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Weinreb amide as an efficient reagent in the one pot synthesis of benzimidazoles and benzothiazoles

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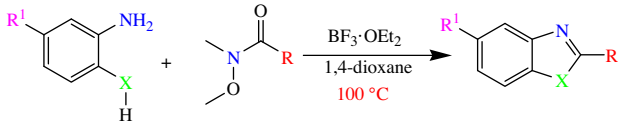
ABSTRACT

One pot synthesis of 2-substituted benzimidazoles/benzothiazoles through condensation is followed by cyclization of Weinreb amide with *o*-diaminoarene or *o*-aminothiophenol is reported. In the presence of boron trifluoride etherate in 1,4-dioxane solvent, a high yield (75–94%) was achieved within 60 min. Weinreb amide shows high selectivity in the reaction, even in presence of other active functional groups such as carboxyl, halogen, cyano, and methoxy.



X : NH, S
R^1 : H, CH_3, Br
R : Alkyl, Alkenyl, Aryl, Heteroaryl

2-Substituted benzimidazoles and benzothiazoles have gained importance in medicinal chemistry. They have been in use as anti-inflammatory,[1a] antimicrobial,[1b] anti-ulcer,[1c] antihelmentic,[1c] antihypertensive,[1d] anti-analgesic,[1e] antivirus,[1f] and anticancer agents.[1g] The general method of synthesis of 2-substituted benzimidazoles involves the reaction between *o*-diaminoarene and a carboxylic acid or an acid chloride or nitrile or imadates or ortho esters. The condensation of arenealdehyde with 1,2-diaminobenzene to form a Schiff base which undergoes intramolecular cyclization generating a dihydrobenzimidazole which undergoes dehydrogenation by 1,4-benzoquinone.[2] Alternative oxidants that can be used are 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[3] manganese dioxide,[4] lead tetraacetate {$Pb(OAC)_4$},[5] potassium-monopersulfate (oxone),[6] and sodium bisulfate.[7] Synthesis of benzimidazoles through transition-metal catalyzed amination followed by condensation has also been reported.[8,9]

Similarly, the classical approach for the synthesis of 2-substituted benzothiazoles is by condensation of *o*-aminothiophenols with aldehydes using oxidants or oxidation process such as MnO_2/SiO_2,[10] silica-sulfuric acid,[11a] *p*-TsOH, or graphite on the surface of solid mineral supports under microwave irradiation,[11b–f] I_2/DMF,[12] 1-phenyl-3-methylimidazolium bromide {[PmIm]Br} under microwave irradiation,[13] activated carbon (Shirasagi KL or Darco® KB) under oxygen atmosphere,[14] O_2 or H_2O_2 in the presence of $Sc(OTf)_3$,[15] ceric ammonium nitrate (CAN),[16] pyridinium chlorochromate,[17] electro oxidation,[18] solvent and catalyst-free microwave irradiation,[19] trichloroisocyanuric acid,[20] and perchloric acid-doped polyaniline.[21] However, the above mentioned methods suffer from several disadvantages like harsh reaction conditions (strong acid, high temperature), high catalyst cost, occurrence of side reactions (which leads to poor yield and difficulty in isolation), low reaction rate, additional oxidation step, tedious work-up pro-

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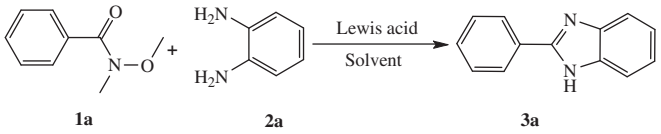
Table 1
Optimization of reaction conditions for the synthesis of 2-phenyl-1*H*-benzimidazole **3a** from *N*-methoxy-*N*-methylbenzamide **1a** with *o*-diamino benzene **2a**



1a **2a** **3a**

Entry	Lewis acid (1.0 equiv)	Temperature (°C)	Time (min)	Yield[a] (%)
01	$ZnCl_2$	RT	—	0
02	$ZnCl_2$	100	60	20
03	$AlCl_3$	100	60	35
04	$FeCl_3$	100	60	27
05	$SnCl_4$	100	60	42
06	$BF_3{\cdot}OEt_2$	100	60	88
07	$Sc(OTf)_3$	100	60	34
08	$InCl_3$	100	60	48
09	PTSA	100	60	54

[a] Isolated yield.

cedure, and lack of selectivity. The present method aims at overcoming all these problems.

N-Methoxy-*N*-methylamide is popularly known as Weinreb amide, which Nahm and Weinreb first employed in the synthesis of ketones from organometallics and also used as acylating agent to synthesize ester enolate.[22] Nowadays, the versatility of this reagent has been increased in organic synthesis for instance, in the preparation of aldehydes,[23a] ketones by classical Wittig reaction,[23b] Grignard reactions,[24a,b] organolithium additions,[24c–e] lithium aluminum hydride reductions,[24f] acylation of oxazole,[25] pyrazoles,[26] nitriles,[27] pyrrole carbaldehyde and pyrrolidinones,[28] trifluoromethyl ketones,[29] etc. The four main reasons for its increased use by chemists as a reagent in organic synthesis are the stability of Weinreb amide functionality, ease of preparation, the scalability of reaction and predictability. As part of our research on Weinreb amide application, we tried one pot syntheses of 2-substituted benzimidazoles and benzothiazoles.

Weinreb amides were synthesized from the carboxylic acid by coupling with *N*,*O*-dimethyl-hydroxyl amine.[30] Optimization of the reaction conditions and parameters were stabilized for the synthesis of 2-phenyl-1*H*-benzimidazole (**3a**) by cyclization of *N*-methoxy-*N*-methylbenzamide (**1a**) with *o*-diamino benzene (**2a**) using various Lewis acids in 1,4-dioxane solvent (Table 1).

The reaction was carried out initially between **1a** and **2a** in the presence of zinc chloride as Lewis acid in 1,4-dioxane at room temperature, but product **3a** was not obtained even after a prolonged time of 24 h (Table 1, entry 1). When the reaction was continued at 100 °C no improvement in yield was observed (Table 1, entry 2). Further, the reaction was done with various Lewis acids such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $InCl_3$ and PTSA to enhance the product yield (Table 1, entries 3–9). Among these reagents, only $BF_3{\cdot}OEt_2$ gave the highest product yield of 88% (Table 1, entry 6).

The solvent and temperature factors on the cyclization reaction between **1a** and **2a** in the presence of boron trifluoride etherate were optimized (Table 2). Although most of the solvents promoted the reaction, 1,4-dioxane and toluene were found suitable media at 100 °C conditions (Table 2, entries 1 and 4).

Finally, the optimized reaction conditions were used to study the generality of the protocol and scope of this cyclization reaction. We have studied the reactivity of various alkyl, alkenyl, aryl, and hetero aryl Weinreb amides and the selectivity of Weinreb amide

Table 2
The reactivity of boron trifluoride etherate in various solvents and at temperatures during the synthesis of 2-phenyl-1*H*-benzimidazole **3a** from *N*-methoxy-*N*-methylbenzamide **1a** with *o*-diaminoarene **2a**

Entry	Equivalent	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
01	1.0	1,4-Dioxane	100	60	89
02	1.0	EDC	90	60	40
03	1.0	DMF	100	60	45
04	1.0	Toluene	100	60	82
05	1.0	Benzene	90	60	76
06	1.0	THF	70	60	32
07	1.0	CH_3CN	90	60	25

[a] Isolated yields.

Table 3
Synthesis of 2-substituted bezimidazoles **3a–l** from Weinreb amides **1a–j**

Entry	R	**1**	R^1	**3**	Yield[a] (%)
01	Phenyl	**1a**	H	**3a**	90
02	4-Carboxyphenyl	**1b**	H	**3b**	81
03	2-Carboxyethyl	**1c**	H	**3c**	78
04	4-Pyridyl	**1d**	H	**3d**	75
05	2-(4-Pyridyl)ethyl	**1e**	H	**3e**	78
06	Allyl	**1f**	H	**3f**	80
07	Me	**1g**	H	**3g**	90
08	4-Bromophenyl	**1h**	H	**3h**	89
09	Phenyl	**1a**	CH_3	**3i**	87
10	Me	**1g**	Br	**3j**	84
11	3-Pyridyl	**1i**	H	**3k**	77
12	Cyclohexylmethyl	**1j**	H	**3l**	86

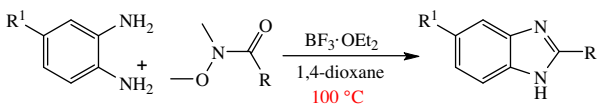
[a] Isolated yields.

was examined in the presence of active carboxyl, halogens, cyano, and methoxy groups.

Weinreb amide showed high reactivity and selectively participated in the cyclization reaction to obtain a very good yield within a short time (Table 3, entries 2 and 3)(Scheme 1).

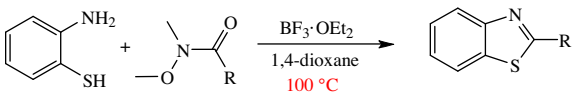
The optimized reaction conditions were further used to synthesize 2-alkyl/aryl/heteroaryl benzothiazoles from Weinreb amides by replacing *o*-diminoarene with *o*-aminothiophenol (Scheme 2).[31] The reaction afforded 2-substituted benzothiazole with good yield (Table 4, entries 1–9). Further, the reaction was carried out with *o*-aminophenol with the expectation to generate 2-arylbenzoxazole, but the yield obtained was very low (~15%) (Scheme 3). This may be due to lower nucleophilicity of oxygen than of nitrogen and sulfur.

In conclusion, Weinreb amide has proved to be an effective reagent to synthesize 2-substituted benzimidazoles and benzothiazoles in the presence of boron trifluoride etherate in 1,4-dioxane solvent at 100 °C. The optimized procedure is a one pot synthesis and shows high selectivity, because the amide function alone participates in the cyclization reaction even in the presence of active functional groups like carboxyl, halogens, cyano, and methoxy on the carbon skeleton of the Weinreb amide. This method may successfully replace the earlier methods for the preparation of 2-substituted benzimidazoles and benzothiazoles which are currently prepared with non-commercial and unstable or sensitive aldehydes and acid chlorides.



2 **1a-j** **3a-l**

Scheme 1. The cyclization of *o*-diaminoarene **2a** with various Weinreb amides **1a–j** in the presence of boron trifluoride etherate.



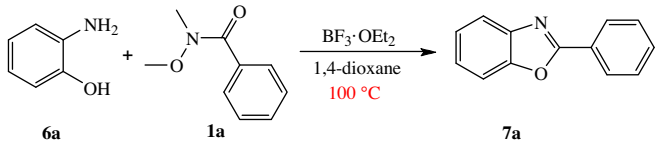
5a **1a,b,d,f,j-n** **4a-i**

Scheme 2. The cyclization of *o*-aminothiophenol **5a** with various Weinreb amides **1a**,**b**,**d**,**f**,**j**–**n** in the presence of boron trifluoride etherate.

Table 4
Synthesis of 2-substituted benzothiazoles **4a**–**i** from Weinreb amides **1a**,**b**,**d**,**f**,**j**–**n**

Entry	R	1	4	Yield[a] (%)
01	Phenyl	**1a**	**4a**	94
02	4-Carboxyphenyl	**1b**	**4b**	76
03	3-Cyano phenyl	**1k**	**4c**	81
04	4-Pyridyl	**1d**	**4d**	75
05	4-Fluoro-3-methoxyphenyl	**1l**	**4e**	89
06	4-Ethylphenyl	**1m**	**4f**	92
07	Benzo[1,3]dioxolyl	**1n**	**4g**	94
08	Allyl	**1f**	**4h**	88
09	2-Carboxyethyl	**1j**	**4i**	89

[a] Isolated yields.



6a **1a** **7a**
15%

Scheme 3. The cyclization of *o*-aminophenol **6a** with *N*-methoxy-*N*-methyl-benzamide **1a** in the presence of boron trifluoride etherate.

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Supplementary data

Supplementary data (Supplementary data ^{1}H NMR and ^{13}C NMR of the synthesized compounds described in Schemes 1 and 2 are associated with this article are available, in the on-line version) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.075.

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31. *General Procedure:* To a stirred solution of Weinreb amide (5 mmol), *o*-diaminoarene or *o*-aminothiophenol (5 mmol) in 1,4-dioxane (10 mL) was added $BF_3{\cdot}OEt_2$ (5 mmol). The resulting mixture was heated at 100 °C under nitrogen atmosphere for the specified time (Table 3 and 4). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated ammonium chloride solution (40 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), brine solution (2 × 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The resulting residue was purified by column chromatography on silica gel (Merck, 60–120 mesh, appropriate ethyl acetate and hexane mixture, 1:1 or 3:7) to afford the pure product.