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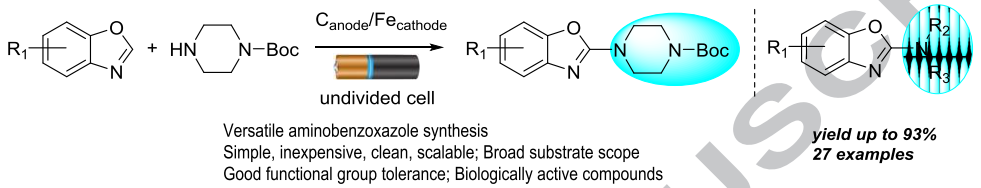

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Synthesis of aminobenzoxazoles *via* simple, clean and efficient electrochemical redox reactions[#]

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[#]Dedicated to the memory of Professor Gilbert Stork (Columbia University, New York, USA)

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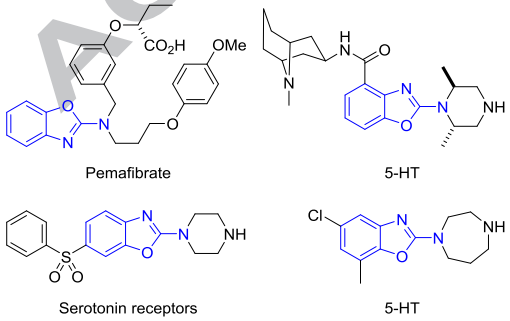
ABSTRACT

An efficient single step process for the construction of pharmaceutically relevant substituted aminobenzoxazoles have been described in this report. Various electrodes and electrolytes combinations have been carried out to harvest optimum coupling results. The presented C-N bond formation reaction methodology has applied for the synthesis of biologically active compounds. This methodology saves reaction steps over traditional functionalization reactions.

1. Introduction

Aminobenzoxazoles are an integral part of pharmacophores[1] in medicinal chemistry discovery programs. Some of the recently disclosed biologically active benzoxazole compounds are shown in Scheme 1. Pemafibrate[2] is a potent PPARα agonist used for the management of atherogenic dyslipidaemia. The other three compounds[3] shown in the Scheme 1 are active in serotonin receptors. Easy access to such types of aminobenzoxazoles are always an interesting portion of research for the medicinal chemists.



Scheme 1. Some of the biologically active aminobenzoxazoles.

Electrochemical reactions attracted considerable amounts of interest over the years due to its versatility and applicability[4]. The electrochemical processes have been utilized in the classical production of polymers and pigments over a century ago and the methods have been lasting till today[5]. One of the very early notable applications of Kolbe electrolysis reaction has been reported by Stork[6] in the synthesis of α-onocerin. Over the last few years, significant amount of complex organic chemistry transformations have been reported from the labs of Baran and others[7]. Quite often, multiple chemical transformations occurs under the electrochemical environments. Electrochemistry provides a powerful tool for the late-stage functionalization of many complex molecules. These electrochemical transformations are considered to be clean, nonpolluting and atom economic. Recent example from Fu and co-workers on the diazidation of inactive olefin represents an excellent process[8] indicating all facets of electro organic chemistry. In this paper, a combination of electrochemistry and organic catalysis transforms alkenes into hard-to-make vicinal diamines. We were intrigued by the recent report of benzoxazole coupling of morpholine[9] and majority of other amines does not participate in the coupling reactions. At this point in time we planned to study amines of pharmaceutically valued substrates to accelerate the synthesis of advanced intermediates. We also planned to survey electrodes, electrolytes and reaction solvents to get maximum output for these reactions. Effect of input voltage also included in the proposed studies.

Based on the extensive study of common functional groups present in FDA approved drugs (nitrogen containing hetero-cycles) compiled by Njardarson and co-workers[10], we focused

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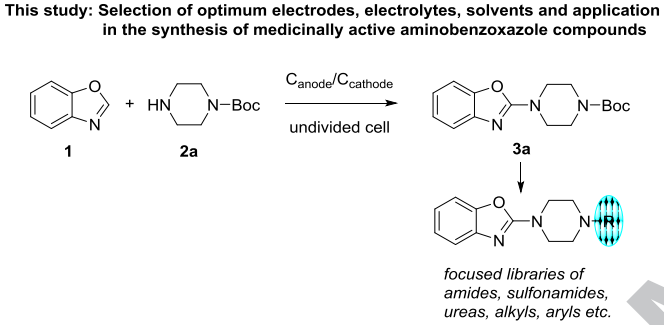
our attention on the coupling reactions of piperidines and piperazines in our proposed electrochemical reactions with benzoxazoles and benzothiazoles. According to the above mentioned mini perspective compiling all FDA approved drugs, non-aromatic heterocycles are widely present in active pharmaceutical ingredients. There are 72 drugs with piperidine substructure, 59 drugs with piperazine moiety, 37 drugs with pyrrolidine substructure, 13 drugs with morpholine subunit and 11 compounds with tetrahydroisoquinoline substructure[10]. We planned a systematic study of the above mentioned subunits under electrochemical coupling conditions.

2. Results and Discussions

At the beginning of our investigation, we chose simple benzoxazole (**1**) and N-Boc piperazine (**2a**) as our model substrates. These nitrogen heterocycles were chosen aiming at the possibility of further derivatization to get focused libraries of aminobenzoxazoles.



Scheme 2. Electrochemical coupling of benzoxazoles with amines.

Our initial studies utilizing carbon electrodes and 9V batteries were extremely encouraging and then later we used regular cell phone charger (5V) as described by Aubé and co-workers[11]. The undivided cells made from simple vials were safe and economical and this simple set up produced reproducible results with a variety of substituted amines. The successful reactions were repeated with different electrodes, electrolytes and solvents as shown in the following Tables 1-3.

Table 1. Screening of conditions for electrodes.

Entry	Cathode	Anode	Electrolyte	% Conversion	Time
1	Cu	C	TBAI	50	3 h
2	Al	C	TBAI	90	3 h
3	Fe	C	TBAI	<5	3 h
4	C	C	TBAI	<5	3 h
5	Al	Fe	TBAI	<5	3 h
6	C	Al	TBAI	<5	3 h

As shown in Table 1, a wide variety of electrodes have been screened for optimal conditions keeping TBAI as electrolyte and entry 2 gave us the best conversion of starting material to the product **3a**. Other electrodes furnished poor results as compared to aluminum as cathode and carbon rod as anode.

Table 2. Screening of conditions for electrolytes.

Entry	Electrolyte	% Conversion	Time
1	Lithium perchlorate ($LiClO_4$)	<5	16 h
2	Sodium iodide (NaI)	<5	16 h
3	Tetraethylammonium-*p*-toluenesulphonate	60	16 h
4	Tetrabutylamonium tetrafluoroborate (TBATFB)	35	16 h
5	Tetrabutylammonium iodide (TBAI)	90	3 h

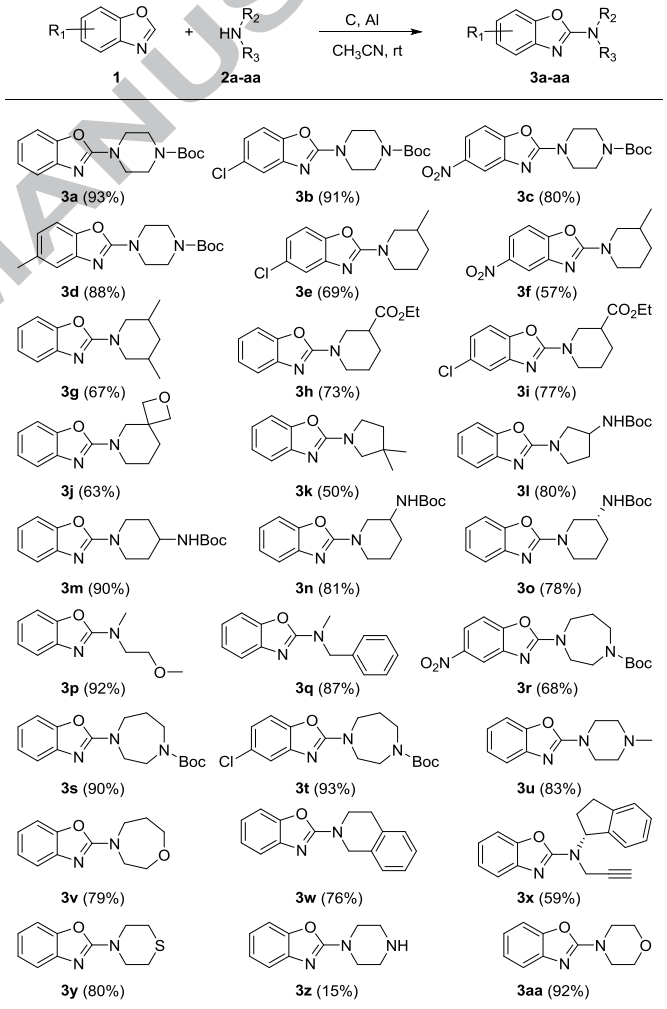
Next, we focused our attention on the selection of best electrolytes as shown in Table 2. Among five commonly used electrolytes tried, tetrabutylammonium iodide (TBAI) furnished the best results. The reactions were conducted at room temperature and monitored periodically and then allowed to be stirred overnight.

Table 3. Screening of conditions for solvents.

Entry	Cathode	Anode	Solvent	% Conversion	Time
1	Al	C	Acetone	14	3 h
2	Al	C	DCM	<5	3 h
3	Al	C	Methanol	<5	3 h
4	Al	C	Acetonitrile	90	3 h

Table 3 shows the optimal solvent as acetonitrile for the electrochemical transformations.

Table 4. Study of pharmaceutically relevant secondary amines and their coupling with benzoxazoles.

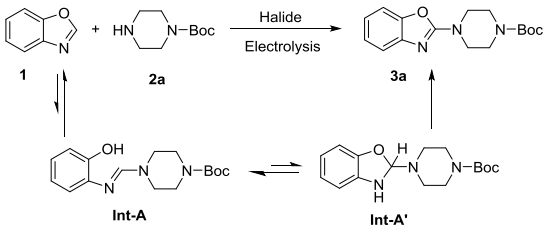


Conditions: Undivided cell, C anode/Al cathode, TBAI (10 mol %), HOAc (5 equiv.), Acetonitrile (20 mL) at RT. Isolated yields are shown.

It is evident from the above tables that the optimum condition for this particular transformation is entry number 2 in Table 1. It should also be noted that each experiments were carried out in the presence of acetic acid (5 mmol). The best results obtained by the use of aluminum rod as cathode, carbon rod as anode and TBAI as electrolyte in acetonitrile solvent at room temperature. These results might be described based on the higher conductivity of aluminum metal and better solubility of TBAI in acetonitrile solvent. This optimized condition has been used for all our substrates described in this paper. It should also be noted that all reactions were conducted using 5V cell phone charger as the power source. We carried out control experiments with all

reagents and electrodes without passing electricity and as expected, we have not detected any desired product formation. In order to extend the utility of this user friendly procedure, we started to couple medicinally relevant subunits with benzoxazoles and benzothiazoles.

Preliminary experiments were successful with *N*-Boc piperazine, however the reactions with simple piperazine were only partially successful (15% conversion to the product **3z**) under a variety of experimental conditions. We assumed that this might be due to the poor solubility of piperazine under the regular electrochemical reaction conditions. This prompted us to choose soluble substrates such as *N*-Boc or ester derivatives. From our initial optimization studies, compound **3a** was obtained in 93% isolated yield with a clean reaction profile[12]. Our results are summarized in Table 4. It has been proposed previously that the Schiff base (**Int-A**) would undergo electrochemically initiated dehydrogenative oxidation to form the desired aminobenzoxazole **3a** as shown in Scheme 3[9].



Scheme 3. Suggested direct electrochemical amination for the formation of 2-aminobenzoxazoles.

The intermediate **A** was detected under the LC-MS conditions[13] and as the reaction time increases, intermediate **A** would undergo aromatization to yield the required product **3a**.

Substrate scope of the benzoxazole moiety was immediately considered and the reactions were as smooth as that of simple unsubstituted benzoxazoles. Substitutions like chloro, nitro and methyl groups were included in the present study. It has been found that there is not much effect on the substitution patterns on the overall reactivity of benzoxazoles towards electrochemical reactions. Compounds **3b**, **3c** and **3d** were isolated in >80% yield. It should be noted that these products can be hydrolyzed to the free amines under mild conditions and further quick SAR developments are possible.

Subsequently we focused our attention on another abundant functional groups in the list of approved drugs namely piperidine moiety. Though simple piperidine should be able to produce the required compounds, our aim is to functionalize further to generate more SAR points. In this situation, we chose pipecolic ester as our major substrate hoping to derivatize further. The reaction under our standard conditions afforded compound **3h** in 73% isolated yield. This compound is proved to be amenable to further functionalization at the acid functional group to generate focused libraries of amide compounds for direct SAR studies. Methyl substitutions on the piperidine moiety was also studied. Recent literature on the incorporation of oxetanes[14] in drug molecules prompted us to study this functional group as well. It has been found that the oxetane functional group tolerated well under the electrochemical conditions. Compound **3j** was isolated in 63% isolated yield. Substituted pyrrolidines were also afforded aminobenzoxazoles in reasonable yield (Compound **3k**, 50% yield).

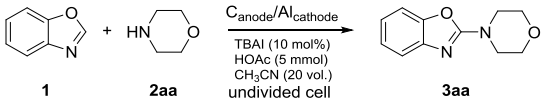
We studied *N*-Boc protected amino piperidines, hoping to develop a strategy for further functionalization at the 3 or 4-position of the piperidine ring. These pharmacophores were valuable in many commercial drugs existing in the market. One particular example is alogliptin[15] which contains aminopiperidine moiety. Under our electrochemical conditions, both racemic as well as single enantiomers of *N*-Boc protected aminopiperidines (**3n**, 81% and **3o**, 78% respectively) produced the same results as anticipated. Similar results were obtained with *N*-Boc protected aminopyrrolidines.

It is interesting to note that acyclic secondary amines also very well participated in electrochemical reactions as illustrated by compounds **3p** and **3q**. Excellent yields were observed in these cases, however the reactions failed to provide any results in the case of primary amines.

Recent literature discloses that many compounds with homopiperazine moieties are biologically active especially as serotonin antagonists[3,16]. As expected, the reactions between benzoxaxoles and *N*-Boc homopiperazine went uneventful to furnish compound **3s** with around 90% isolated yields. A slight decrease in yield was noted in the case of compound **3r**.

Tetrahydroisoquinolines constitute yet another major moiety in approved drugs and we were interested in these groups as well. The coupling reactions went well and the product **3w** was isolated in 76% yield. Homomorpholine also tolerated under our electrochemical conditions (**3v**; 79% yield). All compounds described in this paper have been fully characterized by NMR and mass spectral analysis.

Since we have a robust methodology to attach secondary amines to benzoxazoles, we planned to explore the scalability of some of the reactions. We chose simple benzoxazole and morpholine as substrates. The scale-up results are shown in Table 5 and the reactions were consistent even at 10 g scale (Compound **3aa**) with a very clean profile. It should be scalable even at larger scale and the profile should be clean as well[17].

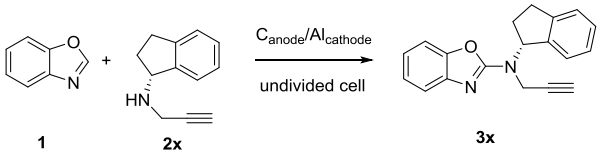


Scheme 4. Scale-up reaction of compound **3aa**.

Table 5. Summary of scale-up reactions.

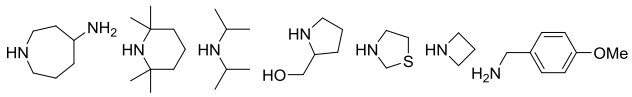
Entry	Compound **1**	Compound **2aa**	Isolated yield of **3aa**
1	50 mg, 0.42 mmol	73 mg, 0.84 mmol	79 mg; 92%
2	500 mg, 4.2 mmol	730 mg, 8.4 mmol	746 mg; 87%
3	2.5 g, 21.0 mmol	3.65 g, 42 mmol	3.6 g; 84%
4	10 g, 84.0 mmol	16.6 g, 168 mmol	14.6 g; 85%

Another interesting result is that we were able to attach one of the marketed drugs such as rasagiline[18] to benzoxazoles in a single step with 59% isolated yield as shown in Scheme 5. This methodology could be utilized for the late stage functionalization of pharmaceutically relevant compounds containing secondary nitrogen moieties. More SAR studies would be generated from this simple one step reaction set up. Further work is in progress to explore the substrate scope of this versatile chemistry that includes benzothiazoles and benzimidazoles and the results will be published in due course.



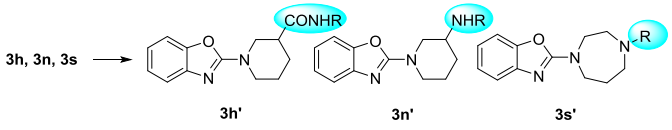
Scheme 5. Electrochemical coupling of rasagiline with benzoxazole.

Shown below are some of the unsuccessful substrates attempted in our electrochemical reactions. These subunits are present in some of the biologically active compounds and may require further rigorous methodology developments.



Scheme 6. Some of the unreacted amines in coupling reaction.

The aminobenzoxazole compounds obtained (e.g. **3h**, **3n** and **3s**) from our studies are amenable to further chemical transformations. Scheme 7 shows our plans to derivatize these newly synthesized aminobenzoxazoles to make focused libraries of amides, sulfonamides, ureas, reductive amination products and so on.



Scheme 7. Further transformations of compounds **3h**, **3n** and **3s**

3. Conclusion

In conclusion, we have presented that pharmaceutically relevant amino substituted benzoxazoles can be synthesized in a single step that is clean, environmentally friendly and atom economic. Moreover, the process eliminates the use of toxic reagents and the reactions are easily scalable.

Acknowledgements

We thank Mr. Vivek Sharma (Piramal Enterprises Limited) for valuable support.

Supplementary Material

Supplementary data associated with this article can be found in the online version.

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12. Typical electrochemical experimental details are shown here. **Compound 3a** (*tert*-Butyl 4-(benzo[d]oxazol-2-yl)piperazine-1-carboxylate): A 30 mL screw capped vial with a septum was inserted carbon anode and aluminum cathode (**CAUTION**: *Electrodes should not come in contact with each other*). The electrodes were connected to a cell phone charger (5V) by use of alligator clips. To the reaction vial were added benzoxazole **1** (119 mg, 1 mmol), *N*-Boc piperazine **2a** (372 mg, 2 mmol), acetic acid (300 mg, 5 mmol, 5 equiv.) and TBAI (37 mg, 10 mol %) and the mixture was dissolved in 20 mL of acetonitrile and stirred gently at room temperature. Electric current was passed through the reaction vial at room temperature for 3 hours. The progress of the reaction was monitored by TLC and LC-MS. After the completion of the reaction, the solvent was removed in vacuo and the crude material was re dissolved in ethyl acetate (25 mL) and then washed with saturated aqueous sodium carbonate solution (3X10 ml). The organic layer was separated, washed with water and then dried over sodium sulfate. The product was purified by column chromatography using hexane and ethyl acetate as eluent to afford 282 mg of compound **3a** (93% yield).
The compound **3a** was characterized by NMR and mass spectral analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.42 (d, *J* = 8 Hz, 1H), 7.30-7.32 (d, *J* = 8 Hz, 1H), 7.20-7.24 (t, 1H), 7.06-7.10 (t, 1H), 3.70-3.73 (t, 4H), 3.59-3.62 (t, 4H), 1.53 (s, 9H). LC-MS (m/z): 304.7 $[M+1]^+$.
13. Intermediate **A** was observed in the LC-MS and as the reaction proceeds, intermediate **A** converts completely to the product **3a** over a period of time. See supplementary details for crude LC-MS trace and analytical details.
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17. Scale-up of **Compound 3aa** (2-Morpholinobenzo[*d*]oxazole): A 250 mL three neck flask was equipped with carbon anode and aluminum cathode (**CAUTION**: *Electrodes should not come in contact with each other*). The electrodes were connected to a cell phone charger (5V) by use of alligator clips. To the reaction flask were added benzoxazole **1** (10.0 g, 84 mmol), morpholine **2aa** (16.6 g, 168 mmol), acetic acid (25.2 g, 5 equiv.) and TBAI (3.1 g, 10 mol %) and the mixture was dissolved in 150 mL of acetonitrile and stirred gently at room temperature. Electric current was passed through the reaction flask at room temperature for overnight. The progress of the reaction was monitored by TLC and LC-MS. The work up was done according to ref. 12. The product was purified by column chromatography using hexane and ethyl acetate as eluent to afford 14.6 g of compound **3aa** (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.42 (d, *J* = 7.6 Hz, 1H), 7.30-7.32 (d, *J* = 7.6 Hz, 1H), 7.20-7.24 (t, 1H), 7.07-7.10 (t, 1H), 3.85-3.88 (t, 4H), 3.72-3.75 (t, 4H). LC-MS (m/z): 205.1 $[M+1]^+$.
Note: Use of 12V adaptor furnished less clean reaction profile as compared to 5V adaptor.
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Highlights:

- Substituted aminobenzoxazoles play an integral role in medicinal chemistry and drug development.
- Single step synthesis of aminobenzoxazoles from benzoxazoles using electrochemical conditions.
- These electrochemical transformations are simple, clean and scalable with a broad substrate scope and functional group tolerance.