ORGANIC LETTERS

2010
Vol. 12, No. 10
2334−2337

Metal-Free Coupling of Azoles with 2- and 3-Haloindoles Providing Access to Novel 2- or 3-(Azol-1-yl)indole Derivatives

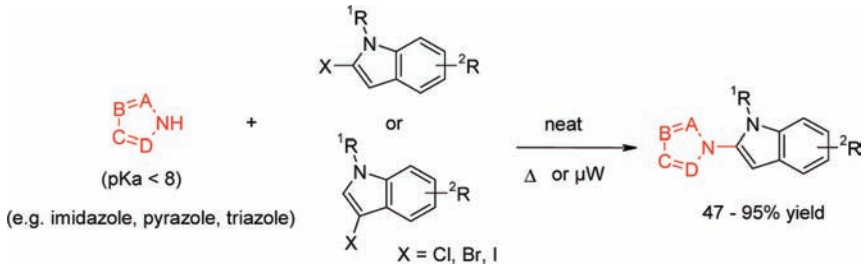
Martin Poirier,* Sébastien Goudreau, Jason Poulin, Jolaine Savoie, and Pierre L. Beaulieu*

Chemistry Department, Boehringer Ingelheim (Canada) Ltd., Research and Development, 2100 Cunard Street, Laval, Québec, Canada H7S 2G5

pierre.beaulieu@boehringer-ingelheim.com; martin.poirier@boehringer-ingelheim.com

Received March 23, 2010

ABSTRACT



Thermal or microwave-mediated heating of 2- or 3-haloindoles with azoles (pK_a < 8) provides a straightforward, metal-free, and environmentally friendly access to novel 2-(azol-1-yl)indoles. Furthermore, previously unknown 2,3-bis(azolyl-1-yl)indoles can be prepared from 2,3-dihaloindoles by sequential reaction with two distinct azoles. This operationally simple acid-catalyzed process delivers novel indole derivatives in fair to excellent yields and expands the chemical diversity of substitutions that can be introduced on this medicinally important scaffold.

The indole core, present in numerous biologically active natural products and marketed drugs, stands as a privileged structure in pharmaceutical research.[1,2] In an effort to expand the diversity of substitutions that can be positioned on this scaffold, we became interested in accessing indole derivatives substituted at the 2-position with various *N*-linked aromatic heterocycles (**A**, Figure 1). Such derivatives, in addition to incorporating structural elements that expand the potential for interaction with biological receptors, also provide an opportunity for manipulating the electronic characteristics of the indole scaffold itself. Surprisingly, 2-(azol-1-yl)indoles are not generally represented in the chemical literature. Exceptions include isogranulatimide, a G2 checkpoint inhibitor,[3] antifungal azole derivatives,[4] and the recently described celogentins and moroidin family of natural antimitotics (Figure 1), which are potent inhibitors of tubulin polymerization.[5] The latter all contain a 2-(imidazol-1-yl)indole moiety imbedded within their structures. A 2-(pyrazol-1-yl)indole melatonin derivative with cardiopro-

(1) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. S. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473.

(2) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F., Bird, C. W., Eds.; Pergamon: Oxford, 1996; Vol. 2, p119. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F., Bird, C. W., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 207.

(3) (a) Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850. (b) Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530.

(4) Benkli, K.; Demirayak, S.; Gundogdu-Karaburun, N.; Kiraz, N.; Iscan, G.; Ucucu, U. *Indian J. Chem.* **2004**, *43B*, 174.

(5) (a) Morita, H.; Shimbo, K.; Shigemori, H.; Kobayashi, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 469. (b) Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626. (c) Suzuki, H.; Morita, H.; Iwasaki, S.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 5307. (d) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 2489.

10.1021/ol100685p
Published on Web 04/19/2010

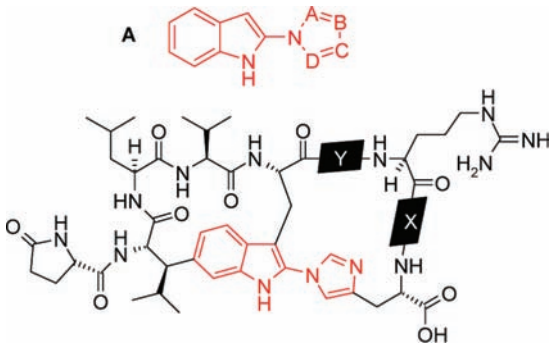


Figure 1. Structure of celogentin C (X = bond, Y = Pro) and moroidin (X = Gly, Y = bond).

tective activity was also recently described.[6] The synthesis of 2-(azol-1-yl)indoles has so far been limited to the nucleophilic displacement on 2-chloroindole derivatives activated at C-3 with an electron-withdrawing group.[4,7] Although a route to a 2-(imidazole-1-yl)indole derivative via oxidative coupling and the first total syntheses of celogentin C have recently been published,[8] a general and direct access to 2-(azol-1-yl)indoles from unactivated indoles and azoles has not been reported.

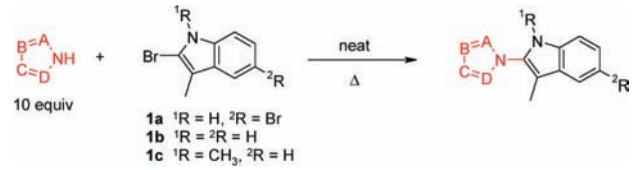
On the basis of precedent for coupling azoles with aryl halides,[9] we attempted a copper-catalyzed cross-coupling of 2-bromo-3-methylindole (**1b**) with imidazole and obtained the dehalogenated indole as sole product. Palladium-catalyzed amination of 2- and 3-bromoindoles with secondary anilines is also known in the literature,[10] but application to azoles also failed to provide the desired product.

In our attempts to promote the desired reaction, we found that simple heating of neat 2,5-dibromo-3-methylindole (**1a**) with 10 equiv of pyrazole at 120 °C for 6 h provided the desired N−C coupled 2-(azol-1-yl)indole exclusively in 78% yield (Table 1, entry 1). Substitution occurred specifically at the 2-position of the indole and the 5-bromo substituent remained unaffected.

A preliminary evaluation of the scope of this new methodology (Table 1) revealed that this reaction also proceeded with other azoles (e.g., triazole and imidazole), providing access to various 2-(azol-1-yl)indoles in moderate to excellent yields (entries 2−4). More basic aliphatic amines (entries 5 and 6) did not react, suggesting that the reaction did not proceed via a direct nucleophilic aromatic substitution mechanism. Indeed, an inverse correlation was established between reaction rates and the aqueous pK_a of the azole conjugate acid, or increasing basicity of the nucleophile (Table 1).[11] 2-Bromo-3-methylindole **1b** led to comparable yields of the desired indole derivatives (entries 7−10). The more hindered 2-bromo-1,3-dimethylindole **1c** required longer reaction times and/or higher temperatures to reach acceptable yields (entries 11−13), and no product was observed in the sterically demanding case of 2-methylimidazole (entry 14).

Reactions were usually performed using excess azole under solvent-free conditions. Attempts to use solvents such as DMF or DMSO led to drastic reductions in yield or to decomposition. Sulfolane, however, was found to be a suitable solvent for this reaction, providing the product in 90% yield after 9 h using only 2 equiv of azole substrate (Figure 2).

Table 1. Reaction of Azoles and Amines with 2-Bromoindoles



entry	azole	pK_a[a] (H^+)	R^1	R^2	time[b] (h)	yield[c] (%)
1	pyrazole	2.5	H	Br	6	78
2	1,2,3-triazole[d]	1.2	H	Br	6	95
3	imidazole	7	H	Br	23	77
4	2-methylimidazole	7.6	H	Br	72	52
5	pyrrolidine	11.3	H	Br	72	0
6	benzylamine	9.3	H	Br	72	0
7	pyrazole	2.5	H	H	2	80
8	1,2,3-triazole[d]	1.2	H	H	1	78
9	imidazole	7	H	H	32	73
10	2-methylimidazole	7.6	H	H	68	47
11	pyrazole	2.5	Me	H	2	92
12	1,2,3-triazole[d]	1.2	Me	H	1	63
13	imidazole	7	Me	H	42	65
14	2-methylimidazole	7.6	Me	H	68	0

[a] Aqueous pK_a values.[11] [b] Reaction conditions: entries 1 and 7 heat at 120 °C, 2 and 8 heat at 100 °C, 3−6 and 9−14 heat at 150 °C. [c] Yield of isolated product. [d] 5 equiv, only 1-triazolyl isomer observed as product.

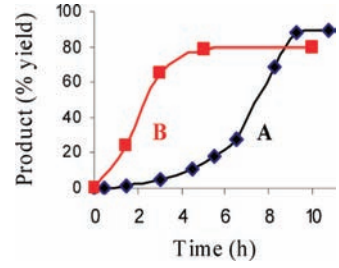


Figure 2. Indole **1a** (1 equiv) and pyrazole (2 equiv) in sulfolane, 0.5 M: (A) without TFA; (B) with 0.25 equiv of TFA.

(6) Ahmed, H. H.; Mannaa, F.; Elmegeed, G. A.; Doss, S. H. *Bioorg. Med. Chem.* **2005**, *13*, 1847.

(7) (a) Comber, M. F.; Moody, C. J. *Synthesis* **1992**, 731. (b) Harrison, J. R.; Moody, J. *Tetrahedron Lett.* **2003**, *44*, 5189.

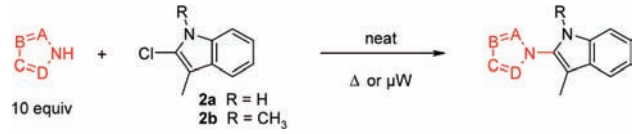
(8) (a) He, L.; Yang, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1165. (b) Ma, B.; Litvinov, D. N.; He, L.; Banerjee, B.; Castle, S. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 6104. (c) Ma, B.; Banerjee, B.; Litvinov, D. N.; He, L.; Castle, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1159. (d) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (e) Hu, W.; Zhang, F.; Xu, Z.; Liu, Q.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 956.

(9) (a) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190, and references therein. (b) Zhu, L.; Li, G.; Luo, L.; Guo, P.; Lan, J.; You, J. *J. Org. Chem.* **2009**, *74*, 2200.

(10) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

(11) (a) Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc.* **1958**, *80*, 148. (b) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441.

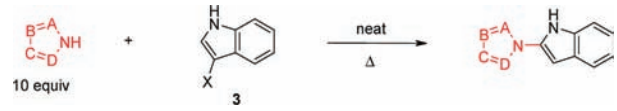
Table 2. Reaction of Azoles with 2-Chloroindoles



entry	azole	R	t (°C)	time	yield[a] (%)
1	1,2,3-triazole[b]	H	80	1.5 h	84
2	1,2,3-triazole[b]	Me	80	2 h	83
3	1,2,3-triazole[b]	Me	120	5 min	84[c]
4	pyrazole	H	100	4 h	63
5	pyrazole	Me	80	70 h	47
6	pyrazole	Me	140	15 min	2[d]
7	pyrazole	Me	140	15 min	80[c]
8	imidazole	H	120	65 h	59
9	imidazole	Me	150	9 days	51
10	imidazole	Me	180	40 min	71[c]
11	2-methylimidazole	H	140	105 h	59
12	2-methylimidazole	Me	150	4 days	0
13	2-methylimidazole	Me	210	225 min	68[c]

[a] Yield of isolated product. [b] 5 equiv of triazole, only the 1-triazolyl-isomer observed. [c] Microwave used as heating source, in sulfolane (2 M). [d] Percent conversion by HPLC.

Table 3. Reaction of Azoles with 3-Haloindoles



entry	azole	X	t (°C)	time (h)	yield[a] (%)
1	1,2,3-triazole[b]	Br	70	2	23/60[c]
2	1,2,3-triazole[b]	I	70	3	23/27[c]
3	1,2,3-triazole[b]	Cl	80	1.5	48/33[c]
4	pyrazole	Br	70	4	88
5	pyrazole	I	70	1	69
6	pyrazole	Cl	150	3	74
7	imidazole	Br	90	24	dec
8	imidazole	I	90	2.5	50
9	imidazole	Cl	115	25	84
10	2-methylimidazole	Br	140	24	dec
11	2-methylimidazole	I	140	1.5	49
12	2-methylimidazole	Cl	150	27	76

[a] Yield of isolated product. [b] 5 equiv of triazole. [c] Yield of triazol-1-yl and triazole-2-yl isomers, respectively.

Reaction kinetics suggested that conversion is autocatalyzed, most likely by HBr formed during the course of the reaction. To test this hypothesis, using sulfolane as solvent, TFA (0.25 equiv) was added to the reaction, and an accelerated conversion of starting material to product was observed (Figure 2, trace B). The slight reduction in yield in this case (80%) we believe is the result of decomposition of the bromindole substrate under strongly acidic reaction conditions. In general, however, reactions performed under neat conditions were preferred over the use of sulfolane as solvent (with/without added TFA) and provided the broadest scope of substrate, yields, and reaction times.

A similar study was undertaken to assess the potential of 2-chloroindoles[12] as substrates in this reaction since in some cases they are easier to prepare and are more stable than the corresponding 2-bromoindoles (Table 2). Gratifyingly, 2-chloroindoles (**2**) also led to the desired 2-(azol-1-yl)indoles, but longer reaction times were necessary in some instances to achieve comparable yields as the corresponding bromoindoles (entries 1, 4, 8, 11). As before, steric hindrance resulted in lower reaction rates for 2-chloro-1,3-dimethylindole **2b** (entries 2, 5, 9), and no product was obtained with 2-methylimidazole (entry 12).

Microwave irradiation often provides a beneficial alternative to reactions performed under harsh thermal conditions with sensitive substrates. Increased reaction temperature and shorter reaction times can minimize decomposition and lead to improved yields. The coupling of 2-chloroindoles with azoles was performed under microwave irradiation. The desired 2-(azol-1-yl)indoles were obtained in similar or better yields than under thermal conditions, and reaction times were drastically reduced (Table 2, entries 3, 7, 10, 13). Entries 6 and 7 illustrate the effect of microwave irradiation on the outcome of the reaction when performed under comparable medium temperature (140 °C) and reaction times (15 min). Local heating phenomena ("hot spots") may account for the observed dramatic increase in yield from 2% to 80%.[13]

Furthermore, the previously unsuccessful coupling of the sterically demanding 2-bromo or 2-chloroindoles **1c** and **2b** with 2-methylimidazole proceeded in 68% isolated yield under microwave irradiation in the case of **2b**, extending the scope of the reaction to more hindered substrates (Table 2, entry 13).

To further increase the scope of this new metal-free coupling methodology, we attempted the substitution reaction on readily available and stable 3-haloindoles **3**.[7] To our surprise, 2-(azol-1-yl)indoles were once again obtained as sole product (Table 3). Because 3-haloindoles are generally easier to prepare and more stable than C-3 unsubstituted 2-haloindoles, this method provides convenient access to C-3 unsubstituted 2-(azol-1-yl)indoles. As shown in Table 3, 3-bromoindole readily reacted at 70−80 °C with 1,2,3-triazole and pyrazole to give the desired coupled heterocycles in good yield (entries 1 and 4). In the case of triazole, a separable mixture of 2-(1- and 2-triazolyl)indole isomers was obtained. This is to be contrasted with the more sterically hindered 3-substituted-2-haloindoles, which had delivered the unsymmetrical 1-triazolyl isomer exclusively (Tables 1 and 2).

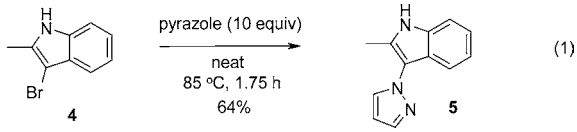
3-Bromoindole was unstable under the conditions required for reaction with imidazoles (Table 3, entries 7 and 10). The lower chemical stability of 3-bromindoles was circumvented by the use of the more reactive 3-iodoindole (Table 3, entries

(12) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495.

(13) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.

2, 5, 8, 11), which allowed access to the desired 2-(azol-1-yl)indoles, including imidazole derivatives, albeit in moderate yields.

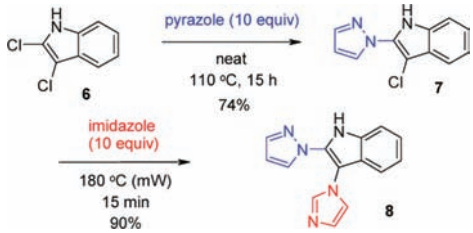
Although somewhat less reactive and requiring longer reaction times, the more stable 3-chloroindole (entries 3, 6, 9, 12) was the substrate of choice for this transformation, providing uniformly good yields of products for all azoles investigated in this study. Interestingly, 3-haloindoles in which the 2-position is blocked by substitution react with azoles in the expected manor to provide 3-(azol-1-yl) derivatives. For example, 3-bromo-2-methylindole **4** gave 2-methyl-3-(pyrazole-1-yl)indole **5** in 64% yield (eq 1).



(1)

Finally, sequential and selective displacement of the two chlorine atoms of 2,3-dichloroindole **6** was achieved, to afford novel, highly functionalized 2,3-di(azol-1-yl)indole derivatives such as **8** as illustrated in Scheme 1.

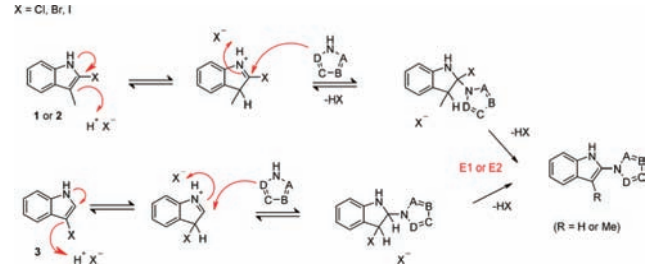
Scheme 1. Sequential Substitution of 2,3-Dichloroindole



In this case, thermal conditions led to initial substitution at C-2 exclusively, to provide intermediate **7** in 74% yield, which reacted further with imidazole under microwave irradiation to provide highly functionalized indole **8** in 90% yield. This latter sequence illustrates the versatility and potential of this methodology for constructing unprecedented and highly functionalized indole derivatives.

A mechanism for the transformation is proposed (Scheme 2) that is consistent with the observed inverse correlation between the pK_a of the nitrogen nucleophile and reactivities (Table 1).[11] In the absence of added TFA, a trace of HBr

Scheme 2. Proposed Mechanisms



from decomposition of starting material likely initiates the reaction. Consistent with this hypothesis, we observed some variability in initiation time between runs. Protonation of the indole nitrogen generates a reactive iminium intermediate that can be trapped by nucleophilic azoles. Subsequent E1 or E2 elimination of HX provides the observed products. Basic amines with pK_a > 8−9 (e.g., pyrrolidine) prevent protonation of the indole system and do not engage in this reaction. A similar acid-catalyzed mechanism can be invoked in the case of 3-haloindoles.

In summary, we have developed a metal-free amination of 2- and 3-haloindoles that provides general access to novel *N*-linked 2- or 3-(azol-1-yl)indoles via an acid-catalyzed process. It is operationally simple and is performed under environmentally friendly metal- and solvent-free conditions. Straightforward access to such novel derivatives should find broad application in medicinal chemistry since the indole core is a privileged structure in drug discovery. Extension of this methodology to more functionalized indole substrates and other nitrogen nucleophiles is currently under investigation and will be reported in due course.

Acknowledgment. From Boehringer Ingelheim (Canada) Ltd., we thank Dr. Angelo Filosa, Sylvain Bordeleau, Colette Boucher, and Michael Little for analytical support and Dr. Nathalie Goudreau and Norman Aubry for NMR structure confirmations.

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

OL100685P