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Synthesis of 3-oxadiazolyl/triazolyl morpholines: Novel scaffolds for drug discovery

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ABSTRACT

Synthesis of isomeric 3-oxadiazolyl/triazolyl morpholines was performed based on a common intermediate on the gram scale. The target compounds were designed as novel scaffolds for the medicinal chemistry. The key reaction was an electrochemical CH-oxidation of *N*-Boc morpholine.

1. Introduction

The morpholine moiety has been used extensively in the pharmaceutical industry for drug design often due to the resulting improvement of the pharmacokinetic properties it can provide. The World Drug Index includes well over 100 drugs that comprise this structural feature, including its presence as a side-chain, a scaffold, and a component of the fused-ring systems. All these structures may be divided into two classes, where the major part includes side-chain morpholines.

The minor part includes 2- and/or 3-substituted morpholines, where a specified heterocyclic core is a decisive factor. The biological potential of 2-aryl/heteroaryl scaffolds is well developed in pre-clinical studies[1] and some examples are used in actual clinical practice such as the well-known antidepressant drug Reboxetine and the appetite stimulator Phenmetrazine (Fig. 1).[2] At the same time, the first substantive investigations of the biological activity of 3-heteroaryl-substituted morpholines have been made during the last 10 years. Promising references state that such compounds can inhibit NS5A protein in Hepatitis C virus,[3] can be antagonists of the metabotropic glutamate receptor,[4] and inhibitors of p38 Mitogen-activated protein kinase.[5] Moreover, it was reported that said compounds could be selective blockers for the N-type calcium channels.[6]

The synthesis of 3-arylsubstituted morpholines includes acylation of 2-amino-2-phenylethanol with 2-chloroacetyl chloride, further cyclization with formation of morpholin-3-one, and reduction of the amide bond with $LiAlH_4$.[7] The synthesis of the 3-heteroaryl-substitued morpholines is a more complicated task. The synthetic kit was limited by electrolysis[8] or UV irradiation[9] of mixture of morpholine and heterocycle for a long time. In this

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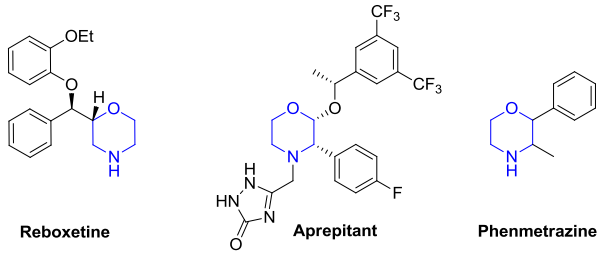


Fig. 1. Marketed morpholine drugs.

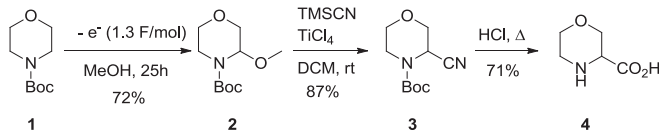
decade were reported Fe-catalyzed oxidative coupling[10] of morpholines with heterocycles, and very original transformation of aldehydes and ketones into azoles with a stannyl amine protocol.[11] Unfortunately, the final morpholines were obtained in milligram amounts with the above methods. We found several publications with the synthesis of 3-heteroaryl-substitued morpholines starting from morpholine-3-carboxylic acid or its nitrile, but detailed analysis revealed the lack of synthetic protocols or the usage of the commercial inaccessible starting materials.[4a,5-6,12] In conclusion, *N*-unsubstituted 3-heteroarylmorpholines are prospective compounds for the drug development. The goal of our research is the development of a gram-scale synthetic protocol for the preparation of the above scaffolds.

2. Results/discussion

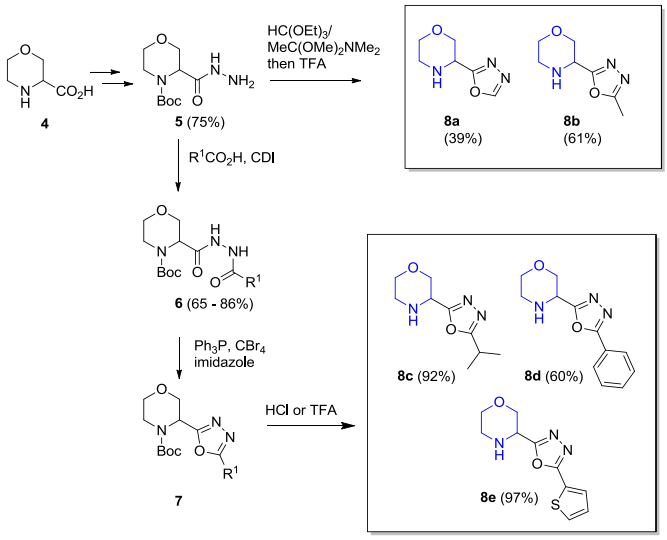
Using a single initial material allows the development of a large library in a short time period. We determined that the nitrile **3** is best suited to the further construction of diverse heterocyclic cores (Scheme 1).

Several protocols for the anodic introduction of a methoxylic anion to the N-protected morpholine have been published before.[13] The anodic oxidation of morpholine **1** was carried out with current 7.5 A and tension 24 V on graphite electrode. It was finished after 1.3 F/mol of electricity in 25 h resulting in the 72% yield. The optimal current density is 20–25 mA/cm^2. We were unable to find more efficient reaction conditions for the electrolysis, and all our experiments resulted in a mixture of *tert*-butyl 3-methoxymorpholine-4-carboxylate **2** and starting morpholine **1** which was purified by column chromatography to get target compound in 90% purity. The analytical sample was prepared by HPLC purification of the above material. The anodic oxidation resulted in a racemic mixture. (S)-Morpholine-3-carboxylic acid and its Boc-protected derivative were synthesized before.[14] The desired nitrile **3** was obtained using the treatment crude **2** with trimethylsilyl cyanide on an 18 g scale.

The synthesis of 1,3,4-oxadiazol-2-yl derivatives was based on the intramolecular cyclization of *N*-acylated hydrazines.[15] Acid **4** was obtained in 71% yield using acid hydrolysis of nitrile **3** (Scheme 1). It was then N-protected with Boc-anhydride, and the intermediate acid was heated with hydrazine hydrate in 2-propanol for 15 h to get hydrazine **5** in 75% yield (Scheme 2). The H- and Me-substituted compounds **8a,b** were obtained using heating of **6**



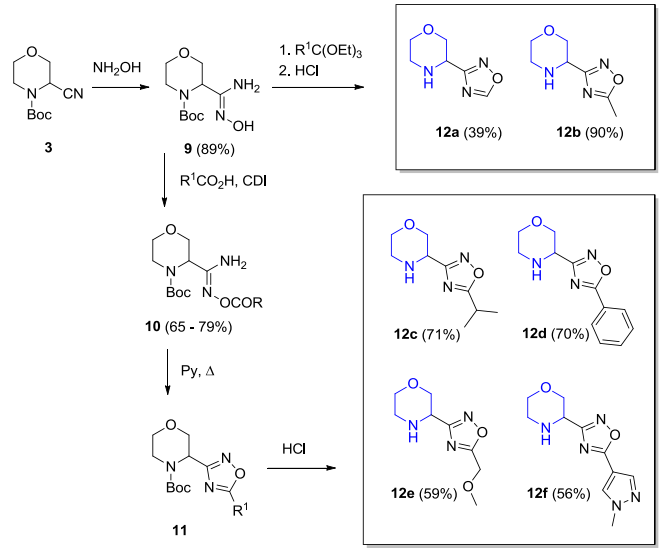
Scheme 1. A quick, 3 steps only, synthesis of key starting materials, *tert*-butyl 3-cyanomorpholine-4-carboxylate and morpholine-3-carboxylic acid.



Scheme 2. Synthesis of 1,3,4-oxadiazol-2-yl derivatives.

with triethoxymethane or 1,1-dimethoxy-*N*,*N*-dimethylethanamine resulting in 39% and 61% yields, accordingly. At the same time, the synthesis of isopropyl, phenyl, and thiophen-2-yl derivatives **8c-e** was carried out in 2 steps. First, hydrazide **5** was acylated with the relevant carboxylic acid and then the resulting imidamide **7** was cyclized into 1,3,4-oxadiazol in a presence of Ph_3P. The treatment of aryl-substituted **7d,e** with hydrochloric acid resulted in smooth removal of the protective group. Hydrochlorides of alkyl-substituted **7a-c** decomposed on standing within several hours. Thus, the preparation of trifluoroacetates that are stable at the room temperature for a long time without decomposition is suggested.

The synthesis of the isomeric 1,2,4-oxadiazol-3-yl derivatives was based on the cyclization of *N*-acylated carboximidamides in the basic medium.[16] Initially, *N*'-hydroxymorpholine-3-carboximidamide **9** was obtained by treatment of nitrile **3** with hydroxylamine in 89% yield (Scheme 3). Reaction of compound **9** with triethoxymethane and 1,1-dimethoxy-*N*,*N*-dimethylethanamine resulted in Boc-protected oxadiazoles. The subsequent



Scheme 3. Synthesis of 1,3,4-oxadiazol-3-yl derivatives.