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A novel and easy two-step, microwave-assisted method for the synthesis of halophenyl pyrrolo[2,3-*b*]quinoxalines via their pyrrolo precursors. Evaluation of their bioactivity

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ABSTRACT

A novel, two-step, facile route for the synthesis of pyrrolo[2,3-*b*]quinoxalines via 2,3-dioxopyrroles, enhanced by microwave irradiation, is presented. The newly synthesized 2,3-dioxo-5-halophenyl pyrrolo precursors **4a–c** as well as the non-aromatized ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c** and the aromatized ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c** were evaluated for their antioxidant, cytostatic, and antiviral properties. Most of them proved to be potent hydroxyl radical scavengers and inhibited in vitro lipid peroxidation. The compounds showed moderate antiproliferative activity, while **6a** inhibited vaccinia virus at an EC_{50} value of 2 μM, and **4c** and **6c** inhibited Sindbis virus at EC_{50} values of 4 μM.

Microwave (MW) technology and multicomponent reactions (MCRs) have attracted significant attention from synthetic organic chemists as they accelerate a wide variety of chemical transformations. MWs impart many chemical reactions with attributes such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimization of reactions, and several ecofriendly advantages,[1,2] while MCRs are extremely useful tools for the synthesis of diverse and complex compounds, as well as small and drug-like heterocycles.[3,4] According to current synthetic requirements, environmentally benign multicomponent procedures employing microwave methodology are particularly welcome.

Among various classes of heterocyclic compounds, pyrrolyl[5–7] and quinoxalinyl[8,9] derivatives are well known as antioxidants, presenting potent lipid peroxidation inhibition in vitro and significant hydroxyl radical scavenging activity. The quinoxaline nucleus is present in many pharmaceutical agents exhibiting a broad spectrum of biological activities, such as antitumor, antiviral, antiglaucoma, antitubercular, and anti-inflammatory.[10–13] 2-Oxopyrroles are important substructures in a variety of drugs, including those active against viral infections (HIV,[14] influenza,[15] cytomegalovirus[16]), microbiological diseases[17,18] (bacterial or fungal), and cancer.[19] Finally, pyrroloquinoxaline derivatives[20] are also known as anti-HIV,[21] antimalarial,[22] antagonist,[23] anticancer,[24–26] and antioxidant[27]agents, as well as PARP-1[28] and Akt kinase[29] inhibitors.

Based on the pharmacological interest in compounds that belong to the pyrrolo and quinoxaline families, and considering that only a few methods have been reported for the synthesis of pyrrolo[2,3-*b*]quinoxalines,[27,30–32] we present herein a novel two-step process for the synthesis of 4-chloro, 4-fluoro, and 4-iodophenyl pyrrolo[2,3-*b*]quinoxalines via 2,3-dioxo-pyrroles using microwave irradiation, and a comparison of this methodology with conventional heating.

Our approach to the key intermediates, 2,3-dioxo-5-(4-halophenyl) pyrroles **4a–c**, involved the operationally simple, practical, and economical, three-component condensation of sodium

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diethyl oxalacetate (**3**) with an equimolar amount of an aromatic aldehyde (**1a–c**) and methylamine (**2**), in refluxing ethanol.[33] This reaction provided the desired pyrroles **4a–c** in a one-pot reaction and in moderate yields (36–48%), depending on the halogen on the aromatic aldehyde used (Scheme 1). All the products could be easily filtered from the reaction mixture and could be prepared on multigram scale.

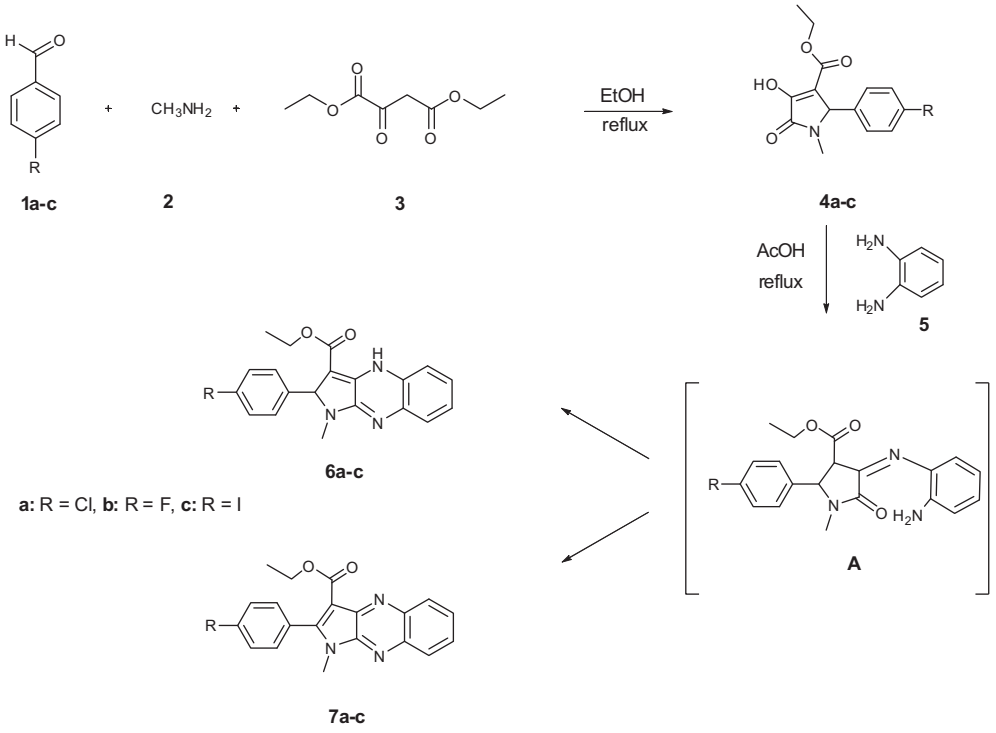
These substituted pyrroles are useful intermediates for the synthesis of pyrrolo[2,3-*b*]quinoxalines **6a–c** and **7a–c**. Therefore, pyrroles **4a–c** were condensed with *o*-phenylenediamine (**5**) in refluxing glacial acetic acid for one hour to give a mixture of two products, which were separable by thin-layer chromatography. The slower moving derivatives were isolated in 39–46% yields and were identified as the non-aromatized ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c**, while the less polar analogues corresponding to the aromatized ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c**, were obtained in slightly higher yields (50–58%) (Scheme 1). When the condensation reaction was performed for two hours, the aromatized isomers **7a–c** were afforded exclusively (65–72%). When oxygen or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used, the starting materials were recovered together with some degradation products. It should be noted that the nature of the halogen on the aromatic ring at position 5 of the heterocycle, in compounds **4a–c**, did not affect the reaction course.

A possible reaction mechanism probably includes an imine–enamine exchange (intermediate A, Scheme 1), which may lead to a favorable situation for the second step (cyclization) to operate; this can directly result from the hydrogen atom on the nitrogen leading to compounds **6**, or from the hydrogen atom on the carbon after cyclic hemiaminal formation leading to compounds **7**.

Since thermally driven organic transformations take place either by conventional heating or microwave accelerated heating, all the reactions were also conducted under MW conditions. Thus, the three-component reaction between aldehydes **1a–c** and methylamine (**2**) with sodium diethyl oxalacetate (**3**) under MW irradiation (100 W) at 110 °C for 20 min produced pyrroles**4a–c**, which were condensed upon irradiation (200 W) with *o*-phenylenediamine (**5**), to afford solely after 3 min at 40 °C the non-aromatized quinoxalines **6a–c** and the aromatized isomers **7a–c** after 10 min at 180 °C (Table 1). When compared to conventional heating, the MW technology completed the two-step synthesis much faster, while the yields of the products were slightly increased (by 4–11%).

All new compounds were characterized by NMR and IR spectroscopy, mass spectrometry, and elemental analysis. Regarding the structures of products **4**, **6**, and **7**, their IR spectra showed the typical absorptions of an α,β-unsaturated ethyl carboxylate at 1625–1698 cm^{-1}. Their ^1H NMR spectra showed signals that could be attributed to the carboethoxy group at 1.00–1.22 ppm (t, 3H) and at 3.97–4.30 ppm (q, 2H). In the ^1H NMR spectra of dihydro analogues **6a–c**, prominent 3-proton methyl signals appeared, which were ascribed to the *N*-methylamino group (**6a**: δ 2.76, **6b**: δ 1.25, **6c**: δ 1.25), while following aromatization the same protons were remarkably deshielded (**7a**: δ 3.78, **7b**: δ 3.78, **7c**: δ 3.77). The ^1H NMR spectra of compounds **6a–c** exhibited signals for the H-2′ protons of the pyrrole ring at 4.85–5.02 ppm as characteristic singlets, contrary to compounds **7a–c**, whose ^1H NMR spectra revealed the absence of such signals.

All the products were evaluated for their antioxidant, cytostatic, and antiviral properties. The interactions of the examined compounds with the 1,1-diphenyl-2-picryl-hydrazyl (DPPH) stable free radical[34] are listed in Table 2, in comparison to the well-known antioxidant agent, nordihydroguaiaretic acid (NDGA). The best DPPH radical scavenging activity was presented by **6b** (at 20 min) and **6a** (at 60 min), while the results for all the analogues at a concentration of 100 μM were time-dependent with the exception of **4c**. A



Scheme 1. Synthesis of the novel 2,3-dioxo-5-(4-halophenyl) pyrroles **4a–c**, ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c**, and ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c**.