



A New Synthetic Route to 2-Oxazolines. The Electrochemical Reduction of N-(2,2-Dichloroethyl)amides as a Key Step

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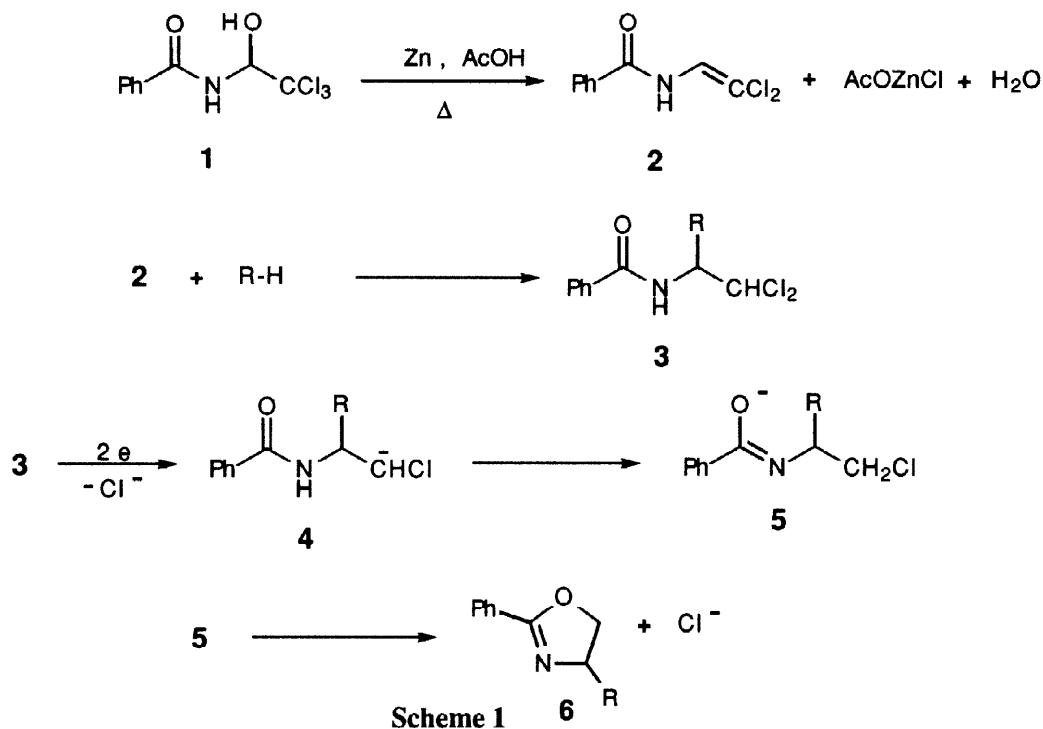
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Abstract : A convenient new method for the synthesis of 2-oxazolines has been established involving the preparation of N-(2,2-dichloroethyl)amides followed by electrochemical reductive cyclizations. It has been applied successfully in preparing previously unknown 4-alkylamino-2-phenyl-2-oxazolines in fair to good yields. © 1998 Elsevier Science Ltd. All rights reserved.

Over the years the chemistry of 2-oxazolines has been excellently reviewed.¹ These compounds are of great interest because they can be used as versatile synthetic intermediates,^{1e-g} as therapeutic agents^{1c} as well as in a wide variety of applications.^{1c} Especially remarkable is the vast number of transformations recently reported that have caused a renewed interest in the progress of the synthesis of 2-oxazolines.^{1g} Regarding the described methods for the formation of this heterocyclic system, it is apparent that β -amino alcohols are commonly preferred for simple preparations. Carboxylic acids and some β -amino alcohols lead directly to 2-oxazolines by reaction at high temperature assisted by water removal. A related but more general procedure involves the use of previously prepared hydroxyamides followed by treatment with thionyl chloride. Then cyclization of chloroamides formed is carried out in a strong basic medium. The drastic experimental conditions and the indiscriminate reactivity of thionyl chloride are severe limiting factors for the scope of these procedures, which have been substantially improved by using specific reagents.² However, the number of β -amino alcohols or β -chloroamines available is another important synthetic limitation. Given the above, the development of alternative methods to increase the number of available 2-oxazolines has been a subject of intensive and permanent activity since many years.¹ A number of intermediates (enamines, epoxides, aziridines, ylides, isocyanides, etc.) have been found useful for specific preparations.^{1g}

As a result of our research project in electrochemical synthesis of heterocyclic compounds,³ we herein report a new and efficient entry to 2-oxazolines which is shown in Scheme 1. Chloralamides⁴ are easily

available from chloral and amides, and are efficiently transformed into N-(2,2-dichlorovinyl)amides⁵ whose particular reactivity⁶ allows the addition of alkylamines under mild conditions. The addition of aromatic compounds⁷ also takes place at low temperature under strong acid catalysis. Following this reaction sequence products **1**, **2** and **3** were prepared. A direct electrochemical conversion of intermediates **3** into the corresponding oxazolines **6** was attempted successfully. Products **6 a - g** were isolated in fair to good yields.



*Table 1. Preparation of oxazolines **6** by cathodic reduction of **3**.*

Entry	R	Yield (%)
6a	C ₆ H ₅ CH ₂ NH	72
6b	C ₆ H ₁₁ NH	60
6c	(CH ₃) ₂ CHNH	68
6d	CH ₃ CH ₂ CH ₂ NH	65
6e	CH ₃ NH	92
6f	(CH ₃ CH ₂) ₂ N	73
6g	C ₆ H ₅	78

Cathodic reductions of products **3** were carried out in aprotic medium. The electricity consumption was 2 F/mol. After electrolysis, fully dechlorinated products were isolated and were identified by IR, EI MS, FAB MS, NMR spectroscopy and microanalyses as the corresponding 2-oxazolines **6**. The results are summarized in Table 1. 4-alkylamino-2-phenyl-2-oxazolines **6 a - f** were new 2-oxazolines, whereas the preparation of 2,4-diphenyl-2-oxazoline **6 g** has been previously described.^{2a,e} The reported data were coincident. The formation of products **6** (Scheme 1) can be reasonably explained on the basis of a two-electron selective cathodic cleavage of one carbon - chlorine bond with generation of the chlorocarbene intermediates **4** which would

generate the amide anions **5**. Therefore, the cyclization would occur by nucleophilic displacement of the remaining chlorine atom.

It should be noted that the described preparative procedure shows several valuable synthetic features: (1) Inexpensive and commercially available starting materials are used. (2) In contrast with other procedures involving halogenoamides, many synthetic problems associated with the lack of selectivity of halogenating reagents can be avoided. (3) As mentioned above, the cyclization of halogenoamides commonly requires strongly basic media. However, the intermediates **3** contain a probase⁸ centre which upon electron transfer is activated and internally neutralized. Therefore, the reaction medium remains close to neutrality. (4) Since there is a great variety of well known addition reactions to alkenes, type **2** products seem to be promising intermediates in allowing the preparation of a diversity of substituted 2-oxazolines.

In conclusion, an effective new method for the synthesis of 2-oxazolines is reported. Good yields, easy availability of starting materials and the mild reaction conditions are valuable advantages of the procedure which gives access to previously unattainable compounds.

On the other hand, it is also to be pointed out that electroreductive dehalogenation of gem-polyhalogenated compounds has been studied from different points of view.⁹ However, the cathodic reductions of derivatives of type **3** had remained unknown. In this work a specially useful reaction mode has been found. Crucially, after the generation of the carbanionic intermediates **4** the negative charge can be transferred to a remote heteroatom. Due to structural peculiarities of the formed intermediates **5** (presence of two suitably placed centres with opposite activity) a heterocyclization process takes place easily. It seems feasible that other classes of gem-polyhalides would also be useful intermediates for preparing a variety of heterocyclic compounds.

General Electrolysis Procedure

Preparative electrolyses were carried out under a constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reductions were performed in anhydrous MeCN - Bu₄NClO₄, 0.4 M of which 35 mL and 15 mL, approximately, were placed respectively in the cathodic and the anodic compartments. Anhydrous sodium carbonate (3 g) was placed in the anode compartment to prevent accumulation of electrogenerated acid. Solutions of compounds **3** (5 mmol) were electrolyzed under a cathodic potential of - 2.05 V vs SCE. The electricity consumption was 2 F/mol in all cases. All electrolysis products were isolated by removing the solvent in vacuo. The residue was then shaken with ether (3 x 50 mL) over a period of 30 min. The ethereal solutions were combined and concentrated leaving oily crude products **6** in high purity state¹⁰ which were purified by column chromatography on silica gel (ethyl acetate or ethyl acetate - hexane 1:1). The isolated purified products **6** were viscous oils that gave satisfactory elemental and spectroscopic analyses.¹¹

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10. i.r. and ^{13}C n.m.r. spectra for crude and purified products were recorded showing negligible differences.
11. The spectral data for product **6a** are reported as an example of spectroscopic properties of this class of compound: ^1H n.m.r. δ (CDCl_3 , 300 MHz): 2.79 (br s, 1H), 3.91 (d, 1H, $J = 13.2$ Hz), 4.03-4.08 (m, 2H), 4.45 (t, 1H, $J = 9.0$ Hz), 5.22 (dd, 1H, $J = 8.7$ Hz, $J = 6.6$ Hz), 7.22-7.47 (m, 8H), 7.98 (dd, 2H, $J = 8.4$ Hz, $J = 1.5$ Hz); ^{13}C n.m.r. δ (CDCl_3 , 75.4 MHz): 49.19, 71.93, 80.85, 126.89, 127.60, 128.14, 128.24, 128.28, 128.31, 131.47, 139.90, 164.56; m.s.; m/z (%): 251 ($\text{M}^+ - \text{H}$, 28), 131 (72), 118 (44), 104 (63), 91 (100), 77 (31); FAB: 253 [$(\text{M} + \text{H})^+$, 100]; i.r.: 3268, 1643, 1452, 1372, 1249, 1139, 1088, 1025, 956, 744, 694 cm^{-1} .