ORGANIC LETTERS

2009
Vol. 11, No. 5
1055−1058

Palladium-Catalyzed Indolization of *N*-Aroylbenzotriazoles with Disubstituted Alkynes

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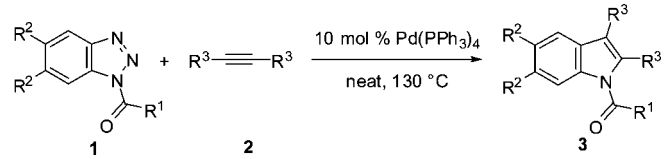
Received November 28, 2008

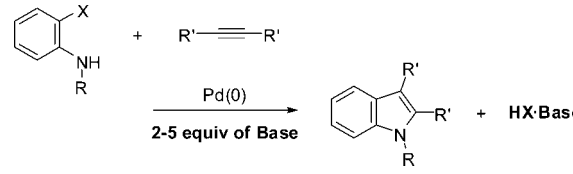
ABSTRACT



The palladium-catalyzed denitrogenative indolization of *N*-aroylbenzotriazoles 1 and internal alkynes 2 produced the corresponding polysubstituted indoles 3 in good to high yields. For example, the reaction of 5,6-dimethyl-1-[4-(trifluoromethyl)benzoyl]benzotriazole (1j) with 6-dodecyne (2a), 4-octyne (2b), and diphenylacetylene (2f) in the presence of 10 mol % of $Pd(PPh_3)_4$ without solvent at 130 °C gave the corresponding indoles 3i, 3l, and 3p in 74, 71, and 41% yields, respectively. In the present reaction, the aroylbenzotriazole acts as a synthetic equivalent of a 2-haloanilide in Larock's indole synthesis.

Indoles have been widely utilized in pharmaceutical and material sciences. Therefore, the efficient construction of indole derivatives in organic synthesis is of great importance.[1] One of the most powerful synthetic methods to make these compounds is the palladium-catalyzed cyclization of 2-haloanilines with alkynes. This is generally recognized as Larock's indole synthesis[2] and has been widely utilized for the synthesis of indole-containing biologically active compounds (Scheme 1).[3] This method, however, still suffers from

Scheme 1. Larock's Indole Synthesis



the viewpoint of atom efficiency. That is, the formation of stoichiometric amounts of halogenoic acid derived from 2-haloanilines as byproducts is unavoidable, and therefore, an excess (2−5 equiv) of base has to be used in order to capture the halogenoic acid. We envisioned the use of *N*-acylbenzotriazoles to replace 2-haloanilides in palladium-catalyzed reactions by combining two concepts, that is, thermal isomerization of the benzotriazole to the corresponding 2-iminobenzenediazonium species **A**[4,5] and oxidative

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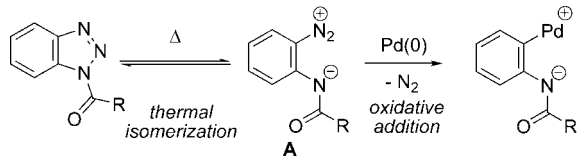
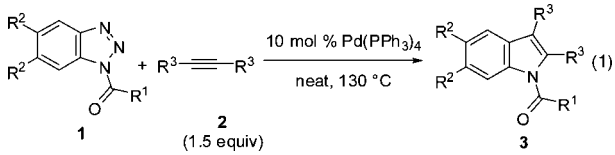
10.1021/ol900113f CCC: $40.75
Published on Web 02/09/2009

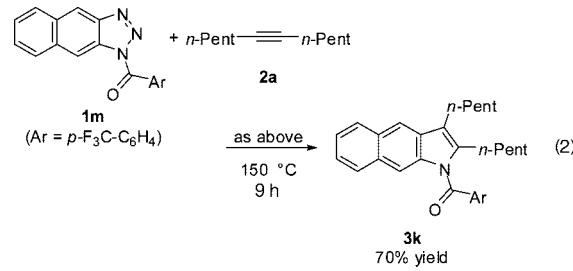
addition of the $Ar-N_2^+$ bond of **A** to palladium(0), which is an initial step of palladium-catalyzed cross-coupling reaction of diazonium salts (Scheme 2).[6] Herein, we report the palladium-catalyzed denitrogenative indolization of *N*-aroylbenzotriazoles **1** with disubstituted alkynes **2** to produce the corresponding indoles **3** in good to moderate yields with high atom efficiencies (eq 1).[7]

Scheme 2. *N*-Acylbenzotriazoles as Synthetic Equivalents for 2-Haloanilides



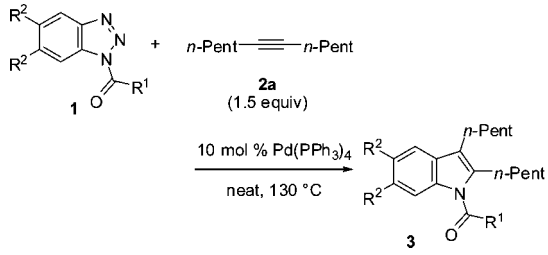


The results of the palladium-catalyzed reactions of benzotriazoles **1** with 6-dodecyne **2a** are summarized in Table 1. The reaction of 1-[4-(trifluoromethyl)benzoyl]benzotriazole (**1b**) with 1.5 equiv of **2a** in the presence of 10 mol % of $Pd(PPh_3)_4$ without solvent at 130 °C for 8 h gave 2,3-dipentyl-1-[4-(trifluoromethyl)benzoyl]indole **3b** in 69% yield (entry 2).[8] When acetonitrile was used as the solvent, the yield decreased to 54%. Other palladium catalyst systems, such as $Pd_2(dba)_3 \cdot CHCl_3-PPh_3$ and $Pd(OAc)_2-PPh_3$, were not effective, and the reaction in the absence of palladium catalysts did not proceed at all (see the Supporting Information). The reaction at 100 °C afforded **3b** in 10% yield along with 84% of recovered **1b**. The reaction using 1 equiv of **2a** gave **3b** in 42% yield. The electronic character of the arylcarbonyl group on the nitrogen atom of the benzotriazole significantly influenced the reaction. The yield of **3** increased with the order of the electron-withdrawing ability of the arylcarbonyl group. However, the reaction of **1a** with **2a** gave **3a** in a lower yield due to fast decomposition of **1a** under the reaction conditions (entries 1−6). In contrast, the reaction of **1g** bearing an electron-donating methoxy group proceeded slowly, affording **3g** in a moderate yield (entry 7). The reaction of benzotriazoles having an acetyl group on the nitrogen atom did not afford the desired product (entry 8). The benzotriazole **1i** bearing an ethoxycarbonyl group was quickly converted to *N*-ethylbenzotriazole under the reaction conditions (entry 9).[9] The reaction of **1j** having slightly electron-donating methyl groups at the 5 and 6 positions of the benzotriazole skeleton gave **3i** in good yield (entry 10), while that of **1k** bearing strongly electron-donating methoxy groups afforded **3j** in a moderate yield along with a mixture of unidentified products (entry 11). The reaction of **1l**, which has electron-withdrawing cyano groups at R^2, did not afford the desired product at all; decomposition of **1l** was observed (entry 12). The reaction of *N*-unsubstituted benzotrizole with **2a** did not proceed at all. The reaction of the naphthotriazole **1m** with **2a** at 150 °C gave the 1*H*-benzo[*f*]indole derivative **3k** in a good yield (eq 2).



Various alkynes were treated and results are summarized in Table 2. The reaction of **2b**, which has normal alkyl groups

Table 1. Palladium-Catalyzed Denitrogenative Indolization of 1-Acylbenzotriazoles **1** and 6-Dodecyne **2a**[a]



entry	**1**	R^1	R^2	time/h	**3**	yield[b]/%
1	**1a**	3,5-$(F_3C)_2$-C_6H_3	H	12	**3a**	39
2	**1b**	4-F_3C-C_6H_4	H	8	**3b**	69
3	**1c**	3,5-F_2-C_6H_3	H	24	**3c**	66
4	**1d**	4-Ac-C_6H_4	H	18	**3d**	64
5	**1e**	3-F-C_6H_4	H	8	**3e**	54
6	**1f**	Ph	H	18	**3f**	42
7	**1g**	4-MeO-C_6H_4	H	72	**3g**	47
8	**1h**	Me	H	72		nr
9	**1i**	OEt	H	9	**3h**	trace
10	**1j**	4-F_3C-C_6H_4	Me	8	**3i**	74
11	**1k**	4-F_3C-C_6H_4	OMe	11	**3j**	41
12	**1l**	4-F_3C-C_6H_4	CN	41		-[c]

[a] The reaction of **1** (0.25 mmol) and **2a** (0.375 mmol) was carried out in the presence of 10 mol % of $Pd(PPh_3)_4$ without solvent at 130 °C. [b] Isolated yield. [c] Decomposition of **1l** was observed.

(4) For a review of benzotriazoles, see: (a) Katritzky, A. R.; Kirichenko, K. *ARKIVOC* **2006**, (iv), 119. (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656. (c) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

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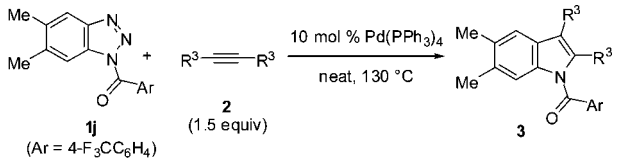
(6) For a review, see: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. Recent reports: (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Persiani, D. *Org. Lett.* **2008**, *10*, 1597. (c) Masllorens, J.; González, I.; Roglans, A. *Eur. J. Org. Chem.* **2007**, 158. (d) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.

(7) For the concept of using a "triazole" moiety in the coupling reaction for the synthesis of heterocycles, see: (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (c) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, in press.

(8) The present reaction proceeded smoothly at larger scale. For example, the reaction of 2 mmol of **1b** and 3 mmol of **2a** gave **3b** in 69% isolated yield.

Table 2. Palladium-Catalyzed Denitrogenative Indolization of **1j** and Alkynes **2**[a]



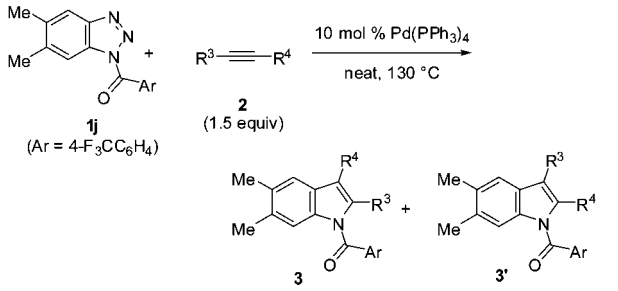
entry	**2**	R^3	**3**	yield[b]/%
1	**2b**	*n*-Pr	**3l**	71
2	**2c**	$(CH_2)_3OAc$	**3m**	64
3	**2d**	$(CH_2)_3OMOM$	**3n**	67
4	**2e**	$(CH_2)_3OTBS$	**3o**	51
5[c]	**2f**	Ph	**3p**	41

[a] The reaction of **1j** (0.25 mmol) and **2** (0.375 mmol) was carried out in the presence of 10 mol % of $Pd(PPh_3)_4$ without solvent at 130 °C for 8−9 h. All reactions were conducted in a pressure vial. [b] Isolated yield. [c] For 41 h.

at the alkynyl moiety, with **1j** proceeded smoothly (entry 1). Several protective groups of the hydroxy groups, such as acetyl, methoxymethyl (MOM), and *tert*-butyldimethylsilyl (TBS) groups, were tolerated under the reaction conditions (entries 2−4). Diphenylacetylene **2f** reacted with **1j**, affording **3p** in a moderate yield (entry 5).

In the reaction of the asymmetric alkynes **2g**−**k**, **3q**−**u**, in which a bulkier substituent (R^3) was located at the 2 position of the indole ring, were obtained as major products, respectively (Table 3). The alkyne **2g** having a

Table 3. Palladium-Catalyzed Denitrogenative Indolization of **1j** and Unsymmetrical Alkynes **2g**−**l**[a]



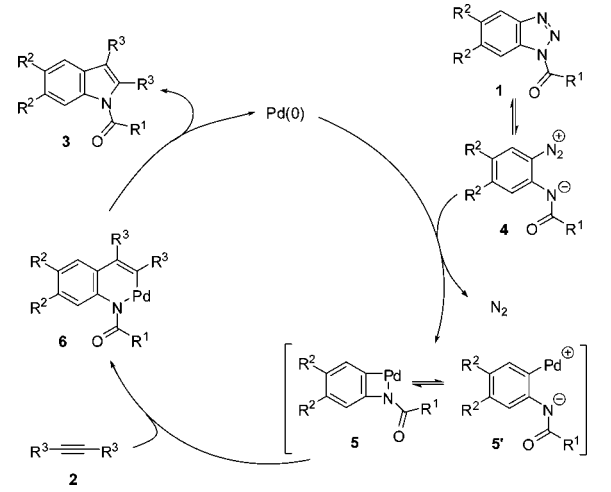
entry	**2**	R^3	R^4	**3**	yield[b]/%	**3**:**3′**[c]
1	**2g**	Cy	Me	**3q, 3q′**	65	55:45
2[d]	**2h**	*t*-Bu	Me	**3r, 3r′**	22[e]	78:22
3	**2i**	Ph	*n*-Bu	**3s, 3s′**	72	74:26
4	**2j**	*p*-MeO-C_6H_4	*n*-Bu	**3t, 3t′**	66	52:48
5	**2k**	*p*-F_3C-C_6H_4	*n*-Bu	**3u, 3u′**	59	82:18
6	**2l**	Ph	H	**3v**	trace	

[a] The reaction of **1j** (0.25 mmol) and **2** (0.375 mmol) was carried out in the presence of 10 mol % of $Pd(PPh_3)_4$ without solvent at 130 °C for 8−9 h. All reactions were conducted in a pressure vial. [b] Isolated yield. [c] The ratio was determined by ^1H NMR spectroscopy. [d] For 3 days. [e] 20% of **2h** was recovered.

cyclohexyl group at R^3 reacted with **1j** smoothly, whereas a bulky *tert*-butyl group interfered with the cycloaddition (entries 1 and 2). The reaction of **2k**, which had an electron-deficient aromatic ring at the alkynyl terminus, with **1j** led to better regioselectivity than that of **2j** having electron-rich anisyl group at R^3 (entries 4 and 5). The reaction of **1j** with phenylacetylene gave a trace amount of the desired product; phenylacetylene was quickly decomposed under the reaction conditions (entry 6). Further improvement of the regioselectivity is currently ongoing in our laboratory.

A plausible mechanism of the present reaction is illustrated in Scheme 3. Palladium(0) oxidatively inserts

Scheme 3. Plausible Mechanism



into a C−N bond of the diazonium moiety of the 2-iminobenzenediazonium species **4**, which is thermally generated from benzotriazole **1**.[4,10] Insertion of the internal alkyne **2** into the C−Pd bond of the resulting intermediate **5** or **5′** leads to the palladacycle species **6**. Reductive elimination of palladium(0) from **6** gives the product **3**. Higher reaction temperature is required for ring opening of the triazole ring.[4,5] Both the electron-withdrawing group on the nitrogen atom and the slightly electron-donating methyl groups at R^2 play a role in stabilizing the 2-iminobenzenediazonium species **4** (see the Supporting Information). Perhaps displacement of the thermodynamic equilibrium to the intermediate **4** accelerates the desired reaction pathway relative to decomposition of **1** under the reaction conditions.[11] Presumably, alkyne insertion takes place so as to generate steric strain in the vicinity of the shorter C−C bond rather than the longer C−Pd bond, similar to Larock's indole synthesis.[2b,12] Further mechanistic studies are currently underway in our laboratory.

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(11) When the benzotriazole **1f** was heated with 1 equiv of $Pd(PPh_3)_4$ in CH_3CN for 18 h, **1f** decomposed.

(12) Shen, M.; Li, G.; Lu, B. Z.; Hossian, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129.

In conclusion, we are now in the position to construct polysubstituted indole derivatives by the palladium-catalyzed denitrogenative [3 + 2] cycloaddition of benzotriazoles and internal alkynes under neutral conditions. The present results suggest that benzotriazoles can be synthetic equivalents of 2-haloanilides in palladium-catalyzed reactions. Since this reaction is free from the use of bases and the formation of byproducts except for nitrogen gas, the present methodology synthesizes polysubstituted indoles in an efficient and atom-economic manner.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research from Japan Society for Promotion in Science (JSPS).

Supporting Information Available: Experimental procedures and characterization of the benzotriazoles **1** and the products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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