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PII: S0040-4039(15)30467-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.12.052
Reference: TETL 47099

To appear in: *Tetrahedron Letters*

Received Date: 2 June 2015
Revised Date: 23 November 2015
Accepted Date: 9 December 2015

Please cite this article as: El-Remaily, M.A.E., Elhady, O.M., Cobalt (III)-porphyrin Complex (CoTCPP) as an efficient and recyclable homogeneous catalyst for the synthesis of tryptanthrin in aqueous media, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.052

Cobalt (III)-porphyrin Complex (CoTCPP) as an efficient and recyclable homogeneous catalyst for the synthesis of tryptanthrin in aqueous media.

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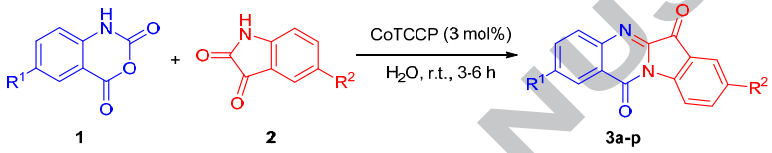
Graphical Abstract:

Cobalt (III)-porphyrin Complex (CoTCPP) as an efficient and recyclable homogeneous catalyst for the synthesis of tryptanthrin in aqueous media.



Abstract:

The water soluble cobalt (III) porphyrin complex (CoTCPP) was employed as an efficient catalyst for the synthesis of the biologically active natural product tryptanthrin. The reaction proceeded under mild conditions in aqueous media at room temperature from various isatoic anhydride and isatin derivatives. The advantages of these reactions were excellent yields, short reaction times and a recoverable catalyst.

Keywords: CoTCPP, tryptanthrin, efficient catalyst, aqueous medium, recoverable catalyst.

Introduction

Catalytic reactions performed using 5,10,15,20-tetrakis-(4-carboxlatophenyl)-porphyrin-cobalt(III) chloride (CoTCPP) fulfill the prerequisite criteria of green chemistry such as water-solubility,[1] low toxicity, and high stability of the complexes. Porphyrins, are typical examples of functional molecular materials and have attracted great interest in the materials field because of their large conjugated electronic molecular structures. They have also been extensively investigated in diverse areas, such as physics, chemistry, medicine, and biology.[2] The search for broadly applicable metal catalysts that operate in aqueous solvent is currently a subject of high interest.[3]

Applications have been reported in preparative organic synthesis, and also in the degradation of bio renewables (e.g., lignin) as an important sources of chemical feedstocks. However, most metal-based catalytic applications have been reported in organic solvents, due to the sensitivity of these complexes to moisture. Accordingly, the number of metal complexes suitable for catalysis in an aqueous environmental remains limited and the need for such catalysts has resulted in detailed studies.[4,5] Tryptanthrin can be isolated from *Candida lipolytica* in the presence of tryptophan.[6] Its structure is slightly twisted with aromatic character according to single crystal X-ray analysis.[7] Tryptanthrin and its derivatives are indoloquinazoline alkaloids which are found in many plants.[8] For example, eight indoloquinazolines were isolated from the methanol extract of *Phaius mishmensis*. Among these compounds, tryptanthrin was shown to have excellent cytotoxicity against human breast carcinoma (MCF-7)[9a], lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines.[9b] Several tryptanthrin derivatives were also found to exhibit remarkable antileishmanial activity and are potential succedaneums of sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime), which are current treatments for leishmaniases that unfortunately show hazardous side effects and alarming cardiotoxicity.[10] More recently, it was also discovered that tryptanthrins are potential antitubercular agents.[11]

Previous method for the synthesis of tryptanthrin focus on its construction from isatin. For example, cathodic reduction of isatin afforded tryptanthrin in moderate yield.[12] Treatment of isatin with $POCl_3$,[9b,13] $KMnO_4$[14a] $NiCl_2{\cdot}6H_2O/NaBH_4$[14b] or Cu-catalyzed reactions[15] also led to the formation of tryptanthrin. However, the structural diversity of tryptanthrins is confined by these methods due to the use of a single starting material. Structured diversity could be achieved by the condensation reaction between isatins and isatoic anhydrides in the presence of triethylamine[16] or in an aqueous solution of β-cyclodextrin. [17] An alternative condensation uses the reaction of isatin and *ortho*-aminobenzoic acid in the presence of $SOCl_2$.[18] The lithiation of orthobromophenyl isocyanide, followed by addition of electrophilic methyl 2-isocyanatobenzoate, is an unusual method which has also been utilised.[19]

One of our aims in the last years have been the development of new tools and methodologies for synthesizing bioactive compounds.[20-22]

In this communication, CoTCPP was found to be an efficient catalyst for the synthesis of tryptanthrin derivatives in aqueous medium from isatoic anhydrides and isatins at room temperature using an environmentally benign protocol.

Results and discussion:

The preparation of the CoTCPP catalyst was performed according to reported literature procedures.[23-26] Firstly, metal free 5,10,15,20-tetra(4-carboxyphenyl)-porphyrin was prepared by the reaction of pyrrole and 4-carboxy benzaldehyde in propanoic acid. Coordination of cobalt into the porphyrin core was carried out by the reaction of $CoCl_2$ with the metal-free porphyrin at reflux, giving 5,10,15,20-tetrakis-(4-carboxlatophenyl)-porphyrin-cobalt(III) chloride in 83% yield (Figure 1).

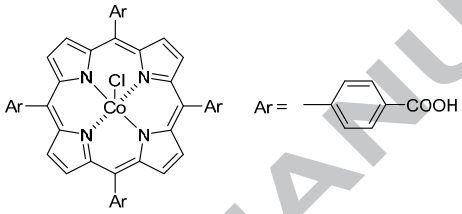
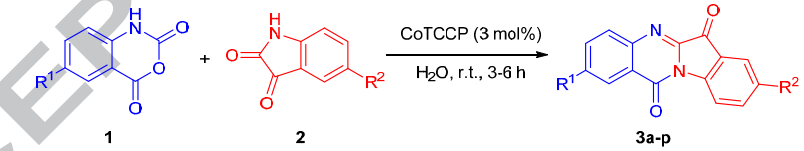


Fig. 1 Structure of the CoTCPP catalyst.

CoTCPP was then examined as an efficient and recoverable catalyst for the synthesis of tryptanthrin derivatives **3a-p** (Scheme 1). Due to the low solubility of some starting materials in water, a mixed solvent of water and ethanol (5:1) was used.



Scheme 1: Synthesis of tryptanthrin derivatives **3a-p**.

The role of CoTCPP as a catalyst was confirmed when the model reaction between isatoic anhydride **1a** and isatin **2a** was carried out in the absence of any catalyst; no product was obtained even with a long reaction time (Table 1, entry 1). We examined the influence of a variety of different Lewis acids, using the selected reaction conditions (Table 1, entries 2-11). It is noteworthy that the CoTCPP catalyst performed much better in comparison with all of the other water-soluble Lewis acids

investigated. Thus, CoTCPP was found to be the most effective catalyst and afforded the desired product **3a** in 96% yield (Table 1, entry 12). We screened different solvents such as CH_3OH, $CHCl_3$, DMF, DMSO, THF, CH_3CN and water with CoTCPP as a catalyst and found promising results with water as a solvent due to better solubility of CoTCPP (Table 1, entries 13-18).

Table 1. Use of different Lewis acids for the reaction to form **3a**[b]

Entry	Cat (mol%)	Conditions[b]	Yield (%)[a]
1	No catalyst	H_2O, r.t, 3 d	0
2	$CoCl_2•6H_2O$ (3)	H_2O, r.t, 3 h	37
3	$Co(NO_2)_2•6H_2O$ (3)	H_2O, r.t, 3 h	38
4	CoO (3)	H_2O, r.t, 3 h	21
5	$FeCl_2•6H_2O$ (3)	H_2O, r.t, 3 h	33
6	$FeCl_3•6H_2O$ (3)	H_2O, r.t, 3 h	31
7	$AlCl_3$ (3)	H_2O, r.t, 3 h	28
8	$ZnBr_2$ (3)	H_2O, r.t, 3 h	18
9	$MgCl_2$ (3)	H_2O, r.t, 3 h	23
10	$CuCl_2$(3)	H_2O, r.t, 3 h	22
11	$TiCl_4$ (3)	H_2O, r.t, 3 h	14
12	**CoTCPP(3)**	**H_2O, r.t, 3 h**	**95**
13	CoTCPP(3)	CH_3OH, r.t, 3 h	73
14	CoTCPP(3)	$CHCl_3$, r.t, 3 h	68
15	CoTCPP(3)	DMF, r.t, 3 h	61
16	CoTCPP(3)	THF, r.t, 3 h	66
17	CoTCPP(3)	DMSO, r.t, 3 h	70
18	CoTCPP(3)	CH_3CN, r.t, 3 h	72

[a]Isolated yield based on **3a**, [b]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (3 mol%), water:ethanol (5:1), room temperature.

With the optimized reaction conditions in hand, we investigated the model reaction further by varying the amount of the CoTCPP catalyst. It was observed that 3 mol% gave the highest yield of 95% and further increases were not beneficial to the process.

Table 2: the amount of CoTCPP catalyst for the synthesis of tryptanthrin **3a**[b].

Entry	Cat. (mol%)	Yield %[a]
1	1	51
2	2	83
3	3	95
4	4	95

[a]Isolated yield based on **3a**, [b]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), CoTCPP (3 mol%), water:ethanol (5:1), room temperature.

The substrate scope was explored under the optimized condition to give a series of tryptanthrin derivatives **3a-p** (Table 3).

Table 3: Synthesis of tryptanthrin derivatives[a].

Entry	Compound	R^1	R^2	Time (h)	Yield (%)[b]
1	**3a**	H	H	3	95
2	**3b**	H	CH_3	5	91
3	**3c**	CH_3	H	5	90
4	**3d**	CH_3	CH_3	6	88
5	**3e**	H	OCH_3	3	93
6	**3f**	OCH_3	OCH_3	4	95
7	**3g**	CH_3	OCH_3	4	91
8	**3h**	OCH_3	CH_3	4	89
9	**3i**	H	Cl	5	92
10	**3j**	Cl	Cl	3	94
11	**3k**	Cl	CH_3	6	91
12	**3l**	CH_3	Cl	5	92
13	**3m**	H	Br	4	93
14	**3n**	Br	Br	3	95
15	**3o**	Br	CH_3	6	91

16	**3p**	CH_3	Br	5	90

[a]Reaction conditions: **1a-p** (1 mmol), **2a-p** (1 mmol), CoTCPP (3 mol%), water:ethanol (5:1), room temperature. [b]Isolated yields.

A possible mechanism for the formation of product **3a** in the presence catalytic CoTCPP involves CoTCPP activating the carbonyl carbon at position 4 of the isatoic anhydride **1a** for nucleophilic attack by isatin **2a,** leading to cleavage of the anhydride ring and formation of the intermediate. This then reacts at position 2 of isatin to form the product **3a**.

The catalyst reusability was studied in the model reaction to from **3a**. Despite an inevitable loss of catalyst in the recovery process, no significant loss in catalytic activity was observed (Figure 2). The catalyst was used directly several times in other reactions under similar conditions without a loss of efficiency.

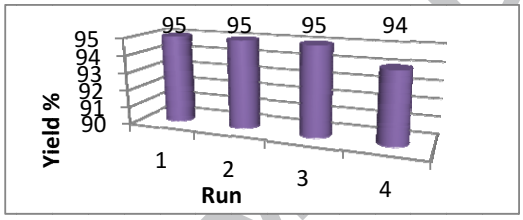


Fig 2: Recyclability of CoTCPP in the model reaction.

Conclusion:

In conclusion, we report CoTCPP as an efficient and environmentally benign catalyst for the synthesis of the biologically active natural product tryptanthrin in aqueous medium at room temperature. This method is has merits such as high yields and cost effectiveness, using aqueous conditions, as well as being environmentally benign in nature and using a recoverable catalyst. This represents the first example of using CoTCPP as a catalyst in water for the synthesis of tryptanthrin derivatives.

Supporting Information:

General procedures spectra and data for all compounds is located in the supporting information.

Acknowledgment:

The author is deeply grateful to Sohag University in Egypt for supporting and facilitating this study.

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