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An efficient microwave-assisted synthesis of dihydropyrazinones and bis-benzoylketones

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ABSTRACT

Microwave-assisted modified Sandmeyer reactions of oximinoacetanilides, themselves obtained from substituted primary aromatic amines, in concentrated H_2SO_4 give isatins. *N*-Acetylisatins undergo ring cleavage and subsequent ring closing with alkanediamines in the presence of ethanol under MW irradiation to give the corresponding dihydropyrazinones in excellent yields. Modification of the reaction conditions affords bis-benzoylketones under MW irradiation.

Since the publication of the first paper on organic synthesis under microwave (MW) dielectric heating, the field has expanded dramatically.[1–4] The use of MW irradiation minimizes the formation of unwanted by-products and reduces the need for organic solvents to a minimum, or even solvent-free.[5,6] Isatins and related compounds have beneficial biological effects, including antifungal, antiviral, and antiproliferative activities.[7,8] Hence, there is significant interest in the design of various isatins and related compounds as drugs in the field of medicinal organic chemistry.[9–11] In addition, the reactions of carbonyl moieties at the β-position of various isatins and *N*-acetylisatins, are important.[12–14] Accordingly, we report on the MW-assisted synthesis and the characterization of several *N*-acetylisatins and their transformations into dihydropyrazinones and bis-benzoylketones using alkanediamines in excellent yields.

A microwave oven (Shikoku Instrumentation Co. Ltd, Japan, power range: 0–650 W at 2.45 GHz) was used. The temperature gradient of the reactor was 2–5 °C/s and each reaction was carried out at least three times to ensure accuracy.

The ring closing reaction of oximinoacetanilides **4a–c** with concentrated H_2SO_4 to give isatins **3a–c** in 85–95% yields (conventional yields below 80%) was carried out under MW conditions for 10 s. It is worth noting that the interaction of H_2SO_4 with MW irradiation was found to be problematic. In particular, prolonged exposure to MW irradiation resulted in decomposition of the products. To prevent decomposition, a short pulse irradiation technique was applied (5 s/irradiation). Two 5 s pulses were sufficient to complete the cyclization to give isatins **3a–c**. Acetylation of **3a–c** in Ac_2O/pyridine under MW irradiation for 50–70 s afforded the corresponding *N*-acetylisatins **2a–c** in excellent yields (**2a**: yield 81%, conventional yield 66%, decomposed at 298 °C). The IR (KBr, disc) spectrum of **2a** showed absorptions at 1758 (s, C=O, lactam), 1684 (s, C=O), and 1625 (s, C=O, amide) cm^{-1} for the three carbonyl groups, respectively. In addition, **2a** showed signals in the ^1H NMR spectrum (DMSO-d_6) at δ 7.82 for the aromatic proton (C_4-H) as a doublet and the C_6-H proton appeared at δ 7.64 as a doublet of doublets. The CH_3 protons appeared as a singlet at δ 2.41. The microanalysis data were consistent with the structures of products **2a–c**.

An important aspect of this work was the ring cleavage of *N*-acetylisatins **2a–c** with ethanol and their subsequent cyclization with alkanediamines (Scheme 1). The *N*-acetylisatin **2** (3.0 mmol) was dissolved in distilled ethanol and the appropriate diamine (3.0 mmol) was added to the mixture. The reaction mixture was irradiated under MW conditions for 40–50 s. The extent of the reaction was monitored by TLC (EtOAc–MeOH–*n*-hexane, 2:1:5) after irradiation. Cooling, followed by neutralization of the reaction mixture with 2% aq HCl solution gave a yellow solid mass. Recrystallization of the crude solid from EtOAc afforded compounds **1a–d** (>80% yield, conventional yield was found to be <70%). A few reactions of acetylisatins with alkanediamines were studied previously using conventional heating.[14–16] A plausible mechanism involves nucleophilic attack by ethanol at the lactam carbonyl carbon of *N*-acetylisatin and subsequent ring cleavage to generate keto ester **B** (Scheme 2). Next, nucleophilic attack of the alkanediamine on the ester carbonyl carbon followed by elimination of ethanol and intramolecular cyclization gives dihydropyrazinone **C**.

The NMR spectra and microanalyses of pyrazinones **1a–d** were consistent with the structures shown.[17] The melting point (190–192 °C, lit.[14] 189–191 °C) and the spectral data of bromopyrazinone **1b** corresponded well with that reported earlier for the same compound obtained by conventional heating.

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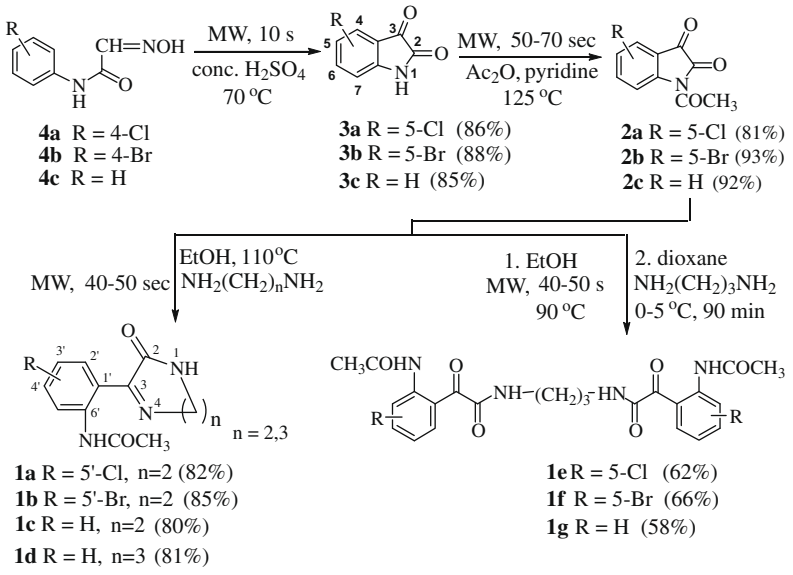
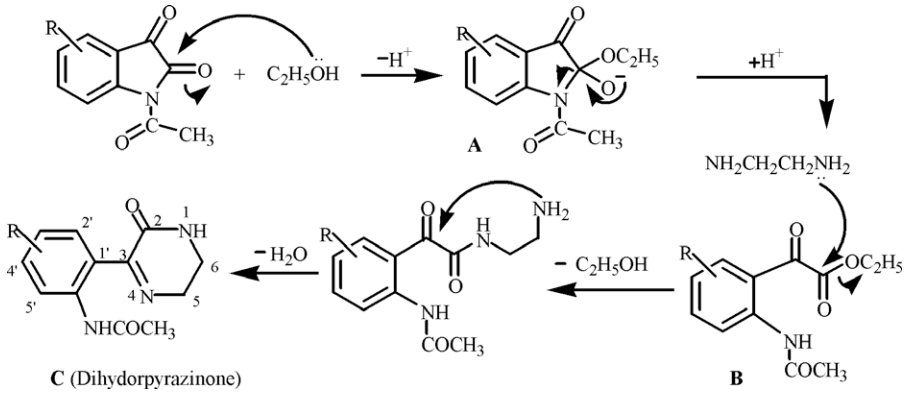


Scheme 1.



Scheme 2.

Alternatively the *N*-acetylisatin **2** (3.0 mmol) in distilled ethanol (5.0 mL) was irradiated under MW conditions for 40–50 s followed by cooling.[18] Next, dioxane (8.0 mL) and 1,3-diaminopropane (1.5 mmol) were added and reaction mixture was stirred at 0–5 °C for 90 min. The crude solid obtained after work-up was chromatographed on silica gel (cyclohexane, ethyl acetate, and methanol as eluents). Removal of the solvent under reduced pressure gave a brown crystalline solid, which was recrystallized from a mixture of $CHCl_3$ and EtOAc. The above-mentioned reaction conditions facilitated the addition of the intermediate ester **B** (Scheme 2) to the diamine in a 1:2 molar ratio and afforded the bis-benzoylketones **1e–g** in fairly good yields. The analytical data for compounds **1e–g** were consistent with the structures shown.

Typically, MW-dielectric heating plays an important role in the rapid formation of molecules in higher yields compared to reactions carried out using classical heating. In conclusion, we have demonstrated that microwave irradiation could be employed efficiently for the synthesis of biologically important isatins and their related heterocyclic compounds. The MW-assisted synthesis was more advantageous over classical heating with regard to reaction time, solvent quantity, and product yield in almost every case. A possible explanation for the formation of the products in short reaction times lie in the fact that the MW provides elevated heating rates which shortens reaction times.

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17. *Compound **1a***: ^{1}H NMR (400 MHz, CD_3OD): δ 10.68 (br s, NH), 9.88 (br s, NH), 7.58 (d, 1H, *J* = 1.6 Hz, C2′–H, ArH), 7.37 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, C4′–H, ArH), 7.15 (d, 1H, *J* = 7.6 Hz, C5′-H, ArH), 4.12 (t, 2H, *J* = 8.1 Hz, C-5), 3.21 (br m, 2H, C-6), 2.50 (s, 3H, CH_3). *Compound* **1e:** ^{1}H NMR (400 MHz, CD_3OD): δ 9.21 (s, 2H, 2 × NH), 7.76 (d, 2H, *J* = 1.9 Hz, C6–H, ArH × 2), 7.54 (dd, 2H, *J* = 8.1 Hz, *J* = 1.9 Hz, C4–H, ArH × 2), 6.84 (d, 2H, *J* = 8.1 Hz, C3–H, ArH × 2), 3.52 (m, 4H, 2 × CH_2), 2.55 (s, 6H, 2 × CH_3), 1.38 (m, 2H, CH_2).
18. *Representative procedures*: *Compounds* **3a–c**: Oximinoacetanilide **4a** (0.99 g, 5.0 mmol) was mixed with concentrated sulfuric acid (5.0 mL) and the resulting mixture was irradiated (20% radiation) using a microwave oven for 10 s (5 s × 2 irradiation). The extent of the reaction was monitored by TLC (CH_2Cl_2–EtOAc, 5:1). Neutralization of the reaction mixture with 20% aq Na_2CO_3 solution gave an orange solid mass. Recrystallization of crude solid from methanol afforded compound **3a**.

Compounds **1a–d**: *N*-Acetylisatin **2a** (545.5 mg, 3.0 mmol) was dissolved in distilled ethanol and the appropriate diamine (3.0 mmol) was added to the mixture. The reaction mixture was irradiated using a microwave for 40–50 s. Cooling followed by neutralization of the reaction mixture with 2% aqueous HCl solution gave a yellow solid mass. Recrystallization of the crude solid from EtOAc gave compound **1a.**

Compounds **1e–g**: *N*-Acetylisatin **2a** (545.5 mg, 3.0 mmol) was dissolved in distilled ethanol (5.0 mL) and the resulting reaction mixture was irradiated using a microwave for 40–50 s. The mixture was cooled to rt and dioxane (8.0 mL) was added followed by propan-1,3-diamine (1.5 mmol) and the reaction mixture was stirred at 0–5 °C for 90 min. The obtained crude solid was chromatographed on silica gel using cyclohexane, EtOAc and MeOH as eluent. Removal of the solvent under reduced pressure gave a brown crystalline solid, which was recrystallized from a mixture of $CHCl_3$ and EtOAc to give **1e**.