Synthesis of 3,3-Spiroindolines via FeCl_3 -Mediated Cyclisation of Aryl or Alkene-Containing 3-Substituted N-Ac Indoles

Raj Kumar Nandi, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent

► To cite this version:

Raj Kumar Nandi, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent. Synthesis of 3,3-Spiroindolines via FeCl_3 -Mediated Cyclisation of Aryl or Alkene-Containing 3-Substituted N-Ac Indoles. *Organic Letters*, 2016, 18 (8), pp.1716-1719. 10.1021/acs.orglett.6b00174 . hal-01509939

HAL Id: hal-01509939

<https://hal.science/hal-01509939>

Submitted on 18 Apr 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis of 3,3-Spiroindolines via FeCl₃-Mediated Cyclisation of Aryl or Alkene-Containing 3-Substituted N-Ac Indoles.

Raj Kumar Nandi, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent*

Univ Paris Sud, CNRS, Université Paris-Saclay, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Equipe Méthodologie, Synthèse et Molécules Thérapeutique (MS&MT), Bat. 410, 91405, Orsay, France.

Supporting Information Placeholder

ABSTRACT: We report the cyclisation of 3-substituted N-acetylindoles for the straightforward synthesis of 3,3-spiroindolines via the Friedel-Crafts reaction of an appended aryl group or the formal [2+2] cycloaddition of an appended alkene. Our strategy involves an Umpolung of the C2=C3 bond of the indole nucleus during FeCl₃-mediated hydroarylation or annulation reactions.

The 3,3-spiroindoline motif is found in several biologically active natural products¹ such as spiroindimicin B or vindoline and it is a privileged scaffold for the design of medicinally relevant compounds (Figure 1).² For example, NITD609 is an anti-malaria agent,^{2a} XEN907 is a promising compound for the treatment of pain^{2b} and SYN351 is an insecticidal^{2c} (Figure 1).

Figure 1. 3,3-spiroindolines of interest.

Various methods to access 3,3-spiroindolines have been reported³ including dearomative cyclisation of indoles.⁴⁻⁸ However the access to 3-aryl-containing spiroindolines is less encountered.^{9,2b} In particular spirocyclisation by 3-arylate dearomatization of indole is uncommon (Scheme 1).¹⁰ Harrowven reported one example of a radical spirocyclisation of a 2-iodoaryl-containing 3-substituted indole **1** mediated by tin hydride to give spiroindoline **2**.¹¹

Scheme 1. Strategies for the spiroarylation of indoles

The group of You¹² and the group of Xu and Liang¹³ reported a palladium catalyzed cyclisation process from bromo or iodoarenes **3-5** involving the intramolecular nucleophilic attack of the C3 position of indole into an aryl palladium complex **6** which led to 3,3-spiroindolines **7**.

Given our interest in arylative functionalization of indoles,¹⁴ we propose a mechanistically distinct approach to the synthesis of arylated 3,3-spiroindolines.

To access the spiroindoline framework **9** from substrates **8** (Scheme 1), we intend to deploy the FeCl₃-mediated hydroarylation reaction of the C3=C2 bond of N-Ac indoles that we developed and reported recently in the intermolecular mode.^{14a,b,15} We believe that this reaction proceeds via both the activation of the acetyl and the C2=C3 bond of indole in intermediates **10a** or **10b** which would be electrophilic to trigger a Friedel-Crafts type reaction and would indeed result in the transformation of a C-H bond into a C-C bond.¹⁶

The hydroarylation cyclisation proved to best proceed with 2.4 equivalents of anhydrous FeCl₃ in dichloromethane in dilute conditions (0.05 M) at room temperature in air. The generality of the reaction was evaluated and we found that *para*- and *meta*-methoxyphenyl as well as *para*-tolyl or phenyl substituents on the C3-chain of the indole led efficiently to the desired spiroindolines **9a-d** (Scheme 2).

Scheme 2. Spirocyclisation via hydroarylation of N-Ac indoles: substitution of the aryl group.

We then studied the substitution of the benzene part of the indole (Scheme 3). We noticed that electrondonating methoxy and methyl groups were well tolerated at the C5-position and led to the respective formation of spiroindolines **9e-h** and **9i-l**. Halogens were also tolerated since the 5-bromo-3,3-spiroindolines **9m-p** and the 6-chloro-3,3-spiroindolines **9q-t** were obtained.

We then found that it is also possible to use a heterocyclic substituent such as a thienyl to obtain heteroarylspiroindolines **9u,v** in moderate yields (Scheme 4).

Finally, we also introduced a *gem*-diester on the tether between the indole and the phenyl parts (Scheme 4). We observed that the conversion was incomplete at room temperature probably due to sequestration of iron chloride by the ester groups. However, performing the reaction at 80 °C in 1,2-dichloroethane resulted in complete conversion of the starting indole and isolation of the spiroindoline **9w** in 62 % yield. Unfortunately, no conversion of **8x**, the precursor of the 7-membered ring **9x**, was observed.¹⁷

X-ray crystallography of crystals of spiroindolines **9a**, **9d** and **9u** allowed us to unambiguously assign their structures.¹⁸

Scheme 3. Spirocyclisation via hydroarylation of N-Ac indoles: substitution of the indole nucleus

Scheme 4. Spirocyclisation via hydroarylation of N-Ac indoles: use of a heteroaryl and substitution of the tether.

Figure 2. X-ray structures of spiroindolines **9a**, **9d** and **9u**.

We next wished to evaluate other π nucleophiles to access the spiroindoline framework. Therefore, we replaced the aryl group on the C3-side chain by a terminal alkene. We believed that activation of the C2=C3 bond of indole **11** by FeCl₃ would trigger the addition of the alkene at C3 via intermediate **12** to form a 3,3-spirocyclic compound **13** bearing an *endo*-cyclic double bond (Scheme 5).^{9a}

Scheme 5. Planned 3-spirocyclisation of an N-Ac indole by intramolecular addition of a terminal alkene.

However, when we performed the reaction of **11** with FeCl_3 , we obtained a different 3,3-spirocyclic indoline **14** (Scheme 6). The terminal alkene and the $\text{C2}=\text{C3}$ bond of indole have been involved in a dearomative [2+2] annulation which led to the formation of a cyclobuta[*b*]indoline framework fused with a cyclopentane, as determined by X-ray analysis (Figure 3).¹⁸ Few dearomative [2+2] cycloaddition between indoles and alkenes are known which are photoinduced, in contrast with our reaction.^{7d-e,19-21} We can postulate that upon activation of the $\text{C2}=\text{C3}$ bond of the indole, the alkene adds onto the electrophilic C3 position of the indole by its more substituted carbon. It is also possible that FeCl_3 only activates the carbonyl group to promote a [2+2] cycloaddition.²²

Scheme 6. Spirocyclisation via a formal [2+2] cycloaddition.

This result proves that the activation of *N*-acyl indole by FeCl_3 is not limited to induce C3 -regioselective hydroarylation. Other dearomative reactions of indole could be promoted by this mode of activation such as a formal [2+2] cycloaddition.

In conclusion, we report a straightforward access to spiroindoline derivatives via the intramolecular hydroarylation of *N*-Ac indoles mediated by FeCl_3 . This Friedel-Crafts reaction of the appended aryl leads to the concomitant C3 -regioselective formation of a quaternary carbon center and dearomatization of the indole nucleus. This reaction is operationally simple and proceeds at room temperature in air with a cheap and non-toxic promoter. Moreover, in presence of a terminal alkene on the C3 -side chain of the indole, iron trichloride mediates a rare non-photoinduced dearomative [2+2] annulation which led to a constrained cyclopenta[2,3]cyclobuta[1,2-*b*]indoline holding also a spirocyclic structure.

ASSOCIATED CONTENT

Supporting Information

Additional experiment, experimental procedures, characterizations, and ^1H and ^{13}C NMR spectra copies of all new compounds (PDF file) and cif files for compounds **9a**, **9d**, **9u** and **14**. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* guillaume.vincent@u-psud.fr

Author Contributions

All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/ under REA grant agreement n° 623422 (IIF-2013 postdoctoral fellowship to R.K.N.). We also gratefully acknowledge the ANR (ANR-12-JS07-0002), the Université Paris Sud and the CNRS for financial support.

REFERENCES

1. Spiroindimicins: (a) Zhang, W.; Liu, Z.; Li, S.; Yang, T.; Zhang, Q.; Ma, L.; Tian, X.; Zhang, H.; Huang, C.; Zhang, S.; Ju, J.; Shen, Y.; Zhang, C. *Org. Lett.* **2012**, *14*, 3364–3367; vindoline: (b) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058–1059.
2. (a) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagona, T. T. *Science* **2010**, *329*, 1175–1180; (b) Chowdhury, S.; Chafeev, M.; Liu, S.; Sun, J.; Raina, V.; Chui, R.; Young, W.; Kwan, R.; Fu, J.; Cadieux, J. A. *Bioorg. Med. Chem. Lett.* **2011**, *21* (12), 3676–3681; (c) Sluder, A.; Shah, S.; Cassayre, J.; Clover, R.; Maienfisch, P.; Molleyres, L.-P.; Hirst, E. A.; Flemming, A. J.; Shi, M.; Cutler, P.; Stanger, C.; Roberts, R. S.; Hughes, D. J.; Flury, T.; Robinson, M. P.; Hillesheim, E.; Pitterna, T.; Cederbaum, F.; Worthington, P. A.; Crossthwaite, A. J.; Windass, J. D.; Currie, R. A.; Earley, F. G. P. *PLoS ONE* **2012**, *7*, e34712.
3. For reviews: (a) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. – Eur. J.* **2016**, *22*, 2856–2881; (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104–6155; (c) Trost, B.; Brennan, M. *Synthesis* **2009**, 3003–3025; (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758.
4. For a general review on dearomatization of indoles, see: Roche, S. P.; Youte Tendoung, J.-J.; Tréguier, B. *Tetrahedron* **2015**, *71*, 3549–3591.
5. Selected examples of dearomative 3-cyclisation of indoles using their C3 nucleophilicity: (a) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772; (b) Medley, J. W.; Movassaghi, M. *Angew. Chem.* **2012**, *124*, 4650–4654; (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.
6. Selected examples of metal-catalyzed dearomative 3-cyclisations of indoles: (a) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795; (b) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418–11419; (c) Cai, Q.; Zheng, C.; Zhang, J.-W.; You, S.-L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8665–8669; (d) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 1680–1683; (e) Zhang, X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Org. Lett.* **2013**, *15*, 3746–3749; (f) Gao, R.-D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett.* **2014**, *16*, 3919–3921; (g) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3480–3483; (h) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350–1353; (i) James, M. J.; Cuthbertson, J. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7640–7643; (j) James, M.

- J.; Clubley, R. E.; Palate, K. Y.; Procter, T. J.; Wyton, A. C.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2015**, *17*, 4372–4375; (k) Xu, W.; Wang, W.; Wang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 9546–9549; (l) Zheng, N.; Chang, Y.-Y.; Zhang, L.-J.; Gong, J.-X.; Yang, Z. *Chem. – Asian J.* **2016**, *11*, 371–375.
7. Selected examples of a dearomative 3-cyclisation of indoles by cycloaddition, [3+2]: (a) Mejía-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275–3278; (b) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012; (c) Zheng, Y.; Cleaveland, J.; Richardson, D.; Yuan, Y. *Org. Lett.* **2015**, *17*, 4240–4243; [2+2]: (d) Winkler, J. D.; Scott, R. D.; Williard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 8971–8975; (e) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081–1084.
 8. Selected examples of dearomative 3-cyclisations of indoles by oxidative coupling: (a) Zuo, Z.; Ma, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 12008–12011; (b) Fan, F.; Xie, W.; Ma, D. *Org. Lett.* **2012**, *14*, 1405–1407; (c) Fan, F.; Xie, W.; Ma, D. *Chem. Commun.* **2012**, *48*, 7571–7573; (d) Wei, Y.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991; (e) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702–711; (f) Kaïm, L. E.; Grimaud, L.; Goff, X.-F. L.; Menes-Arzate, M.; Miranda, L. D. *Chem. Commun.* **2011**, *47*, 8145–8147; (g) Watanabe, T.; Umezawa, N.; Kato, N.; Higuchi, T. *Chem. – Eur. J.* **2013**, *19*, 4255–4261.
 9. Selected examples: (a) England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805–3807; (b) Gorokhovik, I.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 5536–5539; (c) Piou, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11561–11565; (d) Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lébl, T.; Smith, A. D. *Org. Lett.* **2012**, *14*, 2762–2765; (e) Katayev, D.; Jia, Y.-X.; Sharma, A. K.; Banerjee, D.; Besnard, C.; Sunoj, R. B.; Kündig, E. P. *Chem. – Eur. J.* **2013**, *19*, 11916–11927.
 10. For a review on 3-arylate dearomatization of indoles: Denizot, N.; Tomakinian, T.; Beaud, R.; Kouklovsky, C.; Vincent, G. *Tetrahedron Lett.* **2015**, *56*, 4413–4429.
 11. Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795–1798.
 12. Wu, K.-J.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 3772–3775.
 13. Wu, X.-X.; Shen, Y.; Chen, W.-L.; Chen, S.; Xu, P.-F.; Liang, Y.-M. *Chem. Commun.* **2015**, *51*, 16798–16801.
 14. (a) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 12546–12550; (b) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. – Eur. J.* **2014**, *20*, 7492–7500; (c) Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11881–11885; (d) Denizot, N.; Pouilhès, A.; Cucca, M.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Org. Lett.* **2014**, *16*, 5752–5755; (e) Beaud, R.; Tomakinian, T.; Denizot, N.; Pouilhès, A.; Kouklovsky, C.; Vincent, G. *Synlett* **2014**, *26*, 432–440; (f) Tomakinian, T.; Kouklovsky, C.; Vincent, G. *Synlett* **2015**, *26*, 1269–1275; (g) Denizot, N.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. – Eur. J.* **2015**, *21*, 18953–18956.
 15. For a review on hydroarylation: de Haro, T.; Nevado, C. In *Comprehensive Organic Synthesis (Second Edition)*; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; pp 1621–1659.
 16. For a highlight on the electrophilicity of indoles: Bandini, M. *Org. Biomol. Chem.* **2013**, *11*, 5206–5212.
 17. The reaction of 3-phenethyl-N-Ac-indoles does not lead to 5-membered ring 3,3-spiroindolines but to 2-hydroarylated indolines: Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun.* **2016**, doi 10.1039/C6CC01654E.
 18. CCDC 1446909-1446912 (**9a**, **9d**, **9u** and **14**) 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.
 19. For a review: Firooznia, F.; Kester, R. F.; Berthel, S. J. In *Heterocyclic Scaffolds II*; Gribble, G. W., Ed.; Topics in Heterocyclic Chemistry; Springer Berlin Heidelberg, 2010; pp 283–326.
 20. Selected examples: (a) Ikeda, M.; Ohno, K.; Takahashi, M.; Uno, T.; Tamura, Y.; Kido, M. *J. Chem. Soc. Perkin 1*, **1982**, 741–748; (b) Ikeda, M.; Ohno, K.; Mohri, S.; Takahashi, M.; Tamura, Y. *J. Chem. Soc. Perkin 1*, **1984**, 405–412; (c) Hastings, D. J.; Weedon, A. C. *J. Org. Chem.* **1991**, *56*, 6326–6331; (d) Hastings, D. J.; Weedon, A. C. *Tetrahedron Lett.* **1991**, *32*, 4107–4110; (e) Oldroyd, D. L.; Weedon, A. C. *J. Chem. Soc. Chem. Commun.* **1992**, 1491–1492.
 21. Related dearomative [2+2] annulations of indoles with alkenes: (a) Jia, M.; Monari, M.; Yang, Q.-Q.; Bandini, M. *Chem. Commun.* **2015**, *51*, 2320–2323; (b) Ocello, R.; De Nisi, A.; Jia, M.; Yang, Q.-Q.; Monari, M.; Giacinto, P.; Bottoni, A.; Miscione, G. P.; Bandini, M. *Chem. – Eur. J.* **2015**, *21*, 18445–18453; (c) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1658–1664; (d) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; with alkynes: (e) Davis, P. D.; Neckers, D. C. *J. Org. Chem.* **1980**, *45*, 456–462; with carbonynes: (f) Zhao, D.; Zhang, J.; Xie, Z. *J. Am. Chem. Soc.* **2015**, *137*, 9423–9428.
 22. When we replaced the terminal monosubstituted alkene by a trisubstituted alkene, we did not obtain the desired cyclobutane but a tetrahydrocarbazole, see the supporting information.