Electrochemically Induced Aza-Henry Reaction: A New, Mild, and Clean Synthesis of α-Nitroamines

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Abstract: The addition reaction of nitro compounds to azomethine functions, known as the aza-Henry (or nitro-Mannich) reaction was performed electrochemically under solvent and supporting electrolyte-free conditions. Reaction yields are very good and the method is very clean, avoiding the use of any classical solvent or catalyst.

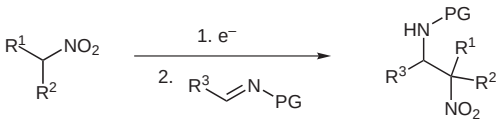
Key words: carbanions, green chemistry, imines, Michael additions, nucleophilic additions

The nucleophilic addition reaction of nitro compounds to imines to give α-nitroamine derivatives, known as the aza-Henry (or nitro-Mannich) reaction[1] is an important tool for carbon–carbon bond formation. The further reduction of 1,2-nitroamine adducts to 1,2-diamines[2,3] or their Nef oxidation[4] to α-amino acids greatly enhance the interest for the aza-Henry reaction. In particular, the 1,2-diamine structural motif is important in biologically active natural products,[5] in medicinal chemistry,[6] and more recently as a core unit in chiral auxiliaries and chiral ligands for use in asymmetric catalysis.[3,7] Aza-Henry reactions are usually catalyzed or promoted by bases, metal salts, or Brønsted and Lewis acids. Several drawbacks are related to the above-mentioned procedures such as the cost and the toxicity of the metal species. Moreover, the use of organic solvents that are often ecologically harmful is often required.[8]

Over the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically practicable,[9] and an important area of green chemistry deals with solvent minimization.[10] Although several papers reported the nitroaldol reaction performed under solvent-free conditions,[11] only one note reports a methodology for an organocatalyzed solvent-free aza-Henry reaction.[12]

Among the different green methodologies recently elaborated, organic electrochemistry[13] could be rightly considered a powerful tool for clean and safe organic syntheses. Reactions are carried out using a nonpolluting reagent, the electron in a medium consisting of a solvent-supporting electrolyte system. The principal limitations of the method are related to the use of large amounts of supporting electrolyte (usually an ammonium or phosphonium salt that needs to be separated at the end of the reaction) and particular solvents (usually with high dielectric constant and wide 'potential window'). Clearly, if an excess of reagent could be used as solvent, a particularly simple and green methodology would be possible. Recently, some of us reported the electrochemically induced Henry reaction[14] carried out in the absence of solvent. Cathodic reduction of pure nitromethane followed by addition of an aldehyde to the cathodic compartment of the electrochemical cell at the end of the electrolysis afforded 2-nitroalcohols in good yields.

Herein we report a new and significantly simplified and environmentally friendly approach to the catalytic aza-Henry reaction using solvent-free conditions. The direct electrochemical reduction of nitroalkanes is conveniently used for the selective synthesis of α-nitroamines by addition of an imine to the cathodic compartment of the cell at the end of the electrolysis. No classical solvent or supporting electrolyte is required (Equation 1).



Equation 1 Electrochemically induced aza-Henry reaction

The groups bound at the nitrogen atom of the imine (PG) could affect both stability and electrophilicity of the imine, so we tested the reaction with different N-protected imines such as tosyl- and phosphinoylimines. Also the reaction was extended to different nitro compounds such as 1- and 2-nitropropane. The results are reported in Table 1.

To test the efficiency of the electrochemical system, the reaction of 4-methyl-*N*-(phenylmethylene) benzenesulfonamide (**1a**) with nitromethane was performed under several different electrolysis conditions. In particular it was found that only a catalytic amount of current was necessary. If related to the amount of imines used in the reaction, a current quantity of only 0.01 F·mol^{-1} was required to perform the reaction. However, to obtain very high yields and shortest reaction time, a current quantity of 0.1 F·mol^{-1} was needed. In this case, the transformation was practically complete after five minutes. (see Table 1, entries 1–3).

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Table 1 Solvent-Free Electrochemically Induced Aza-Henry Reaction[a]

Entry	R^1	R^2	Imine	R^3	PG	Adduct	Q[b]	Time (min)	Yield (%)[c]
1	H	H	**1a**	Ph	Ts	**2a**	0.01	1000	81
2	H	H	**1a**	Ph	Ts	**2a**	0.05	30	86
3	H	H	**1a**	Ph	Ts	**2a**	0.1	5	92
4	Et	H	**1a**	Ph	Ts	**3a**	0.1	5	81
5	Me	Me	**1a**	Ph	Ts	**4a**	0.1	5	82
6	H	H	**1b**	Ph	$P(O)Ph_2$	**5a**	0.1	5	91
7	H	H	**1c**	2-furyl	Ts	**2b**	0.1	5	85
8	H	H	**1d**	2-furyl	$P(O)Ph_2$	**3b**	0.1	5	88
9	H	H	**1e**	4-$MeOC_6H_4$	Ts	**2c**	0.1	5	90
10	H	H	**1f**	4-$MeOC_6H_4$	$P(O)Ph_2$	**3c**	0.1	5	89
11	H	H	**1g**	2-naphthyl	Ts	**2d**	0.1	5	88
12	H	H	**1h**	2-naphthyl	$P(O)Ph_2$	**3d**	0.1	5	95
13	H	H	**1i**	4-$O_2NC_6H_4$	Ts	**2e**	0.1	5	78
14	H	H	**1j**	4-$F_3CC_6H_4$	Ts	**2f**	0.1	5	86
15	H	H	**1k**	4-Cl-C_6H_4	Ts	**2g**	0.1	5	66

[a] Electrolyses were carried out according to the general procedure.
[b] Numbers of faradays per mol of added imine supplied to the electrode.
[c] Isolated yields based on the starting imine **1a**–**k**.

This behavior could be explained assuming that the reaction proceeds by direct electrochemical reduction of the suitable nitroalkane with the formation of the corresponding stabilized carbanion that acts as a nucleophile towards the imine. The adduct thus obtained extracts a proton from a new molecule of nitroalkane rendering the whole a catalytic process.

The potential of the solvent-free aza-Henry reaction was then investigated varying both the imine and the nitroalkane partners. Several examples of the aza-Henry reaction of sulfonylimines **1a**,**c**,**e**,**g**,**i**,**j**,**k** are reported. Moreover, phosphinoylimines **1b**,**d**,**f**,**h** were used as substrates. The diphenylphosphinoyl moiety, easily removable at the end of the synthetic sequence,[15] should guarantee, just as the tosyl moiety should, a sufficient reactivity toward nucleophilic species. Very good yields and selectivity were obtained using aromatic and heteroaromatic imines. Unsubstituted aromatic imines **1a**,**b** and heteroaromatic imines **1c**,**d**,**g**, as well as imines **1h**,**i**,**j**,**k** bearing an electron-withdrawing group, reacted smoothly under standard conditions with nitromethane to afford, after a very short time (5 min), the expected products in very good yields. Quite surprisingly, the presence of an electron-releasing group in **1e** and **1f** did not have any effect on either the reaction rates or the reaction yields. Increasing the length (entries 4) or the branching (entry 5) of the nitroalkane chain did not affect the reaction rate or yields.

A large-scale experiment was also performed using 1.0 mmol of **1a** and 3.7 mmol of nitromethane; this afforded a 75% isolated yield for **2a**.

In all cases, the reactions proceed smoothly to give the corresponding addition products in very high yields under extremely mild, clean, and safe conditions. Furthermore, the use of solvents is also avoided during work-up, as the product can be obtained by simple evaporation of the nitroalkane from the crude reaction mixture. Otherwise, a simple silica gel filtration of the crude reaction mixture is required.

In summary we have reported a new catalytic, mild, clean, and convenient electrochemical methodology for the synthesis of α-nitroamines starting from imines and nitroalkanes. The use of any solvent, supporting electrolyte, or metal or basic catalyst is avoided. When compared to the classical chemical methods, the conditions of the electrochemical reaction are mild and the reaction times are very short. In addition, the work-up procedure is extremely simple.

Imines **1a**–**k** were prepared according to the procedure reported by Jennings.[16] All the known isolated imines gave spectral and physical data in accordance with those reported in the literature.[16–18]

All the experiments were performed using a two-compartment cell equipped with a Pt anode and cathode using an Amel 555B potentiostat, equipped with an Amel 731 integrator. The working electrode was a platinum spiral cathode (apparent area 0.8 cm^2), the

counter electrode was a cylindrical platinum spiral. Anodic and cathodic compartments were separated by a G3-glass diaphragm fitted with an agar gel (methyl cellulose 0.5% vol. dissolved in 1 M TEAP/DMF solution).

General Procedure for the Solvent-Free Aza-Henry Reaction

A nitroalkane (1.0 mL) was added to the cathodic compartment of the electrochemical cell. No supporting electrolyte was added to the cathodic compartment. The electrolysis was carried out under galvanostatic control (J = 40 mA·cm^{-2}), under an inert atmosphere (Ar), until the necessary amount of current quantity (0.1 F mol^{-1} related to the imine) was passed. At the end of the electrolysis, the imine (0.2 mmol) was added and the resulting mixture was stirred for 5 min at r.t. The reaction was practically immediate [TLC monitored $CHCl_3$–MeOH (9:1) for *P*,*P*-diphenyl-*N*-arylmethylene phosphinic amides and Et_2O–hexanes (4:6) for *N*-arylmethylenesulfonamides] and afforded the crude nitroamine adduct which was purified by simple evaporation of the residual nitroalkane and, if necessary, filtration through a pad of silica gel. All the known isolated nitroamines gave spectral data in accordance with those reported in the literature.[17c,19]

4-Methyl-*N*-[2-nitro-1-(4-nitrophenyl)ethyl]benzenesulfonamide (2e)

Mp 136–137 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.7 Hz, 2 H), 7.55–7.30 (m, 4 H), 7.22 (d, J = 7.7 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 2 H), 5.25–5.10 (m, 1 H), 4.90–4.55 (m, 3 H), 2.27 (s, 3 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 148.4, 144.1, 142.8, 136.8, 129.7, 127.9, 127.0, 124.0, 78.3, 54.9, 21.4.

4-Methyl-*N*-{2-nitro-1-[4-(trifluoromethyl)phenyl]ethyl}benzenesulfonamide (2f)

Mp 122–124 °C. ^{1}H NMR (200 MHz, acetone-d_6): δ = 7.60–7.40 (m, 7 H), 7.20–7.05 (d, J = 8.1 Hz, 2 H), 5.53–5.25 (m, 1 H), 5.00–4.85 (m, 2 H), 2.30 (s, 3 H). ^{13}C NMR (50.3 MHz, acetone-d_6): δ = 144.7, 142.4, 139.7, 130.8, 129.6, 129.0, 128.4, 126.9, 126.8, 122.7, 117.7, 78.3, 57.2, 21.3.

4-Methyl-*N*-(2-methyl-2-nitro-1-phenylpropyl)benzenesulfonamide (3a)

Mp 129–131 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.9 Hz, 1 H), 7.49 (d, J = 7.9 Hz, 2 H), 7.40–7.25 (m, 1 H), 7.20–6.80 (m, 5 H), 5.80–5.70 (m, 1 H), 5.15 (br s, 1 H), 4.70–4.55 (m, 1 H), 2.33 (s, 3 H), 0.91 (t, 3 H). ^{13}C NMR (50.3 MHz, acetone-d_6): δ = 143.5, 139.5, 137.2, 129.9, 129.4, 128.4, 127.7, 94.4, 61.5, 25.4, 21.3, 10.3.

***N*-[1-(4-Methoxyphenyl)-2-nitroethyl]-*P*,*P*-diphenylphosphinic Amide (3c)**

Mp 163–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90–7.70 (m, 4 H), 7.60–7.30 (m, 6 H), 7.20 (d, J = 8.7 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 5.00–4.65 (m, 3 H), 4.35–4.15 (m, 1 H), 3.77 (s, 3 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 159.7, 132.5, 132.3, 132.2, 131.9, 131.7, 130.1, 130.0, 128.8, 128.5, 127.7, 114.4, 80.9, 80.8, 55.3, 53.0.

4-Methyl-*N*-(2-methyl-2-nitro-1-phenylpropyl)benzenesulfonamide (4a)

Mp 134–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.3 Hz, 2 H), 7.60–6.80 (m, 7 H), 6.20 (d, J = 10.4 Hz, 1 H), 4.96 (br s, 1 H), 2.27 (s, 3 H), 1.64 (s, 3 H), 1.54 (s, 3 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 143.2, 136.9, 134.6, 129.2, 128.4, 127.8, 126.7, 90.6, 64.0, 25.0, 23.0, 22.3.

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