Synthesis of Isoquinolinium-2-yl Amides via Silver(I)-Catalyzed Ring Closure of *N*′-(2-Alkynylbenzylidene)hydrazides

Vsevolod A. Peshkov, Olga P. Pereshivko, Sofie Van Hove, Denis S. Ermolat'ev,* Erik V. Van der Eycken*

Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax +32(16)327990; E-mail: denis.ermolatev@chem.kuleuven.be; E-mail: erik.vandereycken@chem.kuleuven.be

Received 26 June 2011; revised 21 July 2011

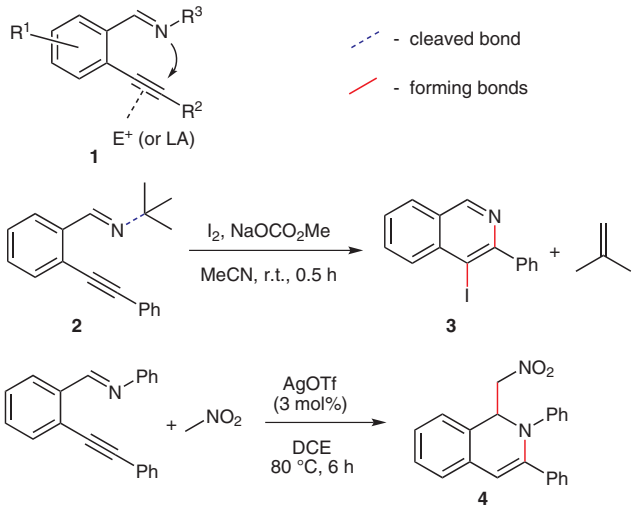
Abstract: An efficient one-pot protocol for the synthesis of isoquinolinium-2-yl amides starting from readily available hydrazides and 2-alkynylbenzaldehydes is described. The key step of the protocol is a silver(I)-catalyzed ring-closure of *N*′-(2-alkynylbenzylidene)hydrazides that are generated in situ. Isoquinolinium-2-yl amides derived from *tert*-butoxycarbonyl hydrazide could be further deprotected, delivering 2-aminoisoquinolinium trifluoroacetates.

Key words: alkynes, hydrazides, isoquinolines, annulation, ylides, silver catalysis

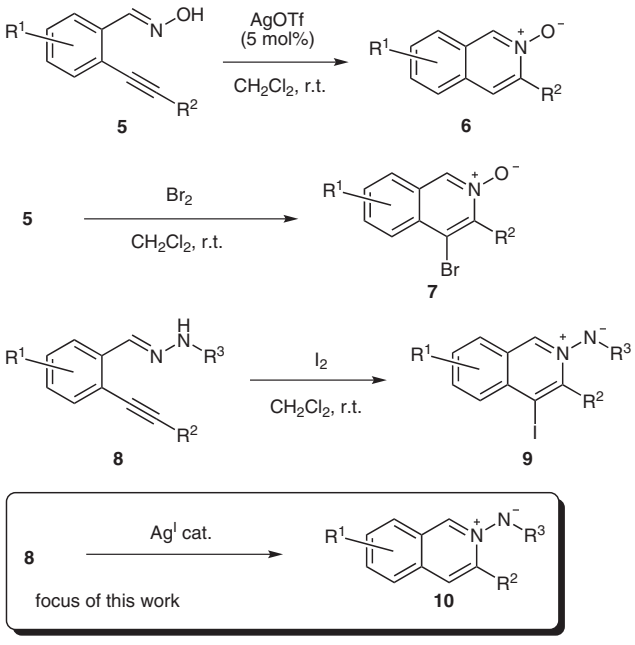
In recent years, a cluster of reports devoted to the synthesis of various isoquinoline derivatives involving *6-endo*-dig ring-closure of alkynylimines **1** have appeared in the literature (Scheme 1). The pioneering work of Larock and co-workers describes efficient protocols involving Lewis acid catalysts (Ag^I, Cu^I, Pd^0, Pd^{II}) or electrophilic reagents (I_2, ICl, PhSeCl, ArSCl) that cyclize *N*-*tert*-butyl-2-alkynylaryl aldimines **2** into isoquinolines **3**.[1] One C–N bond or C–N and C–E (E = I, Br, SPh etc.) bonds are efficiently formed in these processes, however, this is accompanied by the cleavage of another C–N bond with concomitant liberation of isobutene.[2] In contrast, Lewis acid-catalyzed tandem reactions involving external nucleophiles deliver 1,2-dihydroisoquinolines **4** without cleavage of any group (Scheme 1).[3]

Other examples of atom-economical processes are the Lewis acid catalyzed[4] or electrophile-mediated[5] cyclization of 2-alkynylbenzaldoximes **5** into isoquinoline 2-oxides **6** and **7**, respectively (Scheme 2). The electrophile-mediated[6] cyclization of *N*′-(2-alkynylbenzylidene)hydrazides **8** into isoquinolinium-2-yl amides **9** is also well-established (Scheme 2). However, a general protocol for the preparation of isoquinolinium-2-yl amides **10** via Lewis acid-catalyzed cyclization of *N*′-(2-alkynylbenzylidene)hydrazides is not described in the literature, although a great number of efficient one-pot/tandem procedures are reported in which compounds of type **6**, **7**, **9**, or **10** are generated in situ and used as highly reactive intermediates.[7–9] In order to fill this gap, we herein describe an optimized protocol for the silver(I)-catalyzed ring-closure of *N*′-(2-alkynylbenzylidene)hydrazides **8** that provides general access to isoquinolinium-2-yl amides of type **10**.

Initially, we prepared *N*′-(2-alkynylbenzylidene)hydrazide **8a** via reaction between 2-(phenylethynyl)benzaldehyde (**11a**) and *tert*-butoxycarbonyl hydrazide (**12a**;



Scheme 1

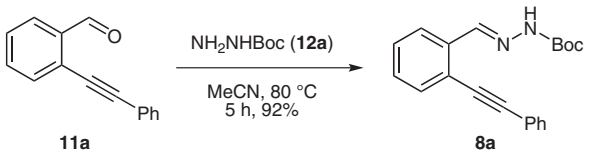


Scheme 2

SYNTHESIS 2011, No. 20, pp 3371–3374
Advanced online publication: 08.09.2011
DOI: 10.1055/s-0030-1260219; Art ID: Z64411SS

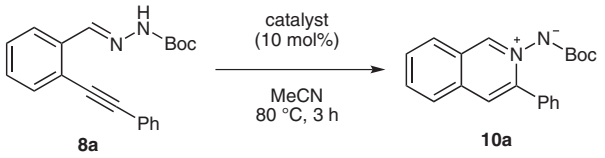
Scheme 3). This reaction proceeds efficiently within five hours in acetonitrile at 80 °C, delivering **8a** in 92% yield.

We then performed a catalyst screening for the cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **8a** into isoquinolinium-2-yl amide **10a**. Several silver(I) salts were evaluated that delivered the desired isoquinolinium-2-yl amide **10a** in good yields. The best result was obtained with silver triflate (Table 1, entry 2); copper(II) triflate was found to be less efficient (Table 1, entry 5).



Scheme 3

Table 1 Catalyst Screening for the Ring Closure of *N*′-(2-Alkynylbenzylidene)hydrazide **8a** into Isoquinolinium-2-yl Amide **10a**



Entry	Catalyst (10 mol%)	Yield (%)[a]
1	$AgOOCCF_3$	74
2	AgOTf	80
3	$AgSbF_6$	77
4	$AgNO_3$	74
5	$Cu(OTf)_2$	17 (70)[b]

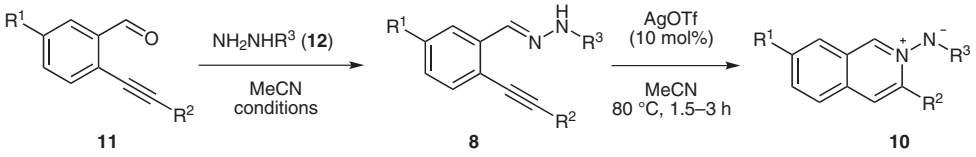
[a] Isolated yield.
[b] Yield of recovered **8a** given in parenthesis.

With these preliminary results in hand, we evaluated the possibility of performing the formation and subsequent cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **8a** in a one-pot fashion. Gratifyingly, by applying a one-pot protocol, the target isoquinolinium-2-yl amide **10a** was obtained in a good overall yield of 62% (Table 2, entry 1). We then investigated the scope of the one-pot procedure by employing various hydrazides **12** (Table 2).[10] To our satisfaction, all reactions worked well and provided the target isoquinolinium-2-yl amides **10a–j** in good to excellent yields. The lower yields in the reactions with *tert*-butoxycarbonyl hydrazide (**12a**) could probably be ascribed to the less electron-withdrawing character of the Boc group, implying that the negative charge in the formed isoquinolinium-2-yl amides **10a**, **10i**, and **10j** is less stabilized (Table 2, entries 1, 9, and 10).

Finally, we attempted Boc-deprotection of the isoquinolinium-2-yl amides **10a**, **10i**, and **10j**. By treatment with trifluoroacetic acid (TFA) in dichloromethane (1:2) at room temperature for three hours, the 2-aminoisoquinolinium trifluoroacetates **13a–c** were obtained in good yields (Table 3).[11]

In conclusion, we have elaborated a protocol for the synthesis of isoquinolinium-2-yl amides via silver(I)-catalyzed ring-closure of *N*′-(2-alkynylbenzylidene)hydrazides. The current report is the first focused study of this transformation, which was previously described only

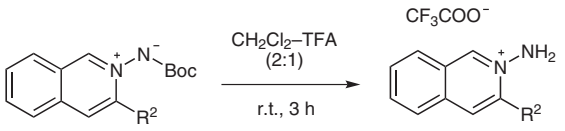
Table 2 One-Pot Synthesis of Isoquinolinium-2-yl Amides **10**



Entry	**11**	R^1	R^2	**12**	R^3	Conditions[a]	Product	Yield (%)[b]
1	**11a**	H	Ph	**12a**	Boc	A	**10a**	62
2	**11a**	H	Ph	**12b**	Ac	A	**10b**	80
3	**11a**	H	Ph	**12c**	formyl	A	**10c**	70
4	**11a**	H	Ph	**12d**	COBn	A	**10d**	76
5	**11a**	H	Ph	**12e**	Ts	B	**10e**	99
6	**11b**	F	Ph	**12d**	COBn	C	**10f**	89
7	**11b**	F	Ph	**12e**	Ts	B	**10g**	97
8	**11b**	F	Ph	**12f**	*p*-Tol	B	**10h**	80
9	**11c**	H	3-thienyl	**12a**	Boc	A	**10i**	70
10	**11a**	H	Bu	**12a**	Boc	A	**10j**	53

[a] Conditions A: 80 °C, 3–5 h; B: 80 °C, 15 min; C: 100 °C, 5 h.
[b] Isolated yield based on **11**.

Table 3 Boc-Deprotection of Isoquinolinium-2-yl Amides **10a**, **10i**, and **10j** to 2-Aminoisoquinolinium Trifluoroacetates **13a–c**



10 **13**

Entry	**10**	R^2	Product	Yield (%)[a]
1	**10a**	Ph	**13a**	52
2	**10i**	3-thienyl	**13b**	57
3	**10j**	Bu	**13c**	49

[a] Isolated yield.

as part of a complex one-pot/tandem process. A significant expansion of the hydrazide substrate scope has been achieved.

^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance 300 instruments. The ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS using the residual solvent signal as the internal reference. Mass spectra were recorded with a Thermo Finnigan LCQ Advantage apparatus (ESI).

One-Pot Synthesis of Isoquinolinium-2-yl Amides 10; Typical Procedure

2-(Phenylethynyl)benzaldehyde (**11a**; 206 mg, 1 mmol) and *tert*-butoxycarbonyl hydrazide (**12a**; 145 mg, 1.1 mmol) were dissolved in anhydrous MeCN (3.5 mL). The reaction mixture was heated at 80 °C for 5 h in a glass tube with a screw-cap. AgOTf (26 mg, 0.1 mmol) was added and the reaction mixture was degassed and flushed with argon. After heating at 80 °C for 3 h, the reaction mixture was directly loaded onto a silica gel column and purified by column chromatography (EtOAc–MeOH, 9:1), to provide isoquinolinium-2-yl amide (**10a**).

***tert*-Butoxycarbonyl(3-phenylisoquinolinium-2-yl)amide (10a)**

Yield: 199 mg (62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.08–8.01 (m, 1 H), 7.98–7.90 (m, 2 H), 7.89–7.81 (m, 1 H), 7.80–7.71 (m, 1 H), 7.70–7.63 (m, 2 H), 7.50–7.40 (m, 3 H), 1.38 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 148.3, 148.0, 134.8, 133.5, 129.6, 129.5, 129.4, 128.1, 127.9, 127.5, 126.6, 125.8, 77.3, 28.8.

MS (ESI): m/z = 321.8 $[M + H]^+$.

Boc-Deprotection of Isoquinolinium-2-yl Amides 10 To Give 2-Aminoisoquinolinium Trifluoroacetates 13; Typical Procedure

Isoquinolinium-2-yl amide (**10a**; 192 mg, 0.6 mmol) was dissolved in CH_2Cl_2 (4 mL) and TFA (2 mL) was added. The reaction mixture was stirred at r.t. for 3 h and then concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and loaded onto a short pad of silica for flash chromatography (EtOAc–MeOH, 4:1), providing 2-aminoisoquinolinium trifluoroacetate (**13a**).

2-Amino-3-phenylisoquinolinium Trifluoroacetate (13a)

Yield: 104 mg (52%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 8.37–8.26 (m, 1 H), 8.05–7.94 (m, 3 H), 7.92–7.80 (m, 1 H), 7.71–7.54 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.43, 142.39, 135.2, 134.9, 131.3, 131.1, 129.9, 129.53, 129.49, 129.3, 127.4, 126.8, 126.7.

MS (ESI): m/z = 221.7 $[C_{15}H_{13}N_2]^+$.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are spectral data for all compounds and copies of NMR spectra.

Acknowledgment

Support was provided by the Fund for Scientific Research (FWO), Flanders, and by the Research Fund of the Katholieke Universiteit Leuven. P.V.A. is grateful to the EMECW (Triple I) for obtaining a doctoral scholarship.

References

(1) (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (c) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (d) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557. (e) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (f) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (g) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. (h) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920.

(2) For a Ag(I)-promoted protocol in which indole acts as a leaving group (N–N bond cleavage), see: (a) Ghavtadze, N.; Fröhlich, R.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2010**, 1787. Similarly, N_2 acts as a leaving group in the Lewis acid catalyzed or electrophile-mediated cyclization of 2-alkynylbenzyl azides, see: (b) Zhang, H.-P.; Yu, S.-C.; Liang, Y.; Peng, P.; Tang, B.-X.; Li, J.-H. *Synlett* **2011**, 982. (c) Zhang, H.-P.; Yang, X.-H.; Peng, P.; Li, J.-H. *Synthesis* **2011**, 1219. (d) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893. (e) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4764. (f) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720.

(3) (a) Ye, Y.; Ding, Q.; Wu, J. *Tetrahedron* **2008**, *64*, 1378. (b) Ding, Q.; Wang, B.; Wu, J. *Tetrahedron* **2007**, *63*, 12166. (c) Markina, N. A.; Mancuso, R.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2011**, *13*, 265.

(4) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924.

(5) (a) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850. (b) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.

(6) Ding, Q.; Chen, Z.; Yu, X.; Peng, Y.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 340.

(7) For one-pot/tandem procedures involving intermediates of types **6** and **7**, see: (a) Ding, Q.; Wang, Z.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 198. (b) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746. (c) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem.* **2010**, 6436. (d) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702. (e) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921.

(8) For one-pot/tandem procedures involving intermediates of types **9** and **10**, see: (a) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (b) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (c) Yu, X.; Ye, S.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 2050. (d) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 5238. (e) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (f) Yu, X.; Yang, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 4526. (g) Chen, Z.; Pan, X.; Wu, J. *Synlett* **2011**, 964. (h) Yu, X.; Pan, X.; Wu, J. *Tetrahedron* **2011**, *67*, 1145.

(9) For other related processes, see: Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744.

(10) So far, only the application of tosyl hydrazide (**12e**) was sufficiently explored in related processes; see refs. 6 and 8.

(11) Compounds of this type can alternatively be prepared by direct N-amination of the isoquinolines or other heterocycles, see: (a) Legault, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7119. (b) Tamura, Y.; Matsugashita, S.; Ishibashi, H.; Ikeda, M. *Tetrahedron* **1973**, *29*, 2359. (c) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1; and references therein.