metal catalysis,[7] so this aryl ketone pathway must be considered.

Scheme 2. Proposed Mechanistic Pathways



To test the mechanistic hypothesis involving initial alkyne hydration (pathway B), monoalkyne **5**, a putative intermediate on this pathway, was prepared via an oxy-Michael addition[13] of commercial 3-pentyn-1-ol with enone **4**[14] (Scheme 3). However, when **5** was subjected to the In(III)-catalyzed hydrative cyclization, no reaction to **2a** was observed. This lack of reactivity disproves pathway B.

Scheme 3. Initial Mechanistic Study



Pathway A (Scheme 2) accounts for several experimental observations. First, the propargylic substituent must be electron-rich in order for the reaction to proceed. In particular, sufficient nucleophilicity would be required to

promote the initial ring closure, stabilize vinyl carbocation **II**, and may also assist in the elimination to enone **V**. The absence of a sufficiently electron-rich propargylic group explains the inability of 1,7-diynyl ethers **1c** (Table 2) and **1j** and **1k** (Table 3) to produce THF products. Additionally, the failure of dialkynyl amides **6** and **7** (Figure 1) to give cyclized products may be due to either inability to eliminate the amide group to the acyclic intermediate analogous to **V** or inability to form the appropriate In(III) chelate complex analogous to **I** in the first place.

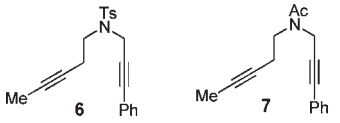
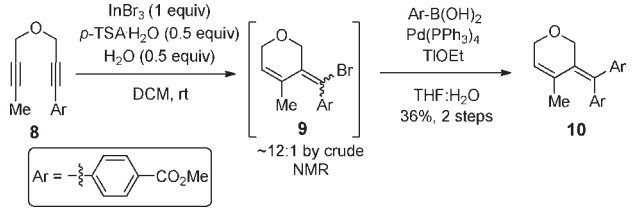


Figure 1. Unsuccessful *N*-tethered cyclization substrates.

After observing the formation of THF products **2** from 1,7- and 1,8-diynyl ethers, the reactivity of dipropargyl ethers in this hydrative cyclization was examined. Interestingly, when 1,6-diyne **8** was subjected to stoichiometric $InBr_3$, a new product, vinyl bromide **9**, was isolated as a mixture of stereoisomers by NMR (12:1, Scheme 4).[15]

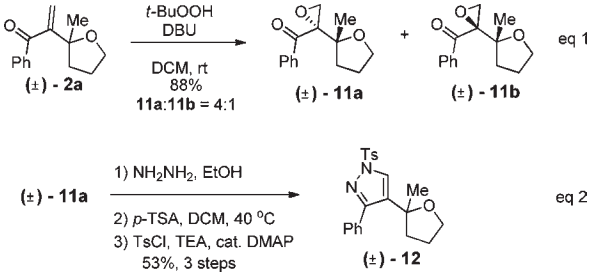
Scheme 4. Hydrobromination of 1,6-Diynyl Ether **8**



Since **9** was unstable after storage at ambient conditions, the crude product was subjected to a TlOEt-promoted Suzuki coupling,[16] giving exocyclic alkene **10** in 36% over 2 steps. Presumably, angle strain prohibits formation of the initial In(III) complex with the ether oxygen and one of the alkyne units of **8**, leading to the alternative reaction pathway.

The 2,2-disubstituted tetrahydrofuran products **2** with the enone substituent are intriguing substrates for scaffold postmodifications in library synthesis. Attempts to use the parent enone **2a** in reactions with traditional condensation partners such as urea and hydrazine failed, so preparation of the α-keto epoxide as a handle for reactivity was considered (Scheme 5). Treatment of racemic **2a** with excess *t*-BuOOH led to the isolation of separable diastereomeric epoxides **11a** and **11b** in a 4:1 ratio (eq 1).[17] The major isomer was further subjected to a condensation with excess hydrazine[18] followed by aromatization under acidic conditions[19] and tosylation to produce pyrazole **12** in 53% yield over 3 steps (eq 2). This structural motif mimics a *C*-nucleoside, which typically are potent antiviral agents.[20]

Scheme 5. Postmodifications of THF Products



In conclusion, a novel hydrative cyclization of 1,7- and 1,8-dialkynyl ethers was achieved using InI_3 and *p*-TSA cocatalysis. The resulting 2,2-disubstituted THF systems contain an exocyclic enone, and the highest yields were obtained for substrates bearing propargylic termini with nucleophilic aryl groups. Current work is focused on additional optimization, a more extensive mechanistic study, and investigation of an enantioselective variant.

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Supporting Information Available. Full experimental procedures, characterization data, and copies of ^1H and ^{13}C spectra of **1a**–**i**,**l**,**m**, **2a**,**b**,**d**–**i**,**l**, **5**, **8**, **10**, **11a**–**b**, **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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