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$BF_3{\cdot}Et_2O$ promoted one-pot expeditious and convenient synthesis of 2-substituted benzimidazoles and 3,1,5-benzoxadiazepines

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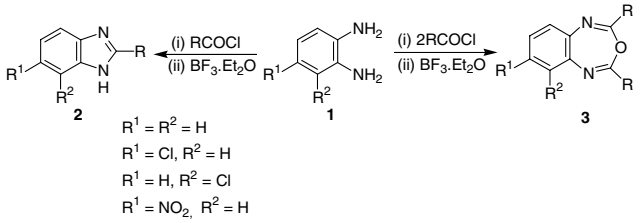
Abstract—2-Substituted benzimidazoles and 3,1,5-benzoxadiazepines have been synthesized in excellent yields in a single pot by cyclodehydration of *N*-acyl-1,2-phenylenediamines and *N*,*N*′-diacyl-1,2-phenylenediamines prepared in situ from the corresponding 1,2-phenylenediamines and an acid chloride, respectively.

The benzimidazole ring is a crucial pharmacophore in drug discovery. Benzimidazole derivatives are an unique and broad-spectrum class of antirhino/enteroviral agents.[1] Benzimidazoles exhibit significant activity against several viruses including HIV,[2] herpes (HSV-1),[3] RNA,[4] influenza[5] and human cytomegalovirus (HCMV).[2a] In recent years benzimidazoles have been reported to act as topoisomerase I inhibitors,[6] selective neuropeptide Y Y1 receptor antagonists,[7] angiotensin II (AII) inhibitors,[8] inhibitors of HCMV replication, [2a] 5-HT_3 antagonists in isolated guinea pig ileum,[9] potential antitumour agents,[10] antimicrobial agents,[11] smooth muscle cell proliferation inhibitors,[12] a treatment for interstitial cystitis,[13] as factor Xa inhibitors[14] and in diverse areas of chemistry.[15]

Benzoxadiazepines have been found to possess marked biological effects as CNS stimulants,[16] muscle relaxants,[17] tranquilizers, anticonvulsants,[18] antibacterial and antiinflamatory agents[19] and pesticides and insecticides.[18]

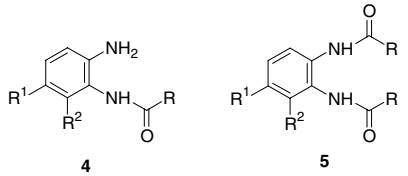
A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of 2-substituted benzimidazoles.[20–26] However, the yields reported in the above methods are moderate or poor. Moreover more than one step is involved in the synthesis of these compounds. Few methods are available in the literature for the synthesis of benzoxadiazepines.[27–30]



Scheme 1.

During the course of our studies towards the development of new routes to the synthesis of heterocycles, we employed $BF_3{\cdot}Et_2O$ as a selective reagent for cyclodehydration of *N*-acyl-1,2-phenylenediamines and *N*,*N*′-diacyl-1,2-phenylenediamines, resulting in the formation of 2-substituted benzimidazoles and 2,4-disubstituted benzoxadiazepines (Scheme 1).

We envisaged that cyclodehydration of *N*-acyl and *N*,*N*′-diacyl derivatives **4** and **5** with $BF_3{\cdot}Et_2O$ would lead to the formation of 2-substituted benzimidazoles **2** and 2,4-disubstituted 3,1,5-benzoxadiazepines **3**.



A typical reaction procedure involves the addition of 1,2-phenylenediamines **1** to the acid chloride (1 equiv) at

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Table 1. Isolated 2-substituted benzimidazoles **2** and 3,1,5-benzoxadiazepines **3** from 1,2-phenylenediamines **1**. All the reactions were complete in 1–2.5 h

Entry	R	R^1	R^2	Product yield (%)	
				2	**3**
1	CH_3	H	H	95	82
2	C_6H_5	H	H	97	88
3	4-Cl–C_6H_4	H	H	98	91
4	4-MeO–C_6H_4	H	H	97	93
5	4-O_2N–C_6H_4	H	H	98	90
6	2-C_5H_4N	H	H	94	92
7	4-C_5H_4N	H	H	93	90
8	CH_3–CH_2–CH_2	H	H	92	83
9	2-Furyl	H	H	94	86
10	CH_3	Cl	H	92	85
11	CH_3	H	Cl	93	87
12	C_6H_5	Cl	H	94	92
13	CH_3	NO_2	H	93	88
14	C_6H_5	NO_2	H	95	92

0 °C in dry dioxane and stirring for 30 min at rt to furnish the corresponding *N*-acyl-1,2-phenylenediamine **4**. $BF_3{\cdot}Et_2O$ in dry dioxane was added to crude **4** and the reaction mixture refluxed for 1–2.5 h at 130 °C. The yields of the 2-substituted benzimidazoles[31] were excellent (92–98%) and independent of the various substituents present in the precursor (Table 1).

Employing the same procedure reported above but using 2 equiv of acid chloride, 2,4-substituted-3,1,5-benzoxadiazepines **3** were synthesized.[32] The yields of **3** were 82–93% and independent of various substituents present in the precursor (Table 1).

Our method for the synthesis of 2-substituted benzimidazoles and 2,4-disubstituted-3,1,5-benzoxadiazepines[33] has the following advantages over previous known methods of synthesis: (i) the precursors *N*-acyl and *N*,*N*′-diacyl-1,2-phenylenediamines need not be isolated before cyclodehydration; (ii) the cyclodehydration and deacylation can be accomplished in situ in one pot; (iii) $BF_3{\cdot}Et_2O$ is efficient and tolerant towards a number of substituted aromatics, unsubstituted aliphatics and heterocycles.

In summary, the present communication describes a simple, efficient and convenient synthesis of 2-substituted benzimidazoles and 2,4-disubstituted 3,1,5-benzoxadiazepines in excellent yields using $BF_3 \cdot Et_2O$ as the cyclodehydrating and deacylating agent.

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31. Substituted benzimidazoles **2** reported in Table 1 are known compounds to which the spectroscopic data was compared. Data for entry 8: 2-*n*-propylbenzimidazole: mp 160–162 °C (lit.[29] 157–159 °C); ν_{max} (KBr/cm): 1604 (C=N), 3110 (NH); ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 0.80 (3H, t, $J = 6.5$ Hz, CH_3), 1.93 (2H, m, CH_2), 2.14 (2H, t, $J = 6.5$ Hz, CH_2), 6.80–7.42 (5H, m, Ph and NH); m/z M^+, 161 (M+1), 160.
32. Some of the 3,1,5-benzoxadiazepines reported in Table 1 are known compounds for which satisfactory spectroscopic data were obtained. Data for 2,3-bis(4-methoxyphenyl)-3,1,5-benzoxadiazepine (entry 4): pale yellow powder, mp 124 °C; ν_{max} (KBr/cm): 1680 (C=N), 1026 (C–O–C); ^{1}H NMR ($CDCl_3$, 200 MHz, δ ppm): 3.85 (6H, s, OCH_3), 6.95 (8H, m, Ph), 7.87 (4H, m, Ph); m/z M^+, 359 (M+1), 105, 77; ^{13}C: 56.0, 114.2, 123.5, 128.3, 130.0, 146.7, 164.0, 164.3; Analysis: calcd for $C_{22}H_{18}N_2O_3$; C, 73.74; H, 5.02; N, 7.82; found: C, 73.92; H, 5.08; N, 7.94.
33. The detailed spectral data of other benzimidazoles and benzoxadiazepines will be reported in a full paper.