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Platinum(II)-catalyzed intramolecular cyclization of alkynylbenzonitriles: synthesis of 1-alkoxyisoquinolines and isoquinolones

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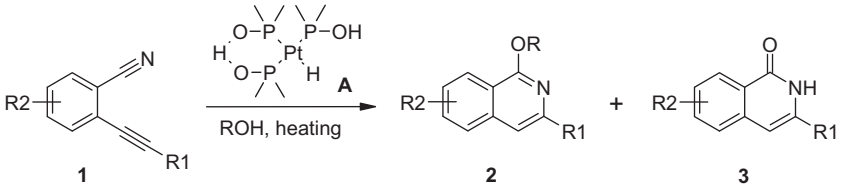
ABSTRACT

A facile synthesis of a series of 1-alkoxyisoquinolines and (2*H*)-isoquinolones by an intramolecular 6-*endo*-*dig* cyclization of *ortho*-alkynylbenzonitriles in the presence of a catalytic amount of hydrido(dimethylphosphinous acid-κP)[hydrogen bis(dimethylphosphinito-κP)]platinum(II) in various alcohols at 65–90 °C is described for the first time.

Isoquinolines and isoquinolones are a unique class of heterocyclic frameworks which are frequently found in many natural products, biologically active compounds, and clinical candidates.[1–4] In particular, the 1-alkoxyisoquinoline moiety is an essential component of a class of potent hepatitis C virus (HCV) protease inhibitors.[3,4] There are extensive methodologies regarding the synthesis of isoquinolines and isoquinolones available in the literature.[5,6] Although there have been reports utilizing transition metals for the construction of isoquinolines and isoquinolones,[7] applications of platinum metal complexes involved in such cyclization transformations have not received much attention until recently.[8] Numerous examples reported in the literature describe the use of metal complexes, such as Au, Ag, Pd, and Cu, to catalyze cyclizations of arylalkynes bearing nucleophilic *ortho*-substitutions.[9–12] Platinum complexes are well known for their ability to coordinate to an alkyne moiety and have the potential to initiate the subsequent transformations.[13] We reasoned that this Pt–alkyne coordination feature would regioselectively direct an intramolecular ring cyclization with *ortho*-substituted nucleophilic functionalities, such as nitriles, amides, acids, esters, and hydroxyl groups. Applying this new approach, we studied the constructions of isoquinolones and isoquinolones from *ortho*-alkynylbenzonitriles in a catalysis manner under mild neutral conditions that have not been reported before. Herein, we describe the first application of platinum(II)-catalyzed regioselective intramolecular 6-*endo*-*dig* cyclization of *ortho*-alkynylbenzonitriles that lead to isoquinoline and isoquinolone rings under simple and mild neutral reaction conditions illustrated in Scheme 1.

Our initial successful attempt for this transformation was conducted with hydrido(dimethylphosphinous acid-κP)[hydrogen bis(dimethylphosphinito-κP)]platinum(II) (**A**), which is a catalyst used for hydrolyzing nitriles to primary amides under neutral conditions.[14] A mixture of *ortho*-CN-diphenylacetylene[15,16] (**1a**) and 5 mol % of this Pt(II) catalyst in refluxing MeOH for 16 h afforded 18% of 1-methoxyisoquinoline **2a**, 32% of methyl benzoate **4a**, and 27% of primary benzamide **5** (Table 1, entry 1). To our dismay, only a trace amount of the isoquinolone **3a** was observed in the product mixture although none of the 5-*exo*-*dig* products were observed. Both the reaction time and the catalyst loading influenced the product formation during the preliminary studies. Increasing the Pt(II) catalyst loading to 10 mol % not only improved both yields of 1-methoxyisoquinoline **2a** and isoquinolone **3a** (26% and 6%, respectively), but also produced less methyl benzoate **4a** and benzamide **5** (entry 2). Prolonging the reaction time by heating **1a** with 10 mol % Pt(II) catalyst in MeOH from 16 to 48 h further enhanced the yields of 1-methoxyisoquinoline **2a** and isoquinolone **3a** to 35% and 10%, respectively (entry 3). We observed that



Scheme 1. Synthesis of 1-alkoxyisoquinolines **2** and isoquinolones **3** from *ortho*-alkynylbenzonitriles **1**.

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the formation of both isoquinolines **2a**–**2d** and isoquinolone **3a** was inversely proportional to that of benzoate esters **4a**–**4d** and benzamide **5** in the product mixture.

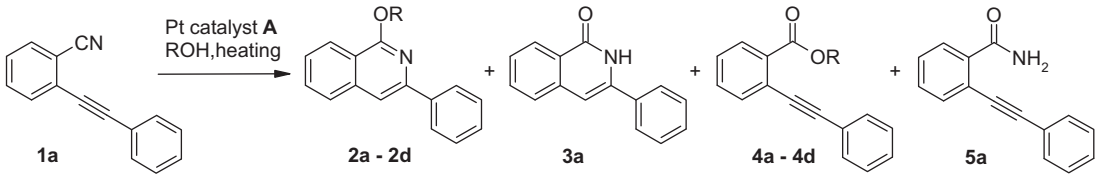
Next, we investigated solvents other than MeOH for this reaction. Results from the reactions with *ortho*-CN-diphenylacetylene (**1a**) are summarized in Table 1. We initially found that polar solvents such as MeOH worked well with 5–10 mol % Pt(II) catalyst under reflux to afford **2a** in 18–35% yield, accompanied by 2–10% of **3a** and 20–32% of **4a** (entries 1–3). Elevating the reaction temperature further enhanced this intramolecular cyclization. We observed an increase in the overall yields of isoquinolines and isoquinolones while the yield of benzamide diminished as the solvent went from MeOH to cyclopentanol. Heating **1a** with 10 mol % of Pt(II) catalyst in EtOH for 16 h gave 48% of 1-ethoxyisoquinoline **2b**, 15% of isoquinolone **3a** and 20% of ethyl benzoate **4b** (entry 4). In addition, only a very small amount of benzamide **5** was observed in the product mixture. Increasing the Pt(II) catalyst loading from 10 to 20 mol % only slightly improved the yields of **2b** from 48% to 52% and **3a** from 15% to 20%, respectively (entry 5). Employing bulkier *i*-PrOH was able to give the corresponding 1-isopropoxyisoquinoline **2c** and isoquinolone **3a** (45% and 17% yields, respectively) after heating at reflux temperature for 16 h (entry 6). Heating **1a** in cyclopentanol at 90 °C for 16 h afforded 2-cyclopentoxyisoquinoline **2d** and isoquinolone **3a** in 41% and 20% yields, respectively (entry 7).

Once the desired reaction conditions[17] [10 mol % of the Pt(II) catalyst in refluxing EtOH] were established, we proceeded to investigate the scope of this transformation for a series of *ortho*-alkynylbenzonitriles. This Pt(II)-catalyzed intramolecular cyclization seemed to be generally applicable for various substrates (Table 2). We first investigated the electronic and steric effects of substituents on the distal group of the β-position on the alkyne (entries 1–8). We found that electronic factors played a small role for this ring cyclization process. Substrates (**1e** and **1f**) bearing both of electron-donating and electron-withdrawing substituents at the *para*-position gave the cyclized products in similar yields (entries 2 and 3). However, both substrates (**1g** and **1h**) bearing an *ortho*-substituent with an electron-donating or a withdrawing moiety (Me and Cl) provided nearly no cyclization reaction at all (entries 4 and 5). The corresponding primary benzamides were isolated as the major products after the reactions were heated at reflux temperature in EtOH for 36 h. We believed steric hindrance from the *ortho*-substitutions disfavored the required Pt–alkyne coordination step and hence prevented the subsequent intramolecular cyclization. The intramolecular cyclization of substrates with heteroaromatic rings, such as 3-pyridyl (**1i**) and 3-thenyl (**1j**), also provided 1-ethoxyisoquinolines **2i** and **2j** in 30% and 49% yields, and isoquinolones **3i** and **3j** in 12% and 14% yields, respectively (entries 6 and 7). Substrate **1k** bearing a distal cyclohexyl group also gave the corresponding 1-ethoxyisoquinoline **2k** and isoquinolone **3k** in 43% and 19% yields, respectively.

Next we examined the electronic effect of substitutions on the backbone benzonitrile ring system (entries 9–15). Substrates with an electron-poor system seemed to be more favorable toward this intramolecular cyclization. Both benzonitriles **1l** and **1m** bearing fluorine moieties afforded 1-ethoxyisoquinolines **2l** and **2m** (42% and 37% yields, respectively) and isoquinolones **3l** and **3m** (~5% and 11% yields, respectively) upon refluxing for 16 h in EtOH (entries 9 and 10). In contrast, the intramolecular cyclizations of electron-rich benzonitriles **1n** and **1o** required longer reaction times of 48 and 24 h in refluxing EtOH to provide 1-ethoxyisoquinolines (16% of **2n** and 40% of **2o**, respectively) and isoquinolones (<5% of **3n** and 16% of **3o**, respectively). We also studied this intramolecular cyclization of substrates with backbone heteroaromatic ring (entries 13–14). Cyclization of 3-cyano-pyridine **1p** occurred upon refluxing in EtOH for 16 h to afford 32% of 1-ethoxyisoquinoline **2p** and 46% of isoquinolone **3p**. Under the same conditions, 4-cyanopyridine **1q** provided 24% of 1-ethoxyisoquinoline **2q** and 13% isoquinolone **3q**. In the case of **3p**, the nitrogen atom in the pyridine ring of **1p** was either likely involved in coordination with the Pt–alkyne complex or its electron-withdrawing nature made the carbon–carbon triple bond more electrophilic for the subsequent nucleophilic addition of the amide group.

The newly formed 1-alkoxyisoquinolines (**2a**–**2q**) can be further converted into the corresponding isoquinolones (**3a**–**3q**) under the acidic deprotection conditions illustrated in Scheme 2. We demonstrated this transformation with 1-methoxyisoquinoline (**2a**) and 1-ethoxyisoquinoline (**2b**) to the corresponding isoquinolone **3a** in 97% and 92% yields respectively, upon heating with 4 equiv of 48% HBr in acetic acid at 50 °C for 2 and 5 h, respectively.[18]

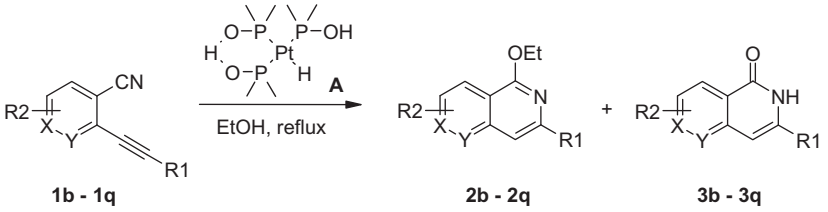
Table 1
Effects of Pt(II) catalyst loading and solvents[a]



Entry	1	Pt(II) catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Product yield[b] (%)			
						2	3	4	5
1	**1a**	5	MeOH	65	16	18	2	32	27
2	**1a**	10	MeOH	65	16	26	6	27	16
3	**1a**	10	MeOH	65	48	35	10	20	5[c]
4	**1b**	10	EtOH	78	16	48	15	20	<5[c]
5	**1b**	20	EtOH	78	16	52	20	17	<5[c]
6	**1c**	10	*i*-PrOH	82	16	45	17	18	<5[c]
7	**1d**	10	Cyclopentanol	90	16	41	20	14	0

[a] All reactions were performed with benzonitrile substrates (100 mg) and Pt(II) catalyst in various alcohols (4 mL) at the indicated temperature and reaction time.
[b] Isolation yields.
[c] Based on the analysis of the crude product mixture.

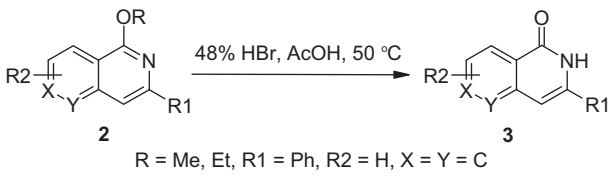
Table 2
1-Ethoxyisoquinolines and isoquinolones from Pt(II)-catalyzed intramolecular cyclization[a]



1b - 1q **2b - 2q** **3b - 3q**

Entry	Alkyne	R^1	R^2	X	Y	Time (h)	Yield[b] (%)	
							2	**3**
1	**1b**	Ph	H	C	C	16	48	15
2	**1e**	*p*-MeO-C_6H_4–	H	C	C	16	31	6
3	**1f**	*p*-F-C_6H_4–	H	C	C	16	40	5
4	**1g**	*o*-CH_3–C_6H_4–	H	C	C	36	0[c]	0[c]
5	**1h**	*o*-Cl-C_6H_4–	H	C	C	36	0[d]	5[d]
6	**1i**	3-Pyridyl	H	C	C	16	30	12
7	**1j**	3-Thiophene	H	C	C	16	49	14
8	**1k**	Cyclohexyl	H	C	C	16	43	19
9	**1l**	Ph	3-F	C	C	16	42	~5[e]
10	**1m**	Ph	5-CF_3	C	C	16	37	11
11	**1n**	Ph	5-MeO	C	C	48	16	<5[e]
12	**1o**	Ph	4-Me	C	C	24	40	16
13	**1p**	Ph	H	C	N	16	32	46
14	**1q**	Ph	H	N	C	16	24	13

[a] All reactions were performed with benzonitrile substrates (100 mg) and Pt(II) catalyst (10 mol %) in refluxing EtOH (4 mL) for the indicated reaction time.
[b] Isolation yields.
[c] The corresponding primary benzamide **5g** was isolated in 93% yield.
[d] The corresponding primary benzamide **5h** was isolated in 89% yield.
[e] Based on analysis of the crude product mixture.



Scheme 2. Synthesis of isoquinolones **3** from 1-alkoxyisoquinolines **2**.

In summary, we describe a facile route to regioselectively synthesize both 1-alkoxyisoquinoline and isoquinolone skeletons from various readily accessible *ortho*-alkynylbenzonitriles via hydrido(dimethylphosphinous acid-κP)[hydrogen bis(dimethylphosphinito-κP)]platinum(II)-catalyzed intramolecular 6-*endo-dig* cyclization for the first time. The advantage of this versatile method is able to provide easy access to a variety of 3-substituted 1-alkoxyisoquinolines and isoquinolones under simple catalytic and favorable neutral conditions. Further work to study the scope of this reaction and its mechanism are ongoing and the results will be reported in due course.

Acknowledgments

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17. *Representative experimental procedure*: A mixture of benzonitrile **1a** (100 mg, 0.49 mmol) and hydrido(dimethylphosphinous acid-κP)[hydrogen bis (dimethylphosphinito-κP)]platinum(II) (21 mg, 0.05 mmol) in EtOH (4 mL) was heated to refluxed for 16 h. The reaction was cooled to room temperature and concentrated. The crude product mixture was purified to afford 2-ethoxyisoquinoline **2b** (59 mg, 48% yield) as a viscous oil and isoquinolone **3a** (16 mg, 15% yield) as a solid upon standing at room temperature.
18. *Representative experimental procedure*: A mixture of isoquinoline **2a** (0.30 mmol, 70 mg) and 48% HBr (1.19 mmol, 200 μL) in AcOH (0.5 mL) in a sealed tube was heated at 50 °C for 2 h. The reaction was cooled to room temperature and poured into a mixture of ice and saturated aq $NaHCO_3$ solution. The reaction was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated to provided analytical pure isoquinolone **3** (64 mg, 97% yield) as a creamy-colored solid.