ORGANIC LETTERS

2011
Vol. 13, No. 6
1429–1431

Palladium-Catalyzed Denitrogenation Reaction of 1,2,3-Benzotriazin-4(3*H*)-ones Incorporating Isocyanides

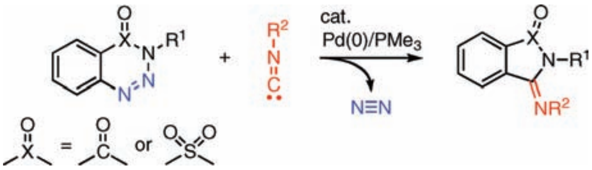
Tomoya Miura, Yui Nishida, Masao Morimoto, Motoshi Yamauchi, and Masahiro Murakami*

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

murakami@sbchem.kyoto-u.ac.jp

Received December 27, 2010

ABSTRACT



1,2,3-Benzotriazin-4(3*H*)-ones and 1,2,3,4-benzothiatriazine 1,1(2*H*)-dioxide reacted with isocyanides in the presence of a palladium catalyst to give 3-(imino)isoindolin-1-ones and 3-(imino)thiaisoindoline 1,1-dioxides, respectively, in high yield. An intermediate azapalladacycle was generated through denitrogenation of the triazine moiety, and an isocyanide was incorporated therein.

Transition-metal-catalyzed annulation reactions triggered by extrusion of gaseous small molecules have emerged as a powerful strategy for efficient construction of heterocyclic compounds. A heterometalacyclic intermediate is generated as the key intermediate from an organic platform and then incorporates an unsaturated molecule to form a new heterocyclic framework. In addition to rhodium(II)[1] and palladium(0) complexes,[2] nickel(0) complexes are also employed[3,4] as the precatalyst for such transformations. For example, phthalimide,[3a] phthalic anhydride,[3b] and isatoic anhydride[3c] reacted with alkynes in the presence of a nickel catalyst to give isoquinolin-1(2*H*)-ones, isochromen-1-ones, and quinolin-4(1*H*)-ones, respectively, with concomitant extrusion of CO or CO_2. We have recently developed the nickel-catalyzed annulation reactions of 1,2,3-benzotriazin-4(3*H*)-ones with unsaturated compounds such as alkynes,[5a] allenes,[5b] 1,3-dienes, and electron-deficient olefins.[5c] In these reactions, the triazinone moiety is activated by nickel(0), and with extrusion of N_2, a five-membered azanickelacycle is generated as the key intermediate.

---

(1) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (c) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034. (d) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510.

(2) (a) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (b) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118. (c) Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11*, 1055. (d) Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7508 and references cited therein.

(3) (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226. (c) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494. (d) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470. (e) Ooguri, A.; Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 13194. (f) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955. (g) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4548.

(4) For related reaction evolving CO, see: O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498.

(5) (a) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (b) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54. (c) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359.

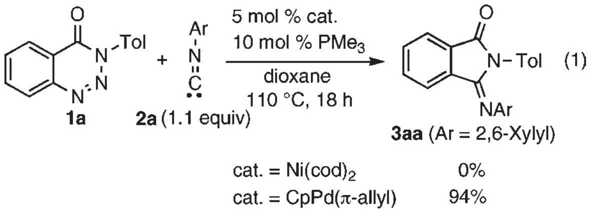
(6) For examples of transition-metal-catalyzed cyclization reactions incorporating isocyanides, see: (a) Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498. (b) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940. (c) Shibata, T.; Yamashita, K.; Katayama, E.; Takagi, K. *Tetrahedron* **2002**, *58*, 8661. (d) Onitsuka, K.; Suzuki, S.; Takahashi, S. *Tetrahedron Lett.* **2002**, *43*, 6197. (e) Park, S.; Shintani, R.; Hayashi, T. *Chem. Lett.* **2009**, *38*, 204. (f) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4835.

(7) For examples of the synthesis of 3-(imino)isoindolin-1-ones, see: (a) Nan'ya, S.; Tange, T.; Maekawa, E. *J. Heterocycl. Chem.* **1985**, *22*, 449. (b) Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2149. (c) Scherbakow, S.; Namyslo, J. C.; Gjikaj, M.; Schmidt, A. *Synlett* **2009**, 1964. (d) Wang, J.; He, Z.; Chen, X.; Song, W.; Lu, P.; Wang, Y. *Tetrahedron* **2010**, *66*, 1208.

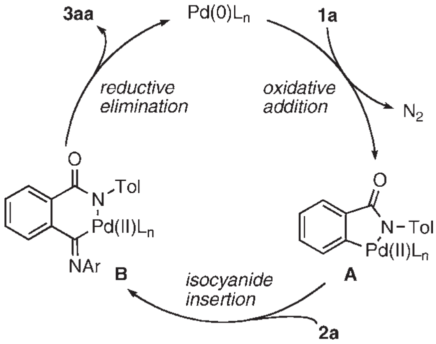
10.1021/ol103143a

Subsequent insertion of a carbon−carbon double or triple bond leads to the formation of the corresponding isoquinolin-1(2*H*)-one derivatives. As a whole, the N=N moiety of the six-membered heterocycle is replaced with a two-carbon unit to give a new six-membered heterocyclic compound. We next examined the possibility of incorporating isocyanides as the C1 source.[6] Herein, we report that a palladium catalyst efficiently promotes the annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones and 1,2,3,4-benzothiatriazine 1,1(2*H*)-dioxide with isocyanides. The reactions present new synthetic methods for 3-(imino)isoindolin-1-ones and 3-(imino)thiaisoindoline 1,1-dioxides,[7] which are substructures found in bioactive compounds.[8]

We initiated our study by conducting a reaction of *N*-tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**) with 2,6-xylyl isocyanide (**2a**, 1.1 equiv) in the presence of a nickel(0) catalyst generated in situ from Ni(cod)$_2$ (5 mol %) and PMe$_3$ (10 mol %) in 1,4-dioxane. No reaction occurred, and the starting substrate **1a** remained intact after heating at 110 °C for 18 h. This unsuccessful result with the Ni(0)/PMe$_3$ catalyst led us to examine the use of palladium catalysts. When a palladium(0) catalyst generated in situ from CpPd(π-allyl) (5 mol %)[9] and PMe$_3$ (10 mol %) was used, the substrate **1a** was consumed in 18 h, and after chromatographic isolation on silica gel, the desired 3-(imino)isoindolin-1-one **3aa** was obtained in 94% yield (eq 1). The following phosphine ligands gave inferior results: P(*n*-Bu)$_3$ (92%), PCy$_3$ (92%), P(*t*-Bu)$_3$ (11%), PPh$_3$ (17%), and Dppf (15%).



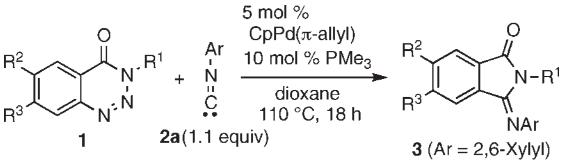
Scheme 1. Proposed Reaction Mechanism

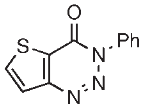


We assume the following reaction mechanism which is analogous to that we previously proposed for the nickel-catalyzed annulation reactions of 1,2,3-benzotriazin-4(3*H*)-ones with alkynes (Scheme 1).[5a] Oxidative addition of a C(O)N−N bond to palladium(0) prompts extrusion of N$_2$ to generate the five-membered ring azapalladacyclic intermediate **A**. Subsequent insertion of isocyanide **2a** into the palladium−carbon bond results in a formation of six-membered ring azapalladacyclic intermediate **B**.[10] Finally, reductive elimination affords **3aa**, regenerating the palladium(0) catalyst.

The scope of benzotriazinones **1** was examined in the reaction with **2a** using the CpPd(π-allyl)/PMe$_3$ complex as the catalyst (Table 1). Substrates **1b−g** possessing a variety of aryl groups on the nitrogen atom reacted nearly quantitatively with **2a** to afford the corresponding products **3ba−ga** in yields ranging from 95% to 99% (entries 1−6). Carbamoyl-substituted substrate **1h** also participated in

Table 1. Pd(0)-Catalyzed Annulation Reaction of 1,2,3-Benzotriazin-4(3*H*)-ones **1b−n** with 2,6-Xylyl Isocyanide (**2a**)[a]



entry	1	R^1	R^2	R^3	3	yield (%)[b]
1	**1b**	Ph	H	H	**3ba**	99
2	**1c**	4-MeOC$_6$H$_4$	H	H	**3ca**	99
3	**1d**	4-ClC$_6$H$_4$	H	H	**3da**	95
4	**1e**	4-CF$_3$C$_6$H$_4$	H	H	**3ea**	96
5	**1f**	2-MeOC$_6$H$_4$	H	H	**3fa**	98
6	**1g**	2-Pyridyl	H	H	**3ga**	97
7	**1h**	CONPh$_2$	H	H	**3ha**	91
8	**1i**	Me	H	H	**3ia**	0
9	**1j**	Ph	MeO	H	**3ja**	93[c]
10	**1k**	Ph	H	MeO	**3ka**	99
11	**1l**	Ph	MeO	MeO	**3la**	99[c]
12	**1m**	Ph	H	CO$_2$Me	**3ma**	99
13	**1n**				**3na**	90

[a] Reactions conducted on a 0.2 mmol scale. [b] Isolated yield. [c] 130 °C.

---

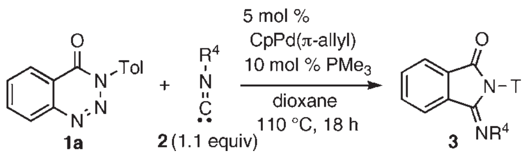
(8) (a) Murthy, A. R. K.; Wong, O. T.; Reynolds, D. J.; Hall, I. H. *Pharm. Res.* **1987**, *4*, 21. (b) Butner, L.; Huang, Y.; Tse, E.; Hall, I. H. *Biomed. Pharmacother.* **1996**, *50*, 290. (c) Wada, K.; Gomibuchi, T.; Yoneta, Y.; Otsu, Y.; Shibuya, K.; Okuya, H. (Bayer CropScience LP). US 2007/0031514 A1, Feburary 8, 2007. (d) Renold, P.; Huetter, O. F.; Maienfisch, P.; Zambach, W.; Pitterna, T.; Grimm, C. (Syngenta Crop Protection, Inc.). US 2010/0173959 A1, July 8, 2010.

(9) Pd(dba)$_2$ was also effective as the precatalyst and gave **3aa** in 99% NMR yield under the same reaction conditions. However, it was difficult to separate **3aa** and dibenzylideneacetone (dba) by PTLC.

(10) For examples of isocyanide insertion into the palladium−carbon bond, see: (a) Yamamoto, Y.; Yamazaki, H. *Inorg. Chim. Acta* **1980**, *41*, 229. (b) Albert, J.; D'Andrea, L.; Granell, J.; Zafrilla, J.; Font-Bardia, M.; Solans, X. *J. Organomet. Chem.* **2007**, *692*, 4895. (c) Vicente, J.; Saura-Llamas, I.; García-López, J.-A.; Bautista, D. *Organometallics* **2009**, *28*, 448 and references cited therein.

the annulation reaction, giving the product **3ha** in 91% yield (entry 7). However, methyl-substituted substrate **1i** was far less reactive and failed to undergo the annulation reaction with **2a** (entry 8). Benzotriazinones **1j−m** having electron-donating and -withdrawing substituents on the benzene ring were all competent substrates to afford the corresponding products **3ja−ma** in yields ranging from 93% to 99% (entries 9−12). In addition, thienotriazinone **1n** was also converted to the desired product **3na** in 90% yield (entry 13).

Table 2. Pd(0)-Catalyzed Annulation Reaction of *N*-Tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**) with Isocyanides **2b−f** [a]



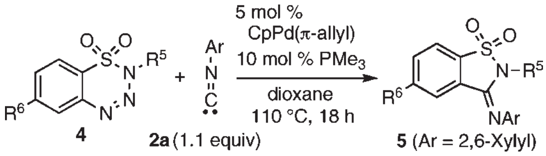
entry	2	R^4	3	yield (%)[b]
1	**2b**	2-MeC$_6$H$_4$	**3ab**	92[c]
2	**2c**	4-MeOC$_6$H$_4$	**3ac**	89[c]
3	**2d**	Bn	**3ad**	84[c,d]
4	**2e**	Cy	**3ae**	99[d]
5	**2f**	1,1,3,3 -Tetramethylbutyl	**3af**	99

[a] Reactions conducted on a 0.2 mmol scale. [b] Isolated yield. [c] 130 °C. [d] Including a small amount (<2%) of the hydrolyzed product (*N*-tolylphthalimide).

Next, various isocyanides **2b−f** were subjected to the annulation reaction of **1a** (Table 2). Aryl isocyanides such as 2-tolyl isocyanide (**2b**) and 4-methoxyphenyl isocyanide (**2c**) were incorporated well to give the corresponding products **3ab** and **3ac** in 92% and 89% yields, respectively (entries 1 and 2). The annulation reaction with aliphatic isocyanides **2d−f** proceeded also cleanly to give the corresponding products **3ad−af** in high yield (entries 3−5). It was interesting that benzyl isocyanide (**2d**) and cyclohexyl isocyanide (**2e**), which are prone to polymerization by transition metal catalysis,[11] were inserted in a desired manner.

We also examined the use of 1,2,3,4-benzothiatriazine 1,1(2*H*)-dioxide **4** as the triazo substrate (Table. 3).[3f] The same type of denitrogenation reaction took place in the presence of the CpPd(π-allyl)/PMe$_3$ catalyst. The reaction of aryl-substituted substrates **4a** with **2a** afforded the corresponding products **5aa** in 78% yield (entry 1). Unlike the reaction using 1,2,3-benzotriazin-4(3*H*)-ones **1**, alkyl-substituted substrates **4b−f** including even a *tert*-butyl-substituted one could readily participate in the reaction with **2a** (entries 2−6). The sulfone moiety of a highly electron-withdraing character might facilitate oxidative addition of the S(O)$_2$N−N bond to palladium(0).

Table 3. Annulation Reaction of 1,2,3,4-Benzothiatriazine 1,1(2*H*)-Dioxides **4a−f** with 2,6-Xylyl Isocyanide (**2a**) [a]



entry	4	R^5	R^6	5	yield (%)[b]
1	**4a**	Mes	H	**5aa**	78
2	**4b**	Me	H	**5ba**	91
3	**4c**	Bn	H	**5ca**	90
4	**4d**	*i*-Pr	H	**5da**	98
5	**4e**	*t*-Bu	H	**5ea**	87
6	**4f**	Me	MeO	**5fa**	93

[a] Reactions conducted on a 0.2 mmol scale. [b] Isolated yield.

In summary, we have demonstrated that isocyanides are efficiently incorporated into the skeleton of 1,2,3-benzotriazin-4(3*H*)-ones with extrusion of a dinitrogen molecule in the presence of the CpPd(π-allyl)/PMe$_3$ catalyst. In addition, an analogous denitrogenation reaction proceeds also with 1,2,3,4-benzothiatriazine 1,1(2*H*)-dioxides. The annulation reactions provide unique methods for the synthesis of 3-(imino)isoindolin-1-ones and 3-(imino)thiaisoindoline 1,1-dioxides.

Acknowledgment. This work was supported in part by MEXT (Grant-in-Aid for Challenging Exploratory Research, No. 21656033), the Mitsubishi Chemical Corporation Fund, the Sumitomo Foundation, and the Astellas Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available. Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[11] For a review of transition-metal-mediated polymerization of isocyanides, see: Suginome, M.; Ito, Y. *Adv. Polym. Sci.* **2004**, *171*, 77.