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One-Pot Synthesis of Pyrrolo[1,2-*a*]quinoxaline Derivatives via Iron-Promoted Aryl Nitro Reduction and Aerobic Oxidation of Alcohols

Maria de Fatima Pereira*,†,‡ and Valérie Thiéry†

Université de La Rochelle, UMR CNRS 7266 -LIENSs, LIttoral ENvironnement SociétéS, Pôle Sciences et Technologie, Bâtiment Marie-Curie, Avenue Michel Crépeau, 17042 La Rochelle, France, and Université de Caen Basse-Normandie, EA 4258 CERMN - FR CNRS 3038 INC3M, UFR des Sciences Pharmaceutiques, 14032 Caen, France

maria_de_fatima.pereira-rosenfeld@univ-lr.fr

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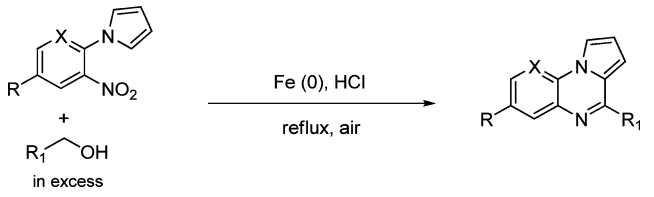
ABSTRACT



Here, we describe a new one-pot method to synthesize 4,7-substituted pyrrolo[1,2-*a*]quinoxalines and related heterocyles through a cascade of redox reactions/imine formation/intramolecular cyclization. This procedure tolerates readily available substituted 1-(2-nitrophenyl)pyrrole derivatives and aliphatic or benzylic alcohols as starting materials using iron powder and acidic conditions. This is the first example of constructing *N*-heterocycles via iron-mediated aryl nitro reduction and aerobic oxidation of alcohols in one pot.

The pyrrolo[1,2-*a*]quinoxaline skeleton is present in various heterocyclic compounds possessing interesting biological activities. This nucleus substituted at the C-4 position gives various derivatives with 5-HTR affinities,[1] in vitro antiparasitic activities,[2] potential nonpeptide glucagon receptor antagonist activities,[3] and fluorescence properties for amyloid fibril detection.[4] Some of these classes of compounds are of particular interest in antiproliferative activity.[5] They inhibit human leukemic cell lines U937, K562 and the breast cancer cell line MCF7 (IC_{50} in the range of 4.5 and 8 μM). These three human cell

† Université de La Rochelle.
‡ Université de Caen Basse-Normandie.

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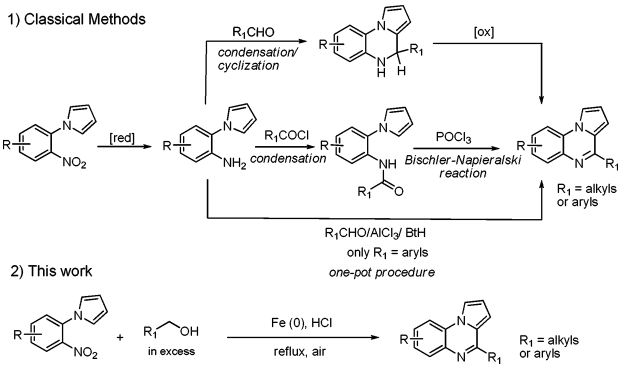
lines exhibit an active phosphorylated form of Akt Kinase. Therefore, the development of novel and highly efficient methods to construct these fused angular heterocyclic architectures is highly desirable for drug discovery.

Many methods for syntheses of 4,5-dihydropyrrolo-[1,2-*a*]quinoxalines,[6] pyrrolo[1,2-*a*]quinoxalin-4-ones,[7] and unsubstitued pyrrolo[1,2-*a*]quinoxalines[8] have been developed; however, to the best of our knowledge, only a few synthetic procedures have been reported for fused aromatic pyrrolo[1,2-*a*]quinoxalines substituted in C-4 by aryl or alkyl groups. As shown in Scheme 1, all of the reported 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives were obtained by the reduction of the 1-(2-nitrophenyl)pyrroles to provide the amino intermediates. The main synthetic method utilized various alkyl- and aryl-acid chlorides with the amino group to obtain the corresponding acetamides. Subsequently, 4-substituted pyrrolo[1,2-*a*]quinoxalines were prepared by intramolecular cyclization of theses amides according to the Bischler−Napieralski reaction.[9] The other approach involved the reaction between the corresponding 1-(2-aminophenyl)pyrroles with aldehydes in an acidic medium followed by oxidation of the 4,5-dihydropyrrolo[1,2-*a*]quinoxaline intermediates.[10] More recently, a modified Pictet−Spengler reaction using benzotriazole methodology reported the one-pot synthesis of these fused aromatic heterocycles.[11] This is the first example of constructing 4-aryl pyrrolo[1,2-*a*]quinoxalines between aromatic aldehydes and the amino intermediates. In all cases, these multistep syntheses led to modest overall yields using volatile and environmentally toxic reagents such as aliphatic aldehydes. Therefore, the use of alcohols with nitroarenes as starting materials to form a direct C−N bond is highly attractive, and great progress has been made during the past decade to develop environmentally friendly processes toward this subject.[12]

Herein, we reported the first one-pot synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitrophenyl)-pyrrole derivatives and various alcohols in redox conditions. In this process, alcohols were oxidized in situ from a nitroarene reduction step and no external oxidant reagent was added to the reaction mixture.

Scheme 1. Different Pathways for the 4-Substituted Pyrrolo[1,2-*a*]-quinoxalines Formation



Until now, whereas aryl nitro reduction with iron powder as a reducing agent has already been studied, there are only a few reports of using cheap and less toxic iron catalysts for the oxidation of alcohols to carbonyls. In the literature, the oxidation catalyzed by ferrous ions and hydrogen peroxide (the Fenton reaction) has been carefully investigated,[13] unlike oxidations with ferric ions which have received considerably less attention. More recently, a few methods have been developed using iron(III)−Schiff base−triphenylphosphine complexes,[14] iron(III) bromide,[15] iron(III) nitrate,[16] and iron(III) porphyrin and nonporphyrin complexes,[17] but all of the reagents need the presence of hydrogen peroxide (or a peroxide) as a reagent.

This new method provided a route for the construction of a variety of substituted pyrrolo[1,2-*a*]quinoxaline derivatives via iron-mediated aryl nitro reduction and aerobic oxidation of alcohols in the one-pot procedure. Moreover, we have extended this reaction to novel pyrido[3,2-*e*]-pyrrolo[1,2-*a*]pyrazines.

Performed in usual reduction conditions (3 equiv of iron, 6 equiv of HCl), the reaction led mainly to the expected amino **3a** besides a trace of pyrrolo[1,2-*a*]quinoxaline **2a** (Table 1, entry 1). In order to understand and optimize this surprising result, we decided to reinvestigate the experimental conditions to obtain the tricyclic aromatic skeleton in one pot. When a large excess of iron powder (9 equiv) and HCl 12 M (11 equiv) were used, only the desired compound **2a** was observed (74%) and no trace of the amino compound **3a** was identified (entry 2). The best yield was obtained with the same equivalents of iron and chlorhydric acid in refluxing ethanol (80%) (entry 3). It should be noted that when more than 14 equiv of iron, the yield decreased to 60% because of the complex mixture of

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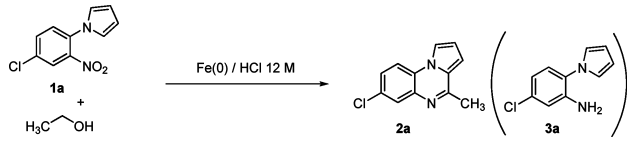
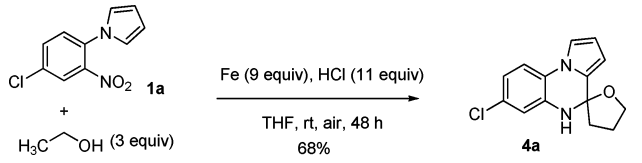
Table 1. Reactions of 1-(4-Chloro-2-nitrophenyl)pyrrole and Ethanol under Various Conditions[a]



entry	Fe (equiv)	HCl (equiv)	solvent	**1a**	**2a**	**3a**
1	3	6	EtOH	0	trace	70
2	9	11	EtOH	0	74	0
3	**9**	**11**	**EtOH**[b]	**0**	**80**	**0**
4	14	15	EtOH	0	60	0
5	9	11	EtOH[c]	0	0	70
6	9	none	acetic acid	0	30	10[d]
7[e]	9	11	AcOEt	0	58	0
8[e]	9	11	MeCN	0	54	0
9[e]	9	11	dioxane	0	0	50[d]
10[e]	9	11	toluene	75	0	10[d]
11[e]	9	11	DCM	80	0	5[d]
12[e]	9	11	Et_2O	trace	trace	50[d]
13[e,f]	9	11	THF	0	0	0

[a] Conditions: solvent (15 mL), 72 h, rt, air. [b] Reflux, 48 h, air. [c] Under N_2 atmosphere. [d] Determined by ^1H NMR analysis of the crude reaction product. [e] 3 equiv of ethanol as substrate were used. [f] Scheme 2, 68% of spirocyclic compound **4a**.

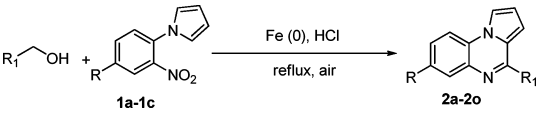
Scheme 2. Access to Spirocyclic Compound **4a** When the Reaction Was Performed in THF as Solvent

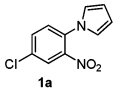
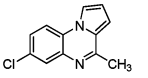
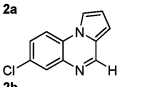
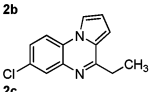
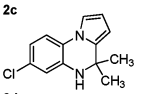
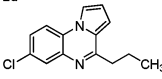
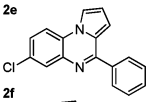
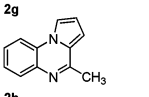
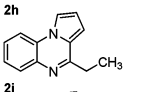
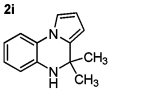
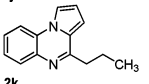
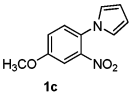
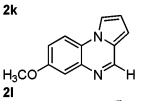
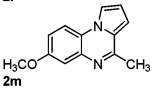
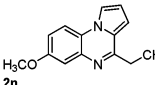
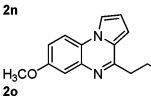


unidentified byproducts (entry 4). Interestingly, we noticed that only the amino compound was identified (70% yield) when the reaction was performed under an inert atmosphere (N_2) (entry 5). It seems that oxygen should play a key role in the reaction. The desired product was obtained in 30% yield when the reaction was carried out in acetic acid without addition of HCl 12 M and ethanol as the substrate (entry 6).

The effect of solvents was also investigated. The use of AcOEt and MeCN resulted in lower yields with 3 equiv of ethanol as substrate (relative to the amount of 1-(4-chloro-2-nitrophenyl)pyrrole) (entries 7–8). The reaction was not efficient in other solvents such as ether, DCM, toluene, and dioxane; only the starting material or/and amino intermediate were isolated (entries 9–12). Interestingly, when THF was used as solvent, none of the three compounds was observed (entry 13). However, we identified a novel spirocyclic compound **4a** in good yield 68% (Scheme 2). It supposed that THF should be oxidized and then reacted with the amino intermediate to provide the new molecule **4a**.

Table 2. Reactions of 1-(2-Nitrophenyl)pyrrole Derivatives with Various Alcohols[a]

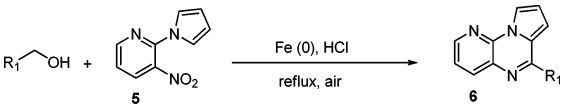


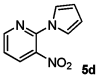
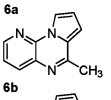
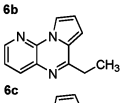
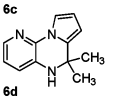
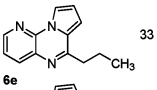
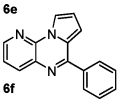
entry	substrate	alcohol	product	yield (%)[b]
1	 **1a**	EtOH	 **2a**	80
2	**1a**	MeOH	 **2b**	40
3	**1a**	*n*-PrOH	 **2c**	56
4	**1a**	*i*-PrOH	 **2d**	61
5	**1a**	*n*-BuOH	 **2e**	58
6	**1a**	BnOH	 **2f**	54
7	 **1b**	MeOH	 **2g**	31
8	**1b**	EtOH	 **2h**	81
9	**1b**	*n*-PrOH	 **2i**	56
10	**1b**	*i*-PrOH	 **2j**	60
11	**1b**	*n*-BuOH	 **2k**	50
12	 **1c**	MeOH	 **2l**	20
13	**1c**	EtOH	 **2m**	69
14	**1c**	*n*-PrOH	 **2n**	47
15	**1c**	*n*-BuOH	 **2o**	44

[a] Conditions: **1** (2.25 mmol), iron powder (9.0 equiv), HCl 12 M (11.0 equiv), alcohol (15 mL), reflux, 48 h. [b] Isolated yield.

In light of these interesting results, we decided to study and extend this new methodology in order to develop an available library of pyrrolo[1,2-*a*]quinoxaline derivatives. We started the reaction with readily available substituted

Table 3. Reactions of 3-Nitro-2-pyrrolopyridine with Various Alcohols Leading to Pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazines **6** under Optimal Conditions[a]



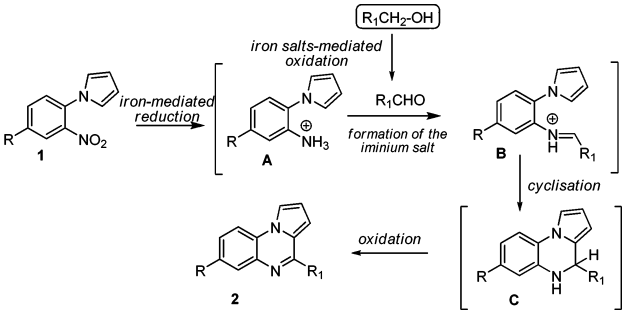
entry	substrate	alcohol	product	yield (%)[b]
1	 **5d**	MeOH	 **6a**	25
2	**5d**	EtOH	 **6b**	63
3	**5d**	*n*-PrOH	 **6c**	50
4	**5d**	*i*-PrOH	 **6d**	61
5	**5d**	*n*-BuOH	 **6e**	33
6	**5d**	BnOH	 **6f**	54

[a] Conditions: **5** (2.25 mmol), iron powder (9.0 equiv), HCl 12 M (11.0 equiv), alcohol (15 mL), reflux, 48 h. [b] Isolated yield.

1-(2-nitrophenyl)pyrroles and various alcohols. As shown in Table 2, for all combinations of 1-(2-nitrophenyl)-pyrrole derivatives and aliphatic or benzylic alcohols, the desired 4-substituted pyrrolo[1,2-*a*]quinoxaline was observed as the only product. Most of the substrates examined provided good yields. The lowest yield was obtained when substituted 1-(2-nitrophenyl)pyrroles reacted with methanol as the substrate (entries 2, 7, 12) whereas ethanol was the best substrate for this reaction (entries 1, 8, 13). The reactions with 1-(2-nitrophenyl)pyrroles bearing an electron-donating group such as a methoxy group *meta* to the nitro group decrease the product yields (entries 12−15). To our delight, besides simple aliphatic alcohols, benzyl alcohol also reacted with the 1-(4-chloro-2-nitrophenyl)-pyrrole to give the desired product in moderate yield (entry 6). Furthermore, reactions between a secondary alcohol such as isopropanol and substituted 1-(2-nitrophenyl)pyrroles gave 4,5-dihydropyrrolo[1,2-*a*]quinoxaline derivatives (entries 4, 10). To further explore the scope

(18) It should be noted that byproduct was identified in the reaction when methanol, ethanol, and butyl alcohol were used as starting materials. Characterization data confirmed the presence of trace amounts of the 2-chloropyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine derivatives.

Scheme 3. Proposed Mechanism



of the reaction, all alcohols were also employed to react with 3-nitro-2-pyrrolopyridine. In general, good to moderate yields were obtained under standard optimized reaction conditions. Interestingly, the reaction of 3-nitro-2-pyrrolopyridine with methanol and butyl alcohol resulted in a much lower yield (Table 3, entries 1, 5).[18]

The most likely mechanism to rationalize this transformation is illustrated in Scheme 3. In an acidic medium, iron could catalyze the reduction of the nitrophenylpyrrole (**1**) to its amine counterpart (**A**) giving ferric salts (or ferrous salts) which in turn would be able to oxidize alcohols into aldehydes. Condensation of these latter with the amine (**A**) gives the iminium salts (**B**) which spontaneously cyclize leading to the dihydroquinoxalines (**C**) as previously described. Finally, a final oxidation produces the 4-alkyl or 4-phenylpyrroloquinoxalines (**2**) in moderate to good yield.

In conclusion, we have developed a rare one-pot reaction for assembling pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitrophenyl)pyrroles and various alcohols. The nitro reduction, alcohol oxidation, heterocycle formation, and heterocycle oxidation were realized in a cascade. A wide range of these fused heterocycles bearing in position 4 different alkyl and aryl groups have been elaborated from suitable substrates; thereby 3-nitro-2-pyrrolopyridine was also compatible with this process, giving the corresponding fused tricyclic compounds. The synthetic applications of this reaction are under investigation.

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Supporting Information Available. Detailed experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.