RECENT PROGRESS OF PHTHALIMIDINE SYNTHESES†

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Abstract - Phthalimidine (2,3-dihydro-1*H*-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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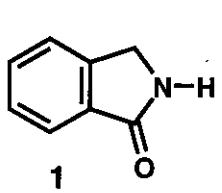
†This review is dedicated to the 25th Anniversary of HETEROCYCLES.

1. Introduction

Heterocyclic compounds containing phthalimidine (**1**; 2,3-dihydro-1*H*-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]



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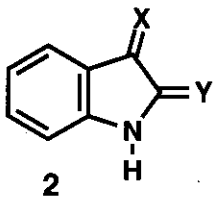
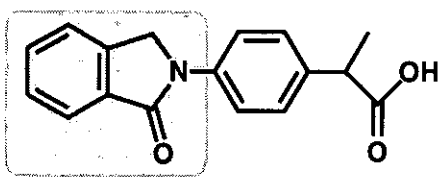
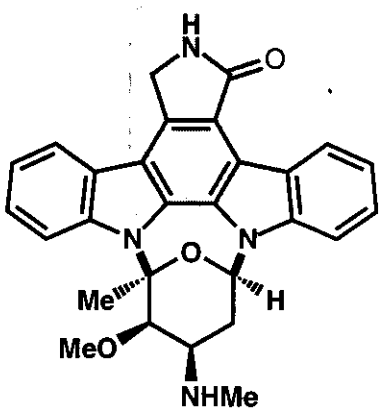


2

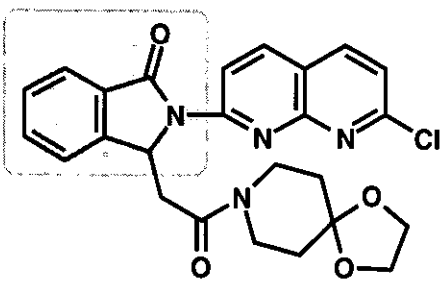
Recently focused phthalimidine derivatives involve indoprofen (**3**; anti-inflammatory agent), staurosporine (**4**; protein kinase C inhibitor), and DN-2327 (**5**; anxiolytic agent, formerly known as pazinaclone).[2-4] Reports on such evaluated skeletons as fluorescent markers to biochemical uses and precursors of electrically conductive polymers have appeared frequently.[1a,5,6] Theoretical studies have extensively evolved, too.[7]



indoprofen (**3**)



staurosporine (**4**)



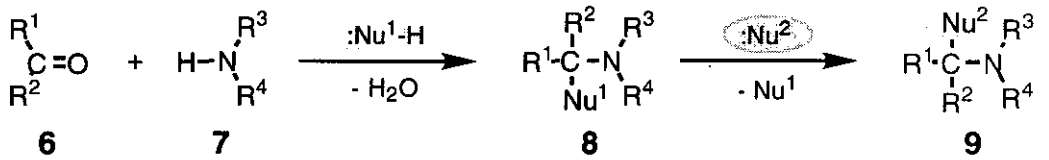
DN-2327 (**5**)

Except for side chain conversions of existing phthalimidine derivatives,[2b,c,5c] 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 "protic" nucleophile (Nu^1-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 Nu^1 contained in adducts (**8**) may be substituted by second nucleophile (Nu^2) to give compound (**9**) in principle, but often in vein.



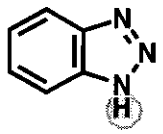
6 **7** **8** **9**

Scheme 1

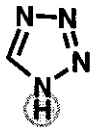
The arising threshold was first overcome by Katritzky *et al.* in 1987. With use of 1,2,3-1*H*-benzotriazole (Bt-H) as the auxiliary (Nu^1-H) of Scheme 1, the condensation reaction of aldehyde (**6**; R^1 and/or R^2 = H), amine (**7**), with Bt-H readily gives a mixed aminal (**8**; Nu^1 = Bt), which is in turn converted into the corresponding Nu^2-substituted product (**9**) when attacked by a second nucleophile (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.[8]

According to the definition described above, those compounds which dissociate proton(s) at neutral pH region are candidates of synthetic auxiliaries.[9] Utilities as such have been

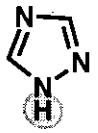
recognized to tetrazole,[8a] 1,2,4-triazole,[8a] pyrazole,[8a] 2-mercaptoethanol (MET),[10] and 2-aminopyridine.[11]



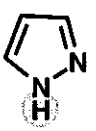
Benzotriazole (Bt-H)
*pK*a ~8



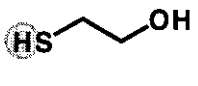
Tetrazole
~5



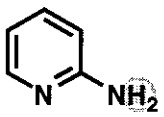
1,2,4-Triazole
~10



Pyrazole
~14



2-Mercaptoethanol (MET)
~11



2-Aminopyridine
~12

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

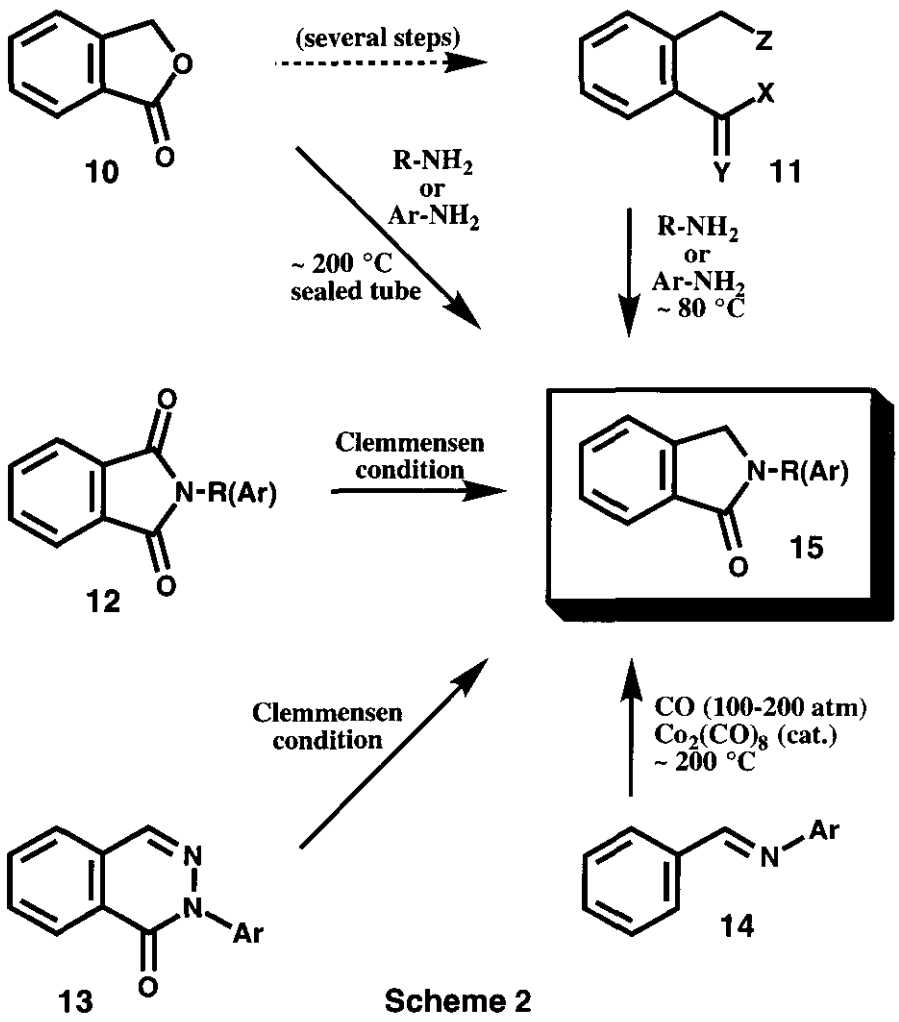
For lactam-forming reactions only, more than thirty synthetic methods of phthalimidines have been known on literatures, however, only six of which have been used frequently. In this chapter, representative methods for phthalimidine syntheses are described except for the Thiele method, which is to be stated in the next chapter in detail (Scheme 2).[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**; Ar = Ph) and (**1**), respectively (no yields available).[12a,b] In 1943, Sugasawa *et al.*, unsuccessful in reproducing the results by Hessert, carried out the condensation reaction in the presence of $ZnCl_2$ to give the desired phthalimidine (**15**; Ar = 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).[12c] Irrespective of a number of other variants, phthalimidines have never been obtained under mild conditions along this category.[12d-f]

This method is favorable to prepare simple phthalimidine derivatives, however, less useful to those possessing heat-sensitive and/or acid-sensitive functionalities.



Scheme 2

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**; Ar = 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 [C(:Y)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-C_6H_4) 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-halogenomethylbenzoic 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 phthalimidines.[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,e] 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-$BaSO_4$/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 ($NaBH_4$/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 phthalimidines, 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*-phthalaldehydic acid and phenylhydrazine derivative.[13b,15b] Reductants have long been Zn/HCl, however, $Na_2S_2O_4$ 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 phthalaldehydic 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)

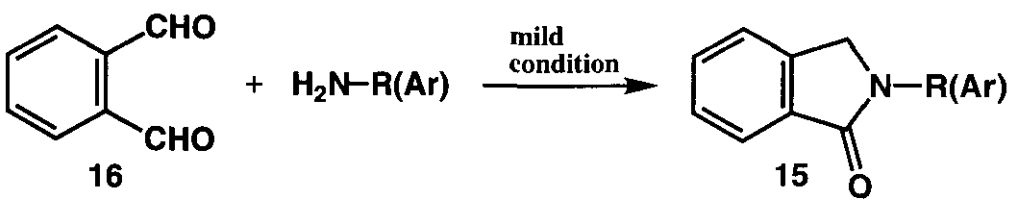
Debut of the organometallic reagent to phthalimidine syntheses was done by Gilman *et al.* in 1943. Its key step portrays the dilithiation of dibenzylamine by *n*-BuLi, which on treatment with CO_2 followed by the cyclization during work-up affords 2-benzylphthalimidine in *ca.* 30% yield. This method 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 [$Co_2(CO)_8$] 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 ^{15}N-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**).

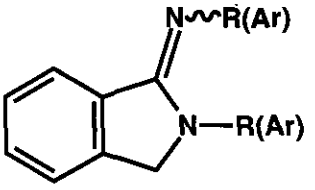
4. Direct condensation of *o*-phthalaldehyde (OPT) with primary amines (Thiele method): scope and limitation

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**.



Scheme 3

In 1909, Thiele *et al.* first examined the 1:1 condensation reaction between **16** and aniline in Et_2O 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]



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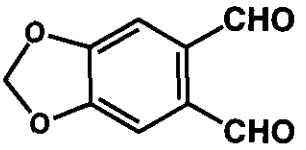

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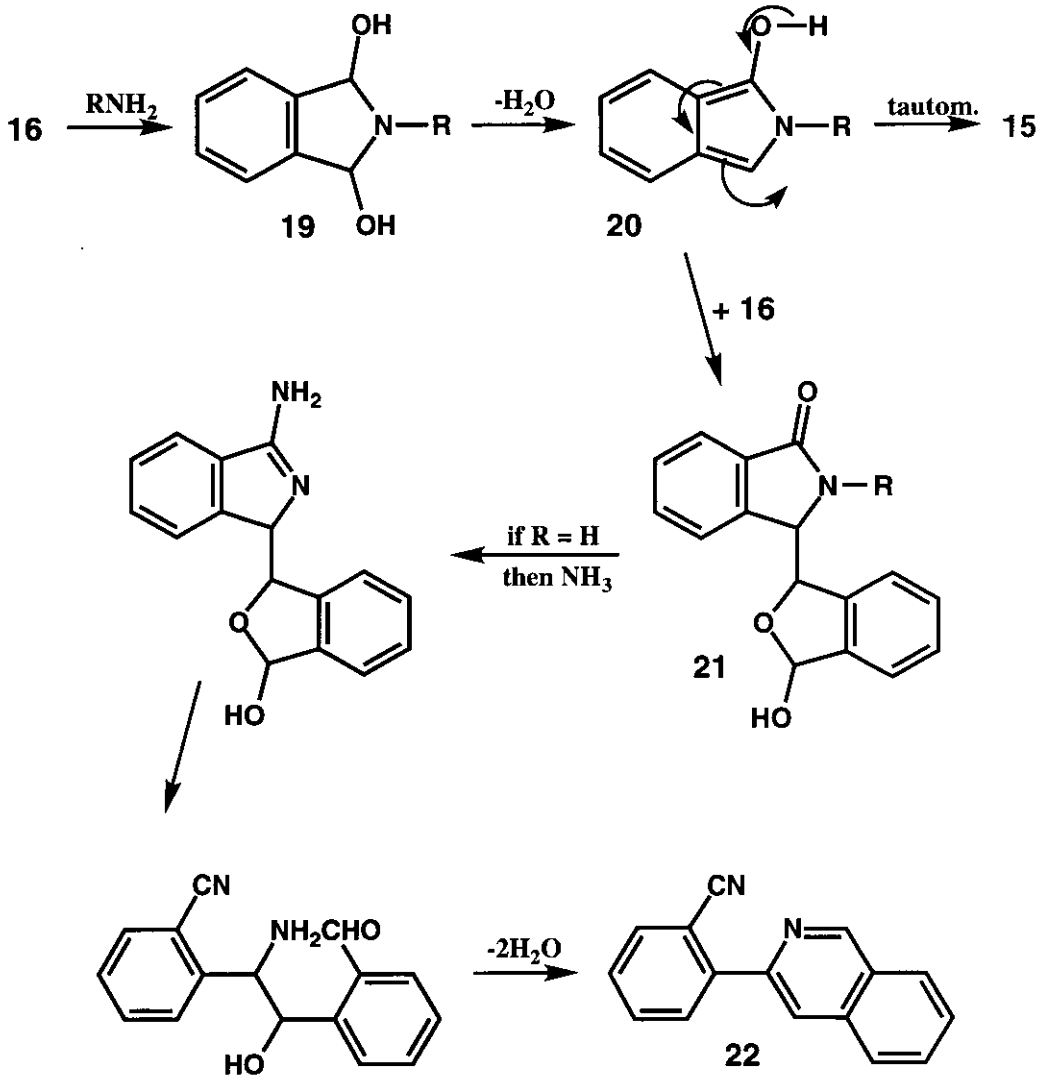
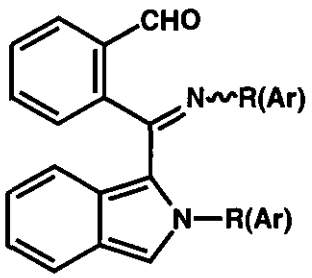
In 1965, Amano *et al.* reexamined the Thiele method and obtained a number of 2-arylphthalimidines systematically, during the quantitative analysis of biomolecular primary amino groups by fluorescence spectroscopy.[5a,18] As the results, the isolated yields of pure phthalimidines out of the 1:1 condensation 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-2*H*-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]



Scheme 4

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*-BuOH 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]



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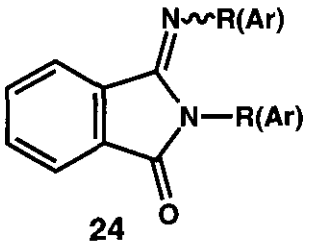

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As a whole, although the original Thiele method appears to be simple at first look, it practically concerns with a number of reaction paths; the inhibition of phthalimidine-forming path brings about the progress of some other by-paths to give complicated 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

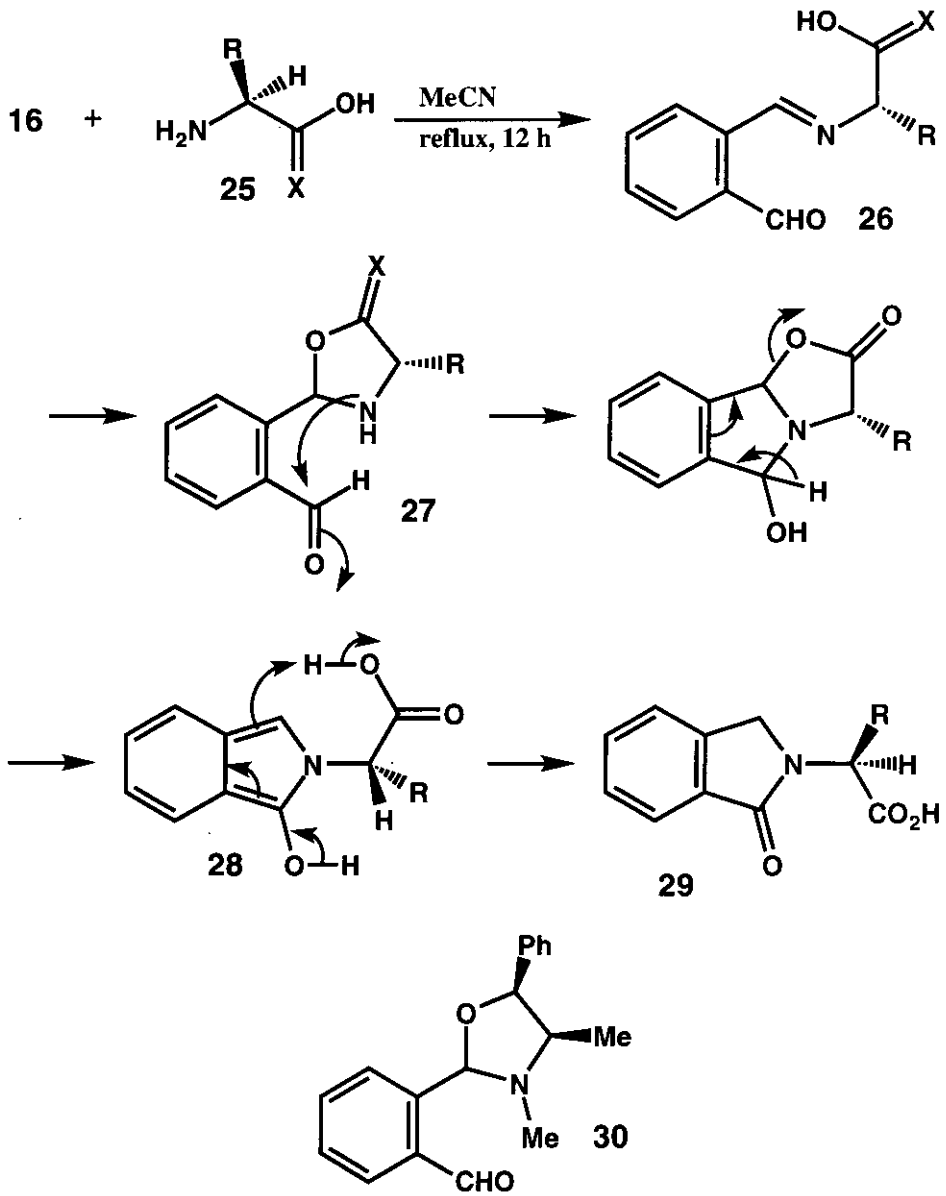
In principle, the presence of intramolecular functional groups, which improve the function of both dehydration and keto-enol tautomerization described in Chapter 4, would enable to keep the phthalimidine-forming path exclusively. Thus far, examples using primary amines possessing reaction-promoting functionalities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

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

In 1985, Grigg *et al.* carried out the 1:1 condensation reactions between **16** and α-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-deuteriophthalimidines (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.

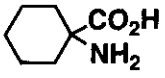
In 1996, shortly after authors' report using dual synthetic auxiliaries, Allin *et al.* exposed a fine modification to the Grigg method described above.[20b] They carried out the same reaction system using MeCN under reflux for 12 h to give phthalimidines in 33-87% yield (Table 1). In addition, with use of β-aminoethanols (**25**; X = H_2) instead of α-amino acids, desired

phthalimidines were obtained in 56-69% yields. In these runs, CO_2H 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.



Scheme 5

Table 1. Yields of Phthalimidine Syntheses Using α-Amino Acids.

Method / 25 (X = O)	Grigg[a]	Allin[b]
Val	80	87 (L)
Phe	80	64 (L)
Ser	91	73 (L)
Ala	60	68 (L)
Phenyl-Gly	67	------
Gly	76	------
	65	------
Leu	----	77 (DL)
Ile	----	33 (DL)

(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 = ^{i}Pr) 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-aminopripionitrile, 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).

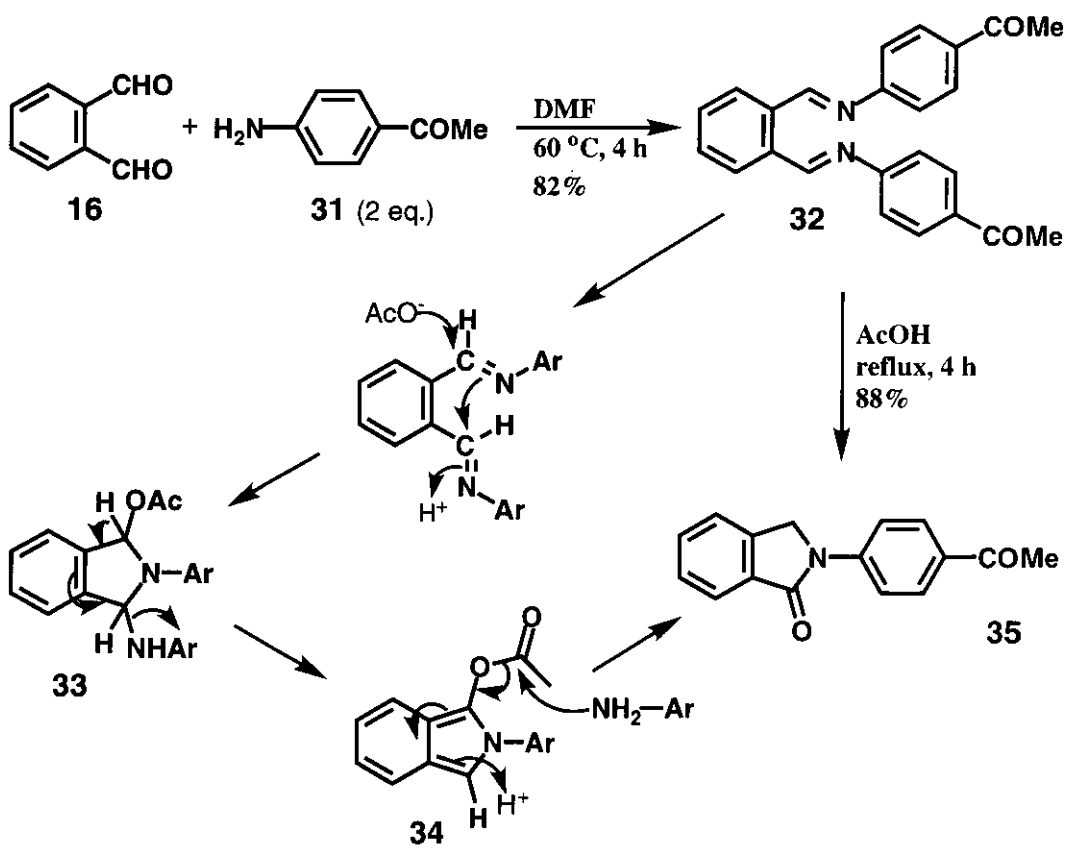
6. Phthalimidine syntheses using intermolecular synthetic auxiliaries during Mannich type condensation reactions as key steps

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)

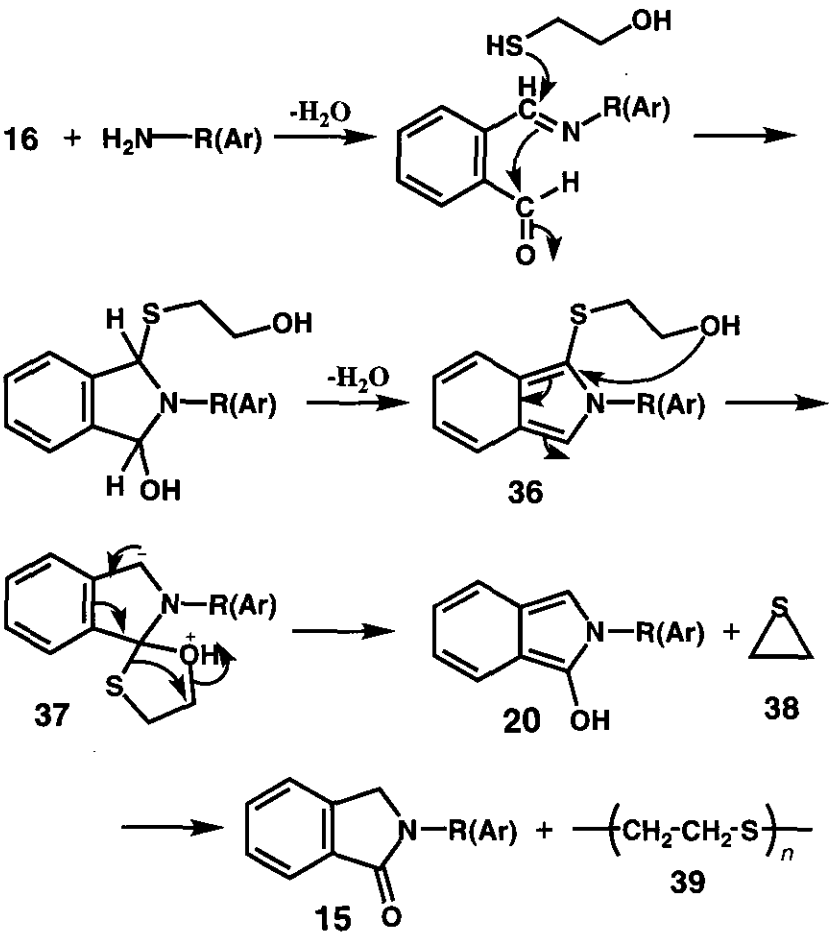
In 1978, on an occasion of preparing 2-(4-acetylphenyl)phthalimidine (**35**) as a key precursor to the optically active indoprofen (**3**) derivatives, Kametani *et al.* exhibited a novel strategy, along with some of representative methods (Chapter 3). The 1:2 condensation reaction between OPT (**16**) 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 isoindolinol (**33**), which in turn transforms into **35** *via* 2*H*-isoindole (**34**) (Scheme 6).[2b]



Scheme 6

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)

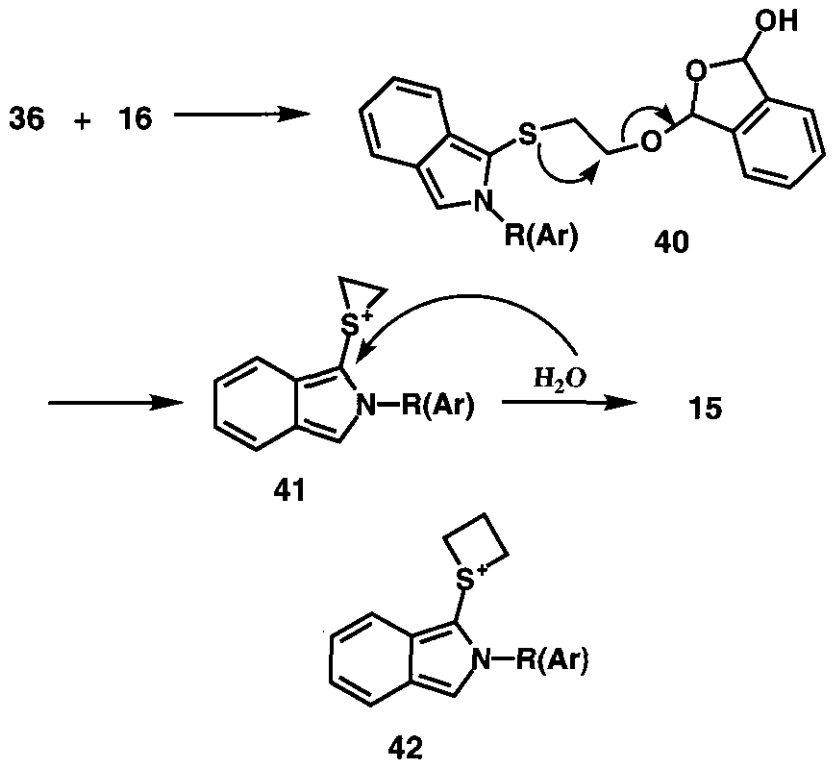


Scheme 7

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 = ^{n}Pr) 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]



Scheme 8

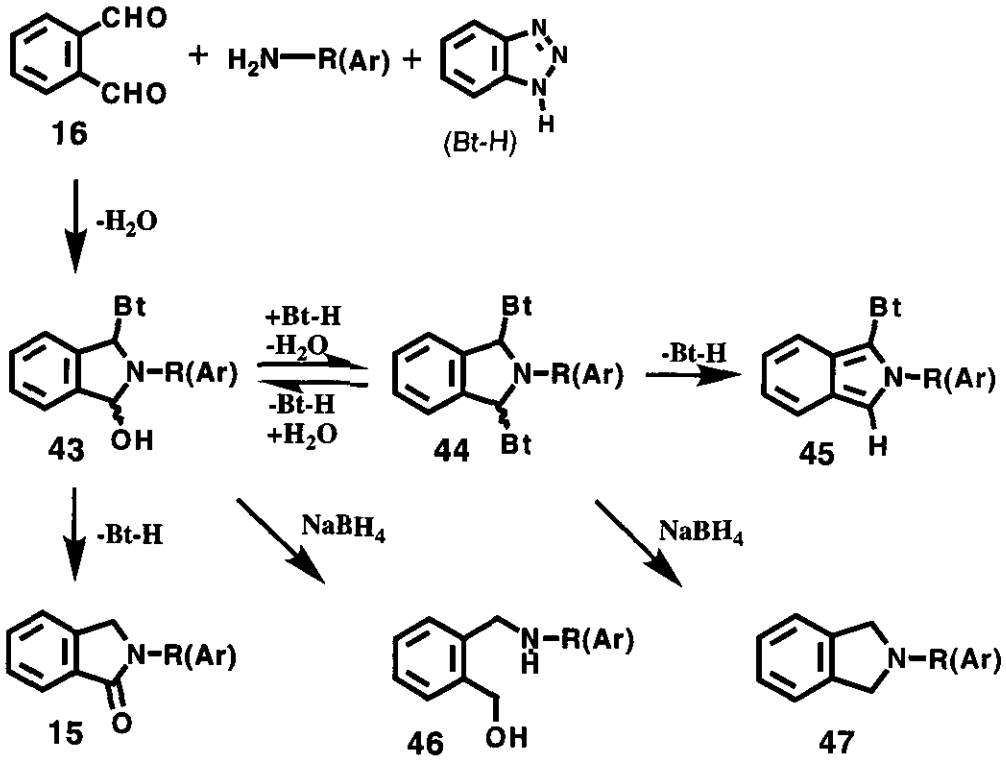
The 1:1 addition of **36** with **16** gave the adduct (**40**), which in turn undergoes the elimination to afford thiaranium (**41**) as an intermediate to phthalimidine (**15**). Additional evidence was shown by experiments using 3-mercaptoethanol instead of MET that the formation of **15** was slower; 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[18] in which the excessive use of **16** affords **15** quantitatively (based on amines), but not presume at all the results by Simmons *et al.* [10a,b]

Authors also examined the hydrolysis of isoindole derivative (**36**; Ar = *p*-Me-C_6H_4). 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.[20c]

6.3. Utility of 1,2,3-1*H*-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.[8] 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 2*H*-isoindole derivatives (**43-45**, **47**),[21] of which *skeletons have been evaluated as the antihypertensives/antihyperglycemics*[22] *and as the* unit compounds for electrically conductive polymers (Scheme 9).[6,23]



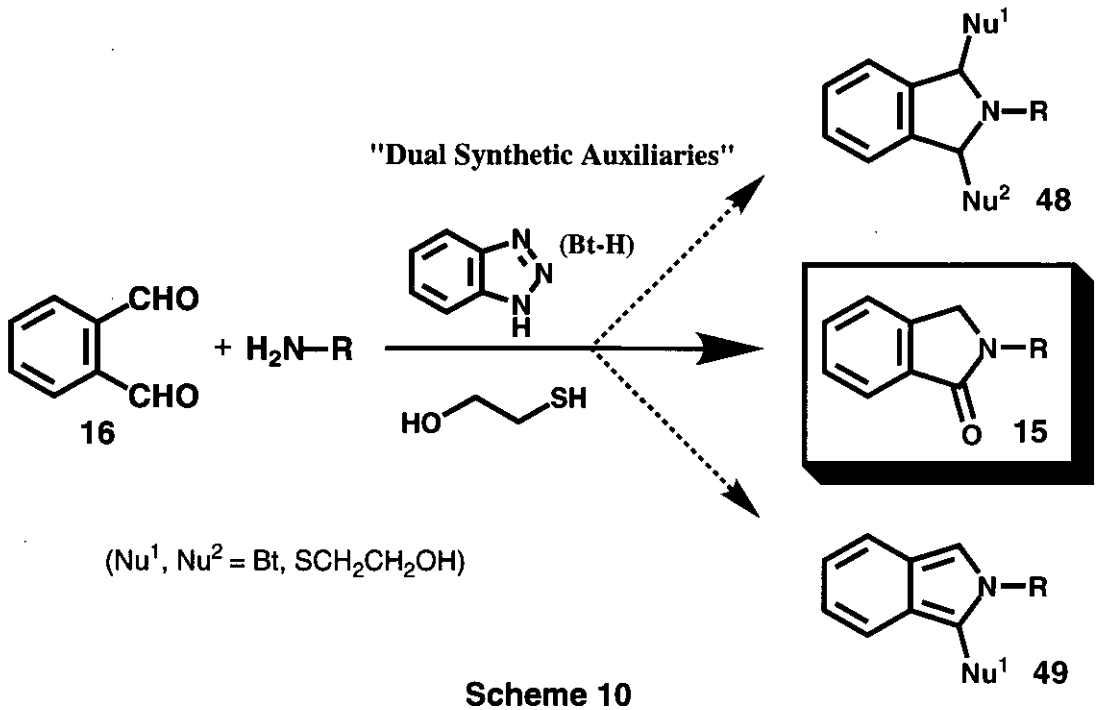
Scheme 9

Out of systematic investigations using a series of *p*-substituted anilines, reactions in MeCN at room temperature were found to afford isoindoline (**44**) and 2*H*-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 **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** → **43** → **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)

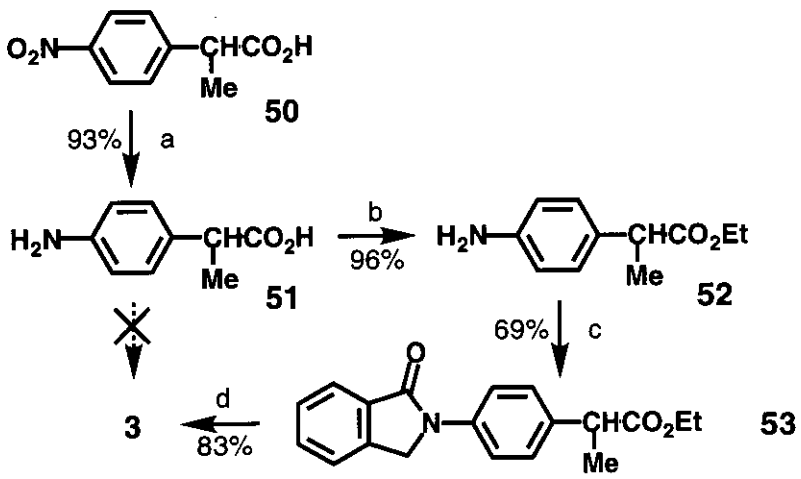
Failure of authors' isoindoline syntheses described in Section 6.3 are attributable to the basicity of alkylamines by far stronger than that of anilines, which urges the elimination of Bt-H from isoindolines to form 2*H*-isoindoles, and promotes quick polymerization of the latter. In order to obtain *N*-alkylisoindolines properly, we examined a number of literally known synthetic methods for 2*H*-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 2*H*-isoindole (**49**) but 2-(*p*-tolyl)phthalimidine (**15**; R = *p*-Me-C_6H_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]



Scheme 10

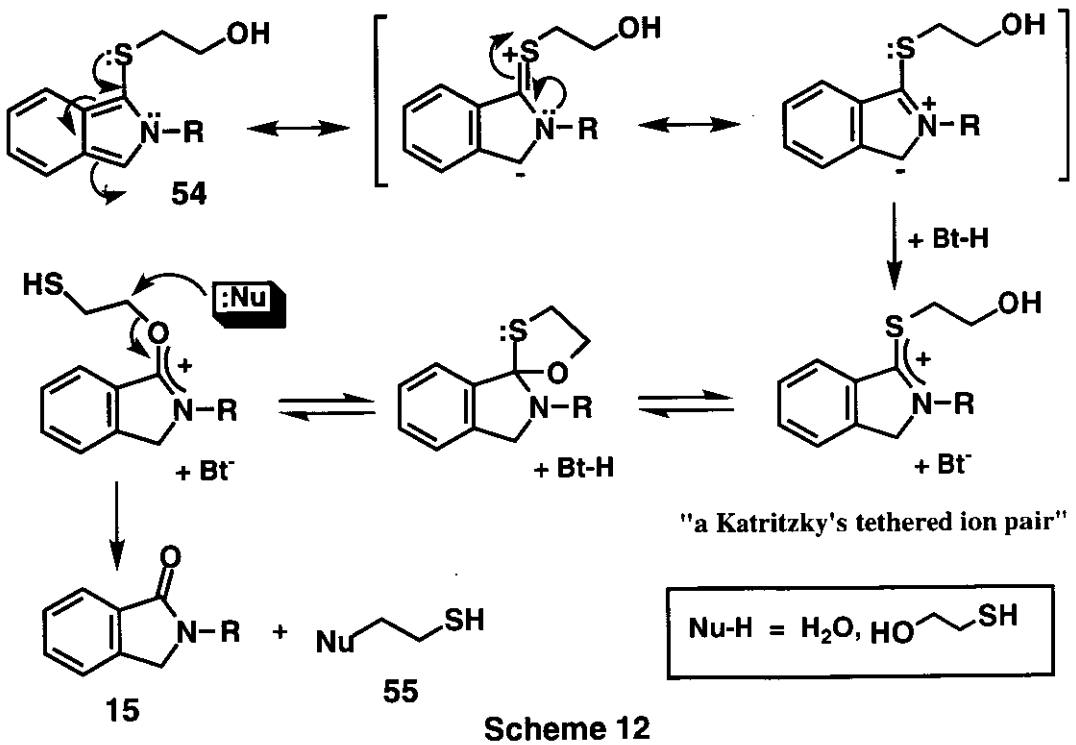
This "by chance found" phthalimidine-forming reaction proceeds under mild condition, and obtained high purity materials even at crude stage implied its potential as a useful synthetic method in common. In order to compare with results by Amano *et al.*, the 1:1 condensation reactions between **16** and 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 (*o*-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.



a) H_2 (50 kg/cm^2), 5% Pd-C, EtOH, rt, 45 min;
b) EtOH, toluene, *p*-TsOH (1 eq.), reflux, 18 h;
c) OPT (1 eq.), Bt-H (1 eq.), MET (9 eq.), MeCN, borate buffer (pH 9.6), rt, 13 h;
d) KOH, 95% EtOH, 70 °C, 3 h.

Scheme 11



Scheme 12

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 upto the formation of 2*H*-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 = OCH_2CH_2SH) 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 method[17] has literally become the representative synthetic method of phthalimidines, effected by the successful variants exhibited from research groups of Grigg, Allin, and authors.

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

$ArNH_2$ or RNH_2 \ Method	Takahashi	Thiele	Fischer	Graebe	Gabriel	Murahashi
C_6H_5-NH_2	66[a]	79[d]	80[g]	78[h]	85[j]	80[m]
o-Cl-C_6H_4-NH_2	27[c]	10[e]	---	---	84[k]	---
o-NO_2-C_6H_4-NH_2	33[b]	12[e]	---	---	---	---
m-OMe-C_6H_4-NH_2	77[c]	3[e]	---	---	---	---
m-Me-C_6H_4-NH_2	60[a]	9[e]	---	---	---	---
m-Cl-C_6H_4-NH_2	44[c]	27[e]	---	---	84[l]	---
m-NO_2-C_6H_4-NH_2	59[a]	10[e]	---	---	---	---
p-OMe-C_6H_4-NH_2	70[a]	13[e]	---	---	---	86[n]
p-Me-C_6H_4-NH_2	82[c]	16[e]	---	---	---	---
p-Cl-C_6H_4-NH_2	72[a]	6[e]	---	---	---	75[n]
p-Br-C_6H_4-NH_2	62[a]	57[e]	---	---	---	---
p-I-C_6H_4-NH_2	44[b]	37[e]	---	---	---	---
p-NO_2-C_6H_4-NH_2	39[a]	5[e]	---	---	---	complex[n]
1-$C_{10}H_7$-NH_2	62[c]	11[e]	---	---	---	---
$C_6H_5CH_2$-NH_2	75[a]	---	88[g]	66[i]	---	82[n]
Me-NH_2	47[c]	---	---	86[i]	---	49[n]
t-Bu-NH_2	60[c]	---	---	92[i]	---	---
c-C_6H_{11}-NH_2	60[a]	---	86[g]	---	---	---
Oleylamine	66[c]	---	70[g]	---	---	---
$C_6H_5CH(Me)$-NH_2	68 (*RS*)[c]	21 (*S*)[f]	---	---	---	---

(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.

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.

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