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Unexpected Formation of 4-[(1-Carbamoyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl)amino]benzoic Acid from 4-[(3-Amino-1-oxo-1*H*-2-benzopyran-4-yl)amino]benzoic Acid

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Abstract: With the aim of obtaining derivatives belonging to 2′,3′-diphenyl-3*H*-spiro[[2]benzofuran-1,4′-imidazole]-3,5′(3′*H*)-dione nucleus, we synthesized 4-[(3-amino-1-oxo-1*H*-2-benzopyran-4-yl)amino] benzoic acid (a 3,4-diaminoisocoumarine derivative), a known precursor of 4-[(1-carbamoyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl)amino]benzoic acid (a phthalide–carboxamide-bearing system) by a novel methodology that we report here. The reaction conditions were optimized to afford the latter in 62% yield.

Keywords: phthalides; isobenzofuranones; diaminoisocoumarins; ring contracting rearrangement

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Citation: Rodríguez, R.; Quiroga-Suavita, F.; Dotor Robayo, M.Y. Unexpected Formation of 4-[(1-Carbamoyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl)amino]benzoic Acid from 4-[(3-Amino-1-oxo-1*H*-2-benzopyran-4-yl)amino]benzoic Acid. *Molbank* **2022**, *2022*, M1407. https://doi.org/10.3390/M1407

Academic Editor: Fawaz Aldabbagh

Received: 3 June 2022
Accepted: 8 July 2022
Published: 12 July 2022

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1. Introduction

Isocoumarins (1*H*-isochromen-1-ones or 1*H*-2-benzopyran-1-one) are notable organic compounds due to their key role in pharmaceutical research and a vast range of pharmacological activities [1–3]. These molecules have been obtained from various sources, including natural organisms such as fungi, lichens, marine sponges, and higher plants as protagonists [3–7]. Their extensive application areas have attracted the interest of organic and medicinal chemists, developing, and designing diverse synthetic methodologies to form it, not only from traditional, but also from metal-catalyzed pathways [8–10].

Isobenzofuranones (Isobenzofuran-1(3*H*)-ones), commonly named as phthalides, are considered to be privileged structures in organic, biological, and medicinal chemistry. Specifically, those nuclei have exhibited a wide variety of biological activities, such as herbicidal **1** [11,12], antioxidant **2** [13,14], anti-rotavirus **3** [15], anti-inflammatory **4** [16], antibacterial **5** [17], antifungal **6** [18,19], as well as antileishmanial [20] activities (Figure 1), deriving from natural or synthetic products.

Different routes to obtain phthalides have been designed due to the growing interest in these important compounds, from the cyclization of *ortho*-functionalized benzoic acids, the reduction of phthalic anhydrides and phthalaldehydic acids to cyclocarbonyl, or the cyclocarboxylation of halogen-benzyl alcohols [21], situating isobenzofuranones as leading products in the discovery of new drugs. Furthermore, isobenzofuranones have been used as precursors in the synthesis of other relevant heterocyclic compounds [22–24], demonstrating the versatility and applicability of this important organic scaffold.

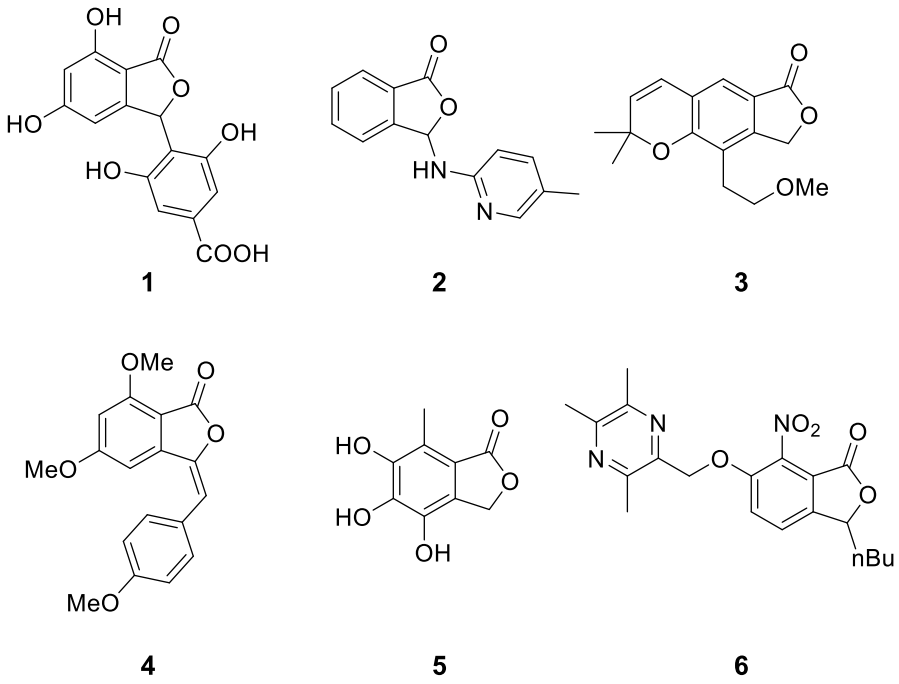
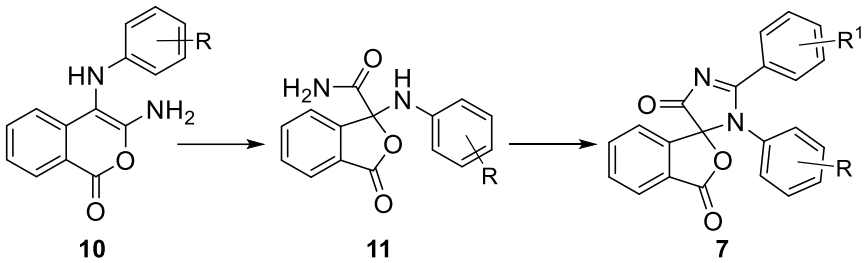


Figure 1. Some relevant examples of isobenzofuranones derivatives with demonstrated biological activities.

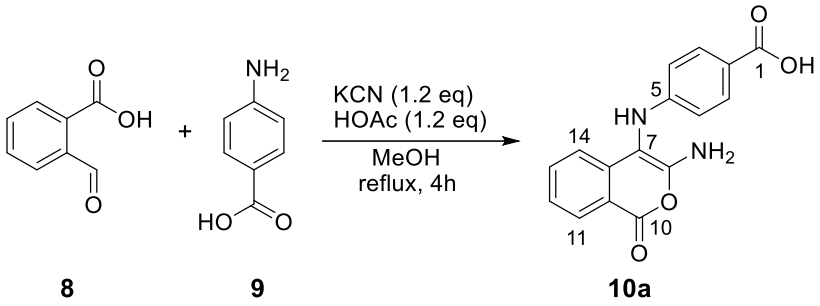
2. Results and Discussion

During our recent work, we have designed the synthesis of spiro-compounds **7** through a three-step methodology, where synthesized diaminoisocoumarins **10** and subsequently **11**-type compounds are involved, as shown in Scheme 1. Herein, we report two of the obtained precursors derivatives (**10a** and **11a**) which, according to the SciFinder^n database, are new molecules.



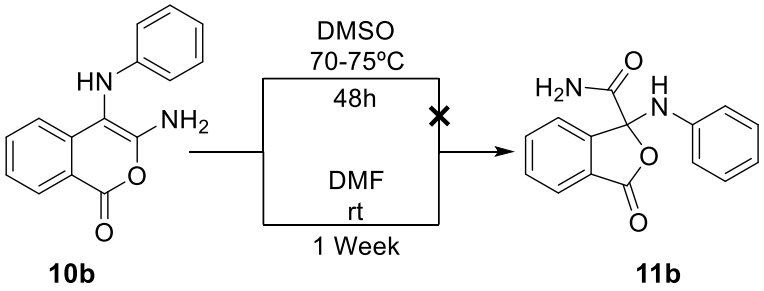
Scheme 1. Summarized pathway of phthalide–imidazolinone spiro-compound target obtention.

The first step of the procedure consisted of the methodology previously reported by Opatz and Ferenc [25], where 2-formylbenzoic acid (**8**), arylamines (anilines) and KCN undergo a Strecker-type reaction to afford 3-amino-4-(4-arylamino)-1*H*-isochromen-1-ones, also named as diaminoisocoumarins. In one of our ongoing investigations, we needed to introduce a para-carboxy group into the diaminoisocoumarin structure; therefore, we evaluated the reaction behavior using 4-aminobenzoic acid (**9**) as an arylamine-reagent and carried out the reaction under the same reported conditions, achieving the expected diaminoisocoumarin **10a** in a remarkable 71% yield as a bright yellow solid. (Scheme 2).



Scheme 2. Synthesis of 4-[(3-amino-1-oxo-1*H*-2-benzopyran-4-yl)amino]benzoic acid (**10a**).

Additionally, we found a novel, simple, and reasonable method to achieve previously reported amide–aniline-bearing phthalides (1-(arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides) from diaminoisocoumarin (3-amino-4-(4-arylamino)-1*H*-isochromen-1-ones) moieties, based on an oxidative ring contracting rearrangement. To the best of our knowledge, there is only one report which describe the synthesis of those specific molecules [26], where Opatz and Ferenc used **10b**-type compounds as reagents to obtain the aforementioned isobenzofuranones. We attempted the same procedure, carrying out the reaction without an argon atmosphere, unfortunately with no successful results. Serendipitously, we noticed that when the initial reagent was dissolved in DMF at room temperature, a subsequent precipitate was observed after 1 week of constant stirring. Controlling the reaction mixture by TLC, we concluded that a new product was forming. Further isolation and purification resulted in a white solid with 52% yield. ^{1}H, ^{13}C, and APT NMR experiments were carried out to characterize and identify the molecular structure of the product, showing us the unexpected formation of the phthalide moiety **11b** (Scheme 3).



Scheme 3. Synthesis attempts of 1–phenylamino–3–oxo–1,3–dihydroisobenzofuran–1–carboxamide (**11b**) from 3–amino–4–phenylamino–1*H*–isochromen–1–one (**10b**).

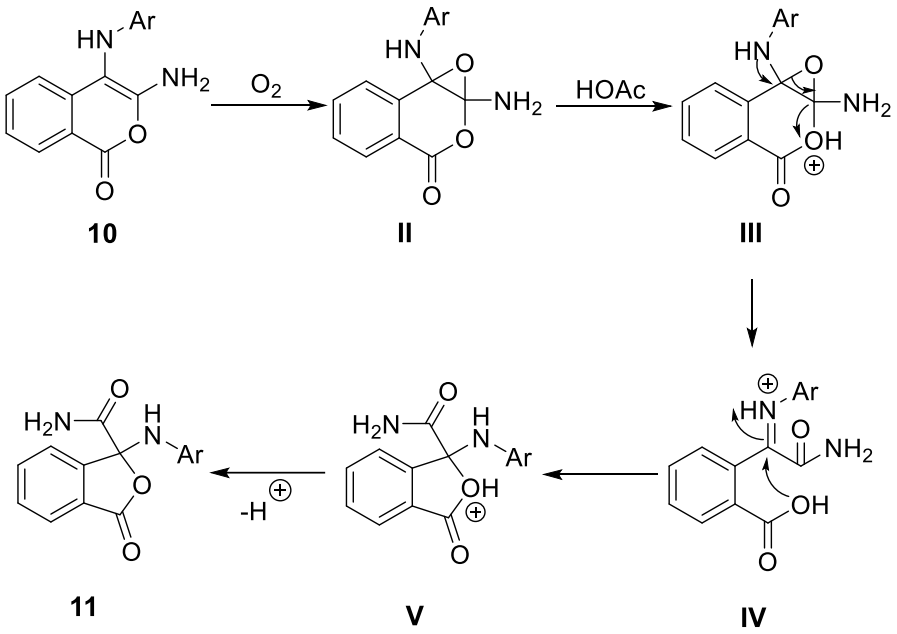
Aiming to synthetize the product in better yields, we added glacial HOAc to the aforementioned conditions. Interestingly, we afforded no significant improvement, but achieved a noticeable reaction time reduction as well as a slightly higher yield. In addition, another attempt with HOAc and higher temperature were performed, reaching a lower yield of the product within the same reaction time; the specific parameters and results are presented in Table 1.

Table 1. Optimization of reaction conditions of **10b** to afford **11b**; all procedures were performed in DMF.

Entry	Conditions	Time	Yield (%)
1	r.t.	1 week	52
2	HOAc/r.t.	48 h	57
3	HOAc/60 °C	48 h	43

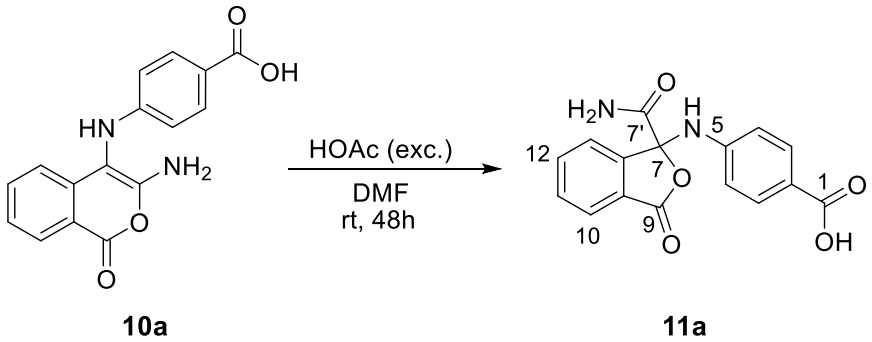
According to the observations reported by Opatz, when 3-amino-4-(4-tolylamino)-1*H*-isochromen-1-one was dissolved in DMSO at room temperature, the formation of a single

product could be observed. Further NMR analysis elucidated the compound structure to be 3-oxo-1-(4-tolylamino)-1,3-dihydroisobenzofuran-1-carboxamide. A mechanistic pathway was proposed, where DMSO behaved as an oxygen source. However, this hypothesis is not applicable to our case, basically due to the reaction solvent being DMF. Herein, we propose another approach of how this reaction occurs (Scheme 4), suggesting the air to be the oxygen source for the ring contracting rearrangement. Subsequent protonation of **II** to produce **III** leads to the lactone ring opening intermediate **IV**. Finally, a nucleophilic attack from the carboxylic oxygen recyclizes the system, forming **11**. Notably, clear elucidation of the reaction pathway based on mechanistic studies is still necessary.



Scheme 4. Proposed reaction scheme for the formation of compound **11**.

Having established the optimum conditions for the procedure, we decided to test the same reaction with **10a**. Satisfactorily, we synthesized compound **11a** in a competent yield of 64% (Scheme 5).



Scheme 5. Synthesis of 4-[(1-carbamoyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl)amino]benzoic acid (**11a**).

Compound **11a** was characterized with a set of spectroscopic techniques (NMR and IR) and by its melting point. In the IR spectrum at 3428 and 3305 cm^{-1}, a couple of absorption bands characteristic of N–H bonds of the carboxamide and aryl amino moieties were observed. Strong bands at 1770, 1675, and 1606 cm^{-1} were assigned to the carboxylic, lactone, and amide carbonyl groups, respectively. At 1325 cm^{-1}, a strong band was assigned to the =C–N bond of the aromatic amine. Finally, absorption bands corresponding to C–O

and C–N bonds appeared at 1249 and 1169 cm^{-1}, respectively. The HR-MS featured a peak at m/z = 313.08211, which is in accordance with the $[M + H]^+$ ion.

The ^{1}H-NMR spectrum of the purified product showed a complete set of signals corresponding to the proposed structure. Therefore, the first at 6.86 ppm was a doublet assigned to H-4 protons. Two signals resonating at 7.68 and 8.20 ppm corresponded to both amide protons. Two broad multiplets, centered at 7.78 and 7.92 ppm, were determined to be the two H-3 and the H-11 protons for the former, and H-10, H-12, the H-13 protons for the latter. A well-defined singlet at 8.12 ppm was attributed to the ArNH proton, whereas a broad singlet at 12.48 ppm was designated as the signal of the carboxylic proton.

Additionally, as expected, 14 signals were observed in the ^{13}C-NMR spectrum. Furthermore, ATP experiments supported these findings exhibiting eight signals for quaternary carbons. Three of them corresponded to the carbonyl groups at 168.4 (C-9) (lactone group), 167.8 (C-7′) (carboxamide group), and 167.2 ppm (C-1) (carboxylic group). At 93.7 ppm, there was another quaternary signal, which was characteristic of the single aliphatic carbon of the molecule (C-7). The other signals were assigned to aromatic carbons. All these observations are supported by ^{1}H- ^{1}H-COSY, ^{1}H-^{13}C-HSQC, and ^{1}H-^{13}C-HMBC spectra (see the Supplementary Materials); thus, this is in strong agreement with the proposed structure for **11a**. Moreover, assignations were compared with Opatz and Ferenc's report [26] of 1-(4-Trifluoromethyl-phenylamino)-3-oxo-1,3-dihydroisobenzofuran1-carboxamide, finding clear correlation between the aforementioned author findings and those reported here.

3. Conclusions

We have developed a new synthetic methodology to afford the carboxamide-phthalide **11a** through an oxidative contraction ring rearrangement from a novel 3,4-diaminoisocoumarin derivative **10a** obtained from a previously described procedure. We surmise that the proposed reaction scheme and the established conditions could shed some light on understanding the behavior of this unusual reaction. Additionally, we consider that the final product, **11a**, could, prove useful to achieve more complex heterocyclic systems, as is the case of the aforementioned 2′,3′-diphenyl-3*H*-spiro[[2]benzofuran-1,4′-imidazole]-3,5′(3′*H*)-dione nucleus (**7**).

4. Materials and Methods

4.1. General Information

The reagents and solvents used were obtained from commercial sources and were used without previous purification. The reaction progress was monitored by TLC with 0.2 mm precoated plates of silica gel 60 F254 (Merck). The melting points were measured using Stuart SMP3 melting point apparatus (Cole-Parmer, Staffordshire, UK), and were corrected. The IR spectrum was recorded on a Shimadzu IR Affinity (Shimadzu, Kyoto, Japan) with an ATR probe. The ^{1}H, ^{13}C-NMR, ^{1}H- ^{1}H-COSY, ^{1}H-^{13}C-HSQC, and ^{1}H-^{13}C-HMBC spectra were recorded on a BRUKER DPX 400 spectrophotometer (Bruker, Bruker BioSpin GmbH, Rheinstetten, Germany), operating at 400 and 100 MHz, respectively (^{1}H, ^{13}C), using DMSO-*d6* as the solvent. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; and m, multiplet. High-resolution mass spectra (HRMS) were recorded using an Agilent Technologies Q-TOF 6520 spectrometer by electrospray ionization (ESI).

*4.2. Preparation of 4-[(3-Amino-1-oxo-1H-2-benzopyran-4-yl)amino]benzoic Acid (**10a**)*

4-aminobenzoic acid (1.03 g, 7.5 mmol), acetic acid (0.43 mL, 7.5 mmol) and potassium cyanide (0.39 g, 6 mmol) were added to a stirred solution of 2-formylbenzoic acid (0.75 g, 5 mmol) in methanol (12 mL). The reaction mixture was refluxed for 4 h (the reaction progress was controlled by TLC). Once cooled, the yellow precipitate was filtered and washed with methanol, yielding **10a** as a bright yellow solid.

Yield: 1.05 g, 71%. M.p. 168 °C (dec). FT-IR (KBr disk) $\overline{v}$ (cm^{-1}): 3508, 3366, 3183, 1703, 1647, 1603, 1551, 1468, 1268, 1169, 770, 594.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.58 (d, *J* = 7.7 Hz, 2H, 4-H), 6.70 (s, 2H, NH_2), 6.99 (d, *J* = 8.1 Hz, 1H, 14-H), 7.09 (ddd, *J* = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H, 12-H), 7.52–7.55 (m, 2H, 13-H, NH), 7.67 (d, *J* = 9.1 Hz, 2H, 3-H), 7.92 (dd, J = 8.0 Hz, 1.1 Hz, 1H, 11-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 89.4 (C-7), 112.1 (C-4), 114.0 (C-10a), 119.0 (C-2), 119.4 (C-14), 122.3 (C-12), 129.4 (C-11), 131.2 (C-3), 135.1 (C-13), 141.3 (C-14a), 152.0 (C-5), 156.0 (C-8), 160.3 (C-10), 167.6 (C-1 (COOH)). HR-MS (ESI): *m/z* calculated for $[M + H]^+$: 297.28532, found: 297.08630.

*4.3. Preparation of 4-[(1-Carbamoyl-3-oxo-1,3-dihydro-2-benzofuran-1-yl)amino]benzoic Acid (**11a**)*

An excess of acetic acid (1.2 mL) was added to a stirred solution of **10a** (0.59 g, 2 mmol) in DMF (4.7 mL) at room temperature and in open air. Once TLC indicated the complete conversion of **10a** (48 h), distilled water was added to precipitate the product. The crude solid was filtered and washed with dichloromethane until a clear white solid was obtained, yielding **11a**.

Yield: 0.39 g, 62%. M.p. 246 °C (dec). FT-IR (KBr disk) $\overline{v}$ (cm^{-1}): 3428, 3305, 1770, 1675, 1606, 1525, 1427, 1325, 1249, 1169, 1098, 903, 776, 748, 609. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.86 (d, *J* = 8.8 Hz, 2H, 4-H), 7.68 (s, 1H, $CONH^b$), 7.76–7.80 (m, 3H, 3-H,11-H), 7.90–7.94 (m, 3H, 10,12,13-H), 8.12 (s, 1H, ArNH), 8.20 (s, 1H, $CONH^a$), 12.48 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 93.7 (C-7), 114.8 (C-4), 121.2 (C-2), 123.7 (C-13), 125.2 (C-10), 125.8 (C-9a), 130.6 (C-3), 131.4 (C-11), 135.0 (C-12), 146.1 (C-5), 148.2 (C-13a), 167.2 (C-1(COOH)), 167.8 (C-7′($CONH_2$)), 168.4 (C-9). HR-MS (ESI): *m/z* calculated for $[M + H]^+$: 313.28472, found: 313.08211.

Supplementary Materials: The following supporting information can be downloaded online: Figure S1. ^{1}H-NMR spectrum for compound **10a**, Figure S2. ^{13}C-NMR spectrum for compound **10a**, Figure S3. APT spectrum for compound **10a**, Figure S4. ^{1}H- ^{13}C-HSQC spectrum of compound **10a**, Figure S5. ^{1}H- ^{13}C-HMBC spectrum for compound **10a**, Figure S6. FT-IR spectrum of compound **10a**, Figure S7. HR-MS of compound **10a**, Figure S8. ^{1}H-NMR spectrum for compound **11a**, Figure S9. ^{13}C-NMR spectrum for compound **11a**, Figure S10. APT spectrum for compound **11a**, Figure S11. ^{1}H- ^{1}H-COSY spectrum of compound **11a**, Figure S12. ^{1}H- ^{13}C-HSQC spectrum of compound **11a**, Figure S13. ^{1}H- ^{13}C-HMBC spectrum of compound **11a**, Figure S14. FT-IR spectrum of compound **11a**, Figure S15. HR-MS spectrum of compound **11a**.

Author Contributions: R.R., F.Q.-S. and M.Y.D.R. designed and performed the research. Additionally, they analyzed data and wrote the paper together. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. Part of the APC was sponsored by MDPI.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article.

Acknowledgments: The authors wish to thank the Universidad Nacional de Colombia-Sede Bogotá and Dirección de Investigación y Extensión, Sede Bogotá for financial support.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds **10a** and **11a** are available from the authors.

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