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SYNTHESIS OF ISOCOUMARINS: RHENIUM COMPLEX-CATALYZED CYCLIZATION OF 2-ETHYNYLBENZOIC ACIDS

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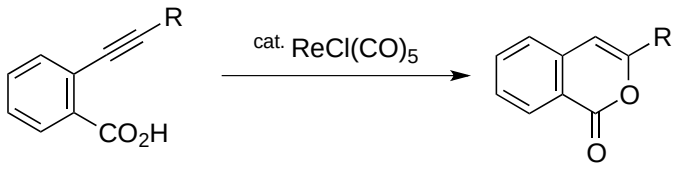
Abstract – When 2-ethynylbenzoic acids were treated with a catalytic amount of a rhenium complex, such as $ReCl(CO)_5$, 6-*endo* cyclization of 2-ethynylbenzoic acids proceeded with a high selectivity to give the corresponding isocoumarins in moderate to good yields.

Isocoumarin (1*H*-2-benzopyran-1-one) is one of the important structural subunits in numerous natural products that exhibit a wide range of biological properties[1] and is a useful intermediate for the preparation of hetero- and carbocyclic compounds including isocarbostyrils, isochromenes and isoquinolines.[2] Therefore, the development of synthetic methods of the isocoumarins has significantly contributed to organic and medicinal chemistries.[3]

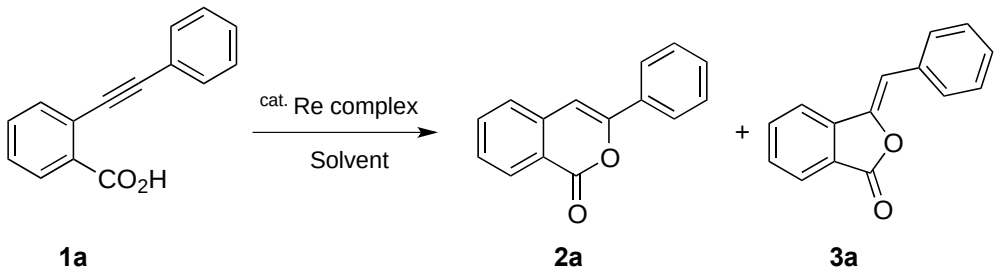
We and some groups showed that $ReX(CO)_5$ (X = Cl or Br) can be used as a catalyst for organic reactions instead of various Lewis acid complexes.[4,5] Recently, Hou reported that the rhenium complex-catalyzed addition of carboxylic acids to terminal alkynes proceeded with a high regioselectivity affording the *anti*-Markovnikov adduct, *i.e.*, α,β-unsaturated carboxylic acids, in moderate to good yields.[6] Based on these results, it is expected that the treatment of 2-ethynylbenzoic acids in the presence of rhenium catalyst would provide the one of the preparation methods of cyclic esters, isocoumarins or vinylphthalides, *via* the intramolecular cyclization of 2-ethynylbenzoic acids.[7] We now wish to report the successful example of the rhenium-catalyzed 6-*endo* intramolecular cyclization of 2-ethynylbenzoic acids for the synthesis of isocoumarins (Scheme 1).



Scheme 1

When 2-(phenylethynyl)benzoic acid (**1a**) was stirred in the presence of a catalytic amount of $ReCl(CO)_5$ (5 mol%) in a hexane at 80 °C for 5 h, the 6-*endo* cyclization of **1a** smoothly proceeded with a high selectivity to give 3-phenyl-1*H*-isochromen-1-one (**2a**) in 80% yield with a small amount of the 5-*exo* cyclized product, 3-(1-benzylidene)phthalide (**3a**) (1%) (Entry 1 in Table 1). No reaction took place in the absence of the rhenium complex (Entry 2). The yield of **2a** was improved by the extended reaction time (10 h) (Entry 3). At a lower reaction temperature (60 °C), the yield and selectivity of **2a** decreased (Entry 4). To explore the effect of the solvents and rhenium complexes, the reaction of **1a** was carried out in various solvents and rhenium complex catalysts. In the toluene solvent, a decrease in both the yield and selectivity of **2a** were observed (Entry 5). In the cases of THF and acetonitrile, which were coordinated solvents to metals, the yields of **2a** dramatically decreased (Entries 6 and 7).

Table 1. Reaction of 2-(phenylethynyl)benzoic acid (**1a**)[a]



1a **2a** **3a**

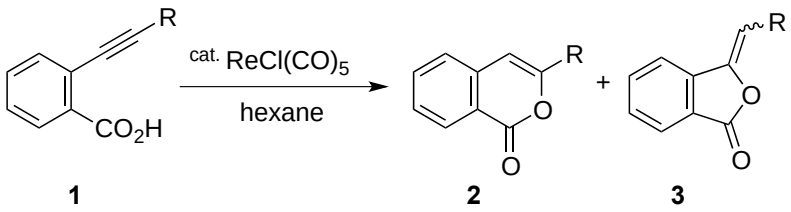
Entry	Catalyst	Solvent	Temp (°C)	Yield (%) (**2a** : **3a**)[b]
1	$ReCl(CO)_5$	hexane	80	81 (80 : 1)
2	-	hexane	80	0
3[c]	$ReCl(CO)_5$	hexane	80	93 (90 : 3)
4	$ReCl(CO)_5$	hexane	60	60 (53 : 7)
5	$ReCl(CO)_5$	toluene	80	66 (53 : 13)
6	$ReCl(CO)_5$	THF	80	24 (24 : 0)
7	$ReCl(CO)_5$	MeCN	80	3 (2 : 1)
8	$ReCl(CO)_5$	$ClCH_2CH_2Cl$	80	87 (80 : 7)
9	$ReBr(CO)_5$	hexane	80	77 (72 : 5)
10	$Re_2(CO)_{10}$	hexane	80	19 (2 : 17)
11	$ReCl_5$	hexane	80	22 (17 : 5)
12	$(C_5H_5)Re(CO)_3$	hexane	80	8 (2 : 6)

[a] Reaction conditions: **1a** (0.3 mmol), Re catalyst (5 mol%), solvent (2 mL), 5 h.
[b] ^1H NMR yield. The number in parenthesis shows the ratio of **2a** and **3a**.
[c] 10 h.

The use of 1,2-dichloroethane, which is often used for the rhenium-catalyzed reaction, led to the good yield of **2a** (80%), but the selectivity slightly decreased (Entry 8). When $ReBr(CO)_5$ was used instead of $ReCl(CO)_5$ as the catalyst, both the yield and selectivity of **2a** were lower than those of $ReCl(CO)_5$ (Entry 9). Other rhenium complexes, such as $Re_2(CO)_{10}$, $ReCl_5$ and $(C_5H_5)Re(CO)_3$, did not show any high catalytic activity (entries 10-12).[8]

To clear the scope and limitation of the rhenium complex catalytic system, various 2-(arylethynyl)benzoic acids were treated with a catalytic amount of rhenium complex. These results are shown in Table 2. The 6-*endo* cyclization of 2-(arylethynyl)benzoic acids bearing electron-donating groups on the aromatic ring, such as the 2-((4-methylphenyl)ethynyl)- and 2-((4-methoxyphenyl)ethynyl)benzoic acid, proceeded with excellent selectivity to give the corresponding 3-aryl-1*H*-isochromen-1-one, **2b**,**c**, in 96 and 87% yields, respectively (Entries 2 and 3). For the reaction of 2-((4-chlorophenyl)ethynyl)benzoic acid, in which the electron withdrawing group was substituted on the aromatic ring, the yield of 3-(4-chlorophenyl)-1*H*-isochromen-1-one (**2d**) decreased (Entry 4). In the case of the 2-((3-methoxyphenyl)ethynyl)benzoic acid, the yield of 3-(3-methoxyphenyl)-1*H*-isochromen-1-one (**2e**) decreased due to the decreasing selectivity (Entry 5). For the sterically hindered 2-(arylethynyl)benzoic acids, 2-((2-methoxyphenyl)- and 2-((2-methylphenyl)ethynyl)benzoic acid, the yields of products decreased (Entries 6 and 7). The preparation of the naphthyl and alkyl substituted 1*H*-isochromen-1-ones **2** was successfully achieved using the rhenium catalytic system (Entries 8-12).

Table 2. Synthesis of 1*H*-isochromen-1-ones[a]



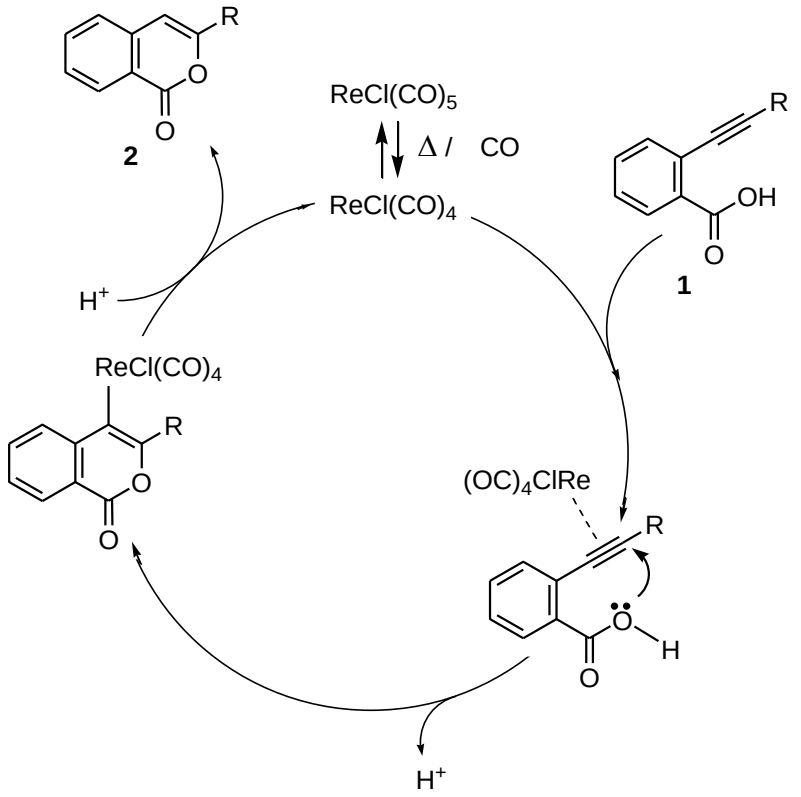
1 **2** **3**

Entry	R	Yield (%) (**2** : **3**)[b]
1	Ph (**1a**)	93 (90 : 3)
2	4-MeC_6H_4 (**1b**)	99 (96 : 3)
3[c]	4-$MeOC_6H_4$ (**1c**)	87 (87 : 0)
4	4-ClC_6H_4 (**1d**)	77 (72 : 5)
5	3-$MeOC_6H_4$ (**1e**)	94 (54 : 40)
6	2-$MeOC_6H_4$ (**1f**)	68 (53 : 15)
7	2-MeC_6H_4 (**1g**)	45 (40 : 5)

8[c]	1-$C_{10}H_7$ (**1h**)	80 (80 : 0)
9	*n*-C_3H_7 (**1i**)	70 (70 : 0)
10	*n*-C_4H_9 (**1j**)	77 (77 : 0)
11	*c*-C_6H_{11} (**1k**)	81 (81 : 0)
12	*t*-C_4H_9 (**1l**)	20 (20 : 0)

[a] Reaction conditions: **1** (0.3 mmol), $ReCl(CO)_5$ (5 mol%), hexane (2 mL) at 80 °C for 10 h.
[b] Isolated yield. The number in parenthesis shows the ratio of **2** and **3**.
[c] $ClCH_2CH_2Cl$ was used as a solvent.

We cannot fully explain the reaction pathway for the reaction, however, one of the plausible reaction pathways for the rhenium-catalyzed reaction is shown in Scheme 2. First, the decarbonylation of $ReCl(CO)_5$ to form $ReCl(CO)_4$, which is the coordinatively unsaturated 16-electron complex, is the first step of the catalytic reaction.[9] The carbon-carbon triple bond of the 2-ethynylbenzoic acids **1** is activated by the coordination of the rhenium species. The nucleophilic addition of the carboxy group to the carbon-carbon triple bond activated by the rhenium complex followed by the protonation then gave the 1*H*-isochromen-1-ones **2**.



Scheme 2

We developed a new synthetic method of isocoumarins by the rhenium complex-catalyzed 6-*endo* cyclization of 2-ethynylbenzoic acids. The application of the reaction and determining the reaction mechanism are now in progress.

EXPERIMENTAL

Reagents. $ReBr(CO)_5$, $ReCl(CO)_5$, $(C_5H_5)ReO_3$, $Re_2(CO)_{10}$, and $ReCl_5$ were commercially available and were used without further purification. 2-(Arylethynyl)benzoic acids were prepared by the hydoration of corresponding methyl esters, which were prepared by the Sonogashira coupling of methyl 2-iodobenzoate and arylethyny, 1-pentyne, 1-hexyne, ethynylcyclohexane or 3,3-dimethyl-1-butyne. Other chemical agents were obtained commercially and were purified if necessary by distillation.

General procedure for rhenium-catalyzed cyclization of 2-ethynylbenzoic acids. A hexane (2.0 mL) solution of 2-ethynylbenzoic acid (0.3 mmol) and $ReCl(CO)_5$ (5 mol%) was stirred under an atmosphere of nitrogen at 80 ºC for 10 h. After the reaction was complete, H_2O was added to the reaction mixture and extracted with EtOAc. The organic layer was dried with $MgSO_4$. The resulting mixture was filtered, and the filtrate was concentrated. Purification of the residue by silica gel column chromatography afforded isocoumarins. The structures of the products were assigned by their ^1H and ^{13}C-NMR, and mass spectra. The products were characterized by comparing its spectral data with those of authentic samples or previous reports **2a**,[3e] **2b**,[3e] **2c**,[3e] **2d**,[3e] **2e**,[10] **2f**,[3e] **2g**,[7b] **2h**,[3e] **2i**,[7b,11] **2j**,[3e] **2k**,[12] **2l**,[13] **3a**,[14] **3b**,[14] **3d**,[15] and **3g**.[7b] The structures of the products (**3e** and **3f**) were assigned by their ^1H and ^{13}C NMR, IR and mass spectrum.

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