Tetrahedron Letters 53 (2012) 620–622

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ionic diamine rhodium complex catalyzed reductive N-heterocyclization of *N*-(2-nitroarylidene)amines

Kazumi Okuro, Joanna Gurnham, Howard Alper *

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Canada K1N 6N5

ARTICLE INFO

Article history:
Received 21 October 2011
Revised 14 November 2011
Accepted 18 November 2011
Available online 25 November 2011

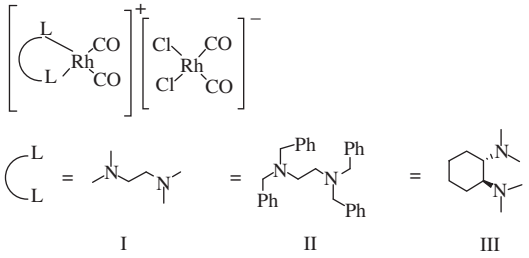
Keywords:
Rhodium
Heterocycles
2*H*-Indazole
Reductive N-heterocyclization

ABSTRACT

Ionic diamine rhodium complexes catalyze the reductive N-heterocyclization of *N*-(2-nitroarylidene)amines under carbon monoxide to afford the corresponding 2*H*-indazoles in up to 75% yields.

Indazoles, which are regarded as isoteres of indoles, are an important class of heterocycles often occurring as constituents of biologically active compounds. For example, it has been reported that N-substituted indazoles exhibit high affinities for estrogen receptor β, and exhibit analogestic and anti-angiogenic activities.[1] Due to the pharmaceutical and agricultural importance of these heterocyclic systems, it is somewhat surprising that the syntheses of 2*H*-indazoles have been less explored than those of other heterocycles including 1*H*-indazoles.[2] Recent advances in organometallic chemistry have provided several straightforward approaches to 2*H*-indazoles. Examples include the Pd/$SnCl_2$ catalyzed reductive N-heterocyclization of (2-nitroarylidene)amines,[3] and the Pd catalyzed domino reaction of 2-halophenylacetylenes with phenylhydrazine.[4]

We have recently reported the synthesis of a novel, air stable diamine rhodium complex, $[Rh(CO)_2(Me_2NCH_2CH_2NMe_2)]^+[RhCl_2(CO)_2]^-$ (**I**).[5] The complex is an excellent catalyst for the regioselective hydroformylation of olefins,[5] and for the inter- and intra-molecular hydroaminomethylation of anilines containing an olefinic unit.[6] In further exploring the catalytic activity of **I**, we recently found that **I** can catalyze reductive N-heterocyclization of 2-nitroarenes under carbon monoxide affording indole derivatives.[7] In this Letter, we describe the reductive N-heterocyclization of *N*-(2-nitroarylidene)amines to give 2*H*-indazole derivatives, where carbon monoxide is used as a reducing agent for the nitro group.

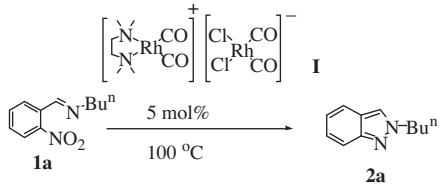


We initially employed *N*-(2-nitrobenzylidene)butylamine (**1a**) to optimize the reaction conditions. When **1a** was treated with 5 mol % of the complex **I** in THF at 100 °C for 24 h under CO (100 psi), conditions used for the reductive N-heterocyclization of 2-nitroarenes affording indoles,[7] 2-butyl-2*H*-indazole (**2a**) was produced in a 56% yield (Table 1, entry 1). Performing the reaction in toluene increased the yield to 75% (entry 2). Other solvents such as CH_2Cl_2 and CH_3CN were inferior to toluene. Decreasing the temperature to 80 °C in toluene significantly reduced the conversion of **1a** (entry 6) and prolonged reaction time increased the yield of **2a** (entry 7). Higher (200 psi) or lower (42 psi) pressure of carbon monoxide did not have a positive effect on the yield of **2a** (entries 5 and 8). The effect of the diamine ligands was also examined. Use of the rhodium complex with the diamines, *N*,*N*,*N*′,*N*′-tetrabenzylethylenediamine(tipeda) (**II**)[5] or trans-1,2-bis(dimethylamino)cyclohexane (**III**)[5] was evaluated, and although both complexes catalyzed the reaction to some extent, they were not as effective

* Corresponding author. Tel.: +1 613 562 5189; fax: +1 613 562 5871.
E-mail address: howard.alper@uottawa.ca (H. Alper).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.101

Table 1
Reductive N-heterocyclization of **1a**



Entry	Cat.	CO (psi)	Solvent	Yield (%)	
				2a	**1a**
1	**I**	100	THF	56	0
2	**I**	100	Toluene	75	0
3	**I**	100	CH_2Cl_2	43	Trace
4	**I**	100	CH_3CN	58	0
5	**I**	200	Toluene	65	0
6[a]	**I**	100	Toluene	42	39
7[a,b]	**I**	100	Toluene	64	11
8	**I**	42	Toluene	29	42
9	**II**	100	Toluene	11	83
10	**III**	100	Toluene	46	Trace

[a] Reaction at 80 °C.
[b] Reaction for 48 h.

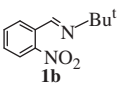
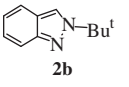
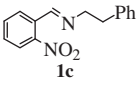
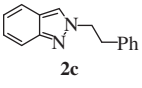
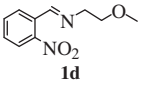
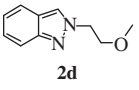
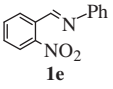
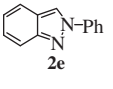
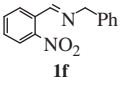
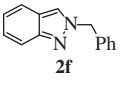
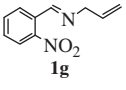
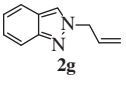
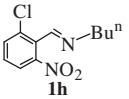
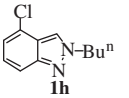
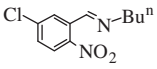
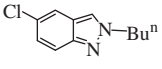
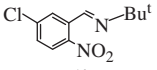
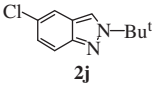
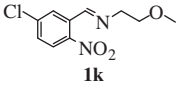
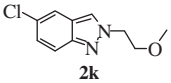
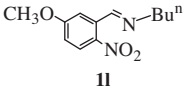
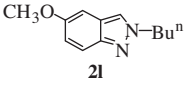
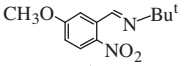
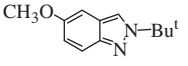
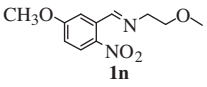
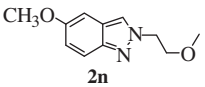
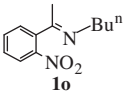
as complex **I** (entries 9 and 10). When the reaction was carried out using the catalyst system of $[Rh(COD)Cl]_2$ and standard phosphines such as PPh_3, PCy_3, dppe, dppp, dppb, and dppf, no reaction took place at all, indicating that similar catalytic performance with **I** cannot be obtained for the system with phosphine ligands.

Having found the optimal conditions using **1a**, the reaction was applied to a variety of *N*-(2-nitroarylidene)amines. At first, the effect of the substituents on nitrogen was examined. The reaction of *N*-(2-nitrobenzylidene)-*t*-butylamine (**1b**), *N*-(2-nitrobenzylidene)-2-phenylethylamine (**1c**), and *N*-(2-nitrobenzylidene)-2-methoxyethylamine (**1d**) proceeded smoothly to afford the corresponding 2-substituted 2*H*-indazoles in 65–85% yields (Table 2, entries 1–3). On the other hand, the substrate having phenyl-, benzyl-, and allyl- substituted *N*-(2-nitrobenzylidene)amine derivatives gave unsatisfactory results (entries 4–6). Several *N*-(2-nitroarylidene)amines having methoxy and chloro groups on the aromatic ring were reacted under the optimal conditions to afford the corresponding 2*H*-indazole derivatives in 32–65% yields. In contrast, the ketimine **1o** was totally unreactive, with **1o** being recovered unchanged. These results were comparable to those reported using a Pd complex as the catalyst,[3] except for *N*-(2-nitrobenzylidene)arylamines (i.e., **1e**). In the latter case, *N*-(2-nitrobenzylidene)arylamine derivatives successfully reacted to afford the corresponding *N*-aryl-2*H*-indazoles in moderate yields whereas the present catalyst system resulted in a poor yield of **2e** described above.

The reaction mechanism is not known; however it would be reasonable to consider the involvement of the nitrene-rhodium intermediate, **3**[3b,7,8] where carbon monoxide serves as a reducing agent (Scheme 1). Thus, the diamine rhodium complex catalyzed deoxygenation of the nitro group can give a nitrene-rhodium intermediate of an electrophilic nature, and then the latter could undergo intramolecular ring closure onto the imino nitrogen atom, resulting in the formation of 2*H*-indazole. Considering that the nitrene would strongly coordinate to the metal, it is conceivable that the reaction behavior of the nitrene intermediate is affected by the nature of its metal species, depending on its coordination environment, which could lead to no comparable outcome for the reaction of **1e** using the Pd catalyst.

In conclusion, we have demonstrated that the reductive N-heterocyclization of *N*-(2-nitroarylidene)amines catalyzed by the ionic diamine rhodium complex under carbon monoxide affords 2*H*-indazole derivatives in up to 75% yields.

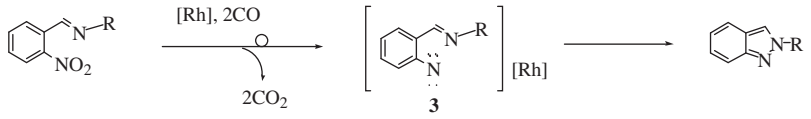
Table 2
Results of the Rh-catalyzed reductive N-cyclization of a variety of (2-nitroarylidene)amine[a]

Entry	Nitro compound	2*H*-indazole	Yield (%)
1	 **1b**	 **2b**	75
2	 **1c**	 **2c**	85
3	 **1d**	 **2d**	65
4	 **1e**	 **2e**	25
5	 **1f**	 **2f**	34(36)[b]
6	 **1g**	 **2g**	Trace
7	 **1h**	 **1h**	32
8	 **1i**	 **2i**	65
9	 **1j**	 **2j**	58
10	 **1k**	 **2k**	56
11	 **1l**	 **2l**	57
12	 **1m**	 **2m**	50
13	 **1n**	 **2n**	47
14	 **1o**		0

[a] Conditions: **1** (1.0 mmol), **I** (0.05 mmol), toluene, 100 °C, CO 100 psi.
[b] The yield in parenthesis at 80 °C.

Acknowledgment

We are grateful to the Natural Sciences and Engineering Council of Canada (NSERC) for the support of this research.



Scheme 1. Possible reaction mechanism for indazole formation.

References and notes

1. (a) Cerecetto, A.; Gerpe, A.; González, V.; Arán, V. J.; Ochoa de Ocáriz, C. *Mini-Rev. Med. Chem.* **2005**, *5*, 869; (b) Amgelis, M. D.; Stossi, F.; Carson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, *48*, 1132; (c) Huang, L. J.; Shih, M. L.; Chen, H. S.; Pan, S. L.; Teng, C. M.; Lee, F. Y.; Kuo, S. C. *Bioorg. Med. Chem.* **2006**, *14*, 528.
2. (a) Stadlbauer, W. *Science of Synthesis* **2002**, *12*, 227; (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. C., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 1–75; (c) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. C., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 167–303; (d) Behr, L. C. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1967; Vol. 22, pp 289–382; (e) Schmidt, A.; Beutler, A.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073; (f) Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Iizuka, T.; Horaguchi, T. *J. Heterocycl. Chem.* **2009**, *46*, 1309.
3. (a) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1466; (b) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1995**, *59*, 3375.
4. Halland, N.; Nazare, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6879.
5. Kim, J. J.; Alper, H. *Chem. Commun.* **2005**, 3059.
6. (a) Vieira, T. O.; Alper, H. *Chem. Commun.* **2007**, 2710; (b) Vieira, T. O.; Alper, H. *Org. Lett.* **2008**, *10*, 485; (c) Okuro, K.; Alper, H. *Tetrahedron Lett.* **2010**, *51*, 4959.
7. Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem.* **2011**, *76*, 4715.
8. (a) Abramovitch, R. A.; Davis, B. A. *Chem. Rev.* **1964**, *64*, 149; (b) Weigert, F. J. *J. Org. Chem.* **1973**, *38*, 1316; (c) Dieck, H. A.; Laine, R. M.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 2819; (d) Watanabe, Y.; Tsuji, Y.; Takeuchi, R. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3343; (e) Cenini, S.; Pizzotti, M.; Crotti, C.; Porata, F.; La Monica, G. *J. Chem. Soc., Chem. Commun.* **1984**, *53*, 1243; (f) Watanabe, Y.; Tsuji, Y.; Kondo, T.; Takeuchi, R. *J. Org. Chem.* **1984**, *49*, 4451; (g) Watanabe, Y.; Tsuji, Y.; Takeuchi, R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3011; (h) Allessio, E.; Mestroni, G. *J. Organomet. Chem.* **1985**, *291*, 117; (i) Tsuji, Y.; Takeuchi, R.; Watanabe, Y. *J. Organomet. Chem.* **1985**, *290*, 249; (j) Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1986**, 784; (k) Crotti, C.; Cenini, S.; Ragaini, F.; Porta, F. *J. Mol. Catal.* **1992**, *72*, 283.