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, research in this field is still in demand today, mostly due to the importance of the indole core in drug design, which is attributed to the wide range of biological activity they demonstrate. 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, inhibitor of tumor-related protein kinases 2, antithrombotic factor Xa inhibitors, and 5-HT6 receptor ligand 3. 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.

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

As for 1,2-disubstituted-3-tosyl indoles, the most efficient strategies for their preparation are the intramolecular cyclization of o-aminobenzenses, oxidation of their corresponding thioethers, or direct construction of the indole ring from a suitable starting material. It is also worth mentioning that 2-trifluoromethylindoles are promising bioactive compounds. Moreover, 1,3-disubstituted-2-trifluoromethylindoles can show biological activity, for example, the selective inhibitor activity against cyclooxygenase-2, which can be used for optical imaging. However, despite the synthetic availability of various 2-trifluoromethyl indoles, 1-substituted-2-trifluoromethyl-3-cyano indoles are poorly describe-d, 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.

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 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-TolSO₂Na made it possible to obtain compound 5 at 90% yield after 12 h in DMSO at 25 °C.
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 5a 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$^-$ is a stronger base than p-TolSO$_2$; 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)$^{ac}$

| $^{ac}$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. | 38506 | http://dx.doi.org/10.1021/acsomega.2c03754 | ACS Omega 2022, 7, 38505–38511 |
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

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

| 5a-5o | p-TolSO₂Na, 12 h; then DBN 12 h | 6a-8o |
|-------|-------------|-------|
| Ts    | Ph          |       |
| 6a, 89% | 6b, 87% | 6c, 88% |
| Ts    | Ph          |       |
| 6d, 79% | 6e, 72% | 6f, 83% |
| Ts    | Br          |       |
| 6g, 84% | 6h, 81% | 6l, 80% |
| Ts    | Br          |       |
| 6j, 61% | 6k, 86% | 6l, 83% |
| Ts    | CF₃         |       |
| 6m, 81% | 6n, 82% | 6o, 78% |
| Ts    | CF₃         |       |
| 6p, 71 | 6q, 44% |

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

| 5a-5o, 5n-5o | KCN, 12 h; then DBN 12 h | 7a-7l, 7n-7o |
|---------------|-----------------|--------------|
| CN            | Ph              |               |
| 7a, 88% (69%) | 7b, 87% (81%) | 7c, 84% (81%) |
| CN            | Ph              |               |
| 7d, 71% (66%) | 7e, 51% (56%) | 7f, 78% (72%) |
| CN            | Br              |               |
| 7g, 85% (31%) | 7h, 77% (22%) | 7i, 84% (43%) |
| CN            | Br              |               |
| 7j, 77% (67%) | 7k, 81% (76%) | 7l, 85% (80%) |
| CN            | MeO             |               |
| 7n, 77% (74%) | 7r, 84% (74%) | 7o, 74% (73%) |
| CN            | Ph              |               |
| 7p, 75% (70%) | 7q, 61% (56%) |              |

*Reaction conditions: 5 (0.5 mmol), p-TolSO₂Na (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.
indoles on its own. In turn, DBN 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 H₂O 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 substituents, even those that could not be obtained before: 1-aryl-2-(trifluoromethyl)-3-cyano 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 together with the halogen lamp was wrapped in aluminum foil. Shortly after the start of illumination of the reaction flask, the reaction mixture was submitted to column 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 1H NMR, 13C NMR, 19F NMR, FTIR, and high resolution mass spectrometry (HRMS). NMR spectra were obtained using a Bruker "Ascend 400" (400 MHz 1H, 101 MHz 13C, 376 MHz 19F). 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. 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 CH₂Cl₂. The combined organic phase was dried over Na₂SO₄, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH₂Cl₂ 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. 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/CH₂Cl₂ as eluent) to afford 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 CCl₄. 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
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 (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 CH₂Cl₂. The combined organic layer was washed three times with water, dried over Na₂SO₄, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH₂Cl₂ 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 (0.5 mmol), p-TolSO₂Na (0.357 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 CH₂Cl₂. The combined organic layer was washed three times with water, dried over Na₂SO₄, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (a mixture of PE/CH₂Cl₂ as eluent) to give the desired product 6 as white to pale yellow solid.

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5b–5fsh–5p

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