Accepted Manuscript

Rhodium(III)-catalyzed synthesis of indoles from 1-alkylidene-2-arylhydrazines and alkynes via C–H and N–N bond cleavages

Takanori Matsuda, Yuki Tomaru

PII:	S0040-4039(14)00613-3
DOI:	http://dx.doi.org/10.1016/j.tetlet.2014.04.016
Reference:	TETL 44478
To appear in:	Tetrahedron Letters
Received Date:	24 February 2014
Revised Date:	2 April 2014
Accepted Date:	7 April 2014



Please cite this article as: Matsuda, T., Tomaru, Y., Rhodium(III)-catalyzed synthesis of indoles from 1-alkylidene-2-arylhydrazines and alkynes via C–H and N–N bond cleavages, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.016

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.





Tetrahedron Letters

journal homepage: www.elsevier.com

Rhodium(III)-catalyzed synthesis of indoles from 1-alkylidene-2-arylhydrazines and alkynes via C-H and N-N bond cleavages

Takanori Matsuda * and Yuki Tomaru

Department of Applied Chemistry, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online Keywords:

Alkyne Annulation C-H bond functionalization Hydrazine Indole Rhodium

Because of the importance of indoles as a privileged structure in the manufacture of pharmaceuticals, agrochemicals, and functional materials, the continued development of increasingly efficient methods for the preparation of indoles has been a pervasive topic in organic synthesis.¹ The Fischer indole cyclization (synthesis) has arguably become one of the most studied and successful approaches to indole synthesis since its discovery in 1883, and it remains under active development. The vintage synthesis and its modern variants employ 1-alkylidene-2arylhydrazines or their tautomers, 1-alkenyl-2-arylhydrazines, as substrates.

Transition-metal-catalyzed C-H bond functionalization has witnessed tremendous growth in recent years because it offers an innovative and elegant pathway for the construction of organic molecules. As such, a wide variety of annulation and cyclization reactions based on the functionalization of C-H bonds² have been devised for indole synthesis^{3,4} and have addressed some of the issues pertaining to the traditional methods. Reports of a rhodium(III)-catalyzed indole synthesis involving the cleavage of N-N bonds appeared in succession last year (Figure 1).^{4,5} During our ongoing investigation into transition-metal-catalyzed reactions of hydrazine derivatives,⁶ we discovered an indoleforming annulation reaction of alkylidenehydrazines with alkynes under rhodium(III) catalysis, which we report herein.⁷



E-mail address: mtd@rs.tus.ac.jp (T. Matsuda).

Figure 1. N-N Compounds used in rhodium(III)-catalyzed annulation with alkynes to give indoles

2009 Elsevier Ltd. All rights reserved.

1-Alkylidene-2-arylhydrazines undergo annulative coupling with internal alkynes in presence of

a rhodium(III) catalyst and a copper(II) salt. The reaction proceeds through cleavage of the C-H

and N-N bonds of the hydrazines to afford 1,2,3-trisubstituted indole derivatives.

Subjection of 1-ethylidene-2-methyl-2-phenylhydrazine (1a) and diphenylacetylene (2a) to [Cp*RhCl₂]₂ (2.5 mol%, 5 mol%) Rh) and Cu(OAc)₂ (2 equiv) in DMF at 120 °C under nitrogen resulted in the formation of 1-methyl-2,3-diphenylindole (3a) in 34% yield through the annulative coupling involving cleavage of the C-H and N-N bonds under rhodium(III)-catalyzed oxidative conditions (Table 1, entry 1). Because a cationic system ([Cp*RhCl₂]₂/AgSbF₆) proved to be more effective (entry 2), the preformed cationic rhodium(III) catalyst [Cp*Rh(MeCN)₃](SbF₆)₂ was used; the reaction gave 3a in 58% vield (entrv Furthermore. the addition of 3). tetraphenylcyclopentadiene ($C_5H_2Ph_4$) as the ligand boosted the yield to 67% (entry 4).8 A control experiment revealed that the use of an excess (1.5 equiv) of 2a was pivotal for obtaining the product in good yield. The reaction performed at a lower temperature (100 °C) led to a reduced yield (entry 5), and a complex mixture of products was obtained when the reaction was performed under air. Almost no indole formation was observed in the absence of either the Rh(III) catalyst or the Cu(II) oxidant.

Table 1

`R

Optimization of reaction conditions^a



CEPTED M

2				Tetr
Entry	Catalyst	Temp	Time	Yield ^b
		(°C)	(h)	(%)
1	2.5 mol% [Cp*RhCl ₂] ₂	120	3	34
2	2.5 mol% [Cp*RhCl ₂] ₂	120	3	46
	20 mol% AgSbF ₆			
3	$5 \text{ mol}\% [Cp*Rh(MeCN)_3](SbF_6)_2$	120	1.5	58
4	$5 \text{ mol}\% [Cp*Rh(MeCN)_3](SbF_6)_2$	120	1.5	67 ^c
	20 mol% C ₅ H ₂ Ph ₄			
5	$5 \text{ mol}\% [Cp*Rh(MeCN)_3](SbF_6)_2$	100	2	54
	$20 \text{ mol}\% \text{C}_5\text{H}_2\text{Ph}_4$			

^a 1a (0.20 mmol) and 2a (0.30 mmol) were reacted in the presence of 5 mol% Rh(III) catalyst and 2 equiv Cu(OAc)₂ in DMF (1.0 mL) under nitrogen.

^b Isolated yield.

^c 50% yield with 1 equiv 2a.

We subsequently investigated the effect of the alkylidene moieties of hydrazines 1 that are dismantled during the reaction (Table 2).⁹ The reaction of N'-propylidene hydrazine **1b** with **2a** resulted in a comparable yield (entry 1). N'-Isobutylidene hydrazine 1c was among the most efficacious substrates for the reaction, giving 90% yield of 3a (entry 2). However, the product 3a was not obtained with neopentylidene hydrazine 1d because of the decomposition of the substrate (entry 3), and no reaction was observed with benzylidene hydrazine 1e (entry 4). We also examined ketone-derived substrates; the use of cyclohexylidene derivative 1f led to the decomposition of the starting hydrazine (entry 5).

Table 2



^a 1 (0.20 mmol) and 2a (0.30 mmol) were reacted in the presence of 5 mol% [Cp*Rh(MeCN)₃](SbF₆)₂ and 2 equiv Cu(OAc)₂ in DMF (1.0 mL) under nitrogen.

^b Isolated yield.

Some experiments were conducted to probe the mechanism of the reaction. The reaction with 1-methyl-1-phenylhydrazine

Table 3

Substrate scope of the rhodium(III)-catalyzed annulative coupling of 1 with 2



ahedron

(PhMeN-NH₂) under our reaction conditions afforded 3a in trace amount. suggesting that a mechanism involving hydrohydrazination of alkynes followed by the Fischer indole cyclization¹⁰ is improbable in this case.

The proposed mechanism for the rhodium(III)-catalyzed indole-forming annulation reaction between 1c and 2a is shown in Scheme 1. A rhodium(III) acetate species is presumably generated from ligand exchange, and the nitrogen of the hydrazine 1c directs the C-H bond cleavage event to generate five-membered rhodacycle A with an accompanying loss of acetic acid.^{11,12} Next, the C–C triple bond of **2a** coordinates to the rhodium, after which migratory insertion occurs to form sevenmembered rhodacycle B. The N-N bond in intermediate B is then cleaved, and the amino group migrates to the rhodium to forge six-membered rhodacycle C with the concomitant release of acetic acid and isobutyronitrile.¹³ Finally, reductive elimination of C furnishing indole 3a extrudes a rhodium(I) species, which is oxidized by Cu(II) to restore the catalytically active rhodium(III) complex. Under our oxidative conditions, the putative byproduct, nitrile, was so unstable that its detection and isolation were not possible.



Scheme 1. Proposed mechanism for the rhodium(III)-catalyzed indole-forming annulation

Using N'-isobutylidene hydrazines as coupling partners of choice, we subjected a range of alkynes to the optimized indoleforming reaction conditions (Table 3).¹⁴ The reaction of 1c with diaryl alkynes afforded the corresponding 2,3-diaryl indoles 3bf. A thienyl group was tolerated in this reaction to provide dithienyl indole 3g. An aliphatic alkyne was also used that resulted in 2,3-dipropylindole 3h being isolated in 54% yield. In the case of the unsymmetrical alkyne 1-phenyl-1-propyne, product 3i was obtained as an 80:20 mixture of regioisomers. In addition to N-methylindoles, N-ethyl-, N-benzyl-, and Nphenylindoles **3***j*-**m** were also prepared through the reaction. In the reaction of 3-tolyl derivative, the C-H bond cleavage process occurred at the more sterically accessible sites to give and 6methylindole **30**, respectively, as the exclusive products.

EPTED MA SCRIPT NU



In conclusion, we developed a method for the synthesis of indoles from alkylidenehydrazines and alkynes under rhodium(III)-catalyzed oxidative conditions. This annulation reaction proceeds via the cleavage of C-H and N-N bonds and allows access to a range of 1,2,3-trisubstituted indoles.

Acknowledgments

This work was supported by JSPS, Japan (Grant-in-Aid for Scientific Research (C) No. 25410054) and the Sumitomo Foundation.

References and notes

- 1. For recent general reviews on indole synthesis, see: (a) Cacchi, S.; Fabrizi, G. Chem. Rev. 2005, 105, 2873. (b) Humphrey, G. R.; Kuethe, J. T. Chem. Rev. 2006, 106, 2875. (c) Krüger, K.; Tillack, A.; Beller, M. Adv. Synth. Catal. 2008, 350, 2153. (d) Cacchi, S.; Fabrizi, G. Chem. Rev. 2011, 111, PR215. (e) Taber, D. F.; Tirunahari, P. K. Tetrahedron 2011, 67, 7195. (f) Vicente, R. Org. Biomol. Chem. 2011, 9, 6469. (g) Shiri, M. Chem. Rev. 2012, 112, 3508. (h) Inman, M.; Moody, C. J. Chem. Sci. 2013, 4, 29.
- For most recent reviews, see: (a) Louillat, M.-L.; Patureau, F. W. Chem. Soc. Rev. 2014, 43, 901. (b) Rouquet, G.; Chatani, N. Angew. Chem., Int. Ed. 2013, 52, 11726. (c) Jeffrey, J. L.; Sarpong, R. Chem. Sci. 2013, 4, 4092. (d) Wencel-Delord, J.; Colobert, F. Chem. Eur. J. 2013, 19, 14010. (e) Engle, K. M.; Yu, J.-Q. J. Org. Chem. 2013, 78, 8927. (f) Yan, G.; Wu, X.; Yang, M. Org. Biomol. Chem. 2013, 11, 5558. (g) Shibahara, F.; Murai, T. Asian J. Org. Chem. 2013, 2, 624. (h) Li, B.; Dixneuf, P. H. Chem. Soc. Rev. 2013, 42, 5744. (i) Yoshikai, N.; Wei, Y. Asian J. Org. Chem. 2013, 2, 466. (j) Wencel-Delord, J.; Glorius, F. Nat. Chem. 2013, 5, 369. (k) Pan, S.; Shibata, T. ACS Catal. 2013, 3, 704. (1) Liu, H.; Gu, Z.; Jiang, X. Adv. Synth. Catal. 2013, 355, 617. (m) Ferraccioli, R. Synthesis 2013, 45, 581. (n) Kozhushkov, S. I.; Ackermann, L. Chem. Sci. 2013, 4, 886. (o) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. Catal. Sci. Technol. 2013, 3, 562. (p) Zhang, M.; Zhang, A.-Q.; Peng, Y. J. Organomet. Chem. 2013, 723, 224. (q) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Chem. Rev. 2012, 112, 5879. (r) Chen, D. Y.-K.; Youn, S. W. Chem. Eur. J. 2012, 18, 9452. (s) Zhu, C.; Wang, R.; Falck, J. R. Chem. Asian J. 2012, 7, 1502. (t) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. Synthesis 2012, 44, 1778. (u) Song, G.; Wang, F.; Li, X. Chem. Soc. Rev. 2012, 41, 3651.
- (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. Angew. Chem., Int. Ed. 2008, 47, 7230. (b) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. J. Am.

Chem. Soc. 2008, 130, 16474. (c) Tsuchikama, K.; Hashimoto, Y.k.; Endo, K.; Shibata, T. Adv. Synth. Catal. 2009, 351, 2850. (d) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. Angew. Chem., Int. Ed. 2009, 48, 4572. (e) Chen, J.; Song, G.; Pan, C.-L.; Li, X. Org. Lett. 2010, 12, 5426. (f) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. J. Am. Chem. Soc. 2010, 132, 18326. (g) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. Org. Lett. 2010, 12, 5462. (h) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. Angew. Chem., Int. Ed. 2011, 50, 1338. (i) Chen, J.; Pang, Q.; Sun, Y.; Li, X. J. Org. Chem. 2011, 76, 3523. (j) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. Chem. Eur. J. 2011, 17, 7298. (k) Ackermann, L.; Lygin, A. V. Org. Lett. 2012, 14, 764. (1) Wei, Y.; Deb, I.; Yoshikai, N. J. Am. Chem. Soc. 2012, 134, 9098. (m) Nanjo, T.; Tsukano, C.; Takemoto, Y. Org. Lett. 2012, 14, 4270. (n) Song, W.; Ackermann, L. Chem. Commun. 2013, 49, 6638. (o) Cajaraville, A.; López, S. S.; Varela, J. A.; Saá, C. Org. Lett. 2013, 15, 4576.

- (a) Wang, C.; Sun, H.; Fang, Y.; Huang, Y. Angew. Chem., Int. Ed. 2013, 52, 5795. (b) Wang, C.; Huang, Y. Org. Lett. 2013, 15, 5294. (c) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. J. Am. Chem. Soc. 2013, 135, 16625. (d) Zhao, D.; Shi, Z.; Glorius, F. Angew. Chem., Int. Ed. 2013, 52, 12426.
- For other rhodium(III)-catalyzed annulations involving N-N bond 5. cleavage, see: (a) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. Angew. Chem., Int. Ed. 2011, 50, 5927. (b) Liu, W.; Hong, X.; Xu, B. Synthesis 2013, 45, 2137. (c) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. Org. Lett. 2013, 15, 5750. (d) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. J. Org. Chem. 2014, 79, 1025.
- Matsuda, T.; Tomaru, Y.; Matsuda, Y. Org. Biomol. Chem. 2013, 6. 11, 2084.
- 7. Just prior to the submission of this manuscript, we became aware of closely related results. Zheng, L.; Hua, R. Chem. Eur. J. 2014, 20. 2352
- For the successful use of tetraphenylcyclopentadiene in the 8. rhodium(III)-catalyzed reactions, see: (a) Uto, T.; Shimizu, M.; Ueura, K.; Tsurugi, H.; Satoh, T.; Miura, M. J. Org. Chem. 2008, 73, 298. (b) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. J. Org. Chem. 2011, 76, 13. (c) Shi, Z.; Schröder, N.; Glorius, F. Angew. Chem., Int. Ed. 2012, 51, 8092.
- The N'-methylene derivative was too unstable to examine.
- (a) Cao, C.; Shi, Y.; Odom, A. L. Org. Lett. 2002, 4, 2853. (b) 10 Schwarz, N.; Alex, K.; Sayyed, I. A.; Khedkar, V.; Tillack, A.; Beller, M. Synlett 2007, 1091. (c) Banerjee, S.; Barnea, E.; Odom, A. L. Organometallics 2008, 27, 1005. (d) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. Angew. Chem., Int. Ed. 2008, 47, 2304.
- 11. Use of KOAc instead of Cu(OAc)2 as the source of acetate ion was unsuccessful.
- When 1c was heated at 120 °C in DMF-CD₃OD (5:1) in the 12. presence of $[Cp*Rh(MeCN)_3](SbF_6)_2$ (5 mol%) and $Cu(OAc)_2$ (50 mol%), deuteration at the ortho positions of 1c was observed.

3

ACCEPTED MANUSCRIPT

Tetrahedron

 For a similar acetate-induced C–H bond cleavage process via a seven-membered intermediate, see: Nakamura, I.; Shiraiwa, N.; Kanazawa, R.; Terada, M. Org. Lett. 2010, 12, 4198. See also ref 7.

4

14. Use of terminal alkynes resulted in homocoupling to yield 1,3diynes, and formation of indoles was not observed. Accerbatic