ChemComm

Silver-Catalyzed Cyclization of 2-Pyridyl Alkynyl Carbinols with Isocyanides: Divergent Synthesis of Indolizines and Pyrroles

Journal:	*ChemComm*
Manuscript ID:	CC-COM-06-2014-004905.R2
Article Type:	Communication
Date Submitted by the Author:	08-Aug-2014
Complete List of Authors:	Meng, Xianyu; Northeast Normal University, Department of Chemistry Liu, Jianquan; Northeast Normal University, Department of Chemistry Liao, Peiqiu; Northeast Normal University, Department of Chemistry Bi, Xihe; Northeast Normal University,

SCHOLARONE™
Manuscripts

ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Silver-Catalyzed Cyclization of 2-Pyridyl Alkynyl Carbinols with Isocyanides: Divergent Synthesis of Indolizines and Pyrroles

Xianyu Meng,[a] Peiqiu Liao,[a] Jianquan Liu,[a] Xihe Bi*[a,b]

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

Divergent syntheses of indolizines and 2,4-disubstituted pyrroles by the silver-catalyzed cyclization of 2-pyridyl alkynyl carbinols with isocyanides are reported. These methods provide an effective route to highly functionalized indolizines and 2,4-disubstituted pyrroles in good to excellent yields. The synthesis of 2,4-disubstituted pyrroles is an unprecedented regioselective [3 + 2] cycloaddition of terminal alkynes with isocyanides.

Indolizines are an important class of *N*-containing heterocycles found in many natural products and synthetic pharmaceuticals.[1] They generally possess remarkable biological activities, such as anti-inflammatory,[2] antimicrobial and anti-tubercular,[3] anti-fungal,[4] antioxidants,[5] and anticancer (Figure 1a).[6] Thus, efficient and versatile synthetic methods for the synthesis of indolizines have been actively investigated in the past few decades.[7] Among these methods, the cycloisomerization of propargylic pyridines represents an attractive pathway to construct indolizine framework (Figure 1b).[8-11] For example, a series of transition-metal-catalyzed cycloisomerization or cyclization reactions on the basis of propargylic pyridines have been developed by the research groups of Gevorgyan,[8] Sarpong,[9] and Liu,[10] allowing the synthesis of highly functionalized indolizines. Moreover, a metal-free *5-endo-trig* iodocyclization of propargylic pyridines to indolizines has also been developed by Lee and coworkers.[11] However, the *O*-protection of 2-pyridyl alkynyl carbinols in all these transformations, *i.e.*, $R^3 \neq H$, appears to be essential for the success of the reactions, because indolizinones were obtained when 2-pyridyl alkynyl carbinols were directly used as the reactants (Figure 1b).[9a,10] To the best of our knowledge, only two examples are known to date that the indolizine ring was formed by the cyclization of 2-pyridyl alkynyl carbinols using ruthenium catalysis.[12] As our ongoing efforts to develop novel organic reactions based on functionalized alkynes,[13] we previously have discovered silver-catalyzed reactions of alkynes with isocyanides, which involved in the strategic insertion of isocyanides into the in situ generated carbon-silver (*sp*C–Ag) bond.[13c,d] Herein, we report a novel chemoselective silver-catalyzed cyclization reactions between 2-pyridyl alkynyl carbinols and isocyanides, which divergently afforded indolizines and 2,4-disubstituted pyrroles in good to excellent yields (Figure 1c).

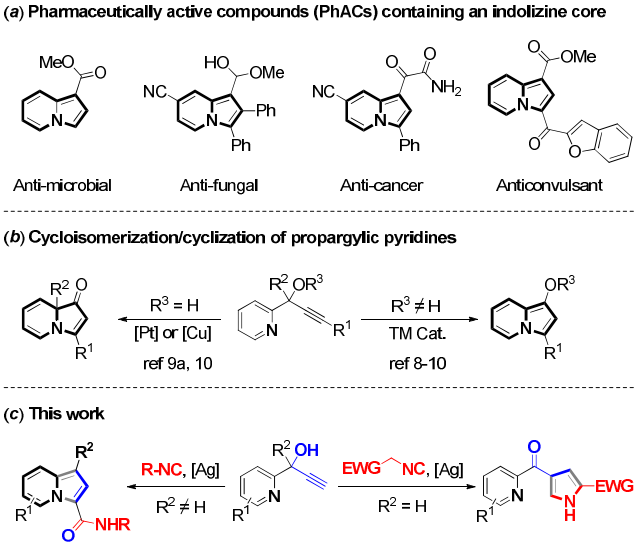
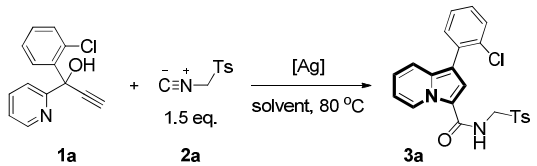


Figure 1

Table 1 Optimization of the Reaction Conditions.[a]

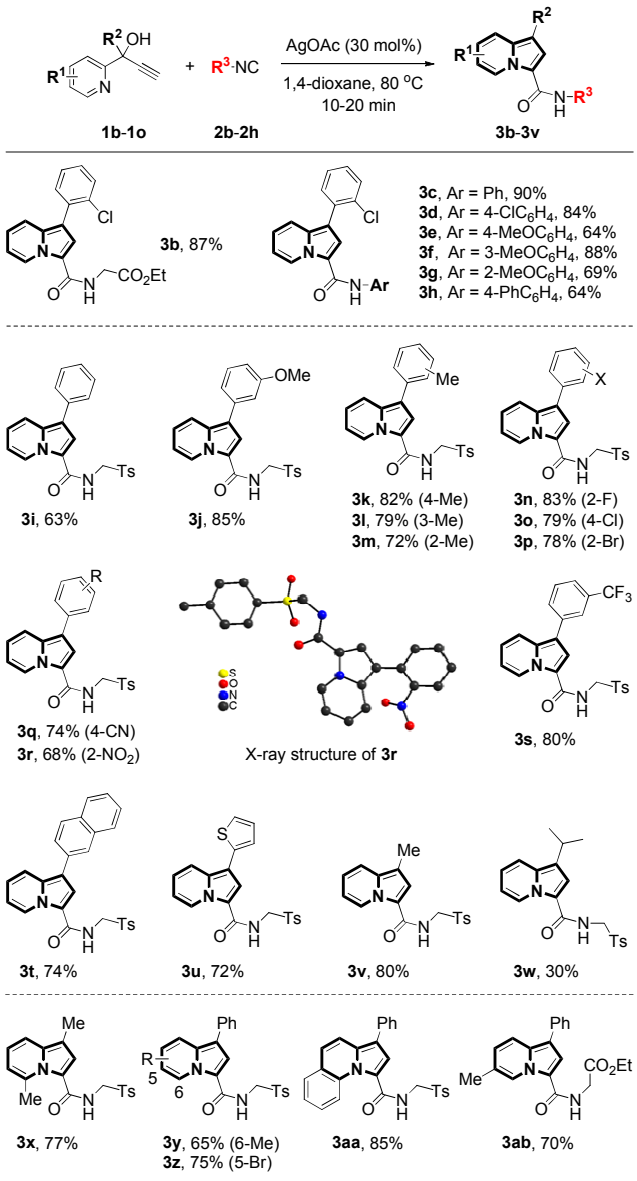


Entry	[Ag]	Solvent	Time	Yield (%)[b]
1	AgOAc	Toluene	12 h	52
2	AgOAc	NMP	4 h	0
3	AgOAc	DMF	12 h	0
4	AgOAc	MeCN	12 h	trace
5	AgOAc	MeOH	3 h	0
6	AgOAc	1,4-dioxane	10 min	82
7	Ag_2CO_3	1,4-dioxane	40 min	67
8	$AgNO_3$	1,4-dioxane	3 h	68
9	AgF	1,4-dioxane	1 h	trace

[a] Reactions were performed on a 0.5 mmol scale of **1a** and a 0.75 mmol scale of **2a** in 2.0 mL solvent at 80 °C. [b] Isolated yields.

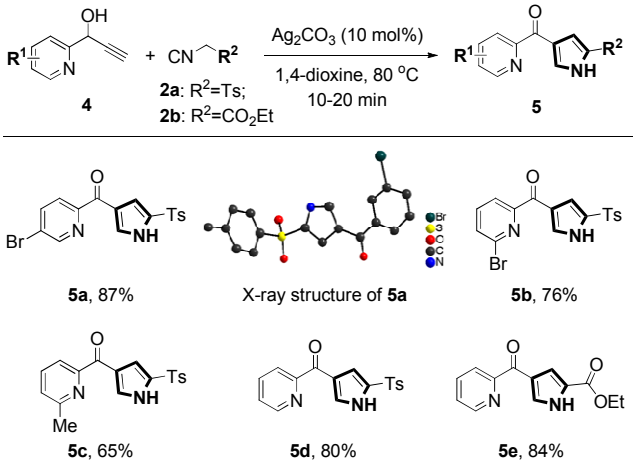
First, the reaction of a tertiary propargylic alcohol (**1a**) with *p*-toluenesulfonylmethyl isocyanide (TosMIC) (**2a**) was selected as the model reaction to optimize the reaction conditions (Table 1).[14] Delightfully, the indolizine product (**3a**) was obtained in 52% yield using 30 mol% AgOAc catalyst at 80 °C in toluene for 12 h (Table 1, entry 1). Encouraged by this promising result, solvents were screened. The use of *N*-methylpyrrolidone (NMP), DMF, acetonitrile (MeCN), and methanol (MeOH) proved to be ineffective, because no reaction took place or only trace amount of product **3a** was observed (Table 1, entries 2–5). When 1,4-dioxine was used as the solvent, the reaction yield was

significantly increased to 82% within a shorter reaction time (10 min) (Table 1, entry 6). Further, the silver catalyst was varied in 1,4-dioxane at 80 °C. Ag_2CO_3 and $AgNO_3$ afforded **3a** in similar yields, 67% and 68%, respectively, whereas AgF only afforded a trace amount of **3a** (Table 1, entries 7–9). Therefore, the reaction conditions listed in entry 6 (30 mol% AgOAc, in 1,4-dioxane at 80 ºC) were found to be optimal and selected for further investigations.



Scheme 1 Synthesis of Indolizines.

With the optimal conditions in hand, the substrate scope for the synthesis of indolizines was investigated by varying both isocyanides and tertiary propargylic alcohols. The experimental results are summarized in Scheme 1. First, the reactions of tertiary propargylic alcohol **1a** with a series of differently substituted isocyanides (**2b**–**2h**) were carried out. Similar to TosMIC **2a**, the reactions of other isocyanides such as ethyl isocyanoacetate (**2b**) and several aryl isocyanides with **1a** for 10–20 min smoothly afforded the corresponding 1,3-disubstituted indolizines (**3b**–**3h**) in good to excellent yields (64–90%). Notably, the substituents at the *para* or *ortho* positions on the phenyl ring slightly affected the reaction outcome; for example, indolizines **3e**, **3g** and **3h** were obtained in relatively lower yields. Next, the 2-pyridyl alkynyl carbinols were varied using the commercially available and inexpensive TosMIC as the isocyanide component. Diverse 2-pyridyl alkynyl carbinols with different types of R^2 groups such as aryl, heteroaryl, and alkyl groups participated in the tandem cyclization reaction with TosMIC, thus affording the corresponding 1,3-disubstituted indolizines (**3i**–**3w**) in good to excellent yields. In addition to the structural analysis by $^1H/^{13}C$ NMR and HRMS spectra, the indolizine structure was further unambiguously confirmed by the X-ray diffraction (XRD) analysis of product **3r** (CCDC 1010662). The variation of the pyridine unit of 2-pyridyl alkynyl carbinols nearly has no influence on the reaction outcome. Therefore, the corresponding indolizines (**3v**–**3ab**) including pyrrolo[1,2-α]quinoline **3aa**, were obtained in good yields. The bromine substituent on compound **3z** provided an opportunity for further synthetic transformation, such as the utilization in diverse cross-coupling reactions.



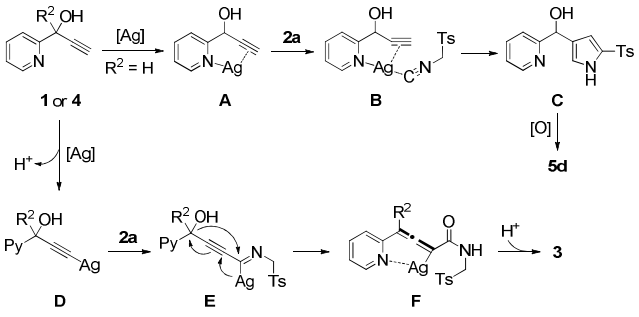
Scheme 2 Synthesis of 2,4-Disubstituted Pyrroles.

Encouraged by the results of tertiary propargylic alcohols, the reactivity of secondary propargylic alcohols was investigated. Unexpectedly, the reaction of 2-pyridyl alkynyl carbinol (**5a**) with TosMIC **2a** under the silver-catalyzed conditions afforded a 2,4-disubstituted pyrrole (**4a**) (Scheme 2). The structure of the product was unambiguously confirmed by X-ray diffraction analysis (CCDC 1010663). Further, the yield of **5a** was increased to 87% using Ag_2CO_3 as the catalyst instead of AgOAc. The variation of the substituents on the pyridyl unit of substrates **4** had no significant influence on the reaction outcome, thus affording the corresponding 2,4-disubstituted pyrroles (**5b**–**5d**) in good yields. Similar to TosMIC, ethyl isocyanoacetate (**2b**) also participated in the tandem reaction with 2-pyridyl alkynyl carbinol **4d**, affording the desired product **5e** in 84% yield. The [3 + 2] cycloaddition of isocyanides with alkynes is an atom-economic reaction for the synthesis of oligosubstituted pyrroles.[15] Recently, the Lei group[16] and we[13d] reported the first transition-metal-catalyzed method that could be applied to *unactivated* terminal alkynes; however, only 2,3-disubstituted pyrroles were obtained

This journal is © The Royal Society of Chemistry [year]

regioselectively. To the best of our knowledge, the synthesis of 2,4-disubstituted isomers in the cycloaddition of isocyanides with alkynes has not been reported yet. The unexpected reactivity of 2-pyridyl alkynyl carbinols **4** in the reaction with isocyanides can be attributed to the directing effect of 2-pyridyl group. Oligosubstituted pyrroles are important subunits in natural products, pharmaceuticals, and functional materials, and also valuable intermediates in organic synthesis.[17] Herein, we have provided a novel and practical method for the synthesis of 2,4-disubstituted pyrroles.[18]

Based on related precedents[8-10] and our previous reports on the silver-catalyzed reactions of isocyanides with terminal alkynes or propargylic alcohols,[12c,f] a plausible reaction mechanism for the synthesis of indolizines and pyrroles is proposed (Scheme 3). Because of the coordination effect of pyridyl and alkynyl units, complex **A** is formed. The coordination of an isocyanide to the silver center affords complex **B**. This complex provides a suitable configuration for the [3 + 2] cycloaddition of the alkynyl unit with the isocyanide unit, thus affording 2,4-disubstituted pyrrole **C** regioselectively. Finally, the oxidation of secondary alcohol to carbonyl group affords 4-picolinoyl pyrrole **5d**. In the synthesis of indolizines from tertiary propargyl alcohols **1**, the reaction of **1** with Ag catalyst affords silver acetylide intermediate **D**.[19] Next, 1,1-insertion of the isocyanide into the Ag–C bond affords acetylenic imido complex **E**. This imido complex subsequently undergoes a possible intramolecular rearrangement to produce 2,3-allenamides **F**. Finally, the one-step intramolecular cycloisomerization of **F** affords indolizines **3**. The different reactivities of tertiary and secondary propargylic alcohols **1** and **4** can be attributed to the steric hindrance and the easy cleavage of the hydroxyl group in tertiary propargyl alcohols.



Scheme 3 A Plausible Reaction Mechanism.

In summary, we have developed a novel chemoselective silver-catalyzed cyclization reactions between 2-pyridyl alkynyl carbinols and isocyanides, which divergently afforded indolizines and 2,4-disubstituted pyrroles in good to excellent yields. For the first time, the regioselective formation of 2,4-disubstituted pyrroles by the [3 + 2] cycloaddition of terminal alkynes with isocyanides was accomplished. Considering the readily available starting materials, mild reaction conditions, and highly functionalized products, these novel reactions would have great potential in organic synthesis.

Financial supports by the NNSFC (21172029, 21202016, 21372038), the Ministry of Education of the People's Republic of China (NCET-13-0714), and the Jilin Provincial Research Foundation for Basic Research (20140519008JH).

Notes and references

[a] *Department of Chemistry, Northeast Normal University, Changchun 130024, China; E-mail: bixh507@nrenu.edu.cn*
[b] *State Key Laboratory and Institute of Elemento-Organic Chemistry, Tianjin 300071, China.*

† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, and spectra copies of all compounds. See DOI: 10.1039/b000000x/

1 For reviews, see: (*a*) J. P. Michael, *Alkaloids*, 2001, **55**, 91; (*b*) C. Bailly, *Curr. Med. Chem. Anti-Cancer Agents*, 2004, **4**, 363; (*c*) J. P. Michael, *Nat. Prod. Rep.,* 2008, **25**, 139.
2 A. K. Das, S. Som, *Orient. J. Chem.*, 2006, **2**, 415.
3 S. Lingala, R. Nerella; R. Cherukupally, A. K. Das, *Int. J. Pharmaceut. Sci. Rev. Res.*, 2011, **6**, 128.
4 P. Sharma, A. Kumar, S. Sharma, N. Rane, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 937.
5 S. Teklu, L.-L. Gundersen, F. Rise, M. Tilset, *Tetrahedron*, 2005, **61**, 4643.
6 D. A. James, K. Koya, H. Li, G. Q. Liang, Z. Q. Xia, W. W. Ying, Y. M. Wu, L. J. Sun, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1784.
7 For examples, see: (*a*) U. Bora, A. Saikia, R. C. Boruah, *Org. Lett.*, 2003, **5**, 435; (*b*) D. Basavaiah, A. J. Rao, *Chem. Commun.*, 2003, 604; (*c*) V. Specowius, F. Bendrath, M. Winterberg, A. Khurshid, P. Langer, *Adv. Synth. Catal.*, 2012, **354**, 1163; (*d*) E. L. Kostik, A. Abiko, A. Oku, *J. Org. Chem.*, 2001, **66**, 2618.
8 (*a*) I. V. Seregin, V. Gevorgyan, *J. Am. Chem. Soc.*, 2006, **128**, 12050; (*b*) Z. Li, D. Chernyak, V. Gevorgyan, *Org. Lett.*, 2012, **14**, 6056; (*c*) I. V. Seregin, A. W. Schammel, V. Gevorgyan, *Org. Lett.*, 2007, **9**, 3433; (*d*) D. Chernyak, C. Skontos, V. Gevorgyan, *Org. Lett.*, 2010, **12**, 3242.
9 (*a*) C. R. Smith, E. M. Bunnelle, A. J. Rhodes, R. Sarpong, *Org. Lett.*, 2007, **9**, 1169; (*b*) A. R. Hardin, R. Sarpong, *Org. Lett.*, 2007, **9**, 4547.
10 B. Yan, Y. Zhou, H. Zhang, J. Chen, Liu, Y. *J. Org. Chem.*, 2007, **72**, 7783.
11 (*a*) I. Kim, J. Choi, H. K. Won, G. H. Lee, *Tetrahedron Lett.*, 2007, **48**, 6863; (*b*) I. Kim, H. K. Won, J. Choi, G. H. Lee, *Tetrahedron*, 2007, **63**, 12954.
12 (*a*) C. H. Zhang, H. Zhang, L. Y. Zhang, T. B. Wen, X. M. He, H. P. Xia, *Organometallics*, 2013, **32**, 3738; (*b*) L.-H. Chung, C.-Y. Wong, *Organometallics*, 2013, **32**, 3583.
13 For examples, see: (*a*) Z. Fang, J. Liu, Q. Liu, X. Bi, *Angew. Chem. Int. Ed.*, 2014, **53**, 7209; (*b*) Z. Liu, J. Liu, L. Zhang, P. Liao, J. Song, X. Bi, *Angew. Chem. Int. Ed.,* 2014, **53**, 5305; (*c*) J. Liu, Z. Fang, Q. Zhang, Q. Liu, X. Bi, *Angew. Chem. Int. Ed.*, 2013, **52**, 6953.
14 For a review on the applications of *p*-toluenesulfonylmethyl isocyanide (TosMIC), see: V. K. Tandon, S. Rai, *Sulfur Rep.*, 2003, **24**, 307.
15 (*a*) H. Saikachi, T. Kitagawa, H. Sasaki, *Chem. Pharm. Bull.*, 1979, **27**, 2857; (*b*) S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9260; (*c*) O. V. Larionov, A. de Meijere, *Angew. Chem. Int. Ed.*, 2005, **44**, 5664; (*d*) A. V. Lygin, O. V. Larionov, V. S. Korotkov, A. de Meijere, *Chem. Eur. J.*, 2009, **15**, 227; (*e*) Q. Cai, F. Zhou, T. Xu, L. Fu, K. Ding, *Org. Lett.*, 2011, **13**, 340.
16 M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem. Int. Ed.*, 2013, **52**, 6958.
17 (*a*) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264; (*b*) N. T. Patil, Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395. (c) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084.
18 For examples on the synthesis of 2,4-disubstituted pyrroles, see: (*a*) L. Meng, K. Wu, C. Liu, A. Lei, *Chem. Commun.*, 2013, **49**, 5853; (*b*) Z. Shi, M. Suri, F. Glorius, *Angew. Chem. Int. Ed.*, 2013, **52**, 4892; (*c*) Q. Zeng, L. Zhang, J. Yang, B. Xu, Y. Xiao, J. Zhang, *Chem. Commun.*, 2014, **50**, 4203.

19 U. Létinois-Halbes, P. Pale, S. Berger, *J. Org. Chem.*, 2005, **70**, 9185.

This journal is © The Royal Society of Chemistry [year]