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Study of the Effect of Substituents of *ortho*-Phenylenediamines in the Opening of Lactones and Lactams for Access to Benzimidazol-2-yl Alkanols and Benzimidazol-2-yl Alkylamines

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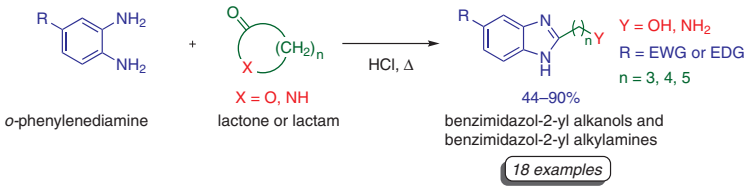

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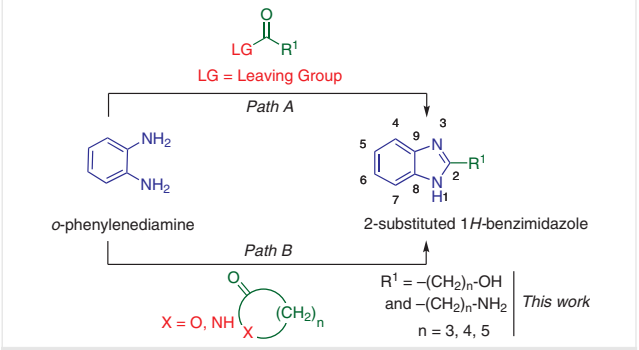
Abstract Benzimidazoles represent common chemical moieties in bioactive compounds. The synthesis of this heterocycle often involves a condensation of an *ortho*-phenylenediamine with a carboxylic acid derivative. The observed dialkylation of the starting *ortho*-phenylenediamine is avoided by opening of lactones or lactams. This strategy can directly yield 1*H*-benzimidazoles substituted at the 2-position by a functionalized chain. We present herein a study of the effect of different electron-withdrawing or electron-donating groups at the 4-position of *ortho*-phenylenediamines on the opening of lactones or lactams to synthesize benzimidazol-2-yl alkanols and benzimidazol-2-yl alkylamines.

Key words 2-benzimidazol-2-yl alkanols, 2-benzimidazol-2-yl alkylamines, *ortho*-phenylenediamines, lactones, lactams

Benzimidazoles represent a common chemical moiety in bioactive compounds such as antimicrobials, food preservatives, antiulcer, antiviral and anti-cancer agents (Figure 1).[1–3] The synthesis of this heterocycle often involves condensation of an *ortho*-phenylenediamine with a carbonyl derivative (Scheme 1)[4,5] and, most recently, with orthoesters.[6] The dialkylation of the starting *ortho*-phenylenediamine with a carboxylic acid, aldehyde, acid anhydride, acid chloride, or nitrile (Scheme 1, path A), can be avoided by ring-opening of lactones or lactams under acidic conditions (Scheme 1, path B).[7–14] Advantageously, path B directly yields 1*H*-benzimidazoles substituted at the 2-position by a functionalized chain and these are of particular interest in synthesis. In fact, as part of the synthesis of a bioactive chemical library in our team, we used this efficient pathway to afford different benzimidazol-2-yl alkanols and benzimidazol-2-yl alkylamines as synthetic stating materials. We focused on exploring the effect of different substituents at the 4-position of the monosubstituted *ortho*-phenylenediamine in the reaction with different lactones or lactams.

2-Substituted 1*H*-benzimidazoles with a side chain containing either a hydroxyl group or a primary amine were obtained by a one-pot reaction under acidic conditions of *ortho*-phenylenediamine with a lactone or a lactam, respectively. One equivalent of 4-(*tert*-butyl)benzene-1,2-diamine reacts with an excess (4–6 equivalents, adjusted to obtain a full reaction) of a lactone or a lactam in 4N HCl at reflux in a sealed tube during 12–24 hours or until disappearance of the limiting reagent monitored by TLC (experimental conditions A).[15] This reaction was initially explored with lac-



Scheme 1 Principal synthetic pathways to obtain 1*H*-benzimidazoles

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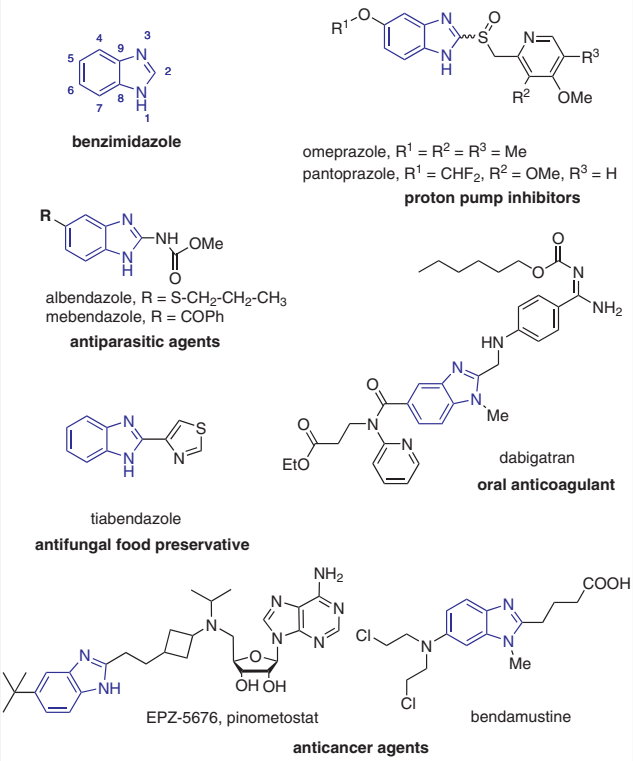


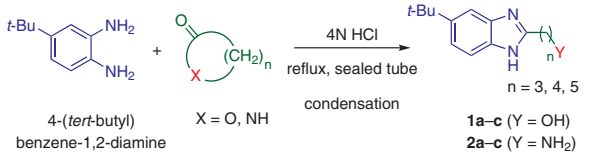
Figure 1 Examples of benzimidazole-containing bioactive compounds

tones and lactams of different size (Table 1). The benzimidazol-2-yl alkanols were obtained in very good yields (69–93%). The reaction yield with γ-butyrolactone (entry 1) was slightly better than those obtained with higher homologues (entries 2 and 3). The benzimidazol-2-yl alkylamines were obtained in lower yields, from 9 to 49% (entries 4–6). Use of γ-butyrolactam seems to adversely affect the yield of **2a**, possibly due to the relatively poor stability of the starting five-membered lactam.

Experimental conditions A were then applied to explore the impact on the reaction of donating groups (*t*-Bu, Me, OMe, OH) and withdrawing groups (Cl, CF_3, NO_2, CN) at the 4-position of the *ortho*-phenylenediamine. The six-membered lactone (δ-valerolactone) and lactam (δ-valerolactam), the most stable rings, were chosen to examine the scope of the synthesis of benzimidazol-2-yl alkanols and benzimidazol-2-yl alkylamines (Table 2). We observed that the isolated yield of the reaction was higher in the presence of both types of substituents compared to that obtained using unsubstituted *ortho*-phenylenediamine (entries 1 and 6), except for 4-chlorobenzene-1,2-diamine (entry 13). This positive effect of the substituents on the yield has also been observed at the 3-position of monosubstituted *ortho*-phenylenediamines.[16] Furthermore, we observed that the overall average time of reaction was shortened in the presence of electron-donating groups (EDG). In fact, all electron-donating substituents at the *para*-position positively affect the reactivity of the NH_2 (Scheme 2).[17–20] Electron-withdrawing groups (EWG) reduce the nucleophilicity of the *para*-NH_2 without affecting the nucleophilicity of the *meta*-NH_2, while electron-donating groups (EDG) increase the nucleophilicity of the *para*-NH_2 without affecting the nucleophilicity of the *meta*-NH_2. In both cases, the carbonyl of the lactone (or lactam) is first attacked by the more activated of the two amino groups of the *ortho*-phenylenediamine, followed by the attack of the other amino group. Although the order of attack is not relevant for the regiochemical outcome of the reaction, due to tautomerism of the resulting benzimidazole the presence of electron-donating groups appears to increase the rate of reaction (Scheme 2C). 4-Chlorobenzene-1,2-diamine shows a reactivity pattern similar to that of the non-substituted *ortho*-phenylenediamine, explained by the well-known simultaneous withdrawing and donating effect of the chlorine atom, common to the other halides.

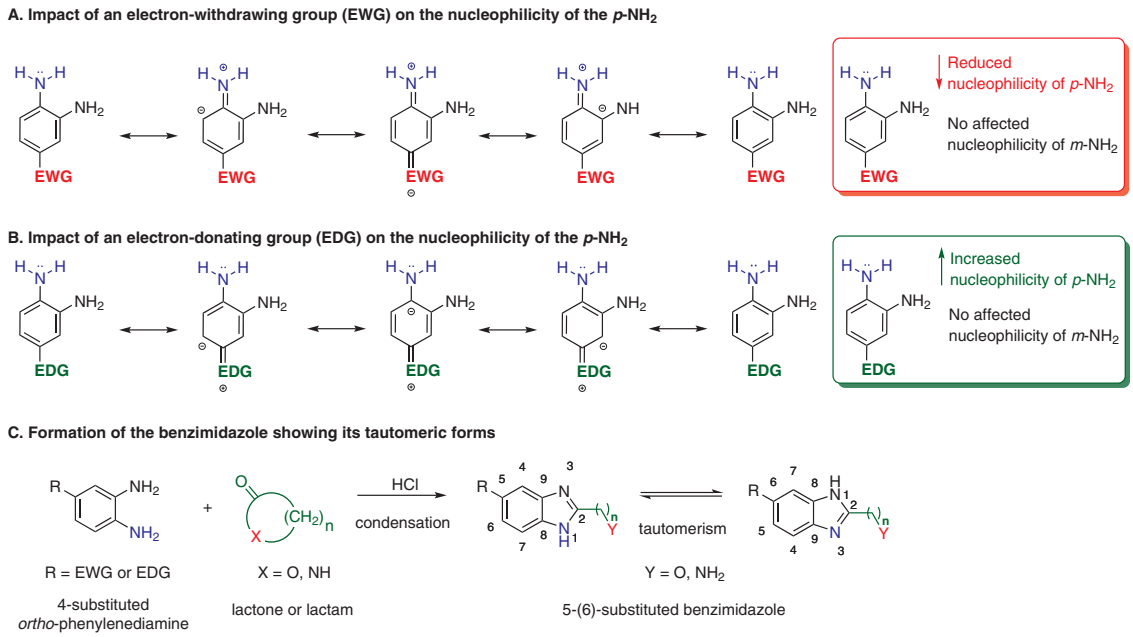
Further benzimidazol-2-yl alkylamines were also synthesized via a three-step synthesis pathway. Thus, the corresponding benzimidazol-2-yl alkanol (1 equiv) previously obtained under conditions A was engaged in a Mitsunobu reaction with phthalimide (2 equiv) in the presence of diisopropyl azodicarboxylate (DIAD, 2 equiv) and triphenylphosphine (2 equiv) in diethyl ether over 12–20 hours at room temperature. The phthalimido-derivative thus obtained subsequently reacts with hydrazine monohydrate (12 equiv) in ethanol over 12 hours at room temperature to release the corresponding primary amine (experimental conditions B) (Table 3).[21] Diethyl ether was preferred over THF for the Mitsunobu reaction in order to favor the precipitation and removal of triphenylphosphine oxide (Ph_3PO) and to facilitate the isolation of the phthalimido derivative. In spite of these precautions, the yield of this step remained low. Thus, the non-isolated phthalimido-derivatives were

Table 1 Synthesis of 2-Substituted 1*H*-Benzimidazoles via the Opening of Lactones and Lactams



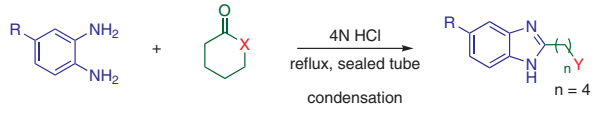
Entry	Reactant	Time (h)	Product	Yield (%)[a]
1	γ-butyrolactone	12	**1a**, *n* = 3	93
2	δ-valerolactone	12	**1b**, *n* = 4	81
3	caprolactone	24	**1c**, *n* = 5	69
4	γ-butyrolactam	12	**2a**, *n* = 3	9
5	δ-valerolactam	24	**2b**, *n* = 4	48
6	caprolactam	24	**2c**, *n* = 5	49

[a] Isolated yield.



Scheme 2 Impact of mono-substitution of *ortho*-phenylenediamine on its nucleophilicity

Table 2 Synthesis of Benzimidazol-2-yl Alkanols and Benzimidazol-2-yl Alkylamines



o-phenylenediamine; δ-valerolactone (X = O); δ-valerolactam (X = NH); **1b,d–g** (Y = OH); **2b,d–k** (Y = NH_2)

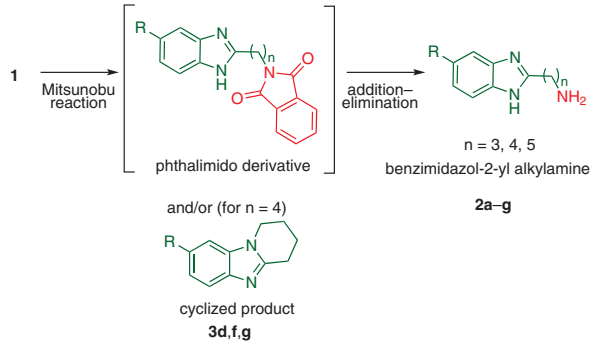
Entry	R	Time (h)	Product	Yield (%)[a]
1	H	16	**1d**	59
2	*t*-Bu	18	**1b**	81
3	OMe	12	**1e**	91
4	CF_3	16	**1f**	68
5	NO_2	16	**1g**	76
6	H	18	**2d**	30
7	*t*-Bu	24	**2b**	48
8	OMe	12	**2e**	73
9	CF_3	48	**2f**	54
10	NO_2	40	**2g**	81
11	Me	48	**2h**	91
12	OH	48	**2i**	87
13	Cl	7	**2j**	44
14	CN	20	**2k**	90

[a] Isolated yield.

directly treated with hydrazine monohydrate, improving the overall yield. Nevertheless, the desired benzimidazol-2-yl alkylamines were obtained in lower yields compared to the one-step synthesis pathway summarized in Tables 1 and 2 (except for Table 3, entry 1), mainly due to the formation of a side product during the Mitsunobu reaction. 1,2,3,4-Tetrahydro-pyrido[1.2,*a*]benzimidazole derivatives **3** were observed (Table 3, entries 4, 6, 7) as the main products of this reaction.[6,16] This might be the result of an intramolecular reaction of the phosphonium intermediate, as shown in Scheme 3.[22] This synthetic pathway could represent an efficient method of synthesis of these heterocyclic compounds.

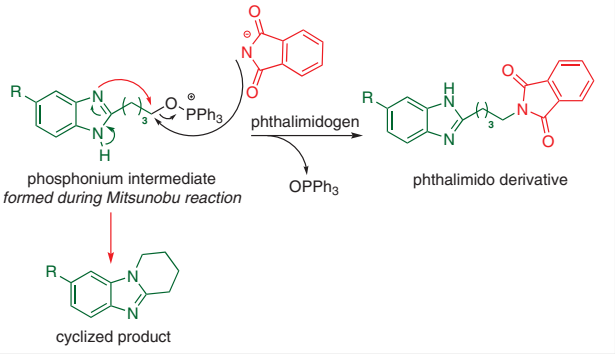
In summary, a range of benzimidazol-2-yl alkylalkanols and benzimidazol-2-yl alkylamines were prepared in a one-step synthesis between an *ortho*-phenylenediamine and a lactone or a lactam, respectively, in yields ranging from 44 to 90%. The presence of electron-withdrawing or electron-donating substituents increased the yield of the reaction, compared to the yield obtained when no substituent or a group with a positive inductive effect and a negative mesomeric effect such as chlorine was present. The formation of benzimidazol-2-yl alkylamines via the lactam opening was compared to a three-step synthetic pathway, involving a Mitsunobu reaction on a benzimidazol-2-yl alkanol followed by hydrazine treatment of the obtained phthalimido derivative, which showed very low yields. This confirms the appeal of this straightforward, efficient one-step formation of 2-substituted-1*H*-benzimidazole derivatives through lactone or lactam opening.

Table 3 Benzimidazol-2-yl Alkylamines Obtained by a Three-Step Synthetic Pathway



Entry	R	*n*	Cyclized product (yield, %)	Product	Three-step yield (%)[b]
1	*t*-Bu	3	–[a]	**2a**	20
2	*t*-Bu	4	–[a]	**2b**	35
3	*t*-Bu	5	–[a]	**2c**	14
4	H	4	**3d** (66)[c,d]	**2d**	0
5	OMe	4	–[a]	**2e**	27
6	CF_3	4	**3f** (42)[c]	**2f**	3
7	NO_2	4	**3g** (51)[b]	**2g**	0

[a] Not observed by LC-MS.
[b] Isolated yield.
[c] Calculated from the crude material by LC-MS.
[d] Characterized by NMR.



Scheme 3 Formation of a cyclized product in the Mitsunobu reaction

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707112.

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(15) **General Conditions A**: A mixture of the corresponding *ortho*-phenylenediamine (1 equiv) and the corresponding lactone or lactam (4–6 equiv) in 4N HCl in a sealed tube was heated overnight (duration is reported in the manuscript). After cooling to room temperature, the pH was adjusted to pH 11 at 0 °C with sat. aq. K_2CO_3. The aqueous layer was extracted three times with EtOAc, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The desired product was obtained by precipitation or by chromatography on silica gel [eluting with CH_2Cl_2–MeOH/ammonia, 9:1 (v/v)]. The final solid or oil obtained was dried over P_2O_5.
Representative example 1a: Yield: 4.3 mmol (93%); white powder obtained from diethyl ether; mp 181–183 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.33 (s, 9 H, *t*-Bu), 1.90 (tt, ^3J = 6.0, 7.5 Hz, 2 H, CH_2), 2.83 (t, ^3J = 7.5 Hz, 2 H, CH_2-Ar), 3.49 (t, ^3J = 6.0 Hz, 2 H, CH_2-OH), 7.17–7.20 (m, 1 H, ArH), 7.35–7.40 (m, 2 H, ArH), 11.86 (br s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.3 (CH_2), 30.8 (CH_2), 31.7 (*t*-Bu), 34.3 (Cq), 60.2 (CH_2-OH),

118.8 (3 CHAr), 143.8 (Cq), 154.9 (Cq). HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}N_2O$: 233.1648; found: 233.1648. IR: 3117 (OH) cm^{-1}.

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(21) **General Conditions B**: Triphenylphosphine (2 equiv, 4.5 g, 17.1 mmol) was added in portions to a solution of **1a** (1 equiv, 2 g, 8.6 mmol), phthalimide (2 equiv, 2.5 g, 17.1 mmol) and DIAD (2 equiv, 3.4 mL, 17.1 mmol) in diethyl ether (40 mL), and the mixture was stirred overnight at room temperature. The triphenylphosphine oxide precipitate was removed by filtration, and the filtrate was concentrated in vacuo. Diethyl ether was added to the residue and the additional precipitate was also removed by filtration. The filtrate was concentrated in vacuo, then ethanol (20 mL) and hydrazine monohydrate (12 equiv, 5 mL, 103 mmol) were added to the viscous residue. After heating at reflux overnight, the reaction mixture was cooled to room temperature and the solid phthalhydrazide was removed by filtration. The filtrate was concentrated in vacuo, and ethanol was added to the residue. The precipitate was again removed by filtration, the filtrate was concentrated in vacuo and the residue was purified by column chromatography over silica gel [eluting with CH_2Cl_2–CH_3OH/ammonia, 9:1 (v/v)]. The oil obtained was dried over P_2O_5.

2-(3-(5-(*tert*-Butyl)-1*H*-benzo[*d*]imidazol-2-yl)propyl)isoindoline-1,3-dione (4): Yellowish powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.30 (s, 9 H, *t*-Bu), 2.09 (tt, ^3J = 6.8, 7.1 Hz, 2 H, CH_2), 2.82 (t, ^3J = 7.1 Hz, 2 H, CH_2-Ar), 3.67 (t, ^3J = 6.8 Hz, 2 H, CH_2-N), 7.13 (m, 1 H, ArH), 7.31 (m, 2 H, ArH), 7.82 (br s, 4 H, ArH), 11.97 (s, 1 H, NH). IR: 1705 (C=O) cm^{-1}.

3-(5-(*tert*-Butyl)-1*H*-benzo[*d*]imidazol-2-yl)propan-1-amine (2a): Yield: 0.4 mmol (overall yield 20%); brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.32 (m, 9 H, *t*-Bu), 1.80 (tt, ^3J = 6.9, 7.6, 2 H, CH_2), 2.66 (t, ^3J = 6.9 Hz, 2 H, CH_2-NH_2), 2.82 (t, ^3J = 7.6 Hz, 2 H, CH_2-Ar), 3.16 (m, 2 H, NH_2), 7.18 (dd, ^3J = 8.4 Hz, ^4J = 1.6 Hz, 1 H, ArH), 7.34 (d, ^3J = 8.4, 1 H, ArH), 7.38 (d, ^4J = 1.6 Hz, 1 H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.0 (CH_2), 30.5 (CH_2), 31.7 (*t*-Bu), 34.3 (Cq), 40.7 (CH_2-NH_2), 118.8 (3 CHAr), 143.9 (Cq), 160.7 (Cq). HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calculated for $C_{14}H_{22}N_3$: 232.1808; found: 232.1801. IR: 3041 (NH) cm^{-1}.

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