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DMSO-mediated transformation of 3-amino-2-hydroxynaphthazarins to natural 2,3-dihydroxynaphthazarins and related compounds

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ABSTRACT

A general and convenient method for the synthesis of naturally occurring and related hydroxylated naphthazarins has been developed. This protocol involves the oxidative DMSO-mediated transformation of 3-amino-2-hydroxynaphthazarins to 2,3-dihydroxynaphthazarins under acidic conditions. Based upon experimental observations, a plausible reaction mechanism is proposed.

Introduction

Naturally occurring quinones are an attractive source for drug discovery due to their wide spectrum of pharmacological activities.[1] Among them, naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) natural products are well-known for their antibacterial,[2] cytotoxic,[3] antitumor,[4] nematicidal,[5] and anti-inflammatory properties.[6] Our continued interest in hydroxylated naphthazarins **1**–**6** (Fig. 1) is due to the high biological activity of echinochrome **4**, used for the treatment of burns and traumas of eyes, ischemia and myocardial infarction.[7] Recent studies have revealed new insights into the mechanisms of cardioprotective[8] and acetylcholinesterase inhibitory[9] activities of echinochrome, as well as its ability to enhance mitochondrial biogenesis in cardiac[10] and skeletal muscles.[11] Also, some natural and synthetic hydroxynaphthazarins are potent antioxidants[12] and possess antiallergic activity.[13]

Hydroxylated quinones are useful substrates for chemical modification. Thus, in the course of our studies for the development of new drugs we have synthesized a series of novel *O*- and *S*-glycosides[14] of naturally occurring quinones, some of which have shown potent antileukemic activity against human promyelocytic leukemia HL-60.[15] Moreover, Margulis and co-workers have revealed that acetylated tris-*O*-glycoside of echinochrome U-133 increases expression of heat shock protein Hsp70 in tumor cells and possesses anticancer activity.[16] These advances motivated us to develop a new and efficient protocol for the synthesis of a wide range of naturally occurring and synthetic polyhydroxylated naphthazarins.

While 2,3-dihydroxynaphthazarins **1**–**6** are well-known,[17] only a few synthetic methods for their production have been reported.[18] Unfortunately, these approaches are multi-step and low-yielding or lead to multicomponent mixtures of products. Currently, the treatment of readily available 2,3-dichloronaphthazarins with MeOH/CsF/Al_2O_3[19] and subsequent demethylation of the resulting methyl ethers with HBr/AcOH[20] is the only method that leads to polyhydroxylated naphthazarins in good yields. However, this protocol is severely limited by poor substrate scope, harsh reaction conditions, and requires using absolute methanol and well-dried CsF, which is an expensive and moisture-sensitive reagent.

In previous work we have developed a short and effective route to 6,7-substituted 3-amino-2-hydroxynaphthazarins by the reaction of 2,3-dichloronaphthazarins with sodium nitrite followed by reduction of the initially formed 2-hydroxy-3-nitronaphthazarins with sodium sulfide or sodium dithionite.[21] In addition, we revealed that 3-amino-2-hydroxynaphthazarin is easily transformed to spinazarin in good yield by heating at reflux in 30% sulfuric acid.[22] Recently, Anufriev and co-workers used our approach for the synthesis of spinochrome E **6**.[23] However, the key step of this protocol, utilizing treatment of an aminoquinone with

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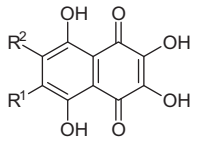


1 spinazarin R^1=H; R^2=H
2 methylspinazarin R^1=Me; R^2=H
3 ethylspinazarin R^1=Et; R^2=H
4 echinochrome R^1=Et; R^2=OH
5 spinochrome D R^1=OH; R^2=H
6 spinochrome E R^1=OH; R^2=OH

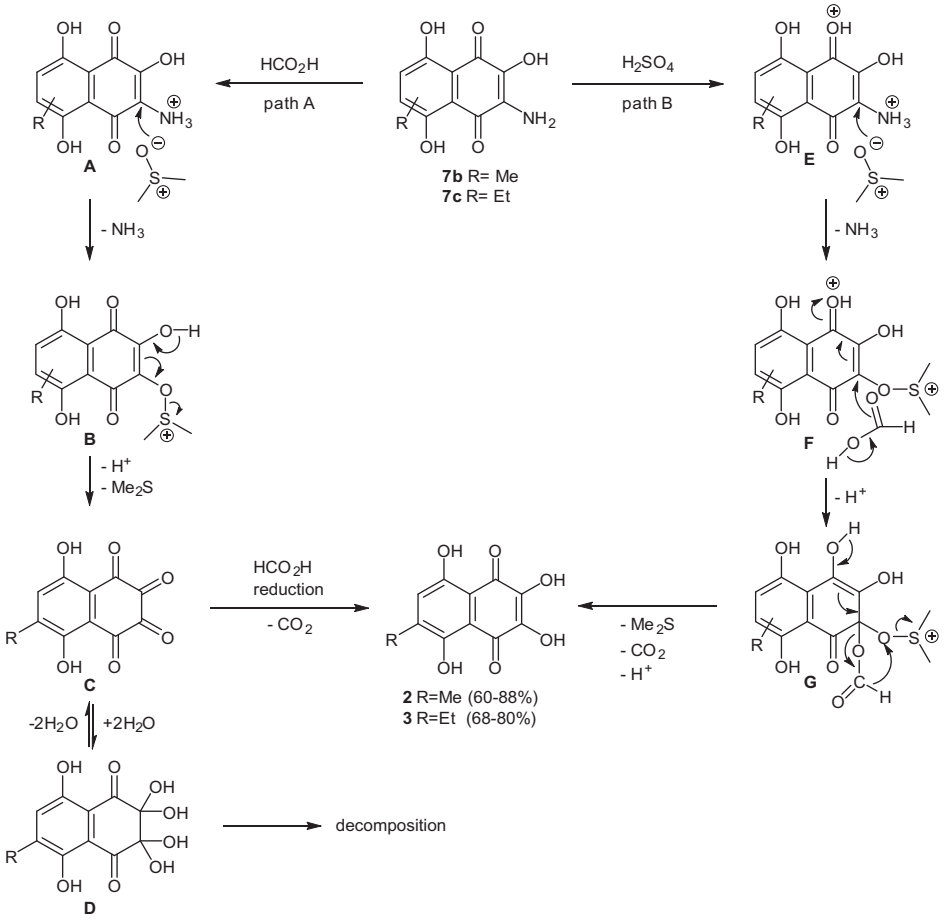
Figure 1. Naturally occurring hydroxylated naphthazarins.

anhydrous $AlCl_3$ in dry nitrobenzene, gave spinochrome E in low yield (43%). Herein, we describe our progress in the development of a general, versatile, and efficient method for the synthesis of various 6,7-substituted 2,3-dihydroxynaphthazarins.

Results and discussion

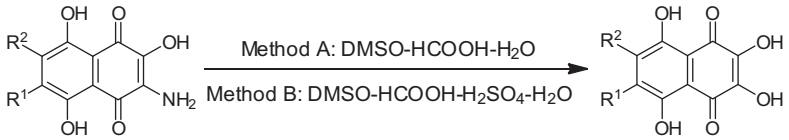
Initially, we examined the utility of various mineral and organic acids for the acid-catalyzed transformation of model aminonaphthazarins **7b** and **7c** to hydroxynaphthazarins **2** and **3**. We found that aminoquinones **7b** and **7c** were only slightly soluble in H_2SO_4 and the conversion to the corresponding 2,3-dihydroxyquinones was very poor (~5%). Moreover, the formation of decomposition products was observed after heating **7b** and **7c** at reflux in 30% sulfuric acid for 4 h. Also, all attempts to apply a protocol utilizing conc. HCl, which was previously used for the synthesis of hydroxyjuglones from aminojuglones,[24] were unsuccessful. When aminoquinones **7b** and **7c** were heated at reflux in H_3PO_4, CH_3COOH, and trifluoroacetic acid, no reaction was observed. Under the same conditions aminonaphthazarins **7b** and **7c** reacted with formic acid to give only N-formylation products in good yield. In our opinion, these unsatisfactory results could be explained by two causes: (1) poor solubility of the starting compounds in mineral acids; (2) insufficient nucleophilicity of water in the acidic medium for nucleophilic substitution of the protonated amino group in aminoquinone.

To circumvent these problems, we tried to apply DMSO as a suitable solvent for the acid-catalyzed transformation. We expected that the combination of DMSO and acid (activated DMSO),[25] would promote substitution of the protonated amino group. Organic acids were used in the following experiments to prevent the decomposition of aminoquinones. When the reaction was carried out in DMSO–CH_3COOH or DMSO–trifluoroacetic acid at reflux for 4.5 h, only the starting compounds were recovered from the reaction mixture. Surprisingly, the treatment of aminonaphthazarins **7b** and **7c** with DMSO–HCOOH (1:1) for 1.5 h afforded non-separable mixtures of the corresponding spinazarins **2**, **3**, and 2,2,3,3,5,8-hexahydroxy-2,3-dihydronaphthalene-1,4-diones **D** (Scheme 1, path A) in a ratio of ~1:1.[26] Naphthalenediones **D** were isolated as the main products when the reaction time was decreased to 45 min. On the other hand, increasing the reaction time to 4.5 h led only to spinazarins **2** and **3** in yields of 60% and 68%, respectively (Table 1, method A, entries 2 and 3). It is noteworthy that the violent outflow of dimethylsulfide was observed in these experiments.



Scheme 1. Two possible mechanisms for the formation of spinazarins: Path A (DMSO–HCOOH–H_2O, reflux, 4.5 h); Path B (DMSO–HCOOH–H_2SO_4–H_2O, reflux, 30 min).

Table 1
Transformation of 3-amino-2-hydroxynaphthazarins to 2,3-dihydroxynaphthazarins



Entry[a]	Aminoquinone[b]			Hydroxyquinone	Yield (%)	
		R^1	R^2		Method A[d]	Method B[e]
1	**7a**[c]	H	H	**1**	80	89
2	**7b**	Me	H	**2**	60	88
3	**7c**	Et	H	**3**	68	80
4	**7d**	*t*-Bu	H	**8a**	76	80
5	**7e**[c]	Me	Me	**8b**	80	88
6	**7f**	Cl	H	**8c**	68	76
7	**7g**[c]	Cl	Cl	**8d**	34	87
8	**7h**	Me	Cl	**8e**	74	86
9	**7i**	Et	Cl	**8f**	63	82
10	**7j**	OMe	H	**8g**	50	85
11	**7k**	OMe	Me	**8h**	57	82
12	**7l**	OMe	Et	**8i**	60	84
13	**7m**	OEt	Me	**8j**	80	82
14	**7n**	OEt	Et	**8k**	44	86
15	**7o**[c]	OH	Me	**8l**[f]	63	80
16	**7p**[c]	OH	Et	**4**[f]	75	81

[a] Reactions were performed on a 0.2-mmol scale.
[b] Mixtures of regioisomers unless otherwise indicated.
[c] Single isomer of the starting aminoquinone.
[d] Reaction conditions: DMSO (2 mL), HCOOH (2 mL, 85%), reflux (4.5 h).
[e] Reaction conditions: DMSO (200 μL, 0.35 mmol), HCOOH (4 mL, 85%), H_2SO_4 (1 mL, 25%), reflux (30 min).
[f] Reflux (10 min).

The reaction was extended to different 3-amino-2-hydroxyquinones (Table 1, entries 1–16, method A). We found that aminonaphthazarins **7a–f**, **7h–p** were converted into 2,3-dihydroxynaphthazarins by heating at reflux in DMSO–HCOOH–H_2O in moderate to good yields. However, aminoquinone **7g,** bearing two chlorine atoms on the benzene ring, was converted to **8d** in only 34% yield (entry 7). Aminoquinones **7o**, **p** reacted with DMSO–HCOOH–H_2O in only 10 min to give pure hydroxyquinones **8l** and **4** in 63% and 75% yields, respectively (entries 15 and 16).

We continued our investigation to develop an effective method of acid-catalyzed transformation. To simplify product isolation, a smaller amount of DMSO (200 μL per 0.2 mmol of aminoquinone) was used in subsequent experiments. It was also established that the addition of sulfuric acid to the DMSO–HCOOH–H_2O system dramatically accelerated the rate of reaction and gave better yields of spinazarins. Thus, heating aminoquinones **7b**, **7c** at reflux for 30 min led to spinazarins **2**, **3** in 88% and 80% yields, respectively (Table 1, method B, entries 2 and 3). Gratifyingly, even traces of tetraone hydrate **D** were not detected and only pure 2,3-dihydroxynaphthazarins were isolated. Nevertheless, the formation of dimethylsulfide was also observed under these conditions.

Reaction mechanisms were proposed for each set of conditions (Scheme 1, path A and B). The conversion of the aminoquinone to the hydroxyquinone involves several stages. In the first step in both pathways, dimethylsulfoxide is added to the C=C–C=O quinonoid core of the protonated aminoquinone followed by elimination of ammonia and the formation of DMSO–quinone conjugates **B** and **F**. Intermediate **B** is easily converted to tetraone **C** with the elimination of dimethylsulfide. For tetraone **C** two feasible transformations are possible. In the first transformation, it can be reduced by HCOOH to give spinazarins **2** or **3**. In the second transformation, hydration of tetraone **C** occurs and tetraone dihydrate **D** is formed. Dihydrate **D** is unstable under the reaction conditions and could decompose or undergo transformation to tetraone **C** by the elimination of two water molecules. In fact an equilibrium between tetraone **C** and its hydrated form **D** has been reported.[27]

We believe that another mechanism for the acid-catalyzed transformation was present using Method B (Scheme 1, path B). In this case sulfuric acid protonates the carbonyl group to give activated quinone **F**. The addition of formic acid to the activated double bond of quinone **F** leads to the unstable intermediate **G**, which is converted to spinazarins **2**, **3** with the elimination of dimethylsulfide and carbon dioxide. Evidently, this step proceeds as a concerted process in contrast with path A. The proposed mechanism explains the critical role of sulfuric acid for the protonation of aminoquinones, as well as quinone intermediates, and shows that formic acid is involved in the reaction as a reducing agent (steps **F**→**G**→**2**, **3**).

With the improved method in hand we synthesized a series of 2,3-dihydroxynaphthazarins **1–4**, **8a–l** (Table 1, entries 1–16, method B). 3-Amino-2-hydroxynaphthazarins **7a–n** reacted smoothly with DMSO–HCOOH–H_2SO_4–H_2O in 30 min to give 2,3-dihydroxynaphthazarins **1–3**, **8a–k** in good to excellent yields. Aminoquinones **7o**, **p** were converted to dihydroxyquinones **8l**, **4** in only 10 min in 80% and 81% yield, respectively. Notably, we did not detect tetraone hydrate **D** in these experiments and pure samples of hydroxynaphthazarins were obtained using this method.

Conclusion

In conclusion, a operationally simple, versatile, and effective route for the synthesis of natural and related 6,7-substituted 2,3-dihydroxynaphthazarins has been developed. The method uses inexpensive and readily available reagents and allows obtaining chloro- and alkoxy- derivatives of various natural 2,3-dihydroxy-

naphthazarins in a regioselective manner. The scope and mechanism of the DMSO-supported transformation are now under investigation.

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Supplementary data

Supplementary data (experimental details, characterization data, ^{1}H NMR and ^{13}C NMR spectra for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.056.

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