



I₂/NaH/DMF as oxidant *trio* for the synthesis of tryptanthrin from indigo or isatin



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ABSTRACT

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

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 photo-electronic materials [1].

Several 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).

Since 1892, when O'Neill described the first synthesis of tryptanthrin through the oxidation of indigo with KMnO₄ [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 KMnO₄ or POCl₃ [5]. *N,N'*-dimethylformamide (DMF) is a commonly used polar aprotic solvent with a high boiling point but it has also the capability to serve as building block for various units namely carbonyl, methyl or dimethylamine groups [6]. Less common is the capability of DMF to act as oxygen source in oxidation reactions, for example the synthesis of ethers from allylic and benzylic bromides by treatment with NaH and DMF [7].

Herein we describe the synthesis of tryptanthrin from indigo or isatin through oxidation using I₂/NaH/DMF as oxidant *trio* and DMF as oxygen source.

2. Results and discussion

With the initial aim of synthesizing *cis-N,N'*-alkylindigo derivatives, we promoted the reaction between indigo and a diiodoalkane in the presence of a base in DMF, under microwave irradiation. When attempting the reaction using diiodomethane (Entry 1- Table 1), some *trans-N*-monoalkylindigo was found, as well as a pale yellow compound. When promoting the reaction using 1,3-diiodopropane (Entry 2), under the same conditions, many side-products were obtained, including the same yellow compound. By using 1,2-diiodoethane as the dihaloalkane (Entry 3), the yellow product was achieved as the major product. After isolation and characterization, and when compared with data reported in the literature [8], the yellow product revealed to be tryptanthrin. Indeed, the gas-chromatography-mass spectrometry (GC-MS) analysis of the reaction media after 15 min of microwave irradiation (50 °C) shows the presence of isatin, isatoic anhydride, tryptanthrin and unreacted indigo, (Figs. S1 and S1).

Intrigued by these findings, we decided to further explore this reaction. Conducting it under conventional heating (15 min, 50 °C), tryptanthrin was also obtained in very low yield (5%). Therefore, we assessed the viability of the formation of tryptanthrin under microwave irradiation, using different conditions.

To verify the influence of the diiodoalkane, we attempted the reaction without the use of this reactant (Entry 4). Under these experimental conditions, only indigo was detected, indicating the absence of reactivity in these circumstances.

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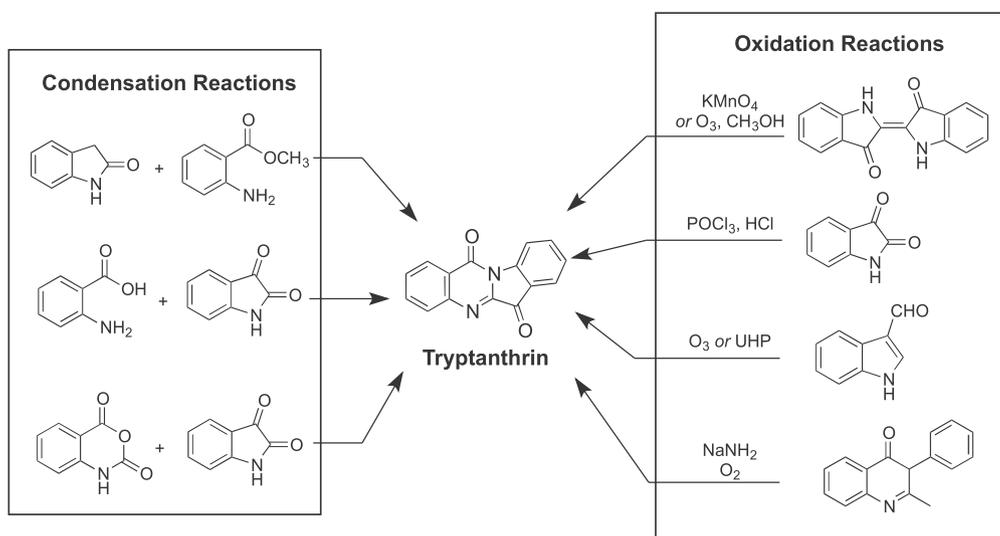
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Scheme 1. Previous approaches for the synthesis of tryptanthrin.

Table 1
Microwave-assisted tryptanthrin synthesis using indigo^{a)} as starting material.



	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.

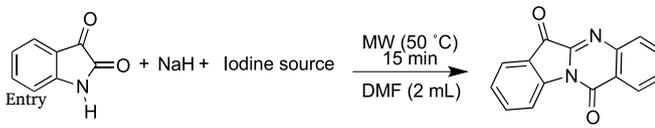
The mechanism would therefore involve oxidation of indigo to isatin, followed by its oxidative cyclization. The evident oxidant in the reaction media of our experiments would be atmospheric oxygen. Therefore, in order to assess the role of oxygen, the reaction was performed under N₂ saturated atmosphere (Entry 5). We found that tryptanthrin is still formed, thus showing that oxygen is not the oxidant in these conditions.

Knowing that DMF is not considered an environmentally friendly option, we decided to evaluate its role as oxygen source using green solvents. Cyrene usually described as a good alternative to DMF and 2-methyltetrahydrofuran (2-MeTHF) was chosen. Knowing the decomposition of cyrene in basic conditions we performed the reaction using a stoichiometric amount of NaH, in the presence of 200 μL of DMF, and just after added the 1,2-diiodoethane in 1.8 mL of cyrene (Entry 6) obtaining only traces of tryptanthrin. Using 2-MeTHF a small amount of tryptanthrin, traces of isatin and a considerable quantity of 1,2-diiodoethane were detected (Entry 7). By adding two equivalents (58 μL) of DMF (Entry 8), a greater amount of isatin and tryptanthrin were obtained, pointing out to the involvement of DMF in the indigo oxidation to isatin and consecutive oxidative cyclization. To verify this hypothesis, we decided to use a solvent with similar properties and structure –

dimethylthioformamide – under the condition in which higher yield was achieved (Entry 9). Using this solvent and keeping all the other variables as previously described no tryptanthrin was detected, only indigo, indicating that the reaction does not occur. Furthermore, this allows us to infer that any dissolved oxygen, water traces or hydroxyl anions can't be considered responsible for the oxidative processes. When a mixture of DMF and dimethylthioformamide (1:1) was used as solvent, tryptanthrin was detected showcasing again the importance of DMF as oxygen source under the conditions described in this work.

To verify the relevance of NaH, two reactions were performed using DMF as solvent, one without the presence of NaH (Entry 10) and other with doubled equivalents (Entry 11). Under these reaction conditions, the GC-MS profile showed only unreacted indigo in the first case and a dramatic increase in the tryptanthrin formation in the second, showcasing the relevance of NaH to the success of the reaction. This yield improvement might be due to several reasons: (i) the involvement of NaH in the decomposition of the dihaloalkane and production of reactive oxidant species; (ii) the need to have deprotonated indigo to promote the reaction; (iii) to the existence of a secondary reaction that might take place between NaH and DMF, as described in the literature

Table 2
Microwave-assisted tryptanthrin synthesis using isatin^{a)} as starting material.



Entry	NaH	Iodine source	Solvent	% Tryptanthrin ^{b)}
13	1 equiv.	C ₂ H ₄ I ₂ (2 equiv.)	DMF (2 mL)	56
14	1 equiv.	–	DMF (2 mL)	0
15	1.5 equiv.	I ₂ (0.2 equiv.)	DMF (2 mL)	0
16	4 equiv.	I ₂ (2 equiv.)	DMF (2 mL)	39
17	–	C ₂ H ₄ I ₂ (2 equiv.)	DMF (2 mL)	0
18	1 equiv.	C ₂ H ₄ I ₂ (2 equiv.)	2-MeTHF (2 mL)	0

^a All reactions were performed using 100 mg (1 equiv.) of isatin.

^b Yields determined by GC-MS.

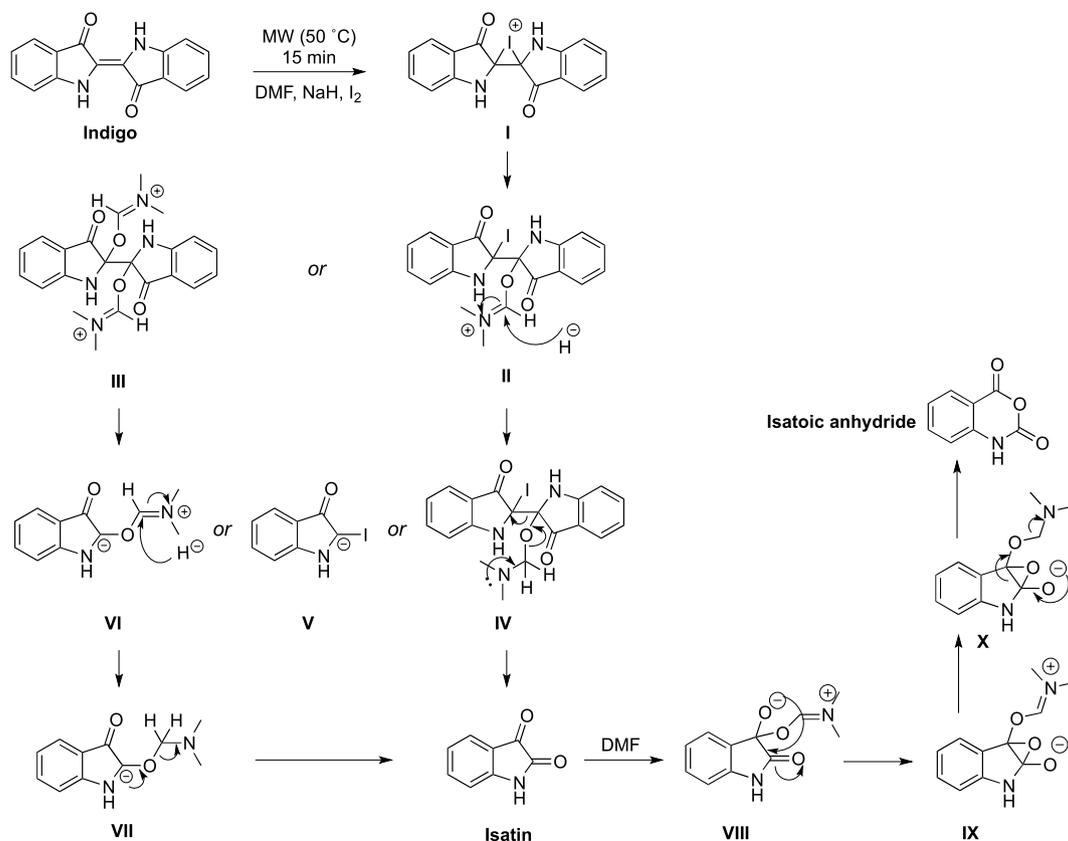
[9]; (iv) it might be involved in an acid-base reaction with isatin increasing its nucleophilicity; and (v) the use of excess of the hydride might promote this secondary reaction that facilitates the formation of tryptanthrin.

Since we observed the formation of a gas immediately after the addition of the 1,2-diiodoethane, we conducted a headspace GC-MS analysis in the closed microwave reactor. The result showed the presence of ethylene, indicating the decomposition of this diiodoalkane in basic conditions, resulting in the formation of iodine or iodide radicals. Iodine is a universal oxidizing agent and a mild and nontoxic Lewis acid catalyst, widely applied in the synthesis of heterocyclic compounds. For these reasons, we pointed it as the oxidant agent in our reaction.

With this information in mind, we decided to conduct the same reaction using molecular iodine I₂ (Entry 12). In this case, we could detect both isatin and isatoic anhydride, confirming the existence of these two

intermediates/side-products and a considerable increase on the tryptanthrin yield (68.8%), with only 17.8% of indigo left unreacted. This data clearly shows that the formation of tryptanthrin from indigo is promoted when iodine (molecular iodine or organic iodine)/DMF/NaH are simultaneously present.

Since isatin and isatoic anhydride have been observed in many reactional conditions, we wanted to understand if the reactant *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 and 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



Scheme 2. Proposed mechanism for the decomposition of indigo to isatin and oxidation to isatoic anhydride.

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 min of reaction (Entry 15). By using 2 equivalents of I₂, tryptanthrin was formed in considerable amount (Entry 16). Overall, the best reaction conditions are achieved when the starting material (indigo or isatin) is deprotonated with an excess of NaH and allowed to react with iodine (as I₂ or C₂H₄I₂) under the described microwave irradiation conditions (see [Supplementary Data](#)). By removing NaH, (Entry 17) or DMF (by substitution with 2-MeTHF) (Entry 18) no tryptanthrin was observed after 15 min under MW irradiation, showcasing the relevance of the I₂/NaH/DMF *trio* for the tryptanthrin formation.

After collecting all this information, and based on the previous reports on the tryptanthrin synthesis and the ability of DMF to act as oxygen donor, we hypothesize the mechanism for the decomposition of indigo to isatin presented in [Scheme 2](#). Iodine addition to indigo double bond (I) followed by the addition of DMF as proposed by Sudalai and co-workers [10], led to the formation of intermediate II. Iodine atom could be further substituted by DMF forming intermediate III, as proposed by Liu et al. [11]. Then, addition-elimination processes where hydride acts as the nucleophile [7] led to the formation of isatin precursors (IV-VII). From there, isatin could be oxidized to isatoic anhydride through DMF addition, intramolecular cyclization (similar to the proposed for the oxidation with peroxide by Wu and Co-workers [12]) and hydride addition-elimination. The condensation of isatin and isatoic acid could form tryptanthrin through a well established mechanism [2a,13].

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 corresponding di- and tetrabromotryptanthrin derivatives were isolated with 36 and 18% yield, respectively.

3. Conclusion

Herein, we describe the oxidation of indigo to isatin and subsequent oxidative cyclization to tryptanthrin, performed using NaH/iodine/DMF under microwave irradiation, being iodine a green oxidant and DMF the oxygen source.

These findings might allow the development of faster and greener methods for the synthesis of this relevant and high-value product and their derivatives using mild reaction conditions in high yields when compared with the previously described methods using indigo as starting material, without the requirement of strong oxidizing agents and complex apparatus.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dyepig.2019.107935>.

References

- [1] a) Jao CW, Lin WC, Wu YT, Wu PL. *J Nat Prod* 2008;71:1275–9.b) Jahng Y. *Arch Pharm Res* 2013;36:517–35.
- [2] a) Kaur R, Manjal SK, Rawal RK, Kumar K. *Bioorg Med Chem* 2017;25:4533–52. b) Tucker AM, Grundt P. *Arkivoc – Rev Acc* 2012:546–69.
- [3] O'Neill C. *Chem. News* 1892;65:124.
- [4] a) Matsui M, Morita M, Shibata K, Takase Y. *Nippon Kagaku Kaishi* 1982;7:1268–9.b) Machemer H. *Ber Dtsch Chem Ges B* 1930;63B:1341.
- [5] a) Moskovkina TV, Denisenko MV, Kalinovskii AI, Stonik VA. *Russ J Org Chem* 2013;49:1740–3.b) Moskovkina TV, Kalinovskii AI, Makhan'kov VV. *Russ J Org Chem* 2012;48:123–6.
- [6] a) Ding S, Jiao N. *Angew Chem Int Ed* 2012;51:9226–37.b) Muzart J. *Tetrahedron* 2009;65. 9313-8323.
- [7] Jin CH, Lee HY, Lee SH, Kim IS, Jung YH. *Synlett* 2007;17:2695–8.
- [8] Antony J, Saikia M, Vinod V, Nath LR, Katiki MR, Murty MS, Paul A, Shabna A, Chandran H, Joseph SM, Nishanth KS, Panakkal EJ, Srirama I, Sridivya I, Ran S, Sankar S, Rajan E, Anto RJ. *Sci Rep* 2015;5:11107.
- [9] Pace V, Hoyos P, Castoldi L, de María PD, Alcántara AR. *ChemSusChem* 2012;5:1369–79.
- [10] Prasad PK, Reddi RN, Sudalai A. *Chem Commun* 2015;51:10276–9.
- [11] Liu W, Chen C, Zhou P. *J Org Chem* 2017;82:2219–22.
- [12] Jia FC, Zhou ZW, Xu C, Wu YD, Wu AX. *Org Lett* 2016;18:2942–5.
- [13] a) Hou H, Li H, Han Y, Yan C. *Org. Chem. Front.* 2018;5:51–4.b) Reissenweber G, Mangold D. *Angew Chem Int Ed* 1980;19:222–3.c) Abe T, Itoh T, Choshi T, Hibino S, Ishikura M. *Tetrahedron Lett* 2014;55:5268–70.