Microwave irradiation for enhancing the regioselective synthesis of 6*H*-indolo[2,3-*b*]quinoxalines

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Microwave irradiation (MWI) promotes the regioselective synthesis of 6*H*-indolo[2,3-*b*]quinoxaline (**5**) by condensation of isatin (**1**) with *o*-phenylenediamine. Ethyl indolo[2,3-*b*]quinoxaline-6-acetate (**8**) was prepared *via* the carbethoxymethylation of **5**, or from the reaction of *N*-(ethoxycarbonylmethyl)isatin (**6**) with *o*-phenylenediamine under MWI. The reaction of **8** with hydrazine hydrate afforded the hydrazide **9**, whose condensation with aromatic aldehydes and monosaccharides gave the hydrazones **10a–d**.

Keywords: isatin, fused indoles, quinoxalines, acylhydrazones, microwave heating

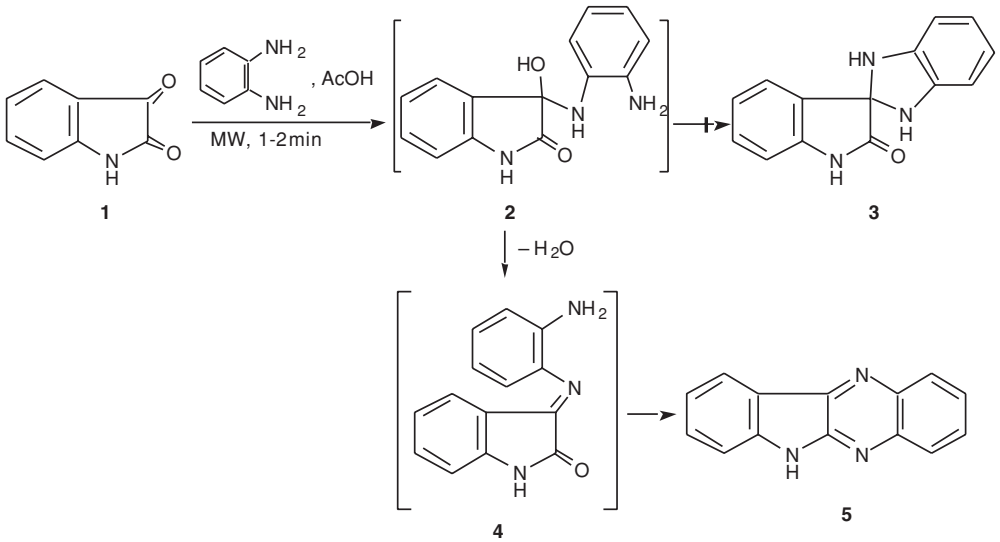
Heterocyclic compounds containing the quinoxaline ring have attracted considerable attention as a consequence of their biological activities.[1] Continuing our interests in the synthesis of quinoxaline derivatives[2] and recently in the use of microwave irradiation in organic synthesis,[3-8] we report the synthesis of some functionalised indoloquinoxalines using microwave irradiation (MWI) as a tool for improving the synthesis, as well as providing better environmental and economical impacts.[9,10]

The reaction of isatin (**1**) with *o*-phenylenediamine has been reported to give the *spiro*benzimidazoline (**3**), the isatin-3-imine (**4**), and/or 6*H*-indolo[2,3-*b*]quinoxaline (**5**).[11] These findings have been rationalised by considering a common intermediate **2**, which could undergo either a nucleophilic substitution reaction to form the *spiro* compound **3** or may suffer dehydration to form the corresponding isatin-3-imine (**4**). This imine may undergo *syn-anti* isomerisation upon protonation in acetic acid to yield the 6*H*-indolo[2,3-*b*]quinoxaline (**5**).[12] Considering the diverse possibilities, it seemed interesting to study this condensation applying MWI.

Results and discussion

We find that the indoloquinoxaline **5** is regioselectively and efficiently obtained (93%) by irradiating a mixture of **1** and *o*-phenylenediamine in acetic acid in a domestic MW oven for 2 min; no spiro compound or Schiff's base were detected (IR and ^{1}H NMR spectra). A shorter time (1 min) was required for completion of the reaction when it was conducted under MWI in a teflon screw-capped vessel, to give **5** in 88% yield. Otherwise, a synthetic approach for **5** involved the use of *p*-toluenesulfonic acid as a catalyst and the reaction was conducted in a focussed MW reactor.[13]

Isatin-1-acetic acid derivatives are important precursors for the synthesis of aldose reductase enzyme inhibitors.[14] When the carbethoxymethylation of **1** with ethyl chloroacetate in the presence of potassium carbonate and sodium iodide as catalyst was carried out under MWI, *N*-carbethoxymethylisatin (**6**) was obtained in 70% yield within 4 min. This could be converted into **8** by reaction with *o*-phenylenediamine in acetic acid under MWI either in an open flask (2 min) or in a teflon screw-capped vessel (1 min). Other possible products, such as **7** or the spirobenzimidazoline, were discounted on the spectral data. Compound **8** was alternatively prepared by the alkylation of **5** with ethyl chloroacetate in *N*,*N*-dimethylformamide in the presence of potassium carbonate and sodium iodide under MWI in a teflon screw-capped vessel for 6 min, to afford 53 % yield of **8** as shown in Scheme 2. Most of the starting material **5** remained unchanged when the reaction was carried out under MWI, using sodium hydride or sodium ethoxide instead of potassium carbonate. The synthesis of **8** from **6** unequivocally confirmed the assigned structure. Moreover, the IR spectrum of **8** showed an absorption band at 1741 cm^{-1} due to the COOEt group, its ^{1}H NMR spectrum



Scheme 1

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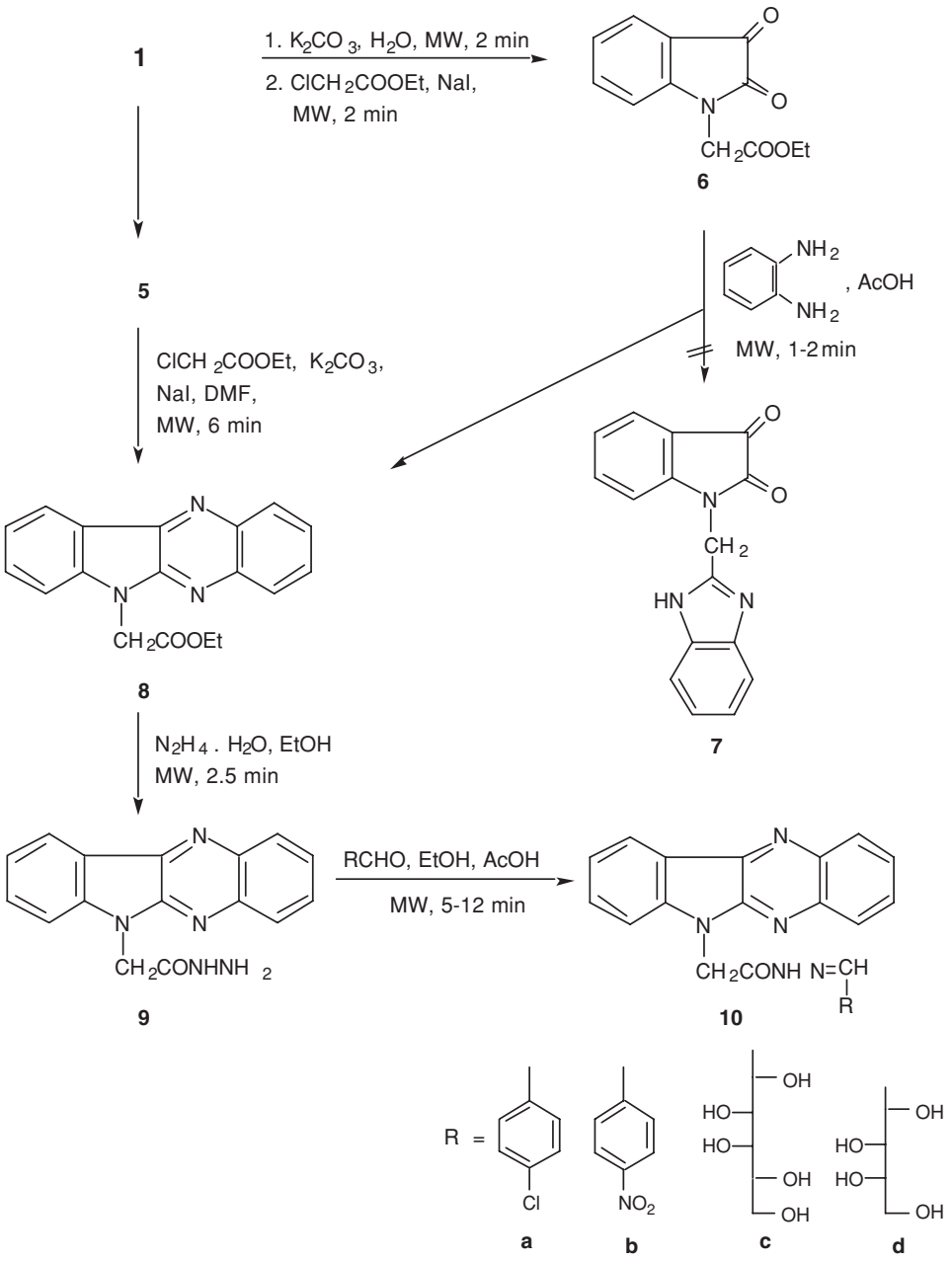

Scheme 2

showed a singlet at δ 5.23 ppm for the methylene group, and the ethyl group appeared as a triplet and quartet at δ 1.26 and 4.24 ppm respectively.

Reaction of **8** with hydrazine hydrate in ethanol under MWI gave the corresponding hydrazide **9** in 84% yield. Its ^{1}H NMR spectrum showed the absence of signals for the ethyl group and its IR spectrum showed a shift of the carbonyl band to a lower frequency than in the ester, confirming that hydrazinolysis had taken place. MWI was also used for condensing **9** with *p*-chloro and *p*-nitrobenzaldehyde in the presence of a catalytic amount of acetic acid for 5 min to yield the benzylidenehydrazine derivatives **10a** and **10b** in 81 and 99% yields, respectively. The prepared compounds were characterised by ^{1}H NMR and IR spectra as well as microanalysis.

Moreover, the reaction of **9** with the monosaccharides D-galactose and L-arabinose was also achieved under MWI for 12 min to give the corresponding sugar hydrazones **10c** and **10d** in 58 and 93% yields, respectively. Their IR spectra showed bands at 3344–3578 cm^{-1} (OH) and 3199–3225 cm^{-1} (NH).

In conclusion the MW irradiation has been found to be a convenient tool to achieve a regioselective synthesis of 6*H*-indolo[2,3-*b*]quinoxaline and their derivatives. The method save much time, energy and provide good yields of the products.

Experimental

Melting points were determined on a Meltemp apparatus. IR spectra were recorded with a Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were determined with Jeol spectrometer at 500 MHz. The chemical shifts are expressed in the δ scale using tetramethylsilane as a reference. TLC was performed on Baker-Flex silica gel 1B-F plates. Irradiation was done in a domestic MW oven EM-230M (800 watt output power), or otherwise when stated in the MW oven Kenwood MW 314 (1000 watt, 67% output power). Microanalyses were performed in the Unit of Microanalysis at Cairo University.

6H-Indolo[2,3-b]quinoxaline (**5**): *Method a*: A mixture of isatin (**1**) (0.10 g, 0.68 mmol) and *o*-phenylenediamine (0.094 g, 0.88 mmol) in acetic acid (1.0 ml) was placed in an Erlenmeyer flask (100 ml) and irradiated by MW (1000 watt) for 2 min. The product was filtered and recrystallised from ethanol/*N*,*N*-dimethylformamide as yellow crystals (0.14 g, 93% yield), m.p. 288 °C, Lit.[15] m.p. 285–287 °C.

Method b: A mixture of isatin (**1**) (0.10 g, 0.68 mmol) and *o*-phenylenediamine (0.094 g, 0.88 mmol) in acetic acid (1.0 ml) was placed in a teflon screw-capped vessel and irradiated by MW (1000 watt) for 1 min. The product (0.132 g, 88% yield) was found to be identical with that obtained from method a.

N-Carbethoxymethylisatin (**6**): A mixture of isatin (**1**) (0.50 g, 3.4 mmol) and anhydrous K_2CO_3 (0.69 g, 5.0 mmol) in water (15 ml) was placed in an Erlenmeyer flask (100 ml) and irradiated by MW till dryness (2 min). Ethyl chloroacetate (0.7 ml, 6.5 mmol) and sodium iodide (1.0 g, 6.7 mmol) were added and the mixture was reirradiated for 2 min. The product was extracted from the solid mixture by boiling in chloroform (15 ml). The extract was concentrated and the product was recrystallised from ethanol as orange crystals (0.554 g, 70% yield), m.p. 129 °C, Lit.[16] m.p. 129–130 °C, Lit.[17] m.p. 128–130 °C. IR (KBr): 1740 (CO) and 1643 cm^{-1}. ^1H NMR ($CDCl_3$): δ =1.26 (t, 3 H, *J*=7.7 Hz, Me), 4.22 (q, 2 H, *J*=6.9 Hz, *J*=7.7 Hz, O-CH_2), 4.47 (s, 2 H, N–CH_2), 6.78 (d, 1 H, *J*=7.7 Hz, Ar–H), 7.13 (t, 1 H, *J*=7.7 Hz, Ar–H), 7.57 (t, 1 H, *J*=7.7 Hz, Ar–H) and 7.62 (d, 1 H, *J*=7.7 Hz, Ar–H).

Ethyl 6H-indolo[2,3-b]quinoxaline-6-acetate (**8**): *Method a.* A mixture of **5** (0.10 g, 0.456 mmol), potassium carbonate (0.065 g, 0.471 mmol), ethyl chloroacetate (0.20 ml, 1.856 mmol) and sodium iodide (0.20 g, 1.34 mmol) in *N*,*N*-dimethylformamide (1.0 ml) was placed in teflon screw-capped vessel and irradiated by MW (1000 watt) for 6 min. The reaction mixture was cooled and poured onto crushed ice. The product was filtered, washed with water and dried. It was recrystallised from ethanol as yellow crystals (0.074 g, 53%), m.p. 202–204 °C, Lit.[18] m.p. 194–195 °C. IR (KBr): 1741 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ = 1.26 (t, 3 H, *J*=7.6 Hz, Me), 4.24 (q, 2 H, *J*=7.6 Hz, *J*=6.7 Hz, OCH_2), 5.23 (s, 2 H, N–CH_2), 7.35 (d, 1 H, *J*=7.7 Hz, Ar–H), 7.41 (t, 1 H, *J*=7.7 Hz, Ar–H), 7.66–7.77 (m, 3 H, Ar–H), 8.11 (d, 1 H, *J*=6.7 Hz, Ar–H), 8.31 (dd, 1 H, *J*=6.7 Hz, *J*=1.9 Hz, Ar–H) and 8.49 (d, 1 H, *J*=7.7 Hz, Ar–H). Analysis for $C_{18}H_{15}N_3O_2$ (305.32); Calcd: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.62; H, 4.60; N, 13.55 %.

Method b: A mixture of **6** (0.10 g, 0.43 mmol) and *o*-phenylenediamine (0.047 g, 0.44 mmol) in acetic acid (1.0 ml) was placed in Erlenmeyer flask (100 ml) and irradiated by MW (1000 watt) for 2 min. The product was filtered and recrystallised from ethanol as yellow crystals (0.126 g, 96%). It was identical with the product obtained from method a.

Method c: A mixture of **6** (0.10 g, 0.43 mmol) and *o*-phenylenediamine (0.047 g, 0.44 mmol) in acetic acid (1.0 ml) was placed in a teflon screw-capped vessel and irradiated by MW (1000 watt) for 1 min. The product (0.109 g, 83%) was found to be identical with that obtained from methods a and b.

6-Hydrazinocarbonylmethylindolo[2,3-b]quinoxaline (**9**): A solution of **8** (0.11 g, 0.36 mmol) in ethanol (20 ml) was treated with hydrazine hydrate (0.5 ml). The reaction mixture was placed in an Erlenmeyer flask (100 ml) and irradiated by MW for 2.5 min. The product was filtered and recrystallised from ethanol/*N*,*N*-dimethylformamide as yellow crystals (0.088 g, 84%), m.p. > 300 °C. IR (KBr): 3314–3191 (NH and NH_2) and 1648 cm^1 (CO). ^1H NMR (DMSO-d_6): δ = 4.29 (s, 2 H, NH_2, D_2O-exchangeable), 5.09 (s, 2 H, N–CH_2), 7.40 (t, 1 H, *J*= 7.7 Hz, Ar–H), 7.61 (d, 1 H, *J*= 8.4 Hz, Ar–H), 7.70–7.73 (m, 2 H, Ar–H), 7.80 (t, 1 H, *J*= 7.7 Hz, Ar–H), 8.07 (d, 1 H, *J*=8.4 Hz, Ar–H), 8.25 (d, 1 H, *J*= 7.7 Hz, Ar–H), 8.37 (d, 1 H, *J*= 7.7 Hz, Ar–H) and 9.43 (s, 1 H, NH, D_2O-exchangeable). Analysis for $C_{16}H_{13}N_5O$ (291.30) Calcd: C, 65.97; H, 4.50; N, 24.04. Found: C, 65.66; H, 4.61; N, 24.18 %.

Reaction of **9** *with aromatic aldehydes*: *General procedure*. A solution of **9** (0.10 g, 0.34 mmol) in ethanol (20 ml), the aromatic aldehyde (0.40 mmol) and one drop of acetic acid was placed in an Erlenmeyer flask (100 ml) and irradiated by MW for 5 min. The product was filtered and recrystallised from ethanol/*N*,*N*-dimethylformamide.

6-(p-Chlorobenzylidenehydrazinocarbonylmethyl)-6H-indolo[2,3-b]quinoxaline(**10a**): Yellow crystals (0.115 g, 81%), m.p. >300 °C. IR (KBr): 3182 (NH) and 1675 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ = 5.69 (s, 2 H, N–CH_2), 7.40 (t, 1 H, *J*= 6.9 Hz, Ar–H), 7.48 (d, 2 H, *J*= 8.4 Hz, Ar–H), 7.67–7.74 (m, 4 H, Ar–H), 7.78 (d, 2 H, *J*= 6.9 Hz, Ar–H), 8.04 (s, 1 H, CH=N), 8.06 (d, 1 H, *J*= 8.4 Hz, Ar–H), 8.26 (d, 1 H, *J*= 8.4 Hz, Ar–H), 8.37 (d, 1 H, *J*= 6.9 Hz, Ar–H) and 11.86 (s, 1 H, NH). Analysis for $C_{23}H_{16}ClN_5O$ (413.85) Calcd: C, 66.75; H, 3.90; N, 16.92. Found: C, 66.43; H, 3.72; N, 17.13 %.

6-(p-Nitrobenzylidenehydrazinocarbonylmethyl)-6H-indolo[2,3-b]quinoxaline (**10b**): Yellow crystals (0.114 g, 99%), m.p. >300 °C. IR (KBr): 3186 (NH) and 1682 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ = 5.74 (s, 2 H, N–CH_2), 7.40 (t, 1 H, *J* = 7.7 Hz, Ar–H), 7.70–7.80 (m, 4 H, Ar–H), 8.00 (d, 2 H, *J* = 7.7 Hz, Ar–H), 8.07 (d, 1 H, *J* = 8.4 Hz, Ar–H), 8.11 (s, 1 H, CH=N), 8.22 (d, 2 H, *J* = 8.4 Hz, Ar–H), 8.25 (d, 1 H, *J* = 8.4 Hz, Ar–H), 8.36 (d, 1 H, *J* = 7.7 Hz, Ar–H) and 12.08 (s, 1 H, NH). Analysis for $C_{23}H_{16}N_6O_3$ (424.41) Calcd: C, 65.09; H, 3.80; N, 19.80. Found: C, 64.72; H, 3.74; N, 19.73 %.

Reaction of 9 with monosaccharides: General procedure: To a solution of **9** (0.10 g, 0.34 mmol) in ethanol (20 ml) was added a solution of the sugar (0.86 mmol) in water (5 ml) and one drop of acetic acid. The reaction mixture was placed in an Erlenmeyer flask (100 ml) and irradiated by MW for 12 min. Water (10 ml) was added and the product was collected by filtration, washed with ethanol and dried. It was recrystallised from ethanol/*N*,*N*-dimethylformamide.

D-Galactose (6H-indolo[2,3-b]quinoxalin-6-yl)acetylhydrazone (**10c**): Yellow crystals (0.09 g, 58%), m.p. 194 °C. IR (KBr): 3578 (OH), 3199 (NH) and 1667 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ = 3.48–5.60 (3 × m, 13 H, N–CH_2 + sugar–H), 7.42–7.43 (m, 1 H, Ar–H), 7.54 (d, 1 H, *J* = 5.4 Hz, CH=N), 7.60–7.82 (m, 4 H, Ar–H), 8.10–8.13 (m, 1 H, Ar–H), 8.29 (d, 1 H, *J* = 7.7 Hz, Ar–H), 8.39–8.40 (m, 1 H, Ar–H) and 11.62 (brs, 1 H, NH, D_2O-exchangeable). Analysis for $C_{22}H_{23}N_5O_6$ (453.44) Calcd: C, 58.27; H, 5.11; N, 15.45. Found: C, 57.93; H, 5.03; N, 15.33 %.

L-Arabinose (6H-indolo[2,3-b]quinoxalin-6-yl)acetylhydrazone (**10d**): Yellow crystals (0.135 g, 93%), m.p. 260 °C. IR (KBr): 3344 (OH), 3225 (NH) and 1687 cm^{-1} (CO). ^1H NMR (DMSO-d_6): δ = 3.44–5.55 (5 × m, 11 H, N–CH_2 + sugar–H), 7.38–7.42 (m, 1 H, Ar–H), 7.47 (d, 1 H, *J* = 6.1 Hz, CH=N), 7.68–7.82 (m, 4 H, Ar–H), 8.09 (d, 1 H, *J* = 7.7 Hz, Ar–H), 8.27 (d, 1 H, *J* = 7.7 Hz, Ar–H), 8.38 (d, 1 H, *J* = 7.7 Hz, Ar–H) and 11.48 (brs, 1 H, NH, D_2O-exchangeable). Analysis for $C_{21}H_{21}N_5O_5$ (423.42) Calcd: C, 59.56; H, 5.00; N, 16.54. Found: C, 59.45; H, 5.03; N, 16.42 %.

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