J|A|C|S COMMUNICATIONS

Published on Web 02/08/2010

A Metal-Catalyzed Intermolecular [5+2] Cycloaddition/Nazarov Cyclization Sequence and Cascade

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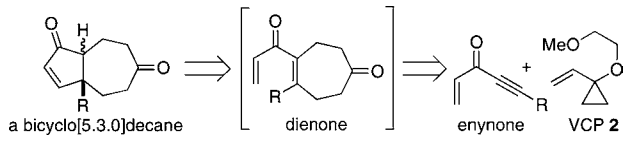
New and serialized[1a−d] reactions play a unique role in efforts to achieve greater step economy in synthesis.[1e] The former create new ways to think about bond construction, thereby providing novel and ideally more efficacious and greener strategic options. Both reduce cost, time, and solvent use (reaction and purification) that generally increase with step count. Prompted in part by these considerations, we previously introduced a new reaction for the synthesis of seven-membered rings based on the metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes (VCPs) and π systems.[2] While applicable to a wide range of 2-carbon π components, this process has not been examined with enynones. However, if successful, the [5+2] cycloaddition of such substrates would set the stage for a subsequent Nazarov[3] cyclization (Scheme 1), providing a strategically novel, one- or two-step route to bicyclo[5.3.0]decane derivatives. This ring system is one of the most commonly encountered subunits in Nature, being a key feature of the tiglianes, including prostratin,[4a] a preclinical candidate for eradication of the HIV/AIDS latent virus; the phorbol esters,[4b,c] the most potent tumor promoters known; the daphnanes,[4d,e] including resiniferatoxin, a clinical lead for treating chronic pain; and many other structurally fascinating families exhibiting significant therapeutic potential.[4f,g] We report herein the first study of the [5+2] cycloaddition of enynones and its utilization in new one- and two-stage routes to bicyclo[5.3.0]decane derivatives.

Scheme 1. [5+2] Cycloaddition/Nazarov Cyclization Sequence



To explore this idea, we first examined the reaction of a variety of en- and aryl-ynones with commercially available VCP **2** using $[Rh(CO)_2Cl]_2$ (2.5−5 mol %) as a catalyst. Significantly, aryl alkynones **1a**−**e**, enynones **1f**,**g**, and α-alkoxy enynones **1h**,**i** all were found to react readily, furnishing upon brief hydrolytic workup the corresponding aryl enones **3a**−**e** and dienones **3f**−**i** in good to excellent isolated yields (Table 1). Both internal and terminal alkynes can be used, and the cycloadditions proceed chemoselectively, occurring only at the alkyne moiety.

To investigate whether the [5+2] cycloaddition could be conducted serially with a Nazarov cyclization, we next screened a variety of Lewis and Brønsted acids for the desired reactions of dienones **3** (see SI for examples). TMSOTf and catalytic $AgSbF_6$ produced optimal results for aryl enones **3a**−**e**, affording the corresponding bicyclo[5.3.0]decane derivatives **4**−**8** in moderate to excellent yields (Table 1, entries 1−5). Catalytic amounts of $AgSbF_6$ also proved effective for the Nazarov cyclization of α-alkoxy dienones **3h**,**i** (entries 8, 9). Proton loss from the cyclopentenyl cation intermediate occurred selectively in favor of rearomatization or enol ether formation, respectively. While the six-membered cyclic enol ether of dienone **3h** was retained in product **11**, the acyclic enol ether in **3i** was hydrolyzed under the reaction conditions (entry 9). For simpler dienone substrates such as **3f**,**g**, bicyclo[5.3.0]decanes **9**,**10** were produced in moderate to good yields using TMSOTf; in these examples, isomers **a**/**b** arise from the commonly observed nonselective proton loss from the cyclopentenyl cation after cyclization (entries 6, 7). The cis-fused diastereomers of bicyclic Nazarov products **4**−**11** are formed preferentially, in ratios ranging from 2.0:1 (entry 1) to >20:1 (entries 2 and 8).[5]

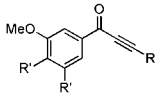
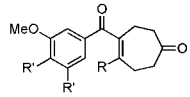
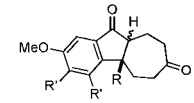
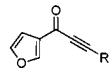
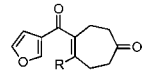
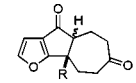
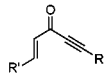
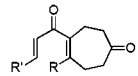
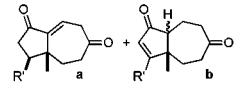
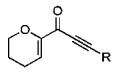
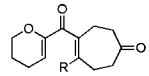
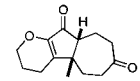
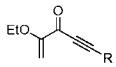
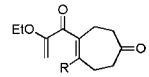
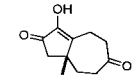
We next examined whether these two reactions could be coupled into a serial, one-flask process to produce bicyclo[5.3.0]decane derivatives in a single operation from VCP **2** and ynones **1**. This proved successful for several substrates (Table 2, conditions A). After completion of the intermolecular [5+2] cycloaddition using $[Rh(CO)_2Cl]_2$ (5 mol %) at 80 °C, $AgSbF_6$ (20 mol %) was added to facilitate the Nazarov cyclization as well as the hydrolysis of the intermediate enol ether (derived from the protecting group of **2**). Significantly, aryl alkynones **1a**−**d** as well as α-alkoxy enynone **1h** were converted into the corresponding cycloaddition/cyclization products **4**−**7** and **11** in this single-flask procedure in isolated yields ranging from 68% to 82%, making this procedure comparable or superior in efficiency to the two-flask (two-purification) protocol (Table 2, conditions A versus Table 1, respectively).

The use of a single catalyst system (cascade catalysis) to mediate both the [5+2] cycloaddition and the Nazarov cyclization was next explored to simplify the procedure operationally. For this purpose, we investigated cationic and more Lewis acidic rhodium catalysts. Significantly, we found that the cationic rhodium complex formed from $[Rh(CO)_2Cl]_2$ and $AgSbF_6$ was capable of carrying out both reactions in a single operation at 40 °C, furnishing product **11** in 56% yield (Table 2, entry 10). Furthermore, just 2 mol % of the cationic rhodium complex $[(C_{10}H_8)Rh(cod)^+SbF_6^-]$, which is highly effective in the intramolecular [5+2] cycloaddition,[6a] was able to catalyze both reaction steps, cleanly providing **11** in a remarkable 95% isolated yield (entry 11). For other substrates (**1a**−**d**), which required the additional use of silver salts to effect serial conversion, combined reaction times could be greatly reduced by activating the Rh(I) precatalyst[6b] $[Rh(cod)Cl]_2$ (2 mol %) with an excess of $AgSbF_6$ (15 mol %). In these cases, the rapid, room temperature [5+2] cycloaddition of VCP **2** was followed by the Nazarov cyclization at 80 °C, presumably facilitated by the additional Ag(I) species, to provide products **4**−**7** in good overall yields (Table 2, conditions B).

In summary, the intermolecular [5+2] cycloadditions of enynones and aryl-ynones proceed readily and chemoselectively, providing a novel route to aryl-enones and dienones in good to excellent yields. The resultant cycloadducts undergo a Nazarov cyclization providing overall a strategy for the facile synthesis of bicyclo[5.3.0]-

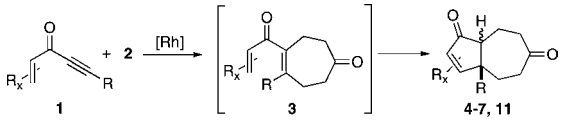
10.1021/ja910696x

Table 1. Rhodium-Catalyzed [5+2] Cycloaddition of Ynones **1a**−**i** and VCP **2**; Nazarov Cyclization of Dienones **3a**−**i**

entry	alkynone **1**		R, R'	Rh cat. (mol %)	*t* (h)	[5+2] product **3**, yield[a]	conditions[b]	t (h)	Nazarov product(s), yield (ratio)[c]
1		**1a**	H, H	2.5	1	 **3a**, 90%	B	2	 **4**, 92% (dr 2.0:1)
2		**1b**	Me, OMe	5	20	**3b**, 93%	B	15	**5**, 89% (dr >20:1)
3		**1c**	H, OMe	5	1	**3c**, 84%	A	1.5	**6**, 64% (dr 3.7:1)
4		**1d**	Me	5	2.5	 **3d**, 95%	B	10	 **7**, 96% (dr 19:1)
5		**1e**	H	5	0.5	**3e**, 88%	A	1	**8**, 80% (dr 2.8:1)
6		**1f**	Me, Me	2.5	16	 **3f**, 74%	A	1	 **9**, 85% (2:1)[d]
7		**1g**	Me, Ph	2.5	20	**3g**, 65%	A	0.5	**10**, 53% (5:1)[d]
8		**1h**	Me	5	15	 **3h**, 90%	B[e]	2.5	 **11**, 95% (dr >20:1)
9		**1i**	Me	5	17	 **3i**, 82%	B[f]	16	 **12**, 90%

[a] [5+2] Reaction conditions: VCP **2** (1.2 equiv), $[Rh(CO)_2Cl]_2$ (2.5−5 mol %), DCE/TFE (95:5), 80 °C; acidic workup. [b] Nazarov reaction conditions: (A) TMSOTf (1.1−2 equiv), DCM, room temp. (B) $AgSbF_6$ (10 mol %), DCE, 80 °C. [c] Isolated yield, ratio of cis:trans diastereomers determined by ^{1}H NMR. [d] Ratio of **a**:**b**. [e] Reaction performed at room temp. [f] Reaction performed at 50 °C.

Table 2. Serial [5+2]/Nazarov Processes and Cascade Catalysis



entry	ynone	conditions[a]	*t* (h)[b]	product(s)	yield (ratio)[c]
1	**1a**	A	15, 1	**4**[d]	82% (dr 2.0:1)
2		B	0.25, 2		71% (dr 2.0:1)
3	**1b**	A	20, 1.5	**5**	76% (dr >20:1)
4		B	0.25, 2		78% (dr >20:1)
5	**1c**	A	20, 1	**6**	82% (dr 3.6:1)
6		B	0.25, 2		89% (dr 3.8:1)
7	**1d**	A	4, 22	**7**	68% (dr 19:1)
8		B[e]	0.25, 20		54% (dr >20:1)
9	**1h**	A[f]	13, 3	**11**	77% (dr >20:1)
10		C	16		56% (dr >20:1)
11		D	24		95% (dr >20:1)

[a] Conditions: VCP **2** (1.2 equiv); (A) $[Rh(CO)_2Cl]_2$ (5 mol %), DCE/TFE (95:5), 80 °C, then $AgSbF_6$ (20 mol %), 80 °C; (B) $[Rh(cod)Cl]_2$ (2 mol %), $AgSbF_6$ (15 mol %), DCE/TFE (75:25), room temp, then 80 °C; acidic workup; (C) $[Rh(CO)_2Cl]_2$ (5 mol %), $AgSbF_6$ (10 mol %), DCE/TFE (95:5), 40 °C; (D) $[(C_{10}H_8)Rh(cod)^+SbF_6^-]$ (2 mol %), DCE, 50 °C. [b] Reaction time for [5+2] and Nazarov phase, respectively. [c] Isolated yield, ratio of cis:trans isomers (^{1}H NMR). [d] There was 7% Nazarov regioisomer also observed. [e] 20 mol % $AgSbF_6$ was used. [f] Nazarov phase run at room temp.

decanes. In many cases, this cycloaddition/cyclization process can be carried out in a single operation with comparable or superior yields and with shorter reaction times using a two-catalyst system. Significantly, the cycloaddition/cyclization can also be conducted with a single catalyst system. Further studies on this facile route to the core ring system of therapeutically promising bicyclo[5.3.0]decanes are in progress.

Acknowledgment. This research was supported by the NSF (Grant CHE-0450638 and graduate fellowship to L.E.S.) and by the German Academic Exchange Service (DAAD, R.T.S.). Jung-Min Kee is thanked for related examples and discussion.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA910696X