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Simultaneously electrogenerated diene and dienophile: A unique access to novel polyfunctionalized 1,4-benzoxazine derivatives as neuroprotective agents

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Abstract

New insights into the scope of a multistep one-pot electrochemical synthesis of polyfunctionalized 2-alkylamino-1,4-benzoxazine derivatives are delineated. This cascade sequence, wherein both cycloaddition partners are generated in situ, at room temperature, under metal-free conditions, should be useful to generate libraries of heterocycles which constitute the molecular framework of medicinally relevant compounds. In this respect, 2-alkylamino-1,4-benzoxazine derivatives proved to be potent neuroprotective agents in vitro, on immortalized HT22 hippocampal cell cultures, and in vivo, in an animal model mimicking the cerebral palsy in human newborns.

Keywords: Anodic oxidation; Enamine; Azaquinone; Cascade reactions; Neuroprotective agents

1. Introduction

The electrochemical methodology becomes more and more attractive compared to conventional chemical procedures, due to increasing environmental problems. It is especially suited for preventive environmental protection because the practically mass-free electrons are used as reagents. It allows indeed the formation of organic compounds without the production of ecologically critical waste which has been to be disposed [1]. The reaction conditions are usually mild using ambient temperature, normal pressure and often alcoholic solvents.

In particular, the electrochemical methods can be used to generate highly reactive species which can be engaged in synthetically useful follow-up reactions [2–8]. Among them, electrochemically induced cycloadditions have proved to be a promising tool for organic chemistry [9–15]. Various unstable electrogenerated dienes [16–19] or dienophiles [20] have been successfully used in Diels–Alder reactions leading to the desired cycloadduct in high yield, with a good stereocontrol.

Recently, we reported the high catalytic performance of the redox mediator 3,4-azaquinone $\mathbf{1}_{ox}$ in the chemoselective indirect electrochemical oxidation of primary aliphatic amines, under metal-free conditions [21]. The catalytic cycle produced the reduced catalyst $\mathbf{1}_{red}$ and an alkylimine as the product of amine oxidation (Scheme 1). However, in the case of $(R^1)_2CHCH_2NH_2$ amines, the catalytic process ceased after a few turnovers, as the catalyst was trapped through [4 + 2] cycloaddition reaction with the simultaneously electrogenerated tautomeric enamine form of the alkylimine extruded during the catalytic process. This unexpected reaction allowed the rapid construction of polyfunctionalized 1,4-benzoxazine derivatives [22]. This cascade sequence, wherein both cycloaddition partners are generated in situ, at room temperature, under metal-free conditions, allowed the inverse-electron-demand Diels–Alder (IEDDA) reaction of an *o*-quinone imine diene with a secondary alkylenamine

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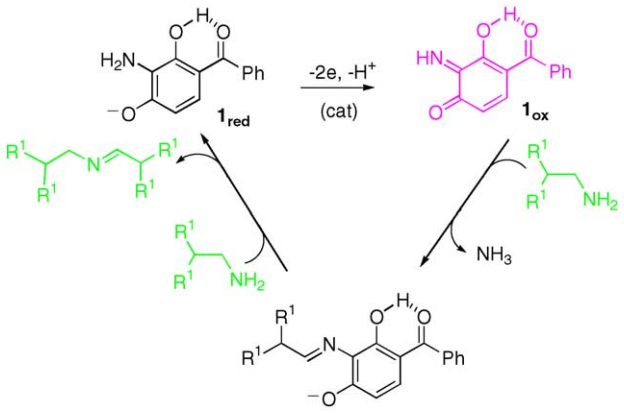


Scheme 1.

dienophile, two chemically nonaccessible unstable entities. Because the reactivity of *o*-quinone imine as an azadiene for IEDDA reactions represented uncharted terrain, though similar reactions with *o*-quinone monoimides [23–28] and *o*-quinone monooximes [29] are known, we then decided to explore further its potential for [4 + 2] cycloaddition reactions with variously substituted enamines. Especially, to increase the molecular diversity, we attempted to generate enamines in which the substituents on the amino group were different from those linked to the double bond. For this purpose, the amine $(R^1)_2CHCH_2NH_2$ was catalytically oxidized by 3,4-azaquinone $\mathbf{1}_{ox}$ in the presence of a second primary aliphatic amine R^2NH_2 (Scheme 2). Then, we showed that the $\mathbf{1}_{ox}$-mediated cascade reactions led to the construction of complex 1,4-benzoxazine derivatives **2**, in a regiospecific manner, and allowing diastereospecific heterocyclic annellation [30].

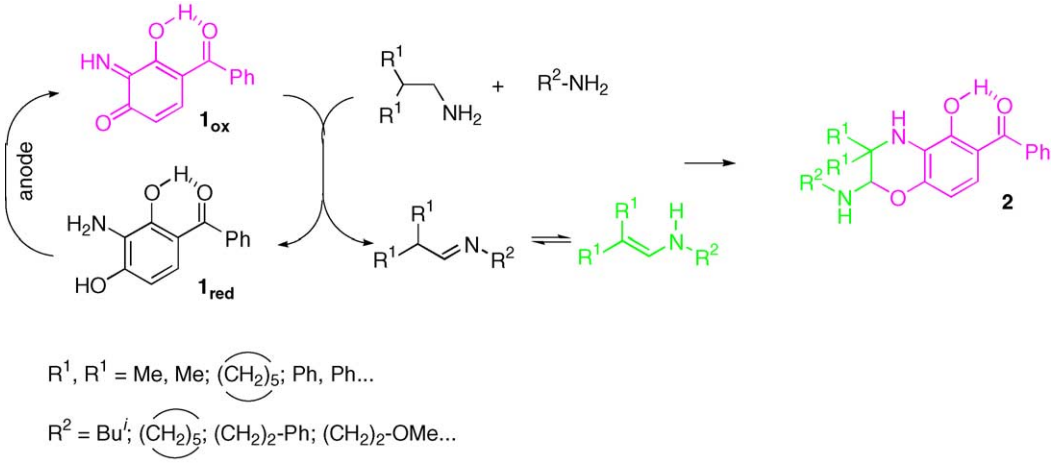
In this paper, we pursue our investigations concerning the extension of the multistep one-pot electrochemical synthesis of 2-alkylamino-1,4-benzoxazine derivatives, because this cascade reaction should be useful to generate libraries of heterocycles which constitute the molecular framework of medicinally relevant compounds. Furthermore, as a result of their structural similarity with a series of topologically different 8-alkylamino-1,4-benzoxazine neuroprotective agents published earlier [31,32], we report briefly, for comparison, the results of in vitro and in vivo assays of some substituted 2-alkylamino-1,4-benzoxazine derivatives.

2. Experimental

Chemicals were commercial products of the highest available purity and were used as supplied. Reduced catalysts $\mathbf{1}_{red}$ and $\mathbf{3}_{red}$ were synthesized as earlier reported [33]. Compounds **2b–f** were prepared according to our published procedures [30]. All apparatus, cells and electrodes were identical with those described previously [34]. The experimental conditions for in vitro and in vivo biological assays are extensively detailed in references [31] (immortalized HT22 hippocampal cell cultures) and [32] (neonatal mice).

*2.1. [(R,S)-3,3-Dimethyl-5-hydroxy-2-isobutylamino-3,4-dihydro-2H-1,4-benzoxazin-6-yl](phenyl)methanone (**2a**)*

3,4-Alkylaminophenol $\mathbf{3a}_{red}$ (142.5 mg, 0.5 mmol) and isobutylamine (1.0 mL, 10 mmol) were added to a 0.02 M solution of tetraethylammonium perchlorate (TEAP) (1.15 g, 5 mmol) as the supporting electrolyte in MeOH. The resulting solution was then oxidized under nitrogen, at room temperature, at a mercury pool whose potential was fixed at 0.0 mV versus SCE (initial current 50 mA). After exhaustive electrolysis (8 h, $n = 16$), that is, when a negligible current was recorded (1 mA), the solution was neutralized with dry ice and the solvent was removed under reduced pressure. The brown oil residue was then poured into diethyl ether (20 mL). Insoluble TEAP was filtered off and the filtrate was evaporated under reduced pressure, at 30 °C. Flash chromatography of the residue on silica gel with toluene as the eluent afforded 2-alkylamino-1,4-benzoxazine **2a** in 62% yield (110 mg,



Scheme 2.