

## Ionic Liquid-promoted Ring-closure Reactions between 1,4-Dihydroxyanthraquinone and Diamines

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**Abstract:** The reaction of 1,4-Dihydroxyanthraquinone with diamines was carried out in the presence of CuCl<sub>2</sub>, CuCl in the ionic liquid [Bmim]PF<sub>6</sub>, [Bmim]BF<sub>4</sub> or [Bmim]Cl·CuCl.

**Keywords:** Ionic liquid, 1,4-dihydroxyanthraquinone, diamines, ring-closure.

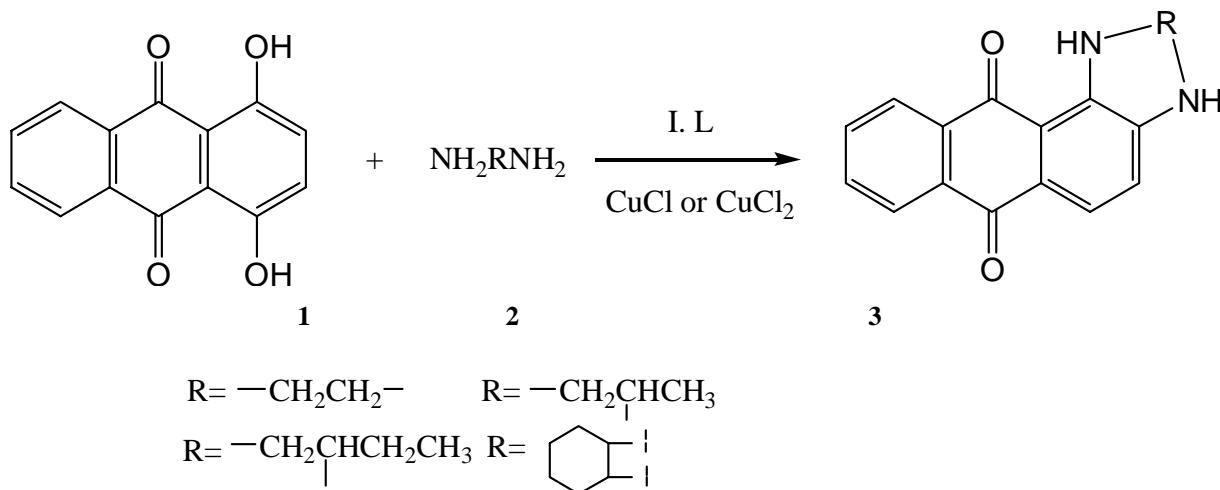
### Introduction

There is currently renewed interest in aminoanthraquinones. The use of mono- and diaminothraquinones in the dyestuffs industry has been well established for many years, but recently a number of other features of aminoanthraquinone chemistry have attracted intense interest. A review of the fascinating enediyne anticancer antibiotics details the role of anthraquinones such as dynemicin A in the cleavages of DNA [1]. In certain cases [2] there is also evidence that an anthraquinone moiety can intercalate into DNA and a side arm of the anthraquinone, for example an alkylamino substituent, can bind to protein and in such cases, due to disruption of DNA-protein interactions there can be interference with topoisomerase II and antitumor activity is observed. Other important aspects of DNA cleavage by anthraquinones have recently been discussed [3]. These exciting biological results with dynemicin A have stimulated synthesis of key sub-units. A tetracycle [4] having a core aminoanthraquinone portion related to dynemicin A has recently been synthesized, and related pentacycles have also been prepared [5]. Other aminoanthraquinones such as mitoxantrone and

ametantrone are now used clinically. A large number of papers and patents have been reported on substitution reactions for introducing amino groups into the anthraquinone moiety, but little is known about the direct amination of this nucleus. The direct amination of anthraquinone or amino-anthraquinones with hydroxylamine catalyzed by iron sulfate or vanadium pentaoxide has been described, but it produces random substitution products. Takei *et al.* have reported direct amination of anthraquinone promoted by copper ions [6]. However, their reaction conditions are rather drastic, requiring the use of copper salt in greater than stoichiometric amounts and the use of toxic pyridine. Therefore, the development of a simple, relatively mild, efficient and environmentally more benign method for the synthesis of aminoanthraquinones would be of great utility.

Our recent research interests have been in the development of new synthetic method using ionic liquids as reaction media and promoters [7]. As part of a program to investigate the range of organic reactions possible in ionic liquids, we examined the reactions of 1,4-dihydroxyanthraquinone and diamines  $\text{NH}_2\text{RNH}_2$  in ionic liquids (Scheme 1).

**Scheme 1**



## Results and Discussion

First, the ring-closure reaction of 1,4-dihydroxyanthraquinone and ethylenediamine was investigated. The results are presented in Table 1. We found that in the presence of 20 mol %  $\text{CuCl}_2$ , the reaction of 1,4-dihydroxyanthraquinone and ethylenediamine in the ionic liquid  $[\text{Bmim}]PF_6$  resulted in the formation of 6-hydroxy-1,2,3,4-tetrahydronaphtho[2,3-f]-quinoxaline-7,12-dione in 99% yield, and that the reaction proceeded smoothly at room temperature and was complete within 2 hours. In a similar fashion, the reactions of 1,4-dihydroxyanthraquinone and ethylenediamine in different ionic liquids and classical solvents were investigated. The results demonstrated that the ionic liquids  $[\text{Bmim}]PF_6$ ,  $[\text{Bmim}]BF_4$ ,  $[\text{Bmim}]Cl \cdot \text{CuCl}$  were effective and promoted ring-closure reaction between 1,4-dihydroxyanthraquinone and the diamine (Table 1, Entries 1–5). The yields in classical solvents were lower than those observed using ionic liquids (Table 1, Entries 6–9).

The scope of the reaction of different diamines with 1,4-dihydroxyanthraquinone was investigated next. We found that the reaction occurred easily in  $[\text{Bmim}]PF_6$  in the presence of 20 mol %  $\text{CuCl}_2$  to form the corresponding products. The yields with 1,2-propanediamine and 1,2-cyclohexanediamine

were excellent, while the yields with *N*-methylenediamine and *N*-ethylmethylenediamine were modest (Table 1, Entries 10-13). All the products gave satisfactory M.p., IR and <sup>1</sup>H-NMR data, which were consistent with the literature data.

The ionic liquid and copper salt could typically be recovered by extracting the product and washing with a mixture of Et<sub>2</sub>O-EtOAc (1:1), followed by drying under vacuum. The recovered ionic liquid and copper salt could be reused at least up to five times with no appreciable decrease in yield.

**Table 1.** Reaction of 1,4-Dihydroxyanthraquinone and Diamines catalyzedcopper salt in ionic liquids <sup>a</sup>.

Entr y	Diamine	Solvent and Copper salt	Reaction time (h)	Yield <sup>b</sup> (%)
1	ethylenediamine	[Bmim]PF <sub>6</sub> + CuCl <sub>2</sub>	2	99
2	ethylenediamine	[Bmim]PF <sub>6</sub> + CuCl	2	95
3	ethylenediamine	[Bmim]Cl·CuCl	2	87
4	ethylenediamine	[Bmim]BF <sub>4</sub> + CuCl	2	90
5	ethylenediamine	[Bmim]BF <sub>4</sub> + CuCl <sub>2</sub>	2	96
6	ethylenediamine	CuCl <sub>2</sub> + DMF	8	56
7	ethylenediamine	CuCl + DMF	8	42
8	ethylenediamine	CuCl <sub>2</sub> + CH <sub>2</sub> Cl <sub>2</sub>	8	50
9	ethylenediamine	CuCl + CH <sub>2</sub> Cl <sub>2</sub>	8	40
10	1,2-propanediamine	[Bmim]PF <sub>6</sub> + CuCl <sub>2</sub>	2	92
11	1,2-cyclohexanediamine	[Bmim]PF <sub>6</sub> + CuCl <sub>2</sub>	2	80
12	<i>N</i> -methylenediamine	[Bmim]PF <sub>6</sub> + CuCl <sub>2</sub>	2	48
13	<i>N</i> -ethylmethylenediamine	[Bmim]PF <sub>6</sub> + CuCl <sub>2</sub>	2	31

<sup>a</sup> All the reaction were run with 1,4-dihydroxyanthraquinone (2 mmol), diamine (4 mmol) and 0.4 mmol copper salt in ionic liquid (2 mL).

<sup>b</sup> Isolated yields based on 1,4-dihydroxyanthraquinone.

## Conclusions

In summary, we have demonstrated that the ring closure reaction between 1,4-dihydroxyanthraquinone and diamines can be performed effectively at room temperature in the ionic liquids 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF<sub>6</sub>) or 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF<sub>4</sub>) or with copper (I) chloride-1-butyl-3-methylimidazolium chloride ([Bmim]Cl·CuCl), thus providing a simple and efficient synthetic method. This method has many obvious advantages compared to those previously reported in the literature, including being environmentally more benign, the simplicity of the methodology, the higher yields obtained and the potential for recycling of the ionic liquids and catalyst copper salt.

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## Experimental Section

### General

Melting points were determined on a digital melting point apparatus and were not corrected. Infrared spectra were recorded on a Bruker VECTOR 22 instrument. Nuclear magnetic resonance spectra were recorded on a Bruker AVANCE DMX 200 spectrometer. The ionic liquids [Bmim]BF<sub>4</sub>, [Bmim]PF<sub>6</sub> and [Bmim]Cl·CuCl were synthesized according to reported procedures [8]. The other materials are commercially available and were used without further purification.

### General synthetic procedure

1,4-Dihydroxyanthraquinone (2 mmol), the appropriate diamine (4 mmol) and copper salt (0.4 mmol) were added to the selected ionic liquid ([Bmim][PF<sub>6</sub>] or [Bmim]BF<sub>4</sub>, 2 mL) and the mixture was stirred at room temperature for 2 h. The product was then extracted with ether (3x10 mL). The combined ethereal phase was evaporated under reduced pressure to give the crude product, which was purified by recrystallization to give the corresponding pure compound. After removal of the product, the residue of the viscous ionic liquid and copper salt was further washed with a 1:1 mixture of ether-ethyl acetate, dried at 80°C under reduced pressure for several hours and reused in subsequent runs.

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