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Microwave-Assisted Synthesis of 2-Methyl-1*H*-indole-3-carboxylate Derivatives via Pd-Catalyzed Heterocyclization

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Abstract: Indole moiety is well-known as a superlative framework in many natural products and synthetic pharmaceuticals. Herein, we report an efficient procedure to synthesize a series of functionalized 2-methyl-1*H*-indole-3-carboxylate derivatives from commercially available anilines properly functionalized by different electron-withdrawing and -donating groups through a palladium-catalyzed intramolecular oxidative coupling. The conversion of a variety of enamines into the relevant indole was optimized by exposing the neat mixture of reactants to microwave irradiation, obtaining the desired products in excellent yields and high regioselectivity. The synthesized compounds were confirmed by ^{1}H and ^{13}C spectroscopic means as well as by high-resolution mass spectrometry.

Keywords: indoles; C-H activation; Pd-catalyzed coupling; microwave irradiation; *N*-aryl enamines

1. Introduction

The indole nucleus is a very widespread motif used in drug discovery and found in many pharmacologically active compounds [1,2]. Bioactive indole-based molecules have been isolated from plants, bacteria, fungi, and marine products, such as tryptamine and serotonin derivatives [3,4], bufotenine [3], ergot and vinca alkaloids [5,6]. In addition, a large pool of drugs containing the indole ring was approved by the Food and Drug Administration (FDA) as antiviral, anticancer, antimalarial, and antitubercular agents [7,8]. Some of these molecules are mainly featured by axially chiral indole-based units [9,10], which are typical building blocks present in natural alkaloids, chiral phosphine ligands, and catalysts [11,12].

The construction of the traditional indole core may occur through conventional strategies, such as those described by Fischer [13], Julia and Bartoli [14,15], or through organometallic catalyzed cross-coupling C–N/C–C bond formations [16,17], which are highly versatile and suitable for indole derivatization. The catalytic asymmetric approaches can be also used to access chiral indole-based compounds [18]. These substituted indole derivatives can be considered key intermediates for the synthesis of molecules of medicinal chemistry interest (Figure 1). For instance, 3-nitroindoles are essential structural moiety for the development and synthesis of novel antidiabetic agents [19], whereas halogenated indoles represent a key structural moiety of human 15-lipoxygenase-1 inhibitors [20], and indole-3-carboxylic acids, along with their related esters, are key moieties for mast cell tryptase inhibitors [21]. As part of chiral-indole-based skeletons, there are chiral

tryptamines that constitute bioactive molecules acting in the central nervous system [22], while many axially chiral indoles have proved potent anticancer activity [23].
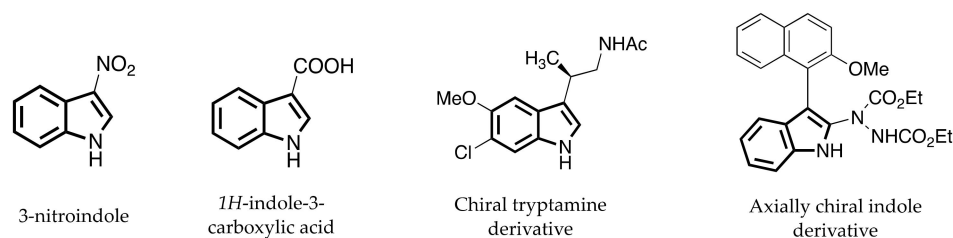

Figure 1. Representation of some indole-based compounds containing biologically active compounds.

An efficient route to obtain indole-3-carboxylate derivatives from several substituted anilines has been developed by Wurtz et al. by performing palladium-catalyzed intramolecular oxidation [24]. This strategy involves the use of four players: (*i*) a copper source, (*ii*) a ligand, (*iii*) a base, and (*iv*) an *N*-aryl enamine, to efficiently get a series of 2-methyl-1*H*-indole-3-carboxylate derivatives [24]. Starting from this study and considering the numerous advantages the microwave (μW)-assisted synthesis has over the traditional organic synthesis, which includes reduction of reaction time, improved conversions, and cleaner product formation [25–28], we have explored the palladium-catalyzed oxidative cyclization reaction for the preparation of several indole-3-carboxylate derivatives via μW-heating technology. Previously, μW-heating has been exploited for the preparation of indole analogs in the classical reaction of Fischer [28], and other transition metal-mediated cyclizations, leading to final products yields >80% and excellent purity (>90%) [29]. In this light, we have synthesized *N*-aryl enamine carboxylates starting from commercially available anilines bearing different electron-withdrawing (-NO_2, -Cl, -Br) and donating groups (-CH_3, -OPh) (Scheme 1), then converted into their corresponding indoles under both μW-assisted and conventional heating conditions by palladium-catalyzed oxidation. By varying both the amount of oxidant agent (copper source) and the type of solvent, 2-methyl-1*H*-indole-3-carboxylate derivatives have been obtained with improved yields (>90%) and strikingly reduced reaction time with respect to conventional conditions.
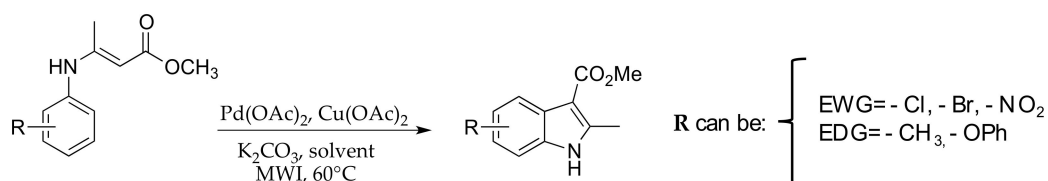
Scheme 1. Microwave-assisted palladium-catalyzed cyclization of *N*-aryl enamine substituted with electron-withdrawing (EWG) and -donating (EDG) groups that were used in our study.

2. Materials and Methods

2.1. Materials and General Procedures

All solvents and commercial reagents were purchased from Sigma-Aldrich (Saint Louis, MO, USA). TLC sheets (silica gel 60 F254 with plates 5 × 20, 0.25 mm) were purchased from Merck (Kenilworth, NJ, USA). High-resolution MS analysis (positive mode) was performed on a Thermo LTQ Orbitrap XL mass spectrometer (Thermo-Fisher, San Josè, CA, USA) through the infusion of compounds **11–28** into the ESI source using MeOH as solvent. [1]H (700, 600, and 400 MHz) and [13]C (175 and 125 MHz). NMR spectra were recorded on a Bruker Avance Neo spectrometer equipped with an RT-DR-BF/1H-5 mm-OZ SmartProbe (Bruker BioSpin Corporation, Billerica, MA, USA); chemical shifts (δ_H and δ_C) were referenced to the residual CHCl$_3$ signal (δ_H = 7.26 and δ_C = 77.0). High-performance liquid chromatography (HPLC) analyses were performed on a Knauer K-501 instrument endowed with a Knauer K-2301 RI detector purchased from LabService Analytica s.r.l., (Anzola dell'Emilia, Italy). Microwave-assisted reactions were performed on an Initiator+

microwave apparatus purchased from Biotage (Bergamo, Italy). The instrument was set on the high-absorption level operating at a frequency of 2.45 GHz with a continuous irradiation power (0–300 W) and a standard absorbance level of 300 W.

2.2. Synthesis of Enamine Derived Compounds 11–19

Each substituted aniline (**1**–**9**, 2.00 mL, 22.0 mmol) was stirred together with methyl acetoacetate ($CH_3COCH_2COOCH_3$, **10**, 2.37 mL, 22.0 mmol, 1 eq) and 10% acetic acid (CH_3CO_2H, 250 μL) into an oven-dried round bottom flask, at room temperature (rt). After 12 h, the crude material was washed with water and extracted with ethyl acetate (EtOAc). The organic phase was washed with water (×3), brine (×3), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. All enamine intermediates (**11**–**19**) were obtained with high yield, ranging from 93–96%, and stored at 4–6 °C. Compounds **11**–**19** were confirmed by ^1H and ^{13}C spectroscopic as well as by HRMS (ESI) analyses.

Methyl-(Z)-3-(phenylimino)butanoate) (11): white crystals (4.03 g, 96%); ^1H NMR ($CDCl_3$): 10.4 (-NH, brs); 7.32 (2H, t, *J* = 15 Hz); 7.15 (1H, t, *J* = 15Hz); 7.10 (2H, d, *J* = 8 Hz); 4.73 (1H, s); 3.69 (3H, s); 1.99 (3H, s). ^{13}C NMR ($CDCl_3$): 170.6, 159.0, 139.3, 129.1, 125.0, 124.5, 85.6, 50.3, 20.4. HRMS (ESI): m/z 192.1018 [M+H]$^+$ (calcd. for $C_{11}H_{14}NO_2$: 192.1019) (Figures S1–S3). δ_H and δ_C agree with literature data [30].

Methyl (Z)-3-(4-bromophenyl)amino)but-2-enoate) (12): dark yellow crystals (5.58 g, 94%); ^1H NMR ($CDCl_3$): 10.3 (-NH, brs); 7.41 (2H, d, *J* = 8.3 Hz); 6.94 (2H, d, *J* = 8.3 Hz); 4.72 (1H, s); 3.67 (3H, s); 1.97 (3H, s). ^{13}C NMR ($CDCl_3$): 170.8, 158.4, 138.4, 132.2, 125.9, 118.2, 86.7, 50.4, 20.2. HRMS (ESI): m/z 270.0131 [M+H]$^+$ (calcd. for $C_{11}H_{13}BrNO_2$: 270.0124) (Figures S4–S6). δ_H and δ_C agree with literature data [31].

Methyl (Z)-3-((3-bromophenyl)amino)but-2-enoate) (13): dark brown oil (5.56 g, 94%); ^1H NMR ($CDCl_3$): 10.3 (-NH, brs); 7.21 (1H); 7.14 (1H); 6.95 (1H, dd, *J* = 17 Hz, 2.6 Hz), 6.79 (1H), 4.73 (1H, s); 3.66 (3H, s); 1.98 (3H, s). ^{13}C NMR ($CDCl_3$): 170.6, 158.2, 140.8, 130.5, 130.3, 127.7, 122.6, 113.6, 87.2, 50.5, 20.4. HRMS (ESI): m/z 270.0130 [M+H]$^+$ (calcd. for $C_{11}H_{13}BrNO_2$: 270.0124) (Figures S7–S9). δ_H and δ_C agree with literature data [31].

Methyl (Z)-3-(naphthalen-1-ylamino)but-2-enoate) (14): dark violet powder (4.93 g, 93%); ^1H NMR ($CDCl_3$): 10.5 (-NH, brs); 7.83–7.79 (1H, m); 7.55–7.51 (2H, m); 7.32–7.27 (3H, m); 6.80 (1H, dd, *J* = 7.2 Hz, 1Hz); 4.82 (1H, s); 3.75 (3H, s); 1.86 (3H, s). ^{13}C NMR ($CDCl_3$): 171.1, 160.7, 135.3, 134.3, 130.5, 128.3, 126.8, 126.7, 126.5, 125.3, 123.7, 122.7, 85.1, 50.4, 20.1 (Figures S10 and S11). δ_H and δ_C agree with literature data [30].

Methyl (Z)-3-(4-chlorophenyl)amino)but-2-enoate) (15): orange powder (4.72 g, 95%); ^1H NMR ($CDCl_3$): 10.2 (-NH, brs); 7.16 (2H, d, *J* = 8.0 Hz); 6.91 (2H, d, *J* = 8.0 Hz); 4.58 (1H, s); 3.58 (3H, s); 2.12 (3H, s). ^{13}C NMR ($CDCl_3$): 170.5, 158.8, 138.1, 129.1, 125.4, 116.5, 89.2, 50.4, 20.0 (Figures S12 and S13). δ_H and δ_C agree with literature data [31].

Methyl (Z)-3-((2,4-dichlorophenyl)amino)but-2-enoate) (16): grey crystals (5.35 g, 94%); ^1H NMR ($CDCl_3$): 10.3 (-NH, brs); 7.24 (1H, s); 7.02 (1H, d, *J* = 8Hz); 6.65 (1H, d, *J* = 8 Hz); 4.81 (1H, s); 3.71 (3H, s); 1.95 (3H, s). ^{13}C NMR ($CDCl_3$): 170.6, 157.9, 135.5, 130.7, 129.8, 128.8, 127.4, 116.6, 88.2, 50.7, 20.3. HRMS (ESI): m/z 260.0241 [M+H]$^+$ (calcd. for $C_{11}H_{11}Cl_2NO_2$: 260.0215) (Figures S14–S16).

Methyl (Z)-3-((4-nitrophenyl)amino)but-2-enoate) (17): yellow crystals (4.83 g, 93%); ^1H NMR ($CDCl_3$): 10.9 (-NH, brs); 8.19 (2H, d, *J* = 8.3 Hz); 7.13 (2H, d, *J* = 8.3 Hz); 4.89 (1H, s); 3.72 (3H, s); 2.21 (3H, s). ^{13}C NMR ($CDCl_3$): 170.6, 156.1, 145.9, 125.5, 120.8, 113.4, 91.1, 50.8, 21.0. HRMS (ESI): m/z 237.0870 [M+H]$^+$ (calcd. for $C_{11}H_{13}N_2O_4$: 237.0869) (Figures S17–S19). δ_H and δ_C agree with literature data [30].

Methyl (Z)-3-((2,4-dimethylphenyl)amino)but-2-enoate) (18): red-brick oil (4.62 g, 96%); ^1H NMR ($CDCl_3$): 10.0 (-NH, brs); 7.02–6.91 (3H, overlapped); 4.70 (1H, s); 3.66 (3H, s); 2.30 (3H, s); 2.23 (3H, s); 1.81 (3H, s). ^{13}C NMR ($CDCl_3$): 170.8, 160.2, 135.8, 135.3, 133.8, 131.4, 127.0, 126.6, 84.4, 50.0, 20.8, 19.9, 17.8. HRMS (ESI): m/z 242.1142 [M+Na]$^+$ (calcd. For $C_{13}H_{17}NO_2Na$: 242.1152) (Figures S20–S22). δ_H and δ_C agree with literature data [31].

Methyl (Z)-3-((4-phenoxyphenyl)amino)but-2-enoate) (19): orange oil (5.91 g, 95%); ^{1}H NMR (CDCl$_3$): 10.1 (-NH, brs); 7.20 (2H, m); 6.97–6.91 (3H, overlapped); 6.87–6.82 (4H, overlapped); 4.54 (1H, s); 3.53 (3H, s); 1.82 (3H, s). ^{13}C NMR (CDCl$_3$): 170.6, 159.4, 156.9, 154.7, 134.4, 129.7, 126.3, 123.3, 119.1, 118.7, 89.5, 50.9, 20.9. HRMS (ESI): m/z 284.1275 [M+H]+ (calcd. for C$_{17}$H$_{18}$NO$_3$: 284.1281) (Figures S23–S25).

2.3. μW-Assisted Palladium-Catalyzed Oxidative Cyclization Yielding Indole Derivatives 20–28

Enamine intermediates (**11–19**) (30.5 mg, 0.16 mmol, 1 eq), catalytic amount of palladium acetate [Pd(OAc)$_2$ (3.6 mg, 0.016 mmol, 0.1 eq], copper acetate [Cu(OAc)$_2$, 29.1 mg, 0.16 mmol, 1 eq], and potassium carbonate (K$_2$CO$_3$, 55.3 mg, 0.40 mmol, 2.5 eq) were dissolved in DMF (2 mL), and placed in a μW reaction vessel, under argon atmosphere (Tables 1 and 2). The resulting mixture was stirred at 60 °C under μW irradiation. As reported in Table 2, when the synthesis of the indole moiety did not succeed in DMF, this was replaced by ACN (2 mL) or DMSO (2 mL). Then, the reaction was cooled down to rt, diluted with DCM, and filtered through a short pad of celite, which was then washed with DCM. The solvent was removed in vacuo and indole derivatives (**20–28**) were isolated by flash chromatography or semi-preparative HPLC using an isocratic mobile phase of H$_2$O (0.1% TFA) and solvent B (0.1% TFA) (95:5, v/v), Luna column (10 μm, C18), and a flow rate of 3 mL/min. The conversion of substituted anilines (**20–28**, Tables 1 and 2) was also performed by conventional oil bath heating (T = 80 °C), as the only change with the respect to the procedure described above.

Table 1. Optimized preparation of 2-methyl-*1H*-indole-3-carboxylate (**20**), passing from conventional to μW-heating conditions.
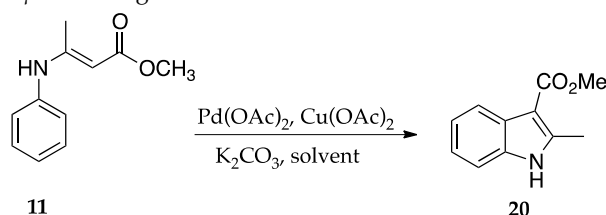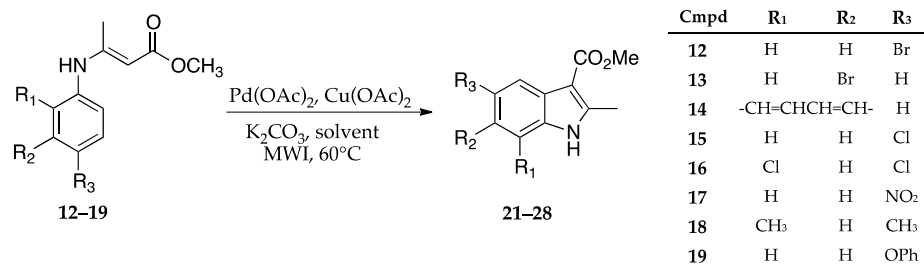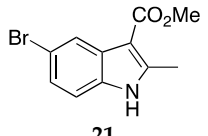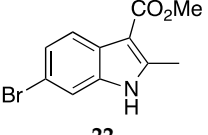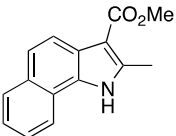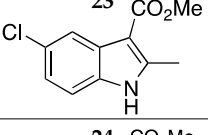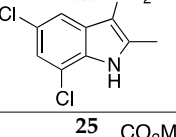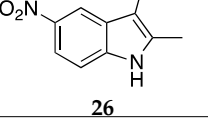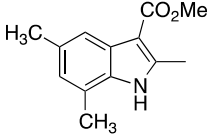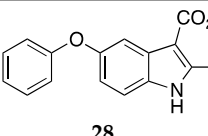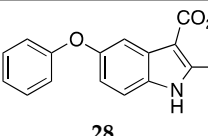

Entry	Solvent	Energy Input	Time (h)	Isolated Yields (%)
1	DMF	a	16	76
2	DMF	b	0.5	93
3	DMF	b	0.25	67
4	DMF	c	0.5	19

[a] Standard reaction conditions: **11** (0.16 mmol), Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (0.16 mmol, 1 eq), K$_2$CO$_3$ (0.4 mmol), DMF (2 mL), 80 °C. [b] Microwave conditions: **11** (0.16 mmol), Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (0.16 mmol), K$_2$CO$_3$ (0.4 mmol), DMF (2 mL), 60 °C. [c] Microwave conditions: **11** (0.16 mmol), Pd(OAc)$_2$ (5 mol%), Cu(OAc)$_2$ (0.16 mmol), K$_2$CO$_3$ (0.4 mmol), DMF (2 mL), 60 °C.

Methyl 2-methyl-1H-indole-3-carboxylate (20). The crude material was purified by flash chromatography (n-hexane/EtOAc, 7:3) to give the product as orangewish powder; ^{1}H NMR (CDCl$_3$): 8.48 (-NH, brs); 8.09 (1H, dd, *J* = 7.5 Hz, 2 Hz); 7.30 (1H, dd, *J* = 7.5Hz, 2 Hz); 7.21 (1H, qd, *J* = 14.5, 7.5, 1.8 Hz); 7.19 (1H, qd, *J* = 14.5, 7.5, 1.8 Hz); 3.94 (3H, s); 2.74 (3H, s). ^{13}C NMR (CDCl$_3$): 166.7, 144.3, 134.6, 127.2, 122.3, 121.6, 121.2, 110.6, 104.3, 50.8, 14.2. HRMS (ESI): m/z 190.0874 [M+H]+ (calcd. for C$_{11}$H$_{12}$NO$_2$: 190.0863) (Figures S26–S28). δ$_H$ and δ$_C$ agree with literature data [24].

Methyl 5-bromo-2-methyl-1H-indole-3-carboxylate (21). The crude material was purified by semi-preparative HPLC (solvent B, MeOH; t$_R$ = 5.2 min). The product was obtained as brown oil; ^{1}H NMR (CDCl$_3$): 8.41 (-NH, brs); 8.21 (1H, s); 7.28 (1H, d, *J* = 8 Hz); 7.17 (1H, d, *J* = 8 Hz); 3.93 (3H, s); 2.74 (3H, s). ^{13}C NMR (CDCl$_3$): 166.1, 145.0, 133.1, 128.8, 125.6, 124.1, 115.4, 112.1, 104.7, 51.2, 14.2. HRMS (ESI): m/z 289.9785 [M+Na]+ (calcd. for C$_{11}$H$_{10}$BrNO$_2$Na: 289.9787) (Figures S29–S31). δ$_H$ and δ$_C$ agree with literature data [32].

Table 2. Screening of solvent conditions for the cyclization reaction of arylenamides **12–19** to indole-based compounds **21–28** under conventional and μW conditions.

Cmpd	R₁	R₂	R₃
12	H	H	Br
13	H	Br	H
14	-CH=CHCH=CH-		H
15	H	H	Cl
16	Cl	H	Cl
17	H	H	NO₂
18	CH₃	H	CH₃
19	H	H	OPh

Compound	Microwave				Conventional Heating			
	Entry	Solvent	Time (h)	Isolated Yield (%)	Entry	Solvent	Time (h)	Isolated Yield (%)
21	**1**	DMF	3	94	**3**	DMF	16	89
	2	DMF	1	55	**4**	DMF	6	51
22	**5**	DMF	3	29	**8**	DMF	16	17
	6	DMSO	3	74	**9**	DMSO	16	33
	7	ACN [a]	3	8	**10**	ACN [b]	16	ND
23	**11**	DMF	1	95	**12**	DMF	6	91
					13	DMF	6	78
24	**14**	DMF	1	90	**16**	DMF	16	73
	15	DMF	0.5	82				
25	**17**	DMF	1	95	**19**	DMF	3	91
	18	DMF	0.5	82	**20**	DMF	1	23
26	**21**	DMF	3	18	**23**	DMF	16	12
	22	DMSO	3	ND	**24**	DMSO	16	ND
	25	ACN [a]	3	91	**27**	ACN [b]	16	24
	26	ACN [a]	1	12				
27	**28**	DMF	3	94	**30**	DMF	6	89
	29	DMF	1	38	**31**	DMF	3	58
28	**32**	DMF	1	95	**34**	DMF	3	90
	33	DMF	0.5	62	**35**	DMF	1	43

Standard reaction conditions: enamine intermediate **12–19** (0.16 mmol), Pd(OAc)₂ (10% mol), Cu(OAc)₂ (0.16 mmol), K₂CO₃ (0.4 mmol), solvent (1.5 mL), 80 °C. Microwave reaction conditions: enamine intermediate **12–19** (0.16 mmol), Pd(OAc)₂ (10% mol), Cu(OAc)₂ (0.016 mmol), K₂CO₃ (0.4 mmol), solvent (2 mL), 60 °C. [a] T = 40 °C; [b] T = 60 °C; ND= not detected.

Methyl 6-bromo-2-methyl-1H-indole-3-carboxylate (22). The crude material was purified by semi-preparative HPLC (solvent B, MeOH; t_R = 6.1 min). The product was obtained as dark brown oil; ^{1}H NMR (CDCl$_3$): 8.34 (-NH, brs); 7.94 (1H, d, *J* = 9 Hz); 7.45 (1H, d, *J* = 1.8 Hz); 7.31 (1H, dd, *J* = 9 Hz, 1.8 Hz); 3.92 (3H, s); 2.73 (3H, s). ^{13}C NMR (CDCl$_3$): 166.1, 144.2, 135.2, 126.0, 125.0, 122.7, 115.7, 113.4, 104.9, 50.9, 14.2. HRMS (ESI): m/z 289.9782 [M+Na]$^+$ (calcd. for C$_{11}$H$_{10}$BrNO$_2$Na: 289.9787) (Figures S32–S34). δ_H and δ_C agree with literature data [32].

Methyl 2-methyl-1H-benzo[g]indole-3-carboxylate (23). The crude material was purified by semi-preparative HPLC (H$_2$O, solvent B, MeOH, 90:10, v,v; t_R = 6.0 min). The product was obtained as dark violet powder; ^{1}H NMR (CDCl$_3$): 8.99 (-NH, brs); 8.21 (1H, d, J = 8.5 Hz); 7.97–7.93 (2H, dd, *J* = 16.5 Hz, 8 Hz); 7.63 (1H, d, *J* = 8.5 Hz); 7.54 (1H, td, *J* = 14.7 Hz, 7.6 Hz, 1 Hz); 7.44 (1H, td, *J* = 14.7 Hz, 7.6 Hz, 1 Hz); 3.97 (3H, s); 2.85 (3H, s). ^{13}C NMR (CDCl$_3$): 166.5, 141.3, 130.4, 129.9, 128.9, 125.8, 124.1, 123.5, 122.3, 120.9, 120.9, 119.1, 106.3, 50.9, 14.4. HRMS (ESI): m/z 240.1018 [M+H]$^+$ (calcd. for C$_{15}$H$_{14}$NO$_2$: 240.1019) (Figures S35–S37). δ_H and δ_C agree with literature data [24].

Methyl 5-chloro-2-methyl-1H-indole-3-carboxylate (24). The crude material was purified by semi-preparative HPLC (solvent B, ACN; t_R = 5.5 min). The product was obtained as dark yellow powder; ^{1}H NMR (CDCl$_3$): 8.43 (-NH, brs); 8.05 (1H, d, *J* = 2 Hz); 7.21 (1H, d, *J* = 8.5 Hz); 7.14 (1H, dd, *J* = 8.5 Hz, 2 Hz); 3.94 (3H, s); 2.74 (3H, s). ^{13}C NMR (CDCl$_3$): 166.1, 145.2, 132.8, 128.3, 127.7, 122.7, 121.1, 111.5, 104.6, 50.9, 14.2. HRMS (ESI): m/z 246.0291 [M+Na]$^+$ (calcd. for C$_{11}$H$_{10}$ClNO$_2$Na: 246.0292) (Figures S38–S40). δ_H and δ_C agree with literature data [24].

Methyl 5,7-dichloro-2-methyl-1H-indole-3-carboxylate (25). The crude material was purified by semi-preparative HPLC (solvent B, MeOH; t_R = 7.1 min). The product was obtained as dark brown oil; ^{1}H NMR (CDCl$_3$): 8.53 (-NH, brs); 7.96 (1H, s); 7.19 (1H, s); 3.93 (3H, s); 2.77 (3H, s). ^{13}C NMR (CDCl$_3$): 165.5, 145.6, 130.4, 128.9, 127.6, 121.9, 119.8, 116.3, 105.7, 51.2, 14.2. HRMS (ESI): m/z 258.0084 [M+H]$^+$ (calcd. for C$_{11}$H$_{10}$Cl$_2$NO$_2$: 258.0083) (Figures S41–S43).

Methyl 2-methyl-5-nitro-1H-indole-3-carboxylate (26). The crude material was purified by flash chromatography (n-hexane/EtOAc, 7:3) and the product was obtained as yellow crystals; ^{1}H NMR (CDCl$_3$): 8.99 (1H, d, *J* = 2 Hz); 8.62 (-NH, brs); 8.12 (1H, dd, *J* = 9 Hz, 2 Hz); 7.36 (1H, d, *J* = 9 Hz); 4.00 (3H, s); 2.81 (3H, s). ^{13}C NMR (CDCl$_3$): 165.4, 147.0, 143.5, 137.5, 126.5, 118.5, 118.3, 113.4, 110.7, 106.7, 51.3, 14.3. HRMS (ESI): m/z 257.0534 [M+Na]$^+$ (calcd. for C$_{11}$H$_{10}$N$_2$O$_4$Na: 257.0533) (Figures S44–S46). δ_H and δ_C agree with literature data [32].

Methyl 2,5,7-trimethyl-1H-indole-3-carboxylate (27). The crude material was purified by semi-preparative HPLC (solvent B, MeOH, t_R = 5.9 min). The product was obtained as red powder; ^{1}H NMR (CDCl$_3$): 8.21 (-NH, brs); 7.72 (1H, s); 6.84 (1H, s); 3.93 (3H, s); 2.74 (3H, s); 2.44 (6H, s). ^{13}C NMR (CDCl$_3$): 166.7, 143.5, 132.2, 131.3, 127.1, 124.7, 119.2, 118.7, 104.6, 50.8, 21.6, 16.5, 14.3. HRMS (ESI): m/z 218.1178 [M+H]$^+$ (calcd. for C$_{13}$H$_{16}$NO$_2$: 218.1176) (Figures S47–S49). δ_H and δ_C agree with literature data [24].
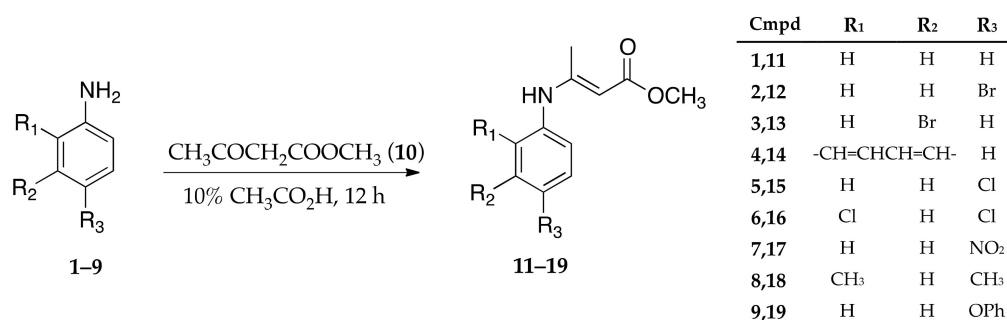
Methyl 2-methyl-5-phenoxy-1H-indole-3-carboxylate (28). The crude material was purified by semi-preparative HPLC (H$_2$O, solvent B, MeOH, 90:10, v,v; t_R = 6.8 min). The product was obtained as dark brown oil; orange oil; ^{1}H NMR (CDCl$_3$): 8.37 (-NH, brs); 7.78 (1H, d, *J* = 1.5 Hz); 7.28–7.27 (3H, overlapped); 7.02 (1H, t, *J* = 15 Hz); 6.96 (2H, d, *J* = 8.5 Hz); 6.93 (1H, d, *J* = 8 Hz); 3.87 (3H, s); 2.76 (3H, s). ^{13}C NMR (CDCl$_3$): 166.2, 159.2, 151.5, 145.1, 131.3, 129.5, 128.2, 122.2, 117.4, 115.9, 112.6, 111.4, 104.8, 50.9, 14.3. HRMS (ESI): m/z 282.1126 [M+H]$^+$ (calcd. for C$_{17}$H$_{16}$NO$_3$: 282.1125) (Figures S50–S52). δ_H and δ_C agree with literature data [33].

3. Results and Discussion

A smart approach for the construction of functionalized indoles consists in transforming substituted enamines via palladium-catalyzed cyclization by oil bath heating conditions [24]. Herein, we investigated and optimized the reaction conditions of the

oxidative enamine-cyclization under μW irradiation, in order to achieve a high-yielding conversion in differently substituted indoles. Given numerous advantages offered by μW irradiation, including high yields, selectivity, and low quantities of side products, many organic reactions are well-assisted by μW radiation, such as the Heck and Suzuki reactions [34]. In our study, we initially explored the palladium-catalyzed intramolecular oxidative coupling of the no-substituted indole **20** under μW irradiation, and then the impact of substituents, such as electron-withdrawing (-NO$_2$, -Cl, -Br) and -donating (-CH$_3$, -OPh) groups on the transformation into indoles were investigated under both conventional heating and μW irradiation.

Firstly, aniline (**1**), as well as commercially available *para-*, *meta-*, and 2,4-substituted anilines and 1-naphtylamine (**1–9**), were converted into their corresponding enamine derivatives (**11–19**) following an efficient synthetic protocol (Scheme 2). In particular, a solution of each aniline, methyl acetoacetate (**10**, 1 eq), and 10% CH$_3$CO$_2$H was prepared and stirred at rt for 12 h [24]. Then, the solvent removal in vacuo afforded crystals for each crude material, which were differently colored depending on the bearing substituents. These were washed with distilled water and extracted with EtOAc. The resulting residues were preliminarily analyzed by NMR spectroscopy (both ^{1}H and ^{13}C) and high-resolution mass spectrometry (HRMS (ESI)). All enamines were obtained with excellent yields (ranging from 93–96%) allowing the desired products (**11–19**) to be directly used for the next synthetic step without further purification. Interestingly, this protocol has also proved to be efficient for the synthesis of two new enamine-derived compounds **16** and **19**, starting from two commercial anilines, that is the 2,4-dichloroaniline (**6**) and *p*-phenoxyaniline (**9**).

Cmpd	R$_1$	R$_2$	R$_3$
1,11	H	H	H
2,12	H	H	Br
3,13	H	Br	H
4,14	-CH=CHCH=CH-		H
5,15	H	H	Cl
6,16	Cl	H	Cl
7,17	H	H	NO$_2$
8,18	CH$_3$	H	CH$_3$
9,19	H	H	OPh

Scheme 2. Synthesis of *N*-aryl enamine derivatives (**11–19**) from substituted anilines (**1–9**).

Our initial studies were focused on the conversion of the methyl-*(Z)*-3-(phenylimino) butanoate (**11**) into indole product **20** under μW radiation (Table 1), which had previously been synthesized by Wurtz et al. using a mixture of catalysts including: (*i*) Pd(OAc)$_2$ (10 mol%) as the catalyst, (*ii*) Cu(OAc)$_2$ as the oxidant (3 eq), (*iii*) K$_2$CO$_3$ (3 eq) as the base required for the catalytic cycle to operate. DMF was selected as a solvent and the reaction was run at 80 °C under argon for 3h (yield 72%) [24].

In our experiments, we successfully demonstrated that a significantly lower amount of Cu II (3 eq→1 eq) was required to improve the quality of the methodology and proven to be environmentally superior; while Pd (II) was kept at the same loading (10% mol) because when we performed the reaction using a low amount of 5% mol, the yield was drastically reduced (19%, entry 4). When the reaction was carried out under conventional oil bath heating (80 °C) the cyclization proceeded slowly and indole **20** was obtained in good yield (76%, Table 1, entry 1) after 16 h.

However, excellent results were obtained by performing the same interconversion under μW irradiation (Table 1, entries 2, 3). The μW-assisted palladium-catalyzed cyclization of enamine **11** was carried out under sub-boiling point conditions, setting a temperature of 60 °C for DMF. In addition, the reaction was monitored at different reaction times to determine the optimum reaction time.

Results collected (Table 1) showed that the conversion of **11** required only 0.5 h providing product **20** in 93% isolated yields (Table 1, entry 2); limiting the reaction time

at 0.25 h, produced a significant reduction of the yield of **20** (Table 1, entry 3) which was obtained in only 63% yield. With this set of optimized conditions in hand, we set up to determine the scope of reaction by subjecting enamines **12–19**, bearing a variety of different electron-donating (-CH$_3$, -OPh) and -withdrawing groups (-NO$_2$, -Cl, -Br), into desired indoles **21–28**.

The preparation of indoles **21–28** was independently studied in various solvents (DMF, DMSO, and ACN) in order to investigate the effect of the media on the reaction rate. It is important to notice that irradiation after full conversion may lead to the formation of products of decomposition, hence, it was important to determine the end point of the reaction in order to obtain compounds as free as possible from products of decomposition. For this reason, the reaction time was gradually reduced from 3 h to 0.5 h when possible (Table 2). Of all three tested solvents, DMF, DMSO, and ACN, DMF gave the best results for most of the substituted *N*-aryl enamine. Additionally, to assess the improvement of the proposed protocol, each *µW*-assisted cyclization has been compared with the same reaction performed under conventional heating in an oil bath.

It is noteworthy that indole-3-carboxylate derivatives such as **21, 22, 24, 25** (Table 2), bearing halogens (-Br and -Cl) and compound **26** bearing a nitro group are key intermediates for the preparation of biologically active compounds [35]. In particular, the formation of brominated indoles in high yields and in short times could be greatly advantageous since these are the main scaffolds for Suzuki–Miyaura cross-coupling reactions, which are widely used for the synthesis of bioactive molecules [32]. In our work, we performed and optimized the synthesis of both 5-bromo and 6-bromo indole 3-carboxylate derivatives under *µW* irradiation, starting from methyl *(Z)*-3-((4-bromophenyl)amino)but-2-enoate (**12**) and methyl (Z)-3-((3-bromophenyl)amino)but-2-enoate) (**13**).

Entries 1 and 2 (Table 2) show that the *µW* irradiation provided a notable reduction of reaction time and high yields. In the case of *para*-Br atom substitution to the benzene moiety, the *µW* heating allowed to synthesize **21** in 3 h (Table 2, entry 1, 94% yield,) vs. 12 h in an oil bath (Table 2, entry 3, 89% yield). Interestingly, our microwave-assisted synthetic strategy did not promote the formation of debrominated indole as a side product, in contrast to under conventional heating as reported by Newman et al. [36]. Specifically, when the conversion was performed in an oil bath at 80 °C, a significant amount of debrominated indole was detected even after 8 min [36]. On the contrary, in our experiments, the formation of this byproduct was not observed, even after a long time of 3 h.

Attractive results regarding the regioselectivity were obtained in the case of the *meta*-Br atom substitution to the benzene moiety. Under conventional heating, the conversion of enamine **13** proceeded very slowly and various solvents were used in order to obtain the best protocol. When we performed the conversion of enamine **13** in DMF as a solvent, the synthesis of indole product **22** was unsatisfactory and required a long reaction time (16 h), yielding 17% of the product (Table 2, entry 8). The synthetic trend resulted similar under *µW* irradiation because we observed a yield of 29% for **22** after 3 h exposure which remained constant over time (Table 2, entry 5). At this stage, on the basis of the high solubility of enamine **13** in solvents such as ACN and DMSO, we decided to change the solvent to improve the cyclization outcome. Firstly, we considered that the use of ACN as solvent makes the reaction mixture more polar, increasing its ability to absorb the *µW* energy taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms [37]. In this context, we performed the reaction under sub-boiling point conditions setting a temperature of 40 °C for ACN and 60 °C for DMSO.

Our results showed that the use of ACN was unideal since **22** was not observed in the oil bath whereas a small amount was isolated from *µW* synthesis (Table 2, entry 7, **8%** yield). Instead, better results were obtained using DMSO (Table 2, entry 9). In particular, the yield of **22** increased to 33% stirring the reaction overnight in an oil bath; meanwhile, **22** was obtained in 74% yield after 3 h (Table 2, entry 6) under *µW* conditions. It is important to note that under all tested conditions, we did not observe the formation of two regioisomers, but **the** formation of **22** only, as demonstrated by NMR spectra and by HPLC analysis of

the crude reaction mixture. Moreover, our optimized conditions allowed us to avoid, as for **21**, the formation of a debrominated side product in contrast to what was previously reported [36].

This striking regioselectivity was also observed for the formation of indole **23,** derived from α-naphthylamine, which contains both α and β C-H bonds available for cyclization. The use of μW-heating allowed to obtain selectively the α- regioisomer in excellent yields (95%) after just 1 h under microwave heating (Table 2, entry 11).

When *para* -Cl substrates were employed even faster cyclizations were observed, as a more electron-withdrawing substituent makes the palladium-catalyzed reaction faster compared to a Br in the same position. Hence, compound **24** was obtained after 1 h in DMF with an improved yield (Table 2, entry 14**,** 90%,) under microwave irradiation, compared to conventional heating that afforded **24** in 73% yield in 16 h (Table 2, entry 16). Similarly, the presence of two chlorine atoms in both *orto* and *para* positions also made the conversion of enamine **16** to indole **25** in a shorter time and higher yield under μW-heating (Table 2, entries 17 and 18).

Interesting results were achieved in presence of a strong electron-withdrawing substituent such as the NO_2 group on the aromatic part of the enaminone. This group, indeed, represents a clear example of a rather sensitive group that can negatively influence oxidative coupling. In the first attempt, our proposed microwave-assisted synthetic strategy afforded the desired indole **26** in a very low yield (Table 2, entry 21**,** 18%,) in DMF, as well as stirring the reaction mixture overnight at 80 °C in an oil bath just 12% of the desired product was observed (entry 23). At this stage, our second attempt consisted in changing the solvent reaction by switching to DMSO and ACN in order to increase the product yield. When we used DMSO no traces of the indole were isolated, neither in the oil bath (entry 24) nor in the μW reactor (entry 22). In contrast, when the enaminone derivative **17** was coupled with the metal catalysts in ACN, which has a lower dielectric constant than DMSO but is comparable with DMF, better results were achieved. In particular, under conventional heating oil bath conditions, ACN did not improve the yield (Table 2, entry 27**,** 24%). On the contrary, it becomes interesting by μW irradiation. As reported in Table 2, the conversion of **17** into the methyl 2-methyl-5-nitro-1*H*-indole-3-carboxylate resulted strongly improved when the oxidative coupling was performed using μW energy (entry 25). Indeed, the yield increased up to 91% after 3 h.

We also have explored the effect of electron-donating groups such as methyl ($-CH_3$) and phenoxy (-OPh) groups. Wurtz et al. have previously been described the synthesis of indole product **27** through the cyclization of methyl (*Z*)-3-((2,4-dimethylphenyl)amino)but-2-enoate (**18**) under conventional heating (110 °C) by adding $Cu(OAc)_2$ (3 eq), $Pd(OAc)_2$ (10% mol), K_2CO_3 (3 eq) in DMF. The indole derivative is afforded in 62% yield [24]. Our protocol, which runs with limited amounts of Cu II provided **27** in high yield (89%, entry 30) when the reaction was performed in DMF at 80 °C for 16 h. Intriguingly, when this cyclization was explored under μW heating conditions (DMF, 60 °C), indole **27** was obtained in an enhanced 94% yield (within 3 h, entry 28).

The palladium-catalyzed oxidation proceeded in high yields also in the presence of -OPh in *para* position as an electron-donating substituent on enamine **19**. Recently, the literature reported the preparation of indole **28** recurring to iridium-based photoredox catalyst in 73% yield in DMF at 120 °C with irradiation from an 11 W lightbulb for 24 h [34]. Herein, we obtained the indole compound **28** in 95% yield within 1h under μW irradiation (entry 32), in comparison to conventional heating (90% yield within 3 h).

4. Conclusions

In conclusion, we have developed a microwave-assisted methodology that provided functionalized 2-methyl-1*H*-indole-3-carboxylate derivatives (*i*) using significantly reduced amounts of Cu II oxidant, (*ii*) required shorted reaction times, and (*iii*) provided substituted indoles in high isolated yields and, in most cases, pure enough for a further reaction; (*iv*) run regioselectivity. The reaction was performed by exposing the *N*-aryl enamines properly

functionalized by different electron-withdrawing and -donating groups to μW irradiations. All the synthesized indoles were obtained in higher yields and reduced reaction time under μW irradiation in comparison to conventional heating. The versatility of the protocol and the possibility of varying the solvent in an eco-friendly manner, with good conversion results, will allow this methodology to be applied to countless generations of suitably functionalized enamines. Indeed, by using the optimized synthetic protocol with a reduced amount of copper source (just 1 eq) as oxidant, the enamines 13 and 14 with α and β C-H bonds underwent a completely regioselective heterocyclization affording only one of the feasible regioisomeric indoles (22 and 23, entries 5–10 and 11–13, Table 2). Moreover, merely by μW heating and in ACN as a solvent, the negative influence that the *p*-NO$_2$ group of **17** exerts on the oxidative coupling to afford 26 (entry 25) has been overpassed increasing the yield up to 91%. Thus, this high-speed μW approach can be considered a fast and highly efficient method to synthesize many indole derivatives with a key role in the development of chiral indole-based compounds.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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