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Preparation of *N*-bornylindoles through Au-catalyzed cyclization of *N*-bornyl-2-ethynylanilines

Egor A. Drokin,[a] Viktoria I. Evdokimova,[a,b] Maxim A. Topchiy,[a] Irina Yu. Chukicheva,[c] Olga A. Shumova,[c] Aleksandr V. Kutchin[a] and Andrey F. Asachenko*[a]

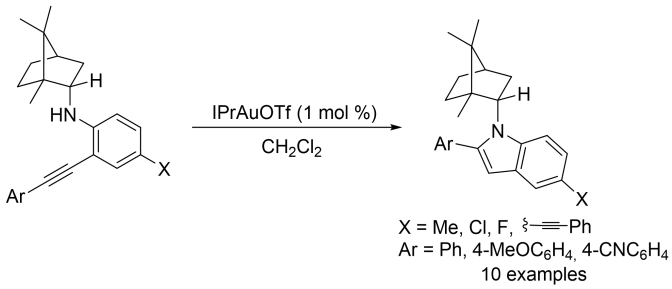
[a] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: aasachenko@ips.ac.ru*

[b] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation*

[c] *Institute of Chemistry, Komi Science Centre, Ural Branch of the Russian Academy of Sciences, 167000 Syktyvkar, Russian Federation*

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Previously undescribed *N*-bornylindoles were synthesized via Au-catalyzed cyclization of *N*-bornyl-2-ethynylanilines. A mild synthetic approach to the corresponding *N*-bornylanilines was developed, enabling access to a series of bornyl-substituted indoles in high to quantitative yields. The key transformations were found to proceed with comparable efficiency for both bornyl and isobornyl substrates, demonstrating that the configuration of the bicyclic terpene fragment has little influence on the outcome of the reactions.



Keywords: N-bornylindoles; indoles; gold catalysis; Au-catalyzed cyclization; Sonogashira coupling; bornyl derivatives.

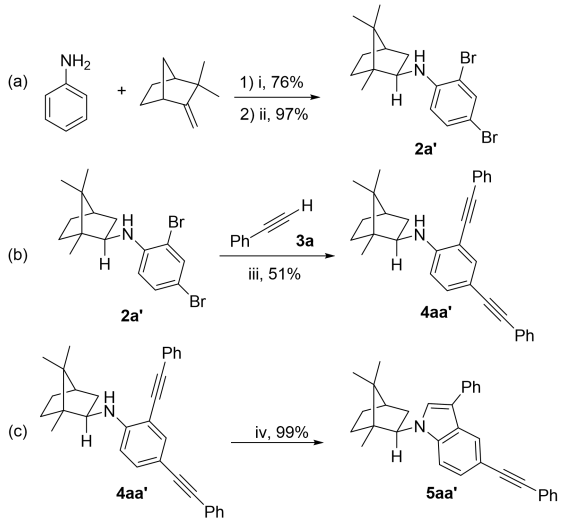
Indole is one of the most important nitrogen-containing heterocyclic scaffolds in natural products and medicinal chemistry [1]. The indole moiety is present in tryptophan, serotonin, melatonin, numerous alkaloids, and a wide range of therapeutically relevant drugs. Indole derivatives exhibit diverse biological activities, including anticancer [2-3], anti-inflammatory [4-5], antimicrobial [6-8] and antiviral [9-10] properties. Regarding the high pharmacological importance of the indole core, the development of new methods for its functionalization and the synthesis of previously inaccessible derivatives remain active areas of the research [11-12]. As part of these studies, our research group has developed several approaches to the synthesis of indoles and related compounds based on the Madelung reaction and gold-catalyzed transformations [13-20].

The introduction of terpene fragments into biologically active molecules is an effective strategy for tuning their physicochemical and pharmacological properties [21]. Special attention is paid to bicyclo[2.2.1]heptane scaffold, since borneol, bornylamine, and their derivatives are characterized by high lipophilicity and diverse biological activities [18, 22-28]. Despite the considerable number of studies devoted to terpenyl- and prenyl-substituted indoles [29-32], no examples of *N*-bornyl-substituted indoles have been reported to date. The presence of a bulky chiral bornyl substituent at the indole nitrogen atom may significantly affect the conformational properties, lipophilicity, and interactions of the molecule with biological targets. Therefore, the development of efficient synthetic approaches to *N*-bornyl- and *N*-isobornylindoles is of considerable interest both for synthetic organic chemistry and for the discovery of new biologically active compounds.

The aim of the present work was to develop an efficient method for the synthesis of previously undescribed *endo*/*exo*-*N*-bornylindoles via gold-catalyzed cyclization of the corresponding ethynylanilines.

The study commenced with optimization of the cross-coupling reaction conditions for the corresponding bromoaniline. The starting 2,4-dibromo-*exo*-*N*-bornylaniline **2a'** was prepared in two steps (Scheme 1, a). Reaction of aniline with camphene in the presence of aluminum phenolate according to the reported procedure [33] followed by bromination, afforded the target product in 74% overall yield over two steps.

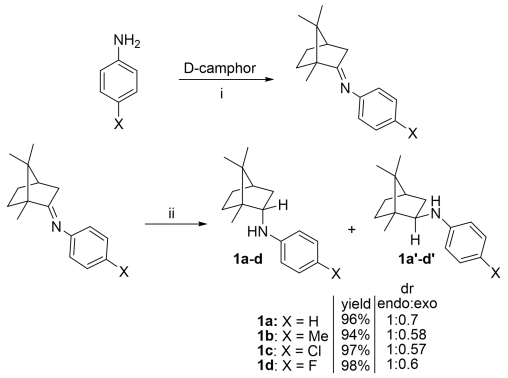
To obtain the target ethynylaniline, Sonogashira coupling with phenylacetylene was performed. While the classical $Pd(PPh_3)_2Cl_2$/CuI catalytic system afforded the desired product in only 20% yield (Table S1), the use of conditions reported to be effective for sterically hindered substrates [34], using $Pd(dppf)Cl_2$ as the catalyst, increased the yield up to 51% (Scheme 1, b).



Scheme 1 *Reagents and condition*: i, $Al(OPh)_3$, 160 °C; ii, NBS, CH_2Cl_2; iii, $Pd(dppf)Cl_2$ (5 mol %), CuI (10 mol %), $PhCH_3/Et_3N$; iv, IPrAuOTf (1 mol %), CH_2Cl_2.

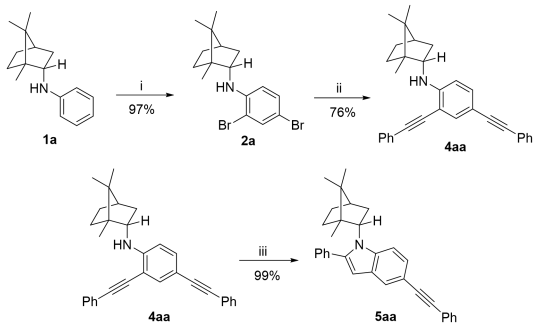
Cyclization of the obtained alkyne was performed using a catalytic system previously investigated by our group [20]. The NHC–gold complex efficiently promoted the reaction under mild conditions, affording the target indole in virtually quantitative yield (Scheme 1, c).

Despite the efficiency of the obtained reaction sequence, the literature method for the preparation of the starting *N*-terpenylanilines leads exclusively to the formation of the isobornyl derivative and requires relatively harsh reaction conditions. This significantly limits access to the corresponding *endo*-bornyl analogues. Therefore, we developed an alternative mild approach to the synthesis of *N*-bornylanilines (Scheme 2). Methyl, chloro, and fluoro substituents were selected for introduction into the aromatic ring, as these groups are known to exert the "magic" effects in medicinal chemistry [35-37]. Reduction of the imines derived from camphor and the corresponding anilines afforded mixtures of *N*-bornyl- (*endo*-) and *N*-isobornylanilines (*exo*-), with the *endo*- diastereomer predominating in all cases (Scheme 4). The structures of the obtained compounds were confirmed by 2D NMR spectroscopy.



Scheme 2 *Reagents and condition*: i, $Si(OEt)_4$, 140 °C;
ii, $NaBH_4$, BF_3•Et_2O, THF.

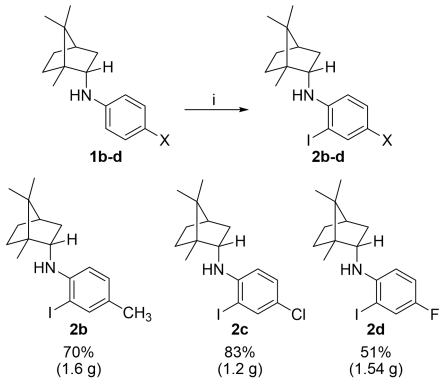
For comparison of the bornyl- and isobornyl-substituted derivatives, a dibromide was obtained from compound **1a**, followed by a Sonogashira reaction and cyclization (Scheme 3). The use of the conditions described above afforded the target compounds. Notably, the *endo*-bornyl isomer provided a significantly higher yield in the Sonogashira coupling. This may be attributed to the lower steric hindrance of the bornyl moiety, which facilitates the oxidative addition step. However, the cyclization reaction proceeded with a virtually quantitative yield for both isomers.



Scheme 3 *Reagents and condition*: i, NBS, CH_2Cl_2;
ii, $Pd(dppf)Cl_2$ (5 mol %), CuI (10 mol %), $PhCH_3/Et_3N$;
iii, IPrAuOTf (1 mol %), CH_2Cl_2.

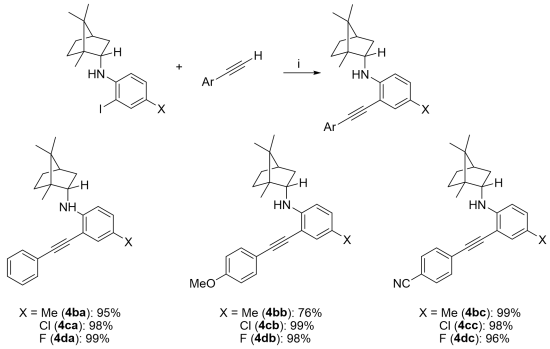
Having demonstrated that both *exo*- and *endo*- bornyl substrates undergo the key transformations efficiently, we next focused on developing a more general route to substituted *N*-bornylindoles. Ortho iodination was chosen to provide more reactive aryl halides suitable for subsequent Sonogashira coupling with various terminal alkynes.

To obtain the corresponding *ortho*-iodoanilines, reaction conditions previously reported for structurally related substrates were evaluated (Table S2). The highest product yield was achieved using benzyltriethylammonium dichloroiodate as the iodinating agent and calcium carbonate as the base. The optimized conditions were successfully applied to the iodination of other *N*-bornylanilines, affording the corresponding products in good yields (Scheme 4). Notably, the method was also readily scalable, and all iodoanilines were obtained on gram scale.



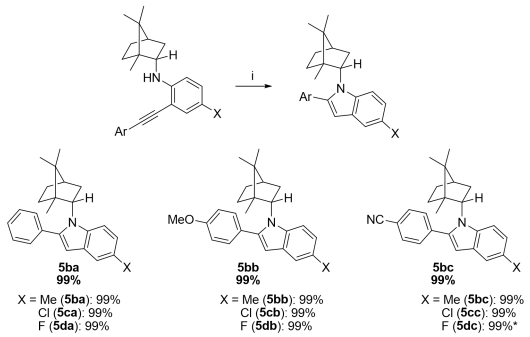
Scheme 4 *Reagents and condition*: i, $BnNEt_3Cl$, ICl, $CaCO_3$, $MeOH/CH_2Cl_2$.

The Sonogashira reaction of iodoanilines proceeded in excellent yields (Scheme 5). Phenylacetylene (**3a**), *p*-methoxyphenylacetylene (**3b**), and *p*-cyanophenylacetylene (**3c**) were employed as representative coupling partners. The high yields obtained with both electron-donating and electron-withdrawing alkynes highlight the broad scope of the developed conditions.



Scheme 5 *Reagents and condition*: i, $Pd(dppf)Cl_2$ (5 mol %), CuI (10 mol %), $PhCH_3/Et_3N$.

The cyclization catalyzed by IPrAuOTf proceeded in virtually quantitative yields for all substrates except **5dc** (Scheme 6). After 12 h of stirring, the reaction mixtures were filtered through a thin layer of silica gel to afford analytically pure products. The presence of two electron-withdrawing substituents in **5dc** resulted in partial conversion, leading to a mixture of product and starting material. Switching to a more active bis(trifluoromethanesulfonyl)imide anion restored full conversion and enabled virtually quantitative product formation.



Scheme 6 *Reagents and condition*: i, IPrAuOTf (1 mol %), CH_2Cl_2; *IPrAuCl (1 mol %) + $AgNTf_2$ (1 mol %)

In summary, an efficient approach to previously unreported *exo/endo*-*N*-bornylindoles has been developed via gold-catalyzed cyclization of *N*-bornyl-2-ethynylanilines. The reaction exhibits broad substrate scope with respect to both electron-donating and electron-withdrawing substituents, providing the corresponding *N*-bornylindoles in high yields. It was found that the key steps proceed with comparable efficiency for both *endo*- and *exo*-bornyl derivatives. The incorporation of an indole core and a bornyl fragment within a single framework opens new

opportunities for the discovery of biologically active compounds within this new class of *N*-bornylindoles.

This work was carried out as part of the A. V. Topchiev Institute of Petrochemical Synthesis (TIPS) Russian Academy of Sciences (RAS) State Program. The synthesis of *exo*-*N*-bornylanilines was carried out as part of the state assignment Reg. No. 125020301261-5. This work was performed using the equipment of the Shared Research Center «Analytical center of deep oil processing and petrochemistry of TIPS RAS».

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.___

References

1. D. I. Bugaenko, A. V. Karchava and M. A. Yurovskaya, *Russ. Chem. Rev.*, 2019, **88**, 99; https://doi.org/10.1070/RCR4844.
2. A. Dhiman, R. Sharma and R. K. Singh, *Acta Pharm. Sin. B*, 2022, **12**, 3006; https://doi.org/10.1016/j.apsb.2022.03.021.
3. W. Zheng, K. Zhang, X. Fan, W. Zheng, D. He and M. Zeng, *Arch. Pharm.*, 2026, **359**, e70246; https://doi.org/10.1002/ardp.70246.
4. L.-L. Song, Y.-L. Mu, H.-C. Zhang, G.-Y. Wu and J.-Y. Sun, *Nat. Prod. Res.*, 2020, **34**, 2283; https://doi.org/10.1080/14786419.2018.1536130.
5. Nisha, S. Singh, N. Sharma and R. Chandra, *Org. Chem. Front.*, 2022, **9**, 3624; https://doi.org/10.1039/D2QO00534D.
6. M. A. Novikov, K. V. Potapov, R. A. Novikov, P. N. Solyev, Y. V. Tomilov, S. N. Kochetkov, A. A. Makarov and V. A. Mitkevich, *Mendeleev Commun.*, 2024, **34**, 255; https://doi.org/10.1016/j.mencom.2024.02.030.
7. N. Chandal, R. Kalia, A. Dey, R. Tambat, N. Mahey, S. Jachak and H. Nandanwar, *Commun. Biol.*, 2024, **7**, 1489; https://doi.org/10.1038/s42003-024-06996-8.
8. H.-L. Qin, J. Liu, W.-Y. Fang, L. Ravindar and K. P. Rakesh, *Eur. J. Med. Chem.*, 2020, **194**, 112245; https://doi.org/10.1016/j.ejmech.2020.112245.
9. A. Singh, C. Bhutani, P. Khanna, S. Talwar, S. K. Singh and L. Khanna, *Eur. J. Med. Chem.*, 2025, **281**, 117017; https://doi.org/10.1016/j.ejmech.2024.117017.
10. M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421; https://doi.org/10.1016/j.ejmech.2014.10.065.
11. E. V. Rozhkov, N. V. Stoletova, A. V. Bachinskiy, M. M. Ilyin, V. I. Maleev and V. A. Larionov, *Mendeleev Commun.*, 2025, **35**, 461; https://doi.org/10.71267/mencom.7701.
12. V. V. Ivanova, A. M. Starosotnikov, M. E. Minyaev, A. A. Kruchinin, A. N. Fakhrutdinov and M. A. Bastrakov, *Mendeleev Commun.*, 2025, **35**, 648; https://doi.org/10.71267/mencom.7793.
13. G. A. Chesnokov, A. A. Ageshina, M. A. Topchiy, M. S. Nechaev and A. F. Asachenko, *Eur. J. Org. Chem.*, 2019, **2019**, 4844; https://doi.org/10.1002/ejoc.201900772.
14. G. A. Chesnokov, A. A. Ageshina, A. V. Maryanova, S. A. Rzhevskiy, P. S. Gribanov, M. A. Topchiy, M. S. Nechaev and A. F. Asachenko, *Russ. Chem. Bull.*, 2020, **69**, 2370; https://doi.org/10.1007/s11172-020-3028-8.
15. G. K. Sterligov, A. N. Lysenko, E. A. Drokin, L. I. Minaeva, M. A. Topchiy, A. A. Ageshina, S. A. Rzhevskiy, M. S. Nechaev and A. F. Asachenko, *Russ. Chem. Bull.*, 2022, **71**, 479; https://doi.org/10.1007/s11172-022-3436-z.
16. G. K. Sterligov, A. A. Ageshina, S. A. Rzhevskiy, O. V. Shurupova, M. A. Topchiy, L. I. Minaeva and A. F. Asachenko, *ACS Omega*, 2022, **7**, 38505; https://doi.org/10.1021/acsomega.2c03754.

17. O. V. Shurupova, E. S. Tarasova, S. A. Rzhevskiy, L. I. Minaeva, M. A. Topchiy and A. F. Asachenko, *Org. Biomol. Chem.*, 2024, **22**, 6742; https://doi.org/10.1039/D4OB00994K.
18. G. K. Sterligov, M. A. Rasskazova, E. A. Drokin, D. K. Isaeva, A. A. Ageshina, S. A. Rzhevskiy, O. V. Shurupova, M. A. Topchiy, L. I. Minaeva and A. F. Asachenko, *J. Org. Chem.*, 2024, **89**, 14028; https://doi.org/10.1021/acs.joc.4c01430.
19. G. K. Sterligov, M. A. Rasskazova, M. A. Topchiy and A. F. Asachenko, *Russ. J. Org. Chem.*, 2025, **61**, 217; https://doi.org/10.1134/S1070428025600779.
20. O. S. Morozov, A. V. Lunchev, A. A. Bush, A. A. Tukov, A. F. Asachenko, V. N. Khrustalev, S. S. Zalesskiy, V. P. Ananikov and M. S. Nechaev, *Chem. - Eur. J.*, 2014, **20**, 6162; https://doi.org/10.1002/chem.201303760.
21. X. Chen, E. Mukwaya, M.-S. Wong and Y. Zhang, *Pharm. Biol.*, 2014, **52**, 655; https://doi.org/10.3109/13880209.2013.853809.
22. S. A. Tishchenko, A. S. Sokolova, O. I. Yarovaya, V. I. Krasnov, A. A. Shtro, A. V. Galochkina, A. M. Klabukov, D. N. Razgulyaeva and N. F. Salakhutdinov, *Russ. J. Gen. Chem.*, 2025, **95**, 79; https://doi.org/10.1134/S1070363224613486.
23. A. S. Sokolova, O. I. Yarovaya, D. V. Korchagina, V. V. Zarubaev, T. S. Tretiak, P. M. Anfimov, O. I. Kiselev and N. F. Salakhutdinov, *Bioorg. Med. Chem.*, 2014, **22**, 2141; https://doi.org/10.1016/j.bmc.2014.02.038.
24. M. Murcia-Soler, F. Pérez-Giménez, F. J. García-March, M. T. Salabert-Salvador, W. Díaz-Villanueva and P. Medina-Casamayor, *J. Mol. Graphics Modell.*, 2003, **21**, 375; https://doi.org/10.1016/S1093-3263(02)00184-5.
25. P. Bottermann, A. Souvatzoglou, K. Schwarz and M. Rettig, *Klin. Wochenschr.*, 1971, **49**, 769; https://doi.org/10.1007/BF01495502.
26. P. D. Williams, P. S. Anderson, R. G. Ball, M. G. Bock, L. Carroll, S.-H. L. Chiu, B. V. Clineschmidt, J. C. Culberson and J. M. Erb, *J. Med. Chem.*, 1994, **37**, 565; https://doi.org/10.1021/jm00031a004.
27. G. A. Chenysheva, V. A. Smol'akova, A. V. Kutchin, I. Y. Chukicheva and M. B. Plotnikov, *Bull. Exp. Biol. Med.*, 2018, **166**, 15; https://doi.org/10.1007/s10517-018-4278-4.
28. I. A. Dvornikova, E. V. Buravlev, O. G. Shevchenko, I. Y. Chukicheva and A. V. Kutchin, *Russ. Chem. Bull.*, 2021, **70**, 2185; https://doi.org/10.1007/s11172-021-3330-0.
29. R. M. Williams, E. M. Stocking and J. F. Sanz-Cervera, in *Biosynthesis: Aromatic Polyketides, Isoprenoids, Alkaloids*, eds. F. J. Leeper and J. C. Vederas, Springer Berlin Heidelberg, Berlin, Heidelberg, 2000, pp. 97; https://doi.org/10.1007/3-540-48146-X
30. M. R. Luzung, C. A. Lewis and P. S. Baran, *Angew. Chem., Int. Ed.*, 2009, **48**, 7025; https://doi.org/10.1002/anie.200902761.
31. B. W. Roose and D. W. Christianson, *Biochemistry*, 2019, **58**, 3232; https://doi.org/10.1021/acs.biochem.9b00399.
32. S. C. Offerman, M. Kadirvel, O. H. Abusara, J. L. Bryant, B. A. Telfer, G. Brown, S. Freeman, A. White, K. J. Williams and H. S. Aojula, *MedChemComm*, 2017, **8**, 551; https://doi.org/10.1039/C6MD00691D.
33. I. Y. Chukicheva, O. A. Shumova, O. G. Shevchenko and A. V. Kutchin, *Russ. Chem. Bull.*, 2024, **73**, 580; https://doi.org/10.1007/s11172-024-4168-z.
34. A. A. Ouahabi, P. N. W. Baxter, J.-P. Gisselbrecht, A. De Cian, L. Brelot and N. Kyritsakas-Gruber, *J. Org. Chem.*, 2009, **74**, 4675; https://doi.org/10.1021/jo802797e.
35. H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256; https://doi.org/10.1002/anie.201303207.
36. D. Chiodi and Y. Ishihara, *J. Med. Chem.*, 2023, **66**, 5305; https://doi.org/10.1021/acs.jmedchem.2c02015.
37. G. Chandra, D. V. Singh, G. K. Mahato and S. Patel, *Chem. Pap.*, 2023, **77**, 4085; https://doi.org/10.1007/s11696-023-02804-5.

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