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Silver-Catalyzed Intramolecular Cyclization of *o*-(1-Alkynyl)-benzamides: Efficient Synthesis of (1*H*)-Isochromen-1-imines

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Abstract: An efficient avenue for the facile and atom-economic synthesis of (1*H*)-isochromen-1-imines has been developed, and a broad spectrum of substrates can participate in the process effectively to produce the desired products in good yields. Significantly, this is the first report of the synthesis of (1*H*)-isochromen-1-imines that involves a silver(I)-catalyzed, regiocontrolled intramolecular addition of the carbonyl group of the amide moiety towards an alkyne.

Keywords: intramolecular cyclization; (1*H*)-isochromen-1-imines; organic catalysis; regioselectivity; silver catalyst; synthetic methods

Isocoumarins are key core structural subunits that occur in a wide variety of biologically active natural products and complex synthetic molecules,[1] as well as being useful and versatile synthetic intermediates.[2] Recently, the activity of isocoumarins as potent anticancer agents invoked additional interest in the investigation of them and their analogues.[3] Since there is a remarkable similarity in reactivity and bioactivities between the oxygen species and their nitrogen counterparts, one would anticipate that (1*H*)-isochromen-1-imine analogues might have potential bioactivities similar to those of the isocoumarins. So far, only four (1*H*)-isochromen-1-imine analogues have been reported in the literature (compounds **1**–**4**, Figure 1). Deady et al. reported the synthesis of **1** *via* the acetylation of α-cyano-*o*-tolunitrile,[4a] and they prepared **2**, **3**, and **4** by thermal cyclization reactions six years later.[4b] Unfortunately, the described method usually

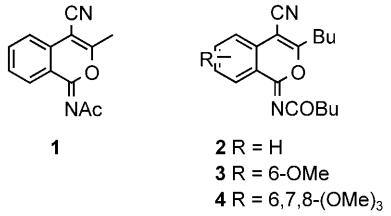


Figure 1. Known (1*H*)-isochromen-1-imine analogues.

requires long reaction time and high reaction temperature, and moreover it suffers from a relatively narrow scope of substrates. Thus, new and improved methodologies for synthesis of (1*H*)-isochromen-1-imine analogues are desired.

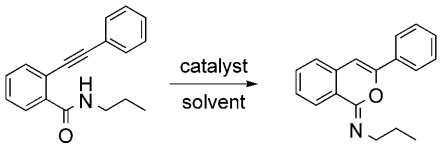
The transition metal-catalyzed construction of heterocycles is one of the frontier areas in organic chemistry, because of the exceptional ability to activate π systems, especially alkynes, towards intermolecular and intramolecular nucleophilic attack.[5] In comparison with other transition metal salts, Ag(I) salts have long been believed to have low catalytic efficiency, and most commonly served as either co-catalysts or Lewis acids. Only recently, have Ag(I) salts have been demonstrated to be important and versatile catalysts for the synthesis of functionalized heterocycles, such as isoquinolines, (2*H*)-isoquinolines, (2*H*)-1,2-oxaphosphorin 2-oxides, 5-substituted proline derivatives, pyrroles, silyl ketene aminals, benzothiazines, and other heterocycles, in efficient and atom-economic ways.[6,7]

However, no investigation has been reported on the synthesis of (1*H*)-isochromen-1-imines using an Ag(I)-catalyzed system. In this communication, we present our preliminary results for the synthesis of diversely substituted (1*H*)-isochromen-1-imines from *o*-(1-alkynyl)benzamides under optimized Ag(I)-cata-

lyzed conditions. Several distinguished features of the process are worthy of mention: (i) it is the first report of the synthesis of (1*H*)-isochromen-1-imines that involves the regiocontrolled intramolecular addition of the carbonyl group of an amide moiety toward alkynes; (ii) it uses $AgSbF_6$ as catalyst without requiring any other additives; and more significantly (iii) *o*-(1-alkynyl)benzamides with a wide range of structural diversity can efficiently participate in the process with good yields.[8]

2-(Phenylethynyl)-*N*-propylbenzamide (**5a**) was first used as the model substrate to optimize the reaction conditions, including different catalysts, various solvents, reaction temperatures, and reaction times (Table 1). Since no desired product was observed without catalysis, various Ag(I) salts were then screened in toluene,[9] and all of them displayed proper catalytic activities (Table 1, entries 1–7). In particular, we identified an exciting lead that stood out unambiguously in the series of experiments. As depicted in Table 1, $AgSbF_6$ seems to be the optimal choice for this reaction. The target product, (1*H*)-3-phenyl-*N*-propylisochromen-1-imine (**6a**), was obtained in 81% yield (Table 1, entry 5). Some other acids, including the ones reported to promote the analogous reactions,[10] were also investigated as activator, but only a trace amount of imine **6a** was detected when utilizing TfOH (Table 1, entries 8–11). Subsequently, we screened different solvents and found that the solvent plays an important role in this transformation (Table 1, entries 5 and 12–17). While no desired product was observed in H_2O under the same catalytic conditions (Table 1, entry 16), the reaction in tetrahydrofuran (THF) afforded the best yield of 85% (Table 1, entry 17).[11] The reaction temperature was found to be an important factor on the process. Compound **6a** was obtained in 65% yield when the temperature was reduced to 60 °C and there is no improvement in yield when the temperature was raised up to 100 °C (Table 1, entries 18 and 19). The decrease in the yield resulting from the decrease in the reaction time under heating was significant (Table 1, entry 20).

Table 1. Cyclization of *N*-propyl-2-(2-phenylethynyl)benzamide (**5a**).[a]



5a **6a**

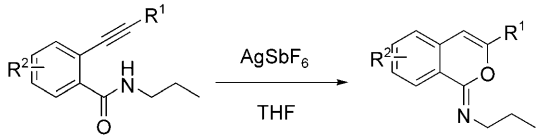
Entry	Catalyst	Solvent	Yield [%][b]
1	–	Toluene	0
2	CF_3COOAg	Toluene	73
3	CH_3COOAg	Toluene	28
4	AgOTf	Toluene	55
5	$AgSbF_6$	Toluene	81
6	$AgNO_3$	Toluene	49
7	Ag_2CO_3	Toluene	30
8	TsOH	EtOH	0
9	TFA	THF	0
10	TfOH	THF	trace
11[c]	HBF_4	CH_2Cl_2	0
12	$AgSbF_6$	CH_2Cl_2	82
13	$AgSbF_6$	CH_3COCH_3	78
14	$AgSbF_6$	CH_3CN	21
15	$AgSbF_6$	DMF	63
16	$AgSbF_6$	H_2O	0
17	$AgSbF_6$	THF	85
18[d]	$AgSbF_6$	THF	65
19[e]	$AgSbF_6$	THF	84
20[f]	$AgSbF_6$	THF	59

[a] The reaction was carried out using **5a** in the presence of catalyst (25 mol%) in the solvent at 80 °C under argon for 8 h.
[b] Yields of isolated products.
[c] The reaction was carried out with HBF_4 (25 equiv.) at room temperature for 5 h.
[d] The reaction was carried out at 60 °C for 8 h.
[e] The reaction was carried out at 100 °C for 8 h.
[f] The reaction was carried out at 80 °C for 4 h.

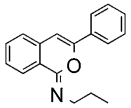
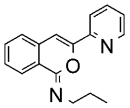
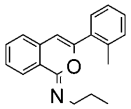
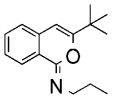
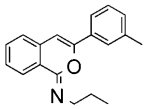
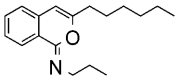
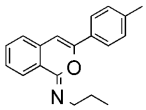
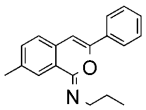
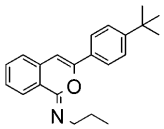
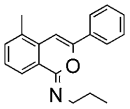
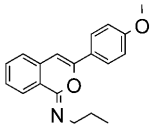
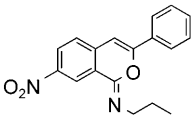
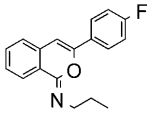
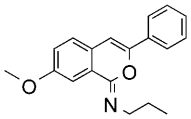
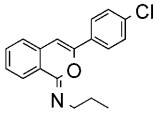
With these promising synthesis conditions (25 mol% of $AgSbF_6$, THF, 80 °C, 8 h), we investigated the substrate scope of the intramolecular cyclization catalyzed by $AgSbF_6$, and the results are summarized in Table 2 and Table 3. As listed in Table 2, 2-(substituted ethynyl)-*N*-propylbenzamides **5** bearing aryl (Table 2, entries 1–9) or alkyl (Table 2, entries 10 and 11) substituents are well suitable for the cyclization reaction. A lower yield was observed in the cases of 2-[(*o*-methylphenyl)ethynyl]-*N*-propylbenzamide, presumably due to steric hindrance (Table 2, entry 2). Excellent yields were obtained irrespective of the presence of electron-withdrawing, electron-donating, or halide groups (Table 2, entries 4–8). Furthermore, good yields were also obtained when the R^1 groups were heteroaromatic or aliphatic groups (Table 2, entries 9–11). When introducing a methyl group into the 5-position of 2-(phenylethynyl)-*N*-propylbenzamide, a good yield of target compound **6l** was obtained. However, introduction of a methyl group to the 3-position resulted in a loss of yield of **6m** (Table 2, entries 12 and 13). In additional, the result was better when R^2 group was an electron-withdrawing substituent, presumably owing to electronic effects (Table 2, entries 12, 14 and 15).

We further examined the cyclization reactions for a wide array of electronically and structurally diverse R^3 groups. As shown in Table 3, the tolerance of the catalytic system was remarkable, and moderate to excellent yields of the desired products were obtained. The substrates bearing aliphatic groups gave excellent yields (Table 3, entries 1 and 2), however, lower yields were observed with substrates involving bulky groups

Table 2. Synthesis of (1*H*)-*N*-propylisochromen-1-imines *via* $AgSbF_6$-mediated cyclization.[a]



5 **6**

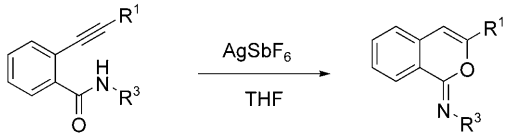
Entry	Product		Yield [%][b]	Entry	Product		Yield [%][b]
1		**6a**	85	9		**6i**	71
2		**6b**	31	10		**6j**	86
3		**6c**	72	11		**6k**	80
4		**6d**	81	12		**6l**	78
5		**6e**	73	13		**6m**	39
6		**6f**	86	14		**6n**	89
7		**6g**	81	15		**6o**	67
8		**6h**	75				

[a] The reaction was carried out using **5** in the presence of $AgSbF_6$ (25 mol%) in the THF at 80 °C under argon for 8 h.
[b] Yields of isolated products.

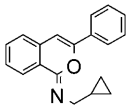
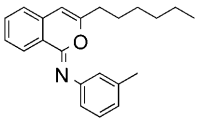
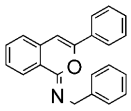
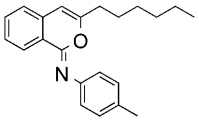
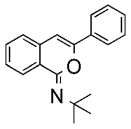
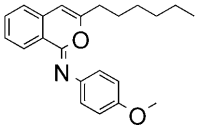
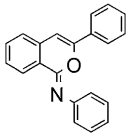
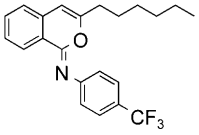
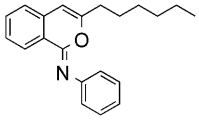
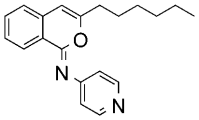
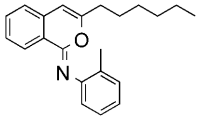
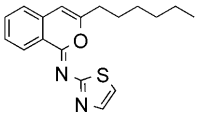
such as the *tert*-butyl group, which causes large steric hindrance under the same reaction conditions (Table 3, entry 3). When both the R^1 and R^3 substituents were aromatic groups, the reaction did not go to completion even after 24 h at 100 °C (Table 3, entry 4), and the situation did not improve until the R^1 group was replaced with an aliphatic group (Table 3, entry 5). Further study showed that relatively higher yields were afforded when the R^3 group was a *para*-substituted aromatic, presumably owing to smaller stereospecific blockade (Table 3, entries 6–8). In addition, electron-donating and electron-withdrawing substituents on the amide moiety had no perceptible effect on the yields (Table 3, entries 9 and 10). Remarkably, a shorter reaction time was needed and excellent yields were obtained for substrates with a heteroaromatic R^3 group (Table 3, entries 11 and 12).

The cyclization of alkynes possessing nucleophiles in proximity to the triple bond can construct various heterocycles in different pathways. As shown in Scheme 1, in principle, there are six possible products for the cyclization of **5**: *O*-cyclization *via 6-endo* or *5-exo* mechanisms, leading to **7** or **7′**, respectively (path a); *N*-cyclization *via 6-endo* or *5-exo* mechanisms, leading to **8** or **8′**, respectively (path b); and hydrolysis of the imino moiety of **7** or **7′**, leading to **9** or **9′**, respectively (path c). The results disclosed in the text suggested that the present Ag-mediated reaction of **5**

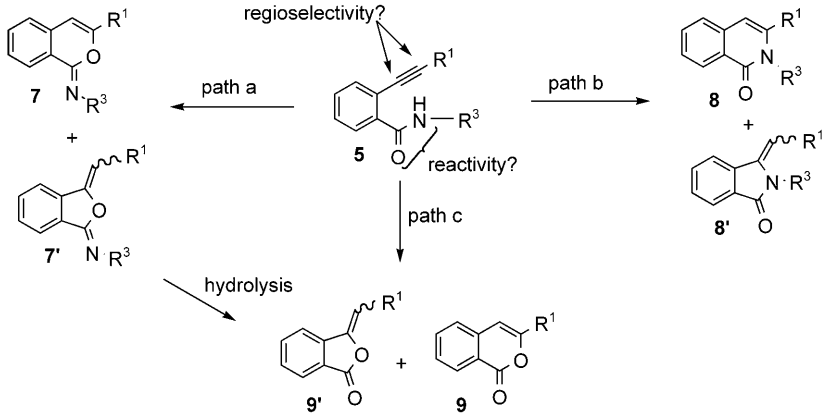
Table 3. Synthesis of (1*H*)-isochromen-1-imines *via* $AgSbF_6$-mediated cyclization.[a]



5 **7**

Entry	Product		Yield [%][b]	Entry	Product		Yield [%][b]
1		**7a**	88	7		**7g**	66
2		**7b**	87	8		**7h**	82
3		**7c**	48	9		**7i**	71
4		**7d**	23[c]	10		**7j**	75
5		**7e**	68	11		**7k**	89[d]
6		**7f**	52	12		**7l**	90[d]

[a] The reaction was carried out using **5** in the presence of $AgSbF_6$ (25 mol%) in the THF at 80 °C under argon for 8 h.
[b] Yields of isolated products.
[c] The reaction was carried out at 100 °C for 24 h.
[d] The reaction was completed within 5 h.



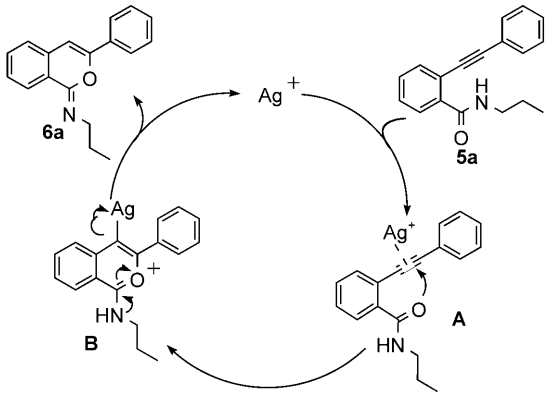
Scheme 1. Intramolecular cyclization of *o*-(1-alkynyl)benzamides **5**.

showed very high reactivity for the oxygen of the amide moiety to form imine **7**. This unique *O*-cyclization is different from *N*-cyclizations catalyzed by palladium where isoquinolin-1-one **8** or isoindolone **8′** could be formed.[12] In parallel, the $AgSbF_6$-catalyzed system, where the imine moiety could be reserved, is distinct from the acid-catalyzed conditions, under which the isocoumarin derivative **9** was obtained directly from amide starting materials.[10] In addition, the regiocontrolled intramolecular cyclization formed the six-membered ring **7** following a "*6-endo-dig*" cyclization probably due to the transition metal nature of $AgSbF_6$ which forms π complexes with alkynes rather than activating the oxygenated functions.[7m] However, the detailed mechanism of this transformation is still unclear.

All the (1*H*)-isochromen-1-imines synthesized were characterized by spectral and analytical data. The relative stereochemistry (*Z*/*E*) of the products was determined by X-ray analyses of **6a** and **7l**, and the absolute configurations are shown in Figure 2.

A plausible catalytic mechanism for the above cyclization is shown in Scheme 2. This scheme is based on the Ag(I)-catalyzed reactions published by Asao[7c] and Patil.[7i] First, the carbon-carbon triple bond of **5a** is activated by coordination with the transition metal salt to form the Ag-alkyne π-complex **A**. Subsequent attack of the oxygen atom at the electron-deficient triple bond leads to the intermediate **B**, which is followed by proton transfer to produce the final product **6a** and regenerate the Ag(I) catalyst.

In summary, we developed a mild and efficient route for Ag(I)-catalyzed intramolecular cyclization of *o*-(1-alkynyl)benzamides. Significantly, the strategy affords an attractive means for the facile and atom-economic synthesis in moderate-to-good yields of a wide range of (1*H*)-isochromen-1-imines, which are important motifs in both useful versatile synthetic intermediates and potent biologically active compounds. It is our expectation that the biologically intriguing structures will find broad applications in our related medicinal chemistry program. This interesting transformation has motivated us to further investigate the reaction pathway as a part of future endeavors.



Scheme 2. Possible mechanism for the Ag(I)-catalyzed intramolecular cyclization.

Experimental Section

General Procedure for the Ag-Catalyzed Synthesis of (1*H*)-Isochromen-1-imines

To a 10-mL reaction flask containing THF (6 mL) under argon was added *o*-(1-alkynyl)benzamides (0.4 mmol) and $AgSbF_6$ (0.1 mmol). The resulting mixture was heated at 80 °C for 8 h, and then diluted with 20 mL of EtOAc, washed with saturated $NaHCO_3$ (twice), and brine, and dried by anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography with petroleum ether (PE)/EtOAc (25/1, v/v) as eluent to yield the desired (1*H*)-isochromen-1-imine products.

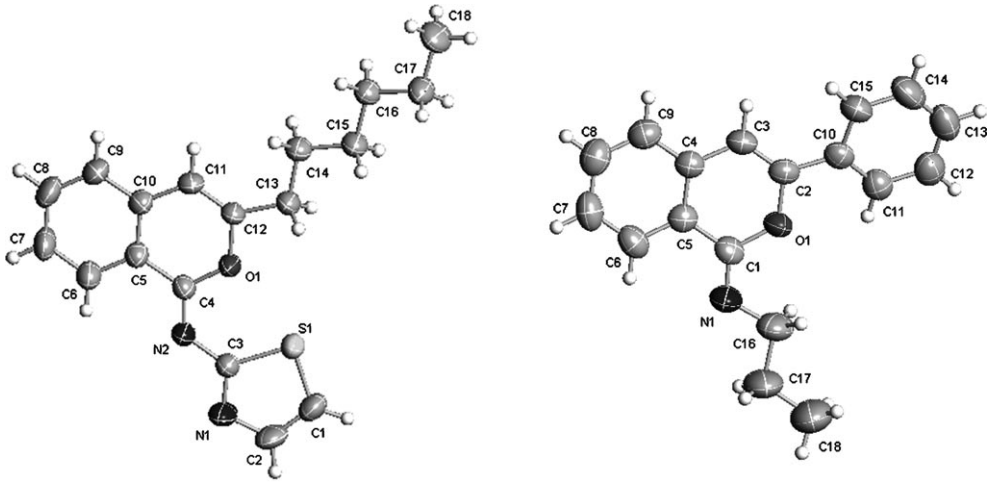


Figure 2. X-ray crystal structures of **6a** and **7l**.[13]

Supporting Information

Experimental details and copies of $^{1}H/^{13}C$ NMR spectra of all products are available as supporting information.

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[13] CCDC 723305 (**6a**) and CCDC 723306 (**7l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

