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Regioselective synthesis of 2-unsubstituted 1-aryl-4- and 1-aryl-5-acylimidazoles

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ABSTRACT

An efficient and simple method for the synthesis of 2-unsubstituted 1-aryl-4- and 1-aryl-5-acylimidazoles has been developed. It consists in the condensation of α-diketone monooximes with aromatic amines and formaldehyde on the presence of boron trifluoride etherate, leading to the formation of stable boron trifluoride complexes of *N*-oxides. Further reduction of these complexes led to the corresponding imidazoles. This method permits broad variations of substituents in the aryl part of these compounds.

1. Introduction

1-Arylimidazoles have a wide range of biological activities[1] and great pharmacological potential.[2–5] 1-Arylimidazoles without a substituent at its position 2 are of particular importance. Several synthetic methods for the preparation of these compounds, are known.[6–10] However, most of them apply for the preparation of only a limited number of compounds, which hinders a comprehensive study of their properties. For this reason developing an efficient method for 2-unsubstituted 1-arylimidazoles synthesis is of considerable interest.

Our synthetic strategy consists of the preparation of 1-arylimidazole *N*-oxides followed by the reduction of the *N*-oxide functional group. First attempts to synthesize 2-unsubstituted 1-arylimidazole *N*-oxides[11–13] involved acid-catalyzed condensation of α-diketone monooximes either with aromatic amines and formaldehyde or previously obtained *N*-arylmethylenamines, but they failed, apparently, due to a rapid isomerization of the *N*-oxides to the corresponding imidazol-2-ones.[13] Other methods[14,15] are also ineffective, since suitable starting materials often prove to be not readily available.

We assumed that 2-unsubstituted imidazole *N*-oxides could be stabilized with respect to a rearrangement to 2-imidazolones by binding them in a complex. In our previous work[16] we have proved that the reaction of primary aromatic amines with formaldehyde and butane-2,3-dione monooxime in the presence of boron trifluoride etherate led to the formation of stable boron trifluoride complexes of 1-aryl-4,5-dimethylimidazole *N*-oxides (Fig. 1).

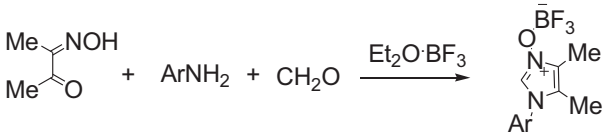

Fig. 1. Synthesis of boron trifluoride complexes of 1-aryl-4,5-dimethylimidazole *N*-oxides.[16]

Aromatic amines containing different substituents, both electron donating and withdrawing groups and aromatic amines with bulky substituents at the *ortho* positions readily participate in this reaction. This shows the prospect of using this as a convenient and general method for the synthesis of 1-arylimidazoles. In the present study, we investigate the viability of this reaction for the preparation of 1-arylimidazoles containing an acyl group at positions 4 or 5.

2. Results and discussion

It is well-known that arylation of imidazoles containing dissimilar substituents at positions 4 and 5 leads to a mixture of

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regioisomers with predominance of the less sterically hindered compound.[6,17] Our method makes it possible to prepare any predetermined regioisomer. The nature of substituents at positions 4 and 5 depends on the structure of α-diketone monooxime.

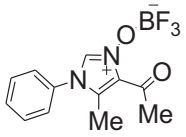
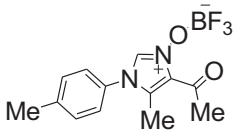
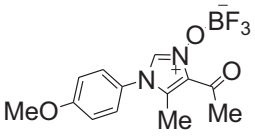
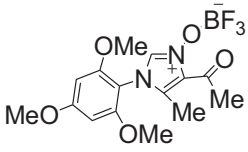
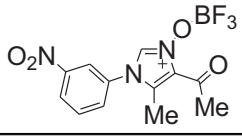
Thus, for the synthesis of 1-aryl-4-acetylimidazoles easily available pentan-2,3,4-trione 3-oxime **7** can be used.[18] Indeed, the condensation of compound **7** with aromatic amines and formaldehyde in the presence of boron trifluoride etherate led to the formation of complexes of boron trifluoride with 1-aryl-4-acetyl-5-methylimidazole *N*-oxides **2** in good yield.

Boron trifluoride etherate not only stabilizes imidazole *N*-oxides but also acts as an excellent acid catalyst facilitating the reaction, so that it may proceed under mild conditions.

It is possible to use various solvents for the condensation (chloroform, alcohols, acetic acid); the choice is mainly determined by features of the isolation of products.

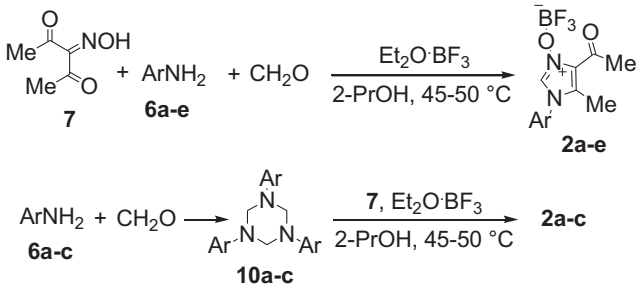
The use of the obtained 1,3,5-triarylhexahydro-1,3,5-triazinanes **10**[19] is an alternative to using a mixture of arylamines **6** and formaldehyde; compounds **10** possess a relatively high reactivity and the greater storage stability. Also, the use of triazinanes **10** makes it possible to minimize the amount of water entering with formaldehyde solution. In this case, the yields of **2** are generally higher (see Table 1, entries 1–3, Scheme 1).

Table 1
Complexes of boron trifluoride with 1-aryl-4-acetyl-5-methylimidazole *N*-oxides **2** produced via Scheme 1

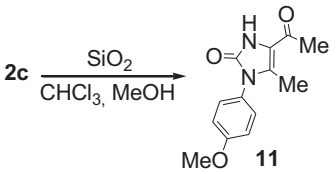
Entry	Compound **2**		Yield, %
1		**2a**	61[a] (80)[b]
2		**2b**	48[a] (71)[b]
3		**2c**	33[a] (47)[b]
4		**2d**	55[a]
5		**2e**	83[a]

[a] Method A: 1.0 equiv oxime **7**, 1.1 equiv $Et_2O{\cdot}BF_3$, 2.0 equiv CH_2O, 1.0 equiv $ArNH_2$ **6** IPA, 45–50 °C, 4 h.
[b] Method B: 1.0 equiv oxime **7**, 1.1 equiv $Et_2O{\cdot}BF_3$, 1.0 equiv triazinane **10**, IPA, room temperature, 4 h.

It is interesting to note that compounds **2** appeared to be less stable than their 4,5-dimethyl analogs. Thus, the attempt to isolate derivative **2c** from the reaction by column chromatography on silica gel led to the isolation imidazole-2-one **11**. Moreover, when pure compound **2c** was passed through a silica gel (eluent: chloroform/methanol) compound **11** was obtained in nearly quantitative yield (Scheme 2). At the same time, complexes of boron trifluoride with 1-aryl-4,5-dimethylimidazole *N*-oxides were smoothly isolated by chromatography in high to moderate yields.

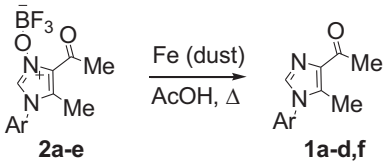


Scheme 1. Synthesis of boron trifluoride complexes **2**.



Scheme 2. Transformation of boron trifluoride complex to the imidazol-2-one.

The reduction of compounds **2** proceeds facile by using various reducing agents and results in corresponding imidazoles **1** in high yields (Scheme 3).



Scheme 3. Reduction of complexes **2**.

The fact that the condensation and reduction can be carried out in the same solvent (e.g., isopropyl alcohol or acetic acid) prompted us to obtain imidazoles **1** using one-pot procedure (see Table 2).

4-Acylimidazoles **3** were also obtained by using a one-pot procedure. As it is known, oxime **8**[20] is unstable under heating in solvents, especially in the presence of acids. For this reason the condensation was performed in acetic acid at room temperature with an increased reaction time (20 h). The reduction step was carried out in the conventional manner (Table 3).

Readily available cyclic dioxime **9**[21] was chosen as a precursor in the synthesis of sterically hindered 5-acylimidazoles. In this case the condensation was carried out with 2 equiv of boron trifluoride etherate because of the potential possibility of complexation of the BF_3 with both *N*-oxide and oxime groups. However, compounds **5** contain only one BF_3 group (Table 4).

The oxime group in these compounds is hidden by the carbonyl function. So, the reduction of compounds **5** by iron dust in boiling acetic acid is accompanied by the hydrolysis of oxime function and led to the formation of imidazoles **4**. The isolation of these compounds is easy and can be carried out even without chromatography (Table 5).