ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

One-Pot Modified Madelung Synthesis of 3-Tosyl- and 3-Cyano-1,2-disubstituted Indoles

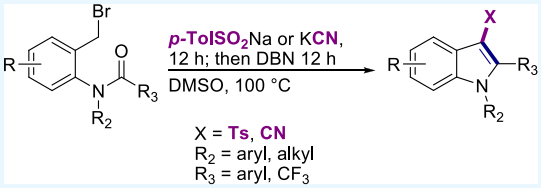
Grigorii K. Sterligov, Alexandra A. Ageshina, Sergey A. Rzhevskiy, Olga V. Shurupova, Maxim A. Topchiy, Lidiya I. Minaeva, and Andrey F. Asachenko*

Cite This: *ACS Omega* 2022, 7, 38505−38511

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A One-pot, two-step procedure for the synthesis of 1,2-disubstituted-3-tosyl and 1,2-disubstituted-3-cyanoindoles from the corresponding *N*-(*o*-tolyl)benzamides is reported. The developed procedure is operationally simple, does not utilize any transition metals, and provides variably substituted indoles in good yields from readily available starting materials.



Indoles are important heterocycles often found in natural products and drugs. The chemistry of indoles has been studied for more than 150 years, and despite the existence of many methods for their synthesis,[1] research in this field is still in demand today,[2] mostly due to the importance of the indole core in drug design, which is attributed to the wide range of biological activity they demonstrate.[3] Among different classes of indoles, 3-tosyl- and 3-cyano-1,2-disubstituted indoles constitute an important class of compounds, which can serve as precursors to a wide range of crucial indole-based targets for medical chemistry. Thus, these heterocyclic scaffolds have been well-known and can be found in many medicinally important molecules, such as the orally available CYP11B2 inhibitor **1**,[4] inhibitor of tumor-related protein kinases **2**,[5] antithrombotic factor Xa inhibitors,[6] and 5-HT6 receptor ligand **3**.[7] Reinhoudt et al. reported on Madelung-type synthesis of 1-benzyl-3-cyano, 1-benzyl-3-tosyl indoles, and annelated 1,2-cycloalkyl-3-cyano and 3-tosyl indoles.[8]

There are two common approaches to 1,2-disubstituted-3-cyano indoles synthesis: construction of the indole ring from cyano-containing starting materials[9] and direct cyanation of indoles.[10] Cyano-group can be also introduced into the C3 position of the indole core by transformation of other functional groups such as formyl[11] and aminomethyl.[10a]

As for 1,2-disubstituted-3-tosyl indoles, the most efficient strategies for their preparation are the intramolecular cyclization of *o*-aminobenzynes,[12] oxidation of their corresponding thioethers,[13] or direct construction of the indole ring from a suitable starting material.[14] It is also worth mentioning that 2-trifluoromethylindoles are promising bioactive compounds;[15] moreover, 1,3-disubstituted-2-trifluoromethylindoles can show biological activity, for example, the selective inhibitor activity against cyclooxygenase-2 **4**,[16] which can be used for optical imaging.[17] However, despite the synthetic availability of various 2-trifluoromethyl indoles,[18] 1-substituted-2-trifluoromethyl-3-cyano indoles are poorly described,[8a,19] whereas 1-substituted-2-trifluoromethyl-3-tosyl indoles are an undescribed class of compounds.

Despite the large number of methods available for the preparation of 3-tosyl- and 3-cyano-1,2-disubstituted indoles, none of them can be called general. All of them have a common disadvantage—low variability in substituents at the C1 and C2 positions of the indole. For example, 1-aryl-2-substituted-3-tosyl indoles, in contrast to 1-alkyl-2-substituted-3-tosyl indoles, are not described in the literature.[20]

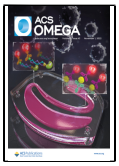
Herein, we report a general synthetic method for the construction of the 1,2,3-trisubstituted indole framework, which is characterized by the following features: (1) ready availability of starting materials, benzyl bromides; (2) large number of tolerated substituents in the first and second positions; and (3) good to excellent isolated yields of final compounds (Figure 1).

RESULTS AND DISCUSSION

The developed method includes the one-pot nucleophilic substitution of bromide to the cyano- or tosyl-containing intermediate, which in turn is further cyclized to indole upon treatment with a suitable base.

Initial screening experiments of the first step were performed employing *N*-(2-(bromomethyl)phenyl)-*N*-phenylbenzamide **5a**, as model substrate, which was obtained by benzylic bromination of the corresponding amide, **4a** (see Supporting information), with sodium *p*-tolylsulfinate. It was found, that using 4 equiv of *p*-TolSO$_2$Na made it possible to obtain compound **5′a** in 90% yield after 12 h in DMSO at 25 °C.

Received: June 16, 2022
Accepted: October 11, 2022
Published: October 19, 2022



https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511

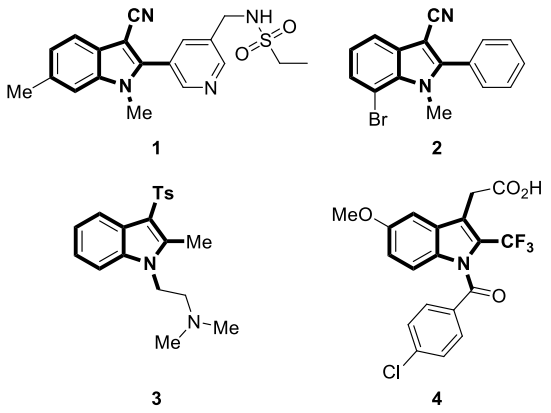


Figure 1. Representative bioactive and medicinal compounds featuring 3-tosyl- and 3-cyano-1,2-disubstituted indoles.

Then, to investigate the performance of the second step, cyclization reaction, under different conditions, and NMR-based screening experiments were performed. The best conditions were found to be: 3 equiv of DBN in DMSO at 100 °C for 12 h (see Supporting information). To confirm the NMR-based experiment, the reaction with the best conditions was performed, which allowed for obtaining indole **6a** from **5′a** in 93% yield. Then, the two-step sequence was performed in a one-pot fashion, which allowed us to obtain the desired 1,2-diphenyl-3-tosylindole (**6a**) in 89% yield. For the operational convenience, it was decided to perform the first stage also at 100 °C (Scheme 1).

In order to determine the scope and limitations of our method, we performed a series of experiments with various substituted benzyl bromides **5a**−**5r**. It was found that 1,2-diaryl-3-tosyl indoles **6a**−**6j** and **6q** (Scheme 2) can be obtained in moderate to high yields. Moreover, sterically hindered substituents at the indole C2 position do not affect their yields (**6g**−**6i**), while bulky substituents on the nitrogen atom decreased the product's yield (**6e**, 72%). The lowest yield of indole was observed in the simultaneous presence of bulky substituents at the first and second positions (**6j**, 61%). As it was mentioned above, 1,3-disubstituted-2-trifluoromethylindoles are an important class of compounds, so the possibility of their synthesis with our one-pot, two-step procedure was investigated. Thus, 1-aryl-2-(trifluoromethyl)-3-tosyl indoles **6k**−**6p** were obtained in high yields, which were not affected by the electronic properties of the substituents on the nitrogen atom. It is especially noteworthy that 1-substituted-2-trifluoromethyl-3-tosyl indoles were synthesized for the first time. As another important class of indole-based compounds, adamantyl-based compounds are used clinically for the treatment of neurological conditions, as potential agents for treating iron overload disease, malaria, type 2 diabetes, tuberculosis, and cancer.[21] Thus, our one-pot, two-step procedure proved to be applicable in this case as well, and 1-adamantyl-2-phenyl-3-tosyl indole **6q** was obtained in 44% yield.

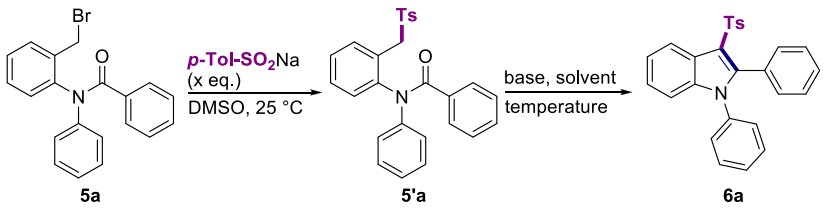
Then, under the same conditions using KCN instead of *p*-TolSO$_2$Na, the one-pot, two-step synthesis of 1,2-disubstituted-3-cyano indoles **7a**−**7l** and **7n**−**7r** (Scheme 3) was investigated. As in 1,2-diaryl-3-tosyl indole, 1,2-diaryl-3-cyano indoles **7a**−**7j** were obtained in high yields. In addition, the dependence of the yields of indoles on the sterically hindered position of the substituents was similar to that of the 3-tosyl indoles: large substituents in the second position had little effect on the product yield, examples **7g**−**7j**, in contrast to large substituents on the nitrogen atom, examples **7d** and **7e**, which significantly reduced it.

It is interesting to note that 3-cyano indole **7j** was obtained in much higher yields than the analogous 3-tosyl indole **6j**, and the lowest yield was observed in case of 3-cyano indole **7e**, which has a methoxy-group on the nitrogen atom in the phenyl *ortho*-position. Then, 1-aryl-2-(trifluoromethyl)-3-cyano indoles **7k**, **7l**, **7n**−**7p**, and **7r** were obtained in high yields for the first time. The yields of indoles were not affected by the presence of electron-donating (**7n** and **7o**) and electron-withdrawing (**7l** and **7r**) substituents. As previously stated, indoles with an adamantyl group are desirable molecules, which is why indole **7q** was also synthesized. Moreover, 1-adamantyl-2-phenyl-3-cyano indole **7q** was obtained in better yield compared to the corresponding 3-tosyl indole **6q**.

During the initial screening study, we noticed that cyclization of benzyl bromides **5** into 3-tosyl indoles **6** occurs only after addition of the external base, whereas 3-cyano indoles **7** were formed under action of KCN only. This result prompted us to perform a series of experiments on the cyclization of benzyl bromides into 3-cyano indoles with and without the addition of an external base. Thus, the possibility of obtaining 3-cyano indoles **7a**−**7l** and **7n**−**7r** in the absence of DBN was shown. The yields were higher in the presence of a base than without it; while in some examples this difference was not perceptible (**7b**−**7f**, **7j**−**7l**, and **7n**−**7r**), in others (**7a** and **7g**−**7i**) it was significant. The greatest difference in yields was observed in case of indoles **7h**−**7i** which have sterically hindered substituents at the C2 position, while bulky substituents on the nitrogen atom of indoles **7d**, **7e**, and **7q** had no effect on the yield of the reaction, depending on the presence of the base in the reaction mixture.

The formation of 3-cyano indoles in the absence of a base can be explained by two factors: first, CN^-[22] is a stronger base than *p*-TolSO$_2^-$,[23] and second, the cyano-group is a more electron-withdrawing group than the tosyl-group. Based on this, it can be concluded, that CN^- is able to deprotonate the benzyl carbon atom, unlike *p*-TolSO$_2^-$; therefore, in the

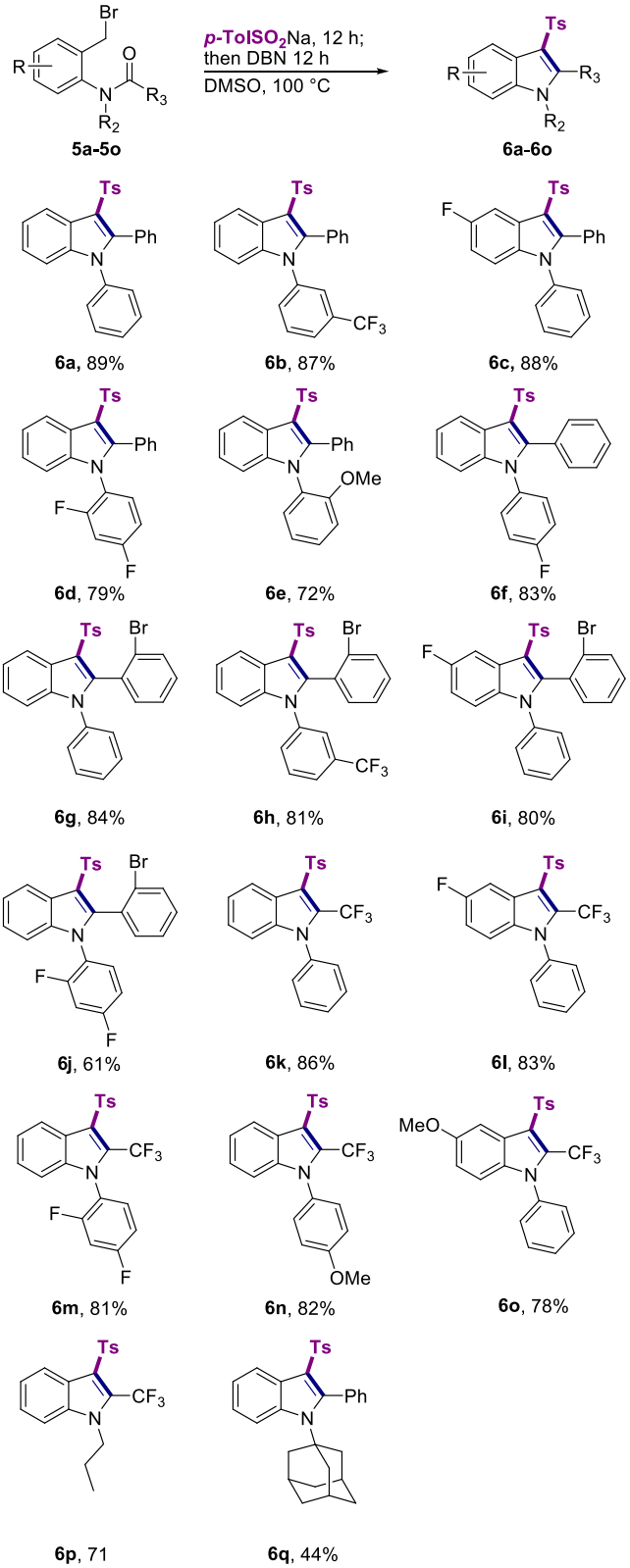
Scheme 1. Optimization of the Formation of 1,2-Diphenyl-3-tosyl Indole (6a)[a]



[a]Reaction conditions for the first stage: **5a** (1 mmol), *p*-TolSO$_2$Na (1, 2 or 4 equiv), DMSO (2 mL), 25 °C, and 12 h.

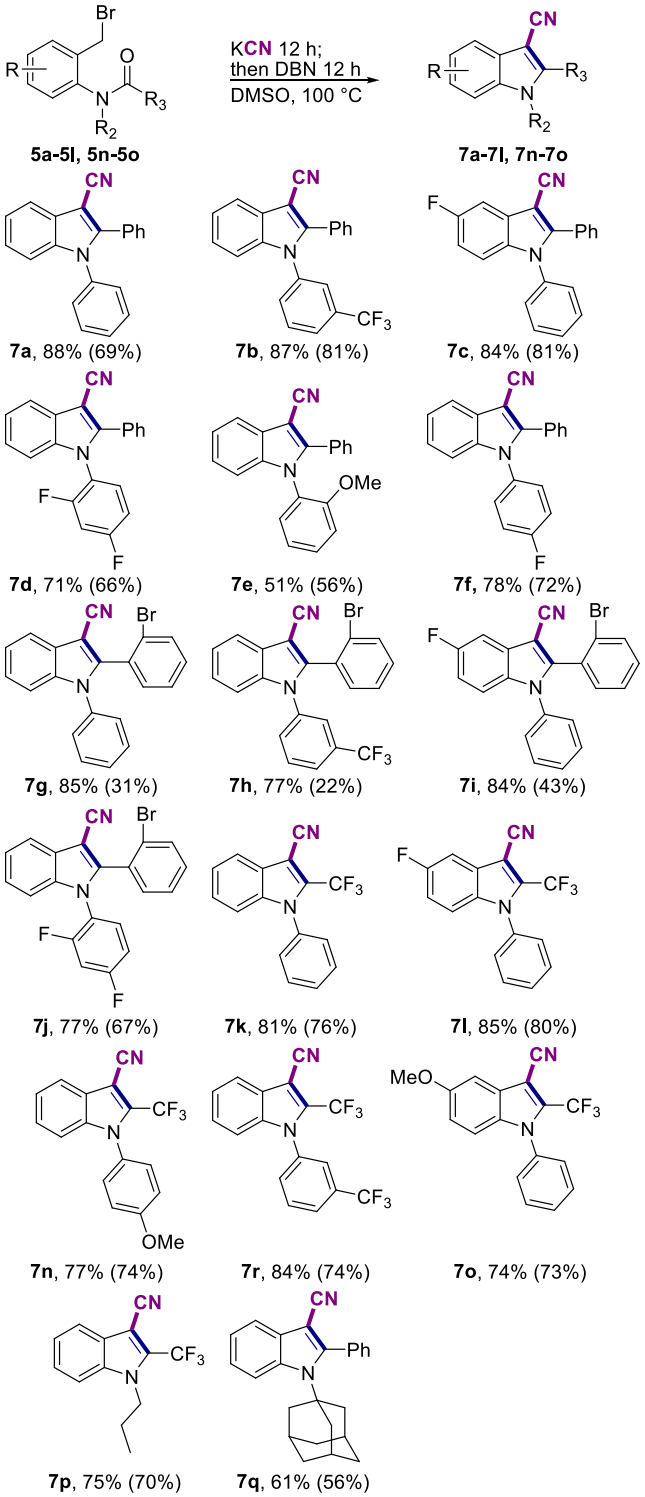
https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511

Scheme 2. Substrate Scope for the Synthesis of 1,2-Disubstituted-3-tosyl Indoles[a]



[a]Reaction conditions: **5** (0.5 mmol), *p*-TolSO$_2$Na (2 mmol, 4 equiv), DMSO (1 mL), 100 °C, and 12 h; then, DBN (1.5 mmol, 3 equiv), 100 °C, and 12 h.

Scheme 3. Substrate Scope for the Synthesis of 1,2-Disubstituted-3-cyano Indoles[a]

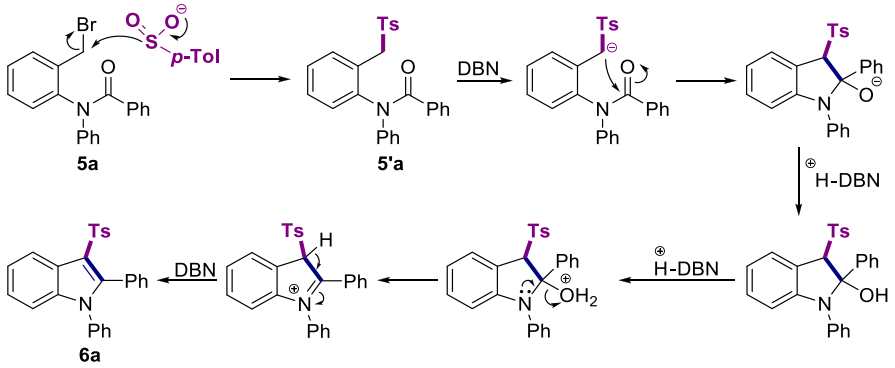


[a]Reaction conditions: **5** (0.5 mmol), KCN (2 mmol, 4 equiv), DMSO (1 mL), 100 °C, 12 h; then DBN (1.5 mmol, 3 equiv), 100 °C, 12 h. The yields in the absence of DBN are shown in parentheses.

absence of a base, benzyl cyanide is obtained together with the corresponding 3-cyano indole, whereas 3-tosyl indoles cannot be obtained in the absence of a base, and the intermediate product of nucleophilic substitution with sodium *p*-tolylsulfinate of benzyl bromides do not cyclize into the corresponding

https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511

Scheme 4. Plausible Mechanism



indoles on its own. In turn, DBN[24] is a stronger base than CN^- and is able to deprotonate a benzyl carbon atom with an electron-withdrawing group as tosyl. This can also explain the higher yield of 3-cyano indoles in the presence of DBN than in its absence.

A probable mechanism for the one-pot, two-step procedure for synthesis of 1,2-diphenyl-3-tosyl indole proposed in Scheme 4. First, a nucleophilic substitution occurs to form **5′a**. Then, DBN deprotonates the benzyl position of **5′a**, which leads to the formation of a carbanion followed by an intramolecular attack of the amide's carbonyl group. In steps 4 and 5, the formation and protonation of the hydroxyl group occurs in the presence of DBN. Then, the nitrogen lone pair assisted elimination of H_2O occurs, after which the indole **6a** is formed, which also becomes possible in the presence of DBN.

CONCLUSIONS

In summary, we have developed a simple cyclization of *N*-(2-(bromomethyl)aryl)-*N*-arylbenzamides with different nucleophiles such as readily accessible sodium *p*-tolylsulfinate and potassium cyanide. This protocol enabled the facile preparation of 1,2-disubstituted-3-tosyl- and 3-cyano indoles in high yields. In comparison to the previously reported methods for indole synthesis, our method makes it possible to obtain a great scope of indoles with various substitutes, even those that could not be obtained before: 1-aryl-2-(trifluoromethyl)-3-tosyl indoles and 1-substituted-2-(trifluoromethyl)-3-cyano indoles.

EXPERIMENTAL SECTION

General Experimental Details. Solvents were purchased from commercial sources and distilled before use. Thin layer chromatography was performed using precoated plates obtained from Merck (TLC silica gel 60 F254). Radical bromination was performed under illumination of the reaction flask by a 230 W halogen lamp (Osram HALOLINE 230 W 230 V R7S) installed 10 cm from the flask. The reaction flask and the lamp were wrapped together with aluminum foil. TLC plates were visualized by exposure to 254 nm ultraviolet light (UV). Silica gel chromatography purifications were performed by flash chromatography using the EM Science silica gel 60 (230−400 mesh). All other reagents were commercially available and were used without further purification. Analytical methods: all new compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, FTIR, and high resolution mass spectrometry (HRMS). NMR spectra were obtained using a Bruker "Ascend 400" (400 MHz ^{1}H, 101 MHz ^{13}C, 376 MHz ^{19}F). Coupling constants J are given in Hertz as positive values regardless of their real individual signs. The multiplicity of the signals is indicated as "s", "d", "t", or "m" for singlet, doublet, triplet, or multiplet, respectively. HRMS spectra were carried out using an AB Sciex TripleTOF 5600+ supported different ionization.

General Procedure for the Synthesis of Amides. Amides were synthesized according to the literature procedures.[2f] Corresponding diarylamine (10 mmol) was charged in the Schlenk tube with a magnetic stir bar equipped, then the Schlenk tube was evacuated and back-filled with nitrogen. Anhydrous THF (20 mL) was added to the flask via a syringe and cooled to −30 °C. *n*-BuLi (2.5 M in hexanes, 4 mL, 10 mmol, 1 equiv) was added dropwise, and the reaction was allowed to warm up to 0 °C and stay for additional 0.5 h. The reaction mixture was cooled again to −30 °C, and benzoyl chloride (10.5 mmol, 1.05 equiv) was added dropwise. The resulting mixture was stirred overnight. A solution of 5% hydrochloric acid was added to the mixture; then, the solution was extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH_2Cl_2 as eluent) to afford corresponding amide **4** as white to yellow solid.

General Procedure for the Synthesis of Trifluoroacetamide. Trifluoroacetamide was synthesized according to the literature procedures with minor changes.[2f] To a solution of diarylamine (10 mmol, 1 equiv) in dry DCM (18 mL), TFAA (2.8 ml, 4.2 g, 20 mmol, 2 equiv) was slowly added at ambient temperature. Then, the reaction mixture was allowed to stir overnight. After having been concentrated under reduced pressure, the reaction mixture was submitted to column chromatography (a mixture of PE/EtOAc as eluent), which afforded the pure trifluoroacetamide **4**.

General Procedure for the Synthesis of Benzyl Bromides. A one neck round bottom 100 mL flask equipped with a reflux condenser and a magnetic stir bar was charged with 6 mmol amide **4**, NBS (1.068 g, 6 mmol, 1 equiv), and 60 mL of dry CCl_4. The solution was irradiated with a 230 W halogen lamp, which was installed in 10 cm from the flask. The reaction flask together with the halogen lamp was wrapped with aluminum foil. Shortly after the start of illumination of the reaction flask with the halogen lamp, the reaction mixture began to reflux. The reaction mixture was allowed to stir and reflux for 1.5 h; then, another portion of NBS (0.267 g, 1.5 mmol, 0.25 equiv) was added, and the reaction mixture was allowed to stir and reflux for another 1 h with halogen lamp illumination. Then, the reaction mixture was cooled to room

https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511

temperature and passed through a short pad of silica to give the crude product. Products **5b−5f** and **5h−5r** were used without further purification. Products **5a** and **5g** were additionally purified by recrystallization from 10 mL of toluene.

General Procedure for the Synthesis of 1,2-Disubstituted-3-tosyl Indoles. A screw-cap vial equipped with a magnetic stir bar was charged with benzyl bromide **5** (0.5 mmol), *p*-TolSO$_2$Na (0.357 g, 2 mmol, 4 equiv) and DMSO (1 mL). The vial was transferred to a preheated oil bath (100 °C). After 12 h, DBN (0.186 g, 1.5 mmol, 3 equiv) was added and the reaction mixture was allowed to stir for another 12 h. Then, the reaction was poured into water and then extracted three times with CH_2Cl_2. The combined organic layer was washed three times with water, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH_2Cl_2 as eluent) to give the desired product **6** as white to pale yellow solid.

General Procedure for the Synthesis of 1,2-Disubstituted-3-cyano indoles. In the presence of DBN, a screw-cap vial equipped with a magnetic stir bar was charged with benzyl bromide **5** (0.5 mmol), KCN (0.131 g, 2 mmol, 4 equiv), and DMSO (1 mL). The vial was then transferred to a preheated oil bath (100 °C). After 12 h, DBN (0.186 g, 1.5 mmol, 3 equiv) was added, and the reaction mixture was allowed to stir for another 12 h. Then, the reaction was poured into water and then extracted three times with CH_2Cl_2. The combined organic layer was washed three times with water, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH_2Cl_2 as eluent) to give the desired product **6** as a white to pale yellow solid. In the absence of DBN, a screw-cap vial equipped with a magnetic stir bar was charged with benzyl bromide **5** (0.5 mmol), KCN (0.131 g, 2 mmol, 4 equiv), and DMSO (1 mL). The vial was then transferred to a preheated oil bath (100 °C). After 12 h, the solution of 15% hydrochloric acid was added. The mixture was extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH_2Cl_2 as eluent) to give the desired product **6** as a white to pale yellow solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03754.

Experimental procedure, characterization of all compounds, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Andrey F. Asachenko − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia;* orcid.org/0000-0001-8638-9261; Email: aasachenko@ips.ac.ru

Authors

Grigorii K. Sterligov − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia*

Alexandra A. Ageshina − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia*

Sergey A. Rzhevskiy − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia*

Olga V. Shurupova − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia*

Maxim A. Topchiy − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia;* orcid.org/0000-0002-6604-7034

Lidiya I. Minaeva − *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c03754

Notes

The authors declare no competing financial interest.
5b−5f5h−5p

■ ACKNOWLEDGMENTS

This work was carried out by G.K.S., A.A.A., S.A.R., O.V.S., M.A.T., L.I.M., and A.F.A. as part of the A. V. Topchiev Institute of Petrochemical Synthesis (TIPS) Russian Academy of Sciences (RAS) State Program. This work was performed using the equipment of the Shared Research Center "Analytical center of deep oil processing and petrochemistry of TIPS RAS".

■ REFERENCES

(1) (a) Sundberg, R. J.; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. S. *Indoles*; Elsevier Science, 1996. (b) Gribble, G. W. *Indole Ring Synthesis: From Natural Products to Drug Discovery*; Wiley, 2016. (c) Bugaenko, D. I.; Karchava, A. V.; Yurovskaya, M. A. Synthesis of indoles: recent advances. *Russ. Chem. Rev.* **2019**, *88*, 99−159.

(2) (a) Panferova, L. I.; Smirnov, V. O.; Levin, V. V.; Kokorekin, V. A.; Struchkova, M. I.; Dilman, A. D. Synthesis of 3-Fluoroindoles via Photoredox Catalysis. *J. Org. Chem.* **2017**, *82*, 745−753. (b) Beletskaya, I.; Desyatkin, V. Asymmetric Friedel−Crafts/Michael Reaction of Indoles and Pyrroles with Coumarin-3-carbonylates. *Synthesis* **2017**, *49*, 4327−4334. (c) Anokhin, M. V.; Feofanov, M. N.; Averin, A. D.; Beletskaya, I. P. The Asymmetric Friedel-Crafts Reaction of Indoles with Arylidenemalonates Catalyzed by MgI2 /PyBox Complexes. *ChemistrySelect* **2018**, *3*, 1388−1391. (d) Bugaenko, D. I.; Dubrovina, A. A.; Yurovskaya, M. A.; Karchava, A. V. Synthesis of Indoles via Electron-Catalyzed Intramolecular C-N Bond Formation. *Org. Lett.* **2018**, *20*, 7358−7362. (e) Aldoshin, A. S.; Tabolin, A. A.; Ioffe, S. L.; Nenajdenko, V. G. One-Pot Synthesis of 3-(2-Fluoroalkenyl)indoles. *Eur. J. Org. Chem.* **2019**, 4384−4396. (f) Chesnokov, G. A.; Ageshina, A. A.; Topchiy, M. A.; Nechaev, M. S.; Asachenko, A. F. Transition-Metal-Free Synthesis of 1,2-Disubstituted Indoles. *Eur. J. Org. Chem.* **2019**, 4844−4854. (g) Chesnokov, G. A.; Ageshina, A. A.; Maryanova, A. V.; Rzhevskiy, S. A.; Gribanov, P. S.; Topchiy, M. A.; Nechaev, M. S.; Asachenko, A. F. Nitromethane as a reagent for the synthesis of 3-nitroindoles from 2-haloarylamine derivatives. *Russ. Chem. Bull.* **2020**, *69*, 2370−2377. (h) Savchuk, M. I.; Kovalev, I. S.; Rusinov, V. L.; Kopchuk, D. S.; Krinochkin, A. P.; Zyryanov, G. V.; Chupakhin, O. N.; Charushin, V. N. Rapid metal free construction of 3-positioned 2-pyridyl substituent in indoles. *Mendeleev Commun.* **2020**, *30*, 712−713. (i) Sterligov, G. K.; Lysenko, A. N.; Drokin, E. A.; Minaeva, L. I.; Topchiy, M. A.; Ageshina, A. A.; Rzhevskiy, S. A.; Nechaev, M. S.; Asachenko, A. F. Solvent-free and transition metal catalyst-free

synthesis of indolo[1,2-f]phenanthridine from 6-chlorophenanthridine. *Russ. Chem. Bull.* **2022**, *71*, 479−483.
(3) (a) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. Biomedical Importance of Indoles. *Molecules* **2013**, *18*, 6620−6662. (b) Sviridova, L. A.; Protopopova, P. S.; Akimov, M. G.; Dudina, M. S.; Melnikova, E. K.; Kochetkov, K. A. Synthesis of new physiologically active (2-oxoimidazolidin-5-yl)-indoles. *Mendeleev Commun.* **2020**, *30*, 347−349.
(4) Papillon, J. P. N.; Lou, C.; Singh, A. K.; Adams, C. M.; Ksander, G. M.; Beil, M. E.; Chen, W.; Leung-Chu, J.; Fu, F.; Gan, L.; Hu, C.-W.; Jeng, A. Y.; LaSala, D.; Liang, G.; Rigel, D. F.; Russell, K. S.; Vest, J. A.; Watson, C. Discovery of N-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide, a Cortisol-Sparing CYP11B2 Inhibitor that Lowers Aldosterone in Human Subjects. *J. Med. Chem.* **2015**, *58*, 9382−9394.
(5) Meine, R.; Blech, M.; Lindhof, J.; Kunick, C. 7-Bromo-1-methyl-2-phenyl-1H-indole-3-carbonitrile. *Molbank* **2017**, *2017*, M941.
(6) Wallnoefer, H. G.; Liedl, K. R.; Fox, T. A challenging system: Free energy prediction for factor Xa. *J. Comput. Chem.* **2011**, *32*, 1743−1752.
(7) Bernotas, R.; Lenicek, S.; Antane, S.; Zhang, G. M.; Smith, D.; Coupet, J.; Harrison, B.; Schechter, L. E. 1-(2-Aminoethyl)-3-(arylsulfonyl)-1H-indoles as novel 5-HT6 receptor ligands. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5499−5502.
(8) (a) Orlemans, E. O. M.; Schreunder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. Synihesis of 3-substituied indoles via a modified madeling reaction. *Tetrahedron* **1987**, *43*, 3817−3826. (b) Verboom, W.; Orlemans, E. O. H.; Berga, H. J.; Scheltinga, H. W.; Reinhoudt, D. N. Synthesis of dihydro-1-pyrrolo-and tetrahydropyrido[1,2-] indoles via a modified madelung reaction. *Tetrahedron* **1986**, *42*, 5053−5064.
(9) (a) Jiang, M.; Xiang, H.; Zhu, F.; Xu, X.; Deng, L.; Yang, C. Efficient Pd-catalyzed domino synthesis of 1-phenyl-1H-indol-2-amine and 5-amino-indolo[1,2-a]quinazoline derivatives. *Org. Biomol. Chem.* **2015**, *13*, 10122−10126. (b) Vijay Kumar, S.; Saraiah, B.; Parameshwarappa, G.; Ila, H.; Verma, G. K. Synthesis of N-Functionalized/NH-Multisubstituted Indoles, Thienopyrroles, Pyrroloindoles, and Pyrazolopyrroles via Sequential One-Pot Base-Mediated and Copper-Catalyzed Inter- and Intramolecular Amination of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles. *J. Org. Chem.* **2014**, *79*, 7961−7978. (c) Du, Y.; Liu, R.; Linn, G.; Zhao, K. Synthesis of N-Substituted Indole Derivatives via PIFA-Mediated Intramolecular Cyclization. *Org. Lett.* **2006**, *8*, 5919−5922. (d) Yugandar, S.; Konda, S.; Ila, H. Amine Directed Pd(II)-Catalyzed C-H Activation-Intramolecular Amination of N-Het(aryl)/Acyl Enaminonitriles and Enaminones: An Approach towards Multi-substituted Indoles and Heterofused Pyrroles. *J. Org. Chem.* **2016**, *81*, 2035−2052. (e) Ren, X.; Chen, J.; Chen, F.; Cheng, J. The palladium-catalyzed cyanation of indole C-H bonds with the combination of NH4HCO3 and DMSO as a safe cyanide source. *Chem. Commun.* **2011**, *47*, 6725−6727.
(10) (a) Ding, S.; Jiao, N. Direct Transformation of N,N-Dimethylformamide to −CN: Pd-Catalyzed Cyanation of Heteroarenes via C-H Functionalization. *J. Am. Chem. Soc.* **2011**, *133*, 12374−12377. (b) Kim, J.; Kim, H.; Chang, S. Copper-Mediated Selective Cyanation of Indoles and 2-Phenylpyridines with Ammonium Iodide and DMF. *Org. Lett.* **2012**, *14*, 3924−3927. (c) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. Palladium-Catalyzed C(sp2)-H Cyanation Using Tertiary Amine Derived Isocyanide as a Cyano Source. *Org. Lett.* **2012**, *14*, 4966−4969. (d) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. Palladium-Catalyzed Direct Cyanation of Indoles with K4[Fe(CN)6]. *Org. Lett.* **2010**, *12*, 1052−1055. (e) Li, L.; Hou, Z.-W.; Li, P.; Wang, L. Site-Selective Electrochemical C-H Cyanation of Indoles. *Org. Lett.* **2021**, *23*, 5983−5987. (f) Dohi, T.; Morimoto, K.; Kiyono, Y.; Tohma, H.; Kita, Y. Novel and Direct Oxidative Cyanation Reactions of Heteroaromatic Compounds Mediated by A Hypervalent Iodine(III) Reagent. *Org. Lett.* **2005**, *7*, 537−540. (g) Yang, Y.; Zhang, Y.; Wang, J. Lewis Acid Catalyzed Direct Cyanation of Indoles and Pyrroles with N-Cyano-N-phenyl-p-toluenesulfonamide (NCTS). *Org. Lett.* **2011**, *13*, 5608−5611.
(11) (a) Becher, J.; Joergensen, P. L.; Pluta, K.; Krake, N. J.; Falt-Hansen, B. Azide ring-opening-ring-closure reactions and tele-substitutions in vicinal azidopyrazole-, pyrrole- and indolecarboxaldehydes. *J. Org. Chem.* **1992**, *57*, 2127−2134. (b) Srinivasan, P.; Jaisankar, P. A Facile Synthesis of 1-Phenylsulfonyl-3-substituted-2-cyanoindoles, 1-Phenylsulfonyl-2-methyl-3-cyanoindoles, and Bifunctional 1-Phenylsulfonylindoles. *Synthesis* **2006**, 2413−2417.
(12) (a) Meesin, J.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Leowanawat, P.; Kuhakarn, C. Synthesis of N-alkyl-3-sulfonylindoles and N-alkyl-3-sulfanylindoles by cascade annulation of 2-alkynyl-N,N-dialkylanilines. *Org. Biomol. Chem.* **2017**, *15*, 3662−3669. (b) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. Gold- and Indium-Catalyzed Synthesis of 3- and 6-Sulfonylindoles fromorthoAlkynyl-N-sulfonylanilines. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284−2287. (c) Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. Palladium-Catalyzed Difunctionalization of Alkynes via C-N and S-N Cleavages: A Versatile Approach to Highly Functional Indoles. *Org. Lett.* **2014**, *16*, 5124−5127. (d) Wu, C.; Zhao, F.; Du, Y.; Zhao, L.; Chen, L.; Wang, J.; Liu, H. Highly selective intramolecular addition of C-N and S-N bonds to alkynes catalyzed by palladium: a practical access to two distinct functional indoles. *RSC Adv.* **2016**, *6*, 70682−70690.
(13) (a) Li, X.; Zhang, B.; Zhang, J.; Wang, X.; Zhang, D.; Du, Y.; Zhao, K. Synthesis of 3-Methylthioindoles via Intramolecular Cyclization of 2-Alkynylanilines Mediated by DMSO / DMSO -d 6 and SOCl 2. *Chin. J. Chem.* **2021**, *39*, 1211−1224. (b) Ma, F.; Qian, J.; Lu, P.; Wang, Y. Convenient synthesis of 2-amino-3-(arylthio)-indoles via the Rh-catalyzed reaction of 3-diazoindol-2-imines with thioesters. *Org. Biomol. Chem.* **2018**, *16*, 439−443. (c) Gilow, H. M.; Brown, C. S.; Copeland, J. N.; Kelly, K. E. Sulfenylation of some pyrroles and indoles. *J. Heterocycl. Chem.* **1991**, *28*, 1025−1034.
(14) (a) Chen, G.; Xu, B. Mild Base-Promoted Tandem Nucleophilic Substitution/Decarboxylation/Hydroamination: Access to 3-Sulfonylindoles and 2-Methyleneindophenols. *Org. Lett.* **2021**, *23*, 9157−9162. (b) Chen, X.; Shatskiy, A.; Liu, J.-Q.; Kärkäs, D. M.; Wang, X.-S. Synthesis of Sulfonylated Heterocycles via Copper-Catalyzed Heteroaromatization/Sulfonyl Transfer of Propargylic Alcohols. *Chem.—Asian J.* **2021**, *16*, 30−33.
(15) (a) Ganesh, T.; Jiang, J.; Yang, M.-S.; Dingledine, R. Lead Optimization Studies of Cinnamic Amide EP2 Antagonists. *J. Med. Chem.* **2014**, *57*, 4173−4184. (b) Trabbic, C. J.; Overmeyer, J. H.; Alexander, E. M.; Crissman, E. J.; Kvale, H. M.; Smith, M. A.; Erhardt, P. W.; Maltese, W. A. Synthesis and Biological Evaluation of Indolyl-Pyridinyl-Propenones Having Either Methuosis or Microtubule Disruption Activity. *J. Med. Chem.* **2015**, *58*, 2489−2512. (c) Trabbic, C. J.; George, S. M.; Alexander, E. M.; Du, S.; Offenbacher, J. M.; Crissman, E. J.; Overmeyer, J. H.; Maltese, W. A.; Erhardt, P. W. Synthesis and biological evaluation of isomeric methoxy substitutions on anti-cancer indolyl-pyridinyl-propenones: Effects on potency and mode of activity. *Eur. J. Med. Chem.* **2016**, *122*, 79−91.
(16) Blobaum, A. L.; Uddin, M. J.; Felts, A. S.; Crews, B. C.; Rouzer, C. A.; Marnett, L. J. The 2′-Trifluoromethyl Analogue of Indomethacin Is a Potent and Selective COX-2 Inhibitor. *ACS Med. Chem. Lett.* **2013**, *4*, 486−490.
(17) Uddin, M. J.; Crews, B. C.; Huda, I.; Ghebreselasie, K.; Daniel, C. K.; Marnett, L. J. Trifluoromethyl Fluorocoxib A Detects Cyclooxygenase-2 Expression in Inflammatory Tissues and Human Tumor Xenografts. *ACS Med. Chem. Lett.* **2014**, *5*, 446−450.
(18) (a) Muzalevskiy, V. M.; Sizova, Z. A.; Abaev, V. T.; Nenajdenko, V. G. An Efficient Approach to 2-CF3-Indoles Based on ortho-Nitrobenzaldehydes. *Molecules* **2021**, *26*, 7365. (b) Muzalevskiy, V. M.; Sizova, Z. A.; Nenajdenko, V. G. An Efficient Synthesis of 2-CF3-3-Benzylindoles. *Molecules* **2021**, *26*, 5084. (c) Muzalevskiy, V. M.; Sizova, Z. A.; Nenajdenko, V. G. Modular Construction of Functionalized 2-CF3-Indoles. *Org. Lett.* **2021**, *23*, 5973−5977.
(19) (a) Bock, L.; Schultheiß, S. K.; Maschauer, S.; Lasch, R.; Gradl, S.; Prante, O.; Zard, S. Z.; Heinrich, M. R. Synthesis of 2-

https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511

(Chlorodifluoromethyl)indoles for Nucleophilic Halogen Exchange with [18 F]Fluoride. *Eur. J. Org. Chem.* **2021**, 6258−6262. (b) Usachev, B. I. 1-/2-/3-Fluoroalkyl-substituted indoles, promising medicinally and biologically beneficial compounds: Synthetic routes, significance and potential applications. *J. Fluorine Chem.* **2016**, *185*, 118−167.

(20) (a) Maassarani, F.; Pfeffer, M.; Spencer, J.; Wehman, E. Selective hetero- and carbo-cycle syntheses via masked cyclo-palladated secondary amine and ketone functions. *J. Organomet. Chem.* **1994**, *466*, 265−271. (b) Unangst, P. C.; Connor, D. T.; Stabler, S. R. Synthesis of novel 1-phenyl-1H-indole-2-carboxylic acids.II.Preparation of 3-dialkylamino, 3-alkylthio, 3-alkylsulfinyl, and 3-alkylsulfonyl derivatives. *J. Heterocycl. Chem.* **1987**, *24*, 817−820.

(21) Liu, J.; Obando, D.; Liao, V.; Lifa, T.; Codd, R. The many faces of the adamantyl group in drug design. *Eur. J. Med. Chem.* **2011**, *46*, 1949−1963.

(22) Anderegg, G. Die Cyanokomplexe des Quecksilbers. *Helv. Chim. Acta* **1957**, *40*, 1022−1026.

(23) Burkhard, R. K.; Sellers, D. E.; DeCOU, F.; Lambert, J. L. The pKa's of Aromatic Sulfinic Acids1. *J. Org. Chem.* **1959**, *24*, 767−769.

(24) Foschi, F.; Tagliabue, A.; Mihali, V.; Pilati, T.; Pecnikaj, I.; Penso, M. Memory of Chirality Approach to the Enantiodivergent Synthesis of Chiral Benzo[d]sultams. *Org. Lett.* **2013**, *15*, 3686−3689.

https://doi.org/10.1021/acsomega.2c03754
ACS Omega 2022, 7, 38505−38511