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COMMUNICATION

Electrochemical Synthesis of 3a-Bromofuranindolines and 3a-Bromopyrroloindolines Mediated by MgBr₂.

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We report an efficient and environmentally friendly electrochemical approach to perform the bromo cyclization of tryptophol, tryptamine and tryptophan derivatives. The 3a-bromofuranindolines and 3a-bromopyrroloindolines obtained are of interest in the total synthesis of natural products. This dearomative procedure relies on the generation of an electrophilic bromine reagent by the electrochemical oxidation of MgBr₂. No organic byproducts are generated with this protocol which avoids the use of an additional electrolyte.

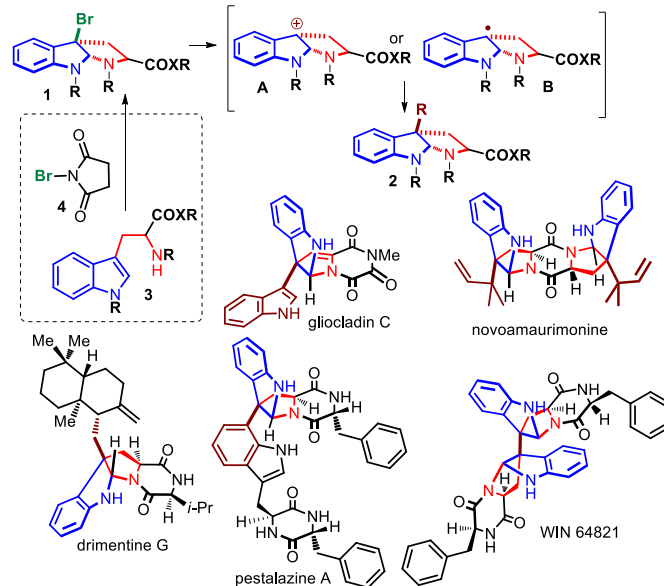
3a-Bromopyrroloindolines **1** are versatile building blocks in which the carbon-bromide bond could be involved in a substitution reaction with retention of configuration in order to form stereospecifically a new C-C, C-N or C-O bond yielding functionalized pyrroloindolines **2** via carbocation **A** or radical intermediate **B**.¹ Such approaches are widely deployed to access tryptophan-derived natural products as exemplified by the total syntheses of WIN 64821, pestalazine A, drimentine G, gliocladin C or novoamaurimonine among others.² 3a-Bromopyrroloindolines **1** are usually synthesized by the treatment of tryptophan derivatives **3** with a stoichiometric electrophilic bromine reagent such as NBS **4**.^{1,2} Reaction with the nucleophilic C3 position of the indole nucleus allows to form 3a-bromopyrroloindolines **1**.

More recently, bromides and others halides salts in combination with stoichiometric oxidants were also employed via the *in-situ* generation of electrophilic halogen reagents to achieve such transformations.^{3,4} In particular, the group of Tong, reported the combination of KBr and oxone to reduce the amount of organic wastes produced.⁴

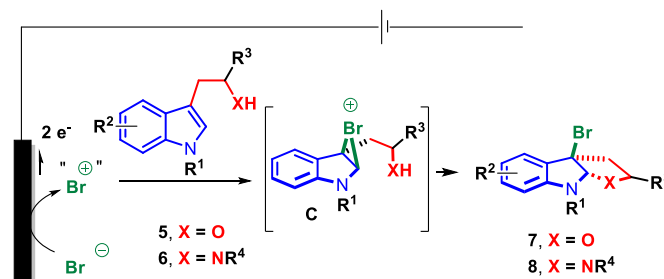
In this context, we would like to report an electrochemical protocol for the dearomative halocyclization of tryptophol **5**,

tryptamine and tryptophan derivatives **6** which avoids the use of an external oxidant and therefore the formation of organic wastes to form the corresponding 3a-bromofuranindolines **7** and 3a-bromopyrroloindolines **8** (Scheme 2).

Scheme 1. Classical synthesis of 3a-bromopyrroloindolines and their importance in natural product synthesis.



Scheme 2. Anodic oxidation of bromide salts for the bromocyclization of indoles.



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Electrochemistry is emerging as a powerful and sustainable tool⁵ to achieve dearomatization reactions of (hetero)arenes⁶ and in particular indoles.⁷

In line with our interest in the development of oxidative dearomatization reactions of indoles,^{8,9} we recently reported a general electrochemical dearomative dialkoxylolation and diazidation of indoles.¹⁰ As in previous works,^{7b,c,e} this reaction proceeds via the direct oxidation at the anode of the indole nucleus into a radical cation. In contrast, to achieve an electrochemical dearomative bromocyclization of 3-substituted indoles into 3a-bromopyrroloindolines, we planned to rely on the anodic oxidation of a bromide salt into an electrophilic specie that would be intercepted by the nucleophilic indole of **5** or **6** to form bromonium ion **C** which would be converted into **7** or **8** while protons would be reduced into H₂ at the cathode.

Indeed, the electrochemical oxidation of halides is known and is a clean halogenation method for alkenes, alkynes or (hetero)arenes¹¹ including indoles.¹² However, in this study, we would like to deploy electrogenerated electrophilic halogen intermediates in dearomatization reactions (Scheme 2).

In addition to be the source of the electrophilic reagent, we expect that the bromide salt would also act as an electrolyte which would avoid the use of an additional electrolyte and therefore reduce the wastes of this process.

After an initial evaluation of different parameters (see SI), we identified that we could achieve the expected electrochemical transformation either in a galvanostatic mode with a constant current of 4.5 mA/cm² or in a potentiostatic mode with a constant cell potential of 5 V. Both these set of conditions involved to perform the electrolysis in an undivided cell with a graphite anode and platinum-plated cathode in a 4:1 mixture of acetonitrile and water at room temperature. Among the bromide salts tested, we found out that it was optimal to use 1 equivalent of MgBr₂ as source of bromide and as electrolyte.

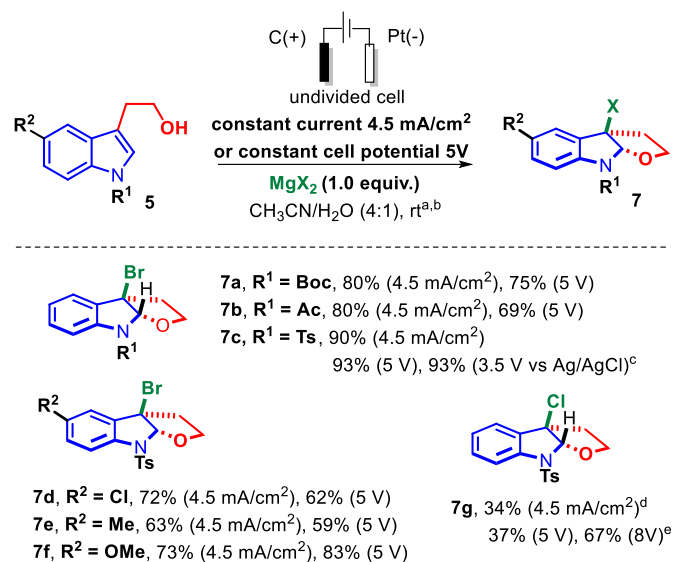
We first studied the scope of the bromocyclisation of tryptophol derivatives **5** into bromofuranoidolines **7** (Scheme 3). Various protecting groups of the indole nitrogen such as Boc, acetyl and tosyl were successfully evaluated leading to **7a-c**. It was also possible to operate at a constant potential of 3.5 V at the anode vs an Ag/AgCl reference electrode instead of a constant potential between the anode and the cathode for **7c**. Tryptophol derivatives bearing substituents on the benzene part of the indole led to the formation of 3a-bromofuranoidolines **7d-f** whether a chloro or a donating group (methyl and methoxy) is present. Replacing MgBr₂ by MgCl₂ delivered the corresponding 3a-chlorofuranoidoline **7g** albeit in a lower yield.

We then turned our attention towards the synthesis of 3a-bromopyrroloindolines from protected tryptamines (Scheme 4). In addition to N,N'-diBoc bromopyrroloindoline **8a**, different combinations of orthogonal protecting groups of the indole and amine nitrogens were assessed. N-Boc,N'-Cbz and N-Boc,N'-CO₂Me bromopyrroloindolines **8b,c** were thus obtained. A tosyl group could also be present on the indole nitrogen in combination with Boc, Cbz and CO₂Me protecting groups of the primary amine leading to compounds **8d-f**. Substitution of the

benzene part is tolerated as demonstrated with 6-bromo indolines **8g-i** and 5-methyl indoline **8j**.

Subsequently, we decided to evaluate the bromo-cyclization of diversely protected (L) and (D)-tryptophan derivatives leading respectively to **8k-m** and **8n,o**. The cyclization proceeded with an *exo* selectivity as demonstrated by the X-ray crystal structure of **8n**.

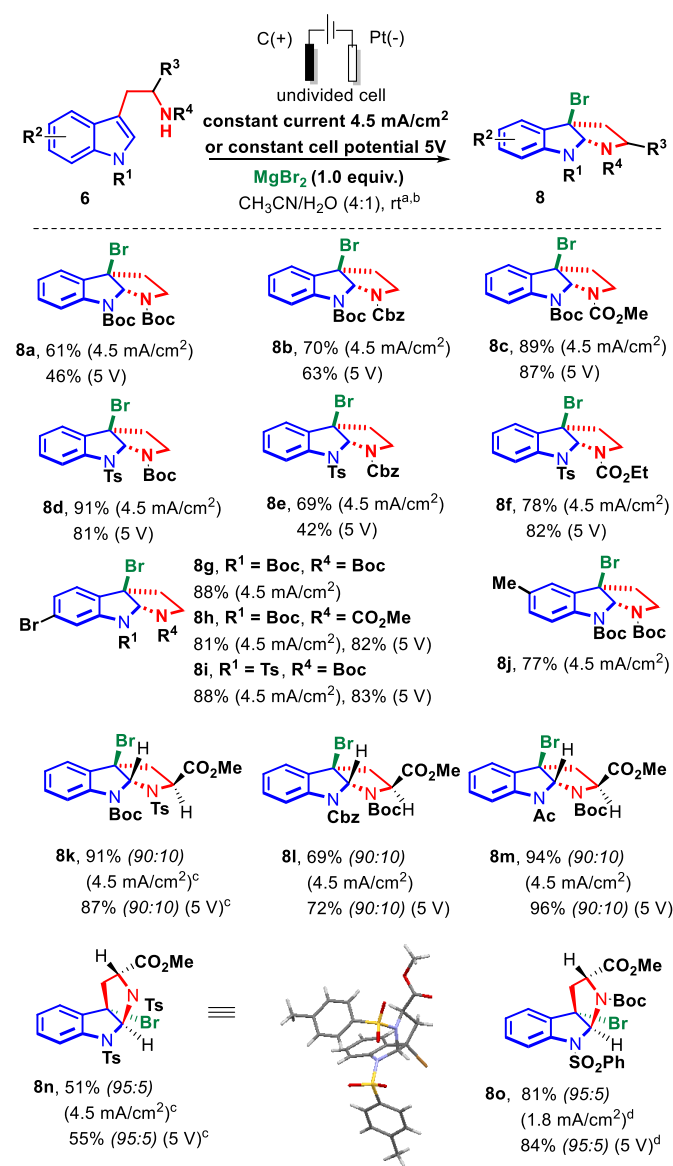
Scheme 3. Electrochemical dearomative halocyclization of tryptophol derivatives.



a) Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), constant current of 5 mA or constant potential of 5 V between the electrodes, **5** (0.2 mmol), MgBr₂ (0.2 mmol), CH₃CN/H₂O (4 mL/1 mL), room temperature; b) isolated yields are indicated (dr > 95:5); c) constant potential of 3.5 V at the anode vs a Ag/AgCl (3M aq. KCl) ref electrode; d) MgCl₂ was used instead of MgBr₂; e) constant cell potential of 8V.

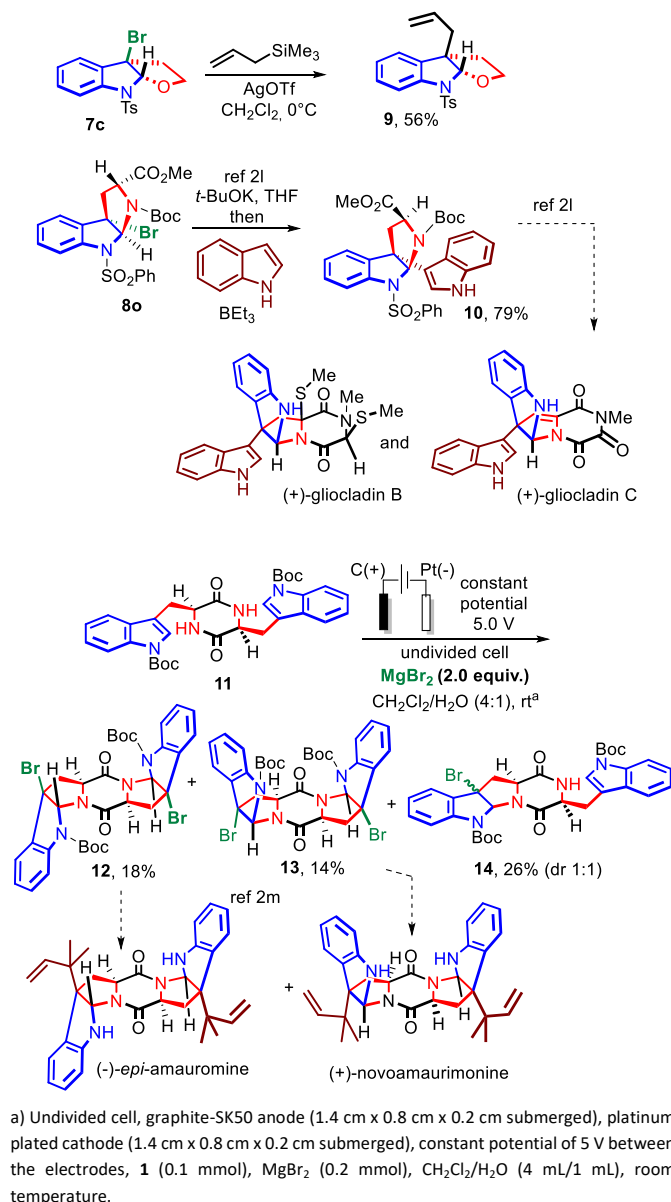
We were then eager to demonstrate the synthetic utility of the products obtained by this electrochemical halocyclization (Scheme 5). Indeed, it is well known that the bromide atom of 3a-bromoidolines such as **8** could be substituted by various functional groups.^{1,2} Therefore, allylfuranoidoline **9** was obtained by treating 3a-bromofuranoidoline **7c** with allylsilane and AgOTf.¹⁸ As described by Ye, *exo*-3a-bromopyrroloindoline **8o** obtained from D-tryptophan could be converted by the addition of indole in presence of *t*-BuOK and triethylborane into *endo*-3a-indolyl-pyrroloindoline **10** which is an intermediate of the synthesis of glioclodins B and C.²¹

Application of the electrochemical bromocyclization to (L)-tryptophan-derived diketopiperazine **11** with 2 equivalents of MgBr₂ resulted in a double bromo-cyclisation to yield *exo-endo* compound **12** and *endo-endo* compound **13** which were respectively converted by Tokuyama into (–)-*epi*-amauromine and (+)-*novo*amauromine.^{2m} This procedure is competitive with the use of NBS by Tokuyama which required to perform 2 steps the double bromocyclisation.^{2m}

Scheme 4. Electrochemical dearomative bromocyclization of tryptamine and tryptophan derivatives.

a) Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), constant current of 5 mA or constant potential of 5 V between the electrodes, **6** (0.2 mmol), MgBr₂ (0.2 mmol), CH₃CN/H₂O (4 mL/1 mL), room temperature; b) isolated yields are indicated (*dr* > 95:5 unless otherwise noted in parenthesis); c) on 0.1 mmol of **6** and MgBr₂ in CH₃CN/H₂O (4 mL/1 mL); d) on 0.6 mmol of **6** and MgBr₂ (0.6 mmol) in CH₃CN/H₂O (12 mL/3 mL), anode (3.4 cm x 0.8 cm x 0.2 cm submerged), cathode (3.4 cm x 0.8 cm x 0.2 cm submerged).

Cyclic voltammetry (CV, see SI) of the reactants in acetonitrile and water showed oxidation of MgBr₂ at a lower potential than NTs-tryptophol **7a**. The oxidation peak observed (1.3 V vs SCE) during the CV of MgBr₂ seems to correspond to the formation of Br₂.^{11,13} In presence of N-Ts tryptophol **7a**, a net increase of the intensity of this oxidation wave is observed. This observation might be in favour of the oxidation of MgBr₂ at the anode into an electrophilic bromine reagent that would react with the C2=C3 bond of indoles to form the bromonium bridge **C** (Scheme 1).¹⁴

Scheme 5. Synthetic applications.

Conclusion

In conclusion we developed a general electrochemical bromocyclization of tryptophol, tryptamine and tryptophan derivatives via the anodic oxidation of MgBr₂ into an electrophilic bromine reagent which could oxidized the indole nucleus into bromofuranoindolines and bromopyranoindolines. This protocol avoids the use of an additional electrolyte and of an external oxidant.

Conflicts of interest

“There are no conflicts to declare”.

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† Electrochemical reactions were performed with ElectraSyn 2.0 package (IKA). CCDC 1910836 (**8n**) contains the supplementary crystallographic data for this paper.

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- In the potentiostatic mode, the difference of potential between the two electrodes may seem high and it could be argue that both bromide ions and the indole nucleus of **6** or **7** could be oxidized simultaneously. However, this high difference of potential may be attributed to the high resistance of the reaction mixture.