Synthesis of Novel 7-methylene-6,7-dihyrobenzo[f]Benzo[4,5] Imidazo[1,2-d][1,4]Oxazepines *via* Base-mediated Regioselective Intramolecular Hydroamination

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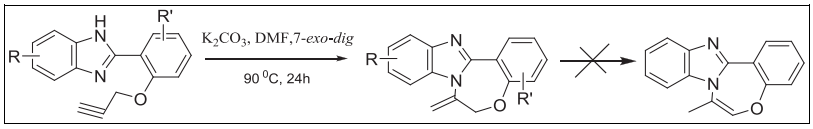

A versatile and transition metal-free approach for the synthesis of new 7-methylene-6,7-dihyrobenzo[f] benzo[4,5]imidazo[1,2-d][1,4]oxazepines were developed by an efficient 7-exo-dig regioselective hydroamination of 2-(2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole in the presence of potassium carbonate in DMF at 90°C.

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INTRODUCTION

Compounds containing "a fused seven-membered benzoxazepine ring" have been of pivotal interest over the past few years because of their wide range of biological activities and pharmacological properties [1–4]. For instance, 5,6-dihydrobenzo[f]imidazo[1,2d] [1,4] oxazepine scaffolds (Fig. 1) are very promising therapeutics for various types of cancer treatments. The connection of benzoxazepines with various biological activities such as anticonvulsant and hypnotic [5], anticancer, and antipsychotic activities [6,7] is well documented in the literature review section. Most syntheses of 2,3,4,5-tetrahydro-1,4-benzooxazepines can be prepared by different synthetic methods: (i) condensation of 2-aryloxyethylamines with 2-formylbenzoic acid to form aminonaphtalides followed by cyclization; (ii) rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzooxazepine-5-yl) benzoate using Bischler–Napieralski conditions; and (iii) scandium or copper triflate-catalyzed acylaminoalkylation of α-methoxy-isoindolones with the formation of 1,4-benzoxazepine [8–10].

Regardless of the fact that the derivatives of benzoxazepine and imidazole have been frequently synthesized and evaluated for their bioactivity, the related literature is in need for the adequate reports about the synthesis of fused benzoxazepine-imidazole derivatives. In recent years, intramolecular and intermolecular hydroamination reactions, the addition of an amine to an unsaturated carbon–carbon multiple bond, are the widely explored reactions for the direct formation of the C—N bond in the synthesis of nitrogen heterocycles [10–15]. The reaction offers an atom-efficient pathway starting from readily accessible alkenes and alkynes. Hydroamination presents an important challenge because of the repulsion between a nitrogen lone pair and the olefin/alkyne π system, and it is also difficult to control the regioselectivity (Markovnikov versus anti-Markovnikov) of hydroamination [16]. The hydroamination reaction is usually categorized as acid-catalyzed, base-catalyzed, and transition metal catalyzed hydroaminations [17–21]. Quite a few researchers have used this strategy as a key step for the total synthesis of various natural products and pharmaceutical agents [22].

RESULTS AND DISCUSSION

In continuation of our research program regarding the synthesis of biologically active nitrogen heterocycles [23–25] and because of the fact that the synthesis of benzo[f] imidazo[1,2-d][1,4]oxazepines is quite infrequent, herein, we developed a new and straightforward approach by the hydroamination strategy for the synthesis of fused benzoxazepine-imidazole derivatives **6** in good yields (Table 1). For this purpose, various *ortho*-phenylenediamines **3**, 2-(prop-2-yn-1-yloxy)benzaldehydes **4** were heated at 80°C in *N,N*-dimethylacetamide (DMA) in the presence of sulfur reagent sodium disulfite (Scheme 1). The required 2-(prop-2-yn-1-yloxy) benzaldehyde derivatives **4** were synthesized by the reaction of various salicylaldehyde derivatives **1** and propargyl bromide **2** under basic conditions in DMF at 80°C (Scheme 1). We later on examined the reaction conditions for the intramolecular cyclization of imidazole

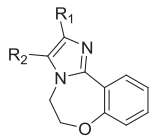


Figure 1. Benzo[f]imidazo [1, 2-d][1,4]oxazepine-5(6*H*)-one derivatives.

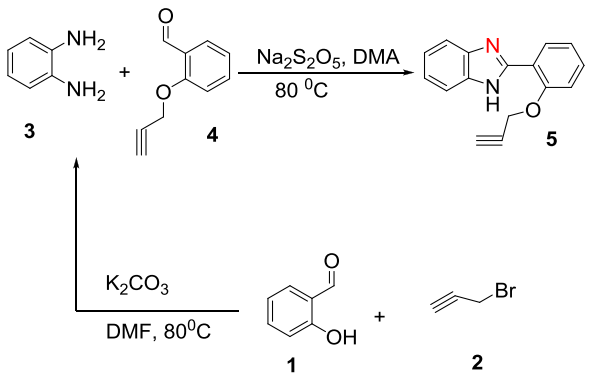
Table 1

Synthesis of 7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d] [1,4]oxazepines **6**.

Entry	R	R′	Product	Yield[a](%)
1	H	H	6a	70
2	7-Me	H	6b	75
3	H	10-Br	6c	65
4	7-Me	10-Br	6d	64
5	H	8-OMe	6e	61
6	7-Me	8-OMe	6f	56
7	H	C_6H_5	6g	58
8	7-Me	C_6H_5	6h	60

[a]Isolated yields.

Scheme 1. Synthetic rout for the preparation of 2-(2-(prop-2-yn-1-yloxy) phenyl)-1*H*–benzo[d]imidazole **5**. [Color figure can be viewed at wileyonlinelibrary.com]

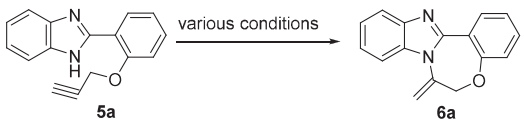


derivative **5** to form 7-methylene-6,7-dihyrobenzo[f]benzo [4,5] imidazo[1,2-d][1,4]oxazepines in moderate to good yields (64-92%). The effect of protic and aprotic solvents such as THF, CH_3OH, EtOH, DMA, and DMF was also tested. Various bases such as alkali metals, alkoxides, and carbonates were then examined, and it was found that the combination of three equivalents of K_2CO_3 in DMF at 90°C was merely effective and led to the formation of the corresponding product **6a** in good yield (92%). Increasing the amount of K_2CO_3 accompanied by the temperature did not lead to an augment in yields (Table 2). Based on these studies, we started to synthesize the various derivatives of 7-methylene-6,7-dihyrobenzo[f]benzo [4,5] imidazo[1,2-d] [1,4] oxazepines.

In our previous work, we took advantage of hydroamination in the presence of KO*t*-Bu in DMF providing the corresponding benzo[f]imidazo[1,2-d][1,4] oxazepines in good yields [23–26]. To our delight, the results revealed that replacing KOt-Bu by K_2CO_3 can lead to the formation of 7-*exo-dig* hydroamination, which did not undergo 1,3 hydrogen shift to afford **7** (Scheme 2).

Table 2

Investigation of various conditions for the hydroamination of **5a** to obtain the corresponding product **6a**.



Entry	Solvent	Base (equiv)	Temperature (°C)	Yield[a] of **6a**(%)
1	DMF	K_2CO_3 (3)	90	92
2	DMF	K_2CO_3 (3)	70	56
3	DMF	K_2CO_3 (3)	60	29
4	DMF	K_2CO_3 (1)	90	70
5	DMF	K_2CO_3 (1.5)	90	79
6	DMF	K_2CO_3 (2)	90	83
8	DMF	t-BuOK (1.5)	90	61
9	DMF	KOH (3)	90	36
10	DMA	K_2CO_3 (3)	90	84
11	DMA	t-BuOK (1.5)	90	50

[a]Isolated yields.

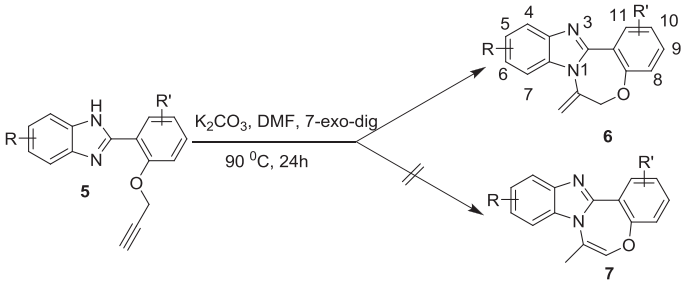
CONCLUSIONS

In summary, a new synthetic strategy for the synthesis of 7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d] [1,4]oxazepine derivatives through regioselective base-mediated 7-exo-dig hydroamination of 2-(prop-2-yn-1-yloxy)benzaldehyde derivatives is described which affords exclusively exo product rather than endo product because of the use of potassium carbonate base. It also offers an efficient access to a large variety of substituted imidazo oxazepine derivatives from readily available *ortho*-phenylenediamines.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus (England) and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker FT-500 (Germany) using tetramethylsilane as an internal standard. IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). The elemental analysis was performed with an Elmentar Analysensysteme GmbH VarioEL CHNS mode (Germany). Mass spectra were recorded on an Agilent Technology (HP, Santa Clara, CA) mass spectrometer operating at an ionization potential of 70 eV.

Scheme 2. Synthetic of 7-methylene-6,7 dihyrobenzo[f]benzo[4,5]imidazo[1,2d][1,4]oxazepine derivatives.



General procedure for the synthesis of 2-(2-(prop-2-yn-1-yloxy)phenyl)-1H–benzo[d]imidazole (5). Mixture of ortho-phenylenediamines (**3**; 1 mmol) and 2-(prop-2-yn-1-yloxy) benzaldehydes (**4**; 1 mmol) was heated at 80°C for 16 h in DMA in the presence of sulfur reagent sodium disulfite (1 mmol). Upon completion of reaction, checked by TLC, the reaction mixture was poured into ice water with stirring. The precipitated products were recrystallized from ethanol to give pure samples **(5)**

General procedure for the synthesis of 7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2d][1,4]oxazepine derivatives (6). A mixture of 2-(2-(prop-2-yn-1-yloxy)phenyl)-1*H*–benzo[d]imidazole (**5**; 1 mmol) and potassium carbonate in DMF was stirred at 90°C for 24 h. Upon completion of reaction, checked by TLC, the reaction mixture was poured into cold water, and the precipitate filtered. The residue was purified using column chromatography, eluting with petroleum ether/ethyl acetate (9:1).

7-Methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (6a). Cream solid; yield: (92%); m.p. 289–291°C. IR: 1618, 1258, 1029. ^{1}H NMR: 4.91 (*s*, 2H of CH_2); 5.74 (*s*, CH); 5.81 (*s*, CH); 7.09 (*d*, *J* = 8.2 Hz, H-C(8)); 7.20 (*t*, *J* = 8.2 Hz, H-C(10)); 7.32–7.34 (*m*, 2H of Ph); 7.45 (*t*, *J* = 7.1 Hz, H-C(9)); 7.73–7.77(*m*, 2H of Ph); 8.69 (*d*, *J* = 10 Hz, H-C(11)). *Anal.* Calcd for $C_{16}H_{12}N_2O$ (248.09): C 77.40, H 4.87, N 11.28. Found: C 77.11, H 4.14, N 11.92.

9-Methyl 7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (6b). Cream solid; yield (75%); m.p. 295–299°. IR: 1608, 1210, 1045. ^{1}H–NMR: 2.43 (*s*, 3H of CH_3); 4.91 (*d*, *J* = 4.8 Hz, 2H of CH_2); 5.64 (*d*, *J* = 19, CH); 5.22 (*d*, *J* = 19,CH); 7.05–7.18 (*m*, 2H of Ph); 7.16 (*t*, *J* = 8, H-C(10)); 7.40 (*t*, *J* = 7.2, H-C(9)); 7.48–7.51 (*m*, 2H of Ph), 7.61 (*d*, *J* = 8.1, H-C(6)); 8.69 (*t*, *J* = 7, H-C(11)). ^{13}C-NMR: 21.5; 71.8, 110.3; 118.9; 119.1; 120.3; 120.4; 122.3; 124.6; 124.7; 131.3; 131.4; 132.9; 137.9; 143.1; 148.6; 156.0. *Anal.* Calcd for $C_{17}H_{14}N_2O$ (262.11): C 77.84, H 5.38, N 10.68; Found: C 77.91, H 5.04, N 10.98.

2-Bromo7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (6c). Cream solid; yield (65%); m.p. 370–372°. IR: 1651, 1112, 1250 cm^{-1}. ^{1}H NMR: 4.90 (s, 2H of CH_2), 5.75 (s, CH), 5.82 (s, CH), 7.09 (d, *J* = 5.5 Hz, H-C(8)), 7.19 (d, *J* = 5.5 Hz, H-C(9)), 7.31–7.34(m, 2H of Ph), 7.70–7.74 (m, 2H of Ph), 8.13 (d, *J* = 2.3 Hz, H-C(6)). ^{13}C NMR: 71.7; 110.6; 117.4; 119.6; 122.8; 123.3; 123.4; 123.7; 123.8; 124.3; 132.9; 137.4; 141.9; 147.7; 155.4. MS: *m/z* (%) = 326[m]$^+$(100), 328[m + 2]$^+$ (91), 290(22), 247(30), 219(41), 191(8). *Anal.* Calcd for $C_{16}H_{11}BrN_2O$ (326.01): C 58.74, H 3.39, N 8.56. Found: C 59.64, H 4.04, N,7.98.

2-Bromo-9-methyl-7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepines (6d). Cream solid; yield (64%); m.p. 375–377. IR: 1651, 1250, 1112. ^{1}H–NMR: 2.47 (*s*, 3H of CH_3); 4.90 (*s*, 2H of CH_2); 5.74 (*d*, *J* = 12.0 Hz, CH); 5.82 (*d*, *J* = 12.0 Hz, CH); 7.09 (*d*, *J* = 8.2 Hz, 1H–C(8)); 7.17 (*d*, *J* = 8.2 Hz, H-C(9)); 7.59–7.55 (*m*, 2H of Ph); 7.63 (*t*, *J* = 8.0 Hz, H-C(5)); 8.7 (*dd*, *J* = 6.6 Hz, 2.3 Hz, H-C(6)). ^{13}C–NMR: 21.5; 71.7; 113.8; 118.8; 119.1; 119.2; 122.9; 125.2; 132.5; 132.8; 133.9; 134.0; 137.5; 142.9; 147.2; 155.4. MS: *m/z* (%) = 340 [m]$^{+\cdot}$(100), 342[m + 2]$^+$(91), 325(14), 261(44), 233(50), 210(19). *Anal.* Calcd for $C_{17}H_{13}BrN_2O$ (340.02): C 59.84, H 3.84, N 8.21. Found: C 59.64, H 4.04, N 7.98.

4-Methoxy 7-methylene-6,7-dihyrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (6e). Cream solid; yield (75%) m.p. 297–301°. IR: 1620, 1215, 1035. ^{1}H NMR: 3.88 (*s*, 3H of OCH_3); 4.69 (*s*, CH); 4.77 (*s*, CH); 5.09 (*s*, 2H of CH_2); 7.25–7.33 (*m*, 4H of Ph), 7.53–57 (*m*, 1H of Ph), 7.73 (*d*, *J* = 8.0, H-C(7)); 7.85 (*d*, *J* = 6.4, H-C(11)). ^{13}C NMR: 56.1; 80.60; 93.3; 110.1; 114.7; 119.3; 121.4; 122.2; 122.5; 124.7; 134.3; 141.4; 142.9; 149.8; 151.3; 157.5. *Anal.* Calcd for $C_{17}H_{14}N_2O_2$ (278.11): C 73.37, H 5.07, N 10.07, Found: C 73.91, H 5.04, N 10.58.

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