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9 **I₂/NaH/DMF as oxidant *trio* for the synthesis of tryptanthrin from Indigo or**
10
11 **Isatin**
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26 **Keywords:** Tryptanthrin; DMF; Oxidation; Isatin; Indigo
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64 **Highlights**

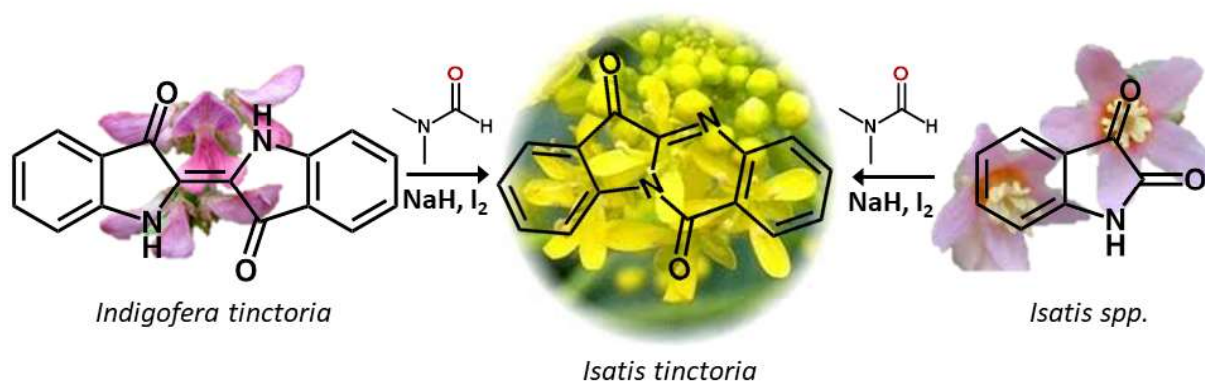
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66 A new method for the synthesis of tryptanthrin in mild oxidant conditions and short reaction
67 times was developed
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73 Using I₂/NaH/DMF as oxidant *trio* tryptanthrin was obtained in high yield from indigo
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77 Using I₂/NaH/DMF as oxidant *trio* tryptanthrin was obtained in high yield from isatin
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81 DMF to act as oxygen donor under microwave irradiation.
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87 **TOC**



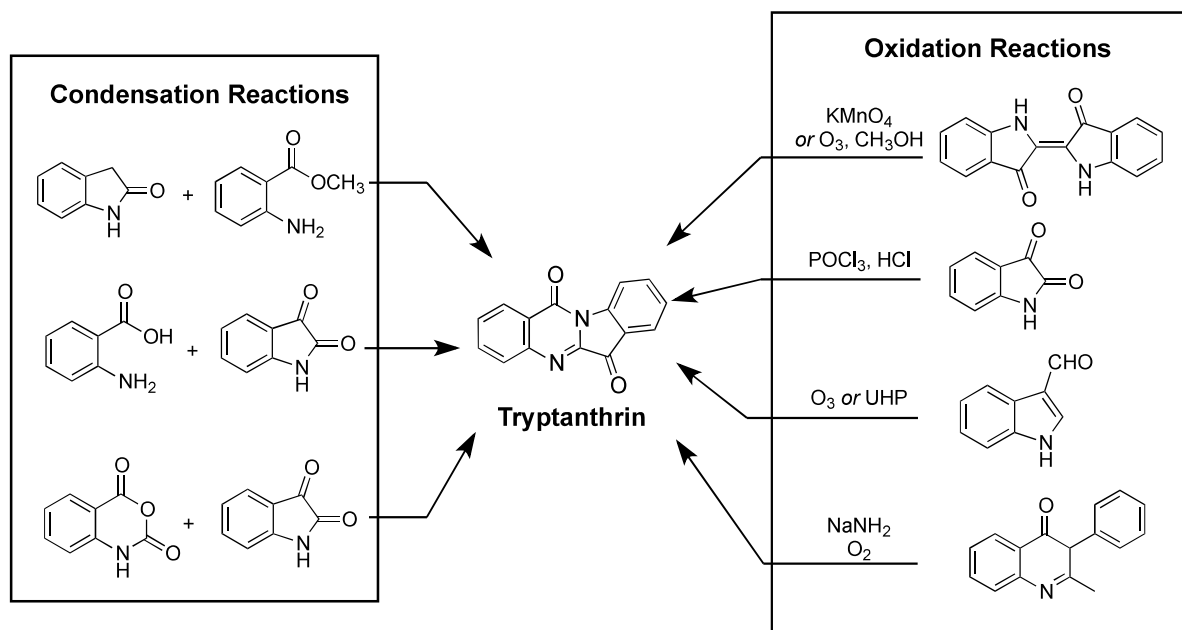
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121 **Abstract**
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124 Tryptanthrin, a product present in several natural sources used as colorants and very relevant in
125 the field of Medicinal Chemistry, was synthesized from indigo and isatin under mild conditions
126 using microwave irradiation. A plausible mechanism for the synthesis of tryptanthrin using the
127 oxidant system formed by iodine, sodium hydride and DMF, the latter acting with dual activity
128 as solvent and as the oxygen source, is proposed.
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1. Introduction

Tryptanthrin (indolo[2.1-b]quinazoline-6,12-dione) is an indoloquinazoline alkaloid isolated from several natural sources. The interest in the synthesis of this alkaloid and its derivatives has been driven by the various applications in the field of Medicinal Chemistry, and in photoelectronic materials [1].

Several synthetic procedures have been reported and recently reviewed for the synthesis of tryptanthrin [2]. The most common approach is the condensation of anthranilic acid derivatives, in particular isatoic acid, with oxindole or isatin derivatives (Scheme 1).



Scheme 1. Previous approaches for the synthesis of tryptanthrin.

Since 1892, when O'Neill described the first synthesis of tryptanthrin through the oxidation of indigo with KMnO_4 [3] only a few oxidative methods for the synthesis of tryptanthrin have been reported. These include the oxidation of indigo using ozone with low yields [4] and the oxidation of isatin with strong oxidants such as KMnO_4 or POCl_3 [5]. *N,N'*-dimethylformamide

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239 (DMF) is a commonly used polar aprotic solvent with a high boiling point but it has also the
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241 capability to serve as building block for various units namely carbonyl, methyl or
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243 dimethylamine groups [6]. Less common is the capability of DMF to act as oxygen source in
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245 oxidation reactions, for example the synthesis of ethers from allylic and benzylic bromides by
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247 treatment with NaH and DMF [7].
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250 Herein we describe the synthesis of tryptanthrin from indigo or isatin through oxidation using
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252 I₂/NaH/DMF as oxidant *trio* and DMF as oxygen source.
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255 256 **2. Results and discussion** 257

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259 With the initial aim of synthesizing *cis-N,N'*-alkylindigo derivatives, we promoted the reaction
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261 between indigo and a diiodoalkane in the presence of a base in DMF, under microwave
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263 irradiation. When attempting the reaction using diiodomethane (Entry 1- Table 1), some *trans-*
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265 *N*-monoalkylindigo was found, as well as a pale yellow compound. When promoting the
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267 reaction using 1,3-diiodopropane (Entry 2), under the same conditions, many side-products
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269 were obtained, including the same yellow compound. By using 1,2-diiodoethane as the
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271 dihaloalkane (Entry 3), the yellow product was achieved as the major product. After isolation
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273 and characterization, and when compared with data reported in the literature [8], the yellow
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275 product revealed to be tryptanthrin. Indeed, the gas-chromatography-mass spectrometry (GC-
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277 MS) analysis of the reaction media after 15 minutes of microwave irradiation (50 °C) shows the
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279 presence of isatin, isatoic anhydride, tryptanthrin and unreacted indigo, (Figure S1, SI).
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281 Considering the moderated yield obtained in the preparation of tryptanthrin from indigo using
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283 oxidative reaction conditions (ref)
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286 Intrigued by these findings, we decided to further explore this reaction. Conducting it under
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288 conventional heating (15 min, 50 °C), tryptanthrin was also obtained in very low yield (5%).
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290 Therefore, we assessed the viability of the formation of tryptanthrin under microwave
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292 irradiation, using different conditions.
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298 To verify the influence of the diiodoalkane, we attempted the reaction without the use of this
299 reactant (Entry 4). Under these experimental conditions, only indigo was detected, indicating
300 the absence of reactivity in these circumstances.
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304 The mechanism would involve oxidation of indigo to isatin, followed by its oxidative
305 cyclization. The evident oxidant in the reaction media of our experiments would be atmospheric
306 oxygen. Therefore, in order to assess the role of oxygen, the reaction was performed under N₂
307 saturated atmosphere (Entry 5). We found that tryptanthrin is still formed, thus showing that
308 oxygen is not the oxidant in these conditions.
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312 Knowing that DMF is not considered an environmentally friendly option, we decided to
313 evaluate its role as oxygen source using green solvents. Cyrene usually described as a good
314 alternative to DMF and 2-methyltetrahydrofuran (2-MeTHF). Knowing the decomposition of
315 cyrene in basic conditions we perform the reaction using a stoichiometric amount of NaH, in
316 the presence of 200 μL of DMF, and just after add the 1,2-diiodoethane in 1.8 mL of cyrene
317 (Entry 6) obtaining only traces of tryptanthrin. Using 2-MeTHF a small amount of tryptanthrin,
318 traces of isatin and a considerable quantity of 1,2-diiodoethane were detected (Entry 7). By
319 adding two equivalents (58 μL) of DMF (Entry 8), a greater amount of isatin and tryptanthrin
320 were obtained, pointing out to the involvement of DMF in the indigo oxidation to isatin and
321 consecutive oxidative cyclization. To verify this hypothesis, we decided to use a solvent with
322 similar properties and structure – dimethylthioformamide – under the condition in which higher
323 yield was achieved (Entry 9). Using this solvent and keeping all the other variables as
324 previously described no tryptanthrin was detected, only indigo, indicating that the reaction does
325 not occur. Further, this allows us to infer that any dissolved oxygen, water traces or hydroxyl
326 anions can not be the responsible for the oxidative processes. When a mixture of DMF and
327 dimethylthioformamide (1:1) was used as solvent, tryptanthrin was detected showcasing again
328 the importance of DMF as oxygen source under the conditions described in this work.
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357 To verify the relevance of NaH, two reactions were performed using DMF as solvent, one
358 without the presence of NaH (Entry 10) and other with doubled equivalents (Entry 11). Under
359 these reaction conditions, the GC-MS profile showed only unreacted indigo in the first case and
360 a dramatic increase in the tryptanthrin formation in the second, showcasing the relevance of
361 NaH to the success of the reaction. This yield improvement might be due to several reasons: (i)
362 the involvement of NaH in the decomposition of the dihaloalkane and production of reactive
363 oxidant species; (ii) the need to have deprotonated indigo to promote the reaction; (iii) to a
364 secondary reaction that might take place between NaH and DMF, as described in the literature
365 [9]; (iv) it might be involved in an acid-base reaction with isatin increasing its nucleophilicity;
366 and (v) the use of excess of the hydride might promote this secondary reaction that facilitates
367 the formation of tryptanthrin.
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380 Since we observed the formation of a gas immediately after the addition of the 1,2-diiodoethane,
381 we conducted a headspace GC-MS analysis in the closed microwave reactor. The result showed
382 the presence of ethylene, indicating the decomposition of this diiodoalkane in basic conditions,
383 resulting in the formation of iodine or iodide radicals. Iodine is a universal oxidizing agent and
384 a mild and nontoxic Lewis acid catalyst, widely applied in the synthesis of heterocyclic
385 compounds. For these reasons, we pointed it as the oxidant agent in our reaction.
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393 With this information in mind, we decided to conduct the same reaction, using molecular iodine
394 I₂ (Entry 12). In this case, we could detect both isatin and isatoic anhydride, confirming the
395 existence of these two intermediates/side-products and a considerable increase on the
396 tryptanthrin yield (68.8%), with only 17.8% of indigo left unreacted. This data clearly shows
397 that the formation of tryptanthrin from indigo is promoted when iodine (molecular iodine or
398 organic iodine)/DMF/NaH are simultaneously present.
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Table 1: Microwave-assisted tryptanthrin synthesis using indigo^{a)} as starting material.

Entry	NaH	Iodine source ^{a)}	Solvent	% Tryptanthrin ^{b)}
1	2 equiv.	CH ₂ I ₂	DMF (2 mL)	9
2	2 equiv.	C ₃ H ₆ I ₂	DMF (2 mL)	2
3	2 equiv.	C ₂ H ₄ I ₂	DMF (2 mL)	23(22 ^{c)}
4	2 equiv.	-	DMF (2 mL)	0
5	2 equiv.	C ₂ H ₄ I ₂	DMF (2 mL)	24
6	2 equiv.	C ₂ H ₄ I ₂	Cyrene (1.8 mL) + DMF (200 μL)	Trace
7	2 equiv.	C ₂ H ₄ I ₂	2-MeTHF (2 mL)	2
8	2 equiv.	C ₂ H ₄ I ₂	2-MeTHF (2 mL) + DMF (58 μL)	7
9	4 equiv.	C ₂ H ₄ I ₂	thioDMF (2 mL)	0
10	-	C ₂ H ₄ I ₂	DMF (2 mL)	0
11	4 equiv.	C ₂ H ₄ I ₂	DMF (2 mL)	83
12	2 equiv.	I ₂	DMF (2 mL)	69(64 ^{c)}

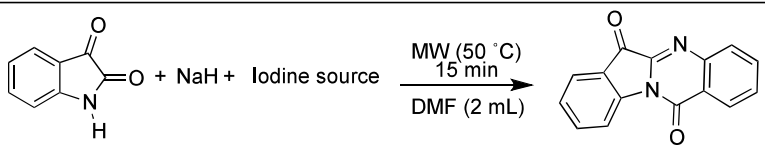
^{a)} All reactions were performed using 100 mg (1 equiv.) of indigo and 2 equiv. of iodine source (except if specified otherwise). ^{b)} Yields determined by GC-MS. ^{c)} Isolated Yields

Since isatin and isatoic anhydride have been observed in many reactional conditions, we wanted to understand if the reactants *trio* was required only to promote the oxidation of indigo to isatin/isatoic anhydride, or if it was also relevant to promote the second step of the oxidative cyclization. To assess such information, we performed some reactions, replacing indigo by isatin (Table 2). First, we promoted the reaction between isatin, NaH, 1,2-diiodoethane in 2 mL of DMF. Tryptanthrin was formed in considerable yield (Entry 13) under such conditions, in opposition to what happens when no iodine source is placed in the reactor vessel (Entry 14), where no tryptanthrin was formed. This indicates that iodine is crucial not only to react with indigo to originate isatin, but also to promote the oxidative cyclization to afford tryptanthrin. We also tested if using a catalytic amount of molecular iodine (0.2 eq.) the reaction would occur, but no tryptanthrin was detected in 15 minutes of reaction (Entry 15). By using 2 equivalents of I₂, tryptanthrin was formed in considerable amount (Entry 16). Overall, the best

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475 reaction conditions are achieved when the starting material (indigo or isatin) is deprotonated
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477 with excess NaH and allowed to react with iodine (as I₂ or C₂H₄I₂) under the described
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479 microwave irradiation conditions (see supp. Inf.). **By removing NaH, (Entry 17) or DMF (by**
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481 **substitution with 2-MeTHF) (Entry 18) no tryptanthrin was observed after 15 min under MW**
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483 **irradiation, showcasing the relevance of the I₂/NaH/DMF trio for the tryptanthrin formation.**
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488 **Table 2:** Microwave-assisted tryptanthrin synthesis using isatin^{a)} as starting material.
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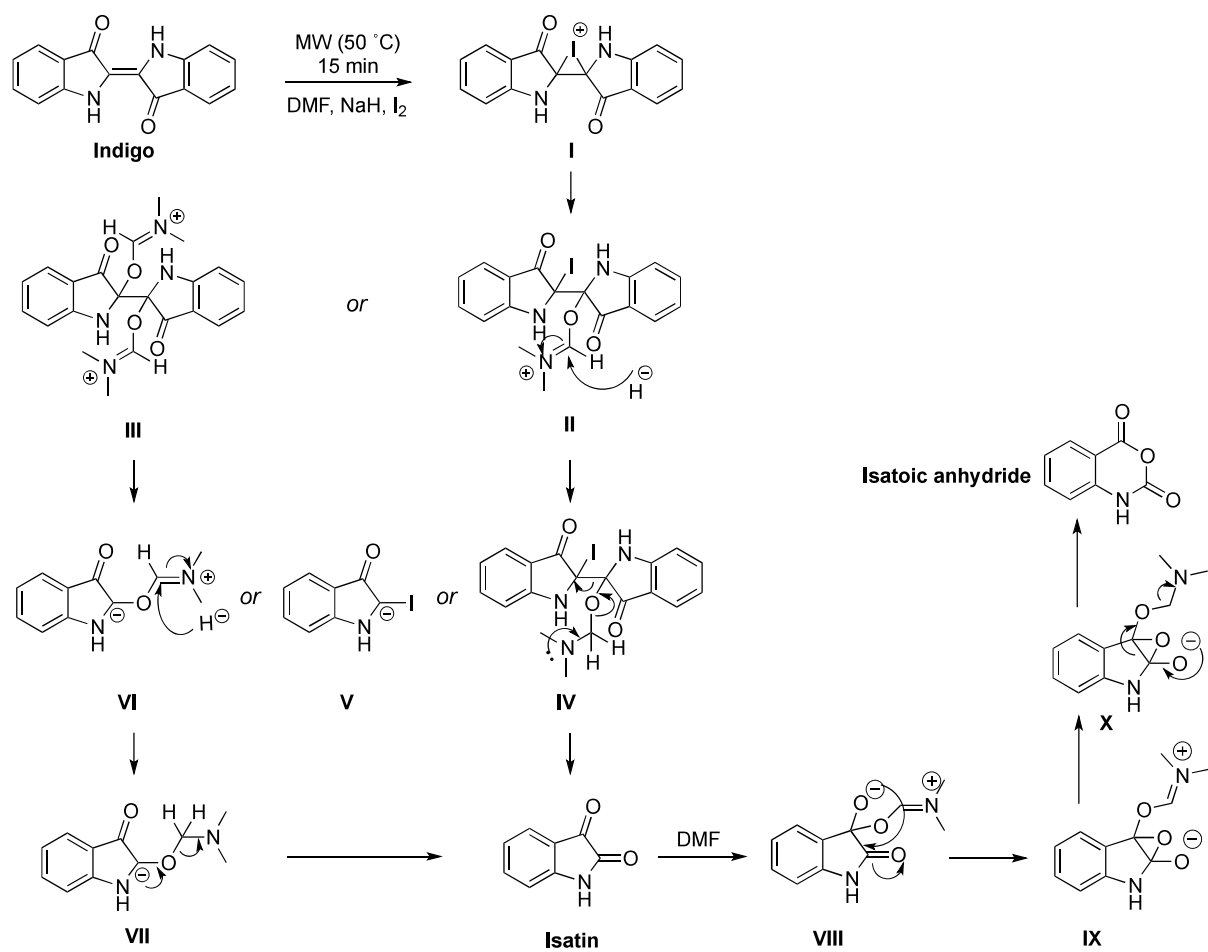
Entry	NaH	Iodine source	Solvent	% Tryptanthrin ^{b)}
13	1 eq.	C ₂ H ₄ I ₂ (2 eq.)	DMF (2 mL)	56
14	1 eq.	-	DMF (2 mL)	0
15	1.5 eq.	I ₂ (0.2 eq.)	DMF (2 mL)	0
16	4 eq.	I ₂ (2 eq.)	DMF (2 mL)	39
17	-	C ₂ H ₄ I ₂ (2 eq.)	DMF (2 mL)	0
18	1 eq.	C ₂ H ₄ I ₂ (2 eq.)	2-MeTHF (2 mL)	0

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503 ^{a)}All reactions were performed using 100 mg (1 equiv.) of isatin. ^{b)}Yields determined by GC-MS.
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506 After collecting all this information, and based on the previous reports on the tryptanthrin
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508 synthesis and the ability of DMF to act as oxygen donor, we hypothesize the mechanism for the
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510 decomposition of indigo to isatin presented in Scheme 2. Iodine addition to indigo double bond
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512 (I) followed by the addition of DMF as proposed by Sudalai and co-workers [10], led to the
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514 formation of intermediate II. Iodine atom could be further substituted by DMF forming
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516 intermediate III, as proposed by Liu *et al* [11]. Then, addition-elimination processes where
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518 hydride acts as the nucleophile [7] led to the formation of isatin precursors (IV-VII). **From**
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520 **there, isatin could be oxidize to isatoic anhydride through DMF addition, intramolecular**
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522 **cyclization (similar to the proposed for the oxidation with peroxide by Wu and Co-workers**
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524 **[12]) and hydride addition-elimination. The condensation of isatin and isatoic acid could form**
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526 **tryptanthrin trough a well stablished mechanism [2a, 13].**
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Scheme 2. Proposed mechanism for the decomposition of indigo to isatin and oxidation to isatoic anhydride.

We apply the developed methodology to the synthesis of bromine derivatives. Starting from 6,6'-dibromoindigo (Tyrian Purple) and 5,5',7,7'-tetrabromoindigo (Tina Blue) the

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593 corresponding di- and tetra-bromotryptathrin derivatives were isolated with 36 and 18% yield,
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600 **4. Conclusion**

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602 Herein, we describe the oxidation of indigo to isatin and subsequent oxidative cyclization to
603 tryptanthrin, performed using NaH/iodine/DMF under microwave irradiation, being iodine a
604 green oxidant and DMF the oxygen source.
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608 These findings might allow the development of faster and greener methods for the synthesis of
609 this relevant and high-value product and their derivatives using mild reaction conditions in high
610 yields when compared with the previously described methods using indigo as starting material,
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612 without the requirement of strong oxidizing agents and complex apparatus.
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620 **Notes**

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622 The authors declare no competing financial interest.
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640 **References**

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I₂/NaH/DMF as oxidant *trio* for the synthesis of tryptanthrin from Indigo or Isatin

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Supplementary Information

Materials

All the reagents for the synthesis, indigo, sodium hydride (60% dispersion in mineral oil stored in a dry box) and 1,2-diodoethane, 1,3-diiodopropane, diiodomethane, were obtained from sigma Aldrich; isatin and dimethylthioformamide were purchased from Fluorochem and used without further purification. DMF (dry and with molecular sieves) was provided by Acros. The solvents were used as commercial P.A. quality.

Equipment and Methods

Microwave-assisted reactions were performed in a CEM Discover S-Class single-mode microwave reactor, featuring continuous temperature, pressure and microwave power monitoring.

Analytical thin-layer chromatography (TLC) was performed on Macherey-Nagel ALUGRAM Xtra silica gel plates with UV₂₅₄ indicator. Visualization was accomplished by an ultraviolet lamp (254 nm). Silica gel column was carried out with silica gel (230-400 mesh).

NMR spectra were recorded at room temperature in CDCl₃ solutions on a Bruker Avance III spectrometer and a Bruker DRX-400 spectrometer, both operating at 400.13 MHz for ¹H and 100.61 MHz for ¹³C. Tetramethylsilane (TMS) was used as internal standard.

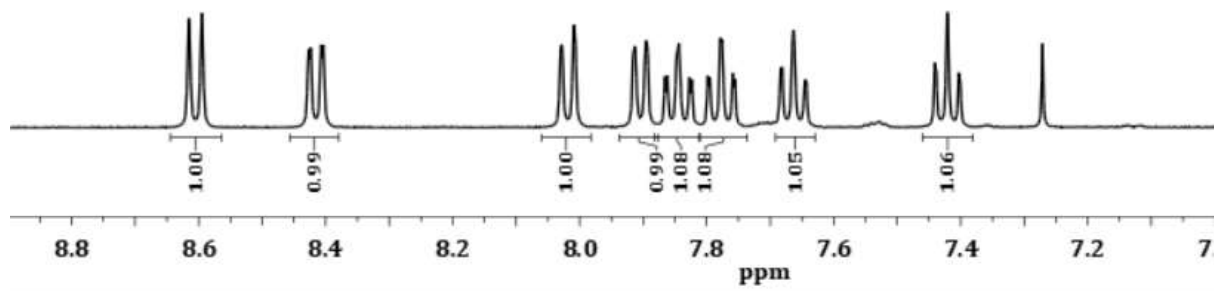
GC-MS analyses were performed on a Hewlett-Packard 5973 MSD spectrometer, using EI (70 eV), coupled to a Hewlett-Packard Agilent 6890 chromatographer, equipped with a HP-5 MS column (30 m x 0.25 mm x 0.25 μ m) and high-purity helium as carrier gas. The initial temperature of 70 °C was increased to 250 °C at a 15 °C/min rate, and held for 10 min. Then the temperature was increased to 290 °C at a 5 °C/min rate and held for 2 min, giving a total run time of 32 min. The flow of the carrier gas was maintained at 1.33 mL/min. The injector port was set at 250 °C.

Tryptanthrin Synthesis

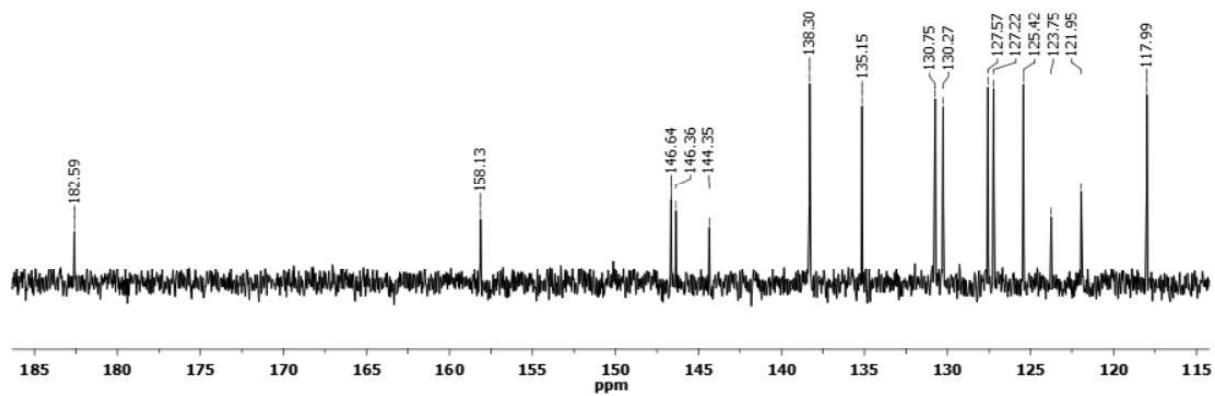
In a thick-glass microwave reactor charged with a magnetic stirring bar, indigo or isatin (100 mg, 0.381 mmol of Indigo or 0.68 mmol of isatin, 1 equiv) and sodium hydride (60% dispersion in mineral oil, stored in a dry box) were dissolved in 1 mL of the appropriate dry solvent. The iodine source was added, and solvent was added to a total volume of 2 mL. The resulting mixture was heated under microwave irradiation (CEM Discover S-Class single-mode microwave reactor) at 50 °C for 15 min. After cooling down to room temperature, a sample was collected, dissolved in 1 mL of dichloromethane and washed with 1 mL of water. The organic layer was analyzed by GC-MS.

Tryptanthrin

^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 8.61 (d, $J=8.1\text{Hz}$, 1H, ArH), 8.42 (dd, $J=7.9\text{Hz}$, $J=1.3\text{Hz}$, 1H, ArH), 8.02 (d, $J=7.8\text{Hz}$, 1H, ArH), 7.90 (d, $J=7.6\text{Hz}$, 1H, ArH), 7.82-7.87 (m, 1H, ArH), 7.76-7.80 (m, 1H, ArH), 7.64-7.68 (m, 1H, ArH), 7.40-7.44 (m, $J=7.5\text{Hz}$, $J=0.4\text{Hz}$, 1H, ArH); ^{13}C NMR (CDCl_3 , 101 MHz) δ (ppm): 182.6 (C=O), 158.1 (C=O), 146.6, 146.4, 144.4, 138.3, 135.1, 130.8, 130.3, 127.6, 127.2, 125.4, 123.8, 122.0, 118.0; GC-MS: m/z [M^+] = 248.0; ESI-TOF-MS: m/z [$\text{M}+1$] $^+$ = 249.0659 for $\text{C}_{15}\text{H}_9\text{N}_2\text{O}_2$.



¹H-NMR of tryptanthrin in CDCl₃

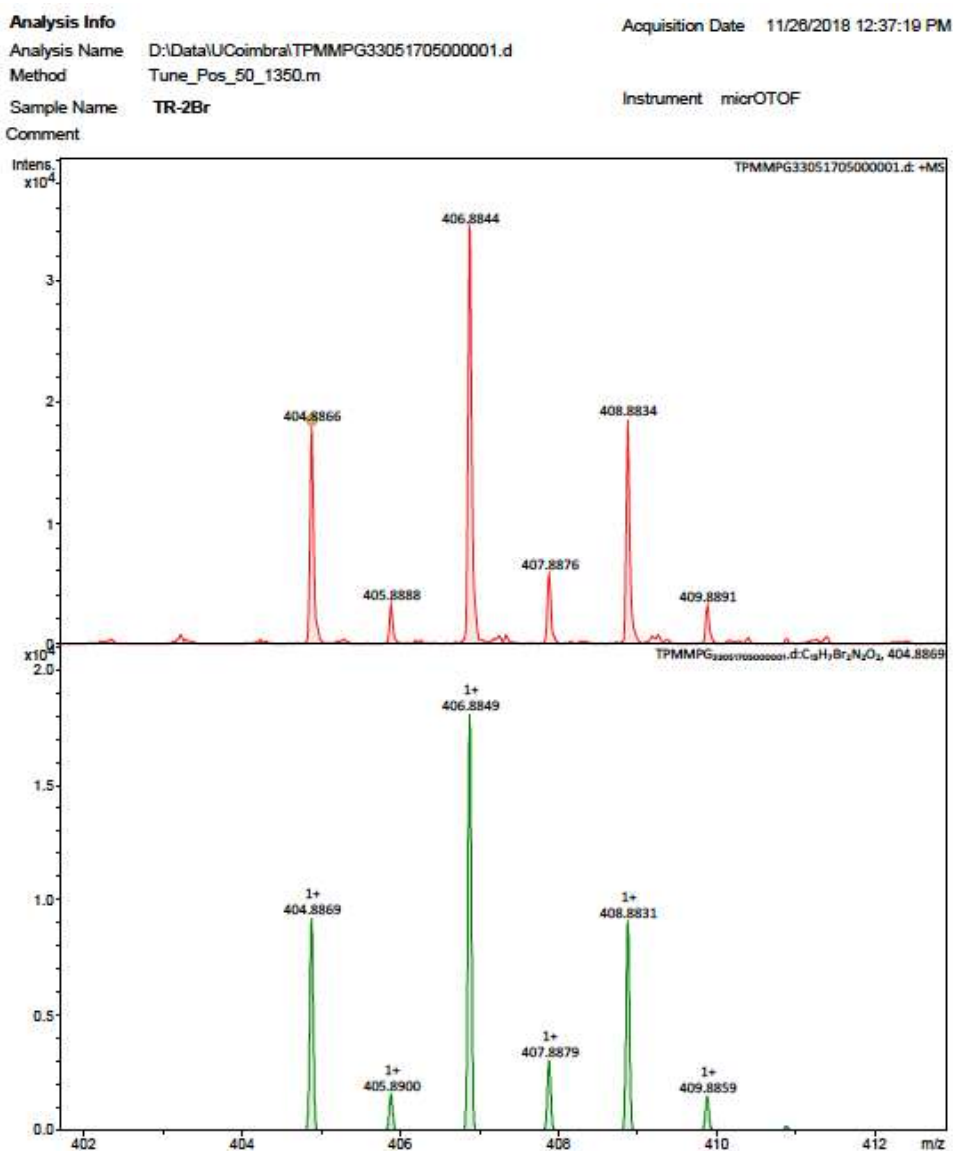


¹³C-NMR of tryptanthrin in CDCl₃

3,9-dibromoTryptanthrin (3,9-dibromoindolo[2,1-*b*]quinazoline-6,12-dione)

^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 8.85 (d, $J=1.5$ Hz, 1H), 8.29 (d, $J=8.5$ Hz, 1H), 8.19 (d, $J=1.8$ Hz, 1H), 7.81-7.76 (m, 2H), 7.61 (dd, $J=8.1$ Hz, $J=1.6$ Hz, 1H). ^{13}C NMR (CDCl_3 , 101 MHz) δ (ppm): 180.03, 156.44, 146.49, 145.47, 143.94, 132.73, 132.69, 132.37, 129.85, 129.22, 127.90, 125.34, 121.26, 120.42, 119.52

HRMS (ESI-TOF-MS): (m/z) found 404.8866, calcd. for $\text{C}_{15}\text{H}_7\text{Br}_2\text{N}_2\text{O}_2$ 404.8869 $[\text{M}+1]^+$.



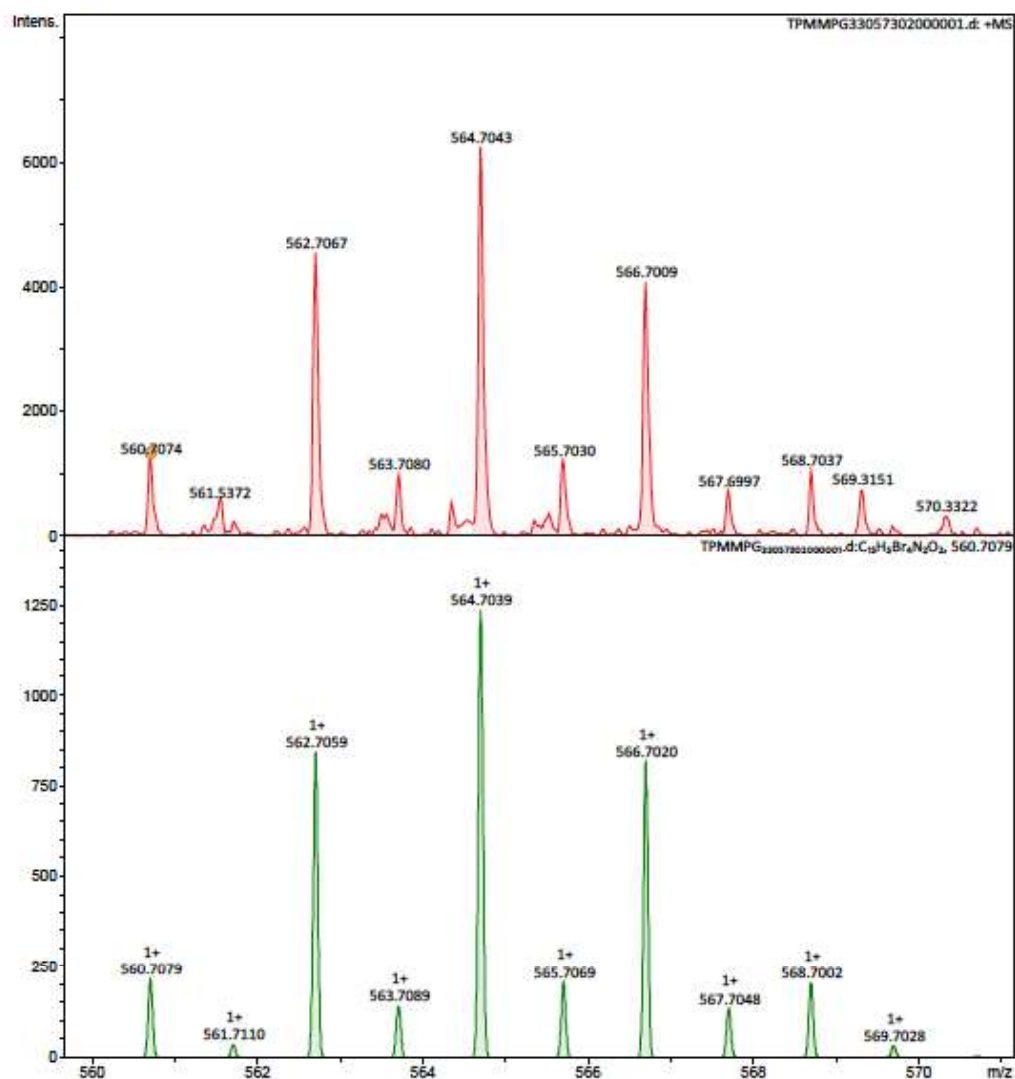
2,4,8,10-tetrabromoTryptanthrin (2,4,8,10-tetrabromoindolo[2,1-*b*]quinazoline-6,12-dione)

^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 8.43 (d, $J = 2.1$ Hz, 1H), 8.22 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 1.9$ Hz, 1H), 8.03 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 101 MHz) δ (ppm): 179.41, 154.72, 145.73, 144.58, 144.52, 143.01, 141.39, 130.04, 127.48, 127.25, 126.67, 126.53, 124.81, 121.96, 112.04

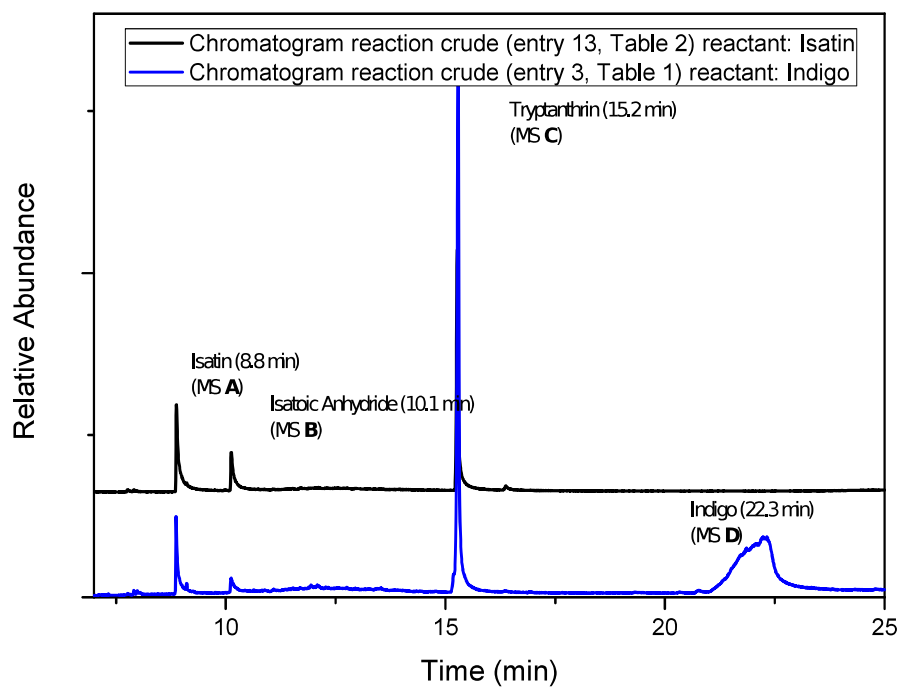
HRMS (ESI-TOF-MS): (m/z) found 560.7074, calcd. for $\text{C}_{15}\text{H}_5\text{Br}_4\text{N}_2\text{O}_2$ 560.7079 $[\text{M}+1]^+$.

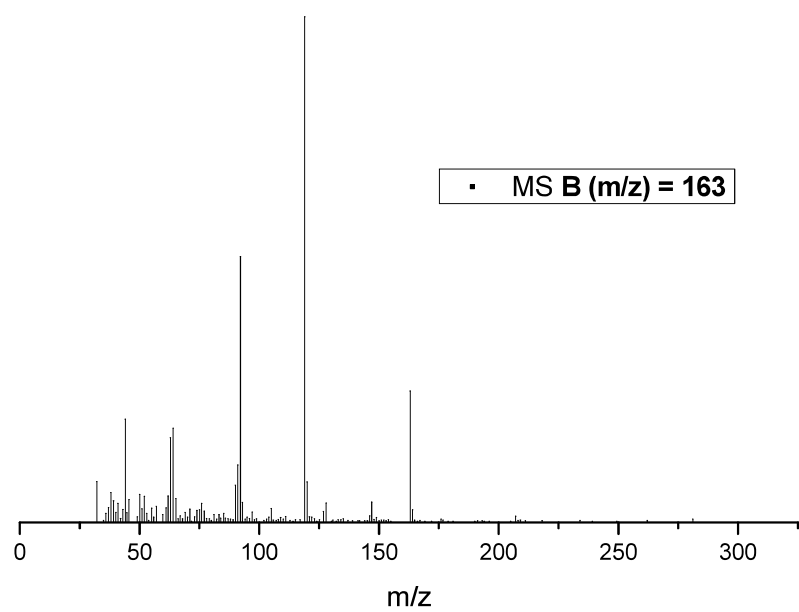
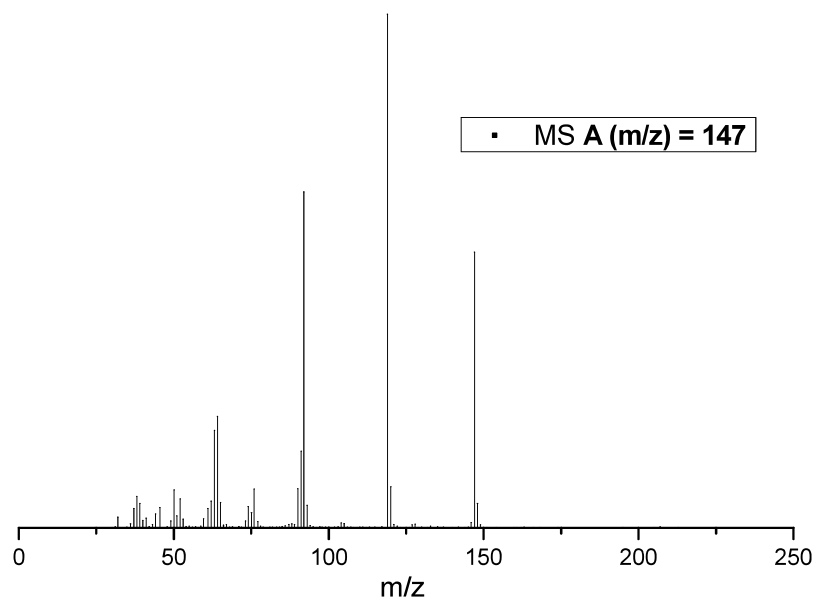
Mass Spectrum Molecular Formula Report

Analysis Info Acquisition Date 2/5/2019 12:50:39 PM
Analysis Name D:\Data\UCoimbra\TPMMPG33057302000001.d
Method Tune_Pos_50_1350.m Instrument micrOTOF
Sample Name TR4Br
Comment



GC-MS analysis of the reaction products





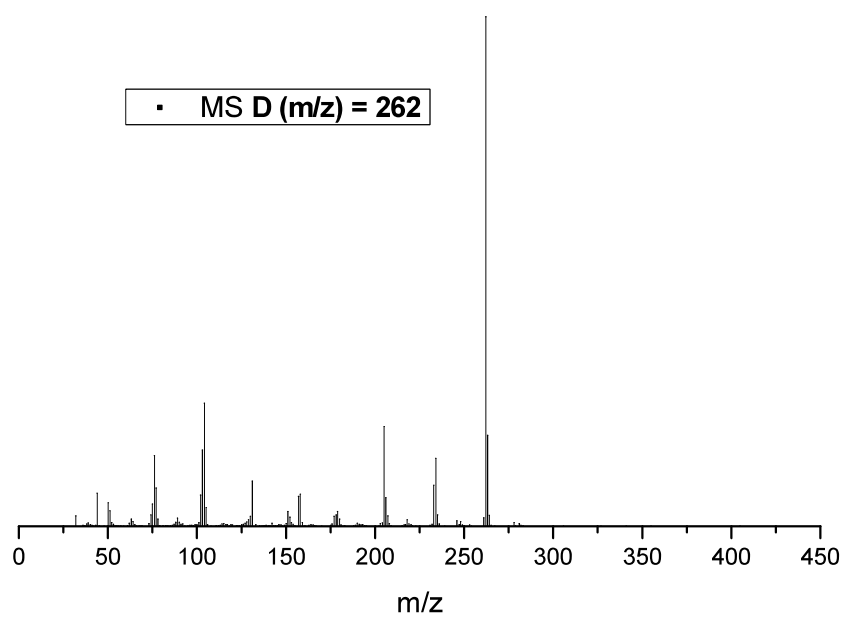
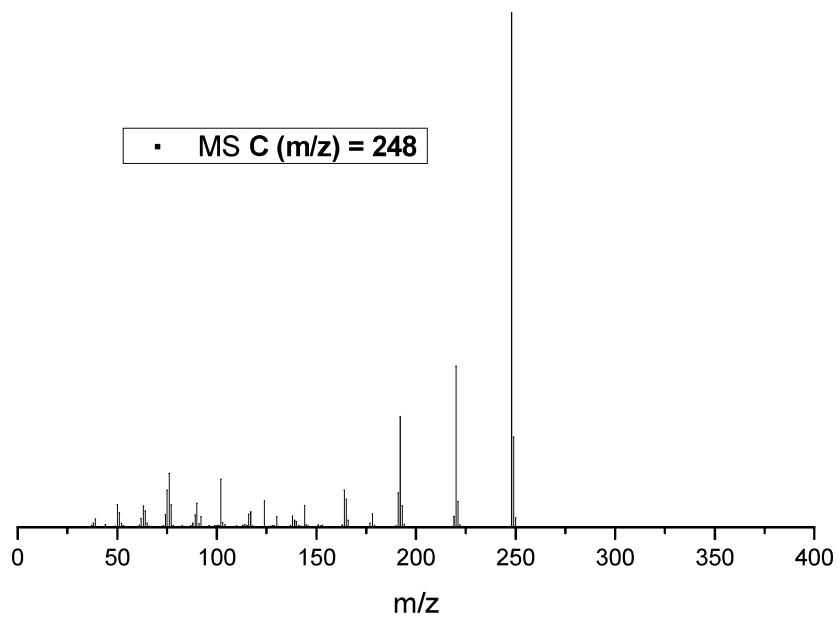


Figure S1. Gas Chromatogram and mass spectra of A: isatin, B: isatoic acid, C: tryptanthrin and D: Indigo after reaction under microwave irradiation.