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6-*endo*-dig Cyclization of heteroarylesters to alkynes promoted by Lewis acid catalyst in the presence of Brønsted acid

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Abstract—We report a regiocontrolled 6-*endo*-dig cyclization of 2-(2-arylethynyl)heteroaryl esters occurred under Brønsted acidic conditions and in the presence of a catalytic amount of Lewis acids such as $Cu(OTf)_2$, $AuCl_3$, or $(CF_3CO_2)Ag$. A variety of heterocyclic lactones are readily prepared in excellent yields.

The alkyne is among the most versatile functional groups in organic chemistry.[1] Significant progress has been made in intramolecular cyclization through alkyne activation.[2] Recently, Uchiyama et al. have reported a regiocontrolled intramolecular cyclization of carboxylic acids to carbon–carbon triple bonds mediated by acid catalyst leading to isocoumarin rings, which constitute an important class of naturally occurring lactones.[3] We report here an efficient Lewis acid-mediated 6-*endo*-dig cyclization of esters to alkynes leading to isocoumarins and their heteroaryl analogs.

We first focused our attention on the cyclization of methyl 2-(2-arylethynyl)benzoate **1a**–**d** (Table 1). Previous theoretical work claimed that under acidic conditions, the electronic bias on both carbons of the triple bond favors Michael-type (6-*endo*-dig) cyclization.[3] In good agreement with this report, the reactions of esters **1a**–**d** in trifluoroacetic acid (TFA), as Brønsted acid, at room temperature led in less than 1 h to the corresponding isocoumarins **2a**–**d** in high yields (Table 1). No 5-*exo*-dig cyclization was detected.[4] Moreover, the presence of electron-donating groups on the aryl moiety seems to favor the cyclization (entries 3 and 4). We next extended this reaction to various heterocyclic esters, such as ethyl 2-(2-phenylethynyl)nicotinate **3** (Table 2).[5] However, the 6-*endo*-dig cyclization of **3** in TFA was never detected, even after 12 h at room temperature (entry 1). Microwave irradiation at 100 °C for 20 min led to the corresponding lactone **4** in only 18% yield (entry 2).[6] Yao and Larock have reported an efficient synthesis of isocoumarin and related lactones via an electrophilic cyclization between alkyne and ester groups by means of HI at room temperature for 4 days.[7] These conditions, applied to nicotinate **3**, did not provide any trace of the corresponding lactone **4**, even after 7 days. Recent reports have highlighted the efficacy of Lewis acids for alkyne activation,[2] so various Lewis acid catalysts were investigated, including derivatives of Cu^0, Cu^I, Cu^{II}, Ag^I, and Au^{III} metals (Table 2).

Generally speaking, the Lewis acidities of copper depends on its oxidation state and on the counterion. So, complexes in the Cu^{II} oxidation state are more Lewis acidic, a property which is increased by the electron-withdrawing capacity of the counterion.[8] Consequently, the cyclization of nicotinate **3** to lactone **4** was carried out under microwave irradiation using a series of copper complexes exhibiting varying Lewis acidity (Table 1, entries 3–13 and 17). Surprisingly, even Cu^0 as turnings was able to provide **4** in 47% yield. Moreover, as expected, Cu^{II} complexes turned out to be more efficient than Cu^I and Cu^0. $Cu(OTf)_2$, bearing the two strongest electron-withdrawing counterions, appeared to be the best catalyst providing lactone **4** in 92% yield.[9] Reaction conditions were optimized following a multivariate screening analysis of the variables involved in this Lewis acid-promoted cyclization. An increase in the quantity of copper catalyst did not improve the reaction (entry 14). Moreover, 20 min of microwave irradiation was

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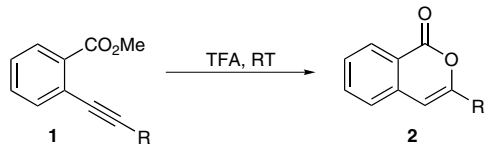
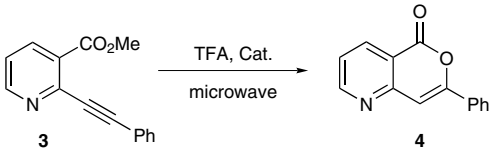
Table 1. Acid-promoted isocoumarin cyclization[a]



Entry	1	R	Reaction time (min)	2	Yield[b] (%)
1	**1a**	Ph	60	**2a**	83
2	**1b**	4-Cl-Ph	60	**2b**	98
3	**1c**	4-MeO-Ph	30	**2c**	96
4	**1d**	3,4-$(MeO)_2$-Ph	15	**2d**	97

[a] The reaction was carried out with **1** (1.86 mmol) in TFA (2 mL) as solvent at rt.
[b] Yield of isolated product.

Table 2. Lewis acid-catalyzed cyclization of **3** to lactone **4**[a]



Entry	Catalyst	Mol %	Conditions[b]	Yield[c] (%)
1[d]	—	—	rt, 12 h	nd[e]
2	—	—	MW (100 °C, 20 min)	18
3	Cu^0 powder	5	MW (100 °C, 20 min)	43
4	Cu^0 turnings	70	MW (100 °C, 20 min)	47
5	Cu^I_2O	5	MW (100 °C, 20 min)	74
6	Cu^ICl	5	MW (100 °C, 20 min)	61
7	Cu^IBr	5	MW (100 °C, 20 min)	65
8	Cu^II	5	MW (100 °C, 20 min)	74
9	Cu^ICN	5	MW (100 °C, 20 min)	86
10	Cu^ITc[f]	5	MW (100 °C, 20 min)	74
11	Cu^IOAc	5	MW (100 °C, 20 min)	68
12	$Cu^{II}Cl_2$	5	MW (100 °C, 20 min)	61
13	$Cu^{II}(OAc)_2$	5	MW (100 °C, 20 min)	86
14	$Cu^{II}(OAc)_2$	10	MW (100 °C, 20 min)	83
15	$Cu^{II}(OAc)_2$	5	MW (100 °C, 5 min)	56
16	$Cu^{II}(OAc)_2$	5	MW (100 °C, 30 min)	83
17	$Cu^{II}(OTf)_2$	5	MW (100 °C, 20 min)	92
18	$Cu^{II}(OTf)_2$	5	CH (100 °C, 20 min)	45
19	$Cu^{II}(OTf)_2$	5	rt, 24 h	29
20	$CF_3CO_2Ag^I$	5	rt, 15 h	32
21	$CF_3CO_2Ag^I$	5	MW (100 °C, 20 min)	75
22	$Au^{III}Cl_3$	5	rt, 15 h	38
23	$Au^{III}Cl_3$	5	MW (100 °C, 20 min)	83

[a] The reaction was carried out with **3** (0.2 mmol) in TFA (1 mL) as solvent.
[b] MW: microwave irradiation; CH: conventional heating.
[c] Yield of isolated product.
[d] Ethyl ester was replaced by a methyl ester.
[e] Not detected.
[f] Copper(I) thiophene-2-carboxylate.

necessary to complete the reaction, and a longer time did not improve the yield (entries 13, 15, and 16). Furthermore, cyclization of **3** achieved under conventional heating for 20 min at 100 °C led to lactone **4** in only 45% yield, clearly supporting the beneficial effects of microwave irradiation (entry 18). Copper is in the Ib column of the periodic table, as well as silver and gold, which are also known to be good Lewis acids.[10] However, $CF_3CO_2Ag^I$ as well as $Au^{III}Cl_3$ was not as efficient as $Cu(OTf)_2$, in providing lactone **4** (entries 21 and 23). As for copper-mediated catalysis, no 5-*exo*-dig cyclization was detected.[4] The choice of trifluoroacetic acid as solvent was critical: use of tetrahydrofuran, dimethylformamide, dichloroethane, or toluene along with TFA as an additive led to a significantly lower yield (Table 3).

We next paid our attention to extend this Lewis acid-promoted cyclization to other heterocyclic esters (**5**–**9**), which were prepared by means of a Sonogashira coupling reaction.[11] The cyclizations were carried out in TFA in the presence of $Cu(OTf)_2$ (5 mol %) under microwave irradiation (20 min, 100 °C) (Table 4). Analogs of nicotinate **3**, bearing electron-donating groups on the phenyl moiety, led to the corresponding lactones in excellent yields (entries 1 and 2). Similar results were obtained starting from pyrimidine **6** (entry 3), indole **7** (entry 4), or tetrahydropyridine **9** (entry 7), providing the corresponding lactones **11**, **12**, and **14** in excellent yields. Surprisingly, under similar conditions, no cyclization was observed in the case of the imidazopyridine scaffold (entry 5). However, the saponification of ester **8a** into the corresponding carboxylic acid **8b** likely allowed a better nucleophilicity of the carbonyl group, leading to lactone **13** in 90% yield under $Cu(OTf)_2$-catalyzed cyclization conditions (entry 6). It is noteworthy that none of these lactones (**10**–**14**) was obtained in the absence of a Lewis acid.

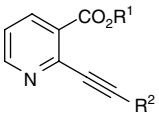
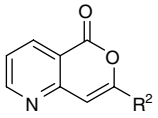
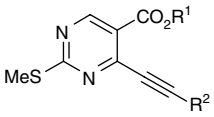
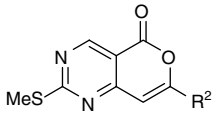
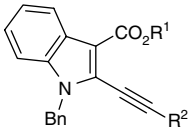
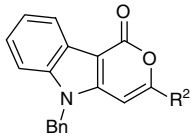
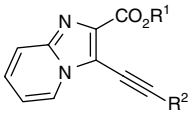
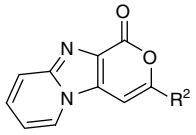
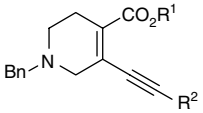
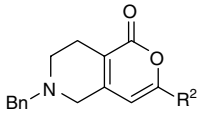
A plausible mechanism for the present reaction is shown in Scheme 1. The pyridine ring and heteroaromatic analogs are known to complex Lewis acids such as copper. However, under strong acidic conditions (TFA as solvent), we observed a protonation of the pyridine ring by ^1H NMR spectroscopy. So the copper catalyst is free to establish a coordination bond with the triple bond of **3**, enhancing the electrophilicity of the alkyne. Moreover, the resulting pyridinium ring acts as an electron-withdrawing group, leading to an electronic bias on both carbons of the triple bonds, which favors Michael-type (6-*endo*) cyclization. The nucleophilic attack of the carbonyl oxygen atom on the electron-deficient alkyne provides the cupric ate complex **3B**, which, after a protonolysis step by means of a Brønsted acid

Table 3. Solvent effect on the Lewis acid-catalyzed cyclization of **3** to lactone **4**[a]

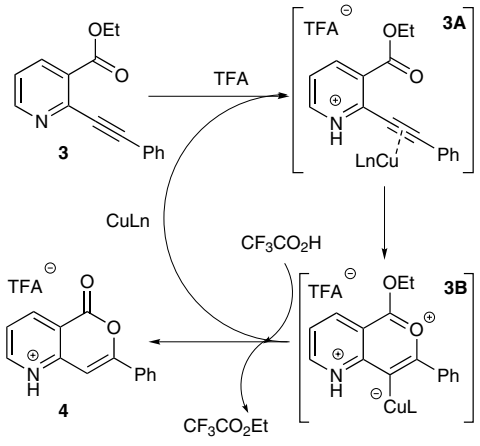
Entry	Solvent	Additive	Equiv	Yield[b] (%)
1	TFA	—		92
2	THF	TFA	1	nd[c]
3	THF	TFA	3	36
4	DMF	TFA	3	nd
5	DCE	TFA	3	38
6	Toluene	TFA	3	63
7	Toluene	TFA	6	61

[a] The reaction was carried out with **3** (0.2 mmol) in the presence of $Cu(OTf)_2$ (5 mol %) in solvent (1 mL) under microwave irradiation (100 °C, 20 min).
[b] Yield of isolated product.
[c] Not detected.

Table 4. Lewis acid-catalyzed cyclization of various heterocycles[a]

Entry	Alkyne		R^1	R^2	Product		Yield[b] (%)
1		**5a**	Et	4-MeO-Ph		**10a**	98
2		**5b**	Et	3,4(MeO)$_2$-Ph		**10b**	94
3		**6**	Et	Ph		**11**	91
4		**7**	Me	Ph		**12**	83
5[c]		**8a**	Et	Ph		**13**	nd[d]
6		**8b**	H	Ph		**13**	90
7		**9**	Et	Ph		**14**	89

[a] The reaction was carried out with alkyne (0.2 mmol) in the presence of $Cu(OTf)_2$ (5 mol %) under microwave irradiation (100 °C, 20 min) in TFA (1 mL) as solvent.
[b] Yield of isolated product.
[c] CuTc (10 mol %) was used in the place of $Cu(OTf)_2$.
[d] Not detected.



Scheme 1. Plausible mechanism for copper-catalyzed cyclization under acidic conditions.

such as trifluoroacetic acid, provides lactone **4**, while regenerating the initial copper catalyst.

In conclusion, an efficient approach to the synthesis of novel heterocyclic lactones has been developed by employing an association between a Brønsted acid and a Lewis acid to catalyze the cyclization of *o*-alkynylaryl esters containing nitrogen atoms. It is noteworthy that this regiocontrolled 6-*endo*-dig cyclization proceeds efficiently through a simple and inexpensive copper catalyst on a wide variety of 2-alkynyl heterocyclic esters.

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Supplementary data

Experimental details, characterization data, and copies of ^1H, ^{13}C, and NOE NMR spectra for each compound are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.020.

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9. *7-Phenyl-5H-pyrano[4,3-b]pyridin-5-one* (**4**): To a solution of **3** (0.2 mmol) in trifluoroacetic acid (1 mL) was added $Cu(OTf)_2$ (5 mol %). The solution was irradiated with microwaves at 100 °C for 20 min. Trifluoroacetic acid was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic layer was further washed with brine (2×20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by chromatography on silica gel R (elution gradient: EtOAc–heptane 3–7 to 1–1) yielded **4** as a white powder in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91 (dd, 1H, $J = 1.3$, 4.7 Hz), 8.52 (dd, 1H, $J = 1.3$, 8.1 Hz), 7.93–7.86 (m, 2H), 7.50–7.45 (m, 3H), 7.40 (dd, 1H, $J = 4.7$, 8.1 Hz), 7.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 157.4, 156.6, 153.3, 137.8, 131.6, 131.1, 129.3, 125.9, 123.2, 117.2, 104.0. IR (neat, cm^{-1}): 3067, 2923, 2853, 2330, 1734, 1633, 1561, 1439, 1280, 1215, 1110, 1079, 774, 752, 688, 530. Mp = 136–137 °C. ESI-HRMS calcd $C_{14}H_{10}NO_2$ $[M+H]^+$ 224.0706, found 224.0694.
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