Efficient Microwave-Assisted Synthesis of Tetrahydroindazoles and their Oxidation to Indazoles

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Abstract: *N*-Acetyl-styrylpyrazoles undergo Diels–Alder cycloaddition reactions with *N*-methylmaleimide under solvent-free conditions to give the corresponding tetrahydroindazoles in good yields and high selectivity. On heating, these reactions do not occur or afford only traces of the cycloadducts. The stereochemistry of obtained cycloadducts was assigned by NMR. Oxidation of the tetrahydroindazoles with DDQ gave the expected indazoles and was accompanied by N-deacylation.

Key words: 4-styrylpyrazoles, Diels–Alder cycloadditions, microwave irradiation, *N*-methylmaleimide, indazoles, dehydrogenation

The indazole nucleus is an important pharmaceutical structure and constitutes the key moiety of many drugs with a broad range of pharmacological activities.[1] Their wide variety of applications in medicinal chemistry can be illustrated by their use as pharmaceutical agents in fields such as CNS disorders (e.g., granisetron),[2] anti-inflammatory (e.g., bendazac and benzydamine)[2,3] and antimicrobial agents,[4] anti-HIV protease inhibition,[5] anti-tumour[6] and nitric oxide synthase inhibitors[7,8] and binding affinity of non-steroidal progesterone receptor.[9] Structural modifications of the anti-inflammatory agent bendazac have been carried out and, in some cases, the synthesised compounds showed analgesic effects along with anti-inflammatory properties.[10]

There are several methods for the synthesis of indazoles;[1,11] most of them start from benzene derivatives, where the pyrazole ring is formed by ring closure. The major part of indazole ring-closure procedures involves creating a bond between the two nitrogen atoms (N–N) as the last step; nevertheless the ring closure by creation of a N–C bond through the formation of N2–C3 or N1–C7a bond is also common (according to the numbering of 1*H*-indazole **1**, Figure 1). A few examples involving a C3–C3a ring closure are also reported. There are also some examples starting from pyrazoles, involving the cycloaddition reactions of 1-phenyl-5-vinylpyrazole,[12] 1-aryl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles[13] and N-unsubstituted pyrazole *ortho*-quinodimethanes[14] with several dienophiles. As part of our continuing work on the synthesis and transformation of styrylpyrazoles,[15] we have investigated the Diels–Alder reaction of 4-styrylpyrazoles with *N*-methylmaleimide and the oxidation of the cycloadducts thus obtained (Scheme 1). This work led us to develop a novel and rapid method for the synthesis of new classes of indazoles.

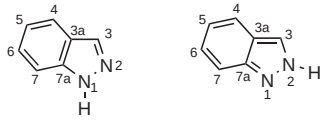

Figure 1 Structure of 1*H*- and 2*H*-indazoles.

Although vinylpyrazole derivatives are very reluctant to participate as dienes in cycloaddition reactions involving the pyrazole ring, owing to the loss of its aromaticity in the reaction,[1b,12] we decided to study the reactivity of styrylpyrazoles as dienes under classical heating conditions or microwave irradiation following our ongoing work with this type of compounds.[15] The reaction of (*E*)-5(3)-(2-hydroxyphenyl)-3(5)-styrylpyrazole (**1a**) with *N*-methylmaleimide in refluxing 1,2,4-trichlorobenzene did not afford the expected cycloadducts but yielded compounds **1d**[16] resulting from a conjugate addition of the pyrazole nitrogen to *N*-methylmaleimide (Figure 2). All attempts to react (*E*)-3-(2-hydroxyphenyl)-1-methy-5-styrylpyrazole (**1b**)[17] with electron-rich or electron-poor dienophiles in refluxing 1,2,4-trichlorobenzene were unsuccessful. Following our work on microwave-assisted reactions,[18] we made several attempts to react (*E*)-3-(2-hydroxyphenyl)-1-methyl-5-styrylpyrazole (**1b**) with *N*-methylmaleimide under microwave irradiation, using solvent or solvent-free conditions, different radiation power and reaction time, but in all cases the starting pyrazole **1b** was recovered and no new products were detected. Our next attempt was to study the reaction of (*E*)-1-acetyl-3-(2-hydroxyphenyl)-5-styrylpyrazole[19] (**1c**) with *N*-methylmaleimide under microwave irradiation, expecting that a deactivating group would facilitate the Diels–Alder reaction. This resulted in less than 20% of the (*E*)-1-acetyl-3-(2-hydroxyphenyl)-5-styrylpyrazole (**1c**) being recovered and (*E*)-3-(2-hydroxyphenyl)-5-styrylpyrazole (**1a**, 9%) could also be detected. Traces of the compound **1d**[16] obtained from the conjugate addition of the pyrazole nitrogen of **1a** to *N*-methylmaleimide and of the desired cycloadduct **2c** were observed (Figure 2). The structure of the latter was supported by the absence of the double bond and H-4 of the pyrazole ring and the presence of aliphatic protons, characteristics of a newly formed cyclohexane ring in the ^{1}H NMR spectrum.

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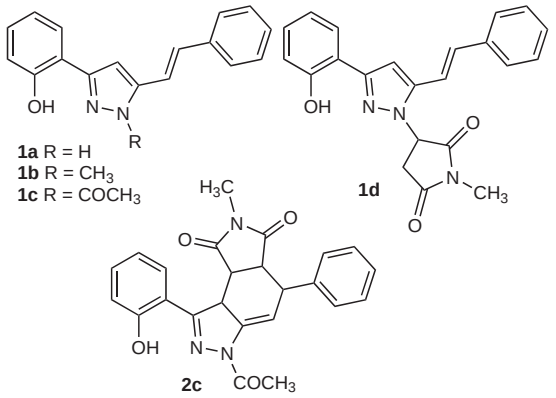


Figure 2 Structures of 3-(2-hydroxyphenyl)-5-styrylpyrazoles **1a**–**d** and cycloadduct **2c**.

As part of our ongoing research into the synthesis and transformation of (*E* and *Z*)-3-styrylchromones we synthesised several (*E* and *Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a**–**d** and **4a**–**c**,[20] which were acetylated with acetyl chloride in dry pyridine yielding in each case the corresponding (*E* and *Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **5a**–**d** and **6a**–**c** (Scheme 1).[21,22] The mixture of each one of the 1-acetyl-4-styrylpyrazoles **5a**–**d** or **6a**–**c** with *N*-methylmaleimide was submitted to microwave irradiation in solvent free conditions[23] and the desired cycloadducts **7a**–**d** or **8a**–**c** were obtained in moderate to very good yields (**7a**–**d**, 68–95%; **8a**–**c**, 32–54%). The NMR spectroscopic characteristics of the products in both cases are: (i) the presence of the hydroxyl group involved in a hydrogen bond (δ_H ca. 10 ppm); (ii) the absence of double bonds; (iii) the presence of the acetyl group noticed, in the ^{13}C NMR spectra, by the signal corresponding to the carbonyl group (δ_C ca. 168 ppm); (iv) the presence of an *N*-methyl group (δ_H ca. 2.5 ppm; δ_C ca. 22 ppm); (v) the presence of several signals in the aliphatic region of the ^1H NMR due to the newly formed cyclohexene ring. These data are consistent with the proposed cycloadduct structures **7a**–**d** and **8a**–**c**.[24,25] The *cis*-configuration of protons H-5, H-5a, H-8a and H-8b in adducts **7a**–**d** and of protons H-5a, H-8a and H-8b in adducts **8a**–**c**, was confirmed by NOE cross-peaks observed in their NOESY spectra (Table 1 and Table 2) and was also supported by a detailed analysis of the coupling constants of some protons ($J_{H8a–H8b}$ ca. 7–8 Hz for both isomers; $J_{H5–H5a}$ ca. 8 Hz for **7a**–**d**; $J_{H5–H5a}$ ca. 0 Hz for **8a**–**c**). These data indicate that the reaction selectively afforded the *endo* adduct in both cases. No traces of the *exo* adduct were detected.

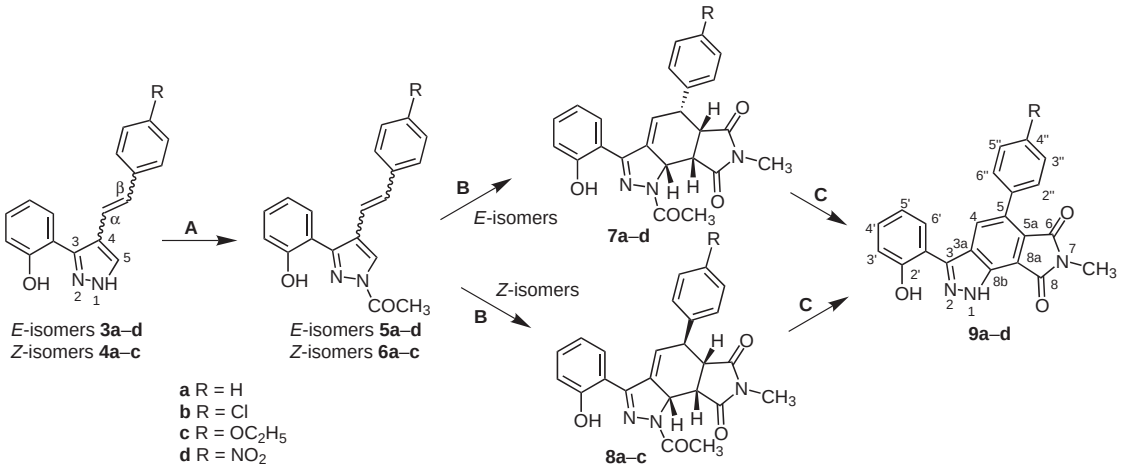
Table 1 Main Results Obtained from NOESY Spectra of Adducts **8a**–**d**

Protons	NOE cross-peaks with
H-5a	H-8a and H-2″,6″
H-8a	H-2″,6″

Table 2 Main Results Obtained from NOESY Spectra of Adducts **7a**–**d**

Protons	NOE cross-peaks with
H-5	H-4 and H-8b
H-5a	H-8b
H-8a	H-5a

In order to determine the scope of this reaction and its utility as a new synthetic methodology to synthesise novel indazole type-compounds, we extended our study to the cycloadduct oxidation following our recently published methodology using DDQ as an oxidant and microwave irradiation as an alternative to conventional heating (Scheme 1).[18] Some of the 1-acetyl-3-(2-hydroxyphenyl)-



Scheme 1 *Reagents and conditions*: (**A**) dry pyridine, CH_3COCl, r.t.; (**B**) *N*-methylmaleimide (6 equiv), MW 800 W, 40 min; (**C**) 1,2,4-trichlorobenzene, DDQ, MW 800 W, 30 min.

7-methy-5-phenyl-6,8-dioxopyrrolo[3,4-*g*]-5,5a,8a,8b-tetrahydroindazoles **7a**,**b**,**d** and **8c** were oxidised[26] and 3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxopyrrolo[3,4-*g*]indazoles **9a**–**d**[27] were the obtained products. These results indicate that the oxidation was accompanied by N-deacylation.[28]

In conclusion we have established a new efficient methodology for the synthesis of novel indazole-type compounds. Our first results indicate that the (*Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **8a**–**c** were less reactive than the (*E*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **7a**–**d**, probably due to the steric hindrance caused by the phenyl ring at the β-position. We can also conclude that electron-withdrawing substituents on the *para*-position of the styryl group increase the reactivity of the pyrazoles,[23] therefore compound **7d** is obtained in better yield (95%). The Diels–Alder cycloadditions described herein were stereoselective and gave the expected *endo*-cycloadducts, which can be aromatised to indazole-type compounds.

Some aspects of this reaction are currently under active investigation in our laboratory and results will be published in due course.

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(16) **Physical Data of (*E*)-1-(1-Methyl-2,5-dioxo-3-pyrrolidinyl)-5-styryl-3-(2-hydroxyphenyl)pyrazole (1d).**
Mp 234–236 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.13 (s, 3 H, NCH_3), 3.30 (dd, 1 H, *J* = 18.3, 9.1 Hz, 4‴-CH_2), 3.45 (dd, 1 H, *J* = 18.3, 5.2 Hz, 4‴-CH_2), 5.46 (dd, 1 H, *J* = 9.1, 5.2 Hz, 3‴-C*H*), 6.90 (s, 1 H, H-4), 6.96 (ddd, 1 H, *J* = 7.7, 7.3, 1.2 Hz, H-5′), 7.00 (dd, 1 H, *J* = 8.4, 1.2 Hz, H-3′), 7.01 (d, 1 H, *J* = 15.8 Hz, H-α), 7.22–7.27 (m, 1 H, H-4′), 7.26 (d, 1 H, *J* = 15.8 Hz, H-β), 7.35–7.44 (m, 3 H, H-3″,5″,4″), 7.53 (dd, 2 H, *J* = 8.1, 1.5 Hz, H-2″,6″), 7.59 (dd, 1 H, *J* = 7.7, 1.7 Hz, H-6′), 10.03 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.5 (NCH_3), 34.8 (4‴-*C*H_2), 55.6 (3‴-*C*H), 100.8 (C-4), 112.6 (C-α), 115.8 (C-1′), 117.1 (C-3′), 119.5 (C-5′), 126.6 (C-6′), 126.9 (C-2″,6″), 128.9 (C-3″,5″), 129.1 (C-4″), 129.9 (C-4′), 135.6 (C-1″), 136.1 (C-β), 143.9 (C-5), 152.5 (C-3), 155.7 (C-2′), 173.3 (2‴-C=O), 172.5 (5‴-C=O). MS (EI): *m/z* (rel. int.) = 374 (30), 373 (100) [$M^{+\cdot}$], 372 (25), 262 (39), 261 (67), 231 (11), 202 (10), 155 (5), 128 (6), 115 (16), 91 (29), 77 (9), 65 (9).

(17) **Physical Data of (*E*)-3-(2-Hydroxyphenyl)-1-methyl-5-styrylpyrazole (1b).**
Mp 159–161 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, 1-CH_3), 6.81 (s, 1 H, H-4), 6.89 (ddd, 1 H, *J* = 7.9, 7.3, 1.1 Hz, H-5′), 6.91 (d, 1 H, *J* = 16.2 Hz, H-α), 7.02 (dd,

1 H, *J* = 8.0, 1.1 Hz, H-3′), 7.13 (d, 1 H, *J* = 16.2 Hz, H-β), 7.21 (ddd, 1 H, *J* = 8.0, 7.3, 1.6 Hz, H-4′), 7.32 (dd, 2 H, *J* = 7.6, 6.8 Hz, H-3″,5″), 7.39 (tt, 1 H, *J* = 7.6, 1.6 Hz, H-4″), 7.51 (dd, 2 H, *J* = 6.8, 1.6 Hz, H-2″,6″), 7.57 (dd, 1 H, *J* = 7.9, 1.6 Hz, H-6′), 10.82 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 36.6 (1-CH_3), 98.9 (C-4), 113.7 (C-α), 116.5 (C-1′), 117.0 (C-3′), 119.2 (C-5′), 126.1 (C-6′), 126.7 (C-2″,6″), 128.6 (C-4″), 128.8 (C-3″,5″), 129.0 (C-4′), 133.5 (C-β), 136.0 (C-1″), 141.8 (C-5), 150.2 (C-3), 155.8 (C-2′). MS (EI): *m/z* (rel. int.) = 276 (100) [M$^{+\bullet}$], 275 (20), 231 (5), 202 (7), 185 (10), 144 (14), 128 (10), 115 (20), 102 (8), 91 (11), 77 (15). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found:C, 77.84; H, 5.79; N, 10.02.

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(19) **Typical Experimental Procedure.**
Acetyl chloride (1 mol equiv) was added to a stirred solution of (*E*)-3-(2-hydroxyphenyl)-5-styrylpyrazole (**1a**) in dry pyridine. The mixture was stirred at r.t. and under nitrogen atmosphere until complete disappearance of the starting 5-styrylpyrazole **1a**. After that period the reaction mixture was poured over ice and H_2O, and acidified at pH 2 with a 10% solution of HCl. The resulting mixture was extracted with $CHCl_3$ and dried over anhyd Na_2SO_4. The solvent was evaporated to dryness and the residue purified by thin layer chromatography with CH_2Cl_2 as eluent giving the expected (*E*)-1-acetyl-3-(2-hydroxyphenyl)-5-styrylpyrazole (**1c**) in moderate yield (44%). Mp 124.4–126.2 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.77 (s, 3 H, 1-COC*H*$_3$), 6.98 (ddd, 1 H, *J* = 7.7, 7.5, 1.1 Hz, H-5′), 7.06 (s, 1 H, H-4), 7.07 (dd, 1 H, *J* = 8.3, 1.1 Hz, H-3′), 7.22 (d, 1 H, *J* = 16.5 Hz, H-β), 7.30–7.43 (m, 4 H, H-4′,3″,4″,5″), 7.57 (d, 2 H, *J* = 7.7 Hz, H-2″,6″), 7.63 (dd, 1 H, *J* = 7.7, 1.6 Hz, H-6′), 7.93 (d, 1 H, *J* = 16.5 Hz, H-α), 10.38 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.0 (1-CO*C*H$_3$), 104.0 (C-4), 114.8 (C-1′), 116.4 (C-α), 117.3 (C-3′), 119.6 (C-5′), 127.2 (C-2″,6″), 127.4 (C-6′), 128.8 (C-3″,5″), 129.0 (C-4″), 131.0 (C-4′), 135.6 (C-β), 136.0 (C-1″), 145.8 (C-5), 153.9 (C-3), 156.5 (C-2′), 170.8 (1-*C*OCH$_3$). MS (EI): *m/z* (rel. int.) = 304 (80) [M$^{+\bullet}$], 262 (73) [M – C_2H_2O]$^+$, 245 (5), 233 (5), 216 (4), 202 (6) [M – C_8H_6]$^+$, 191 (2), 185 (21) [M – C_7H_5NO]$^+$, 178 (4), 171 (100), 155 (3), 140 (4), 128 (5), 115 (23), 102 (6), 89 (5), 77 (8) [$C_6H_5^+$], 65 (4). Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.01; H, 5.26; N, 9.05.

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(21) **Physical Data of (*E*)-1-Acetyl-4-(4-chlorostyryl)-3-(2-hydroxyphenyl)pyrazole (5b).**
Mp 169.1–169.9 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.76 (s, 3 H, 1-COC*H*$_3$), 6.94 (AB, 1 H, *J* = 16.1 Hz, H-β), 6.99 (dd, 1 H, *J* = 7.5, 6.9 Hz, H-5′), 7.04 (AB, 1 H, *J* = 16.1 Hz, H-α), 7.12 (dd, 1 H, *J* = 8.3, 1.1 Hz, H-3′), 7.33–7.36 (m, 1 H, H-4′), 7.36 (d, 2 H, *J* = 8.6 Hz, H-3″5″), 7.42 (d, 2 H, *J* = 8.6 Hz, H-2″,6″), 7.62 (dd, 1 H, *J* = 7.5, 1.6 Hz, H-6′), 8.47 (dd, 1 H, *J* = 0.7 Hz, H-5), 9.82 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.6 (1-CO*C*H$_3$), 115.9 (C-1′), 117.4 (C-3′), 117.9 (C-α), 119.8 (C-5′), 122.9 (C-4), 126.2 (C-5), 127.8 (C-2″,6″), 128.9 (C-6′), 129.0 (C-3″,5″), 130.9 (C-4′), 131.3 (C-β), 133.9 (C-4″), 135.0 (C-1″), 152.4 (C-3), 156.0 (C-2′), 168.1 (1-COCH$_3$). MS (EI): *m/z* (rel. int.) = 340 (36) [M$^{+\bullet}$, ^{37}Cl], 338 (81) [M$^{+\bullet}$, ^{35}Cl], 298 (35), 296 (81), 281 (5), 267 (4), 260 (8), 242 (4), 231 (6), 202 (8), 185 (20), 171 (100), 149 (5), 115 (14), 102 (6), 77 (4). Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.48; H, 4.73; N, 8.30.

(22) **Physical Data of (*Z*)-1-Acetyl-4-(4-chlorostyryl)-3-(2-hydroxyphenyl)pyrazole (6b).**
Mp 141.8–143.6 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, 1-COC*H*$_3$), 6.50 (dd, 1 H, *J* = 11.9, 1.1Hz, H-α), 6.75 (d, 1 H, *J* = 11.9 Hz, H-β), 6.95 (ddd, 1 H, *J* = 7.2, 7.9, 1.2 Hz, H-5′), 7.09 (dd, 1 H, *J* = 8.3, 1.2 Hz, H-3′), 7.17–7.23 (m, 4 H, H-2″,3″,5″,6″), 7.33 (ddd, 1 H, *J* = 7.2, 8.3, 1.6 Hz, H-4′), 7.87 (dd, 1 H, *J* = 7.9, 1.6 Hz, H-6′), 8.00 (d, 1 H, *J* = 1.1 Hz, H-5), 10.23 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.6 (1-CO*C*H$_3$), 115.7 (C-1′), 117.3 (C-3′), 119.6 (C-5′), 119.9 (C-α), 120.0 (C-4), 127.6 (C-5), 128.5 (C-6′), 128.7 (C-2″,6″), 129.8 (C-3″,5″), 131.0 (C-4′), 132.4 (C-β), 133.5 (C-4″), 134.4 (C-1″), 153.1 (C-3), 156.3 (C-2′), 167.8 (C=O). MS (EI): *m/z* (rel. int.) = 340 (31) [M$^{+\bullet}$, ^{37}Cl], 338 (69) [M$^{+\bullet}$, ^{35}Cl], 298 (32), 296 (71), 281 (5), 260 (8), 231 (7), 202 (8), 185 (22), 171 (100), 149 (6), 115 (17), 102 (8), 89 (5), 77 (7). Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.15; H, 4.37; N, 7.98.

(23) **Optimised Experimental Procedure.**
A mixture of (*E* or *Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **5a–d** or **6a–c** and *N*-methylmaleimide (1:6 mole ratio) was irradiated at atmospheric pressure in an Ethos SYNTH microwave (Milestone Inc.), at 800 W for 40 min. The crude product was dissolved in $CHCl_3$ and purified by thin layer chromatography with a 8:2 mixture of $CHCl_3$–EtOAc as eluent. The residue was crystallised from EtOH to give the expected 1-acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxopyrrolo[3,4-*g*]-5,5a,8a,8b-tetrahydro-indazoles (**7a**, 88%; **7b**, 68%; **7c**, 95%; **7d**, 95%; **8a**, 32%; **8b**, 54%; **8c**, 54%).

(24) **Physical Data of 1-Acetyl-5-(4-ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxopyrrolo[3,4-*g*]-5,5a,8a,8b-tetrahydroindazole (7c).**
Mp 236–237 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.44 (t, 3 H, *J* = 7.0 Hz, 4″-OCH$_2$C*H*$_3$), 2.54 (s, 3 H, 1-COC*H*$_3$), 2.76 (s, 3 H, 7-C*H*$_3$), 3.37 (dd, 1 H, *J* = 8.5, 7.4 Hz, H-5a), 3.54 (br dd, 1 H, *J* = 7.4, 4.5 Hz, H-5), 4.07 (dq, 2 H, *J* = 7.0, 1.9 Hz, 4″-OC*H*$_2$CH$_3$), 4.46 (dd, 1 H, *J* = 8.5, 7.1 Hz, H-8a), 4.97 (br dd, 1 H, *J* = 7.1, 3.6 Hz, H-8b), 6.94 (dd, 1 H, *J* = 4.5, 3.6 Hz, H-4), 6.96 (d, 2 H, *J* = 8.6 Hz, H-3″,5″), 6.97 (ddd, 1 H, *J* = 8.6, 7.2, 0.9 Hz, H-5′), 7.10 (dd, 1 H, *J* = 8.0, 0.9 Hz, H-3′), 7.21 (d, 2 H, *J* = 8.6 Hz, H-2″,6″), 7.38 (ddd, 1 H, *J* = 8.0, 7.2, 1.4 Hz, H-4′), 7.66 (dd, 1 H, *J* = 8.6, 1.4 Hz, H-6′), 9.85 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.9 (4″-OCH$_2$*C*H$_3$), 21.5 (1-CO*C*H$_3$), 25.0 (7-*C*H$_3$), 40.6 (C-8a), 42.1 (C-5a), 44.5 (C-5), 57.5 (C-8b), 63.5 (4″-O*C*H$_2$CH$_3$), 114.4 (C-1′), 114.5 (C-3″,5″), 117.7 (C-3′), 119.7 (C-5′), 126.2 (C-4), 127.5 (C-6′;), 129.0 (C-1″), 129.8 (C-2″,6″), 131.9 (C-4′), 137.8 (C-3a), 149.3 (C-3), 157.1 (C-2′), 158.5 (C-4″), 168.6 (1-COCH$_3$), 173.4 (C-6), 174.5 (C-8). MS (EI): *m/z* (rel. int.) = 459 (52) [M$^{+\bullet}$], 417 (28), 348 (100), 306 (70), 277 (18), 257 (10), 171 (35), 160 (7), 91 (10). Anal. Calcd for $C_{29}H_{25}N_3O_5$: C, 67.96; H, 5.48; N, 9.14. Found: C, 67.80; H, 5.49; N, 8.76.

(25) **Physical Data of 1-Acetyl-5-(4-ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxopyrrolo[3,4-*g*]-5,5a,8a,8b-tetrahydroindazole (8c).**
Mp 244–245 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.42 (t, 3 H, *J* = 7.0 Hz, 4″-OCH$_2$C*H*$_3$), 2.46 (s, 3 H, 1-COC*H*$_3$), 2.89 (s, 3 H, 7-C*H*$_3$), 3.56 (br d, 1 H, *J* = 8.6 Hz, H-5a), 4.70 (br d, 1 H, *J* = 7.6 Hz, H-5), 4.02 (dq, 2 H, *J* = 7.0 Hz, 4″-OC*H*$_2$CH$_3$), 4.42 (dd, 1 H, *J* = 8.6, 8.0 Hz, H-8a), 4.80 (dd, 1 H, *J* = 8.0, 3.8 Hz, H-8b), 6.96 (dd, 1 H, *J* = 7.6, 3.8 Hz, H-4), 6.88 (d, 2 H, *J* = 8.7 Hz, H-3″,5″), 6.98 (ddd, 1 H, *J* = 7.6,

7.4, 1.0 Hz, H-5′), 7.09 (dd, 1 H, *J* = 8.2, 1.0 Hz, H-3′), 7.23 (d, 2 H, *J* = 8.7 Hz, H-2″,6″), 7.37 (ddd, 1 H, *J* = 8.2, 7.4, 1.5 Hz, H-4′), 7.70 (dd, 1 H, *J* = 7.6, 1.5 Hz, H-6′), 9.81 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.8 (4″-OCH_2CH_3), 21.5 (1-$COCH_3$), 25.3 (7-CH_3), 41.5 (C-8a), 41.8 (C-5), 43.0 (C-5a), 55.7 (C-8b), 63.6 (4″-OCH_2CH_3), 114.3 (C-1′), 115.2 (C-3″,5″), 117.6 (C-3′), 119.7 (C-5′), 125.9 (C-4), 127.6 (C-6′), 127.9 (C-2″,6″), 128.2 (C-1″), 131.8 (C-4′), 138.2 (C-3a), 149.6 (C-3), 157.0 (C-2′), 158.3 (C-4″), 168.4 (1-$COCH_3$), 173.9 (C-6), 177.7 (C-8). MS (EI): *m/z* (rel. int.) = 459 (46) [$M^{+\bullet}$], 417 (29), 348 (14), 306 (42), 295 (100), 282 (14), 210 (21), 171 (36), 135 (16), 77 (5). Anal. Calcd for $C_{29}H_{25}N_3O_5$: C, 67.96; H, 5.48; N, 9.14. Found: C, 67.91; H, 5.45; N, 9.16.

(26) **Optimised Experimental Procedure.**
A mixture of each of the appropriate 1-acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxopyrrolo[3,4-*g*]-5,5a,8a,8b-tetrahydroindazoles **7a**,**b**,**d** or **8c** and DDQ (1:3 mol ratio) in 1,2,4-trichlorobenzene was irradiated at atmospheric pressure in an Ethos SYNTH microwave (Milestone Inc.), at 800 W for 30 min. The crude product was purified by column chromatography, using light PE as eluent, to remove the 1,2,4-trichlorobenzene, followed by EtOAc to remove the reaction product, which was further purified by TLC with a 9:1 mixture of $CHCl_3$–EtOAc as eluent. The residue was recrystallised from EtOH to give 5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxopyrrolo[3,4-*g*]indazoles (**9a** from **7a**, 85%; **9b** from **7b**, 32%; **9c** from **8c**, 31%; **9d** from **7d**, 34%).

(27) **Physical Data of 3-(2-Hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxopyrrolo[3,4-*g*]indazole (9a).**
Mp >275 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.21 (s, 3 H, NCH_3), 7.05 (ddd, 1 H, *J* = 7.7, 7.6, 1.2 Hz, H-5′), 7.16 (dd, 1 H, *J* = 8.1, 1.2 Hz, H-3′), 7.36 (ddd, 1 H, *J* = 7.6, 8.1, 1.6 Hz, H-4′), 7.48–7.61 (m, 4 H, H-2″,3″,5″,6″), 8.02 (dd, 1 H, *J* = 7.7, 1.6 Hz, H-6′), 8.44 (s, 1 H, H-4), 10.47 (s, 1 H, N*H*), 11.27 (s, 1 H, 2′-O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.0 (NCH_3), 116.2 (C-1′), 117.7 (C-3′), 119.8 (C-5′), 130.2 (C-4), 127.3 (C-6′), 128.2 (C-2″,6″), 129.7 (C-3″,5″), 130.5 (C-4′), 128.5 (C-4″), 133.1 (C-8b), 136.6 (C-5,1″), 145.7 (C-3), 156.3 (C-2′), 133.4 (C-3a), 128.2 (C-5a), 116.5 (C-8a), 167.9 (C-6,8). MS (EI): *m/z* (rel. int.) = 369 (100) [$M^{+\bullet}$], 326 (3), 311 (3), 284 (5), 255 (5), 226 (4), 164 (3), 91 (2).

(28) Lévai, A.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekö, J. *Eur. J. Org. Chem.* **2004**, 4672.