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A Convenient Two-Step One-Pot Electrochemical Synthesis of Novel 8-Amino-1,4-benzoxazine Derivatives Possessing Anti-Stress Oxidative Properties.

Martine Largeron and Maurice-Bernard Fleury*

Laboratoire de Chimie Analytique et Electrochimie associé au CNRS, Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France.

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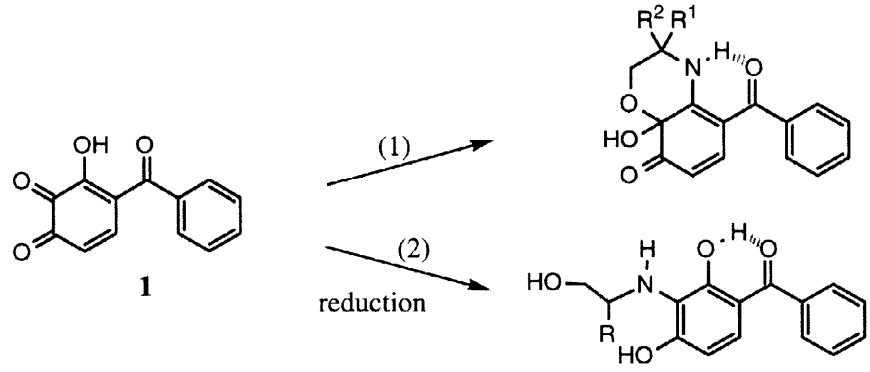
Abstract : Using (3,4-dihydroxy-2-methoxyphenyl) (phenyl) methanone as the starting material, the reaction of the electrogenerated 3,4-quinone with amino alcohols leads to the transient 1,4-benzoxazin-8-one species. The latter can undergo a subsequent addition reaction of an amine at the 8-position affording, after electrochemical reduction, novel 8-amino-1,4-benzoxazine derivatives. The entire sequence can be conducted in one-pot, without isolation of intermediates. © 1998 Elsevier Science Ltd. All rights reserved.

1,4-Benzoxazine derivatives are of interest because they exhibit diverse biological properties[1-4]. Earlier, we have described a simple one-pot electrochemical procedure for the synthesis of novel 1,4-benzoxazin-8-one derivatives possessing efficient anti-stress oxidative activity[5,6]. The key step consisted of the reaction of the transient electrogenerated 3,4-quinone **1** with amino alcohols [CH_2OH-C(R^1, R^2)-NH_2] at the 2-position [eqn.(1), scheme 1]. Nonetheless, the condition that neither R^1 nor R^2 could be an hydrogen atom considerably limited the scope of the electrochemical procedure with respect to synthetic applications. In this connection, we have recently reported that, in the presence of amino alcohols derived from natural amino acids (CH_2OH-CHR-NH_2), a competing reaction arose implying a nucleophilic attack of **1** at the 3-position rather than at the 2-position[7]. This reaction led, after electrochemical reduction, to novel 3,4-alkylaminophenol derivatives [eqn.(2), scheme 1].



Scheme 1

In the course of our investigations aimed at the preparation of molecules of pharmacological interest, we needed a simple procedure which would allow the rapid supply of a large number of diverse 1,4-benzoxazine derivatives for a preliminary *in vitro* screening. So, we envisioned some modifications of our previous electrochemical procedure. First, we chose to replace (2,3,4-trihydroxyphenyl) (phenyl) methanone by the corresponding 2-methoxy derivative as the starting material. Since the methoxy group constitutes a better leaving group than the hydroxy group, we thought that the substitution reaction at the 2-position of the transient electrogenerated 3,4-quinone would take place prior to the addition reaction at the 3-position. Second, in order to increase again the variety of molecules subject to biological evaluation, we planned to introduce an amino group into the 8-position of the 1,4-benzoxazine ring.

**Fax : 01 43 29 05 92, E-mail : fleury@pharmacie.univ-paris5.fr*

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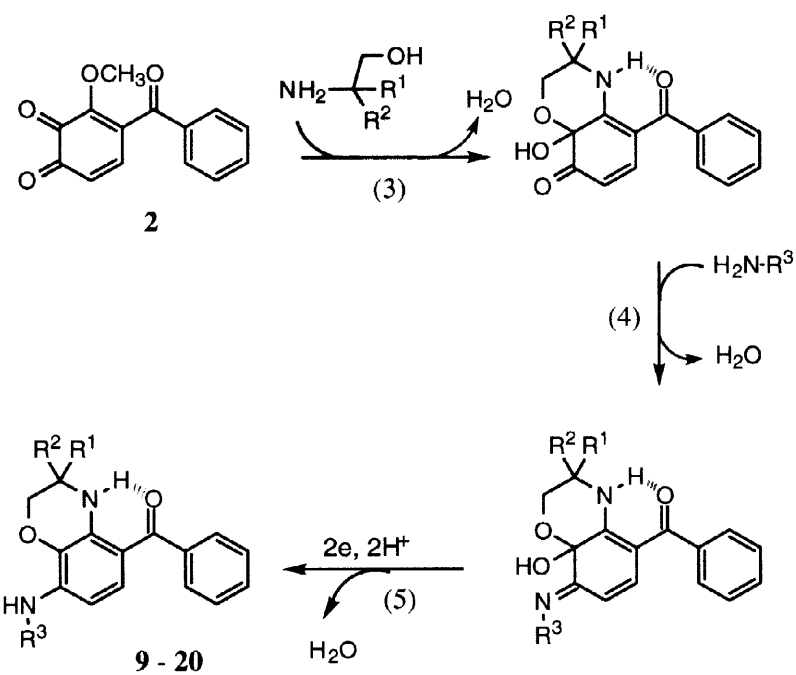
In this paper, we wish to report a convenient electrochemical procedure for the synthesis of 8-amino-1,4-benzoxazine derivatives. It is interesting to note that the entire reaction sequence can be conducted in a one-pot operation, without isolation of intermediates.

(3,4-Dihydroxy-2-methoxyphenyl) (phenyl) methanone was oxidized by controlled potential electrolysis, at room temperature, in methanol, in the presence of tetraethylammonium perchlorate as the supporting electrolyte and an excess of amino alcohol, in a three-compartment cell, at a platinum anode and platinum cathode[8]. When the potential of the platinum anode was fixed at + 0.4 V *vs* saturated calomel electrode (s.c.e.), *i.e.* at a potential immediately following the anodic peak observed in cyclic voltammetry, a coulometric value of 2.0 ± 0.1 was found for the number of electrons involved in the oxidation of one molecule of the starting material into the corresponding transient 3,4-quinone species **2**. As expected, the subsequent step consisted of a substitution reaction of the 2-methoxy group by the amino alcohol, affording, after intramolecular ring closure, the 1,4-benzoxazin-8-one derivatives **3-8** which could be isolated in good yields [eqn. (3), scheme 2]. However, the electrochemical procedure could be pursued without isolation of the latter : after exhaustive anodic electrolysis, an excess of amine R^3-NH_2 was added to the oxidized solution and allowed to react for thirty minutes. At that point, it should be noted that the voltammogram of the exhaustively oxidized solution exhibited a two-electrons cathodic peak Pc, at - 1.2 V *vs* s.c.e., which could be assigned to the reduction of the carbonyl group at the 8-position of the transient 1,4-benzoxazin-8-one species[6]. After the amine R^3-NH_2 was added, a decrease in the Pc intensity was observed, while a new cathodic peak Pc' developed at a less negative potential (- 0.9 V *vs* s.c.e.). The lack of peak Pc indicated that the carbonyl function at the 8-position was converted into a species more easily reducible than the carbonyl group. We hypothesized that Pc' corresponded to the reduction of the imine function generated at the 8-position [eqn. (4), scheme 2]. So, we thought that the latter could be stabilized through a reduction step [eqn. (5), scheme 2]. Therefore, after thirty minutes, the platinum anode was replaced by a mercury pool and the exhaustively oxidized solution was electrochemically reduced at - 1.0 V *vs* s.c.e., *i.e.* at a potential immediately following the cathodic peak Pc' observed in cyclic voltammetry. Finally, preparative scale electrolyses allowed the isolation of 8-amino-1,4-benzoxazine derivatives[8]. The results of some of our experiments are collected in table.

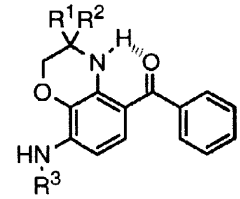
From these results, it appeared that the overall yield of this electrochemical procedure remained moderate. As the transient 1,4-benzoxazin-8-one species **3-8** were produced in good to excellent yields (scheme 2), we thought that the yield determining step consisted necessarily of the reaction of the C-8 carbonyl function with amine R^3-NH_2. So, we focused our attention on this reaction.

Compound	Yield %
3 : R^1 = H, R^2 = Bu^t	95
4 : R^1 = H, R^2 = Ph	68
5 : R^1 = H, R^2 = CH_2OH	65
6 : R^1 = H, R^2 = CH_3	70
7 : R^1 = H, R^2 = H	50
8 : R^1 = Ph, R^2 = Ph	75



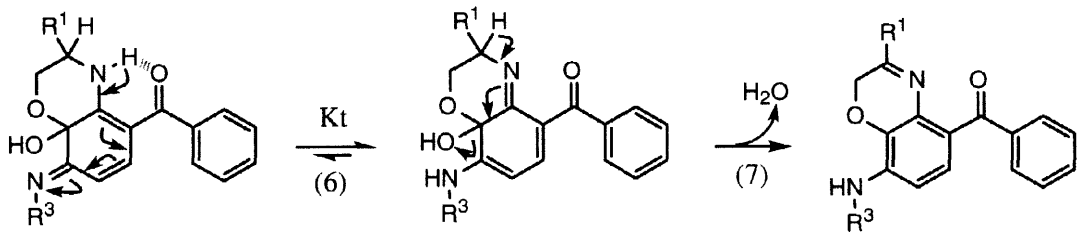
Scheme 2

Table
Yields of 8-amino-1,4-benzoxazine derivatives 9-20 isolated after controlled potential electrolyses in methanolic solution[8].

Entry	NH_2-C(R^1, R^2)-CH_2OH		NH_2-R^3		
	R^1	R^2	R^3	Product	Yield %
1	H	Bu^t	$(CH_2)_2$-Ph	**9**	50
2	H	Bu^t	Pe^i	**10**	45
3	H	Bu^t	CH_2-CH_2OH	**11**	50
4	H	Bu^t	Bzl	**12**	30
5	Ph	Ph	Pe^i	**13**	50
6	Ph	Ph	Bzl	**14**	50
7	CH_2OH	CH_2OH	CH_2-CH_2OH	**15**	60
8	CH_2OH	CH_2OH	Bzl	**16**	30
9	CH_2OH	Me	CH_2-CH_2OH	**17**	50
10	CH_2OH	Me	$CH(CH_2OH)_2$	**18**	25
11	H	CH_2OH	$CH(CH_2OH)_2$	**19**	15
12	H	Me	CH(Me)-CH_2OH	**20**	20

Abbreviations : tertiobutyl (Bu^t), isopentyl (Pe^i), benzyl (Bzl)

From these data, several observations could be drawn : a) within a series of 8-amino-1,4-benzoxazine derivatives bearing the same C-3 substituents, the yield failed with increasing steric hindrance of the R^3 substituents (entries 9-10 of the table). Accordingly, no 8-amino-1,4-benzoxazine derivative could be obtained when amino alcohols possessing a quaternary Cα atom were used as amines R^3-NH_2; b) whatever the nature of amines R^3-NH_2, yields of 8-amino-1,4-benzoxazine derivatives were suitable only when the 3-position was monosubstituted by a bulky group (entries 1-3) or disubstituted (entries 5-7). In contrast, no 8-amino-1,4-benzoxazine was obtained at all, starting from 1,4-benzoxazin-8-ones **4** and **7**. These results could be explained by the occurrence of subsequent tautomerization implying the hydrogen atom at the N-4 position, which shifted towards the C-8 position [eqn. (6)] .The mobility of this hydrogen atom markedly decreased with enhanced steric bulkiness around the amino group at N-4; c) in the particular case of **4**, a subsequent dehydration step [eqn. (7)] would occur leading to an imine function which is conjugated with the phenyl group at C-3. This step would aid the system to recover aromaticity (scheme 3). The resulting Schiff base would decompose, as it no longer could contract intramolecular hydrogen bonding between the 4-amino group of the benzoxazine moiety and the oxygen atom of the benzoyl substituent, needed to the stability of 1,4-benzoxazine derivatives[6].



Scheme 3

In summary, through the replacement of (2,3,4-trihydroxyphenyl) (phenyl) methanone by the corresponding 2-methoxy derivative as the starting material, we have developed a convenient general two-step one-pot electrochemical procedure for the synthesis of a series of novel 8-amino-1,4-benzoxazine derivatives. We thought that the moderate yields of these reactions are redeemed by the simplicity of our approach, as compounds **9-20** very likely would not be accessible by the general chemical methods available so far for the preparation of 1,4-benzoxazine derivatives[2,3,9-12]. These procedures would require indeed, as the starting materials, polysubstituted orthoaminophenols which are difficult to prepare, so that neither of these methods would be well suited to the synthesis of a series of 8-amino-1,4-benzoxazine derivatives for a rapid *in vitro* biological evaluation. As some of these novel compounds have shown promising anti-stress oxidative properties in preliminary assays, they have been protected by a patent[13].

Acknowledgements

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[[3-tertiobutyl-8-(2-hydroxyethyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-5-yl] [phenyl]methanone 11 : ^{1}H NMR (300 MHz, DMSO D_6) : δ 1.00 (s, 9H, Me, Bu^t), 3.10 (q, 2H, CH_2N, J = 6Hz), 3.25 [m, 1H, H(3)], 3.55 (q, 2H, CH_2OH, J = 6Hz), 3.90 [m, 1H, CH_2 (2)], 4.30 [dd, 1H, CH_2 (2), J = 10Hz, J = 3Hz], 4.80 [t, 1H, NH (8), J = 6Hz, D_2O exchanged], 5.60 [t, 1H, OH, J = 6Hz, D_2O exchanged], 6.00 [d, 1H, H (7), J = 8Hz], 6.85 [d, 1H, H (6), J = 8Hz], 7.50 (m, 5H, phenyl), 8.75 [s, 1H, NH (4), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6) : δ 26.9 (Me, Bu^t), 34.0 (Cq, Bu^t), 45.6 (CH_2N), 58.2 [CH(3)], 60.7 (CH_2OH), 65.8 [CH_2(2)], 99.7 [CH(7)], 109.0 (C-5), 127.4 (C-8a), 129.0, 129.2 and 130.8 [CH, phenyl and CH(6)], 139.7 (Cq, phenyl), 142.0 and 142.5 (C-8 and C-4a), 196.0 (CO, methanone); MS (DCI) : m/z = 355 (MH^+).

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