

Microwave synthesis of 2-[(*E*)-2-(1*H*-indol-3-yl)vinyl]hetarenes

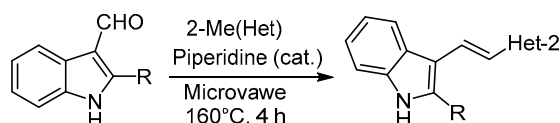
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A new highly efficient method for the condensation of (indol-3-yl)carbaldehydes with 2-methylazoles and 2-methylazines under activation with microwave irradiation is developed. The method provides high yields of structural scaffolds of bishetarylethylene fluorescent sensors that found widespread application in medicinal, bioorganic, and pharmaceutical chemistry.

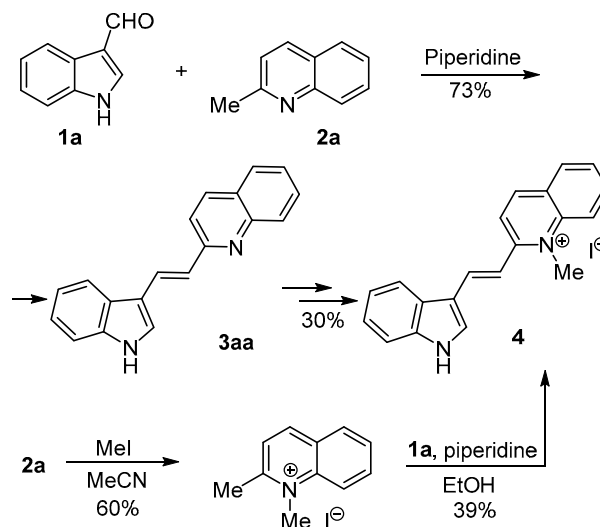
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Clinical treatment of a range of neurological and psychiatric dysfunctions as well as some cardiovascular and oncological conditions calls for diagnostic procedures whose merit strongly depends on efficiency of RNA visualization.^{1,2} Oftentimes the correct choice of RNA-selective sensors suitable for *in vivo* applications becomes a key problem.^{2,3} Among available visualization agents the most commonly used are commercially available cyanine dyes. However, most of these compounds suffer from notable photosensitivity and limited RNA selectivity, which creates certain problems with their utilization for frame-by-frame imaging of live cell samples.⁴

Recently, new luminescent probes of type E36, 2-[(*E*)-2-(1*H*-indol-3-yl)vinyl]-1-methylquinolinium iodide,^{4,5} were introduced. These substances proved suitable for investigation of cell nuclei and identification of particular fragments of RNA in living cells and demonstrated significantly improved photostability and selectivity as compared to traditional cyanine-type sensors, especially for *in vivo* analyses. Furthermore, molecules of this structural type found applications as highly selective contrast fluorescent probes for analyses of nucleic and peptidonic acids.⁶ In addition, important biological properties were discovered for some of related structures, including anticancer⁷ and antimalarial⁸ activity, as well as inhibiting of HIV.⁹ Not surprisingly, there is a great interest to synthesis of compounds of this structural type.

In his recent work Zheng² proposed synthesis of E36 dye (**4**) via *N*-alkylation of heterostilbene **3aa** with a previously protected indolyl nitrogen atom. The overall yield of the target material according to this scheme did not exceed 21% (Scheme 1). A different synthetic approach suggested in the same report involved initial quaternization of quinaldine (**2a**) and subsequent condensation of the formed salt with aldehyde **1a**. However, this alternative protocol also did not provide marked improvement and afforded the yields of about 23–24%.²

Scheme 1



Here and further the corresponding author is marked with*.

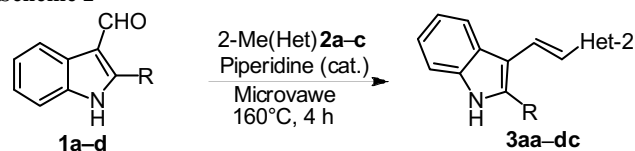
Apparently, the existing synthetic protocols for this condensation, illustrated with the typical examples described above, are greatly limited, which lowers their potential for combinatorial synthesis targeted for building collections of fluorescent analytical probes or libraries for bio-medicinal screening. It should be mentioned, that such condensations involving indol-3-carbaldehydes substituted at position 2 have never been reported.

In the frame of multidisciplinary research project executed in our laboratories concerning the synthetic¹⁰ and medicinal¹¹ chemistry of indole derivatives, we became interested in this challenge. We hypothesized that a general and highly efficient protocol for condensation of indole-3-carbaldehydes with various methylazines and azoles could be developed employing microwave activation. To test this idea, the mixtures of aldehyde **1a** and quinaldine (**2a**), without solvent, in the presence of catalytic amounts of piperidine were heated in a microwave reactor at varied temperatures, and the conversions were monitored by chromatography. Additionally, we found that it was convenient to monitor the reaction progress by ¹H NMR spectroscopy, since the almost equimolar ratio of reactants allowed for easily assessment of the starting aldehyde consumption. This method also provides the opportunity to observe accumulation of well-resolved signals of condensation product **3aa**. Optimized reaction conditions involved isothermic heating of the neat mixtures of starting materials in the presence of catalytic amounts of piperidine (20 mol %) at 160°C for 4 h. Under these conditions, condensation product **3aa** was formed quantitatively, while preparative yield of the purified material was 95% (Scheme 2). The structure and *trans*-configuration of the double bond in this molecule were unambiguously assigned by X-ray crystallography (Fig. 1). Indole-3-carbaldehydes substituted at position 2, (2-methyl-1*H*-indol-3-yl)carbaldehyde (**1b**), (2-phenyl-1*H*-indol-3-yl)carbaldehyde (**1c**), and [2-(naphth-2-yl)-1*H*-indol-3-yl]carbaldehyde (**1d**), also reacted with quinaldine (**2a**) under identical conditions. Although an increase in steric hindrance causes a notable decrease of the process efficacy, the corresponding heterostilbenes **3ba**, **3ca**, and **3da** could be obtained in quite high isolated yields. Similarly, reactions involving 2-methylbenzoxazole (**2c**) proceeded readily under identical conditions leading to formation of vinyloxazoles **3ac**, **3bc**, **3cc**, and **3dc**.

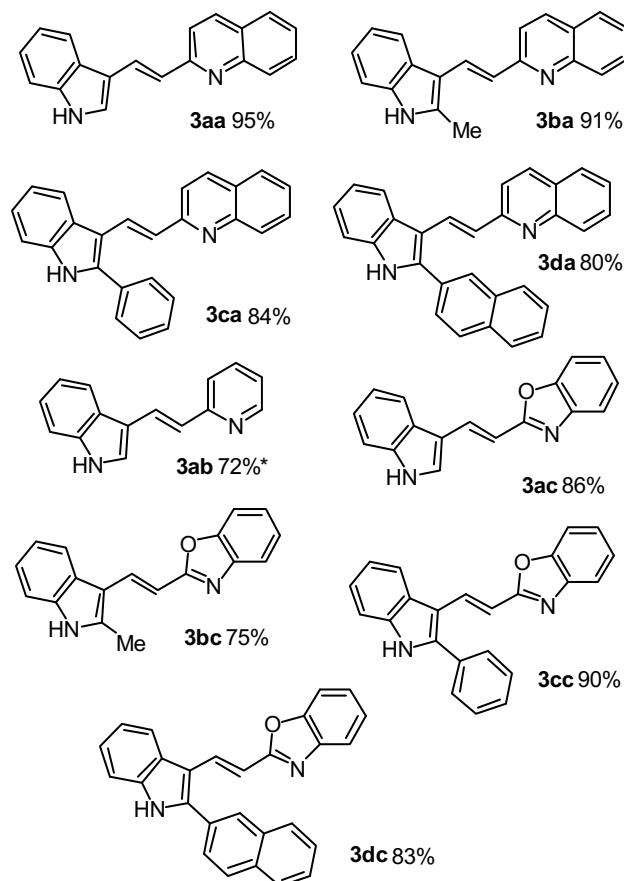
The reaction between 1*H*-indole-3-carbaldehyde (**1a**) and 2-picoline (**2b**) proceeded very sluggishly under standard conditions affording complex mixtures of side products that did not contain a *trans*-double bond according to ¹H NMR spectral analysis. Additional optimization allowed an alternative protocol involving heating the reaction at higher temperature over shorter period of time (2 h at 240°C) in the presence of DBU used as a base. Such modification allowed for isolation of product **3ab**, albeit in somewhat lower yield due to partial decomposition of the reaction mixtures (Scheme 2).

In conclusion, a new green method was developed, allowing for efficient preparative synthesis of compounds that contain non-symmetrical bis(hetarylethylene) structural motif, and are of great interest for bioorganic and medicinal

Scheme 2



1a R = H, **1b** R = Me, **1c** R = Ph, **1d** R = 2-naphthyl;
2a quinaldine, **2b** 2-picoline, **2c** 2-methylbenzoxazole



* Reaction conditions: DBU, MW, 240°C, 2 h.

chemistry. The synthesis involves condensation of indole-3-carbaldehydes with 2-methylated nitrogen heterocycles, and is carried out without solvent in the presence of catalytic amounts of organic base under microwave activation. Compared to previously described analogs, the featured process allowed for significant improvement of yields and successful utilization of even most stubborn sterically hindered aldehydes substituted at position 2.

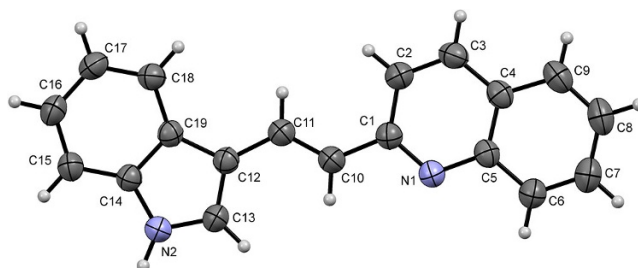


Figure 1. Crystal structure of compound **3aa** showing 50% probability amplitude displacement ellipsoids.

Experimental

IR spectra were registered on a FT-IR spectrometer Shimadzu IRTracer-100 with attenuated total reflectance unit PIKE MIRacle. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer (400 or 100 MHz, respectively) in CDCl_3 , using TMS as internal standard. High-resolution mass spectra (ESI TOF) were measured on a Bruker mAxis Impact spectrometer in $\text{MeCN-H}_2\text{O}$ solutions, employing $\text{HCO}_2\text{Na-HCO}_2\text{H}$ for calibration. Melting points were measured using Stuart SMP30 apparatus. Reaction progress and purity of isolated compounds was controlled by TLC on precoated Kavalier SILUFOL UV-254 plates, eluting with mixture EtOAc-hexane , 1:3. All reactions were carried out in G10 vessels heated in microwave oven Anton Paar Monowave 300 with automated temperature control. The following abbreviations are used to name different aromatic and heterocyclic cores in ^1H NMR spectra: Qu – quinoline; Ind – indole, Py – pyridine, Bxl – benzoxazole, Naph – naphthalene.

Preparation of 2-[(E)-2-(1H-indol-3-yl)vinyl]hetarenes 3aa–dc (General method). A reaction vessel was charged with 1H-indole-3-carbaldehyde **1a–d** (2.5 mmol), 2-methylhetarene **2a–c** (3.0 mmol), and piperidine (0.05 ml, 0.5 mmol), and the mixture was stirred and heated in microwave reactor at 160°C for 4 h. Then, the reaction mixture was cooled down and quantitatively transferred to another vessel employing CH_2Cl_2 (3×10 ml). Solutions of compounds **3aa** and **3ac** were evaporated in vacuum and the residual solids were recrystallized from EtOH. Solutions of other products were concentrated and the residues were purified by flash column chromatography on silica gel eluting with 5% solution of isopropanol in CH_2Cl_2 . Note: DBU (0.075 ml, 0.5 mmol) was used as a base to perform reaction between 1H-indole-3-carbaldehyde (**1a**) and 2-methylpyridine (**2b**); the mixture was microwaved at 240°C for 2 h.

2-[(E)-2-(1H-Indol-3-yl)vinyl]quinoline (3aa). Yield 641 mg (95%), orange crystals, mp $209\text{--}210^\circ\text{C}$ (EtOH) (mp $212\text{--}213^\circ\text{C}^{12}$), R_f 0.45. IR spectrum, ν , cm^{-1} : 3403, 3161, 3053, 2921, 2854, 4600, 1505, 1455, 1423, 1337, 1312, 1221, 1141, 1009, 820, 740. ^1H NMR spectrum, δ , ppm (J , Hz): 8.49 (1H, br. s, NH); 8.14–8.12 (1H, m, H Ind); 8.11 (1H, d, $J = 8.5$, H Qu); 8.08 (1H, d, $J = 9.0$, H Qu); 7.95 (1H, d, $J = 16.4$, CH=); 7.77 (1H, d, $J = 7.9$, H Qu); 7.71–7.68 (1H, m, H Qu); 7.68 (1H, d, $J = 8.5$, H Qu); 7.53 (1H, d, $J = 2.5$, H Ind); 7.47–7.45 (1H, m, H Qu); 7.44 (1H, d, $J = 16.4$, CH=); 7.44–7.42 (1H, m, H Ind); 7.28–7.26 (2H, m, H Ind). ^{13}C NMR spectrum, δ , ppm: 157.3; 148.4; 137.2; 136.4; 129.8; 129.0; 128.1; 127.6; 127.2; 126.1; 125.8; 125.3; 123.1; 121.1; 120.7; 119.2; 115.4, 111.7. Found, m/z : 271.1234 $[\text{M}+\text{H}]^+$. $\text{C}_{19}\text{H}_{15}\text{N}_2$. Calculated, m/z : 271.1230.

3-[(E)-2-(Pyridin-2-yl)vinyl]-1H-indole (3ab). Yield 396 mg (72%), orange crystals, mp $190\text{--}191^\circ\text{C}$ (MeOH) (mp $190\text{--}191^\circ\text{C}^{13}$), R_f 0.34. IR spectrum, ν , cm^{-1} : 3425, 3121, 3078, 3060, 1583, 1506, 1342, 1236, 1160, 985, 930, 802, 738, 693. ^1H NMR spectrum, δ , ppm (J , Hz): 8.50–8.49 (1H, m, H Py); 7.93 (1H, d, $J = 15.3$, CH=); 7.91–7.89

(1H, m, H Ind); 7.50 (1H, d, $J = 3.4$, H Ind); 7.41–7.29 (2H, m, H Py, H Ind); 7.20–7.14 (2H, m, H Ind); 7.16 (1H, d, $J = 15.7$, CH=); 6.94 (1H, br. s, H Py); 6.76 (1H, br. s, H Py). ^{13}C NMR spectrum, δ , ppm: 158.5; 149.2; 136.9; 136.6; 127.7; 127.3; 123.5; 123.4; 122.3; 122.0; 121.9; 120.9; 120.2; 115.9; 111.1. Found, m/z : 221.1074 $[\text{M}+\text{H}]^+$. $\text{C}_{15}\text{H}_{13}\text{N}_2$. Calculated, m/z : 221.1073.

2-[(E)-2-(1H-Indol-3-yl)vinyl]-1,3-benzoxazole (3ac). Yield 559 mg (86%), yellow crystals, mp $182\text{--}183^\circ\text{C}$ (EtOH), R_f 0.56. IR spectrum, ν , cm^{-1} : 3170, 3050, 2934, 2860, 1628, 1490, 1269, 1168, 740. ^1H NMR, δ , ppm (J , Hz): 8.02 (1H, d, $J = 16.4$, CH=); 8.01–7.99 (1H, m, H Ind); 7.67–7.64 (1H, m, H Bxl); 7.52–7.50 (1H, m, H Ind); 7.48–7.46 (1H, m, H Bxl); 7.44–7.42 (1H, m, H Ind); 7.32–7.27 (4H, m, H Bxl, H Ind); 7.06 (1H, d, $J = 16.3$, CH=). ^{13}C NMR spectrum, δ , ppm: 164.5; 151.1; 142.5; 137.4; 136.0; 133.5; 128.1; 125.4; 124.4; 123.4; 123.0; 120.4; 119.4; 114.3; 112.0; 110.2; 109.4. Found, m/z : 261.1018 $[\text{M}+\text{H}]^+$. $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}$. Calculate, m/z : 261.1022.

2-[(E)-2-(2-Methyl-1H-indol-3-yl)vinyl]quinoline (3ba). Yield 645 mg (91%), dark-red oil, R_f 0.46. IR spectrum, ν , cm^{-1} : 3403, 3163, 3055, 2965, 1593, 1456, 1422, 1329, 1222, 949, 816, 741. ^1H NMR spectrum, δ , ppm (J , Hz): 8.09–8.06 (1H, m, H Ind); 8.05–8.02 (2H, m, H Qu); 7.95 (1H, d, $J = 16.4$, CH=); 7.77 (1H, d, $J = 8.0$, H Qu); 7.69–7.66 (2H, m, H Qu); 7.50–7.46 (1H, m, H Qu); 7.44–7.40 (1H, m, H Ind); 7.38 (1H, d, $J = 16.4$, CH=); 7.29–7.27 (2H, m, H Ind); 2.75 (3H, s, CH_3). ^{13}C NMR spectrum, δ , ppm: 157.8; 148.5; 136.8; 136.2; 129.7; 129.3; 127.9; 127.6; 127.1; 126.3; 125.9; 125.5; 124.3; 121.0; 120.8; 120.2; 119.4; 115.5; 111.0; 25.4. Found, m/z : 285.1389 $[\text{M}+\text{H}]^+$. $\text{C}_{20}\text{H}_{17}\text{N}_2$. Calculated, m/z : 285.1386.

2-[(E)-2-(2-Methyl-1H-indol-3-yl)vinyl]-1,3-benzoxazol (3bc). Yield 514 mg (75%), light-yellow oil, R_f 0.58. IR spectrum, ν , cm^{-1} : 3249, 3054, 2967, 2861, 1616, 1456, 1242, 952, 737. ^1H NMR spectrum, δ , ppm (J , Hz): 8.02 (1H, d, $J = 16.4$, CH=); 7.96–7.94 (1H, m, H Ind); 7.66–7.65 (1H, m, H Bxl); 7.47 (2H, m, H Bxl, H Ind); 7.30–7.26 (4H, m, H Bxl, H Ind); 7.05 (1H, d, $J = 16.4$, CH=); 2.64 (3H, s, CH_3). ^{13}C NMR spectrum, δ , ppm: 163.8; 150.5; 146.7; 140.7; 137.2; 135.8; 135.0; 126.1; 124.2; 123.9; 123.6; 123.0; 121.0; 118.9; 115.0; 110.8; 109.9; 12.4. Found, m/z : 275.1184 $[\text{M}+\text{H}]^+$ (1.1 ppm). $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}$. Calculated, m/z : 275.1179.

2-[(E)-2-(2-Phenyl-1H-indol-3-yl)vinyl]quinoline (3ca).¹⁴ Yield 728 mg (84%), dark-red oil, R_f 0.52. IR spectrum, ν , cm^{-1} : 3156, 3058, 2963, 1597, 1450, 1311, 1245, 1073, 952, 743, 695. ^1H NMR spectrum, δ , ppm (J , Hz): 8.20–8.18 (1H, m, H Ind); 8.05–8.02 (2H, m, H Qu); 7.93 (1H, d, $J = 16.4$, CH=); 7.78–7.73 (1H, m, H Qu); 7.70–7.65 (2H, m, H Qu); 7.63–7.61 (2H, m, H Ph); 7.50–7.46 (3H, m, H Ph); 7.43–7.40 (3H, m, H Qu, H Ind, CH=); 7.28–7.24 (2H, m, H Ind). ^{13}C NMR spectrum, δ , ppm: 159.0; 150.1; 148.2; 146.9; 137.5; 136.7; 135.1; 135.3; 131.3; 130.1; 129.6; 129.3; 128.5; 127.5; 126.3; 125.8; 125.0; 124.3; 123.0; 122.1; 121.2; 115.0; 111.1. Found, m/z : 347.1540 $[\text{M}+\text{H}]^+$. $\text{C}_{25}\text{H}_{19}\text{N}_2$. Calculated, m/z : 347.1543.

2-[(E)-2-(2-Phenyl-1H-indol-3-yl)vinyl]-1,3-benzoxazole (3cc). Yield 757 mg (90%), light-yellow oil, R_f 0.63.

IR spectrum, ν , cm^{-1} : 3442, 3230, 3063, 2937, 2858, 2360, 1616, 1451, 1241, 741, 696. ^1H NMR spectrum, δ , ppm (J , Hz): 8.00 (1H, d, $J = 16.3$, CH=); 7.99–7.96 (1H, m, H Ind); 7.63–7.61 (3H, m, H Bxl, H Ph); 7.56–7.51 (3H, m, H Ph); 7.38–7.36 (2H, m, H Bxl, H Ind); 7.32–7.28 (4H, m, H Bxl, H Ind); 7.04 (1H, d, $J = 16.3$, CH=). ^{13}C NMR spectrum, δ , ppm: 165.0; 152.3; 149.0; 147.7; 142.1; 138.4; 137.2; 135.5; 130.3; 129.7; 129.4; 126.3; 124.6; 124.0; 123.4; 123.0; 122.6; 120.5; 115.2; 111.2. Found, m/z : 337.1340 $[\text{M}+\text{H}]^+$. $\text{C}_{23}\text{H}_{17}\text{N}_2\text{O}$. Calculated, m/z : 337.1335.

2- $\{(E)-2-[2-(Naphth-2-yl)-1H-indol-3-yl]vinyl\}$ quinoline (3da). Yield 793 mg (80%), dark-red oil, R_f 0.68. IR spectrum, ν , cm^{-1} : 3180, 3054, 2967, 1597, 1426, 1304, 1237, 950, 818, 745. ^1H NMR spectrum, δ , ppm (J , Hz): 8.29–8.27 (1H, m, H Ind); 8.11 (1H, br. s, H Naph); 8.06–7.99 (4H, m, H Naph, H Qu, CH=); 7.94–7.91 (2H, m, H Naph); 7.79–7.74 (2H, m, H Naph, H Qu); 7.70–7.63 (2H, m, H Qu); 7.58–7.55 (2H, m, H Naph); 7.50–7.42 (3H, m, H Qu, H Ind, CH=); 7.31–7.27 (2H, m, H Ind). ^{13}C NMR spectrum, δ , ppm: 157.8; 148.4; 140.0; 136.4; 129.8; 129.6; 128.9; 128.7; 128.1; 127.9; 127.1; 126.8; 126.7; 126.1; 125.8; 125.6; 124.0; 123.3; 123.2; 122.4; 122.1; 121.3; 121.2; 120.7; 120.2; 118.6; 111.8; 111.1. Found, m/z : 397.1705 $[\text{M}+\text{H}]^+$. Calculated for $\text{C}_{29}\text{H}_{21}\text{N}_2$, m/z : 397.1699.

2- $\{(E)-2-[2-(Naphth-2-yl)-1H-idol-3-yl]vinyl\}-1,3$ -benzoxazole (3dc). Yield 802 mg (83%), light-yellow oil, R_f 0.75. IR spectrum, ν , cm^{-1} : 3213, 3055, 2941, 2858, 1616, 1446, 1241, 820, 743. ^1H NMR spectrum, δ , ppm (J , Hz): 8.95 (1H, br. s, NH); 8.12 (1H, d, $J = 16.3$, CH=); 8.08–8.06 (2H, m, H Ind, H Naph); 7.98–7.95 (1H, m, H Naph); 7.91–7.82 (3H, m, H Naph); 7.66–7.64 (1H, m, H Bxl); 7.57–7.55 (2H, m, H Naph); 7.50–7.42 (2H, m, H Bxl, H Ind); 7.33–7.25 (4H, m, H Bxl, H Ind); 7.13 (1H, d, $J = 16.3$, CH=). ^{13}C NMR spectrum, δ , ppm: 161.7; 151.6; 149.0; 141.9; 138.0; 137.2; 135.8; 133.8; 133.2; 129.8; 129.3; 128.6; 128.1; 127.7; 127.5; 127.4; 126.8; 126.4; 126.3; 124.7; 123.5; 122.6; 122.1; 121.3; 115.4; 112.0; 111.2. Found, m/z : 387.1495 $[\text{M}+\text{H}]^+$. $\text{C}_{27}\text{H}_{19}\text{N}_2\text{O}$. Calculated, m/z : 387.1492.

X-ray structural analysis of compound 3aa was performed on an Agilent SuperNova diffractometer equipped with AtlasS2 CCD detector, using Cu X-ray source ($\text{CuK}\alpha$ 1.54184 Å), scanning at 291.86 K. The structure was solved by the SHELXS software and refined by full-matrix least-squares on all F^2 data using SHELXL¹⁵ in conjunction with the OLEX2 graphical user interface. Full crystallographic data are deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1431568).

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