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New Procedure for the Synthesis of 2-Alkylbenzimidazoles

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New Procedure for the Synthesis of 2-Alkylbenzimidazoles

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Abstract: Simple, economical, and environmentally friendly method to synthesize 2-alkylbenzimidazoles was developed by modifying the conventional method between *o*-phenylenediamine and aldehyde.

Keywords: Benzimidazoles, *o*-phenylenediamine, sodium hydrogen sulfite

Benzimidazole is a key skeleton in the pharmaceutical area, so many compounds with benzimidazole scaffolds were launched as antihistamatic drugs, antiulcer drugs, anti-infectious, and anti-arrhythmic drugs (Fig. 1).

Several reports on the synthesis of benzimidazole derivative have been published[1–11] and applied to industrial methods.

Typical examples for the synthesis of benzimidazoles are (1) reaction of *o*-phenylenediamine and carboxylic acid under strong acidic conditions,[12] (2) ring-closure reaction under mild acidic conditions, of amide derivatives prepared from *o*-phenylenediamine and carboxylic acid,[13]

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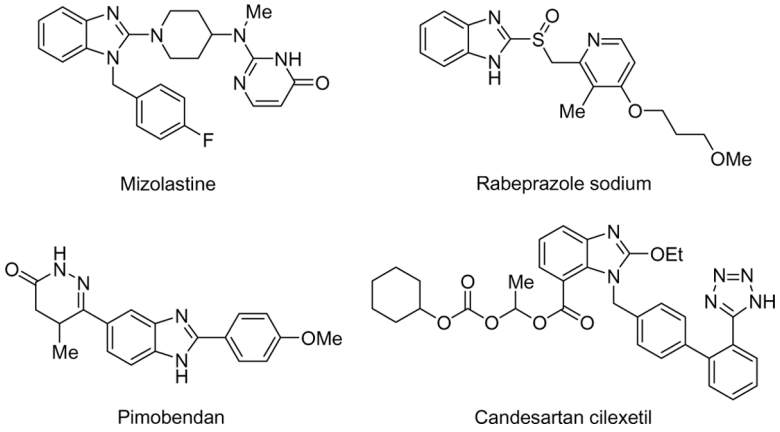


Figure 1. Structures of benzimidazole drugs.

and (3) direct condensation reaction between *o*-phenylenediamine and aldehyde in the presence of an appropriate reagent.[14]

In the area of industrial applications, reasonable cost of chemicals, applicability of reaction conditions, and environmental consciousness are necessary.

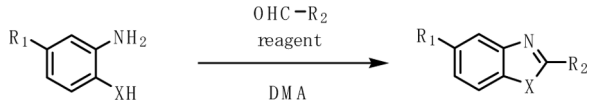
During the process of development of our drug candidate, we needed to establish an ideal reaction procedure to construct a benzimidazole skeleton: 2-substituted benzimidazole derivatives were of particular interest.

Even though a number of reports have been published regarding this kind of reaction, most of them refer to the synthesis of 2-aryl benzimidazoles, and no procedures with satisfactory results were available for 2-alkylbenzimidazole derivatives. To achieve our final purpose, we planned a two-step strategy: (1) select the preferable reaction conditions to synthesize benzimidazole skeleton, and (2) modify and optimize the reaction condition(s) to fit our needs.

Because of its simple operation and mild reaction conditions, we chose the reaction between *o*-phenylenediamine and aldehyde in the presence of a sulfur reagent such as sodium disulfite,[15] sodium hydrogen sulfite,[16] or potassium hydrogen sulfate[17] as a basic strategy, and assessment and optimization were conducted.

At first, the reaction between *o*-phenylenediamine and benzaldehyde was carried out using three types of reagents under identical conditions to compare them. In the case of sodium hydrogen sulfite and sodium disulfite, the yields were almost quantitative: however, potassium hydrogen sulfate gave poor results (Table 1, entries 1, 11, and 20).

Table 1. Synthesis of benzazoles using some sulfur reagents



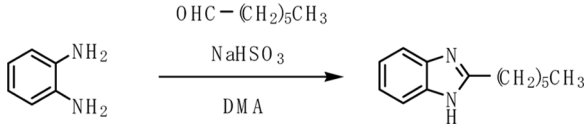
Entry	Reagent	X	R_1	R_2	Yield (%)[a]
1	$NaHSO_3$	NH	H	–Ph	89.6
2	$NaHSO_3$	NH	H	–Ph–4–OMe	91.9
3	$NaHSO_3$	NH	H	–Ph–4–Cl	Quant.
4	$NaHSO_3$	NH	–Me	–Ph	98.9
5	$NaHSO_3$	NH	–Cl	–Ph	89.2
6	$NaHSO_3$	NH	H	$-(CH_2)_5CH_3$	30.6
7	$NaHSO_3$	NH	H	–*c* Hex	56.4
8	$NaHSO_3$	S	H	–Ph	93.2
9	$NaHSO_3$	O	H	–Ph	Trace
10	$NaHSO_3$	O	H	–Ph	19.0[b]
11	$Na_2S_2O_5$	NH	H	–Ph	91.6
12	$Na_2S_2O_5$	NH	H	–Ph–4–OMe	91.9
13	$Na_2S_2O_5$	NH	H	–Ph–4–Cl	91.9
14	$Na_2S_2O_5$	NH	–Me	–Ph	97.5
15	$Na_2S_2O_5$	NH	–Cl	–Ph	95.8
16	$Na_2S_2O_5$	NH	H	$-(CH_2)_5CH_3$	40.5
17	$Na_2S_2O_5$	NH	H	–*c* Hex	58.4
18	$Na_2S_2O_5$	S	H	–Ph	94.2
19	$Na_2S_2O_5$	O	H	–Ph	Trace
20	$KHSO_4$	NH	H	–Ph	25.2
21	$KHSO_4$	NH	H	$-(CH_2)_5CH_3$	13.3
22	$KHSO_4$	NH	H	–*c* Hex	Trace
23	$KHSO_4$	S	H	–Ph	Trace
24	$KHSO_4$	O	H	–Ph	Trace

[a]All yields refer to isolated products.
[b]120°C, 3 days.
Note. Spectroscopic data supported the structures of all compounds.

Simple substitutions on the substrates (−Me, −Cl) did not affect to the yields (Table 1, entries 4, 5, 14, and 15). Similarly, excellent yields of 2-phenylbenzothiazoles were obtained from benzaldehyde and *o*-aminothiophenol; however, in the case of *o*-aminophenol, the yield was very poor even after a longer reaction time (Table 1, entries 8, 9, 10, 18, 19, and 24).

Furthermore, the yield was less when aliphatic aldehydes were used, instead of benzaldehyde as described in the literature[17] (Table 1, entries 6, 7, 16, 17, 21, and 22).

Table 2. Reaction of *o*-phenylenediamine and *n*-heptylaldehyde under various conditions

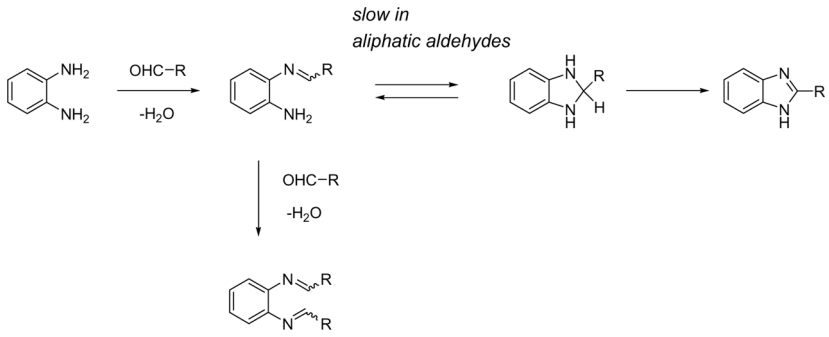


Entry	$NaHSO_3$ (eq.)	Temp. (°C)	Time (h)	Yield (%)[a]
6	1.0	100	2	30.6
25	1.0	120	2	34.6
26	1.5	100	2	26.7
27	1.0	100	4	42.0
28	1.0	100	2	64.8[b]

[a]All yields refer to isolated products.
[b]A solution of aldehyde was added dropwise to a solution of diamine/$NaHSO_3$ mixture.

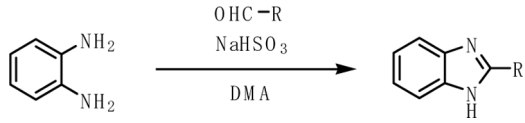
Up to this stage, sodium hydrogen sulfite and sodium disulfite seemed to be candidates for the basic condition to prepare 2-alkylbenzimidazoles. Even though sodium disulfite gave slightly better yields in some cases, we selected sodium hydrogen sulfite because of its economical advantage.

Then, we tried to overcome problems such as poor yield for 2-alkylbenzimidazoles. Greater reaction temperature and an additional amount of reagent had no effects, but longer reaction time improved the yield slightly (Table 2). Considering the speculated reaction mechanism,



Scheme 1. Speculated reaction mechanism.

Table 3. Synthesis of 2-alkylbenzimidazoles under improved conditions



Entry	R	Yield (%)[a]
29	–Et	75.2
30	$-CH(CH_3)CH_2CH_3$	75.2
31	–*t*Bu	97.6
32	$-(CH_2)_7CH_3$	51.7
33	–*c* Hex	73.4

[a]All yields refer to isolated products.
Note. Spectroscopic data supported the structures of all compounds.

reported previously,[16] we expected that the formation of the bis-adduct would be predominant if the final step (ring closure) was slow, and it would cause poor yield of the desired product (Scheme 1). In the case of aromatic aldehydes, ring-closure reaction takes place on the benzylic carbon, proceeds smoothly, and provides a good yield of final products. Therefore, we tried a reaction under a modified procedure, in which a solution of aliphatic aldehyde was slowly dropped into a heated solution of diamine to diminish the formation of bis-adduct. As a result, the yield of the desired compound was dramatically increased (Table 1, entry 28).

To confirm the generality of this condition, several aliphatic aldehydes were applied, and good to excellent yields of the desired compounds were obtained (Table 3).

Furthermore, a similar reaction using cyclohexyl aldehyde was carried out on a preparative scale. In this trial, we attempted to eliminate the chromatographical purification. By adding a 2% sodium carbonate solution to the cooled reaction mixture, the desired product was obtained in 88.8% yield as a solid material.

In conclusion, we found an improved reaction procedure to synthesize 2-alkylbezimidazoles, which could be operated on a preparative scale without chromatographical purification.

GENERAL PROCEDURE

A mixture of phenylenediamine (1.0 mmol), aldehyde (1.0 mmol), and sulfur reagent (1.0 mmol) in N,N-dimethylacetamide (DMA) (2.0 mL)

was heated at 100°C for 2 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography.

Modified Procedure for Aliphatic Aldehyde

A DMA (1.0 mL) solution of aldehyde (1.0 mmol) was added dropwise to a mixture of phenylenediamine (1.0 mmol), and sulfur reagent (1.0 mmol) in DMA (1.0 mL) over a 10-min period at 100°C. After 2 h, the reaction mixture was concentrated, and the residue was purified as described previously.

Preparative Scale Procedure for 2-Cyclohexylbenzimidazole

A DMA (10 mL) solution of cyclohexyl aldehyde (6.1 mL, 50.0 mmol) was added dropwise to a heated mixture of *o*-phenylenediamine (5.41 g, 50.0 mmol) and sodium hydrogen sulfite (5.21 g, 50.0 mmol) in DMA (50 mL) over a 10-min period at 100°C and stirred under the same conditions. After the reaction was completed, the mixture was cooled, and 2% sodium carbonate (10 mL) was less than at a temperature added 40°C. Stirring continued for approximately 2 h. The solid was collected by suction, washed with water, and dried in the air. We obtained 8.9 g (88.8%) of 2-cyclohexylbenzimidazole.

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