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Catalyst-free Mannich reaction of hydroxyanthraquinone: facile access to emodin Mannich bases and anthraoxazines

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ABSTRACT

A simple and efficient method for derivatization of hydroxyanthraquinone natural product emodin through catalyst-free Mannich reaction is described. The method allows the modification of emodin skeleton at 2-position. This new derivatization strategy to emodin provides a clear advantage over traditional approaches, due to its easy operation and efficiency that does not involve the protection and deprotection.

The synthesis of diverse libraries is an important activity in the drug discovery.[1] Using natural products as starting scaffolds to access diverse libraries is particularly attractive because of the rich structural diversity and complexity of natural products.[2] Owing to the diverse biological activities and chemical properties, emodin, a hydroxyanthraquinone natural product, has received considerable attention as a promising candidate for new drug development.[3] Many emodin derivatives have been synthesized in order to get less toxic and more potent antitumor agents. However, most modifications on the emodin structure are mainly focused on the hydroxyl group and methyl group.[4] On the other hand, a number of emodin based natural products with substituents at the 2- and/or 7-position are known to display various biological activities such as variecolorquinones A, which exhibits good antitumor effects,[5] aurantio-obtusin, a potent rat lens aldose reductase (RLAR) inhibitor with IC_{50} value of 13.6 μM,[6] 2-geranylemodin, a potent antimalarial agent with IC_{50} value of 5.3 μM,[7] and laurenquinone A, a potent antibacterial agent.[8] (Fig. 1)

Based on this observation, we have synthesized a series of 7-substituted *O*-trimethyl emodin and screened their antitumor activities (Fig. 2). Unfortunately, most of the newly synthesized derivatives showed lower antitumor activity than emodin.[9] We suspected that the protection of the hydroxyl group as the methyl ether might result in a barrier to intercalation of the anthraquinone ring with DNA, and we decided to investigate an alternative elaboration of emodin that does not involve the protection of the hydroxyl group.

Mannich reaction is among the most useful carbon–carbon bond formation reactions in organic synthesis. Most of the current Mannich reactions are focused on the condensation of enolizable ketones with formaldehyde and amines. Few examples of Mannich reaction of phenols and naphthols have also been reported.[10] In contrast, there are only limited reports on hydroxyanthraquinones.[11] As a continuing interest in the development of new carbon–carbon bond formation reactions,[12] we decide to explore the Mannich reaction of hydroxyanthraquinones using emodin as the starting compound. Herein, we present a highly efficient, simple work-up, and catalyst-free synthesis of a wide range of emodin Mannich bases as potential antitumor agents and building blocks for more complex antitumor anthraquinones.

We initially selected benzaldehyde **2a** as a model substrate and attempted the condensation with emodin **1** and dimethylamine **3a** in H_2O at 65 °C under catalyst-free conditions for 24 h (Table 1). As expected, the emodin Mannich base **4a** was produced, but the yield was low (entry 1). We attributed it to the low solubility of emodin and benzaldehyde in H_2O. Some organic solvents such as DMF (entry 2), EtOH (entry 3), and dioxane (entry 6) were thus screened and dioxane was proven to be the most effective, providing product **4a** in 76% yield with complete consumption of starting material. Next, we studied the influence of the reaction temperature. Carrying out the reaction at room temperature resulted in a lower yield. Prolonged reaction time had no further effect (entry 4). Increasing the temperature to 90 °C decreased the yield and also led to the recovery of emodin **1** (entry 5) presumably due to the volatility of dimethylamine **3a** at an elevated temperature. To verify our assumption, we performed the reaction with 1 equiv dimethylamine **3a** at 65 °C, and a similar result was observed with

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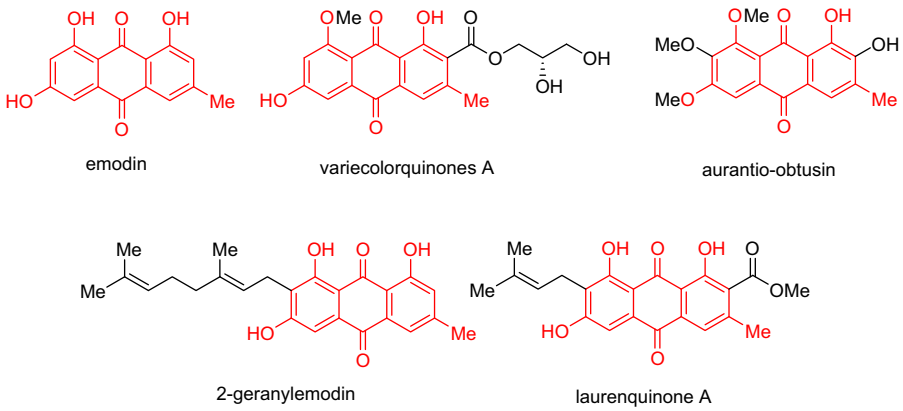


Figure 1. Biologically active emodin and emodin based natural products.

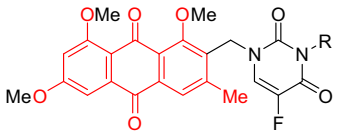


Figure 2. Structure of 7-substituted *O*-trimethyl emodin derivatives.

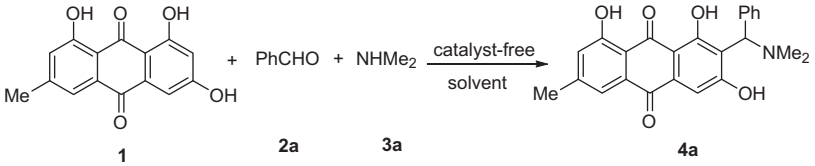
the reaction using 2 equiv dimethylamine **3a** at 90 °C (entry 7). It is disappointing that increasing the amount of dimethylamine from 2 to 4 equiv dropped the yield and afforded some unidentified byproducts (entry 9). Therefore, conducting the reaction in dioxane at 65 °C for 24 h with the 1:2:2 mol ratio of emodin, aldehyde, and dimethylamine is the optimal condition.

Having defined an effective condition for the Mannich reaction, we then explored the substrate scope with other aldehydes including substituted aromatic aldehydes, hetero, and aliphatic aldehydes (Table 2). To our delight, a wide range of substituted benzaldehydes, such as *o*-fluoro, *m*-fluoro, *p*-fluoro, *p*-bromo, *p*-nitro, 2,4-dichloro, 3,5-dichloro, 3,4-dimethyl, *p*-methyl, *o*-methoxyl, and *p*-formyl derivatives, reacted smoothly with emodin **1** affording the corresponding emodin Mannich bases **4b–4l** in 56–83% yields (entries 1–11). Apparently, the substituents in the aryl ring have no significant influence on the product formation. This reaction is also applicable to heterocyclic aldehydes such as 2-thenaldehyde **2m** and nicotinaldehyde **2n**, providing the corresponding products **4m** and **4n** in 71% and 74% yields, respectively (entries 12 and 13). The aliphatic aldehyde **2o** is also compatible and generates product **4o** in 67% yield (entry 14). The structure of product **4a** was unequivocally established by X-ray analysis (Fig. S1 in the Supplementary data).

Inspired by these positive results, we were subsequently interested in exploring other amines instead of dimethylamine. First, we attempted to extend this aminoalkylation to aniline and formaldehyde. To our surprise, the reaction generated a new compound. The unexpected appearance of two different proton signals of CH_2 groups attached to the heteroatom (e.g., ^{1}H NMR: 5.66 and 4.66 ppm) indicated that it was not a simple emodin Mannich base from formaldehyde and aniline. After careful analysis of the ^{13}C NMR and HRMS, the new compound was finally assigned as 3,4-dihydro-5,7-dihydroxy-9-methyl-3-phenyl-2*H*-anthra[2,3-*e*][1,3]oxazine-6,11-dione **5a**. This structure was further confirmed by X-ray crystallography. The formation of **5a** can be rationalized by the condensation of emodin with formaldehyde and amine to give the expected Mannich base **4p**, in which the amino alcohol would subsequently condense with the second formaldehyde to afford the 1,3-oxazine ring (Scheme 1).

Owing to the importance of 1,3-oxazine moiety in biological systems,[13] we turned our attention to investigate other primary amines. We were gratified to find that other primary amines, such as methylamine, also reacted smoothly with emodin **1** and

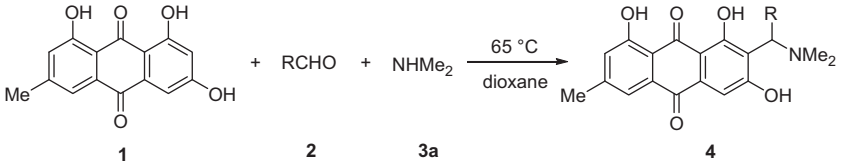
Table 1
Optimization of reaction conditions



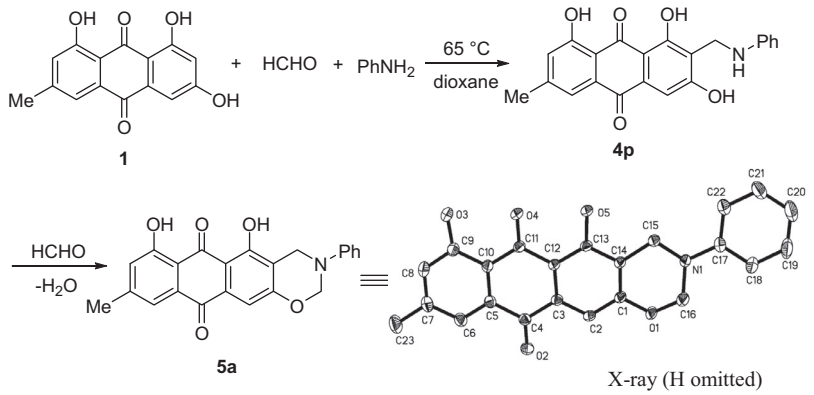
Entry	Solvent	*T* (°C)	Ratio[a]	*t* (h)	**4a**[b] (%)	Recovery of emodin[b] (%)
1	H_2O	65	1:2:2	24	22	Trace
2	DMF	65	1:2:2	24	40	Trace
3	EtOH	65	1:2:2	24	63	28
4	Dioxane	rt	1:2:2	72	27	57
5	Dioxane	90	1:2:2	71	22	49
6	Dioxane	65	1:2:2	24	76	Trace
7	Dioxane	65	1:2:1	60	42	45
8	Dioxane	65	1:1:2	60	41	27
9	Dioxane	65	1:2:4	24	57	Trace

[a] Ratio sequence: emodin/aldehyde/dimethylamine.
[b] Isolated yield.

Table 2
Scope of the emodin Mannich reaction with different aldehydes



Entry	Aldehyde	R	Product	Yield (%)
1	2-Fluorobenzaldehyde **2b**	2-FC_6H_4	**4b**	81
2	3-Fluorobenzaldehyde **2c**	3-FC_6H_4	**4c**	64
3	4-Fluorobenzaldehyde **2d**	4-FC_6H_4	**4d**	69
4	4-Bromobenzaldehyde **2e**	4-BrC_6H_4	**4e**	77
5	4-Nitrobenzaldehyde **2f**	4-$NO_2C_6H_4$	**4f**	73
6	2,4-Dichlorobenzaldehyde **2g**	2,4-$Cl_2C_6H_3$	**4g**	66
7	3,5-Dichlorobenzaldehyde **2h**	3,5-$Cl_2C_6H_3$	**4h**	72
8	3,4-Dimethylbenzaldehyde **2i**	3,4-$(CH_3)_2C_6H_3$	**4i**	56
9	4-Methylbenzaldehyde **2j**	4-$CH_3C_6H_4$	**4j**	83
10	2-Methoxylbenzaldehyde **2k**	2-$CH_3OC_6H_4$	**4k**	64
11	Terephthalaldehyde **2l**	4-$CHOC_6H_4$	**4l**	71
12	2-Thenaldehyde **2m**	2-Thienyl	**4m**	71
13	Nicotinaldehyde **2n**	3-Pyridinyl	**4n**	74
14	Cyclopropanecarbaldehyde **2o**	Cyclopropyl	**4o**	67



Scheme 1. Reaction of emodin with formaldehyde and aniline.

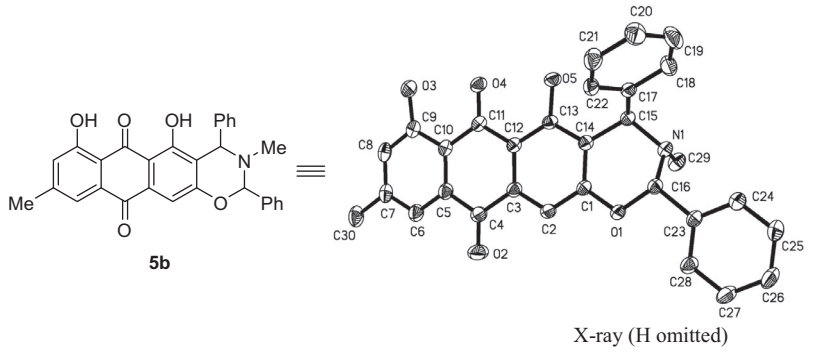


Figure 3. Crystal structure of product **5b** from the Mannich reaction between emodin, benzaldehyde, and methylamine.

benzaldehyde to form the anthraoxazine in moderate yield (68%) (Fig. 3). To the best of our knowledge, emodin incorporating oxazine fragments in the molecule has never been obtained before.

In conclusion, we have developed an efficient catalyst-free hydroxyanthraquinone Mannich reaction using emodin as the starting material. This one-pot procedure allows convenient access to two new classes of molecules depending on the choice of amines. Furthermore, this new derivatization strategy to emodin provides a clear advantage over traditional approaches (modification of the hydroxyl group and methyl group), due to its ease of operation and efficiency that does not involve the protection and deprotection. We believe that the methodology described herein provides a practical method to derivatize and functionalize

hydroxyanthraquinone natural product emodin at rarely modified 2-position.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.059.

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