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A new and efficient electrochemical ring opening of 7-oxanorbornene systems via a modified Ritter reaction: direct approach to bicyclic valienamine analogues

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Abstract—Electrogenerated acids (EGA), produced by controlled potential electrolysis in acetonitrile at a platinum electrode, permitted the oxa-ring opening and the acetamidation of the 7-oxanorbornene system of **4**. It opens in one step a new route to bicyclic valienamine analogues **3**. © 2001 Elsevier Science Ltd. All rights reserved.

Acarbose (**1**) (Fig. 1), an α-glucosidase inhibitor and a clinically useful drug for the treatment of type II diabetes, was isolated from the fermentation broth of *Actinoplanes* sp.[1] The valienamine (**2**), carbocyclic core (Fig. 1) of acarbose, has long been recognized as the crucial element, responsible for the inhibitory effect of this compound. In fact, valienamine (**2**) as well as some of its derivatives, inhibit the same α-processing enzymes.[2] Various methods for the synthesis of these molecules have been developed.[3]

With the aim of the obtaining of new glycosidases inhibitors, we became interested in the racemic synthesis of bicyclic valienamine analogues such as **3**, using 3,7-dinitro-11-oxatricycloundec-9-ene (**4**) as the starting material (Fig. 1). The synthesis of this latter compound was recently reported by our group.[4]

To retain the essential pattern of valienamine (**2**), including amino and hydroxyl substituents as well as an unsatured carbocyclic unit, we envisioned opening the oxa ring of **4** by a Ritter reaction as a means of introducing a potential amino function. In its most general form, the Ritter reaction[5] involves the formation of *N*-substituted amides by the addition of nitriles to alkenes or alcohols. This proceeds via a carbonium ion intermediate in the presence of concentrated sulfuric acid. However, the scope of the method suffers severe limitations, due to the required strong acid medium. Indeed, we observed[4] that treating **4** with triflic anhydride afforded, after dehydration, the tetralin **5** (Scheme 1). This result was confirmed when we tried to open the 7-oxanorbornene system using Vogel's conditions[6] of the modified Ritter reaction. The use of CF_3SO_3H as the acid-promoter gave compound **6** as the major isolated product (Scheme 1).[7]

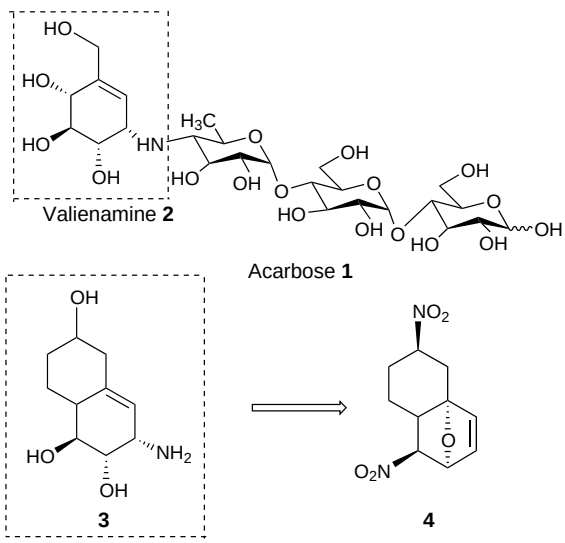

Figure 1.

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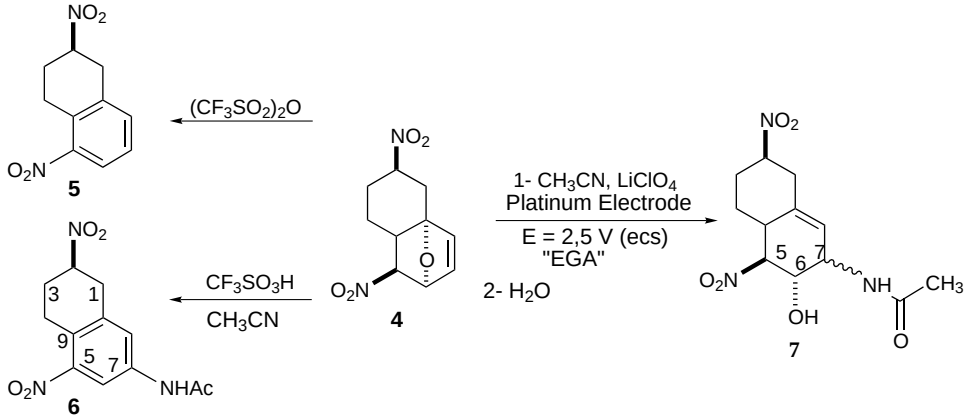


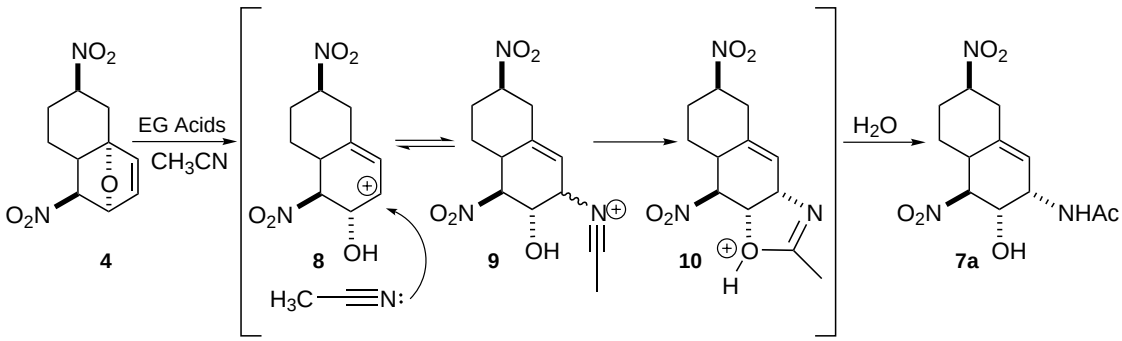
Scheme 1.

Several modified methodologies[8] employing relatively mild conditions have been developed to overcome this problem. The electrogenerated acids (EGA) chemistry[9] can be considered as a 'mild acidic' modification of the Ritter method.[10] EGA are typically formed at an anode as a side product of the electrochemical process. The overall electrolysis generates a base at the cathode and the area surrounding the anode can become acidic. Hence, electrolysis offers an interesting opportunity to promote acid-catalyzed reactions, while maintaining overall neutral conditions.

Although **4** is not oxidizable as shown using cyclic voltametric method, the electrochemical reaction (Scheme 1) was performed in acetonitrile at a platinum anode ($E=2.5$ V ecs) with lithium perchlorate as a supporting electrolyte. Under those conditions EGA were produced and the two diastereomers **7** were obtained in 56% overall yield, as a 8/2 *cis*/*trans* mixture. The relative *cis* configuration of the major product **7a** was easily deduced from the ^{1}H NMR spectra ($J_{\text{H-5/H-6}}=11$ Hz, $J_{\text{H-6/H-7}}=5$ Hz).[11]

A mechanism involving a carbonium ion intermediate, as suggested by Ritter, can be applied to this case, to explain the formation of the two diastereomers of **7**. In contrast, molecular models did not show a sterically hindered face of the carbonium ion intermediate accounting for the 8/2, *cis*/*trans* ratio. Nevertheless, another Ritter type reaction of 1,2-indanediols with acetonitrile has been exploited for their stereocontrolled conversion to *cis*-amino alcohols.[12] The relative configuration of the newly formed amino function was controlled through intermediate formation of a *cis*-methyloxazoline ring involving the configurationally unmodified α-alcohol group. This result may suggest that the mechanism of the reaction (Scheme 2), most probably proceed via an equilibrium between **8** and **9**, which may be displaced by the conformationally driven formation of the *cis*-fused methyl oxazoline ring of **10**, followed by its opening in the presence of water.

In summary, we describe here a new and efficient method for the oxa ring opening of the 7-oxanorbornene system, which gives an easy access to the valienamine pattern system (unsaturation, amino- and hydroxyl- groups in the correct positions). As recently outlined by Moeller[13] electrochemistry complements the existing methodology and opens entirely new strategies for the synthesis of complex molecules. The mild reaction conditions, good yields and convenience of the weakly acidic media, which eliminates the undesired dehydration step, make this method an attractive and useful complement to the present methodology. An entry to new bicyclic valienamine analogues **3** (Fig. 1) from compound **7a**, in two steps by a Nef reaction followed by the reduction of resulting carbonyles, is currently under study.



Scheme 2.

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7. 7-*Acetylamino*-2,5-*dinitro*-1,2,3,4-*tetrahydronaphthalene* (**6**): CF_3SO_3H (288 μL, 3.25 mmol) was added to a solution of 3,7-dinitro-11-oxatricycloundec-9-ene **4** (150 mg, 0.6 mmol) in MeCN and (5 mL) cooled to 0°C. After stirring at 0°C for 5 min, the reaction was allowed to warm to 20°C and stirred for an additional 10 min. The reaction was checked by TLC and then quenched with ice-cold saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL four times). The combined organic extracts were dried (Na_2SO_4), and after solvent evaporation in vacuo the residue was purified by flash chromatography (cyclohexane/ethyl acetate 7:3) giving 60 mg of **6** (36%). IR (ν cm^{-1}): 3274, 2919, 1676, 1532; ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.21 (s, 3H, Me), 2.3–2.5 (m, 2H, H-4 and H-5), 3.05–3.15 (m, 2H, H-4 and H-5), 3.37 (dd, $J=17$, 5 Hz, 1H, H-2), 3.49 (dd, $J=17$, 8 Hz, 1H, H-2), 4.8–4.9 (m, 1H, H-3), 7.46 (s, 1H, NH), 7.74 (s, 1H, H-8 or H-10), 7.89 (s, 1H, H-8 or H-10); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 23.5 (C5), 24.5 (Me), 26.8 (C4), 33.2 (C2), 79.9 (C3), 114.5 (C8 or C10), 124.4 (C8 or C10), 125.0 (C6), 135.9 (C9), 136.8 (C1), 149.4 (C7), 168.6 (CO). MS (CI/NH_3): m/z 297 $(M+18)^+$.
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11. 7-*Acetylamino*-6-*hydroxy*-2,5-*dinitro*-1,2,3,4,5,6,7,10-*octahydronaphthalene* (**7a**): **4** (150 mg, 0.6 mmol) was dissolved in acetonitrile (100 mL) containing lithium perchlorate (500 mg, 5 mmol) as supporting electrolyte. The resulting solution was oxidized ($E=2.5$ V ecs), at a platinum electrode, under nitrogen, using a two compartments cell. When 2.5 F/mol of electricity was passed through the solvent was removed by distillation and the residue was diluted in ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was then purified by flash chromatography (ethyl acetate:cyclohexane; 4:6) to give the bicyclic acetamides **7** (90 mg, 56%). IR (ν cm^{-1}): 3319, 2908, 1649, 1543; ^1H NMR (300 MHz, MeOD, δ, ppm): 1.51 (ddd, $J=13$, 12, 2.5 Hz, 1H, H-5), 1.9–2.2 (m, 5H, H-4, H-5, Me), 2.4–2.5 (m, 1H, H-4), 2.72 (dt, $J=13$, 1.5 Hz, 1H, H-2), 2.8–2.9 (m, 1H, H-6), 3.08 (ddd, $J=13$, 4, 2.5 Hz, 1H, H-2), 4.35 (dd, $J=11$, 5 Hz, 1H, H-8), 4.5–4.6 (m, 1H, H-3), 4.62 (dd, $J=11$, 9 Hz, 1H, H-7), 4.82 (t, $J=5$ Hz, 1H, H-9), 5.69 (d, $J=5$ Hz, 1H, H-10); ^{13}C NMR (75 MHz, MeOD, δ, ppm): 22.7 (Me), 29.1 (C5), 30.5 (C4), 38.7 (C2), 42.2 (C6), 49.5 (C9), 70.4 (C8), 84.2 (C3), 92.2 (C7), 122.6 (C10), 136.8 (C1), 172.5 (CO); MS (CI/NH_3): m/z 317 $(M+18)^+$.
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