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ARTICLE

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Development of Safe One-Pot Synthesis of *N*-1- and *C*-2-Substituted Benzimidazole via Reductive Cyclization of *o*-Nitroarylamine Using $Na_2S_2O_4$

Shinichi Oda,* Hideki Shimizu, Yasunori Aoyama, Tatsuo Ueki, Sumio Shimizu, Hiroshi Osato, and Yoshiyuki Takeuchi

Chemical Development Center, CMC Development Laboratories, Shionogi & Co., Ltd., 1-3, Kuise Terajima 2-Chome, Amagasaki, Hyogo 660-0813, Japan

Supporting Information

ABSTRACT: We report that the reductive cyclization of *o*-nitroarylamine with aldehyde using sodium dithionite ($Na_2S_2O_4$) could be accelerated by addition of H_2O, which made it possible to control the heat release of the reaction by semibatch-type operation. Safety evaluation was performed using DSC, ARSST, in situ IR analysis, and Multimax.

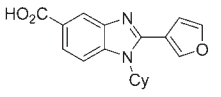
INTRODUCTION

Benzimidazole derivatives are important building blocks for inhibitors of hepatitis C virus (HCV) NS5B polymerase.[1] The discovery and preliminary SAR of the benzimidazole scaffold with a cyclohexyl or cyclopentyl ring at the *N*-1 position, a small aromatic or heteroaromatic ring at *C*-2 position, and a carboxylic acid function at *C*-5 position (e.g., *N*-1 cyclohexyl *C*-5 furyl compound **1**) were reported by Boehringer Ingelheim Inc.[1a] Researchers at our company discovered that *C*-5 heteroaryl, *N*-1- and *C*-2-substituted benzimidazole compounds possess potency as inhibitors of HCV, and one of them was targeted for development as an active pharmaceutical ingredient (API) (Figure 1).[1d]

In the medicinal chemistry route, benzimidazole building blocks were formed via hydrogenation of *o*-nitroarylamine and subsequent oxidative cyclization with aldehyde or the condensation with carboxylic acid and cyclodehydration (Scheme 1).

In order to simplify the steps, we attempted one-pot synthesis via reductive cyclization of *o*-nitroarylamine with aldehyde using sodium dithionite ($Na_2S_2O_4$) according to the literature to obtain benzimidazole **1** from commercially available ethyl 4-chloro-3-nitrobenzoate **2** on small scale (Scheme 2).[2]

The reaction could be an effective method for large-scale synthesis because $Na_2S_2O_4$ is inexpensive and easily available. However, there are known issues with regards to the scale-up of this type of chemistry. Reduction of the nitro group is very exothermic and compounds with the nitro group typically display violent and explosive decomposition[3] Also, accumulation of nitroso or hydroxylamine, which are intermediates of reduction of the nitro group, is dangerous, as these compounds are thermodynamically unstable. And explosion of $Na_2S_2O_4$, probably caused by contamination with water or oxidant, has been reported.[4] It is therefore crucial to investigate how to control the reaction to avoid unexpected accidents. Herein, we report the examination of the reductive cyclization reaction with an aim toward plant-scale synthesis using ethyl 4-(cyclohexylamino)-3-nitrobenzoate **3** and benzaldehyde **6** as model compounds.



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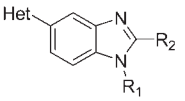
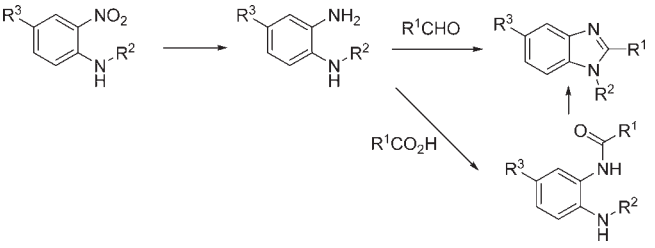


R^1 = alkenyl, cycloalkyl, R^2 = aryl (e.g., phenyl, furyl)

Figure 1. Candidates for an allosteric inhibitor of hepatitis C virus (HCV) NS5B polymerase.

Scheme 1. Synthesis of benzimidazole via the medicinal chemistry route



RESULTS AND DISCUSSION

Screening of Solvents and the Effect of H_2O. First, we screened the solvents by batch-type operation (Table 1). The reaction in ethanol (EtOH), isopropyl alcohol (IPA), and 2-butanol gave only the byproduct diamine **8** instead of benzimidazole **7**. However, the reaction did proceed on addition of

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Scheme 2. Synthesis of 1 using reductive cyclization

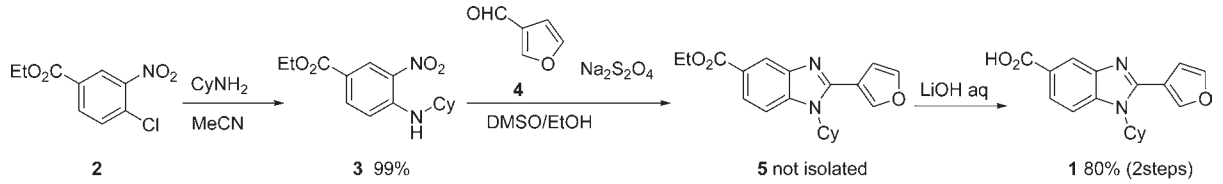
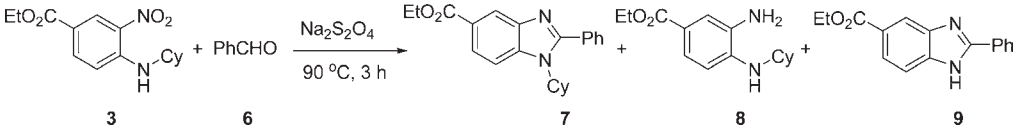


Table 1. Screening of solvents in the reductive cyclization[a]



entry	solvent	yield of 7 (%)[b]	3[b]	8[c]	9[c]
1	EtOH	0	28	42	0
2	EtOH/H_2O (10/1)	63	0	0	2
3	IPA	1	35	41	0
4	IPA/H_2O (10/1)	46	38	0	0
5	2-butanol	1	79	13	0
6	2-butanol/H_2O (10/1)	14	84	0	0
7	DMSO	94	0	0	4
8	DMSO/H_2O (10/1)	87	0	0	3
9	DMA	24	67	0	4
10	DMA/H_2O (10/1)	88	0	0	6
11	DMF	16	82	0	2
12	DMF/H_2O (10/1)	85	0	0	5
13	DMI	61	18	2	6
14	DMI/H_2O (10/1)	85	0	2	6
15	DMSO/EtOH	85	0	1	8

[a] All reactions were performed using **3** (0 2 mrnol), **6** (0 22 mrnol), $Na_2S_2O_4$ (0 6 mmol) in solvent (0 5 mL) [b] All yields and conversions are calculated on the basis of HPLC analysis with an external standard. [c] Peak area % by HPLC analysis at 254 nm was shown.

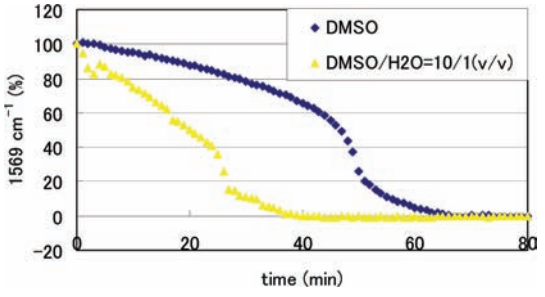


Figure 2. Comparison of the conversion of *o*-nitroarylamine **3** in DMSO and DMSO/H_2O[5].

H_2O, although the yields were moderate (entries 1−6). The reaction in DMSO gave benzimidazole **7** in high yield whether H_2O was added or not (entries 7 and 8). The reaction in other polar solvents such as DMA, DMF, and DMI gave moderate yields, which could be improved by adding H_2O (entries 9−14). The yield in DMSO/EtOH (1:1, v/v) was inferior to that in DMSO due to generation of byproduct **9** by completion of the decyclohexyl reaction (entry 15).

We compared the reaction rate in DMSO with that in DMSO/H_2O (10/1 = v/v) using in situ IR analysis. Addition of H_2O clearly accelerated the reaction (Figure 2). We finally chose DMSO/H_2O and DMA/H_2O as solvents for further examination.

DSC and ARSST experiments. We evaluated the reactivity of the reagents by differential scanning calorimeter (DSC) experiments to determine the explosive potential. A sealed SUS crucible was used, and a heating rate of 10 °C/min was applied. The results are shown in Table 2. *o*-Nitroarylamine **3**, $Na_2S_2O_4$ and the plausible byproduct $NaHSO_3$ exhibited exothermic decomposition of 1016, 480, and 69 J/g beginning at 317, 203, and 266 °C, respectively (entries 1, 4, and 5). On the other hand, benzaldehyde **6** and benzimidazole **7** did not show decomposition below 500 °C (entries 2 and 3). Next, we examined the stability of $Na_2S_2O_4$ in solvents because $Na_2S_2O_4$ contaminated by water is reported to be explosively exothermic.[4] The decomposition onset temperature of $Na_2S_2O_4$ in DMSO or H_2O was lower than that of $Na_2S_2O_4$ (entries 6 and 7). The results suggest that these solvents could promote the decomposition of $Na_2S_2O_4$. On the other hand, $Na_2S_2O_4$ in DMA exhibited exothermic decomposition at the equivalent temperature of $Na_2S_2O_4$ (entry 8).

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Table 2. DSC results for the compounds

entry	cmpds	conc. (wt %)	dec onset temp [°C]	dec energy [J/g]
1	**3**	100	317	1016
2	**6**	100	>500	–
3	**7**	100	>500	–
4	$Na_2S_2O_4$	100	203	32
			226	478
5	$NaHSO_3$	100	266	69
6	$Na_2S_2O_4$in DMSO	18	176	65
			271	45
7	$Na_2S_2O_4$ in H_2O	19	99	29
			274	58
8	$Na_2S_2O_4$ in DMA	21	221	10
			226	173

Next, we measured the thermal stability of the reaction mixture in DMSO/H_2O (10/1 = v/v) and DMA/H_2O (10/1 = v/v) using the Advanced Reactive Systems Screening Tool (ARSST). ARSST experiments were performed starting at 25 °C and heating the samples to 300 °C at the rate of 2 °C/min. The results are shown in Figure 3. The reaction mixture in both solvents did not show a dangerous exothermic peak although a moderate exothermic phenomenon beginning at 150 °C was observed on measurement of the reaction mixture in DMSO/H_2O.

Control of the Reductive Cyclization by Semibatch-Type Operation. We applied a semibatch process in which $Na_2S_2O_4$ (3 equiv) was added slowly to the mixture of **3** and **6** (1.1 equiv) dissolved in DMSO/H_2O or DMA/H_2O at 90 or 80 °C because $Na_2S_2O_4$ was the most thermally unstable reagent in the reaction. As the flash point of DMA (~70 °C) is lower than the reaction temperature, $Na_2S_2O_4$ should not be added as a powder, if possible, in order to avoid the generation of static electricity. We therefore measured the stability of $Na_2S_2O_4$ in H_2O at room temperature using in situ IR analysis. The result is shown in Figure 4. The solution was stable in nitrogen atmosphere but decomposed in air. The results suggest that $Na_2S_2O_4$ can be added as a mixture with excess H_2O under nitrogen atmosphere in a plant although $Na_2S_2O_4$ contaminated by H_2O is dangerous.

We measured the heat flow of the reaction using the operation shown below. A Multimax 250 vessel was charged with *o*-nitroarylamine **3** (6 g 20.5 mmol) and 1.1 equiv of benzaldehyde **6** in DMSO/H_2O and DMA/H_2O (10/1 = v/v 66 mL), and the mixture was heated to 90 and 80 °C, respectively. Next, 3.0 equiv of $Na_2S_2O_4$ was added over 90 min as powder because the addition of a $Na_2S_2O_4$ slurry in water under nitrogen atmosphere was difficult to perform in our laboratory. The reaction mixture was stirred for 2.5 h. The reactions respectively emitted heat of 797, 657 kJ/mol, and the respective adiabatic temperature rises were estimated to be 102 and 94 °C (Figures 5 and 6) (specific heat = 2 J/(g K)). The gross exothermic value was a little higher than the reported value of hydrogenation of nitrobenzene,[3d] but the heat release was proportional to the rate of addition of $Na_2S_2O_4$, and the accumulation of thermally unstable nitroso or hydroxylamine was not observed by HPLC and in situ IR analysis. In the case of DMSO/H_2O, a large exothermic peak (~700 W/mol) was observed when half of the $Na_2S_2O_4$ was added, which was presumed to be the crystallization heat of salt according to the focused beam reflectance measurement (FBRM) data (Figure 7). In summary, both solvents can be used for large-scale synthesis, but considering that DMSO is known as a highly reactive solvent and can cause an unexpected explosion in the presence of impurities, such as transition metal catalysts,[7] DMA/H_2O would be a better choice than DMSO/H_2O. The most important aspect for the safe operation of this reaction is that the $Na_2S_2O_4$ should not be contaminated with water.

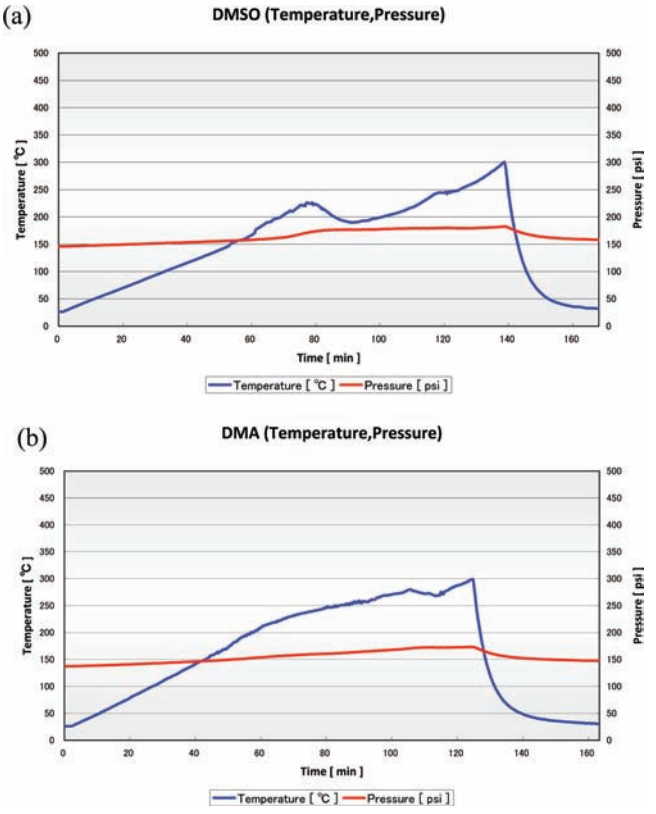

Figure 3. (a) ARSST data for DMSO/H_2O (10/1= v/v). (b) ARSST data for DMA/H_2O (10/1= v/v).[6]

Consideration of the mechanism. In the case of unsubstituted *o*-nitroarylamines, the reaction is presumed to be initiated by imine formation, which could promote reduction of the nitro group by the electronic effect.[2a] In this case, however, iminium ion formation of **3** with **6** was not observed by in situ IR analysis, and the intermediate, detected at less than 2% by HPLC during the addition of $Na_2S_2O_4$, was supposed to be **10**.[8] Thus, the first step of the reaction should be reduction of the nitro group, which requires 2 equiv of H_2O. This may account for the acceleration effect of H_2O (Scheme 3).

■ CONCLUSION

We demonstrated that the reductive cyclization reaction was accelerated by the addition of H_2O and the heat release could be controlled by semibatch-type operation. Safety evaluation by DSC, ARSST, in situ IR analysis, and Multimax removed concerns about using $Na_2S_2O_4$ in DMSO/H_2O or DMA/H_2O. In conclusion, we were able to propose a safe one-pot synthesis of benzimidazole via reductive cyclization of *o*-nitroarylamines with aldehyde using $Na_2S_2O_4$.

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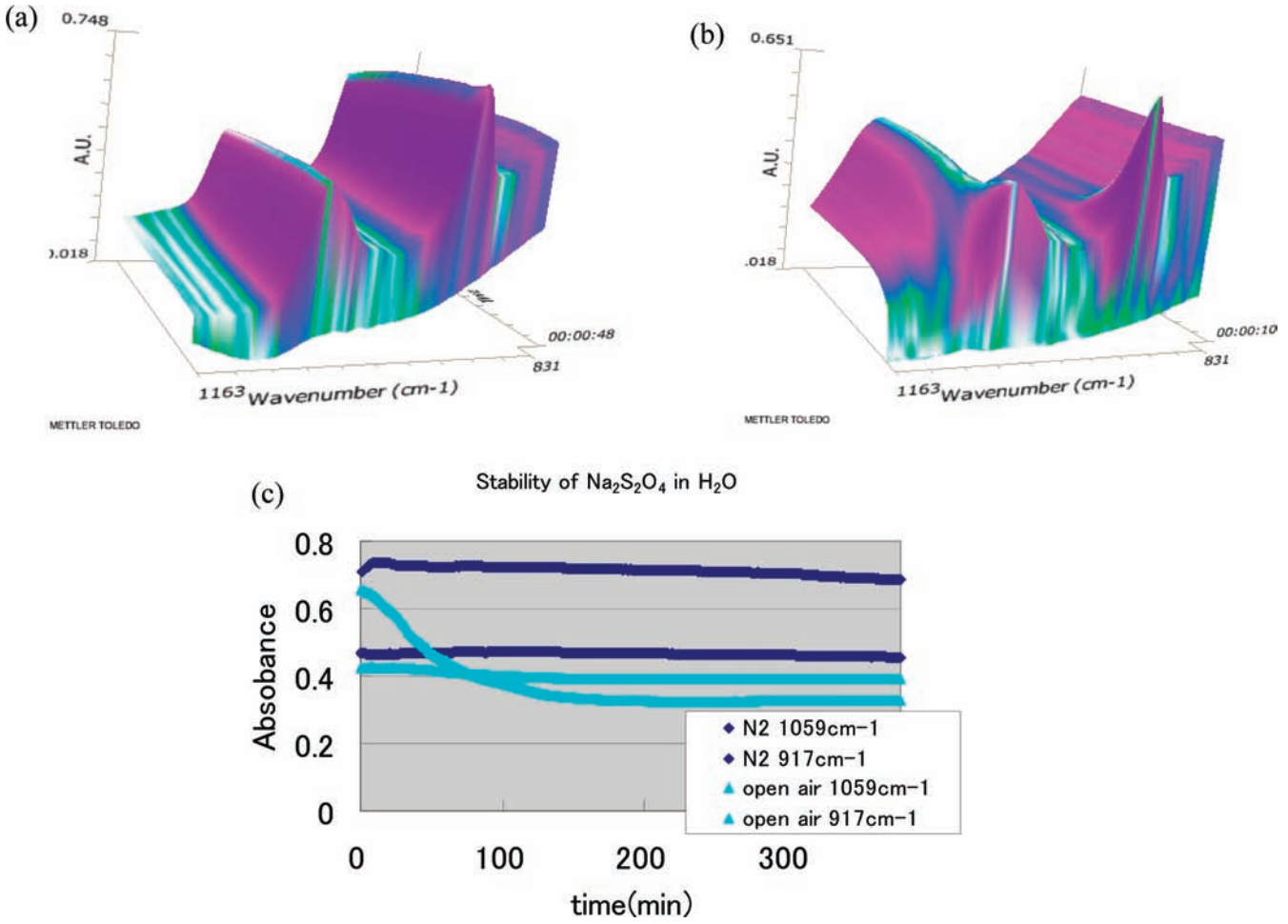

Figure 4. (a) Stability of $Na_2S_2O_4$ in H_2O (20 wt %) in nitrogen atmosphere. (b) Stability of $Na_2S_2O_4$ in H_2O (20 wt %) in air atmosphere, (c) Change of absorbance of in situ IR analysis.

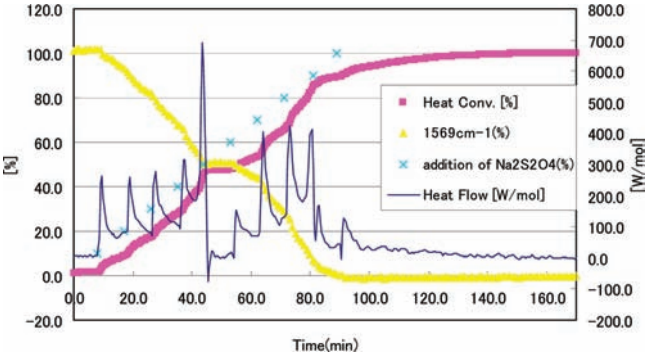

Figure 5. Heat flow of the semibatch-type operation of the reaction in DMSO/H_2O.

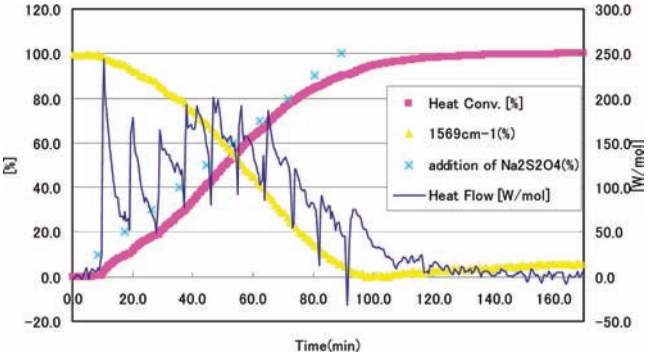

Figure 6. Heat flow of the semibatch-type operation of the reaction in DMA/H_2O.

EXPERIMENTAL SECTION

All reactions were run under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification.

^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Varian FT spectrometer. HRMS were recorded on a JEOL JMS-SX/SX102A. LCMS were recorded on a Shimadzu LCMS2010EV. All in situ infrared spectra were collected using a Mettler Toledo ReactIR iC10 equipped with a 6 mm diameter Diamond ATR probe (DiComp). The heat flow of the reaction was measured by Mettler Toledo MultiMax250. DSC was measured using a Mettler Toledo SDC822e. The total chord length counts were obtained by Lasentec focused beam reflectance measurement (FBRM), i.e., real-time measurement, while the crystallization was taking place. The stability of reaction mixture was measured by Advanced Reactive Systems Screening Tool (ARSST) manufactured by Fauske and Associates.

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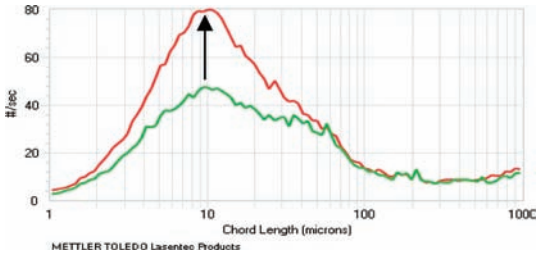
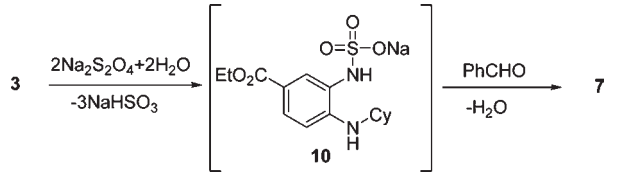


Figure 7. Change of chord length by crystallization.

Scheme 3. Plausible mechanism of the reductive cyclization



1-Cyclohexyl-2-(furan-3-yl)-1*H*-benzo[d]imidazole-5-carboxylic Acid (1). A 200-mL round-bottomed flask was charged with ethyl 4-(cyclohexylamino)-3-nitrobenzoate (5 g), DMSO (25 mL), EtOH (25 mL), 3-furaldehyde (1.81 g), and $Na_2S_2O_4$ (8.93 g). The mixture was stirred at 90 °C for 2.5 h. The mixture was quenched with water (100 mL) and extracted with ethyl acetate (100 mL × 1, 200 mL × 1, 50 mL × 1). The combined organic layers were washed with water (50 mL × 3) and concentrated by rotary evaporation. The crude residue was dissolved in THF (20 mL) and MeOH (10 mL), and then LiOH (1.86 g) dissolved in H_2O (18.6 mL) was added. The mixture was stirred at 30 °C for 1 h, cooled to 0 °C, and adjusted to pH 4 with HCl(aq). The precipitate that formed was obtained by filtration, washed with H_2O (100 mL), and dried at 40 °C under reduced pressure to obtain the title compound (4.22 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (1H, d, J = 0.6 Hz), 8.20 (1H, d, J = 1.8 Hz), 7.94−7.91 (2H, m), 7.83 (1H, dd, J = 8.7, 1.8 Hz), 6.94 (1H, d, J = 2.1 Hz), 4.48−4.39 (1H, m), 2.40−2.20 (2H, m), 2.00−1.80 (4H, m), 1,70−1.60 (1H, m), 1.50−1.30 (3H, m); ^{13}C NMR (300 MHz, DMSO-d_6) δ 168.5, 149.1, 145.2, 144.2, 143.7, 137.6, 125.2, 124.0, 121.7, 116.8, 113.6, 112.0, 57.6, 31.5, 26.5, 25.5; HRMS (FAB) m/z calc'd for $C_{22}H_{25}N_2O_2$ $[M]^+$: 311.1396, found 311.1394.

Ethyl 4-(Cyclohexylamino)-3-nitrobenzoate (3). A 1-L round-bottomed flask was charged with ethyl 4-chloro-3-nitrobenzoate (50.0 g), NMP (150 mL), cyclohexylamine (64.8 g), and triethylamine (66.0 g). The mixture was stirred at 90 °C for 1.5 h. The mixture was quenched by water (300 mL) and extracted by ethyl acetate (500 mL × 2). The combined organic layers were washed with water (300 mL), brine (300 mL), and water (300 mL) and concentrated by rotary evaporation. The residue was dried under reduced pressure at 40 °C to give **3** (63.3 g, 99%). This compound is already known, and the ^{1}H NMR data corresponded to the literature data.[1d] ^{1}H NMR (300 MHz, $CDCl_3$): 8.86 (1H, d, J = 1.8 Hz), 8.35−8.46 (1H, m), 8.01 (1H, dd, J = 8.7, 1.5 Hz), 6.87 (1H, d, J = 9.3 Hz), 4.35 (2H, q, J = 7.2 Hz), 3.65−3.50 (1H, m), 2.14−1.29 (10H, m), 1.38 (3H, t, J = 7.1 Hz)

Ethyl 1-Cyclohexyl-2-phenyl-1*H*-benzo[*d*]imidazole-5-carboxylate (7). The reaction mixtures described in the Results and Discussion section were cooled to room temperature, and then water was added to them. The resulting precipitate was obtained by filtration and washed with water, then purified by recrystallization from acetone and water to give benzimidazole **8** (87%, DMSO/H_2O solvent; 86%, DMA/H_2O solvent). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, d, J = 1.5 Hz), 7.98 (1H, dd, J = 9, 1.8 Hz), 7.62 (1H, s), 7.65−7.60 (2H, m), 7.56−7.25 (3H, m), 4.41 (2H, q, J = 7 Hz), 4.36−4.33 (1H, m), 2.40−2.20 (2H, m), 2.00−1.90 (4H, m), 1.42 (3H, t, J = 7.2 Hz), 1.40−1.28 (4H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.9, 155.3, 143.2, 137.0, 130.5, 129.8, 129.3, 128.6, 124.3, 123.4, 122.3, 112.0, 60.8, 57.1, 31.4, 25.9, 25.3, 14.5; HRMS (FAB) m/z calc'd for $C_{22}H_{25}N_2O_2$ $[M]^+$: 349.1916, found 349.1923.

Ethyl 2-Phenyl-1*H*-benzo[*d*]imidazole-5-carboxylate (9). The title compound was isolated from the reaction mixture (entry 15, Table 2) by flash column chromatography on silica gel using hexane/ethylacetate (3:2) as the eluent to give 5.8 mg of **9** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 8.18 (1H, dd, J = 7.8, 1.8 Hz), 7.93 (1H, dd, J = 8.4, 1.5 Hz), 7.54 (1H, d, J = 8.4 Hz), 7.25−7.40 (3H, m), 4.35 (2H, q, J = 7.2 Hz), 1.35 (3H, t, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.2, 154.7, 130.4, 129.2, 128.9, 127.0, 124.6, 124.1, 61.0, 31.6, 22.6, 14.3, 14.2, 14.1; HRMS (FAB) m/z calc'd for $C_{16}H_{15}N_2O_2$ $[M]^+$: 267.1133, found 267.1141.

■ ASSOCIATED CONTENT

Supporting Information. Copies of DSC, ^{1}H NMR, and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
shinichi.oda@shionogi.co.jp

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(5) The reactions were monitored by the disappearance of N−O antisymmetric vibration peak (1569 cm^{-1}) of *o*-nitroarylamine **3** in *in situ* IR analysis and performed using **3** (1 mmol), **6** (1.1 mmol), $Na_2S_2O_4$ (3 mmol), and solvent (2.5 mL). The yields of benzimidazole **7**

were 96% in DMSO and 91% in DMSO/H_2O, calculated by HPLC using an external standard.

(6) The reaction mixtures were prepared using *o*-nitroarylamine **4** (400 mg), benzaldehyde **7** (159.7 mg), $Na_2S_2O_4$ (714.7 mg) and solvent (4.4 mL).

(7) (a) Schindler, N.; Proger, W. *Chem. Ber.* **1971**, *104*, 969–971. (b) Lam, T. T.; Vickery, T.; Tuma, L. *J. Therm. Anal. Calorim.* **2006**, *85* (1), 25–30.

(8) (a) Kazakov, A. *Bulg. Tr. Nauchnoizsledovatelskiya Khimikofarm. Inst.* **1992**, *18*, 17–28. (b) The structure of the intermediate observed by LCMS was presumed to be **10**, which was supported by the fact that the reaction without benzaldehyde gave the compound in 24% yield (peak area % by HPLC analysis at 254 nm).