RECENT PROGRESS OF PHTHALIMIDINE SYNTHESES†

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Abstract - Phthalimidine (2,3-dihydro-1H-isoindol-1-one) syntheses in recent years are reviewed primarily for those involving synthetic auxiliary-mediated mild Mannich type condensation reactions.

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†This review is dedicated to the 25th Anniversary of HETEROCYCLES.
1. Introduction
Heterocyclic compounds containing phthalimidine (1; 2,3-dihydro-1H-isoindol-1-one) skeletons have attracted considerable interest in recent years. Its publicity has never been competitive to that of isomeric indole analogues (2; \( X \) and/or \( Y = O \)), however, both often occurring crystalline (= easily identifiable) derivatives and a variety of bioactivities have raised its synthetic interest time to time.\(^1\)

Recently focused phthalimidine derivatives involve indoprofen (3; anti-inflammatory agent), staurosporine (4; protein kinase C inhibitor), and DN-2327 (5; anxiolytic agent, formerly known as pazinaclone).\(^2\)\(^4\) Reports on such evaluated skeletons as fluorescent markers to biochemical uses and precursors of electrically conductive polymers have appeared frequently.\(^1\)\(^a\)\(^5\)\(^6\) Theoretical studies have extensively evolved, too.\(^7\)
Except for side chain conversions of existing phthalimidine derivatives, their synthetic methods thus far appeared on literatures are exclusively involved with the formation of energetically feasible 5-membered lactam moieties as key steps. Because of the lack of reaction category varieties from the artificial point of view, representative synthetic methods of 1 have never been reviewed thoroughly. In this writing, we wish to describe the representative phthalimidine syntheses in recent years, focusing on the synthetic auxiliary-mediated "mild" Mannich type condensation reactions.

2. Definition of "synthetic auxiliaries"
Mannich reaction is a dehydrative condensation reaction between carbonyl compounds (6) and primary or secondary amines (7) to form imines or immonium salts known as Schiff's bases. Irrespective of its long time utilities, formaldehyde has been the almost sole carbonyl source to obtain such adducts successfully. In order to overcome this defect, the dual addition reaction of amine and "prootic" nucleophile (Nu1-H) to carbonyl compounds was established to afford Schiff's base-equivalent aminals (Scheme 1). Success of this "Mannich type" condensation reaction enables us to utilize a variety of aldehydes and some ketones as well to give reactive and evaluated intermediates without difficulty.

Substituents \( \text{Nu}^1 \) contained in adducts (8) may be substituted by second nucleophile (\( \text{Nu}^2 \)) to give compound (9) in principle, but often in vein.

\[
\begin{align*}
\text{R}_1^1 \text{C}=\text{O} + \text{H}-\text{N}^3 & \xrightarrow{\text{Nu}^1-\text{H}} \xrightarrow{-\text{H}_2\text{O}} \text{R}_2^1\text{C}-\text{N}^3 \xrightarrow{\text{Nu}^2} \text{R}_2^2\text{C}-\text{N}^3 \\
6 & \quad 7 & \quad \text{H}_2\text{O} & \quad \text{Nu}^1 & \quad \text{Nu}^2 & \quad \text{9}
\end{align*}
\]

Scheme 1

The arising threshold was first overcome by Katritzky et al. in 1987. With use of 1,2,3-1\( H \)-benzotriazole (Bt-H) as the auxiliary (\( \text{Nu}^1\text{-H} \)) of Scheme 1, the condensation reaction of aldehyde (6; \( \text{R}_1^1 \) and/or \( \text{R}_2^2 = \text{H} \)), amine (7), with Bt-H readily gives a mixed aminal (8; \( \text{Nu}^1 = \text{Bt} \)), which is in turn converted into the corresponding \( \text{Nu}^2 \)-substituted product (9) when attacked by a second nucleophile (\( \text{Nu}^2 \)). Success of this feature is attributable to the dual character of Bt-H, performing first as a nucleophile and second as a leaving group (Bt').

Katritzky et al. proposed to call compounds possessing the dual function like Bt-H as synthetic auxiliaries. According to the definition described above, those compounds which dissociate proton(s) at neutral pH region are candidates of synthetic auxiliaries. Utilities as such have been
recognized to tetrazole,\textsuperscript{8a} 1,2,4-triazole,\textsuperscript{8a} pyrazole,\textsuperscript{8a} 2-mercaptopoethanol (MET),\textsuperscript{10} and 2-aminopyridine.\textsuperscript{11}

\[
\begin{align*}
\text{Benzotriazole} & \quad \text{Tetrazole} & \quad \text{1,2,4-Triazole} & \quad \text{Pyrazole} \\
(\text{Bt-H}) & \quad \text{pKa} \approx -8 & \quad \text{pKa} \approx -5 & \quad \text{pKa} \approx -10 & \quad \text{pKa} \approx -14 \\
\end{align*}
\]

\[
\begin{align*}
\text{2-Mercaptopoethanol} & \quad \text{2-Aminopyridine} \\
(\text{MET}) & \quad \text{pKa} \approx -11 & \quad \text{pKa} \approx -12 \\
\end{align*}
\]

3. **Representative methods of phthalimidine syntheses besides Mannich type condensation reactions**

For lactam-forming reactions only, more than thirty synthetic methods of phthalimidines have been known on literatures, however, only six of which have been used frequently. In this chapter, representative methods for phthalimidine syntheses are described except for the Thiele method, which is to be stated in the next chapter in detail (Scheme 2).\textsuperscript{12-16}

3.1. **Direct condensation of phthalide with primary amines**

*(Hessert-Sugasawa method)*

This method is in principle the direct substitution of the ethereal oxygen atom of phthalide (10) by the nitrogen atom of amine to afford phthalimidine derivatives.

First reports were condensation reactions of 10 with aniline by Hessert in 1877 and that of 10 with ammonia by Graebe in 1884, where sealed tube reactions at 200 °C afforded phthalimidines (15; \(\text{Ar} = \text{Ph}\)) and (1), respectively (no yields available).\textsuperscript{12a,b} In 1943, Sugasawa et al., unsuccessful in reproducing the results by Hessert, carried out the condensation reaction in the presence of \(\text{ZnCl}_2\) to give the desired phthalimidine (15; \(\text{Ar} = \text{Ph}\)) in 90% yield. Realization of this variation greatly raised the dependability of this strategy, however, reaction condition was severe still (sealed tube, 210-215 °C for 4 h).\textsuperscript{12c} Irrespective of a number of other variants, phthalimidines have never been obtained under mild conditions along this category.\textsuperscript{12d-f}

This method is favorable to prepare simple phthalimidine derivatives, however, less useful to those possessing heat-sensitive and/or acid-sensitive functionalities.
3.2. Cyclocondensation of 2-halogenomethylbenzoic acids with primary amines (Fischer method)

This method concerns with nucleophilic substitution and subsequent cyclization between primary amine and "phthalide equivalences" possessing good leaving groups (11) to give phthalimidine derivatives, which compensates for a defect described in Section 3.1..

In 1909, Fischer et al. exposed the reaction of 2-chloromethylbenzonitrile with aniline in alkaline solution under heating to give phthalimidine (15; \( \text{Ar} = \text{Ph} \)), which is the first "mild" condition phthalimidine synthesis (no yields available).\(^{13a}\) Since then, Cl or Br has been used as halogen (Z), and ester or nitrile as carboxylic acid derivative \([\text{C}(:\text{Y})\text{X}]\) in the structure of 11, respectively.\(^{13b-f}\) When cyano substituent is used, addition of supplementary base is indispensable to obtain phthalimidine in high yield, since hydrolysis of intermediate imino compound (17) is needed.\(^{2b,13b,e,f}\)
As a recent example in 1978, Kametani et al. examined both ester and cyano substituents in the preparation of 2-((4-acetylphenyl)phthalimidine (15; Ar = p-MeCO-C₆H₄) during their indoprofen (3) synthesis, where isolated yields were high (90% and 70%, respectively).²b This method allows us to produce phthalimidines in 60-80% yield for anilines and ca. 65% yield for alkylamines, which has often been used in the preparation of bioactive compound precursors. Multistep syntheses to convert phthalide into 2-halo-genomethylbenzoic acid derivatives are, however, fatally disadvantageous.

3.3. Reduction of phthalimides (Graebe method)
This method is practically a Clemmensen type reduction, taking advantage of the fact that one-electron reductions of phthalimides go so far as to afford phthalimidine.¹⁴a First examples were given by Graebe in 1884 and 1888.¹²b,¹⁴b In general, 2-substituted phthalimide derivatives (12) are readily available either from the condensation reaction of phthalic anhydride with primary amine or from the alkylation of potassium phthalimide (Gabriel synthesis) in good yields. Common reductants have long been Sn/HCl or Zn/HCl. In 1963, Brewster et al. carried out the reaction using Zn-Hg/HCl or Zn/AcOH under reflux for 12 h to afford 2-alkylphthalimidines (15) in >80% isolated yields.¹⁴d,⁶ Similar results for 2-aryl derivatives were reported by Kametani et al. in 1978.²b,¹⁴c On the other hand, Butula et al. reported Pd-BaSO₄/AcOH in 1972.¹⁴f This method enables us to obtain phthalimidines in high yields and purities out of simple experimental procedures, however, it is less useful to those possessing reduction-sensitive functionalities. As a matter of fact, in a recent report by Danishefsky et al. on the total synthesis of staurosporine, two-step scheme was adopted in the conversion of phthalimide to phthalimidine (NaBH₄/EtOH then PhSeH), so as not to destroy glycoside moiety.³d

3.4. Rearrangement of phthalazones (Gabriel method)
Treatment of phthalazones (13; benzo[d]pyridazin-1-one) under Clemmensen reduction condition undergoes the elimination of nitrogen atom of 3-position as ammonia followed by the ring contraction to give phthalimides, to which first report was exposed by Gabriel in 1893.¹⁵a Phthalazones (13) are readily available as starting materials from the condensation reaction between o-phthalaldehyde acid and phenylhydrazine derivative.¹³b,¹⁵b Reductants have long been Zn/HCl, however, Na₂S₂O₄ is useful, too.¹⁵c According to reports by Rowe et al., isolated yields of 2-arylphthalimidines (15) are fine: 85% for phenyl, and 84% for 3-chlorophenyl and 2-chlorophenyl, respectively.¹⁵d-f Considering that the use of 2-acylbenzoic acid instead of phthalaldehyde acid enables us to obtain 3-substituted phthalimidines in general, this method is a little valuable although no related works had appeared since 1948. Of course, applications to those possessing reduction-sensitive functionalities are obstacle.
3.5. Catalytic insertion of CO to benzylideneanilines (Murahashi method)
Debut of the organometallic reagent to phthalimidine syntheses was done by Gilman et al. in 1943. Its key step portrays the dilithiation of dibenzylamine by n-BuLi, which on treatment with CO2 followed by the cyclization during work-up affords 2-benzylphthalimidine in ca. 30% yield. This method has long been utilized but only as "Gilman's color test" for inspecting in situ prepared alkyllithium reagents.16a Insertion of the carbonyl group of phthalimidine by gaseous CO in the presence of a transition metal catalyst was first extensively examined by Murahashi et al. in 1955. They carried out the insertion reaction of CO (100-200 atm) to benzylideneanilines (14) in benzene in the presence of the catalyst [Co2(CO)8] to obtain phthalimidines in the yields of 70-96%.16b,c Further systematic exploration revealed that this reaction is strongly affected by substituents on aryl rings, i.e., both electron-withdrawing group(s) on aniline side and electron-donating group(s) on benzaldehyde side sabotage good results.16d-f A few of the corresponding N-benzylidene-N-alkylamines have been examined.16e Reaction mechanism was speculated by Rosenthal et al. to a similar reaction system using 15N-containing benzylidenehydrazine derivatives.16g Irrespective of the limitation on aryl ring substituents, this method is simple and highly reliable, which has been industrial standard method for 2-phenylphthalimidine (15; Ar = Ph) synthesis. Huge advantage exists in the fact that readily available benzaldehyde derivatives are useful as starting materials (14).

4. Direct condensation of o-phthalaldehyde (OPT) with primary amines (Thiele method): scope and limitation
Five representative synthetic methods described in Chapter 3 are reliable and therefore standardized in preparing precursors of bioactive compounds, however, limitations apparently arise from severe reaction conditions themselves. An alternative strategy using the 1:1 condensation reaction of phthalaldehyde (16; OPT) with primary amine under mild conditions, which is Mannich type reaction and the main subject of this review, has long been explored, too (Scheme 3).17-19 This reaction involves with the intramolecular simultaneous oxidation-reduction to exchange symmetrical 16 into dissymmetrical 15.

![Diagram](image-url)
In 1909, Thiele et al. first examined the 1:1 condensation reaction between 16 and aniline in Et₂O at room temperature for 24 h to form 2-phenylphthalimidine (15; Ar = Ph) as a sole product (no yields available; recent reexaminations by Tsuruta et al.⁵b,c show its isolated yield as 79%). The corresponding 1:2 condensation reaction gave 2-imino compound (17) in 65% yield.¹⁷

In 1965, Amano et al. reexamined the Thiele method and obtained a number of 2-arylphthalimidines systematically, during the quantitative analysis of biomolecular primary amino groups by fluorescence spectroscopy.⁵a,¹⁸ As the results, the isolated yields of pure phthalimidines out of the 1:1 condensation reactions between 16 and substituted anilines proved to be poor with few exceptions (o-substituted: 5-20%; m-substituted: 3-58%; p-substituted: 5-57%).¹⁸b General cause of low isolated yields is attributable to repetitive recrystallizations necessary for eliminating concomitant polymeric materials (confirmed by authors, too). Further, Amano et al. examined the same reaction system using 4,5-methylenedioxy-OPT (18), in order to obtain phthalimidine derivatives possessing longer and stronger fluorescence. As before, yields were generally low except for anthranilic acid derivatives (73-84%).¹⁸c,d As a recent example in 1991, Shudo et al. carried out the 1:1 condensation reactions of 16 with o-substituted anilines instead in AcOH under reflux (no yields available).⁷d

On the other hand, reaction mechanisms of the Thiele method have been examined, too. In 1977, Dominh et al. explored the condensation reactions of 16 with ammonia, methylamine and aniline using Ir spectra to unveil that the first-formed double adducts (19) underwent dehydration to give phthalimidines (1 or 15), which were promptly formed through the keto-enol tautomerization of intermediate 1-hydroxy-2H-isoindoles (20). In the presence of some electrophiles other than protons, in principle, addition products might be formed. As a matter of fact, the 2:1 reactions between 16 and amines were found to give hemiacetals (21), where intermediate anions were trapped by excessive amount of 16 (9-50% yield). In addition, use of ammonia as amine afforded a quinoline derivative (22; ca. 30% yield), which is explicable by the reaction of 21 with ammonia as shown in Scheme 4.¹⁹a
However, the above described are not all products from the Thiele method. In 1985, Nan'ya et al. examined the 1:1 condensation reactions between 16 and alkylamines in EtOH at room temperature in the presence of 4 equiv. of tert-ButOH to obtain compounds (23) (20-35% yield) and (24) (10-22% yield), which are not explicable from the mechanism by DoMinh et al.. In order for these compounds to come true, *in situ* oxidation/reduction of compounds (21) and (20) are indispensable respectively, however, intermediates have never been specified yet. In addition, the 1:1 condensation reaction between 16 and aniline in EtOH specifically gave imine (17) in 79% yield, which had previously been isolated by Thiele et al., too.\(^{19b,c}\)
As a whole, although the original Thiele method appears to be simple at first look, it practically concerns with a number of reaction paths; the inhibition of phthalimidine-forming path brings about the progress of some other by-paths to give complicated product distribution patterns. Although proton migrations are important, reactions in alcohols are apparently obstacles. In order to utilize the mild-condition phthalimidine syntheses with high dependability and reliability, some tacit devices are needed to induce the dehydrative elimination from DoMinh intermediate (19). Synthetic auxiliaries, the main subjects of this review, are used ultimately for this purpose.

5. Phthalimidine syntheses using intramolecular synthetic auxiliaries during Mannich type condensation reactions as key steps

In principle, the presence of intramolecular functional groups, which improve the function of both dehydration and keto-enol tautomerization described in Chapter 4, would enable to keep the phthalimidine-forming path exclusively. Thus far, examples using primary amines possessing reaction-promoting functionalities have been reported, but none to OPT moieties.

5.1. Utility of \(\alpha\)-amino acid derivatives as primary amines (Grigg-Allin method)

In 1985, Grigg et al. carried out the 1:1 condensation reactions between 16 and \(\alpha\)-amino acids (25; \(X = O\)) in AcOH under reflux for a few minutes to afford phthalimidines (29) in the yields of 60-91% (Table 1).\(^{20a}\) They also examined the same reaction system using AcOH-\(d_4\) instead to find the formation of 3-deuterophthalimides (diastereoselectivities were up to 7:1), out of which they postulated the reaction mechanism via 1,3-hydride shift and/or cyclic intermediates. This method, however, has remained unnoticed for a decade, presumably because both solvents and primary amines are uncommon.

In 1996, shortly after authors' report using dual synthetic auxiliaries, Allin et al. exposed a fine modification to the Grigg method described above.\(^{20b}\) They carried out the same reaction system using MeCN under reflux for 12 h to give phthalimidines in 33-87% yield (Table 1). In addition, with use of \(\beta\)-aminoethanols (25; \(X = H_2\)) instead of \(\alpha\)-amino acids, desired
Phthalimidines were obtained in 56-69% yields. In these runs, CO$_2$H and OH groups contained in primary amino compounds are not merely decorations but perform first as nucleophiles and second as leaving groups, which were called as "intramolecular synthetic auxiliary" by Allin et al. themselves. Whenever phthalimidines need to possess amino acid units, this method is believed to be the best one, accounting for its very simple reaction operations; mere cooling of reaction mixtures to room temperature and giving analytically pure phthalimidines as fine crystals.

\[
\text{Scheme 5}
\]
Table 1. Yields of Phthalimidine Syntheses Using α-Amino Acids.

<table>
<thead>
<tr>
<th>Method</th>
<th>Grigg$^a$</th>
<th>Allin$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td>80</td>
<td>87 (L)</td>
</tr>
<tr>
<td>Phe</td>
<td>80</td>
<td>64 (L)</td>
</tr>
<tr>
<td>Ser</td>
<td>91</td>
<td>73 (L)</td>
</tr>
<tr>
<td>Ala</td>
<td>60</td>
<td>68 (L)</td>
</tr>
<tr>
<td>Phenyl-Gly</td>
<td>67</td>
<td>------</td>
</tr>
<tr>
<td>Gly</td>
<td>76</td>
<td>------</td>
</tr>
<tr>
<td>CO$_2$H</td>
<td>65</td>
<td>------</td>
</tr>
<tr>
<td>NH$_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leu</td>
<td>----</td>
<td>77 (DL)</td>
</tr>
<tr>
<td>Ile</td>
<td>----</td>
<td>33 (DL)</td>
</tr>
</tbody>
</table>

(a) ref. 20a. (b) ref. 20b.

Reaction mechanism was also exposed by them on the bases of the facts as follows: (i) when valinol (25; X = H$_2$, R = iPr) was used, a mixture of 26 and 27 (2:1 at equilibrium) was observed by $^1$H Nmr spectra; (ii) oxazolidine (30) was formed when N-alkylamino alcohol such as ephedrine was used.$^{20b}$ As a matter of fact, diastereoselectivities reported by Grigg et al.$^{20a}$ can rationally be interpreted as the conversion from 28 to 29 (Scheme 5).

5.2. Utility of β-amino acid derivatives as primary amines

Authors were interested in the preparation of phthalimidines bearing hetero functionality-containing substituents at 2-position during the synthetic approaches to heart beat decreasing agents, and so examined the Allin method using primary amines other than α-amino acids.$^{20c}$ In the reaction using β-aminopropionitrile, no phthalimidine was formed. On the other hand, the reaction using β-alanine gave phthalimidine, but isolated yields were fair: 31% for 12 h and 37% for 48 h reactions, respectively. The latter results are attributable to the possible 6-membered ring intermediate, which supports the 5-membered ring intermediates for α-amino acids in the mechanism postulated by Allin et al. (Scheme 5).

6. Phthalimidine syntheses using intermolecular synthetic auxiliaries during Mannich type condensation reactions as key steps

As shown in Chapter 5, synthetic designs involving intramolecular reactions enable to take advantage of some small ring size intermediates in common. On the contrary, in order to
succeed in the corresponding intermolecular reactions, effective enhancements of the keto-enol tautomerization out of Dominh type intermediates are keys. In this Chapter, reactions using those compounds which operate as "synthetic auxiliaries" according to the present definition (Chapter 2) are covered.

6.1. Acetic acid-treatment of diimines derived from OPT and 2 equiv. of amines (Kametani method)

In 1978, on an occasion of preparing 2-(4-acetylphenyl)phthalimidine (35) as a key precursor to the optically active indoprofen (3) derivatives, Kametani et al. exhibited a novel strategy, along with some of representative methods (Chapter 3). The 1:2 condensation reaction between OPT (16) and 31 (acetyl group is converted into propionic acid moiety via a multistep procedure) gave diimine (32) in 82% yield, which was further treated with AcOH under reflux to give 35 in 88% yield. Without water, AcOH must act as the source of oxygen, out of which the reaction mechanism can be assumed as follows (not by Kametani et al.): the primary addition of AcOH to 32 forms isoiindolinol (33), which in turn transforms into 35 via 2H-isoinole (34) (Scheme 6).²

![Scheme 6](image-url)
This method is accounted valuable for its simple reaction procedure and high yield, unless the use of 2 equiv. of amine is problematic. However, this is the one and the only example thus far appeared on literatures. Anyway, it is noteworthy that the desired phthalimidine-forming path was made predominant for the first time among others in a strategy originated from the Thiele method. In Scheme 6, both AcOH and \( p \)-aminoacetophenone play roles defined as synthetic auxiliaries.

### 6.2. Utility of 2-mercaptoethanol (MET) as the synthetic auxiliary (Simons-Stobaugh method)

In 1976, Simons et al. carried out the 1:1 condensation reaction between 16 and \( n \)-propylamine in the presence of 1 equiv. of 2-mercaptoethanol (MET) in MeCN at room temperature to give isoindole (36) quantitatively, which was followed by the addition of 7 equiv. of water to
afford the phthalimidine (15; \( R = nPr \)) in 78% overall yield after stood for 2 weeks.\(^{10a}\) In order to explain the above results rationally, they further proposed the reaction mechanism shown as Scheme 7 on the basis of the isolation of polysulfide (39), which was to be formed from the polymerization of thiarane (38).\(^{10b}\) Thus, the intermediate species is assumed as a spiro compound (37), however, of which charge-separated structure is questionable since solvent system is neutral and less hydrolytic.

In 1983, Stobaugh et al. reexamined the results by Simons et al. in terms of kinetics. In the simpler reaction systems obtained by the addition of pH 9.6 buffer solution to Simons' procedures, founded was that the phthalimidine-forming velocity is close to be proportional to the pseudo first order of the concentration of 16, but hypothesis on a rate-determining intermediate provides better fittings. From these facts on calculations, the following reaction mechanism was given (Scheme 8).\(^{10c}\)

The 1:1 addition of 36 with 16 gave the adduct (40), which in turn undergoes the elimination to afford thiaranium (41) as an intermediate to phthalimidine (15). Additional evidence was shown by experiments using 3-mercaptoethanol instead of MET that the formation of 15 was slower; it is understandable by the stability of thiethanium intermediate (42) compared to that
of 41. As the results, interpretations by Stobaugh et al. can account for the Amano method in which the excessive use of 16 affords 15 quantitatively (based on amines), but not presume at all the results by Simmons et al. Authors also examined the hydrolysis of isoindole derivative (36; Ar = p-Me-C₆H₄). However, different from results by Simons et al., no conversion to phthalimidine (15) took place by the action of water only; the addition of excessive amount of MET enabled hydrolysis to 15 but upto ca. 40% conversion.

6.3. Utility of 1,2,3-1H-benzotriazole (Bt-H) as the synthetic auxiliary

As described in Chapter 2, Katritzky et al. have extensively examined a series of reactions using Bt-H as the synthetic auxiliary. However, past research works were limited to uses of monoaldehydes as substrates, and were done without the aim of constructing practically useful materials. Focusing on this point, authors came to investigate the double Mannich type condensation reaction of 16 (OPT; a representative dialdehyde) with amines in the presence of Bt-H to form Bt-substituted 2H-isoindole derivatives (43-45, 47), of which skeletons have been evaluated as the antihypertensives/antihyperglycemics and as the unit compounds for electrically conductive polymers (Scheme 9).
Out of systematic investigations using a series of \( p \)-substituted anilines, reactions in MeCN at room temperature were found to afford isoindoline (44) and \( 2H \)-isoindole (45) as major and minor products, the latter of which turned out to be major at prolonged reaction periods.\(^{21a,c-e}\) On the other hand, reactions under heating conditions gave none of 44 but phthalimidine (15) as minor product instead.\(^{21b}\) Applications to alkylamines were unsuccessful.\(^{21g}\) Considering that hydride reductions in the meantime gave anilinobenzyl alcohols (46), this reaction is assumed to proceed via intermediate (43), which is analogous to \( \text{19 or 33} \) described before.\(^{21b,g}\) Irrespective of a potential reaction path-controlling ability of this system far better than the direct condensation reactions between 16 and amine (described in Chapter 4), however, 15 was found obtainable but always as a minor product (max. 17% yield).\(^{21b}\) Throughout the examinations using Bt-H as a sole synthetic auxiliary, authors have not succeeded in its refinement yet.

Previously authors established a new sample-sorting technique in the FABms spectrometry in order to observe the molecular ions (\( M^+ \)’s) of isoindolines (44) properly, and during its examination, quite interesting data were obtained.\(^{21f}\) Thus, in the FABms measurements using \( m \)-nitrobenzyl alcohol (MNBA) as an inverse matrix [\( i.e. \), matrix (solvent) is adsorbed into the sample solids], except for fragment ion peaks arose from the matrix itself, those of which mass numbers correspond to phthalimidines (15) were observed as base peaks. Considering that water molecules exist in the chamber (formed from the dehydration of matrix MNBA), the reaction of \( 44 \rightarrow 43 \rightarrow 15 \) was reasonably explained, although it was performed under very special condition (atom bombardment and high vacuum). Unfortunately, realization of this result under ordinary reaction conditions had been unsuccessful.

### 6.4. Utility of Bt-H and MET as the dual synthetic auxiliaries (Takahashi method)

Failure of authors' isoindoline syntheses described in Section 6.3 are attributable to the basicity of alkylamines by far stronger than that of anilines, which urges the elimination of Bt-H from isoindolines to form \( 2H \)-isoindoles, and promotes quick polymerization of the latter. In order to obtain \( N \)-alkylisoindolines properly, we examined a number of literally known synthetic methods for \( 2H \)-isoindoles. As the results, we hoped to obtain isoindolines to which at least one Bt group is attached when Simons-Stobaugh strategy\(^{10}\) was to be performed in the presence of both MET and Bt-H. However, when inspection was done using \( p \)-toluidine as amine, aside from our expectation, none of isoindoline (48) or \( 2H \)-isoindole (49) but \( 2-(p\text{-tolyl}) \)phthalimidine (15; \( R = p\text{-Me-C}_6\text{H}_4 \)) was isolated as a sole product in good yield (Scheme 10). Further exploitations unveiled the optimized standard conditions as follows (max. 82% yield): solvent, MeCN + pH 9.6 borate buffer; Bt-H, 1 equiv.; MET, 9 equiv.; room temperature 13 h.\(^{20c,24a} \)
This "by chance found" phthalimidine-forming reaction proceeds under mild condition, and obtained high purity materials even at crude stage implied its potential as a useful synthetic method in common. In order to compare with results by Amano et al., the 1:1 condensation reactions between 16 and a series of simple aniline derivatives were examined under the optimized condition described above. As the results, pure 2-arylphthalimidines (15) were found to be obtained in fair to good isolated yields with few exceptions (α-substituted: 18-54%; m-substituted: 44-77%; p-substituted: 34-84%). Considering that the results by Amano et al. by the original Thiele method were generally in low yields, authors' improvement of the phthalimidine production using dual synthetic auxiliaries (Bt-H and MET) were evidently recognized. Further, use of primary alkylamines (few examples were previously known) gave desired phthalimidines (15) in 53-80% yield. After all, both generality and dependability of this new synthetic method are proven (Table 2).20c,24a

As a practical application of this method to bioactive skeletons, simple synthesis of (±)-indoprofen (3) was sought. Thus, authors succeeded in a 4-step synthesis (Scheme 11), which is by far shorter than the present industrial (Kametani) method (>10 steps).2b The key to this synthesis is the "in advance preparation" of an appropriately substituted aniline derivatives (52) from a commercially available 50, which enabled all at once construction of indoprofen skeleton (53); direct condensation of 16 with aminoacid (51) was, however, unsuccessful.
**Scheme 11**

![Chemical reaction diagram](image)

\[
\text{H}_2 (50 \, \text{kg/cm}^2), \, 5\% \, \text{Pd-C}, \, \text{EtOH}, \, \text{rt}, \, 45 \, \text{min};
\]

\[\text{EtOH, toluene, } p-\text{TsOH (1 eq.), reflux, 18 h;}\]

\[\text{OPT (1 eq.), Bt-H (1 eq.), MET (9 eq.), MeCN,}
\]

\[\text{borate buffer (pH 9.6), rt, 13 h;}\]

\[\text{KOH, 95\% EtOH, 70 \, ^\circ\text{C}, 3 \, \text{h}.}\]

**Scheme 12**

![Chemical reaction diagram](image)

"a Katritzky's tethered ion pair"
The reaction mechanism of this phthalimidine synthesis is not yet fully specified, however, authors postulate the main path as Scheme 12, on the bases of the following evidences: (i) in the presence of MET as a sole auxiliary, reactions proceed up to the formation of 2H-isoindole (54) but never proceed further; (ii) hydrolysis of 54 requires both MET and Bt-H to give phthalimidine (15); (iii) bis(2-mercaptoethyl) ether (55; Nu = OCH2CH2SH) is formed in common.20c

The mild condition of authors' method is, with no doubt, widely applicative. It is not too much to say that the Thiele method17 has literally become the representative synthetic method of phthalimidines, effected by the successful variants exhibited from research groups of Grigg, Allin, and authors.

(a) ref. 24a. (b) ref. 24a; 49 h reaction. (c) unpublished results (ref. 20c). (d) ref. 5c. (e) ref. 18b. (f) ref. 20b in MeCN. (g) ref. 13e. (h) ref. 2b. (i) ref. 14d. (j) ref. 15f. (k) ref. 15e. (l) ref. 15d. (m) ref. 16b. (n) ref. 16e.

Table 2. Yields of Phthalimidine Syntheses Using Anilines and Alkylamines.

<table>
<thead>
<tr>
<th>ArNH₂ or RNH₂</th>
<th>Method</th>
<th>Takahashi</th>
<th>Thiele</th>
<th>Fischer</th>
<th>Graebe</th>
<th>Gabriel</th>
<th>Murahashi</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅-NH₂</td>
<td></td>
<td>66²⁶</td>
<td>79⁴</td>
<td>80⁴</td>
<td>78⁴¹</td>
<td>85⁴</td>
<td>80⁴</td>
</tr>
<tr>
<td>o-Cl-C₆H₄-NH₂</td>
<td></td>
<td>27⁶</td>
<td>10⁶</td>
<td>---</td>
<td>---</td>
<td>84⁴</td>
<td>---</td>
</tr>
<tr>
<td>o-NO₂-C₆H₄-NH₂</td>
<td></td>
<td>33⁸</td>
<td>12⁸</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>m-OMe-C₆H₄-NH₂</td>
<td></td>
<td>77³</td>
<td>3³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>m-Me-C₆H₄-NH₂</td>
<td></td>
<td>60³</td>
<td>9³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>m-Cl-C₆H₄-NH₂</td>
<td></td>
<td>44⁴</td>
<td>27⁴</td>
<td>---</td>
<td>---</td>
<td>84³</td>
<td>---</td>
</tr>
<tr>
<td>m-NO₂-C₆H₄-NH₂</td>
<td></td>
<td>59³</td>
<td>10³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>p-OMe-C₆H₄-NH₂</td>
<td></td>
<td>70³</td>
<td>13³</td>
<td>---</td>
<td>---</td>
<td>86³</td>
<td>---</td>
</tr>
<tr>
<td>p-Me-C₆H₄-NH₂</td>
<td></td>
<td>82⁴</td>
<td>16⁴</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>p-Cl-C₆H₄-NH₂</td>
<td></td>
<td>72³</td>
<td>6³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>75³</td>
</tr>
<tr>
<td>p-Br-C₆H₄-NH₂</td>
<td></td>
<td>62³</td>
<td>57³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>p-NC₆H₄-NH₂</td>
<td></td>
<td>44⁵</td>
<td>37⁵</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>p-NO₂-C₆H₄-NH₂</td>
<td></td>
<td>39³</td>
<td>5³</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>complex³</td>
</tr>
<tr>
<td>1-C₆H₆-NH₂</td>
<td></td>
<td>62⁵</td>
<td>11⁵</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>C₆H₅CH₂-NH₂</td>
<td></td>
<td>75³</td>
<td>---</td>
<td>88⁵</td>
<td>66²</td>
<td>---</td>
<td>82⁴</td>
</tr>
<tr>
<td>Me-NH₂</td>
<td></td>
<td>47⁵</td>
<td>---</td>
<td>86²</td>
<td>49²</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>t-Bu-NH₂</td>
<td></td>
<td>60⁵</td>
<td>---</td>
<td>92²</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>c-C₆H₆⁵-NH₂</td>
<td></td>
<td>60²</td>
<td>---</td>
<td>86⁵</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Oleylamine</td>
<td></td>
<td>66⁶</td>
<td>---</td>
<td>70⁶</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>C₆H₆(CH(Me))- NH₂</td>
<td></td>
<td>68 (RS)²</td>
<td>21 (S)⁴</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

The numbers in parentheses indicate the references for the yields. The reaction conditions are typically 60°C for 6 h in benzene or acetonitrile, with various auxiliaries such as acetone or dimethyl sulfoxide.
7. Conclusion
As described, many synthetic methods other than "representative six" for phthalimidine derivatives have been known on literatures. Considering that none of these major methods (only in terms of appearing frequencies) are perfect, one of minor methods nowadays may become of importance at any moment.\(^{25}\) It is noticeable that the abundant supply of petroleum-originated products has been bases of representative synthetic methods of phthalimidines. Authors may wish to cover other characteristic synthetic methods in a next occasion of reviewing.

The authors are grateful to Dr. Alan R. Katritzky (University of Florida) and Dr. Hidehiko Kitajima (Professor Emeritus, Fukui University) for useful discussions. We are indebted to Dr. Shingo Yasuda (Fukuju Pharmaceutical Co., Inc.) for patent literature searches. We also thank Dr. Makoto Nakajima (Hokkaido University) for the courtesy of confirming some old references.

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9. The term "synthetic auxiliaries" have intentionally been used only by research groups of Katritzky, Allin, and authors.


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