Cascade Carbocyclizations from Alkynals towards Hydroazulenones Promoted by Brönsted Acids

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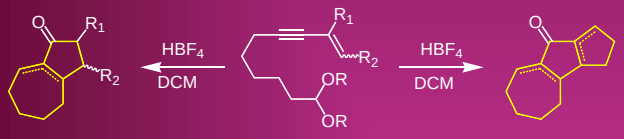
•Cascade carbocyclizations towards hydroazulenones

Hydroazulenones are important synthetic intermediates for pharmaceutical compounds, and their preparation have received important contributions over the last few years.[1]

Recently we have developed the *exo*-carbocyclization of 7-alkynals promoted by Brönsted acids for the construction of synthetically useful seven-membered cycloalkenones.[2]



Scheme 1

We now report the use of this methodology for the carbocyclization of enynacetals **1** to bicyclic [7,5] and tricyclic [7,5,5] hydroazulenones **2** and **3** (Scheme 1, table 1 and table 2).

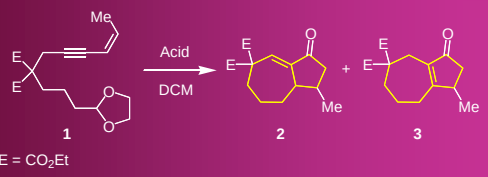
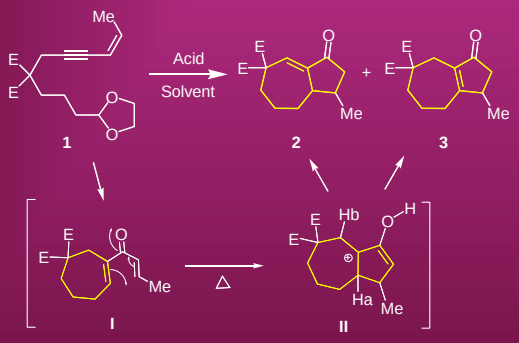


Table 1.- Cascade Carbocyclization/Nazarov Cyclization of Enynacetal **1**

Entry	Brönsted acid	T (°C)	Time (min)	Ratio **2:3**	Yield (%)
1	TFA(20 eq)	20	180	1.8:1	96
2	HBF_4(3 eq)	20	30	3:1	86
3	HBF_4(3 eq)	0	60	3:1	89
4	HBF_4(3 eq)	-15	60	4.5:1	60
5	$BF_3.OEt_2$ (3 eq)	20	90	1:2	39
6	TfOH(3 eq)	20	0.4	1:10	39
7	H_2SO_4(3 eq)	20	0.7h	1:1.6	60

•Mechanism

The transformation begins with a π nucleophile addition to an acid-activated acetal to afford the divinylketone intermediate I that then undergoes a Nazarov cyclization.



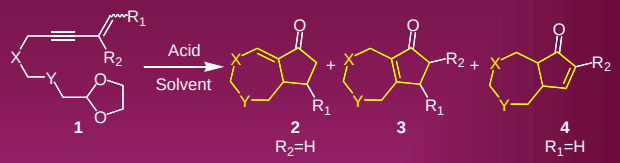
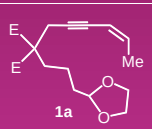
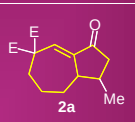
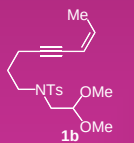
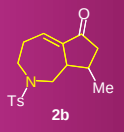
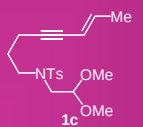
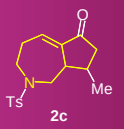
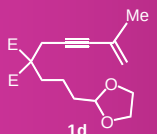
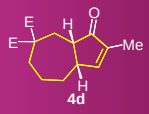
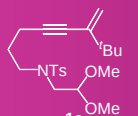
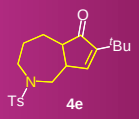
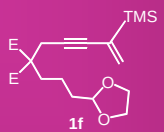
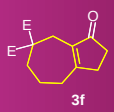
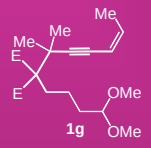
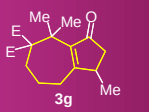
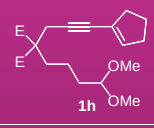
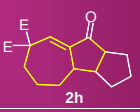


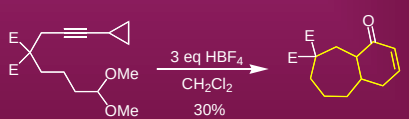
Table 2.- Carbocyclization of conjugated enynacetals **1**

Enynacetal **1**	Bicyclic enone	Ratio 2:3:4	Yield (%)
 **1a**	 **2a**	3:1:0	89 [a]
 **1b**	 **2b**	2:1:0	80 [a]
 **1c**	 **2c**	4.5:1:0	72 [a]
 **1d**	 **4d**	0:1:2	85 [b]
 **1e**	 **4e**	0:0:1	53 [a]
 **1f**	 **3f**	0:5:1	70 [b]
 **1g**	 **3g**	0:1:0	60 [a]
 **1h**	 **2h**	1:0:0	30 [a]

Conditions: [a] 0.5 mmol of enynacetal **1** in 3 mL of DCM and 3 eq HBF_4 , 0 °C, 10-40 min. [b] 20 eq TFA, in 3 mL of DCE, 90°C, 60-180 min. .

•Cascade Carbocyclization/homo-Nazarov Cyclization

Interestingly, cyclopropyl substituted alkyneacetals afford [7,6] bicyclic enones through the homo-Nazarov reaction.[3]



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1) a) Syu, W.J; Shen, C.C; Don, M.J; Ou, J.C; Lee, G.H; Sun, C.M. *J. Nat.Prod*, **1998**, *61*, 1531; b) Brady, S. F; Singh, M. P; Janso, J. E; Clardy, J. *J. Am. Chem. Soc* **2000**, *122*, 2116-2117; c) Wender, P. A.; Stemmler, R. T.; Lauren, S.E. *J. Am. Chem. Soc* **2010**, *132*, 2532-2533.

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3) De Simone, F.; Andrès J.; Torosantucci, R.; Waser, J. *Org. Lett*, **2009**, *11*, 1023.