

Synthesis of Epoxyisoindolinones Via Microwave-Assisted Ugi-4CR/Intramolecular-Diels-Alder Reaction [†]

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Abstract: A series of epoxyisoindolinones were synthesized by microwave-assisted post-IMCR transformation based domino strategy via the Ugi-4CR/Intramolecular-Diels-Alder (U-4CR/IMDA) sequence under mild, solvent-, catalyst free ecofriendly conditions and orthogonal-bifunctional components. Epoxyisoindolinones are a privileged core of high interest in medicinal chemistry mainly for its anticancer activity in several cell lines.

Keywords: multicomponent reactions; Ugi; Diels-alder; epoxyisoindolinone

1. Introduction

Multicomponent reactions (RMC) are one of the most efficient tool in modern organic synthesis, since they have all features that contribute to an ideal synthesis: high atom economy and convergence, efficiency, mild conditions, operational simplicity, broad scope and concomitant step economy compared to other synthetic tools [1–5].

Epoxyisoindolinones are scaffolds present in numerous bioactive molecules. Isoindolinones and epoxyisoindolinones are recognized as privileged cores and are used as building blocks for the design of new pharmacologically active compounds [6,7], they exhibit a wide range of biological activities such as antibiotic, antiviral and anticancer [8–10].

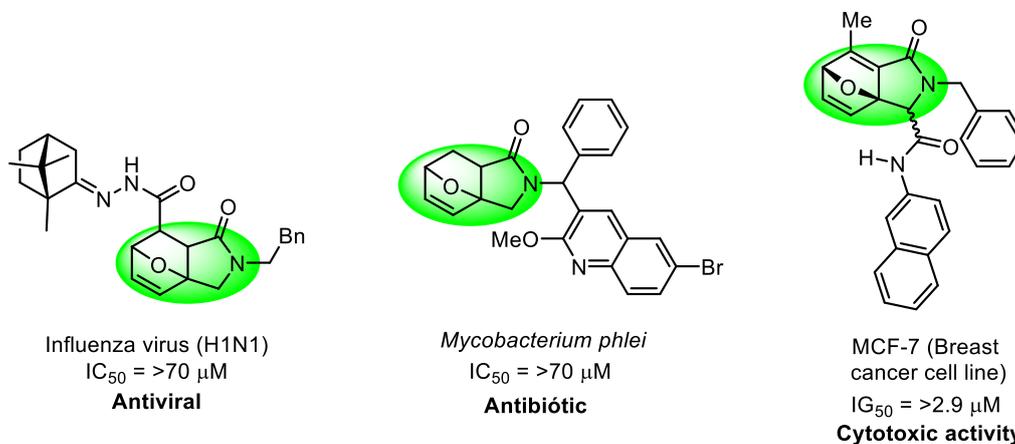
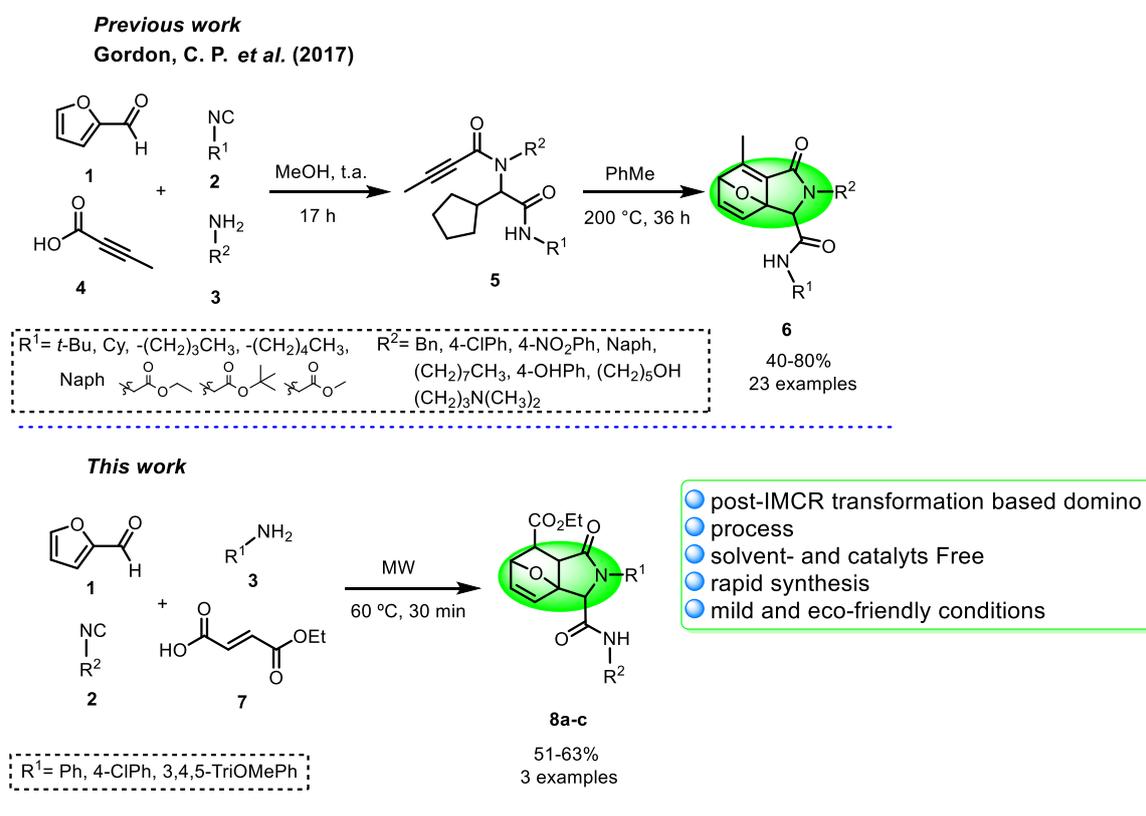


Figure 1. Some representative biological activities of epoxy-isoindolinone.

In a previous report, the synthesis of epoxyisoindolinones were performed under drastic conditions, using high temperatures and long reaction times [6]. Our research group is interested in the design and development of green strategies based on I-MCR's (isocyanide-based multicomponent reactions) toward the synthesis of complex molecules containing several heterocyclic cores. Herein we describe the microwave assisted synthesis of epoxyisoindolinones **8a–c** from 2-furaldehyde **1**, cyclohexyl isocyanide **2a**, anilines **3**, and fumaric acid monoethyl ester **7** without solvent and a short time of reaction (scheme 1).

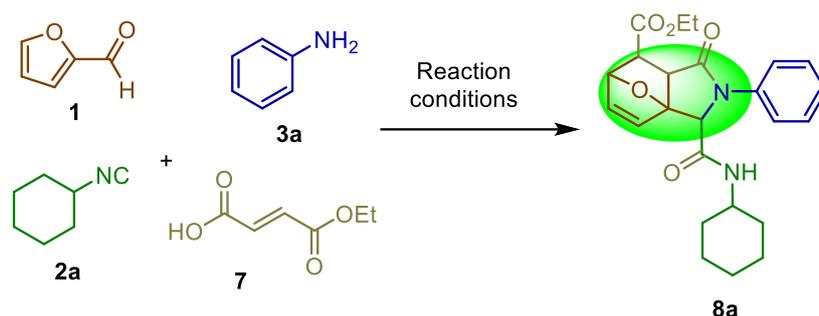


Scheme 1. Previous report and our work.

2. Results and Discussion

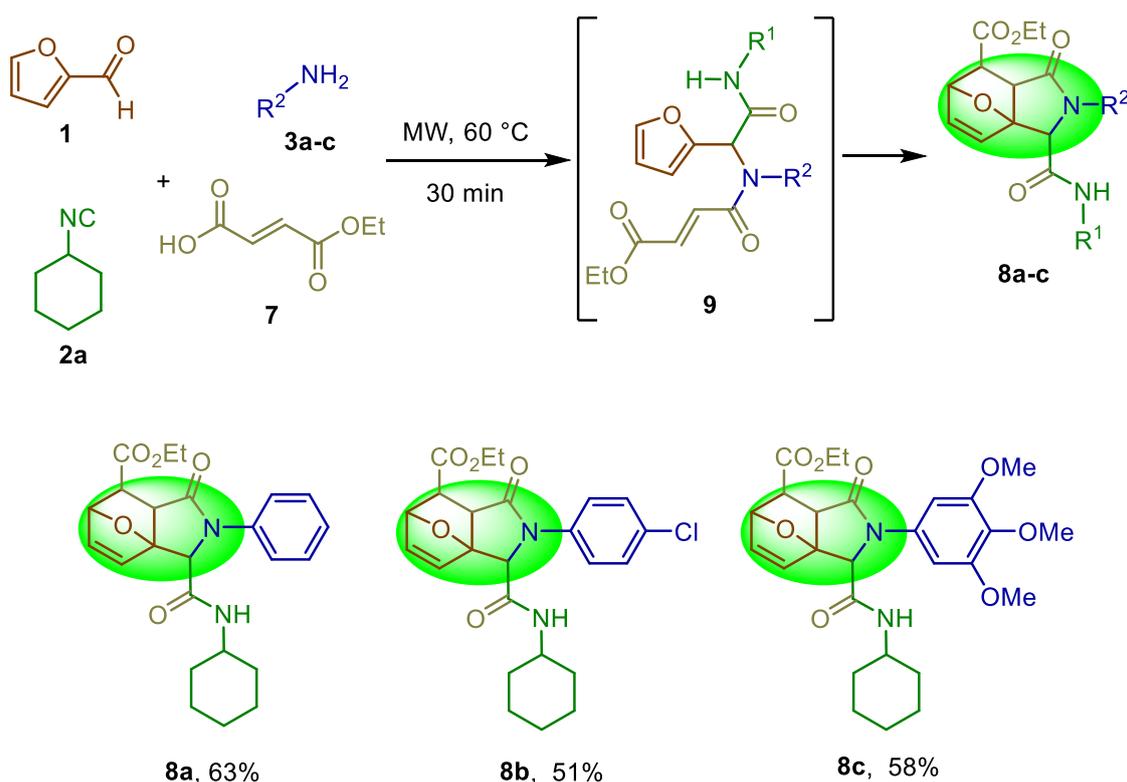
Initially, the U-4CR/IMDA sequence of a domino process for the synthesis of epoxyisoindolinones was performed without solvent at room temperature and conventional stirring using aniline (**3a**), 2-furaldehyde (**1**), cyclohexyl isocyanide (**2a**) and fumaric acid monoethyl ester (**7**), but only traces of desired epoxyisoindoline were obtained (Table 1, entry 1). In a second attempt, it was decided to replace conventional agitation with ultrasound irradiation (USI) for 2 h at room temperature; the yield was 17% (Table 1, entry 2). With these results, we decided to increase the temperature to 40 °C using USI again and it was possible to increase the yield to 35% (Table 1, entry 3). Since temperature is key in this one pot process in domino manner, we decided to change the method of assistance by microwave (MW) at 60 °C for 30 min obtaining the desired epoxyisoindolinone in 63% of yield (Table 1, entry 4).

Using our optimized conditions, we synthesized the series of epoxyisoindolinones shown in Scheme 2. We explored the reaction scope with different anilines (**8a–c**), as 4-chloroaniline, 3,4,5-trimethoxy aniline and aniline derivatives (**a–c**). The products **8a–c** were obtained in moderate to good overall yields (51–63%).

Table 1. Reaction optimizing conditions.

Entry	Time (h)	Solvent	Temperature (°C)	Assistance	Yield (%)
1	2	FS	r.t.	Conventional stirring	Traces
2	2	FS	r.t.	USI ^a	17
3	2	FS	40	USI ^a	35
4	0.5	FS	60	MW ^b	63

FS = free solvent; ^aUSI at 45 kHz; ^b100W; ^creactions performed with 1.0 equiv. aniline (**3a**), 1 equiv. of 2-furaldehyde (**1**), 1 equiv. of cyclohexyl isocyanide (**2a**) and 1 equiv. of fumaric acid monoethyl ester (**7**). ^cisolated yield after after flash column chromatography. r.t. = room temperature.

**Scheme 2.** Substrate scope.

3. Experimental Section

3.1. General Information, Instrumentation, and Chemicals

¹H and ¹³C NMR spectra were acquired on Bruker Avance III spectrometers (500 and 125 MHz respectively). The solvent used was deuterated chloroform (CDCl₃). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for ¹H NMR spectra is trimethylsilane at 0.0 ppm. The internal reference for ¹³C NMR spectra is CDCl₃ at 77.0 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s),

doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 12.0.0–20080. IR spectra were acquired on a Perkin Elmer 100 spectrometer using an Attenuated Total Reflectance (ATR) method with neat compounds. The absorbance peaks are reported in reciprocal centimeters ($\nu_{\max}/\text{cm}^{-1}$). Microwave assisted reactions were performed in closed vessel mode using a monomodal CEM Discover unit. Reaction progress was monitored by Thin-Layer Chromatography (TLC) on precoated silica-gel 60 F₂₅₄ plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (EtOAc) were used to run TLC and for measuring retention factors (R_f). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane with EtOAc in different proportions (v/v) as the mobile phase. All reagents were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

3.2. General Procedure

In a MW vial (10 mL) equipped with a magnetic stirring were sequentially added aniline (1.0 equiv.), 2-furaldehyde (1.0 equiv.), cyclohexyl isocyanide (1.0 equiv.), and fumaric acid monoethyl ester (1.0 equiv.) and the reaction mixture was MW heated (100W, 60 °C) for 30 min, then the crude was immediately purified by silica gel column chromatography using a mixture of hexanes with ethyl acetate (7/3 V/V) to afford the corresponding Epoxyisoindolinones **8a–c**.

3.3. Spectral Data

Ethyl 3-(cyclohexylcarbamoyl)-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylate **8a** Brown solid; $R_f = 0.33$ (Hexanes-AcOEt = 7/3 V/V); $^1\text{H NMR}$ (500 MHz, CDCl_3 , 25 °C, TMS): δ 7.50 (d, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.4$ Hz, 1H), 6.57 (d, $J = 5.9$ Hz, 0H), 6.37 (dd, $J = 5.9, 1.6$ Hz, 0H), 6.06 (d, $J = 8.2$ Hz, 0H), 5.29 (dd, $J = 4.8, 1.6$ Hz, 0H), 4.74 (s, 0H), 4.14 (q, $J = 7.1$ Hz, 1H), 3.92–3.79 (m, 0H), 3.56 (dd, $J = 4.8, 3.5$ Hz, 0H), 3.21 (d, $J = 3.5$ Hz, 0H), 1.91–1.79 (m, 1H), 1.73–1.53 (m, 1H), 1.40–1.30 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 2H), 1.18–1.04 (m, 2H).

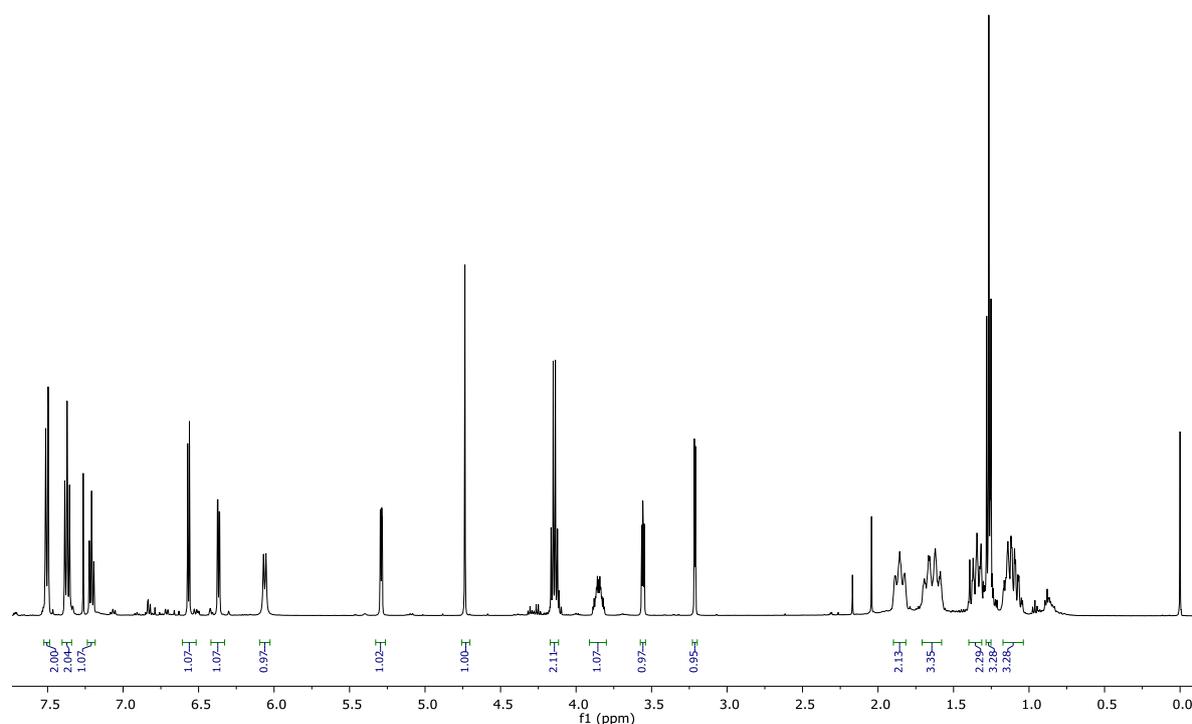


Figure 2. Caption.

4. Conclusions

We developed a green and efficient strategy methodology for the synthesis of epoxyisoindolinones derivatives through of the post-IMCR transformation based domino process with MW-assistance. under mild, solvent-, and catalyst free ecofriendly conditions.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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