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A simple and convenient two-step, one-pot synthesis of hetero-imidazoles from nitroaminoaryls catalyzed by Ytterbium triflate

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ABSTRACT

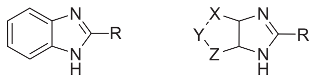
A mild two-step one-pot procedure for the conversion of *ortho*-nitroamino aromatic heterocycles into corresponding benzo and heteroaromatic fused imidazoles is described. The procedure utilizes iron powder, acetic acid, triethylorthoformate, and a catalytic amount of Ytterbium triflate at 75 °C for the nitro group reduction and cyclization reaction. The optimum stoichiometry of each component is highlighted and the broad utility is demonstrated with high compatibility to numerous functional groups.

Introduction

The imidazole ring system is found in important biological building blocks and substances that exhibit diverse biological and pharmaceutical activities.[1] The essential amino acid histidine, the related compound biotin and alkaloids are well known natural products that have the imidazole moiety.[2] Separately, synthetic imidazole containing derivatives are important antifungal, antithyroid, and amoebicidal drugs.[2,3] Benzo and heteroaromatic fused imidazoles such as **1** and **2** (Fig. 1), respectively, represent an equally important class of bio-active compounds due to their therapeutic and pharmaceutical properties.[4,5] Various benzimidazole scaffolds for example, possess applications in numerous different therapeutic areas such as antifungal,[6] antiviral,[4c,7] antihypertensive,[8] anticancer,[9] and antihistaminic.[10] Due to the close similarity of benzo and various heteroaromatic fused imidazoles to the purine base adenine, these structural motifs have also been utilized and incorporated sporadically within protein kinase inhibitors.[11]

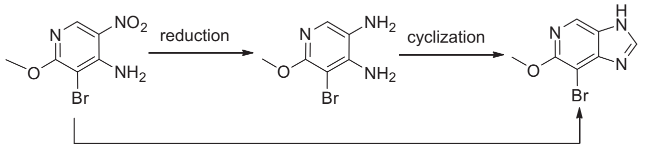
A number of synthetic strategies to access benzo and heterocyclic fused imidazoles such as **1** and **2** are well known and described in the literature.[12–14] The most common route involves condensation of an *ortho*-diamino substituted aromatic heterocycle with an appropriate acid or its derivative such as a nitrile, amide or orthoester.[13e,14b,15] An *ortho*-nitroamino aromatic heterocycle can be another useful starting building block which can be converted into the corresponding benzo and heteroaromatic fused imidazoles.[13d,16] The traditional method is carried out in a two-step process first involving the reduction of the nitro group followed by condensation with the appropriate acid or orthoester. There have also been some reports of two-step one-pot processes in which the reduction and cyclization are performed without isolation of the corresponding intermediate *ortho*-diamine. This has been predominantly exemplified in benzimidazole analog synthesis.

During our effort to synthesize 7-bromo-6-methoxy-3*H*-imidazo[4,5-c]pyridine **5** starting from 3-bromo-2-methoxy-5-nitropyridin-4-amine **3** (Fig. 2), poor yields and long reaction times were observed using published methods. Our initial attempts relied on well known two-step processes involving reduction of the nitro group as the first step leading to **4**. This was followed by



1 **2**

Figure 1. Benzimidazole and heteroaromatic fused imidazoles.



3 **4** **5**

Figure 2. Two-step strategy for azabenzimidazole synthesis.

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condensation of the resulting 5-bromo-6-methoxypyridine-3,4-diamine **4** under acidic conditions (Table 1, entries 1–3). Poor yields were attributed to the unstable nature of the resulting 5-bromo-6-methoxypyridine-3,4-diamine **4**. Therefore, we shifted our synthetic strategy toward known two-step one-pot procedures that would enable us to 'trap' the unstable compound **4**. Entry 4 through 11 in Table 1 describes selected published procedures that gave unsatisfactory results.

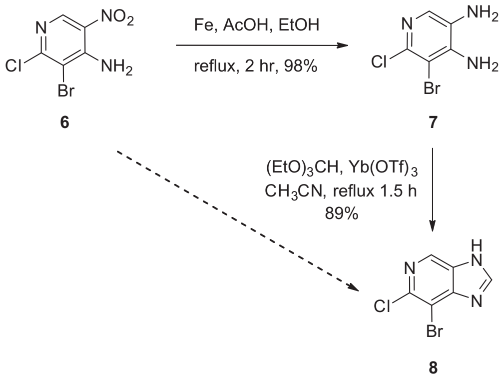
The unsuccessful attempts in obtaining compound **5** in adequate yields lead us to initiate a new synthetic route from a slightly modified starting material, 3-bromo-2-chloro-5-nitropyridin-4-amine **6** (Scheme 1). It was hypothesized that replacing the electron donating methoxy group in **3** with an electron withdrawing chloro group as in **6** would help generate a more stable diamino pyridine intermediate as in compound **7**. The most promising conditions, entry 2 in Table 1, were chosen as a starting point.

Gratifyingly, the two-step procedure using Fe, acetic acid in ethanol to reduce compound **6** followed by Ytterbium triflate catalyzed condensation with triethylorthoformate resulted in compound **8** in 87% overall yield. However, attempts to introduce the methoxy group leading to compound **5** were unsuccessful. Therefore, our focus shifted back to the original synthetic route as depicted in Figure 2. Again, we hypothesized that the unstable nature of 5-bromo-6-methoxypyridine-3,4-diamine **4** limited the success of these conditions in that case. Because condition 2 in Table 1 worked very well when applied in Scheme 1, we attempted to combine the two-step procedure into a one-pot synthesis for the conversion of **3**–**5**, thus avoiding the isolation of **4**. Gratifyingly, treatment of compound **3** with Fe, acetic acid, Yb(OTf)$_3$, and triethylorthoformate at 75 °C for 3 h was successful in producing desired compound **5** in 86% isolated yield.

Table 1
Conditions for the synthesis of compound **5** via Figure 2

Entry	Conditions	Yield (%)
1	(a) Pd/C, H$_2$, EtOAc 22 °C, 16 h (b) HCNNH$_2$·HOAc, HCOOH, EtOH, reflux, 24 h	15
2	(a) Fe, HOAc, EtOH reflux, 2.5 h (b) CH(EtO)$_3$, Yb(OTf)$_3$, CH$_3$CN, reflux, 0.5 h	23
3	(a) Pd/C, H$_2$, EtOAc 22 °C, 16 h (b) CH(EtO)$_3$, Yb(OTf)$_3$, CH$_3$CN , reflux, 0.5 h	45
4	Fe, NH$_4$Cl, HCOOH, 80 °C, 1 h	[a]
5	Fe, HCOOH 100 °C, 16 h	[a]
6	Pd/C, CH(EtO)$_3$, H$_2$, MeOH, HOAc, rt, 16 h	[b]
7	SnCl$_2$, HCOOH, Microwave 130 oC, 20 min	30[c]
8	SnCl$_2$, HCOOH 75 °C, 24 h	5[c]
9	SnCl$_2$, HCOOH 100 °C, 16 h	[d]
10	Pt/C, HCOOH, H2O 95 oC, 1h	[e]
11	Pd/C, HCOOH 100 °C, 66 h	[b]

[a] Formylated intermediate **4**.
[b] Des Bromo **3** and unidentified side products.
[c] By LCMS.
[d] Demethylated product.
[e] Starting material.



Scheme 1. Two-step route to compound **8**.

Table 2
Role of Yb(OTf)$_3$ for the conversion of **3**–**5**

Condition	T (°C)	Product conversion (LCMS)				Yield (%)
		30 min (%)	60 min (%)	3 h (%)	24 h (%)	
A	22	1	3	6	23[a]	N/A
B	22	20	20	25	96	N/A
A	75	12	16	30	74	N/A
B	75	59	81	100	N/A	86

Condition A: Fe, AcOH, CH(OEt)$_3$.
Condition B: Fe, AcOH, CH(OEt)$_3$, Yb(OTf)$_3$.
[a] A significant unidentified byproduct was observed.

We examined the role of Yb(OTf)$_3$ and the results are shown in Table 2. Both room temperature and 75 °C, conditions not containing Yb(OTf)$_3$ (condition A) were sluggish whereas those containing Yb(OTf)$_3$ (condition B) afforded a better reaction profile. It is well know that rare earth metal triflates such as Yb(OTf)$_3$ are uniquely strong Lewis acids compatible with polar protic solvents.[17] Yb(OTf)$_3$ clearly plays a role in accelerating the overall reaction time in both the condensation and cyclization steps as well as improving the isolated yields.

To better understand the importance of each component, the stoichiometry was explored (Table 3). All reactions were performed in 1.0 M of acetic acid. As a preliminary reaction we tested the conversion of compounds **3**–**5** varying the number of equivalents of triethylorthoformate in the presence of 3 equiv of Fe and 0.01 equiv of Yb(OTf)$_3$ (conditions 1–3). Increasing the number of equivalents of triethylorthoformate significantly improved the reaction profile resulting in a better isolated yield (conditions 2 and 3). An improvement of yield is also observed when the amount of iron is increased to 5 equiv (condition 4 vs condition 2 and condition 5 vs condition 3). Further increase of iron to 7 equiv did not affect the reaction profile (conditions 7 and 8). When Yb(OTf)$_3$ is reduced to 0.005 equiv, the reaction profile was not affected and therefore these conditions (entry 6) were considered most desirable.

Having established the optimal reaction conditions, we turned our attention to the scope of the reaction. First, we examined the formation of benzimidazoles from *ortho*-nitroanilines (Table 4, Scheme 2).

Utilizing our optimum conditions, all reactions were completed within 3 h in excellent isolated yields ranging from 82% to 99% (Table 4). Reactions in which the phenyl ring was substituted with electron-withdrawing groups (entries 4 and 5) performed as well as reactions in which the phenyl group was substituted with an

Table 3
Reaction stoichiometry for the conversion of **3**–**5**

Condition	Fe (equiv)	(EtO)$_3$CH (equiv)	Yb(OTf)$_3$ (equiv)	Yield (%)
1	3	1	0.01	[a]
2	3	3	0.01	54
3	3	5	0.01	64
4	5	3	0.01	63
5	5	5	0.01	84
6	5	5	0.005	86
7	7	3	0.01	[b]
8	7	5	0.01	[c]

Reactions were performed with compound **3** (150 mg, 1 equiv) in 1.0 M AcOH at 75 °C.
[a] Trace of product observed by LCMS with intermediate remaining.
[b] Reaction profile by LCMS similar to condition 4. Product not isolated.
[c] Reaction profile by LCMS similar to condition 6. Product not isolated.