



Short Note

3,3,3',3'-Tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole

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Abstract: The palladium-catalyzed homocoupling of 5-iodo-3,3-dimethyl-2-phenyl-3*H*-indole afforded 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole in 65% yield. This previously unreported compound was fully characterized by NMR, IR and HRMS data and its optical properties were studied by UV/vis and fluorescence spectroscopy.

Keywords: biheterocycle; fluorescence; homocoupling; indole; palladium-catalyzed

1. Introduction

Bi(hetero)aryls are common structural motifs in natural products [1,2], numerous industrial chemicals, including pharmaceuticals and agrochemicals, and technology [3–6]. Symmetrical biheterocyclic compounds are particularly important building blocks for the synthesis of functional organic materials. For instance, 4,4'-bipyridine (I) is commonly used in the synthesis of viologen compounds for optoelectronic applications [7], 6,6'-biquinoline (II) was used to prepare luminescent one-dimensional coordination polymers [8], 9*H*,9'*H*-3,3'-bicarbazole (III) was used for the synthesis of a cross-linkable hole-transporting polymer for organic light-emitting diodes (OLEDs) [9], 1*H*,1'*H*-6,6'-biindole (IV) provides a core for glycoprotein 41 targeting HIV-1 fusion inhibitors [10], and 2,2',3,3',3'-hexamethyl-3*H*,3'*H*-5,5'-biindole (V) was used to prepare reversible photoisomerization possessing bis-spiropyran derivatives [11] (Figure 1).

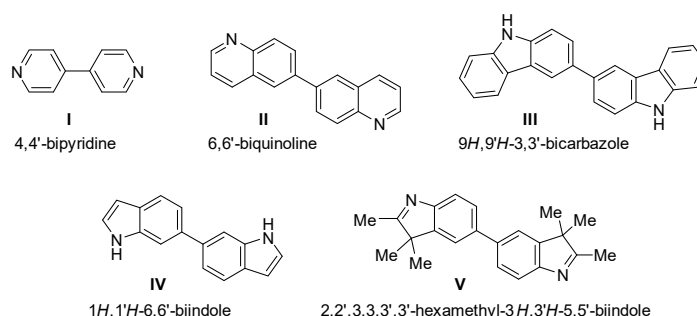


Figure 1. Examples of synthetically relevant biheterocycles.

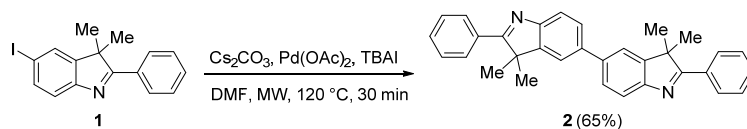
Thus, in a continuation of our work devoted to studying the fluorescence properties of various fused [12–14] and aryl coupled [15–17] indole derivatives, and in view of the importance of biheterocyclic compounds in current organic chemistry, the aim of the present work was the

synthesis of 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole as a novel fluorescent building block, through the Ullmann-type homocoupling reaction of 5-iodo-3,3-trimethyl-2-phenyl-3*H*-indole.

2. Results and Discussion

Synthesis of biaryl compounds is enabled by carbon–carbon coupling reactions that are among the most important tools in current organic synthesis [18]. The Ullmann reaction is a well-known homocoupling method that is commonly used for the synthesis of symmetrical biaryls [19]. The classical Ullmann reaction, however, has limited application due to its major drawback, i.e., the necessity for high reaction temperatures, often reaching as high as 250 °C. To tackle this problem, new methodologies are being extensively developed to assess symmetrical biaryl compounds [20,21]. Among them, palladium-catalyzed Ullmann cross-coupling reactions proved to be superior, proceeding under relatively mild conditions (often under 100 °C) over short periods of time [22].

A fast Pd(OAc)₂-catalyzed homocoupling of 5-iodo-3,3-dimethyl-2-phenyl-3*H*-indole **1** with Cs₂CO₃ as a base and tetrabutylammonium iodide (TBAI) as a phase-transfer catalyst proceeded smoothly under microwave irradiation, affording 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole **2** in 65% yield (Scheme 1).



Scheme 1. Synthesis of 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole.

The structure assignment of symmetrical biheterocyclic Compound **2** was based on spectral data (Figures S1–S9). The high-resolution mass spectrum (HRMS) of the newly formed compound showed a molecular ion peak at m/z 441.2327 [M + H]⁺ that, in combination with advanced nuclear magnetic resonance (NMR) spectroscopy techniques, easily indicated the formation of 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole. Protons of geminal CH₃ groups showed nuclear Overhauser effects (NOEs) both with the neighboring protons from diphenyl (δ 8.18 ppm) and biindole (δ 7.59 ppm) moieties. These assignments were deduced from the total correlation spectroscopy (TOCSY) spectrum that clearly showed two different spin systems of ten and six aromatic protons. Moreover, the examination of homonuclear correlation spectroscopy (COSY) spectrum revealed that the aforementioned protons from the biindole spin system did not share any cross peaks, which suggested a nonprotonated neighboring carbon. The ¹H-¹³C heteronuclear single quantum coherence (HSQC) spectrum indicated that these protons have a one-bond correlation with the carbon at δ 119.9 ppm. In combination with the data from the adequate double quantum transfer experiment (1,1-ADEQUATE), this allowed adjacent quaternary carbons C-5 and C-3a to be assigned to signals at δ 139.3 and 148.4 ppm, respectively. Protonated carbon C-6 showed a correlation with a quaternary carbon C-5 in the 1,1-ADEQUATE spectrum, which also revealed correlations of C-7 with C-7a, respectively. Moreover, data from the ¹H-¹³C heteronuclear multiple bond correlation (HMBC) spectrum allowed us to connect the diphenyl and biindole fragments via long-range correlations, thus eliminating any ambiguity in the elucidation of the target structure (Figure 2).

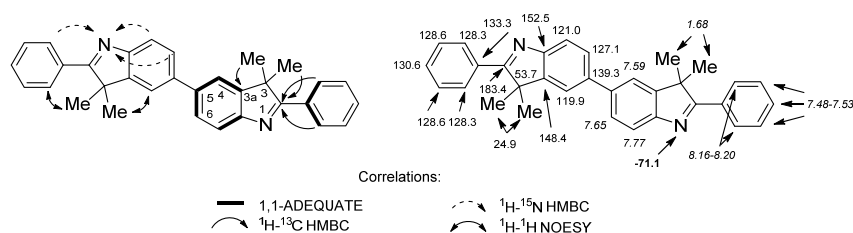


Figure 2. Relevant 1,1-ADEQUATE, ¹H-¹³C HMBC, ¹H-¹⁵N HMBC, ¹H-¹H NOESY correlations and ¹H NMR (in italics), ¹⁵N NMR (in bold) and ¹³C NMR chemical shifts of Compound 2.

The optical properties of Compound 2 were investigated by UV/vis spectroscopy and fluorimetric measurement. The electronic absorption spectra of Compound 2 in tetrahydrofuran (THF) contained intense absorption bands with $\lambda_{\max} = 371, 332,$ and 244 nm, while the fluorescence spectra displayed an emission maximum at 437 nm with a Stokes shift of 66 nm (Figure 3). The fluorescence quantum yield (Φ_f) of the solution was estimated by the integrating sphere method and gave the value of 67% .

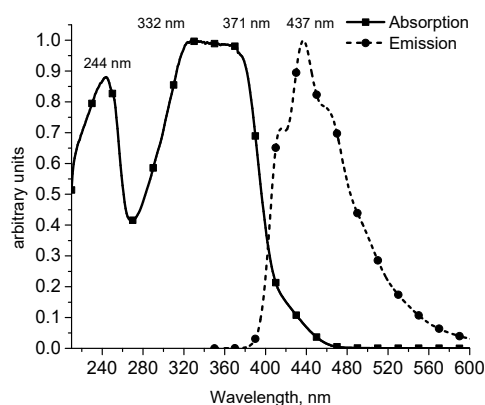


Figure 3. Absorption and emission ($\lambda_{\text{ex}} = 350$ nm) spectrum of Compound 2 in THF.

3. Materials and Methods

3.1. General

5-Iodo-3,3-dimethyl-2-phenyl-3*H*-indole was prepared in accordance to previously published procedure [23]. All other chemicals and solvents were purchased from commercial suppliers and used without further purification unless otherwise specified. Prior to use, *N,N*-dimethylformamide (DMF) was stored over molecular sieves (4 \AA). The ¹H, ¹³C and ¹⁵N NMR spectra were recorded in chloroform-*D* (CDCl₃) at $25 \text{ }^\circ\text{C}$ on a Bruker Avance III 700 (700 MHz for ¹H, 176 MHz for ¹³C, 71 MHz for ¹⁵N) spectrometer equipped with a 5 mm TCI ¹H-¹³C/¹⁵N/D z-gradient cryoprobe (Bruker BioSpin). The chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). The ¹⁵N NMR spectrum was referenced to neat, external nitromethane (coaxial capillary). The full and unambiguous assignments of the ¹H, ¹³C, and ¹⁵N-NMR resonances were achieved using standard Bruker software (TopSpin 3.5.6) and a combination of standard NMR spectroscopic techniques, such as distortionless enhancement by polarization transfer (DEPT), COSY, TOCSY, nuclear Overhauser effect spectroscopy (NOESY), gradient-selected heteronuclear single quantum coherence (gs-HSQC), gradient-selected heteronuclear multiple bond correlation (gs-HMBC), heteronuclear 2-bond correlation (H2BC), and 1,1-ADEQUATE experiments. The infrared (IR) spectra were recorded on a Bruker TENSOR 27 spectrometer (Bruker Optics) using potassium bromide (KBr) pellets. The melting point was determined in open capillary tubes with a Büchi M-565 apparatus (temperature gradient: $2 \text{ }^\circ\text{C}/\text{min}$) and is uncorrected (Büchi Labortechnik AG, Switzerland). HRMS spectrum was obtained in electrospray ionization (ESI) mode on a Bruker MicroTOF-Q III spectrometer (Bruker Daltonics). The UV/vis spectrum was recorded using 10^{-4} M solution of the compound in THF on a Shimadzu

2600 UV/vis spectrometer (Shimadzu Corporation, Japan). The fluorescence spectrum was recorded on a FL920 fluorescence spectrometer from Edinburgh Instruments. The photoluminescence (PL) quantum yield was measured from dilute THF solution by an absolute method using the Edinburgh Instruments (Edinburgh Analytical Instruments Limited, Edinburgh, UK) integrating sphere excited with a Xe lamp. Optical density of the sample solution was ensured to be below 0.1 to avoid reabsorption effects. All optical measurements were performed at rt under ambient conditions. The microwave-assisted reaction was conducted in a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, USA), which consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. The reaction was performed in glass vessel (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the vessel contents was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction was performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Reaction progress was monitored by thin-layer chromatography (TLC) analysis on Macherey-Nagel™ ALUGRAM® Xtra SIL G/UV₂₅₄ plates. TLC plates were visualized with ultraviolet (UV) light (wavelengths 254 and 365 nm) or iodine vapor. Compounds were purified by flash chromatography in a glass column (stationary phase—silica gel, high-purity grade 9385, pore size 60 Å, particle size: 230–400 mesh, supplier Sigma-Aldrich).

3.2. Synthesis

A sealed vessel containing a mixture of 5-iodo-3,3-dimethyl-2-phenyl-3*H*-indole **1** [23] (200 mg, 0.58 mmol), cesium carbonate (188 mg, 0.58 mmol), palladium(II) acetate (17 mg, 0.08 mmol) and tetrabutylammonium iodide (213 mg, 0.58 mmol) in dry dimethylformamide (3 mL) was irradiated (150 W) under Ar atmosphere at 120 °C for 30 min. Upon completion, the reaction mixture was cooled down to room temperature, diluted with distilled water (50 mL) and extracted with ethyl acetate (EtOAc) (4 × 25 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 4:1 v/v) to afford Compound **2** as a yellow solid (82 mg, 65% yield). M.p. 238–239 °C. *R*_f = 0.35 (*n*-hexane/ethyl acetate 4:1 v/v). IR (KBr) $\nu(\text{cm}^{-1})$: 3047 (CH_{arom}), 2983, 2965, 2927, 2864 (CH_{aliph}), 1647, 1598, 1515, 1452, 1439, 1386, 1284, 1223, 1175, 1074 (C=C, C=N, CH₃ bending, C–N), 986, 941, 915, 874, 815, 783, 774, 696, 690 (CH_{aromatic} out-of-plane bending). ¹H NMR (700 MHz, CDCl₃, ppm): δ 1.68 (s, 12H, Ind 3-(CH₃)₂), 7.48–7.53 (m, 6H, C-Ph 3,4,5-H), 7.59 (d, *J* = 1.7 Hz, 2H, Ind 4-H), 7.65 (dd, *J* = 7.9, 1.8 Hz, 2H, Ind 6-H), 7.77 (d, *J* = 7.9 Hz, 2H, Ind 7-H), 8.16–8.20 (m, 4H, C-Ph 2,6-H). ¹³C NMR (176 MHz, CDCl₃, ppm): δ 24.9 (Ind 3-(CH₃)₂), 53.7 (Ind C-3), 119.9 (Ind C-4), 121.0 (Ind C-7), 127.1 (Ind C-6), 128.3 (C-Ph C-2,6), 128.6 (C-Ph C-3,5), 130.6 (C-Ph C-4), 133.3 (C-Ph C-1), 139.3 (Ind C-5), 148.4 (Ind C-3a), 152.5 (Ind C-7a), 183.4 (Ind C-2). ¹⁵N NMR (71 MHz, CDCl₃, ppm): δ –71.1. HRMS (ESI-TOF) for C₃₂H₂₉N₂ ([M + H]⁺): calcd. 441.2325; found 441.2327.

4. Conclusions

In this short note, we reported the synthesis, structure and optical properties elucidation of 3,3,3',3'-tetramethyl-2,2'-diphenyl-3*H*,3'*H*-5,5'-biindole **2**. The fluorescence quantum yield (Φ_f) of the Compound **2** in THF was determined to be 67%.

Supplementary Materials: The following are available online, 2D MDL molfile of Compound **2**. Figure S1: ¹H NMR spectrum of Compound **2**, Figure S2: ¹H 1D selective gradient NOESY spectrum of Compound **2**, Figure S3: ¹³C NMR spectrum of Compound **2**, Figure S4: ¹³C NMR and DEPT-135 ¹³C NMR spectrum of Compound **2**, Figure S5: ¹H-¹⁵N HMBC NMR spectrum of Compound **2**. Figure S6: The overlaid ¹H-¹³C gs-HSQC and 60 Hz 1,1-ADEQUATE NMR spectra of Compound **2**. Figure S7: The overlaid ¹H-¹³C gs-HSQC and gs-HMBC NMR spectra of Compound **2**. Figure S8: ¹H-¹H TOCSY NMR spectrum of Compound **2**. Figure S9: ¹H-¹H COSY NMR spectrum of Compound **2**. Figure S10: HRMS spectrum of Compound **2**.

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References

1. Kozłowski, M.C.; Morgan, B.J.; Linton, E.C. Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. [[CrossRef](#)]
2. Bringmann, G.; Gulder, T.; Gulder, T.A.M.; Breuning, M. Atroposelective total synthesis of axially chiral biaryl natural products. *Chem. Rev.* **2011**, *111*, 563–639. [[CrossRef](#)]
3. Asmar, R. Telmisartan in high cardiovascular risk patients. *Eur. Cardiol.* **2012**, *8*, 10–16. [[CrossRef](#)]
4. Van der Bom, T.; Winter, M.M.; Bouma, B.J.; Groenink, M.; Vliegen, H.W.; Pieper, P.G.; van Dijk, A.P.J.; Sieswerda, G.T.; Roos-Hesselink, J.W.; Zwinderman, A.H.; et al. Effect of valsartan on systemic right ventricular function: A double-blind, randomized, placebo-controlled pilot trial. *Circulation* **2013**, *127*, 322–330. [[CrossRef](#)]
5. Matheron, M.E.; Porchas, M. Activity of boscalid, fenhexamid, fluazinam, fludioxonil, and vinclozolin on growth of *Sclerotinia minor* and *S. sclerotiorum* and development of lettuce drop. *Plant Dis.* **2004**, *88*, 665–668. [[CrossRef](#)] [[PubMed](#)]
6. Zhang, H.C.; Huang, W.S.; Pu, L. Biaryl-based macrocyclic and polymeric chiral (salophen)Ni(II) complexes: Synthesis and spectroscopic study. *J. Org. Chem.* **2001**, *66*, 481–487. [[CrossRef](#)] [[PubMed](#)]
7. Ding, J.; Zheng, C.; Wang, L.; Lu, C.; Zhang, B.; Chen, Y.; Li, M.; Zhai, G.; Zhuang, X. Viologen-inspired functional materials: Synthetic strategies and applications. *J. Mater. Chem. A* **2019**, *7*, 23337–23360. [[CrossRef](#)]
8. Bryleva, Y.A.; Glinskaya, L.A.; Antonova, O.V.; Kokina, T.E.; Larionov, S.V. Coordination polymer [Sm(Biq)(*iso*-Bu₂PS₂)₃]_n: Synthesis, structure, and photoluminescence. *Russ. J. Coord. Chem. Khimiya* **2014**, *40*, 184–188. [[CrossRef](#)]
9. Lee, J.H.; Jeong, C.H.; Godumala, M.; Kim, C.Y.; Kim, H.J.; Hwang, J.H.; Kim, Y.W.; Choi, D.H.; Cho, M.J.; Choi, D.H. Rational design, synthesis, and characterization of a photocrosslinkable hole-transporting polymer for high performance solution-processed thermally activated delayed fluorescence OLEDs. *J. Mater. Chem. C* **2020**, *8*, 4572–4579. [[CrossRef](#)]
10. Zhou, G.; Sofiyev, V.; Kaur, H.; Snyder, B.A.; Mankowski, M.K.; Hogan, P.A.; Ptak, R.G.; Gochin, M. Structure-activity relationship studies of indole-based compounds as small molecule HIV-1 fusion inhibitors targeting glycoprotein 41. *J. Med. Chem.* **2014**, *57*, 5270–5281. [[CrossRef](#)]
11. Lee, S.; Ji, S.; Kang, Y.J. Synthesis and characterizations of bis-spiropyran derivatives. *Bull. Korean Chem. Soc.* **2012**, *33*, 3740–3744. [[CrossRef](#)]
12. Steponavičiūtė, R.; Martynaitis, V.; Bieliauskas, A.; Šačkus, A. Synthesis of new fluorescent building blocks via the microwave-assisted annulation reaction of 1,1,2-trimethyl-1*H*-benzo[*e*]indole with acrylic acid and its derivatives. *Tetrahedron* **2014**, *70*, 1967–1974. [[CrossRef](#)]
13. Buinauskaitė, V.; Martynaitis, V.; Mangelinckx, S.; Kreiza, G.; De Kimpe, N.; Šačkus, A. Facile synthesis of spiro[benzo[*e*]indole-2,2'-piperidine] derivatives and their transformation to novel fluorescent scaffolds. *Tetrahedron* **2012**, *68*, 9260–9266. [[CrossRef](#)]
14. Ragaitė, G.; Martynaitis, V.; Kriščiūnienė, V.; Kleizienė, N.; Redeckas, K.; Voiciuk, V.; Vengris, M.; Šačkus, A. Fast and stable light-driven molecular switch based on a 5*a*,13-methanoindolo [2,1-*b*][1,3]benzoxazepine ring system. *Dye. Pigment.* **2015**, *113*, 546–553. [[CrossRef](#)]
15. Žukauskaitė, Ž.; Buinauskaitė, V.; Solovjova, J.; Malinauskaitė, L.; Kveselytė, A.; Bieliauskas, A.; Ragaitė, G.; Šačkus, A. Microwave-assisted synthesis of new fluorescent indoline-based building blocks by ligand free Suzuki-Miyaura cross-coupling reaction in aqueous media. *Tetrahedron* **2016**, *72*, 2955–2963. [[CrossRef](#)]
16. Voiciuk, V.; Redeckas, K.; Martynaitis, V.; Steponavičiūtė, R.; Šačkus, A.; Vengris, M. Improving the photochromic properties of indolo[2,1-*b*][1,3]benzoxazines with phenylic substituents. *J. Photochem. Photobiol. A Chem.* **2014**, *278*, 60–68. [[CrossRef](#)]

17. Buinauskaitė, V.; Dargytė, M.; Šačkus, A. Synthesis and microwave-promoted Suzuki-Miyaura cross-coupling reactions of 5-bromo-1,3,3-trimethyl-1,3-dihydro-6'H-spiro[indole-2,2'-piperidin]-6'-one. *Chemija* **2012**, *23*, 322–327.
18. Yin, L.; Liebscher, J. Carbon-carbon coupling reactions catalyzed by heterogeneous palladium catalysts. *Chem. Rev.* **2007**, *107*, 133–173. [[CrossRef](#)] [[PubMed](#)]
19. Fanta, P.E. The Ullmann Synthesis of Biaryls, 1945-1963. *Chem. Rev.* **1964**, *64*, 613–632. [[CrossRef](#)]
20. Stefani, H.A.; Guarezemini, A.S.; Cella, R. Homocoupling reactions of alkynes, alkenes and alkyl compounds. *Tetrahedron* **2010**, *66*, 7871–7918. [[CrossRef](#)]
21. Vasconcelos, S.N.S.; Reis, J.S.; de Oliveira, I.M.; Balfour, M.N.; Stefani, H.A. Synthesis of symmetrical biaryl compounds by homocoupling reaction. *Tetrahedron* **2019**, *75*, 1865–1959. [[CrossRef](#)]
22. Khan, F.; Dlugosch, M.; Liu, X.; Banwell, M.G. The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process. *Acc. Chem. Res.* **2018**, *51*, 1784–1795. [[CrossRef](#)] [[PubMed](#)]
23. Tomasulo, M.; Salvatore Sortino, A.; Francisco, M. Raymo Bichromophoric Photochromes Based on the Opening and Closing of a Single Oxazine Ring. *J. Org. Chem.* **2008**, *73*, 118–126. [[CrossRef](#)] [[PubMed](#)]



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