

## Efficient and green synthesis of new polycyclic procyanidin derivatives via tandem dinucleophilic addition of indolin-2-thiones to flavylium salts\*

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**Abstract:** The green synthesis of a new series of polycyclic procyanidin derivatives has been achieved in good yields by tandem dinucleophilic addition of indolin-2-thiones to flavylium salts. The procedure is efficient and simple, and the substrates are easily available.

**Keywords:** dinucleophilic addition; flavylium salts; green synthesis; indolin-2-thione; procyanidin derivatives.

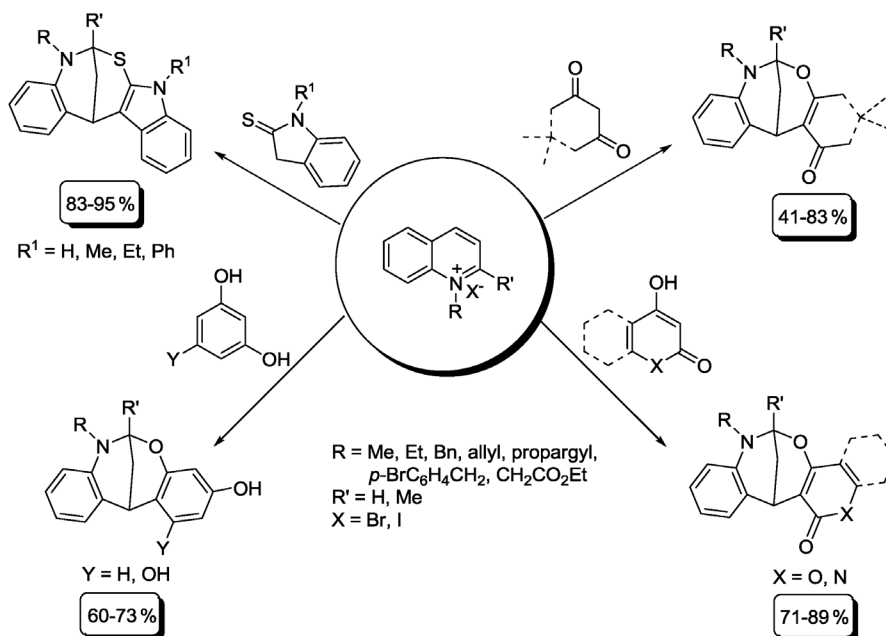
### INTRODUCTION

Procyanidins are widespread in nature, and their applications to biologically active pharmaceuticals and functional materials are becoming more and more important [1]. A variety of molecules containing the procyanidins display a wide range of biological activity and find applications as anticancer, antiallergy, antioxidant, antibacterial, and hair-growing agents [2]. Besides, sulfur-containing procyanidin skeletons are noticeable because they act as scavengers for preventing or treating lifestyle-related diseases like cancer, cardiovascular diseases, premature aging, and food supplement [3]. However, procyanidins are difficult to synthesize, and limited attention has been given to the synthesis of these compounds [4].

Flavylium salts are useful precursors for the synthesis of biologically important heterocyclic compounds [5]. Flavylium compounds are known to undergo addition at C-4 with nucleophiles such as phenols, 4-hydroxycoumarins, dimethylaniline, 1,3-diketone compounds, etc. [6]. On the other hand, tandem reactions (TRs), which result from the combination of multiple transformations in one pot, are highly efficient tools for the synthesis of complex compounds. Over the past few years, there has been a tremendous development in TRs affording novel chemical compounds for drug discovery efforts [7]. We earlier demonstrated an efficient and novel synthesis of a broad spectrum of benzoxazocines via unique tandem 1,3-dinucleophilic addition of different bifunctional nucleophiles to quinolinium and isoquinolinium salts (Scheme 1) [8]. This is a very mild and simple method for the construction of eight-membered ring in fused heterocycles in a one-step process.

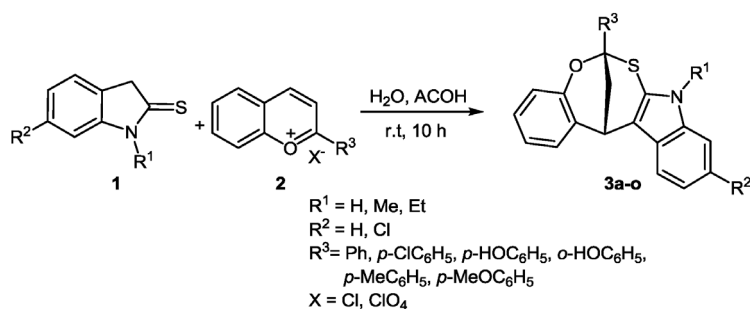
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**Scheme 1** Synthesis of a broad spectrum of benzoxazocines.

Indolin-2-thiones can behave as 1,3-carbon, sulfur dinucleophiles in one-pot reactions. Addition of indolin-2-thiones to quinolinium and isoquinolinium salts yielded indole-annulated pentacyclic indolyltetrahydroquinoline and indolyltetrahydroisoquinoline skeletons, respectively [8a,b]. There has not been any report on the reaction between indolin-2-thiones and flavylium salts. We wish to report herein our results on the green reaction of indolin-2-thiones **1** with flavylium salts **2**, which led to new polycyclic procyanidins **3a-o** in 65–92 % yields (Scheme 2).



**Scheme 2** Synthesis of new polycyclic procyanidins.

## RESULTS AND DISCUSSION

To achieve the optimal reaction conditions for the tandem synthesis of procyanidins, we initially investigated the effects of solvent and pH on the reaction of *N*-methyl indolin-2-thione **1a** and 2-phenylbenzopyrylium perchlorate **2a** as a simple model reaction. The effect of solvent was studied using MeOH, CH<sub>3</sub>CN and H<sub>2</sub>O, at different pH, with water and equal volume of acetic acid providing the highest yield.

The  $^1\text{H}$  NMR spectrum of **3d** showed two resonances ( $\delta$  2.69 and 2.93) for the geminal aliphatic methylene protons of the hydropyran ring, a singlet for the O-Me group ( $\delta$  3.90), a multiplet for the deshielded benzylic proton ( $\delta$  4.54) and a broad singlet for the NH ( $\delta$  7.75). The  $^1\text{H}$ -decoupled  $^{13}\text{C}$  NMR spectrum of **3d** showed 22 distinct resonances in agreement with the proposed structure. The  $^{13}\text{C}$  DEPT experiment showed resonances at  $\delta$  29.9 for the benzylic carbon,  $\delta$  37.6 readily recognized as the methylene carbon,  $\delta$  55.6 (O-Me),  $\delta$  88.9 for the S-C-O carbon, 10 distinct resonances for the aromatic methine carbons, and 8 other quaternary carbons.

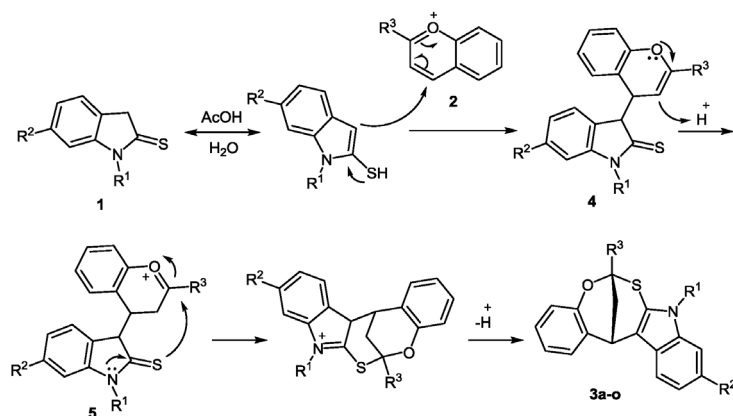
To generalize this methodology, we reacted a series of other indolin-2-thiones **1** and flavylum salts **2** to give the corresponding polycyclic procyanidins (Table 1). The reactions proceeded cleanly under mild conditions at room temperature, and no undesirable side reactions were observed. The same configuration was assumed for the other derivatives on account of their spectroscopic similarities. This chemoselective outcome is in agreement with the results observed in previous nucleophilic substitutions of compounds **1** [8].

**Table 1** Tandem green synthesis of new polycyclic procyanidins.

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yield (%)
1	H	H	Ph	<b>3a</b>	85
2	H	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	88
3	H	Cl	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	89
4	H	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3d</b>	87
5	H	Cl	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3e</b>	80
6	H	H	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>3f</b>	86
7	H	H	<i>o</i> -HOC <sub>6</sub> H <sub>4</sub>	<b>3g</b>	82
8	Me	H	Ph	<b>3h</b>	88
9	Me	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>3i</b>	90
10	Me	H	<i>p</i> -HOC <sub>6</sub> H <sub>4</sub>	<b>3j</b>	75
11	Me	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3k</b>	89
12	Et	H	Ph	<b>3l</b>	77
13	Et	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>3m</b>	92
14	Et	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3n</b>	83
15	Et	H	<i>o</i> -HOC <sub>6</sub> H <sub>4</sub>	<b>3o</b>	65

As a next step, we investigated the scope of the reaction with a linear thioamide, 1-morpholino-2-phenylethanethione as a tertiary thioamide under the optimized reaction conditions, but no reaction was observed and the initial flavylum salt and thioamide remained unchanged.

A plausible mechanism for the formation of the products is shown in Scheme 3. Indolin-2-thione **1** undergoes C-alkylation by attack at C-4 of flavylum salt **2** through the carbon atom of the enethio-late. This would lead to the formation of 4H-chromene **4**, which could be protonated to form a 3,4-dihydrochromenylium ion **5**. Finally, intramolecular nucleophilic cyclization by the sulfur atom gives the desired product **3**.



**Scheme 3** Proposed mechanism for the formation of procyanidin.

## CONCLUSION

In conclusion, we have described a novel and highly efficient method for the synthesis of procyanidins. Good product yield, high selectivity, good functional group tolerance, and low cost of the reagents are the salient features of this method. The starting materials are easily accessible, making this procedure attractive for the preparation of procyanidins in a single step.

## EXPERIMENTAL

*General:* All chemicals were purchased from Sigma–Aldrich and Merck, and were used without any further purification. A Bruker (DRX-500 Avance) NMR instrument was used to record the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. All NMR spectra were determined in  $\text{CDCl}_3$  or DMSO at ambient temperature. Melting points were determined on a Buchi B540 apparatus. Elemental analysis was obtained using a Perkin-Elmer 2004 (II) CHN analyzer. All the reactions were monitored by thin layer chromatography (TLC) carried out on silica gel with UV light. Some of the products were purified by column chromatography carried out on silica gel by using petroleum ether/ethyl acetate.

*General procedure for the synthesis of procyanidins 3a–o:* A mixture of indolin-2-thione **1** (0.5 mmol) and flavylum salt **2** (0.5 mmol) in  $\text{H}_2\text{O}/\text{AcOH}$ (glacial) (5 mL, 1/1) was stirred at room temperature for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid product was filtered and washed three times with water then air dried. In some cases, column chromatography was performed using silica gel eluting with petroleum ether/ethyl acetate (2:1) to obtain pure solid product.

## SUPPLEMENTARY INFORMATION

Experimental procedure and full spectroscopic data for all compounds are available online (doi:10.1351/PAC-CON-10-09-29).

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