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EXPLORATION OF MODERATE CONDITIONS AND SUBSTRATE VARIATION IN THE DIRECT CONDENSATION BETWEEN PHTHALIDE AND PRIMARY AMINE CATALYZED BY $GaCl_3$. ARE ALIPHATIC AMINES LESS REACTIVE THAN AROMATIC ONES?†

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Abstract – Direct condensation between phthalide and a primary amine in the presence of Lewis acid was achieved for the first time in organic solvent-diluted reaction systems catalyzed by $GaCl_3$. The peripheral aspects of this reaction is discussed.

INTRODUCTION

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeletons have attracted considerable interests in recent years. Its publicity has never been comparable to that of isomeric indole analogues, however, trends of often-occurring crystalline (= easily identifiable) derivatives and a variety

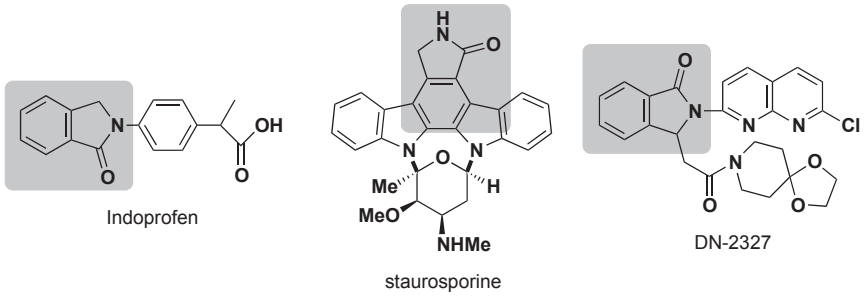


Figure 1. Chemical structures of some bioactive phthalimidines

† Dedicated to Professor Tohru Fukuyama on his 70th birthday

of bioactivities have aroused its synthetic interest increasingly. Recently focused bioactive phthalimidines such as indoprofen (anti-inflammatory agent), staurosporine (protein kinase C inhibitor), and DN-2327 (also known as pazinaclone, anxiolytic agent) have attracted much attention (Figure 1).[1-3]

Since 1877, a number of "famous" phthalimidine skeleton syntheses have been known to literatures, for which the following classification is possible. Thus, condensation of phthalide with primary amine (Hessert-Sugasawa), condensation of 2-hydroxymethylbenzoic acid derivative (e.g., ring-opened type phthalide) with primary amine (Fischer), Clemmensen-type reduction of phthalimide (Graebe), rearrangement of phthalazone (Gabriel), CO insertion to benzimidine (Murahashi), and double Mannich condensation (Thiele), have played major roles ever since.[1-5]

However, applicabilities of all synthetic methods described above are more or less limited and unsatisfactory, due to severe reaction conditions, restrictions in substituents, or difficulties in purification.

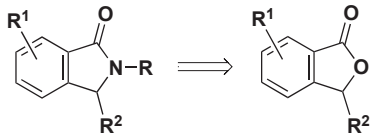
Focusing on this point, we previously reported the 1:1 condensation reaction between *o*-phthalaldehyde (OPT) and primary amine in the presence of 1,2,3-1*H*-benzotriazole and 2-mercaptoethanol as dual synthetic auxiliaries to provide phthalimidines under mild reaction conditions in good isolated yields.[6-11] Our method is believed to be useful in the preparation of phthalimidine framework of "type indoprofen", where unsubstituted or symmetrically substituted benzene precursors are assumed as starting materials.

Recent advancements deeply stem in the categories described above, too. Example of those appeared in literature are as follows: Mannich condensation-based annulation utilizing phthalaldehydic acid,[12,13] use of polymethylhydrosiloxane (PMHS) as reductant for phthalimide,[14] annulations of benzamidomethylide,[15,16] and insertion of Pd catalyst to C-halogen or C-H bondings located ortho to carboxylic amide.[17-20]

However, preparations of phthalimidines exemplified by "type staurosporine" and "type DN-2327" are rather cumbersome business, because in general dissymmetrical substituents' patterns apparently require dissymmetrical substrates, for which at some stage asymmetrization must be applied to distinguish oxidation states between 1-position and 3-position of isoindole moieties. To the best of our knowledge, asymmetrization (redox, *etc.*) of some equi-oxidation stage functionalities (carbonyl groups, aromatic C-H's, *etc.*) have inevitably given rise to all possible isomers in the end, which would bring about difficulties in purification.[21-25] To our surprise, the utility of in-advance-asymmetrized dissymmetrical substrate, which would solve the problems described above, had never been examined intensively.

In this respect, we recently established a 1:1 condensation reaction between phthalide and a primary amine in the presence of a *catalytic* amount of $InCl_3$ under solvent-free conditions to give *single* phthalimidines as sole products,[26] innovating the *oldest* procedure in the history of phthalimidine syntheses (known as the Hessert-Sugasawa procedure), which was introduced 140 years ago.[27,28] Its assumed reaction mechanism is not involved with any intramolecular oxidation/reduction. Therefore,

the patterns of the substituents would directly be imported from those in the phthalide (including the carbonyl group at the 1-position), enabling the quick construction of phthalimidine cores such as "type staurosporine" or "type DN-2327" (Scheme 1).[26] People may consult a number of natural/artificial phthalide derivatives in chemical catalogs at hand (or SciFinder, *etc.*).



Scheme 1. Utility of phthalide as a template of phthalimidine

We also recently categorized the HCC (hourly conversion per catalyst) value, a term numerically identical to the TON (turnover number) per hour, to determine whether a certain reaction is practically fast or slow.[26,29] In this respect, HCC values of our $InCl_3$-catalyzed condensation between phthalide and aniline were ~ 1.25 at the most, indicating that the use of 1 mol% and 5 mol% of the catalyst would require 80 h and 16 h to complete. These estimates are in good accordance with the contemporary standard of organic syntheses, but, some problems remain. These include:

(i) The procedure was solvent-free but had a high concentration of components, which often induced the "solidification" of reaction mixtures, thus inhibiting the reaction itself (when resulting phthalimidines possessed high melting points, *etc.*).

(ii) Dilution of reaction mixtures with a variety of organic solvent systems could be used to overcome the situation described in (i); such dilution did not allow inhibited reactions themselves to proceed.

(iii) High reaction temperature (200 ^{o}C) was needed throughout.

In addition to these *process modifications*, we can demonstrate the following reasons, which have encouraged us greatly:

(i) The procedure involving the direct condensation between phthalide and primary amine (Hessert-Sugasawa) had never encountered *good* reagents, and therefore, it had never been studied enthusiastically.

(ii) Reagents containing In or Ga became convenient to laboratorial uses rather recently, and therefore, examples of their application to the annulation to form heterocycles have still been limited.

(iii) In the present stage, widely applicable mild-condition phthalimidine synthesis is limited to usages of 2-hydroxymethylbenzoic acid derivatives (ring-opened type phthalides), which in themselves require multistep syntheses.

(iv) One-step synthesis to phthalimidine starting from a variety of available phthalides is fascinating to the construction of compounds' library in terms of medicinal chemistry.

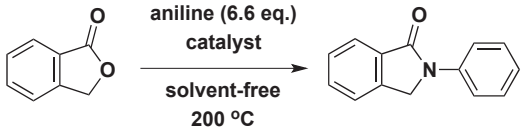
In this report, we describe our attempts to obtain *moderate* reaction conditioned phthalide → phthalimidine conversion, together with some peripheral unforeseen issues.

RESULTS AND DISCUSSION

In principle, the key to finding moderate reaction conditions involves setting temperatures as low as possible. Therefore, catalyst candidates in the present work *had to* show similar or higher reactivity than $InCl_3$ under the optimized conditions in our previous work (heated by bath at 200 °C = aniline reflux).[26] On the other hand, in order to avoid instantaneous solidification of reaction mixtures due to neutralization between components, catalyst candidates must possess similar or lesser affinity than $InCl_3$ towards oxygen and nitrogen.[30] Based on our previous inspections, the usable catalyst candidates in hand were $ZnCl_2$ and $InCl_3$, which belong to groups 12 and 13, respectively.[26] We therefore embarked onto screening of Lewis acids, the central elements of which belong to groups 11 to 14 and *period numbers unlimited*, taking some deviations in catalyst activities into account.[31] In this study, chlorides were examined in terms of commercial availability and ease of handling, based on our past experiences.

In general, aniline (6.6 mmol, used as both reagent and solvent) was added to a flask containing phthalide (1.0 mmol) and a catalyst (an appropriate amount) under Ar atmosphere for a few minutes with stirring, and the whole mixture was heated at gentle reflux (bath temperature = 200 °C) for an appropriate period. Whenever stirring was obstructed due to the viscosity of the solution (or the components themselves), the reaction time was extended as appropriate. After the usual work-up, crude products were purified by column chromatography on silica gel. Isolated components were ascertained by ^{1}H NMR spectral comparison with authentic samples prepared from our former methods (Scheme 2). The results are summarized in Table 1.

As for newly examined catalyst screenings, solidification of reaction mixtures was observed when CuCl, $CuCl_2$, $HgCl_2$, and $TlCl_3$ were utilized as catalysts (Entries 1, 2, 5, and 10), probably due to the strong affinity between metal cation centers with heteroatomic lone pairs; these reactions scarcely progressed, as was the case in past experiments.[26] When $CdCl_2$, $SnCl_2$, and $SnCl_4$ were used as catalysts, the product yields were fair (Entries 4, 11 and 12), but rather lower than when $ZnCl_2$ catalyst was used (Entry 3).[26-28] Meanwhile, when $GaCl_3$ was used as the catalyst (Entries 6-8), the isolated yields of 2-phenylphthalimidine were high and solely comparable to that obtained using $InCl_3$ (Entry 9).[26] Longer reaction-time settings were adopted because the reagent of $GaCl_3$ was in itself very viscous, and had to be dispersed into the reaction mixtures to allow smooth stirring. As a result, hereafter, experiments were conducted using only $GaCl_3$ and $InCl_3$.



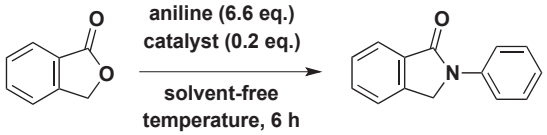
Scheme 2. Solvent-free 2-phenylphthalimidine-forming reaction

Table 1. Catalyst dependence

Entry	Catalyst			Time/h	Yield/%	Recovery/%
	reagent	group	eq.			
1	CuCl	11	2	4	---	---
2	$CuCl_2$		2	4	---	---
3[a]	$ZnCl_2$	12	1	2	51	messy
4	$CdCl_2$		2	4	18	62
5	$HgCl_2$		2	4	---	---
6	$GaCl_3$	13	2	6	95	---
7			0.2	6	84	---
8			0.2	12	95	---
9[a]	$InCl_3$		2	2	95	---
10	$TlCl_3$		2	4	1	49
11	$SnCl_2$	14	2	2	29	3
12	$SnCl_4$		2	2	22	18

(a) Reported results in reference 26.

First, the 2-phenylphthalimidine-forming reaction was settled as the index in connection, and examinations were carried out by altering reaction temperatures (Scheme 3). The results are summarized in Figure 2.



Scheme 3. Temperature-variant 2-phenylphthalimidine-forming reactions

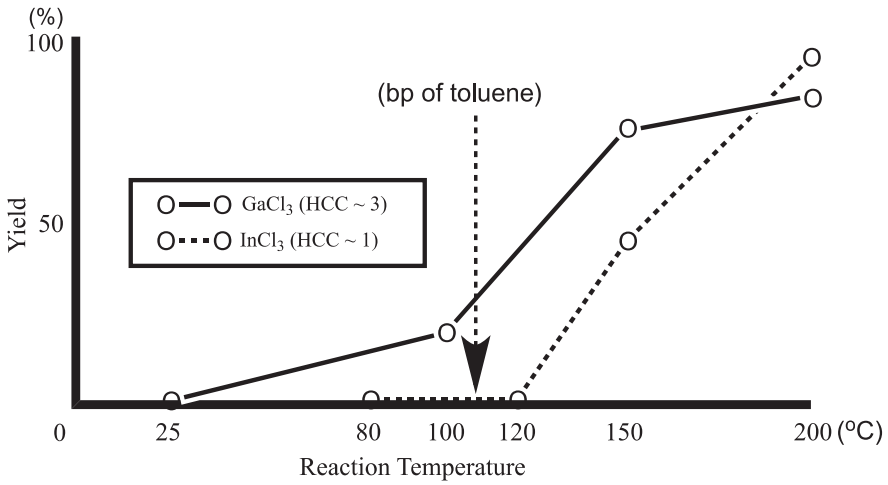
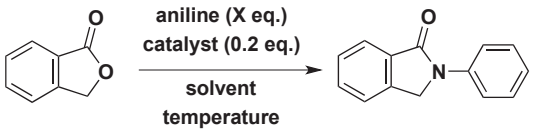


Figure 2. Effects of reaction temperatures on the formation of 2-phenylphthalimidine

As mentioned above, in the very beginning of the reaction, the dispersion process of $GaCl_3$ might be slower than that of $InCl_3$ due to its viscosity producing less reactivity. However, when the systems were compared at the 6-h reaction point, for example, $GaCl_3$ appeared to exhibit higher activity than $InCl_3$. This was as expected from the younger-period central element belonging to group 13, which was supported in terms of our proposed HCC (= Hourly Conversion per Catalyst) index.[29] In addition, the reactions were found to proceed somehow at ~100 °C, which was good news in terms of achieving milder reaction conditions.

We therefore identified a catalyst with activity higher than that of $InCl_3$, which enabled us to examine and optimize the reaction conditions. Related solvent-diluted reaction systems were studied (Scheme 4). The results were summarized in Table 2.



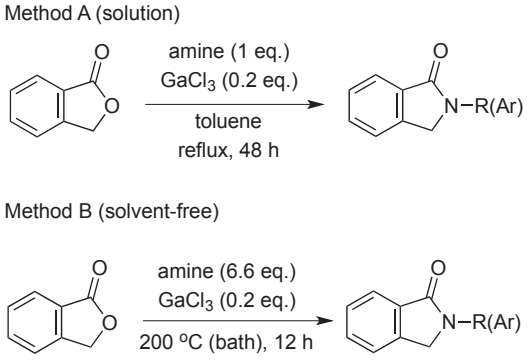
Scheme 4. Solvent-variant 2-phenylphthalimidine-forming reactions

Table 2. Solvent dependency (catalyst = $GaCl_3$)

Entry	Solvent	Time (h)	Temp. (bp/°C)	Yield (%)	X (eq.)
1	dioxane	6	100	15	6.6
2	ethylene glycol	6	196	10	6.6
3	xylene	6	143	48	6.6
4		24	143	59	6.6
5	toluene	6	110	31	6.6
6		24	110	68	6.6
7		48	110	80	6.6
8		48	110	78	2
9		48	110	86	1
10	benzene	6	80	0	6.6

When $InCl_3$ was used as catalyst, as reported in our previous paper,[26] reactions did not proceed at all in solvent-diluted systems (conditions for Entries 1-3 in Table 2; not shown). $GaCl_3$ was then examined as a catalyst, first in polar solvent systems, in the hope that monomeric and active Lewis acid species would emerge. However, the isolated yields of 2-phthalimidine were poor (Entries 1 and 2). On the other hand, when solvent systems were switched to xylene and toluene (hydrocarbons), reactions were unexpectedly found to proceed smoothly at temperatures far lower than 200 °C (Entries 3-7). Additional experiments concerning equivalents of aniline (Entries 8 and 9) completed the optimization of the reaction conditions. Use of benzene as a solvent did not work at all (Entry 10). Entry 9 of Table 2 was thus selected as the protocol.

Further, in order to facilitate the comparison of results, Entry 9 of Table 2 was chosen as the protocol for solvent-free conditions. The two protocols (Methods A and B) described above are shown together as Scheme 5.



Scheme 5. Optimized reaction conditions (Methods A and B)

A number of primary amines other than aniline itself were then tested in the phthalimidine-forming reactions. The results are summarized in Table 3.

Table 3. Results of phthalimidine syntheses catalyzed by $GaCl_3$

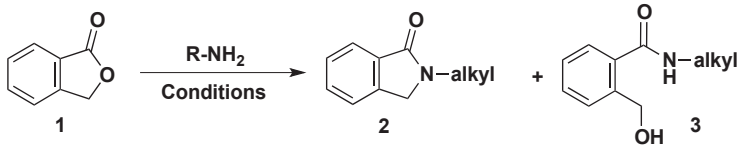
Entry	Amine	Yield/%	
		Method A	Method B
1	*p*-MeO-C_6H_4-NH_2	17	80
2	*p*-Me-C_6H_4-NH_2	41	84
3	C_6H_5-NH_2[a]	86	95
4	*p*-Cl-C_6H_4-NH_2	43	73
5	*p*-Br-C_6H_4-NH_2	41	5
6	*p*-Ac-C_6H_4-NH_2	2	0
7	*p*-NO_2-C_6H_4-NH_2	trace	trace
8	*o*-NO_2-C_6H_4-NH_2	26	trace
9	2-$C_{10}H_7$-NH_2	26	trace
10	C_6H_5-CH_2-NH_2[a]	trace	50
11	*p*-MeO-C_6H_5-CH_2-NH_2	trace	66
12	*n*-$C_{12}H_{25}$-NH_2	2	45[b]

(a) Bp = 184 °C. (b) *N*-Dodecyl-2-hydroxymethylbenzamide (14%) as byproduct.

When aromatic amines (anilines) were used, the isolated yields of products by Method A showed lower yields than those by Method B in principle (Entries 1-4); however, in the case of *p*-bromoaniline, Method A showed yields substantially higher than those by Method B (Entry 5). When strong electron-withdrawing substituent-containing anilines such as *p*-acetyl- and *p*-nitro-anilines were used, the reactions had difficultly proceeded, as expected (Entries 6 and 7). However, when intermediate electron-withdrawing substituent-containing anilines such as *o*-nitroaniline and 2-naphthylamine were used, Method A showed improved yields compared to Method B (Entries 8 and 9). Thus, Method A might be shown to somehow compensate for Method B. In contrast, when aliphatic amines were used instead, the products were obtained in intermediate yields by Method B; however, the reactions were found to barely progress by Method A (Entries 10-12).

These results were surprising, since aliphatic amines are generally believed to advance reactions faster than anilines, owing to the presence of high electron-density-containing nitrogen centers. Incidentally, a benzamide (**3**) derivative was isolated out of Entry 12, together with phthalimidine (**2**). The benzamide (**3**) derivative had never been isolated in our past research, but was considered a key compound in the present reaction system. Therefore, we embarked on a series of experiments to determine the product distribution patterns by altering the primary amine, temperature, and catalyst presence/absence (Scheme 6). In cases with catalytic reactions (containing $GaCl_3$ in the present work), either Method A or B

(Scheme 5) was adopted. On the other hand, in cases of non-catalytic reactions, the components were simply mixed, stirred, and evaporated, and the residues were subjected to chromatographic purifications whenever necessary. The results are summarized in Table 4.



Scheme 6. Reaction between phthalide and aliphatic primary amines

Table 4. Product distribution patterns in the condensation between phthalide and aliphatic primary amines

	R-NH_2						Yield/%[a]		
Entry	Compound	equiv.	Catalyst	Solvent	Temp./°C	Time/h	3	1	2
1	*n*-C_4H_9-NH_2	2	-----	-----	40	3	98	0	0
2		6.6	-----	-----	78	12	71	0	0
3		6.6	$GaCl_3$	-----	78	12	79	0	0
4	*n*-C_6H_{13}-NH_2	2	-----	-----	40	3	80	0	0
5		1	-----	toluene	110	48	30	66	0
6		1	$GaCl_3$	toluene	110	48	0	87	0
7		6.6	-----	-----	131	12	0	70	0
8		6.6	$GaCl_3$	-----	131	12	49	35	9
9	*n*-C_7H_{15}-NH_2	6.6	$GaCl_3$	-----	155	12	7	47	31
10	C_6H_5-CH_2-NH_2	6.6	-----	-----	184	12	0	85	7
11		6.6	$GaCl_3$	-----	184	12	0	0	50
12	C_6H_5-NH_2[b]	6.6	$GaCl_3$	-----	150	6	0	0	76

(a) In cases of mixtures, molar ratio between/among products were determined by integration ratio of benzylic proton signals in ^{1}H NMR spectra. See Experimental for example (Entry 9). (b) Aromatic amine (inserted for data comparisons).

The following tendencies were observed from the data in Table 4.

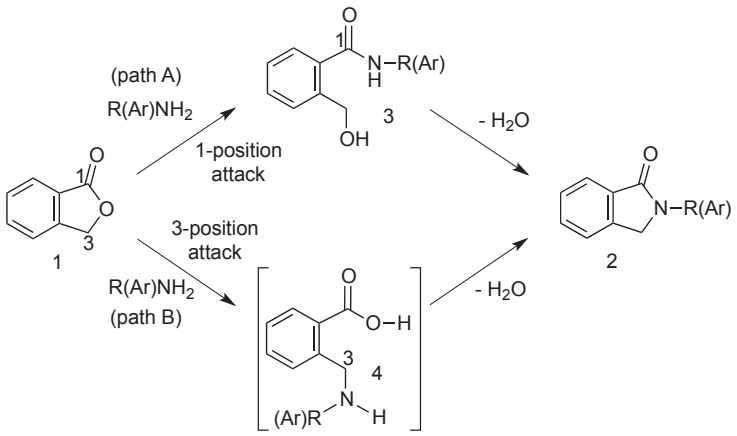
When aliphatic primary amines were used, amides (**3**) were isolated as the sole products irrespective of the presence/absence of catalyst at reaction temperatures <110 °C (Entries 1-4). When the reaction temperature reached ~110 °C, a reverse reaction from **3** to phthalide (**1**) began to be observed (Entry 5); this tendency was intensified by the presence of a catalyst during the temperature increase (Entries 6 and 7). When the reaction temperatures were set to intermediate, phthalimidine (**2**) was observed first, and mixtures containing **1**~**3** were available (Entries 8 and 9). However, when benzylamine was used, the reaction mixtures contained **1** and **2** but not **3** (Entry 10; not explicable in the present stage). Reactions

at high temperatures gave **2** as the sole product (Entries 11 and 12).

In addition, when *N*-butyl- and *N*-hexyl-2-hydroxymethylbenzamide (isolated) were subjected to the reaction conditions for Entries 5 and 6, **1** was recovered as the sole product, and no phthalimidines were detected.[26]

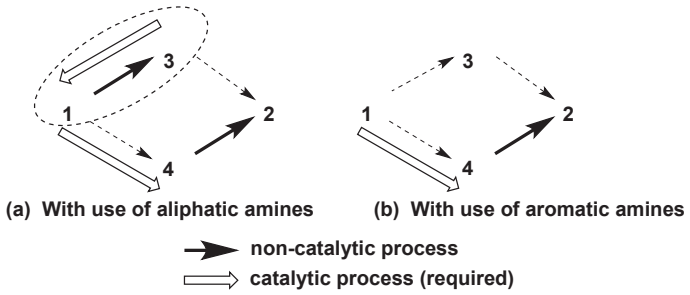
Based on the above results, we assumed that the plausible reaction paths in the present reaction system were those in Scheme 7. In order to clarify this, possible catalyst chelations were abbreviated.

The possible electrophilic reactive centers of phthalide (**1**) towards the primary amine were those at the 1-position (path A) and 3-position (path B). In the case of path A, the benzamide derivative (**3**; isolated) was formed first, followed by dehydrative annulations to afford phthalimidine (**2**). On the other hand, in the case of path B, the benzoic acid derivative (**4**; not determined) was to be formed first, followed by dehydrative annulations to afford phthalimidine (**2**).



Scheme 7. Plausible reaction paths in the present reaction system (1)

From the results in Table 4, reactive amines were limited to aliphatic ones (surprisingly, except for benzylamine) to react at the 1-position and afford the benzamide derivative.[32] The 1-position has a carbon center that is δ+ greater than that of the 3-position, which would match with nucleophilic aliphatic amines in terms of the HSAB rules.[33] On the other hand, open-chain benzamide (**3**) is heated to obtain predominantly phthalide (**1**) and a small amount of phthalimidine (**2**), irrespective of the presence/absence of a catalyst. Therefore, the chance for phthalimidine (**2**) formation is limited to the attack of a nucleophile towards the less electrophilic 3-position, made possible by high reaction temperature settings. The results summarized in Table 4 could be interpreted rationally, taking the matters described above into account. Our working hypothesis is outlined as Scheme 8.



Scheme 8. Plausible reaction paths in the present reaction system (2)

Thus, the reaction between aniline and phthalide (**1**) can progress at a relatively low reaction temperature (Method A) to provide phthalimidine (**2**), since the path to amide (**3**) is practically omitted and no obstacle is expected. In contrast, the reaction between aliphatic amine and phthalide (**1**) preferentially progresses to form amide (**3**) first, and therefore cannot provide **2** until the reverse reaction (**3** to **1**) is intensified to overcome the path (**1** to **3**) to regenerate **1**. This requires additional energy compared to the reaction with anilines. On the other hand, our literature searches showed that *N*-phenyl-2-hydroxymethylbenzamide (a derivative of **4**) was reported to undergo dehydrative annulation upon heating just above melting point (159-161 ^{o}C) for a short preriod.[34] The result described above is not contradictory to the fact that we had never detected the formation of **4** at all in the present study.

In conclusion, though we previously reported the direct condensation reaction between phthalide and amine catalyzed by $InCl_3$, we aimed to determine milder reaction conditions, examined $GaCl_3$ as a proximal catalyst candidate, and succeeded when anilines were used as amines by lowering the temperature and extending usable reactants. However, when aliphatic amines reacted with phthalide, obstructed by the 1-position attack preferentially located even at the low-temperature region, temperature lowering of the phthalimidine-forming reaction itself was unsuccessful.

Further attempts to lower the temperature and apply *N*-substituted-2-hydroxymethylbenzamides for the synthesis of compounds peripheral to phthalimidines are now underway in our laboratories.

EXPERIMENTAL

General Information. All melting points are uncorrected. Infrared (ir) spectra were measured with a JASCO FT/IR-620 Fourier transform infrared spectrometer. ^{1}H (300 MHz) nuclear magnetic resonance (nmr) spectral measurements were carried out with a JEOL JNM-AL300 Fourier transform NMR spectrometer. ^{13}C (125 MHz) NMR spectral measurements were carried out with a JEOL JNM-ECX500 Fourier transform NMR spectrometer. All signals are expressed as ppm downfield from tetramethylsilane (TMS) used as an internal reference (δ value). The following abbreviations are used: singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m), broad(b). Positional numbers are assembled as

follows: no prime, isoindole or benzene ring; single prime, substituent of 1-position, double prime, substituent of 2-position. Mass spectra (ms; FAB mode) were taken with a JEOL JMS DX303 mass spectrometer, where mass numbers of local maxima (relative intensities in parentheses) are recorded.

All chamicals and solvents were commercially purchased in the purest grade and used without further purifications.

Typical Experimental Procedures.

Example of Method A (in solution; Entry 3 of Table 3)

A solution of aniline (0.093 g, 1.0 mmol) in toluene (5 mL) was added to the reaction flask containing phthalide (0.134 g, 1.0 mmol) and $GaCl_3$ (0.01425 g, 0.2 mmol) under Ar atmosphere over *ca.* 3 min with stirring, and the whole mixture was heated at gentle reflux utilizing an oil bath (135 ^oC) for 48 h. During the rise of temperature, powdered phthalide melted off and was fully dissolved in solution. On the other hand, $GaCl_3$ (viscous oil in itself) obstacled stirring in the beginning, but stirring became easier in due course as $GaCl_3$ was partially dissolved in solution. Then, the reaction mixture was cooled to room temperature and poured onto ice-cold 1% HCl, and then extracted with EtOAc. Organic layer was washed by satd. aq. $NaHCO_3$, dried over anhyd. $MgSO_4$, and then filtered. Evaporation gave a crude product, which was purified by column chromatography (silica gel, eluted by hexane-EtOAc) to give pure 2-phenylphthalimidine (0.180 g, 86%).

In addition to the remaining Entries of Table 3, reactions shown as Table 2 and Entries 5 and 6 of Table 4 were carried out using the similar procedure to that described above.

In the case of Entry 7 of Table 3, formation of a trace amount of 2-(*p*-nitrophenyl)phthalimidine was determined by the ^1H NMR spectral comparison of crude mixture with the authentic sample prepared using our former methods.[6-11]

Method B (solvent free; Entry 3 of Table 3)

Aniline (0.614 g, 6.6 mmol) was added to the reaction flask containing phthalide (0.134 g, 1.0 mmol) and $GaCl_3$ (0.0442 g, 0.2 mmol) under Ar atmosphere over *ca*. 3 min with stirring, and the whole mixture was heated at gentle reflux utilizing an oil bath (200 ^oC) for 12 h. During the rise of temperature, powdered phthalide melted off and fully mixed with aniline. On the other hand, $GaCl_3$ (viscous oil in itself) obstacled stirring in the beginning, but stirring became easier in due course as $GaCl_3$ was partially dissolved in solution. Then, the reaction mixture was cooled to room temperature and poured onto ice-cold 1% HCl, and then extracted with EtOAc. Organic layer was washed by satd. aq. $NaHCO_3$, dried over anhyd. $MgSO_4$, and then filtered. Evaporation gave a crude product, which was purified by column chromatography (silica gel, eluted by hexane-EtOAc) to give pure 2-phenylphthalimidine (0.200

g, 95%).

In addition to the remaining Entries of Table 3, reactions shown as Table 1 and Entries 3, 8, 9, 11, and 12 of Table 4 were carried out using the similar procedure to that described above.

Direct Condensation between Phthalide and Aliphatic Primary Amine (Entry 4 of Table 4).

A mixture of phthalide (0.268 g, 2 mmol) and hexylamine (0.404 g, 4 mmol) was stirred at room temperature for 3 h. Then, the reaction mixture was evaporated *in vacuo*, and the crude product was purified by column chromatography (silica gel, eluted by hexane-EtOAc) to give pure *N*-hexyl-2-hydroxymethylbenzamide as a colorless oil (0.240 g, 51%).

Reactions shown as Entries 1, 2, 7, and 10 of Table 4 were carried out using the similar procedure to that described above.

^{1}H NMR spectra of *known* compounds were compatible with those we reported previously. Some other physical data of products are as follows.

2-(*p*-Methoxyphenyl)phthalimidine. White solid, mp 136-138 ºC (lit.,[11] 136-139 ºC).

2-(*p*-Methylphenyl)phthalimidine. White solid, mp 139-141 ºC (lit.,[10] 140-141.5 ºC).

2-Phenylphthalimidine. White solid, mp 158 ºC (lit.,[11] 162-164.5 ºC).

2-(*p*-Chlorophenyl)phthalimidine. White solid, mp 179-181 ºC (lit.,[11] 180-183 ºC).

2-(*p*-Bromophenyl)phthalimidine. White solid, mp 179-181 ºC (lit.,[11] 181-182 ºC).

2-(*p*-Acetylphenyl)phthalimidine. Lemon-yellow solid, mp 236-239 ºC (lit.,[11] 237-239 ºC).

2-(*o*-Nitrophenyl)phthalimidine. Yellow solid, mp 159-160 ºC (lit.,[11] 161-162 ºC).

2-(2-Naphthyl)phthalimidine. Beige solid, mp 183-185 ºC (lit.,[35] 188-189 ºC).

2-(Phenylmethyl)phthalimidine. White solid, mp 87-90 ºC (lit.,[11] 92-95 ºC).

2-(*p*-Methoxyphenylmethyl)phthalimidine. Slightly gray solid, mp 87-90 ºC (lit.,[11] 102-105 ºC).

2-Dodecylphthalimidine. Lemon-yellow oil (lit.,[12] lemon-yellow oil).

***N*-Dodecyl-2-hydroxymethylbenzamide.** Colorless oil (lit.,[36] oil).

***N*-Butyl-2-hydroxymethylbenzamide.** Colorless oil (lit., decomposes,[32] colorless oil[37]).

***N*-Hexyl-2-hydroxymethylbenzamide.** Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.51 (1H, dd, J = 8 Hz and 2 Hz, H-6), 7.38 (1H, ddd, J = 7 Hz, 7 Hz, and 2 Hz, H-4), 7.29 (1H, ddd, J = 8 Hz, 7 Hz, and 2 Hz, H-5), 7.27 (1H, dd, J = 7 Hz and 2 Hz, H-3), 7.16 (1H, bt, J ~ 6 Hz, N$\underline{\text{H}}$C$\underline{\text{H}}_2$), 5.00 (1H, t, J = 6 Hz, ArCH$_2$O$\underline{\text{H}}$), 4.49 (2H, d, J = 6 Hz, ArC$\underline{\text{H}}_2$OH), 3.35 (2H, td, J = 7 Hz and 7 Hz, NHC$\underline{\text{H}}_2$), 1.57 (2H, tt, J = 7 Hz and 7 Hz, NCH$_2$C$\underline{\text{H}}_2$), 1.43-1.22 (6H, m, methylene protons), 0.89 (3H, t, J = 7 Hz, CH$_2$C$\underline{\text{H}}_3$). ^{13}C NMR ($CDCl_3$) δ 170.1 (C=O), 140.1 (C-2), 136.0 (C-1), 131.2 (C-4), 130.8 (C-6), 128.2 (C-3), 127.6 (C-5), 64.8 (C-1”), 40.3 (C-1’), 31.5 (C-2’), 29.6 (C-3’), 26.7 (C-4’), 22.6 (C-5’), 14.2 (C-6’). IR (KBr):

ν_{max} (cm^{-1}) *ca.* 3300 (O-H and N-H), 1629 (C=O), 1536 (amide), 1032 (C-O), 723 (arom). MS (FAB): *m*/*z* (rel. intensities) 236 [$(M+1)^+$, 100], 218 (85), 165 (1), 134 (21), 118 (6), 105 (5), 43 (8). HRMS (FAB): *Calcd.* for $C_{14}H_{22}NO_2$: 236.1650; *Found:* 236.1650.

Mixture of Products from the Reaction between Phthalide and Heptylamine (Entry 9 of Table 4).

Slightly yellow oil. Phthalide (PD) : Benzamide (BA) : Phthalimidine (PI) = 55 : 9 : 36.

^{1}H NMR ($CDCl_3$) δ 7.88 (0.55H, d, *J* = 8 Hz, H-7 of PD), 7.79 (0.36H, d, *J* = 8 Hz, H-7 of PI), 7.69 (0.55H, dd, *J* = 7 Hz and 7 Hz, H-5 of PD), 7.68 (0.36H, dd, *J* = 7 Hz and 7 Hz, H-5 of PI), 7.64 (0.09 H, d, *J* = 8 Hz, H-6 of BA), 7.55-7.33 (1.91H, m, H-4, H-6 of PD, H-4, H-6 of PI, and H-4 of BA), 7.28-7.23 (0.18H, m, H-3 and H-5 of BA), 5.31 (1.1H, s, H-3 of PD), 4.61 (0.18H, s, benzyl of BA), 4.37 (0.72H, s, H-3 of PI), 3.65 (0.18H, td, *J* = 7 Hz and 7 Hz, NHC$\underline{H}_2$ of BA), 3.59 (0.72H, t, *J* = 7 Hz, NC$\underline{H}_2$ of PI), 1.80-1.55 (0.9H, m, $NCH_2C\underline{H}_2$ of PI and BA), 1.45-1.10 (3.6H, m, methylene of PI and BA), 0.87 (1.35H, bt, *J* ~ 6 Hz, C$\underline{H}_3$ of PI and BA).

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