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Quick and easy access to N-Mannich bases of 1-isoindolinones by catalytic electroactivation of primary and secondary amines and tandem reaction with 2-formylbenzonitriles

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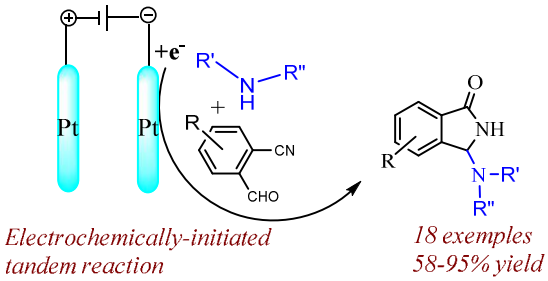

Electrochemically-initiated tandem reaction between 2-formylbenzonitriles and amines successfully leads to N-Mannich bases of 1-isoindolinones. Enantiopure isoindolinones have been obtained by resolution with chiral amines

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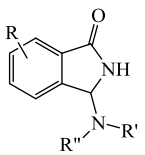
N-Mannich bases of 1-isoindolinones can be rapidly assembled by reacting 2-formylbenzonitriles with electroactivated amines on a Pt cathode, using catalytic amount of electricity. Usefully, chiral non-racemic amines allow the attainment of enantiopure N-Mannich bases by simple chromatographic separation.

The construction of heterocyclic cores and, at once, the introduction of several different functionalities on the selected molecular target is the subject of the big part of the current literature in organic synthesis. Nowadays, cascade and multicomponent reactions[1] are the most common approaches to achieve this goal and are specially applied to the attainment of heterocyclic scaffolds with potential bio- and pharmacological activity. Due to their relevance in medicinal chemistry, in these last years, we have become interested in the design and synthesis of 3-substituted isoindolinone derivatives,[2] easily accessible by reacting 2-formylbenzonitriles with suitable carbon nucleophiles, using chemical[3] or electrochemical[4] catalytic systems. In particular, eco- and atom-economy, efficiency and readiness of the electrochemical approach,[5] prompted us to check if other useful nucleophiles could be electroactivated and used in a similar way. Intrigued by the possibility to introduce an exocyclic nitrogen atom on the third position of the isoindolinonic ring, we firstly focused our attention on amino compounds. In this work we wish to present our results concerning the tandem reaction of 2-formylbenzonitriles with electroactivated primary and secondary amines to afford N-Mannich bases **1**, a class of compounds with easily conceivable versatility for a wide gamut of applications ranging from pharmacology, use as intermediates in drug synthesis, as well as ligands for catalytic purposes.[6]



1

Despite their potential, a literature survey reveals that, after the pioneering study by R. Sato[7] which shows the un-catalyzed access to compounds **1** when a large excess (more than 2000-fold molar excess) of amine is used, no more convenient catalyzed procedures have been reported starting from 2-formylbenzonitriles. However, other routes have been proposed (for ex., the reaction of aldimines with isocyanates by a renhium catalyst),[8] so demonstrating the interest for these kind of heterocyclic scaffolds.[9]

Although simple amines are well-known nonreducible compounds at the Pt-cathode, previous investigations by one of the authors[10] and

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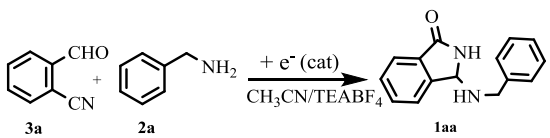
others[11] clearly demonstrated their indirect electrochemical activation in the addition reaction with weak electrophiles as CO_2 gas, *via* electrogenerated cyanomethyl anion or *via* $CO_2^{\cdot-}$. Taking into account these studies, benzylamine (**2a**), chosen as model compound, has been electrolyzed in the cathodic side of a U-shaped two-compartments cell, in the presence of 2-formylbenzonitrile as electrophile, under a variety of experimental conditions (table 1). Interestingly, while pre-electrolyzed solutions of $CH_3CN/Et_4N^+BF_4^-$ and $CH_3CN/Et_4N^+BF_4^-$ / 2-CNC_6H_4CHO (entry 1-2) were found completely ineffective as catalytic system even after long reaction time, N-Mannich base **1aa** was obtained in very good yield by performing constant current electrolysis in the presence of **2a** and 2-formylbenzonitrile **3a** (entry 3). On the other hand, under these last conditions, the current efficiency of the process is strikingly high, since a quantitative conversion of the starting materials is at once achieved by using only 2.5% of electricity. Although the electrochemical mechanism by which the reaction is initiated is not clear in details, such a good turnover of the electron transfer process is highly desirable also in terms of atom-economy since, in parallel, it can drastically reduce the amount of supporting electrolyte required to carry out the electrolysis.[12]

Table 1. Electrochemically-initiated tandem reaction of **2a** with **3a**



Entry	Q (e/molecule of 3a)	3a Conversion	1aa Yield
1[a]	0.05	-	-
2[b]	0.05	-	-
3[c]	0.025	100%	95%

[a)] A solution of $CH_3CN/Et_4N^+BF_4^-$ was pre-electrolyzed under galvanostatic condition using a current quantity as reported in table. **2a** and **3a** were added to the cathodic compartment after the current was switched off. [b)] The electrolysis was performed in the presence of **3a**. **2a** was added after the current was switched off. [c)] The electrolysis was performed in the presence of **2a** and **3a**.

Taking into accounts these experiments, we hypothesized a reaction pathway which involves the electrochemically-iniziated deprotonation of the hemiaminal intermediate **A**, and the subsequent cascade of reactions (cyclization-rearrangement)[7,13] as depicted in figure 1.

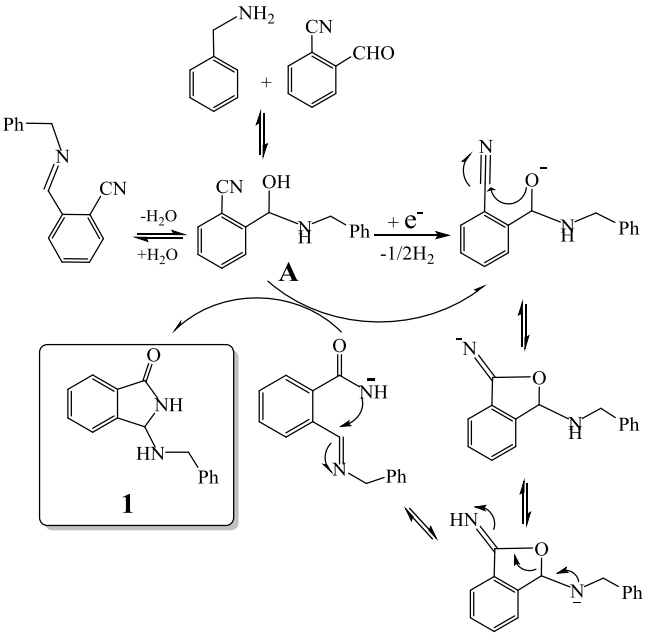


Figure 1. Proposed reaction pathway for the electrochemically-initiated tandem reaction of amines with 2-formylbenzonitriles

With the optimized set of conditions in hand, the electrochemically-induced cascade reaction was investigated using different amines substrates **2a-k** (Figure 2). Table 2 summarizes the variety of N-Mannich bases accessible through the reaction of primary and secondary amines with 2-formylbenzonitriles (**3a,b**). The reaction was found to be general and successful both with primary and secondary alkyl- and benzyl-amines, as the products have been obtained with very good yields and complete regioselectivity in almost the cases. A slight decrease of the yields (as well as an increase of the reaction times) was observed only for amines **2e** and **2g**, probably because of the steric hindrance of these substrates. However, the reaction with amine **2k**, which is scarcely soluble in the electrolysis solvent, did not occur, either by using larger amount of current quantity (up to 1 electron/ molecule) or by prolonging the reaction time.

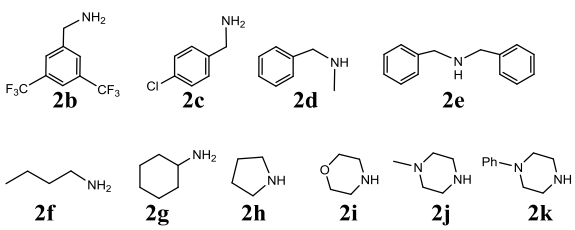


Figure 2. List of amines tested in the tandem reaction with **3a,b**

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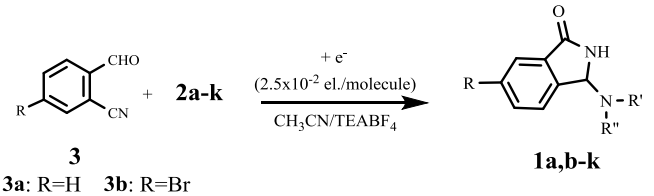
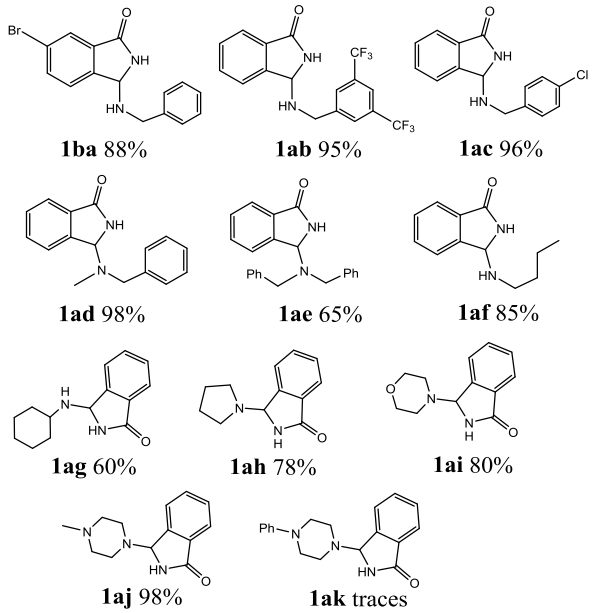
Table 2. Electrochemically-initiated tandem reaction of amines **2a-k** with **3a,b**



3
3a: R=H **3b**: R=Br

1a,b-k



In view of a potential use of compounds **1** as chiral ligands or as pharmaceutical agents, in a follow up of this investigation, we focused our attention on the possibility to obtain the newly created stereogenic center in third position of the isoindolinonic ring in optically pure form. As, at this stage, we were not able to set up a suitable chiral environment that would allow their asymmetric synthesis under the electrochemical conditions, we tested chiral amines as resolving reagents (Figure 3).

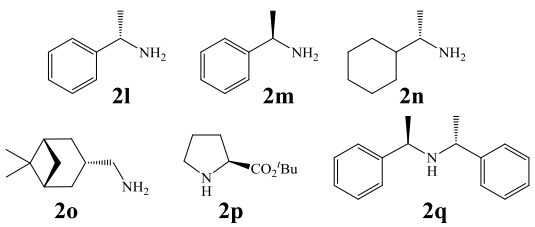
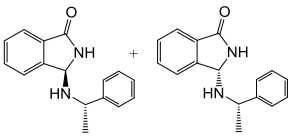
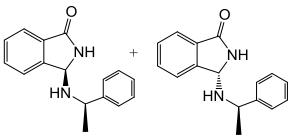
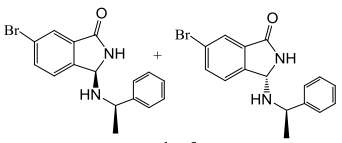
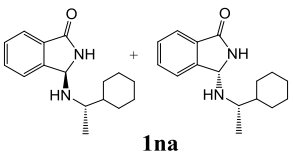
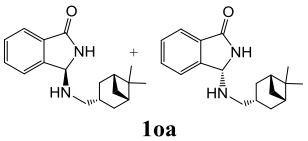
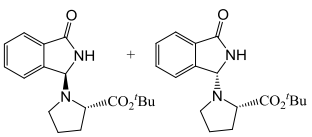


Figure 3. Chiral amines tested in the tandem reaction with **3a,b**

As showed in table 3, with the exception of the bulky substrate **2q**, chiral amines **2l-p** provided the N-Mannich bases **1** with satisfactory to good yields, as epimeric mixtures. Though the diastereoselectivities observed were generally low, we were pleased to ascertain the possibility to access to both the enantiopure diastereoisomers by simple separation on silica gel (entries 1-3 and 6).

Table 3. Electrochemically-initiated tandem reaction of amines **2l-q** with **3a,b**

Entry	2	1	Yield[a]	d.e[b]
1	**2l**	 **1la**	65%	-
2	**2m**	 **1ma**	67%	-
3	**2m**	 **1mb**	80%	-
4[c]	**2n**	 **1na**	45%	28%
5[c]	**2o**	 **1oa**	58%	-
6	**2p**	 **1pa**	82%	33%
7	**2q**	-	-	-

[a] Isolated yields refer to the mixture of diastereoisomers. [b] Diastereoisomeric excesses have been calculated by analysis ^{1}H-NMR of the crude reaction mixtures. [c] ^{1}H-NMR analysis of the crude mixture reveals a competitive reaction of formation of imine.

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In summary, we have succeeded in the electrosynthesis of a series of N-Mannich bases of 1-isoindolinones, a class of heterocyclic compounds which may find applications in medicinal chemistry as well as ligands in catalysis. As postulated, cathodic electrolysis applying catalytic amount of current under simple and handy galvanostatic conditions resulted in the electro-activation of primary and secondary alkyl- and benzyl-amines in the tandem reaction with 2-formylbenzonitriles. The desired products have been generally obtained in good yields and short reaction time, avoiding either metal or basic catalyst and, as a consequence, easy set-up and work-up procedures could be established. Furthermore, the use of chiral non-racemic amines as starting materials has allowed access to enantiopure 3-aminosubstituted isoindolinone derivatives **1** by simple chromatographic separation. We are currently working to develop an asymmetric version of this reaction.

Experimental

Typical experimental procedure for electro-induced synthesis of isoindolinones 1 in CH_3CN: A solution of **2** (0.21 mmol) and **3** (0.2 mmol) in $CH_3CN/TEABF_4$ (0.4 ml/0.03 mmol) was electrolyzed at r.t., under galvanostatic conditions (8 mA, 0.025 electrons/molecule of **3**), using an Hewlett Packard DC Power Supply Mod. E3612A. The experiments were carried out in the cathodic compartment of a U-divided glass cell separated through a porous G-4 glass plug. Platinum spirals (apparent area 1 cm^2) were used as anode and cathode. In all the experiment the anolyte was constituted by a solution of $TEABF_4$ 0.05 M in CH_3CN.

At the end of the electrolysis, TLC analyses showed disappearance of **3** and the reaction was in any case prolonged at r.t. under magnetic stirring for 2h. The mixture was then concentrated *in vacuum* and directly purified by silica gel chromatography (hexane: AcEt= 2:1; CH_3Cl: AcEt = 9:1 or CH_3Cl: MeOH= 9:1).

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental instrumentation and procedures, spectroscopic data, copies of 1H NMR and 13C NMR are provided. See DOI: 10.1039/c000000x/

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