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Highly Efficient Access to Iminoisocoumarins and α-Iminopyrones via AgOTf-Catalyzed Intramolecular Enyne−Amide Cyclization

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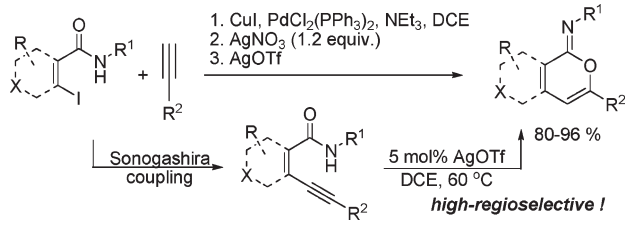

Iminoisocoumarins and α-iminopyrones are prepared via Sonogashira coupling and AgOTf-catalyzed ***6-endo-dig*** *O-cyclization of the enyne−amide system in dichloroethane, in one pot or stepwise, respectively.*

The carbon−carbon triple bond is one of the most important functional groups in organic chemistry and has been widely utilized in organic synthesis as well as mechanistic studies.[1] During the past decade, transition metal-catalyzed cyclization of alkynes possessing a nucleophile in close proximity to the triple bond is one of the most important processes and has emerged as a powerful tool for the construction of a variety of heterocycles.[2] In this context, previous researches related to the annulation of enyne−amide systems **1** were focused on the *N*-nucleophility of the amide group onto C−C triple bonds, giving rise to pyridinone and/or pyrrolone derivatives;[3] however, few *O*-cyclization counterparts which can provide isochromenes or benzofuran imidates exist (Figure 1).[4]

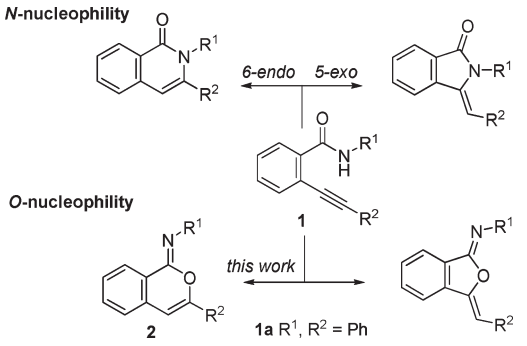

FIGURE 1. Intramolecular cyclization of *o*-(1-alkynyl)benzamides **1**.

Imidates are known to be important pharmacophores and useful synthetic building blocks.[5] Whereas most of the present synthetic approaches take advantage of Pinner-type reactions,[6] some difficulties are often encountered such as low yields, harsh conditions, and rather limited substrate scope. Therefore, new synthetic methods, especially for the production of cyclic imidates, have been investigated.[7] Herein, we report a highly efficient synthesis of iminoisocoumarin and α-iminopyrone imidates via AgOTf-catalyzed intramolecular cyclizations of enyne amide systems.[8]

We initiated our study with the intramolecular cyclization of 2-(phenylethynyl)benzamide **1a** upon treatment with various coin-metal catalysts under nitrogen (Table 1). Whereas copper or gold catalysts afforded low yields or only trace amount of products (entries 6−10, Table 1), we were pleased to discover that such transformation can proceed smoothly to afford the desired product (*Z*)-**2a** with AgOTf (5%mmol) as the catalyst in dichloroethane (DCE) at room temperature (entry 1, Table 1).[9] While at 60 °C in DCE the reaction finished within 2.5 h in excellent yield (96%, entry 2, Table 1), other silver salts including $AgNO_3$ and AgOAc in appropriate solvents only afforded a trace amount of **2a**, respectively (entries 3−5, Table 1). In contrast, the employment of a strong Brønsted acid of TfOH proved unfavorable to this conversion, and the desired product **2a** was isolated in only 5% yield (entry 11, Table 1).

The optimized reaction conditions allowed a wide range of *o*-(1-alkynyl)benzamides **1**, giving 6-*endo-dig* *O*-cyclization

(1) Hart, H. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons Ltd.: New York, 1994.

(2) For reviews, see: (a) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (f) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (g) Patil, N.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

(3) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (b) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (c) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777. (d) Yu, Y.; Gregory, A.; Stephenson, G. A.; Mitchell, D. *Tetrahedron Lett.* **2006**, *47*, 3811.

(4) For 5-*exo-dig* *O*-cyclization of *N*-propargylamides resulting in substituted oxazole derivatives, see: (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (b) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501.

(5) (a) Neilson, D. G. In *The Chemistry of Amdines and Imidates*; Patai, S., Ed.; John Wiley & Sons: London, UK, 1975; Chapter 8. (b) Kantlehner, W. Synthesis of Iminium Salts, Orthoesters and Related Compounds. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 485−599.

(6) (a) Pinner, A.; Klein, F. *Chem. Ber.* **1877**, *10*, 1889. (b) Gavin, D. J.; Mojica, C. A. *Org. Process Res. Dev.* **2001**, *5*, 659. (c) For a review, see: Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179.

(7) (a) Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991. (b) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1999**, *4*, 401. (c) Saluste, C. G.; Crumpler, S.; Furberb, M.; Whitbya, R. J. *Tetrahedron Lett.* **2004**, *45*, 6995. (d) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517.

(8) For recent reviews on silver-mediated heterocyclizations, see: (a) Weible, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174.

(9) The structure of **2a** was confirmed by X-ray crystallography, for details see the Supporting Information.

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TABLE 1. Optimization of Conditions for the Cyclization to 2a[a]

entry	catalyst	solvent	T [°C]	time [h]	yield [%][b]
1	AgOTf	DCE	25	6	76
2	AgOTf	DCE	60	2.5	96
3	$AgNO_3$	DCE	60	48	trace
4	$AgNO_3$	acetone	60	48	trace
5	AgOAc	DMF	60	48	trace
6	$HAuCl_4$	DCE	60	12	20
7	AuCl	DCE	60	24	18
8	$AuCl_3$	DCE	60	24	trace
9	CuI	DCE	60	48	15
10	$Cu(OTf)_2$	DCE	60	48	trace
11	TfOH	DCE	60	24	5

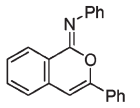
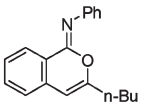
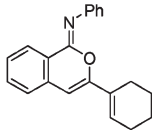
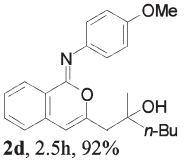
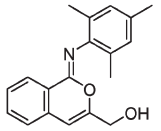
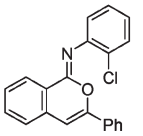
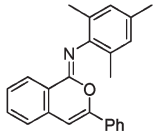
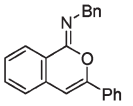
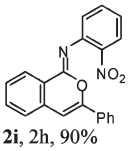
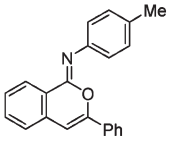
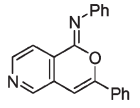
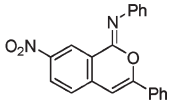
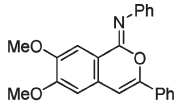
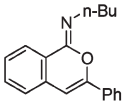
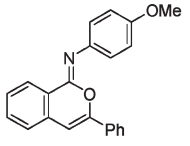
[a]Reaction conditions: **1a** (0.5 mmol), catalyst (5 mol %), solvent (5 mL), under N_2 atmosphere. [b]Yields of isolated products.

products of (*Z*)-**2** in good to excellent yields (Table 2). The presence of aryl or alkyl substitutents (R^2) on the alkyne moiety of **1** presented no difficulties to furnish the expected products. Notably, free hydroxyl groups, primary or β-tertiary, were also tolerated in this conversion, and produced **2d** and **2e** in 92% and 87% yield, respectively (entries 4 and 5, Table 2). On the aromatic tether, not only electron-rich but also electron-poor benzamides **1** underwent the cyclization clearly, although an extended reaction time was required to obtain a good yield for electron-defficient counterpart (entries 12 and 13, Table 2). A heteroaromatic system involving a pyridine unit had also been employed in this process to give **2k** in 91% yield after 3 h (entry 11, Table 2). Finally, there was no obvious difference on the reactivity of *N*-alkyl- and *N*-aromatic-substituted substrates, and they all afforded similar high yields.

This intramolecular reaction was not restricted to the use of (hetero) aromatic systems. Under the standard conditions, the aliphatic analogous **3** performed similar reactions without any problem to provide α-iminopyrones **4** in good to excellent yields (Table 3). During the spectroscopic characterization of **4a**−**e**, we noted the presence of *E*−*Z* isomers arising from the imine group in the solution of $CDCl_3$ at 25 °C by NMR spectra. The ratio of *E*−*Z* isomers is approximately 3:1 in these compounds. However, a similar result was not observed for products **2** and **4f**. As expected, no isomers of **4e** were detected in d_6-DMSO by NMR at 80 °C.[10] These observations can be rationalized by steric and resonance considerations similar to that discussed in previous literature.[11]

Notably, based on these experimental results, the current reaction displayed excellent regioselectivity, and nearly only 6-*endo-dig O*-cyclization products had been observed for those examined substrates, though both 5-*exo-dig* and 6-*endo-dig* cyclizations are favorable according to Baldwin's rule.[12,13]

TABLE 2. Cyclization of *o*-(1-Alkynyl)benzamides 1[a]

Entry	Products **2**, Time, Yield[b]	Entry	Products **2**, Time, Yield[b]
1	 **2a**, 2.5h, 96%	2	 **2b**, 1.5h, 93%
3	 **2c**, 1h, 95%	4	 **2d**, 2.5h, 92%
5	 **2e**, 1.5h, 87%	6	 **2f**, 3h, 92%
7	 **2g**, 2h, 94%	8	 **2h**, 2h, 90%
9	 **2i**, 2h, 90%	10	 **2j**, 2.5h, 93%
11	 **2k**, 3h, 91%	12	 **2l**, 3h, 91%
13	 **2m**, 0.5h, 93%	14	 **2n**, 2h, 91%
15	 **2o**, 2h, 94		

[a]Conditions: 0.5 mmol of *o*-(1-alkynyl)benzamide **1**, 5 mol % of AgOTf in 5 mL of DCE under N_2 atmosphere. [b]Yields of isolated products.

Considering the potential tolerance of Sonogashira coupling and our annulation transformation, we therefore investigated the feasibility of combining these two reactions in one pot. Disappointingly, whereas the Sonogashira coupling of iodides **5** with terminal alkynes proceeded well treated by CuI and $PdCl_2(PPh_3)_2$ in the presence of triethylamine, the subsequent *O*-cyclization cannot take place, no matter when AgOTf was added, before or after the coupling. We envisioned that the byproduct of the coupling reaction, triethylamine hydroiodide salts, as well as the excess amount of NEt_3, might destroy the catalytic activity of AgOTf. To

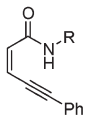
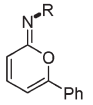
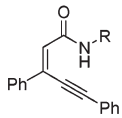
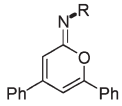
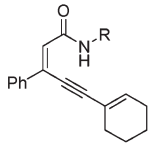
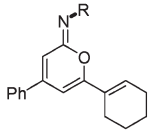
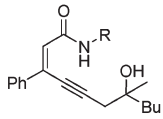
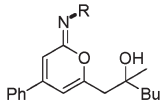
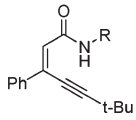
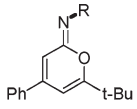
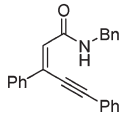
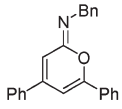
(10) For NMR experiments, see the Supporting Information.

(11) For a review, see: (a) Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475. (b) Nsikabaka, S.; Harb, W.; Ruiz-López, M. F. *J. Mol. Struct. (Theochem)* **2006**, *764*, 161. (c) Lehn, J. M. *Chem.—Eur. J.* **2006**, *12*, 5910. (d) Johnson, J. E.; Silk, N. M.; Arfan, M. *J. Org. Chem.* **1982**, *47*, 1958. (e) Padwa, A.; Albrecht, F. *J. Am. Chem. Soc.* **1974**, *96*, 4849.

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

(13) For some cyclization reactions which cannot be explained in terms of Baldwin's rule, see: (a) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733. (b) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (c) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.

TABLE 3. AgOTf-Catalyzed Cyclization of (*Z*)-Alk-2-en-4-ynamides 3[a]

Entry	Substrate **3**[b]	Product **4**, Yield (%)[c]	E:Z
1	 **3a**	 **4a**, 84	3:1
2	 **3b**	 **4b**, 87	3:1
3	 **3c**	 **4c**, 80	3:1
4	 **3d**	 **4d**, 83	3:1
5	 **3e**	 **4e**, 81	2.6:1
6	 **3f**	 **4f**, 85	–

[a]Conditions: 0.5 mmol of *o*-(1-alkynyl)benzamide **1**, 5 mol % of AgOTf in 5 mL of DCE under N_2 atmosphere. [b]R = *p*-tol. [c]Yields of isolated products.

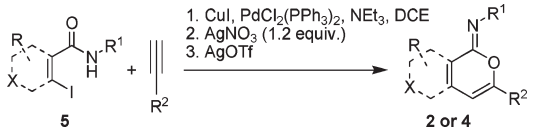
our delight, the employment of $AgNO_3$ (1.2 equiv) could diminish this inhibition effect, and a proposed one-pot three-step protocol, without isolation of intermediates, has been successfully achieved for accessing to product **2a** from iodide **5a** and phenylacetylene in 93% total yield. To evaluate the scope of this one-pot process, we examined several examples randomly, and all entries gave excellent yield of final products as expected (Table 4).

In conclusion, we have developed a highly efficient AgOTf-catalyzed intramolecular cyclization reaction of *o*-(1-alkynyl)benzamide **1** or (*Z*)-alk-2-en-4-ynamides **3** for the synthesis of iminoisocoumarin and α-iminopyrone derivatives, respectively, via a selective 6-*endo*-*dig* type, *O*-nucleophilic attacking onto the tethered C−C triple bond. The current catalyst system tolerates a wide range of aromatic and aliphatic substrates. In addition, we have discovered that the target products are obtainable using an operationally simpler one-pot procedure directly from halide functionalized aromatic/aliphatic amides and alkynes.

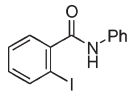
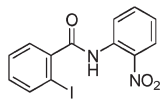
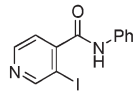
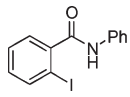
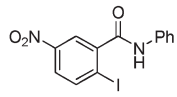
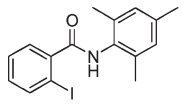
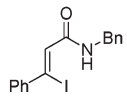
Experimental Section

Typical Procedure for the Cyclzation of 1 and 3. To a solution of alkynylamide **1a** (148 mg, 0.5 mmol) in DCE (5 mL) was added AgOTf (6.5 mg, 0.025 mmol) under nitrogen. The mixture was stirred at 60 °C for 2.5 h. On completion of the reaction, the solvent was removed under vacuum, and the residue was

TABLE 4. One-Pot Formation of 2 and 4[a]



5 **2 or 4**

Entry	Iodide **5**		R^2	**2** or **4**, Yield[b]
1		**5a**	Ph	**2a**, 93%
2		**5b**	Ph	**2i**, 87%
3		**5c**	Ph	**2k**, 91%
4		**5a**	*n*Bu	**2b**, 93%
5		**5d**	Ph	**2l**, 89%
6		**5e**	Ph	**2g**, 92%
7		**5f**	Ph	**4f**, 84%

[a]All reaction were run by mixing 2 mol % of $PdCl_2(PPh_3)_2$, 4 mol % of CuI, 1.2 equiv of Et_3N, 1.1 equiv of the alkyne, and 1.0 equiv of orgnic iodide in DCE (5.0 mL). Once the iodide was consumed, 5 mol % of AgOTf was added followed by 1.2 equiv of $AgNO_3$. [b]Yields of isolated products based on **5**.

purified by column chromatography on silica gel to afford **2a** (142 mg, 96%).

(*Z*)-*N*-(3-Phenyl-1*H*-isochromen-1-ylidene)aniline (2a): pale yellow solid; mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.40 (d, *J* = 8.0 Hz, 1H), 7.61−7.53 (m, 3H), 7.45−7.41 (m, 3H), 7.35−7.33 (m, 4H), 7.30−7.26 (m, 2H), 7.17 (t, *J* = 7.0 Hz, 1H), 6.72 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 151.6, 133.9, 132.4, 132.3, 129.4, 128.8, 128.6, 128.1, 127.5, 125.6, 124.6, 123.6, 122.4, 100.8 ppm; IR (KBr) *v* 3026, 1627, 1660, 1592, 1489, 1340, 1212, 1069 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{15}NONa$ $[M + Na]^+$ 320.1046, found 320.1029.

Typical Procedure for One-Pot Formation of 2 and 4. To a solution of iodide **5a** (323 mg, 1.0 mmol) and phenylacetylene (112 mg, 1.1 mmol) in DCE (5.0 mL) were added CuI (7.6 mg, 0.04 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.02 mmol), and NEt_3 (121 mg, 1.2 mmol) under nitrogen. The resulting mixture was then

heated to refluxing temperature with stirring. Once iodide **5a** was completely consumed, the reaction mixture was cooled to room temperature, and then $AgNO_3$ (202 mg, 1.2 mmol) was added. After 15 min, followed by the addition of AgOTf (12.8 mg, 0.05 mmol), the mixture was stirred for an additional 3 h at 60 °C. On completion of the reaction, salts were removed by filtration and the solvent was evaporated under vacuum, the residue was then purified by column chromatography on silica gel to afford **2a** (276 mg, 93% yield).

4-Methyl-*N*-(6-phenyl-2*H*-pyran-2-ylidene)aniline (4a): the ratio of isomers (3/1) was determined by ^{1}H NMR of the crude product; yellow solid; mp 109−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.58 (t, J = 3.6 Hz, 2H), 7.36−7.35 (m, 3H), 7.19−7.14 (m, 3H), 6.90−6.86 (m, 2H), 6.40 (d, J = 9.6 Hz, 1H), 6.35 (d, J = 6.4 Hz, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 156.9, 151.0, 143.4, 134.5, 132.9, 131.8, 129.9, 129.2, 128.7, 124.6, 122.4, 119.4, 99.9, 20.9 ppm; IR (KBr) v 3026, 1661, 1616, 1548, 1504, 1129, 821, 759 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}NONa$ $[M + Na]^+$ 284.1046, found 284.1053.

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Supporting Information Available: Experimental procedures, compound characterization data, and crystallographic information files (CIFs) of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.