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Synthesis of 1(2*H*)-Isoquinolones by the Nickel-Catalyzed Denitrogenative Alkyne Insertion of 1,2,3-Benzotriazin-4(3*H*)-ones

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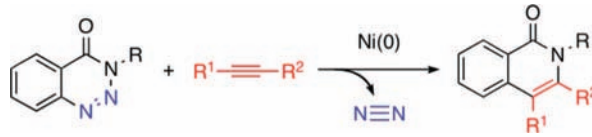
ABSTRACT



1,2,3-Benzotriazin-4(3*H*)-ones reacted with internal and terminal alkynes in the presence of a nickel(0)/phosphine catalyst to give a wide range of substituted 1(2*H*)-isoquinolones in high yield. The reaction proceeded through denitrogenative activation of the triazinone moiety and the following insertion of alkynes.

The 1(2*H*)-isoquinolone ring system is one of the basic units often found in the structures of plant alkaloids[1] and pharmacologically valuable compounds.[2] Therefore, the development of efficient methods for their synthesis is of great importance.[3] Whereas transition-metal-based catalysis has often been utilized for the synthesis of various heterocyclic compounds,[4] only limited examples applicable to the synthesis of 1(2*H*)-isoquinolones have appeared.[5] On the other hand, a rhodium-catalyzed extrusion reaction of a molecular dinitrogen from pyridotriazoles was utilized for construction of a new heterocyclic system by Gevorgyan and co-workers.[6] We report herein a nickel-catalyzed denitrogenative alkyne insertion reaction of 1,2,3-benzotriazin-4(3*H*)-ones, which presents a new synthetic approach to substituted 1(2*H*)-isoquinolones.

1,2,3-Benzotriazin-4(3*H*)-ones can be readily prepared from anthranilic acid derivatives.[7] Initially, the possibility to activate the triazinone moiety was examined using nickel(0)/phosphine complexes;[8] 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one (**1a**, 1.0 equiv) was treated with dec-5-yne (**2a**, 1.1 equiv) in the presence of a nickel(0) catalyst generated

(1) (a) Lewis, J. R. *Nat Prod. Rep.* **1994**, *11*, 329. (b) González, M. C.; Zafra-Polo, C.; Blázquez, A.; Serrano, A.; Cortes, D. *J. Nat. Prod.* **1997**, *60*, 108. (c) Chen, C.-Y.; Chang, F.-R.; Pan, W.-B.; Wu, Y.-C. *Phytochemistry* **2001**, *56*, 753. (d) Zhang, Z.; Li, S.; Zhang, S.; Liang, C.; Gorenstein, D.; Beasley, R. S. *Planta Med.* **2004**, *70*, 1216.

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(3) For a review, see: Glushkov, V. A.; Shklyaev, Y. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 663.

(4) For reviews, see: (a) Varela, J. A.; Saá, C. *Chem Rev.* **2003**, *103*, 3787. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem Rev* **2004**, *104*, 3079. (d) Cacchi, S.; Fabrizi, G. *Chem Rev.* **2005**, *105*, 2873.

(5) (a) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (b) Grigg, R.; Sridharan, V.; Xu, L.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1903. (c) Mahanty, J. S.; De, M.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2577. (d) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (e) Batchu, V. R.; Barange, D. K.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Reddy, E. A.; Pal, M. *Chem Commun.* **2007**, 1966. (f) During the preparation of our manuscript, Matsubara and co-workers reported a nickel-catalyzed decarbonylative alkyne insertion of phthalimides: Kajita, Y.; Matsubara, S.; Kurahashi, T *J. Am. Chem. Soc.* **2008**, *130*, 6058.

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(7) Clark, A. S.; Deans, B.; Stevens, M. F. G.; Tisdale, M. J.; Wheelhouse, R. T.; Denny, B. J.; Hartley, J. A. *J. Med. Chem.* **1995**, *38*, 1493.

(8) For thermolysis of 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones, see: (a) Hey, D. H.; Rees, C. W.; Todd, A. R. *J Chem. Soc. C* **1968**, 1028. (b) Barker, A. J.; Paterson, T. M.; Smalley, R. K.; Suschitzky, H. *J Chem. Soc., Perkin Trans 1.* **1979**, 2203. (c) Cirrincione, G.; Almerico, A. M.; Dattolo, G.; Aiello, E.; Diana, P.; Mingoia, F. *J. Heterocycl. Chem.* **1992**, *29*, 1309.

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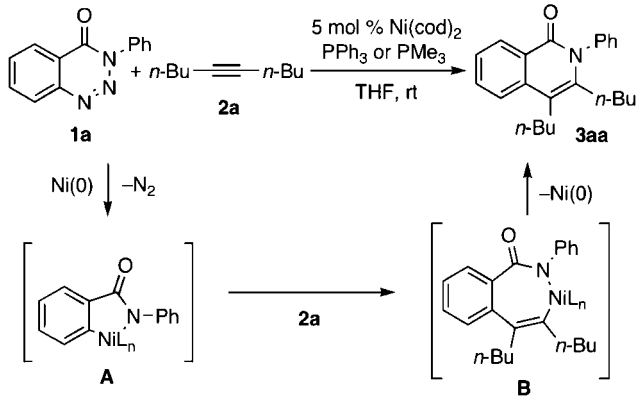
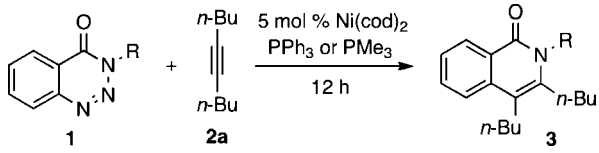
Scheme 1



in situ from $Ni(cod)_2$ (5 mol %, cod = cycloocta-1,5-diene) and PPh_3 (20 mol %) at room temperature in THF. The substrate **1a** was consumed in 10 h, and subsequent chromatographic isolation on silica gel afforded 3,4-dibutyl-2-phenyl-1(2*H*)-isoquinolone (**3aa**) in 91% yield (Scheme 1). Substitution of PMe_3 (10 mol %) for PPh_3 resulted in a faster reaction, which was completed in 3 h affording **3aa** in 93% isolated yield. We assume that the reaction is initiated by insertion of nickel(0) into the N−N linkage of **1a**, which prompts extrusion of a molecular dinitrogen giving azanickelacycle **A**.[5f,9] Subsequent insertion of the alkyne into the nickel−carbon bond leads to the seven-membered-ring nickelacycle **B**.[10] Finally, reductive elimination affords **3aa**, regenerating the nickel(0) catalyst.

The effect of the substituent on the nitrogen of the benzotriazinone was examined (Table 1). Whereas both

Table 1. Ni(0)-Catalyzed Alkyne Insertion: Scope of Substituent on Nitrogen **1**[a]



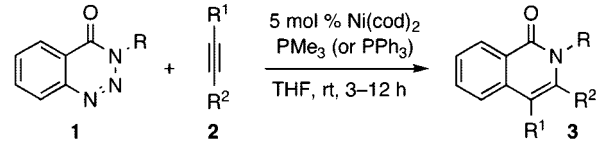
entry	**1** (R)	**3**	T °C)	yield[b] (%)
1	**1b** (4-MeC_6H_4)	**3ba**	rt	98
2	**1c** (4-$MeOC_6H_4$)	**3ca**	rt	95
3	**1d** (4-$CF_3C_6H_4$)	**3da**	rt	99
4	**1e** (Bn)	**3ea**	60	96[c]
5	**1f** (Me)	**3fa**	80	95[d]
6	**1g** (H)	**3ga**	100	0[d]

[a] Conditions: **1** (0.2 mmol), **2** (0.22 mmol), $Ni(cod)_2$ (10 μmol, 5 mol %), and PPh_3 (40 μmol, 20 mol %) in THF (1 mL) for 12 h unless otherwise noted. [b] Isolated yield. [c] PMe_3 (20 μmol, 10 mol %). [d] PMe_3 (20 μmol, 10 mol %) in toluene (1 mL).

electron-donating and -accepting aryl-substituted substrates underwent the denitrogenative insertion reaction in a similar way at room temperature (entries 1−3), the reaction of benzyl- and methyl-substituted benzotriazinones **1e** and **1f** required heating at higher temperatures (entries 4 and 5). On the other hand, simple unprotected benzotriazinone **1g** failed to react with **2a** even at 100 °C (entry 6).[11]

Various internal alkynes **2** were subjected to the denitrogenative insertion reaction with benzotriazinones **1a** and **1b** (Table 2). Symmetrical internal alkynes such as diphenyl-

Table 2. Ni(0)-Catalyzed Insertion of Internal Alkyne **2**[a]



entry	**1**	**2** (R^1, R^2)	**3**	yield (%)[b]
1	**1a**	**2b** (Ph, Ph)	**3ab**	98
2	**1a**	**2c** (CH_2OBn, CH_2OBn)	**3ac**	94
3	**1b**	**2d** (Me, Ph)	**3bd**	99 (86:14)
4	**1b**	**2e** (Me, *p*-$CF_3C_6H_4$)	**3be**	99 (73:27)
5	**1b**	**2f** (Me, *p*-$MeOC_6H_4$)	**3bf**	99 (89:11)
6	**1b**	**2g** (*i*-Pr, Me)	**3bg**	97 (58:42)
7	**1b**	**2h** (*n*-Pr, CO_2Et)	**3bh**	99 (92:8)[c]
8	**1b**	**2i** (*n*-Bu, Bpin)	**3bi**	93 (98:2)[d,e]
9	**1b**	**2j** (TMS, Bpin)	**3bj**	94 (99:1)[e]

[a] Conditions: **1** (0.2 mmol), **2** (0.22 mmol), $Ni(cod)_2$ (10 μmol, 5 mol %), and PMe_3 (20 μmol, 10 mol %) in THF (1 mL) at rt for 3−12 h under N_2 unless otherwise noted. [b] Combined yield of regioisomers unless otherwise noted. Numbers in parentheses describe the regioselectivity. [c] **2** (0.4 mmol) and PPh_3 (40 μmol, 20 mol %) at 60 °C. [d] Isolated yield of the major regioisomer. [e] 60 °C.

ethyne (**2b**) and 1,4-dibenzyloxybut-2-yne (**2c**) reacted with **1a** to give **3ab** and **3ac** in 98 and 94% yields, respectively (entries 1 and 2). With unsymmetrical internal alkynes, the regioselectivity of the insertion reaction was examined wherein 3-tolyl-1,2,3-benzotriazin-4(3*H*)-one (**1b**) was used in order to assign the regiochemistry of the products by NOE experiments.[12] 1-Phenylprop-1-yne (**2d**) reacted smoothly with **1b** to provide **3bd** in 99% yield in a fairly regioselective fashion (86:14, entry 3). In the major product, the phenyl group is bound to C(3) next to nitrogen.[13] The regioselectivity was enhanced by the presence of electron-donating

(9) For precedence of an intermediacy of a similar azanickelacycle, see: (a) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059. (b) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098. (c) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62*, 7552.

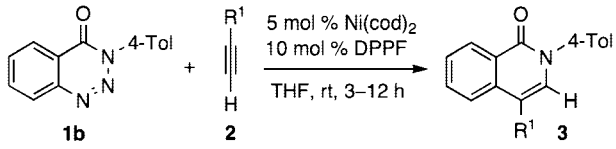
(10) For a previous example of alkyne insertion into a related seven-membered ring nickelacycle intermediate, see: Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179. The authors assumed that a carbon−carbon triple bond can insert into both carbon−nickel and nitrogen−nickel linkages depending on alkynes. The regiochemistry observed in the present reaction using ethyl hex-2-ynoate (**2h**) suggests that a carbon−nickel linkage react with **2h**. In the reaction of other alkynes such as terminal alkynes, however, insertion into a nitrogen−nickel linkage cannot be ruled out.

(11) The benzotriazinone **1g** was recovered.

(12) See the Supporting Information for details.

(13) Although a similar regiochemical preference was explained by assuming stabilization of a partial negative charge on the carbon α to nickel in ref 9b, the effect of the aryl substituent observed with the present reaction is inconsistent with this explanation. Further studies including a theoretical one are necessary for elucidation of the mechanistic and regiochemical issue.

Table 3. Ni(0)-Catalyzed Insertion of Terminal Alkyne **2**[a]

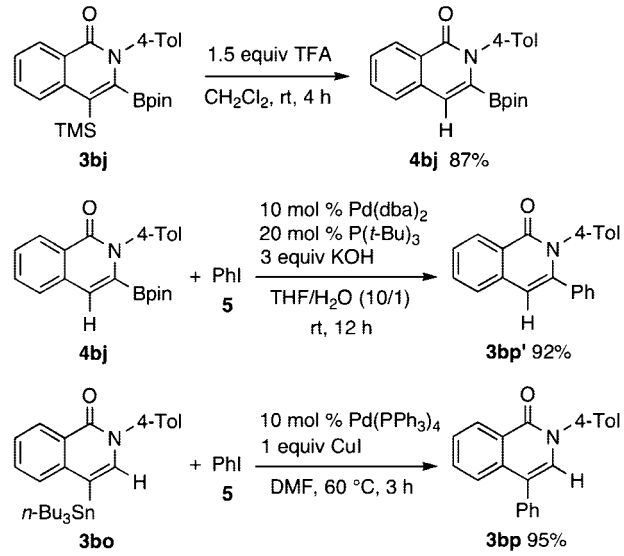


1b **2** **3**

entry	**2** (R^1)	**3**	yield[b] (%)
1	**2k** (*n*-Hex)	**3bk**	98 (73:27)[c]
2	**2k** (*n*-Hex)	**3bk**	99 (98:2)
3	**2l** (*c*-Pent)	**3bl**	98 (99:1)
4	**2m** (*t*-Bu)	**3bm**	99 (>99:1)[e]
5	**2n** (TMS)	**3bn**	94 (99:1)[d,e]
6	**2o** (n-Bu_3Sn)	**3bo**	92 (99:1)[d,f]

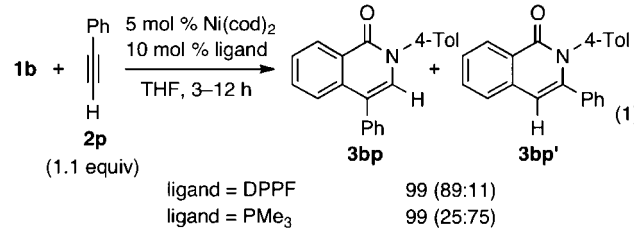
[a] Conditions: **1b** (0.2 mmol), **2** (0.22 mmol), $Ni(cod)_2$ (10 μmol, 5 mol %), and DPPF (20 μmol, 10 mol %) in THF (1 mL) at rt for 3−12 h under N_2 unless otherwise noted. [b] Combined yield of regioisomers unless otherwise noted. Numbers in parentheses describe the regioselectivity. [c] PMe_3 (20 μmol, 10 mol %). [d] Isolated yield of the major regioisomer. [e] 60 °C. [f] $Ni(cod)_2$ (20 μmol, 10 mol %) and DPPF (40 μmol, 20 mol %) at 60 °C. DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

Scheme 2



groups at the para position of the aryl group (entries 4 and 5). In the case of alkynoate **2h**, the regiochemistry of the major isomer was consistent with the electronic demand expected in the carbometalation step (i.e., A → B), although an excess amount of **2h** and the use of PPh_3 were required to get a high yield (entry 7).[14] The high regioselectivity observed with boryl-substituted alkynes[15] can also be understood on similar electronic grounds, which assume stabilization of a partial negative charge on the carbon α to boron by the electron-accepting character of boron (entries 8 and 9).[16]

We then examined the reaction of terminal alkynes with **1b** (Table 3). Although oct-1-yne (**2k**) is capable of undergoing a self-oligomerization reaction, it instead reacted via the insertion reaction giving **3bk** in 98% yield with the Ni(0)/PMe_3 catalyst (entry 1). However, the regioselectivity was modest (73:27). Several phosphine ligands of nickel(0) were tested to improve the selectivity in this case. To our delight, the bidentate phosphine ligand, 1,1′-bis(diphenylphosphino)ferrocene (DPPF), afforded very high regioselectivity (98:2, entry 2).[17,18] This catalyst system proved to be general, catalyzing the insertion reaction of other terminal alkynes **2l**−**2o** with similarly high regioselectivity giving the corresponding products **3bl**−**3bo** in yields ranging from 92% to 99% (entries 3−6). In the case of phenylethyne (**2p**), however, different regioisomers were preferentially obtained depending on the ligand employed, although the selectivity was modest (eq 1).



However, employing the densely functionalized products **3bj** and **3bo**, it was possible to prepare both isomers, **3bp** and **3bp′**, with high regioselectivity (Scheme 2). Starting with compound **3bj**, the silyl group was selectively removed by treatment with trifluoroacetic acid (TFA) at room temperature, giving 3-boryl-1(2*H*)-isoquinolone **4bj** in 87% yield. A subsequent palladium-catalyzed cross-coupling reaction of **4bj** with iodobenzene (**5**) afforded 3-phenyl-1(2*H*)-isoquinolone **3bp′** (92% yield). On the other hand, an analogous cross-coupling reaction performed directly on the stannyl-substituted **3bo** with **5** furnished the other regioisomer, 4-phenyl-1(2*H*)-isoquinolone **3bp** in 95% yield. Thus, **4bj** and **3bo** provide synthetic platforms for the preparation of a wide variety of 3- and 4-substituted 1(2*H*)-isoquinolone.

Finally, we examined the reaction of functionalized triazinones **1h** and **1i** with **2a** (Scheme 3). Methoxy ether and ester functionalities were tolerated on the aryl group of **1**.

In conclusion, we have demonstrated a facile approach for the preparation of substituted 1(2*H*)-isoquinolones. A wide variety of alkyne substrates including borylalkynes were

(14) The major undesired process under the standard conditions using PMe_3 was self-oligomerization of **2h**.

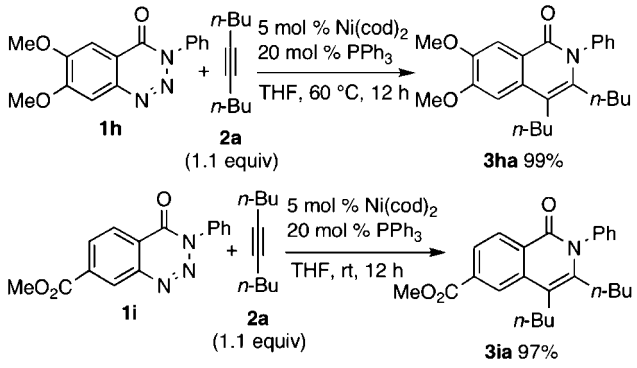
(15) For examples of the regioselective formation of α-boryl-substituted metalacycle intermediates, see: (a) Quntar, A. A. A.; Srebnik, M. *Org. Lett.* **2004**, *6*, 4243. (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 3252. (c) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634. (d) Geny, A.; Lebœuf, D.; Rouquié, G.; Vollhardt, K. P. C.; Malacria, M.; Gandon, V.; Aubert, C. *Chem. Eur. J.* **2007**, *13*, 5408.

(16) For a similar stabilization by a silyl substituent, see: Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870.

(17) Representative results (regioisomers ratio) with other phosphine ligands: PMe_2Ph (75:25), $PMePh_2$ (87:13), P(n-Bu)$_3$ (85:15), DPPPen (92:8), DPEphos (88:12), XANTPHOS (93:7).

(18) The reaction of internal alkynes was retarded when dppf was used in place of PMe_3 as the ligand. For example, the reaction of 1-phenylprop-1-yne using dppf required heating at 80 °C in toluene, giving inferior regioselectivity of 65:35.

Scheme 3



regioselectively incorporated into 1,2,3-benzotriazin-4(3*H*)-ones with loss of a dinitrogen molecule. Further investigation into the reaction mechanism and synthetic applications are underway.

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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.

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