Indole Chemistry

FeCl₃-Mediated Friedel–Crafts Hydroarylation with Electrophilic *N*-Acetyl Indoles for the Synthesis of Benzofuroindolines**

Rodolphe Beaud, Régis Guillot, Cyrille Kouklovsky, and Guillaume Vincent*

The benzofuroindoline core is a unique motif found in the natural products diazonamide A (1),^[1a,b] bipleiophylline,^[1c] and azonazine (**2**, Scheme 1).^[1d] From a biosynthetic point of view, we can assume that the benzofuroindoline skeleton **3** arises from the oxidative coupling of an indole **4** and a phenol **5** (Scheme 1).



Scheme 1. Benzofuroindoline-containing natural products.

The benzofuroindoline motif represents an opportunity for the discovery of new antitumor agents. In fact, diazonamide A is a very potent anticancer agent that has received considerable attention owing to its high antitumor activity ($IC_{50} < 5 \text{ nM}$) and its unique mode of action:^[2] the inhibition of a newly discovered role for the ornithine- δ -aminotransferase (OAT).^[2a] It is suggested that this natural product may have clinical utility for cancer therapy because it is as active in vitro as widely used antimitotic drugs such as taxanes and vinca alkaloids, but does not have their toxicity in normal dividing tissue, as has been demonstrated on mice.^[2b] Owing to the high potential of diazonamide A and its scarce availability, it is highly desirable to identify simplified

[*]	R. Beaud, Dr. R. Guillot, Prof.Dr. C. Kouklovsky, Dr. G. Vincent Université Paris-Sud and CNRS
	Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO)
	UMR 8182, Laboratoire de Chimie des Procédés et Substances
	Naturelles, Bat. 410, 91405 Orsay (France)
	E-mail: guillaume.vincent@u-psud.fr
	Homepage: http://www.icmmo.u-psud.fr/Labos/LPSN/cv/guillau-
	me_eng.php?ID=381
[**]	We thank the CNRS and the Université Paris-Sud (Fellowship to
	R.B.) for financial support, and Didier Gori for HPLC analysis.
	Supporting information for this article is available on the WWW

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206611.

benzofuroindoline analogues as promising as the natural product, but more synthetically accessible.

The attraction of the high antitumor activity of diazonamide A has launched impressive synthetic efforts worldwide towards the benzofuroindoline skeleton, which had been scarcely explored before.^[3–5] Most of the methods developed are neither straightforward nor general, and do not take advantage of the biogenetically inspired direct oxidative coupling between an indole and a phenol. Harran met this objective with a modest yield during his total synthesis of diazonamide A by the hypervalent-iodine(III)-mediated intramolecular coupling between tryptophan and tyrosine residues, presumably through the formation of a phenoxenium ion.^[4] The intermolecular version is little known and only with low yields.^[5] It is also highly substrate dependant, as the corresponding coupling between skatole **4a** and *p*-cresol **5a** unfortunately failed in our hands (Scheme 2).



Scheme 2. Towards benzofuroindolines from indoles and phenols. Ac = acetyl.

Our goal was therefore to develop an oxidative intermolecular process to couple indoles and phenols in order to easily access a wide range of benzofuroindolines. We decided to explore a two-step sequence wherein the two partners would be assembled through the regioselective C3-hydroarylation of a 3-substituted indole (4) by a phenol (5) to generate a 3,3-disubstituted indoline (6).^[6] Oxidation of 6 should then yield the desired benzofuroindoline (3) (Scheme 2).

The hydroarylation of activated alkenes via C–H functionalization of arylating reagents is a well-known process,^[7] however the reaction at the more electron rich C2=C3 bonds of indoles appears far more challenging, as indoles are well known to behave as nucleophiles at C3.^[8] The umpolung of the indole^[9–11] at C3 would therefore require fine tuning of this core by carefully selecting the substituent of the nitrogen.

Interestingly, Nakatsuka et al. have reported the hydroarylation of N-acyl-3-alkyl indoles at C3 with aryl speciesin the presence of a very large excess of $AlCl_3$.^[12] Based on this finding, we explored the coupling between *N*-acetyl skatole **7a** and *p*-cresol **5a**. Disappointingly, the use of up to six equivalents of $AlCl_3$ did not lead to any of the desired product.

Fortunately, we rapidly discovered that 2.4 equivalents of inexpensive and non-toxic iron(III) chloride^[13] in dichloromethane at room temperature promoted the formation of indoline **6a** in 99% yield from 2 equivalents of **5a** (Scheme 3). A small amount of 3-arylated indoline **8a**,



Scheme 3. Optimization of the 3-Hydroarylation of N-acetyl skatole 7a with *p*-cresol 5a. [a] Yield of isolated product based on 7a; [b] Yield of isolated 9 based on 5a. acac=acetylacetonate, Tf=trifluoromethane-sulfonyl.

which is linked at the *para* position of the phenol core, was isolated. This probably results from an electrophilic *ipso* aromatic substitution.^[14] Polyphenol oxidative homocoupling products (9) of *p*-cresol were also isolated.^[15]

Surprisingly, the screening of various Brønsted or Lewis acids in lieu of $FeCl_3$ did not lead to any coupling reaction. Even more intriguing, other sources of iron(III) or iron (II) leave *N*-acetyl skatole untouched. The reason why $FeCl_3$ is so exclusive in achieving this transformation is unclear at the moment. Coordinating solvents, such as ethyl acetate, methanol, acetone, or THF, were unsuited for this reaction, as they probably sequester the iron promoter; moreover, only 37% of **6a** was obtained in heptane because of the low solubility of the starting materials.

Very pleased to have in hand such delicate and mild conditions to achieve the challenging hydroarylation of the usually nucleophilic C2=C3 double bond of indole by phenol, we turned our attention to the scope of the reaction. We explored the reaction between *N*-acetyl skatole **7a** and different *p*-alkyl phenols (Scheme 4). The expected coupling products **6a**-**e** were isolated with yields of 62–99%. Halogenated phenols also furnished the expected indolines **6f**-**i**.



Scheme 4. Hydroarylation of 3-substituted *N*-acetyl indoles with phenols. [a] **7** (2.2 equiv) and FeCl₃ (2.4 equiv). [b] **7** (3.2 equiv) and FeCl₃ (3.4 equiv). [c] About 15% of indoline resulting from *meta* attack of *p*-OEt phenol was also detected.

More electron rich *p*-OEt phenol allowed the synthesis of **6***i*. Evaluation of 3-benzvl and 3-butvl N-acetvl indoles resulted in 3-arylated indolines 6k-m in 92-51% yields. The more hindered 3-phenyl N-acetyl indole gave 24% of indoline 6n. N-acetyl tetrahydocarbazole, a 2,3-substituted indole, delivered cis hydroarylated indoline 60 as the major diastereomer (d.r.: 6.5:1). Varying the electronics of the indole core resulted in the isolation of bromoindoline 6p and ethyl ester indoline 6q from the more electron-poor indole rings, whereas a electron-donating methoxy group on indole allowed the synthesis of methoxyindoline 6r. Unsubstituted phenol reacted in the para position to generate 8a,^[16] whereas 2,4,6-trimethyl phenol delivered a mixture of the ipso substitution para product 8s and compound 10, which results from meta attack of the phenol followed by an oxidative C-C bond formation (Scheme 4).

To gain insight into the stereochemical course of the hydroarylation, the reaction of *N*-acetyl skatole **7a** with the deuterium-labeled phenol 2,6- D_2 -**5a** was performed. The two deuterated indolines, [D]-**6aa** and [D]-**6ab**, which are epimeric at C2, were isolated in a 1.2:1 ratio, whereas the



experiment between 7a and 5a in the presence of D_2O delivered 7% of a 3.2:1 ratio of [D]-6aa and [D]-6ab (Scheme 5).



Scheme 5. Deuterium-labeling experiments.

From a mechanistic point of view, we may postulate that the formation of an iron-phenol complex^[17] was the first event to occur (Scheme 6). Although the formation of polyphenol products **9** proved that some phenol radicals are



Scheme 6. Mechanistic considerations.

formed by the oxidation of phenols with iron(III), we do not believe that this is the operative species that accounts for the hydroarylation of N-acetyl indoles. If this was the case, we would have expected the addition of the phenols at the C2 position of the indoles.^[6d, 18] Moreover, the hydroarylation of indoles is possible with non-phenol aromatic compounds (Scheme 7), where the formation of radicals is unlikely. Therefore, we believe that a Friedel-Crafts pathway occurs with N-acetyl indoles. Activation of the C2=C3 double bond of the indole core with iron could lead to a benzylic tertiary carbocationic species at C3, with the potential coordination of the iron to the oxygen of the N-acetyl group. Nucleophilic attack by the phenol could happen on the same side as the iron, as in intermediate A1, or on the opposite face, as in B1 (Scheme 6). The deuterated experiments of Scheme 5 showed that both possibilities are operative, but syn hydroarylation seems preponderant, as deuteration of the iron intermediate A2 should lead to [D]-6 aa, whereas deuteration of B2 should deliver [D]-6ab.



Scheme 7. Hydroarylation of substituted indoles with aromatic nucleophiles. [a] ArH (2 equiv) and FeCl₃ (2.4 equiv). [b] ArH (3 equiv) and FeCl₃ (2.4 equiv). [c] ArH (3 equiv) and FeCl₃ (3.4 equiv). [d] ArH (7.2 equiv) and FeCl₃ (7.6 equiv).

We have also evaluated non-phenol aromatic nucleophiles under our conditions (Scheme 7). Electron-rich anisole and *N*-acetyl skatole **7a** delivered **11a** in 99% yield, whereas indoline **12** was obtained in 65% yield from a phenolcontaining *N*-acetyl indole. Toluene and *N*-acetyl skatole **7a** produced **11b** in 51% yield, whereas the less electron rich chlorobenzene did not afford any of the desired coupling product **11c**. Heteroaromatic rings, such as *N*-tosyl indole, thiophene, and furan, also proved to be useful nucleophiles for **7a**, as 3-arylated indolines **13**, **14**, and **15** were obtained in 64%, 52%, and 30% yields, respectively.

Our next task required the transformation of 3,3 disubstituted indolines **6** into the targeted benzofuroindolines **3** (Scheme 8). Therefore, we removed the *N*-acetyl substituent of **6a** by acidic hydrolysis, followed by oxidation of the crude N-H indolines with tetrapropylammonium perruthenate (TPAP) and *N*-methyl morpholine-*N*-oxide (NMO),^[19] and we were pleased to isolate 56% of benzofuroindoline **3a**. Diisopropyl azodicarboxylate (DIAD) was also an effective oxidant for this transformation, as 63% of **3a** was obtained.^[20,21] The previously obtained indolines **6a-r** were converted into benzofuroindolines **3a-r** using either TPAP/ NMO or DIAD in yields of 50–86%.^[16,22]

We also desired to access the 3-arylchromenoindoline^[23] framework (Scheme 8), therefore indoline **12** was successively hydrolyzed and treated with a catalytic amount of TPAP and 2.8 equivalents of NMO to deliver aryl chromenoindole **16**.^[16] The use of 1.2 equivalents of DIAD, to prevent overoxidation, allowed the formation and isolation of the expected chromenoindoline **17**.^[24]

To access enantioenriched benzofuroindolines, *N*-mesyl proline^[18] was employed as a chiral auxiliary on the nitrogen of skatole (Scheme 9). The hydroarylation of **18** with **5a** delivers a 2.8:1 ratio of two C3 epimers. Separation on silica gel yielded 63% of the major epimer, **19a**, and 24% of the minor epimer, **19b**. Hydrolysis of **19a** and DIAD oxidation allowed the isolation of (-)-**3a** in 94% *ee*.

In conclusion, we have devised a method to construct benzofuroindolines and chromenoindoline derivatives from the 3-regioselective hydroarylation of N-acetyl indoles by phenols with inexpensive and non-toxic FeCl₃, followed by an oxidation step. This process allows the intermolecular assem-



Scheme 8. Synthesis of benzofuroindolines. [a] TPAP (0.1 equiv) and NMO (1.2–2.8 equiv). [b] DIAD (1.2–2.5 equiv). DIAD = Diisopropyl azodicarboxylate, NMO = N-methyl morpholine-N-oxide, TPAP = tetrapropylammonium perruthenate.



Scheme 9. Asymmetric version. Ms = methanesulfonyl.

bly of phenols and indoles, which is unfavorable by the corresponding hypervalent-iodine-mediated oxidative coupling. The hydroarylation step features a very rare example of electrophilic reactivity of the indole core towards various aromatic nucleophiles. We believe that this procedure has significant potential for the total synthesis of natural products, and in the discovery of new biologically active compounds.

Received: August 16, 2012 Published online: November 5, 2012

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Keywords: benzofuroindoline \cdot diazonamide A \cdot Friedel-Crafts \cdot indoles \cdot umpolung

- a) N. Lindquist, W. Fenical, G. D. Van Duyne, J. Cjardy, J. Am. Chem. Soc. 1991, 113, 2303-2304; b) J. Li, A. W. Burgett, L. Esser, C. Amezscusa, P. G. Harran, Angew. Chem. 2001, 113, 4906-4909; Angew. Chem. Int. Ed. 2001, 40, 4770-4773; c) T.-S. Kam, S.-J. Tan, S.-W. Ng, K. Komiyama, Org. Lett. 2008, 10, 3749-3752; d) Q.-X. Wu, M. S. Crews, M. Draskovic, J. Sohn, T. A. Johnson, K. Tenney, F. A. Valeriote, X.-J. Yao, L. F. Bjeldanes, P. Crews, Org. Lett. 2010, 12, 4458-4461.
- [2] a) G. Wang, L. Shang, A. W. G. Burgett, P. G. Harran, X. Wang, *Proc. Natl. Acad. Sci. USA* 2007, *104*, 2068–2073; b) N. S. Williams, A. W. G. Burgett, A. S. Atkins, X. Wang, P. G. Harran, S. L. McKnight, *Proc. Natl. Acad. Sci. USA* 2007, *104*, 2074– 2079.
- [3] For a review, see: a) M. Lachia, C. J. Moody, Nat. Prod. Rep. 2008. 25. 227-253: for representative examples, see: b) K. C. Nicolaou, M. Bella, D. Y.-K. Chen, X. Huang, T. Ling, S. A. Snyder, Angew. Chem. 2002, 114, 3645-3649; Angew. Chem. Int. Ed. 2002, 41, 3495-3499; Angew. Chem. 2002, 114, 3645-3649; c) K. C. Nicolaou, P. Bheema Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y.-K. Chen, S. A. Snyder, Angew. Chem. 2003, 115, 1795-1800; Angew. Chem. Int. Ed. 2003, 42, 1753-1758; d) C.-M. Cheung, F. W. Goldberg, P. Magnus, C. J. Russell, R. Turnbull, V. Lynch, J. Am. Chem. Soc. 2007, 129, 12320-12327; e) C.-K. Mai, M. F. Sammons, T. Sammakia, Angew. Chem. 2010, 122, 2447-2450; Angew. Chem. Int. Ed. 2010, 49, 2397-2400; f) R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz, D. W. C. MacMillan, Chem. Sci. 2011, 2, 308-311; g) W. Tian, L. Rao Chennamaneni, T. Suzuki, D. Y.-K. Chen, Eur. J. Org. Chem. 2011, 1027-1031.
- [4] A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, Angew. Chem. 2003, 115, 5111-5116; Angew. Chem. Int. Ed. 2003, 42, 4961-4966.
- [5] For a low yielding intermolecular version, see: K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, D. Y.-K. Chen, *Angew. Chem.* 2009, *121*, 7752–7756; *Angew. Chem. Int. Ed.* 2009, *48*, 7616–7620.
- [6] For selected examples of the regioselective synthesis of C3-aryl indoline derivatives, see: a) S. Zhu, D. W. C. Mac Millan, J. Am. Chem. Soc. 2012, 134, 10815-10818; b) K.-J. Wu, L.-X. Dai, S.-L. You, Org. Lett. 2012, 14, 3772-3775; c) J. Kim, M. Movassaghi, J. Am. Chem. Soc. 2011, 133, 14940-14943; d) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, Angew. Chem. 2011, 123, 9829-9833; Angew. Chem. Int. Ed. 2011, 50, 9655-9659; e) R. B. Bedford, N. Fey, M. F. Haddow, R. F. Sankey, Chem. Commun. 2011, 47, 3649-3651; f) V. R. Espejo, X.-B. Li, J. D. Rainier, J. Am. Chem. Soc. 2010, 132, 8282-8284; g) M. W. Boal, A. W. Schammel, N. K. Garg, Org. Lett. 2009, 11, 3458-3461; h) K. Eastman, P. S. Baran, Tetrahedron 2009, 65, 3149-3154; i) K. Matsumoto, H. Tokuyama, T. Fukuyama, Synlett 2007, 3137-3140; j) S. P. Govek, L. E. Overman, J. Am. Chem. Soc. 2001, 123, 9468-9469; k) F. Yamada, A. Goto, M. Somei, Heterocycles 2000, 53, 1255-1258.
- [7] For selected examples of the hydroarylation of alkenes, see: a) Y. Kuninobu, T. Matsuki, K. Takai, J. Am. Chem. Soc. 2009, 131, 9914–9915; b) J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller, Org. Lett. 2006, 8, 19–22.
- [8] M. Bandini, A. Eischholzer, Angew. Chem. 2009, 121, 9786– 9824; Angew. Chem. Int. Ed. 2009, 48, 9608–9644.
- [9] The addition of nucleophiles at the C2-position of indoles as the result of the preliminary activation of the C3-position by electrophiles is known; see: C. C. J. Loh, D. Enders, *Angew. Chem.* **2012**, *124*, 46–49; *Angew. Chem. Int. Ed.* **2012**, *51*, 46–48.

Angew. Chem. Int. Ed. 2012, 51, 12546-12550

Angewandte Communications

- [10] Indoles substituted with electron-withdrawing groups at C3 can react with nucleophiles at C2; see: L. Wang, Y. Shao, Y. Liu, Org. Lett. 2012, 14, 3978–3981.
- [11] For the generation of oxidized C3-substituted indole derivatives which are electrophilic at C3, see references [6c,f,i,k].
- [12] a) K. Nishida, E. Yanase, S.-i. Nakatsuka, *ITE Lett. Batteries New Technol. Med.* 2006, 7, 59–62; b) N. Tajima, T. Hayashi, S.-N. Nakatsuka, *Tetrahedron Lett.* 2000, 41, 1059–1062.
- [13] For iron promoted C-H transformations, see: a) C.-L. Sun, B.-J.
 Li, Z.-J. Shi, *Chem. Rev.* 2011, *111*, 1293–1314; b) K.
 Komeyama, K. Aihara, T. Kashira, K. Takaki, *Chem. Lett.* 2011, *40*, 1254–1256.
- [14] S. M. Bonesi, M. Fagnoni, Chem. Eur. J. 2010, 16, 13572-13589.
- [15] K. Ding, Y. Wang, L. Zhang, Y. Wu, T. Matsuura, *Tetrahedron* 1996, 52, 1005–1010.
- [16] CCDC 850422 (8a), 850423 (3g), and 850424 (16) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [17] For the formation of complexes between phenols and FeCl₃, see:S. Banerjee, B. C. Haldar, *Nature* **1950**, *165*, 1012.
- [18] T. Benkovics, I. A. Guzei, T. P. Yoon, Angew. Chem. 2010, 122, 9339–9343; Angew. Chem. Int. Ed. 2010, 49, 9153–9157.

- [19] A. Goti, M. Romani, Tetrahedron Lett. 1994, 35, 6567-6570.
- [20] a) G. Vincent, Y. Chen, J. W. Lane, R. M. Williams, *Heterocycles* 2007, 72, 385–398; b) X. Xu, X. Li, Org. Lett. 2009, 11, 1027– 1029.
- [21] MnO₂ yields about 20% of **3a**, whereas the Dess–Martin reagent did not afforded the expected product, **3a**.
- [22] Benzofuroindoline $3i(R^4 = I)$ was formed with good conversion, as observed in the crude NMR spectrum; however, we were not able to isolate it by flash column chromatography.
- [23] No 3-arylchromenoindolines are reported in the literature, for 3alkylchromenoindolines, see: a) B. M. Trost, J. Quancard, J. Am. Chem. Soc. 2006, 128, 6314–6315; b) S. L. Crawley, R. L. Funk, Org. Lett. 2003, 5, 3169–3172.
- [24] Chromenoindoline 17 slowly rearranged to indole 20 in CDCl₃ after 1,2 migration of the benzyl group from C3 to C2. For related examples of a 1,2 shift, see: a) W. E. Noland, F. J. Baude, *J. Org. Chem.* 1966, *31*, 3321–3337; b) J.
 Bergman, N. Eklund, *Tetrahedron* 1980, 36, 1445–1450.
- [25] We speculate that the minor enantioerosion from pure (L)-proline has its origin in the preparation of indole **18**.

