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MECHANISTIC ASPECTS OF THE MILD-CONDITION PHTHALIMIDINE SYNTHESIS WITH USE OF 1,2,3-1*H*-BENZOTRIAZOLE AND 2-MERCAPTOETHANOL AS DUAL SYNTHETIC AUXILIARIES †

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Abstract — The mild-condition phthalimidine synthesis based on Mannich-type condensation reaction between *o*-phthalaldehyde and *p*-toluidine was first achieved with use of 1,2,3-1*H*-benzotriazole (Bt-H) and 2-mercaptoethanol (MET) as dual synthetic auxiliaries. Mechanistic aspects based on reaction condition optimization exercises are described.

INTRODUCTION

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeletons have attracted considerable interests in recent years. Its publicity has never been competitive to that of isomeric indole analogues, however, both often occurring crystalline (= easily identifiable) compounds and a variety of bioactivities have aroused its synthetic interest increasingly. Recently focused bioactive compounds, indoprofen (anti-inflammatory agent), staurosporine (protein kinase C inhibitor), and DN-2327 (also known as pazinaclone, anxiolytic agent), which possess phthalimidine skeletons, have been attracted much attention.

Since 1877, a number of "famous" phthalimidine syntheses have been known to literatures, for which the following classification is possible: condensation of phthalide with primary amine (Hessert-Sugasawa),[1]

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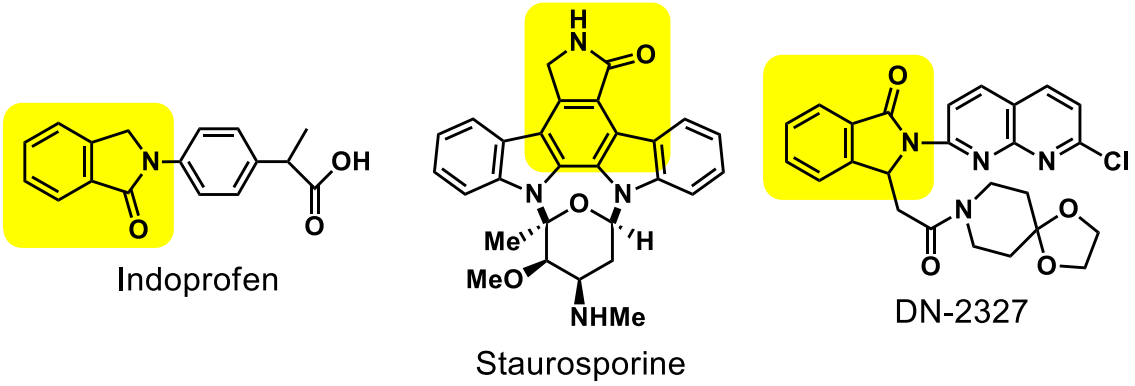
† **Dedicated to Professor Lutz F. Tietze on his 75th birthday**



Clemmensen-type reduction of phthalimide (Graebe),[2] rearrangement of phthalazone (Gabriel),[3] CO insertion to benzimidine (Murahashi),[4] double Mannich condensation (Thiele),[5-8] *etc*.. However, applicabilities of the synthetic methods are quite limited and unsatisfactory, due to severe reaction conditions, restrictions in substituents, or difficulties in purification; they have not been as practical as their fame.[9]

Among them, Mannich condensation-based strategy originally disclosed by Thiele and co-workers[5] in 1909 has appeared to be promising in terms of mild reaction condition (room temperature) and simple experimental procedure [*o*-phthalaldehyde (OPT) and primary amine in Et_2O]. However, extensive studies by Amano and co-workers[6,7] in 1965-1969 using a variety of substituted anilines as primary amines proved that isolated yields of phthalimidines were fair to poor due to concomitant formation of polymeric materials. More recently, Allin and co-workers[8] reported the reaction using α−phenethylamine to afford the desired phthalimidine but in 21% yield. Sole Mannich condensation reaction did not occur when it was confronted with reaction systems involving intramolecular oxidation-reduction.

We grasped the keys to the solution of this uncontrollable-but-promising reaction systems from two independent sectors. As of 1987, Katritzky and co-workers[10] have reported the condensation reaction of *mono*-aldehyde (RCHO; R ≠ H), *secondary* amine (R'R"NH), and 1,2,3-1*H*-benzotriazole (Bt-H; pK_a = 8.2) to give a Mannich base-equivalent mixed aminal [RCH(NR'R")Bt], which is readily converted into the corresponding RCH(NR'R")Nu when attacked by a nucleophile (Nu^-). This feature is attributable to the dual character of Bt-H, operating first as a nucleophile and second as a leaving group. As a first extension of this strategy to multifunctional reactants and formation of practically evaluated skeletons, we reported the "double" Mannich condensation reaction of *o*-phthalaldehyde (**1**; OPT) with *primary* amine **2** in the presence of Bt-H to give 1,3-bis(benzotriazolyl)isoindoline (**3**; $Nu^1 = Nu^2$ =Bt). This method was, however, not tolerant to use of aliphatic primary amines.

On the other hand, in the quantitative formation of a 2*H*-isoindole derivative (**4**; $Nu^1 = SCH_2CH_2OH$)

from **2** with **1** reported by research groups of Simons and Stobaugh, the role of 2-mercaptoethanol (MET; pK_a = 10.5), which is very close to that of Bt-H described above, can also be assigned as the auxiliary.[11] Although the authors did not mention clearly, their reaction systems certainly belong to Mannich-type condensation reactions, and therefore, formation of "some kind of" isoindoline (**3**) type intermediate is assumed on the way to 2*H*-isoindole **4**.

These findings led us to utilize two auxiliaries (Bt-H and MET) simultaneously, hoping to provide isoindoline derivatives **3** possessing 2-*alkyl* substituents. We thus embarked on the preliminary inspection using *p*-toluidine as a primary amine as before.[12-14] When the reaction was first carried out without Bt-H, the sole product was 2*H*-isoindole **4** as reported.[11] The effect of the addition of Bt-H to this reaction system was amazing; neither isoindoline **3** nor 2*H*-isoindole **4** was detected as isolable non-polymeric products and phthalimidine **5** was obtained as a sole product. It was the moment at which "uncontrollable-but-promising reaction systems" *would* be realized.

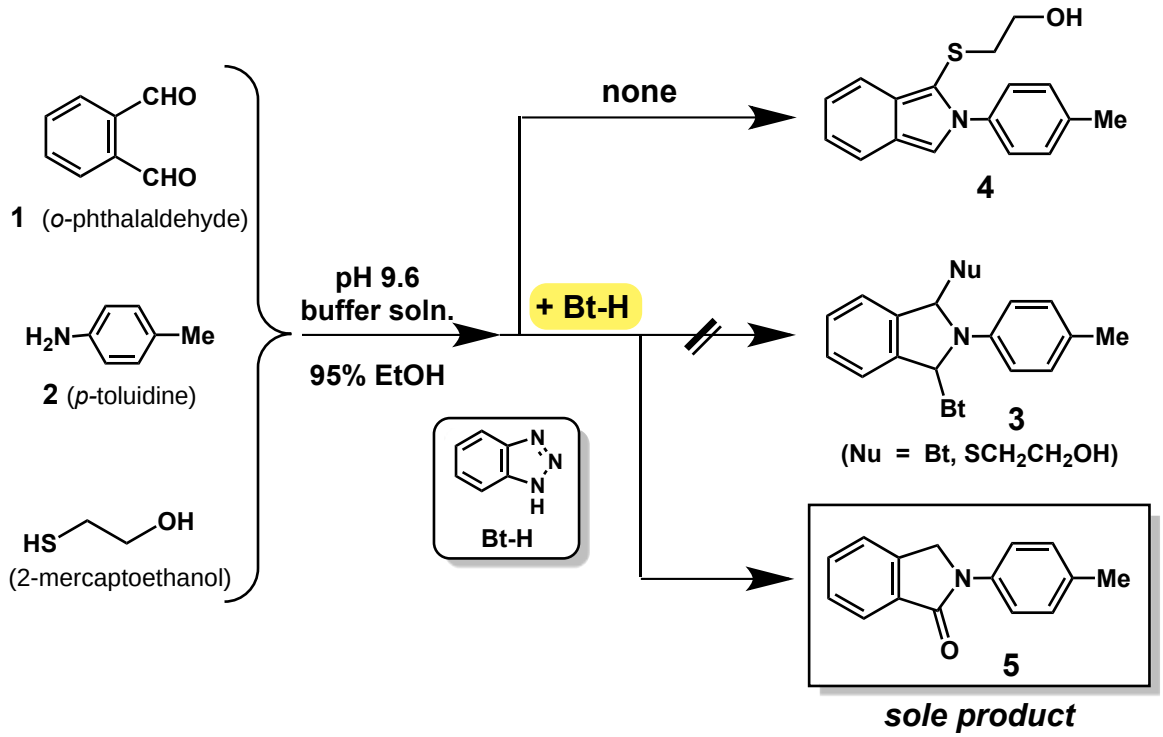
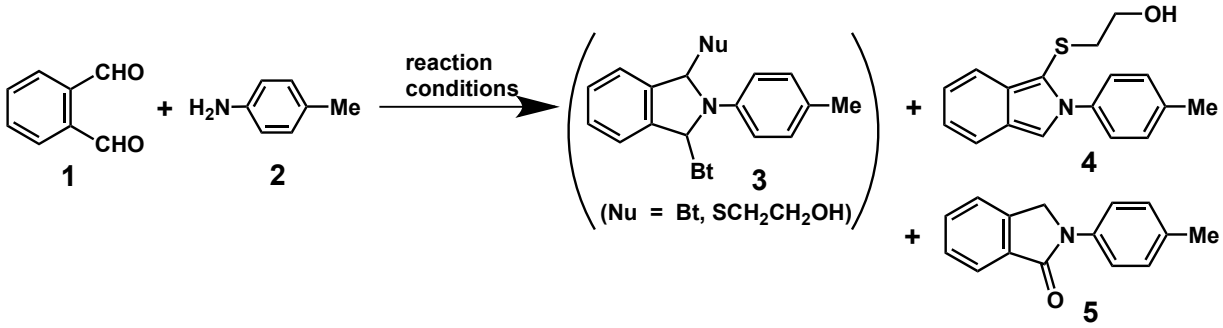


Figure 1. Realization of a New Phthalimidine Synthesis

In this report, we wish to describe the success in "controlling" Thiele's strategy to provide phthalimidines of appreciable purities and good isolated yields under mild reaction conditions for the first time.[15] A plausible reaction mechanism is also proposed in terms of product distribution patterns through optimization of reaction conditions.[16]

RESULTS AND DISCUSSION

Molar ratio between OPT (**1**) and *p*-toluidine (**2**) was fixed as 1:1 during our reaction condition-optimizing experiments. Possible isolable products were isoindoline **3**, 2*H*-isoindole **4**, and phthalimidine **5**, out of which isoindoline **3** was never detected during our expeditions probably due to its lability in the present reaction systems (Scheme 1).[17]



Scheme 1

During the Mannich-type condensation reaction (water-producing on the way) involved with OPT, primary amine, and excessive amount of Bt-H,[12,13] use of water-miscible solvents was favorable. Therefore, in the first stage of the present study, we explored solvent systems among Et_2O, EtOH and MeCN.[15] Amount of Bt-H was also examined. The results were summarized in Table 1.

Table 1. Solvent & Bt-H Dependence[a]

Entry	Solvent	Bt-H (eq.)	pH	Yield (%) 4	Yield (%) 5
1	Et_2O	-----	-----[b]	< 5[c]	-----
2	EtOH	-----	-----[b]	90	-----
3	MeCN	-----	-----[b]	67	-----
4	MeCN	0.1	9.6	72	7
5	MeCN	1	9.6	37	22
6	MeCN	2	9.6	29[b]	22

(a) Reaction conditions: 2-mercaptoethanol (MET; 3 eq.) and reaction time (13 h).
(b) Water was added instead of buffer solution.
(c) Polymeric materials were formed concomitantly.

Formation of 2*H*-isoindole **4** was quite slow in Et_2O (Entry 1). On the other hands, yields of 2*H*-isoindole **4** varied among experiments and non-reproducible in EtOH (Entry 2). Therefore, both solvents were omitted in further experiments. We then fixed the use of MeCN, where no phthalimidine **5** was detected without Bt-H (Entry 3). As Bt-H was added to the reaction system, phthalimidine **5** emerged (Entries 4-5). However, the use of excessive amount of Bt-H led to form polymeric materials

(checked by ^{1}H NMR spectra) rather than the induction of desired reactions (Entry 6). Accordingly we decided to fix the additive Bt-H at 1 equivalent.

In the second stage, the amount of additive MET was examined. Product distribution patterns (**4** and **5**) varied depending on the amount of MET (0.3-9 equiv.) (Table 2).

Table 2. MET Dependence[a]

Entry	MET (eq.)	Yield (%) **4**	Yield (%) **5**
1	0.3	-----	trace
2	1	57	9
3	2	48	11
4	3	37	22
5	6	43	26
6	9	-----	68

(a) Reaction conditions: solvent (MeCN), 1,2,3-1*H*-benzotriazole (Bt-H; 1 eq.), pH (9.6), and reaction time (13 h).

As we reported previously, no Mannich-type condensation product was obtained when OPT was reacted with *p*-toluidine (**2**) in the presence of 1 equiv. of Bt-H without MET in MeCN.[12] Reaction proceeded as MET was added to the reaction system (Entry 1). As the equivalence of MET increased, ratio of phthalimidine **5** increased (Entries 2-5), and when 9 equiv. of MET was added, phthalimidine **5** was given as a sole product (Entry 6). Therefore, in the further experiments, the use of MET was decided to fix at 9 equivalents.

In the third stage, the length of reaction time was examined. Product distribution patterns (**4** and **5**) were changed by a various reaction time (0.5-49 h) (Table 3).

Table 3. Reaction Time Dependence[a]

Entry	Time (h)	Yield (%) **4**	Yield (%) **5**
1	0.5	53	25
2	1	33	35
3	3	21	40
4	7	12	48
5	13	-----	68
6	25	-----	37[b]
7	49	-----	40[b]

(a) Reaction conditions: solvent (MeCN), 1,2,3-1*H*-benzotriazole (Bt-H; 1 eq.), 2-mercaptoethanol (MET; 9 eq.), and pH (9.6).
(b) Polymeric materials were also formed concomitantly.

When reactions were run for shorter periods, both 2*H*-isoindole **4** and phthalimidine **5** existed in reaction mixtures (Entries 1-4). However, as the reaction time increased, formation of 2*H*-isoindole **4** was suppressed and instead phthalimidine **5** turned out to be a sole product (Entry 6). When reaction time was further elongated, isolated yields of phthalimidine **5** decreased as concomitant polymeric materials increased, and therefore, in the further exploitations, the reaction time was fixed at 13 h.

In the last stage, pH dependence was tested by altering buffer (or aqueous) solutions. The results were shown in Table 4.

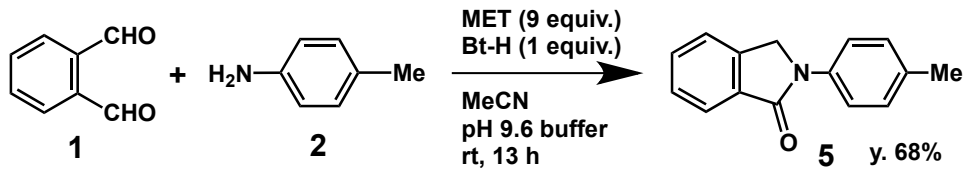
Table 4. pH Dependence[a]

Entry	MET (eq.)	pH	Yield (%)	
			4	**5**
1	3	1.7	-----	48
2	3	4	29	39
3	3	9.6	37	22
4	3	11	31	35
5	3	14[b]	83	-----
6	9	1.7	-----	58
7	9	4	-----	61
8	9	-----[c]	-----	62
9	9	9.6	-----	68

(a) Reaction conditions: solvent (MeCN), 1,2,3-1*H*-benzotriazole (Bt-H; 1 eq.), and reaction time (13 h).
(b) 0.05 *M* NaOH was added instead of a buffer solution.
(c) Water was added instead of a buffer solution.

The reaction proceeded to afford phthalimidine **5** except for under strongly basic pH values (Entry 5). Although the reaction was tolerant to a wide range of pH values between 1.7-9.6 with use of 9 equiv. of MET, taking into account the possibility to utilize amino substituents other than the reactant primary amino group, pH 9.6 buffer was adopted.

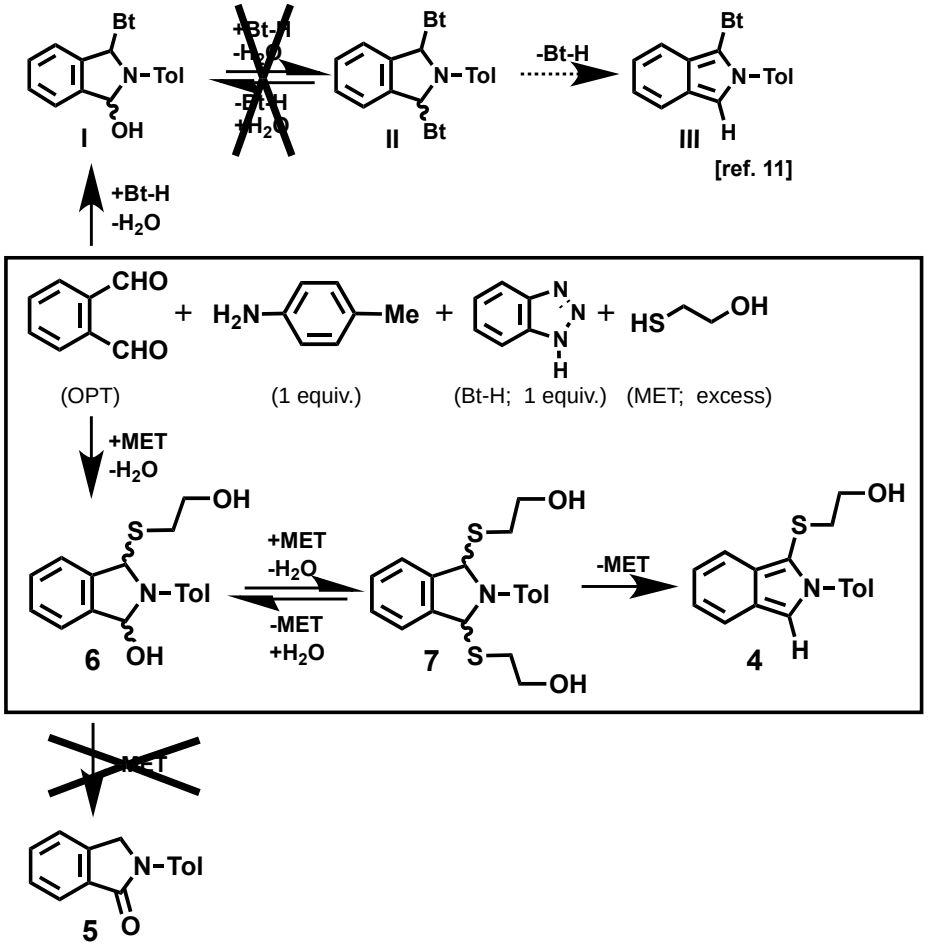
Our finally optimized reaction condition (Table 4, Entry 9) was depicted as Scheme 2.



Scheme 2

In due course of our present study, shortly after the first evaporation of reaction mixtures, formation of non-negligible amount of bis(2-mercaptoethyl) ether was checked, whenever phthalimidine **5** was formed. Different from our expectations, disulfide derived from MET was not detected at all. Combining these

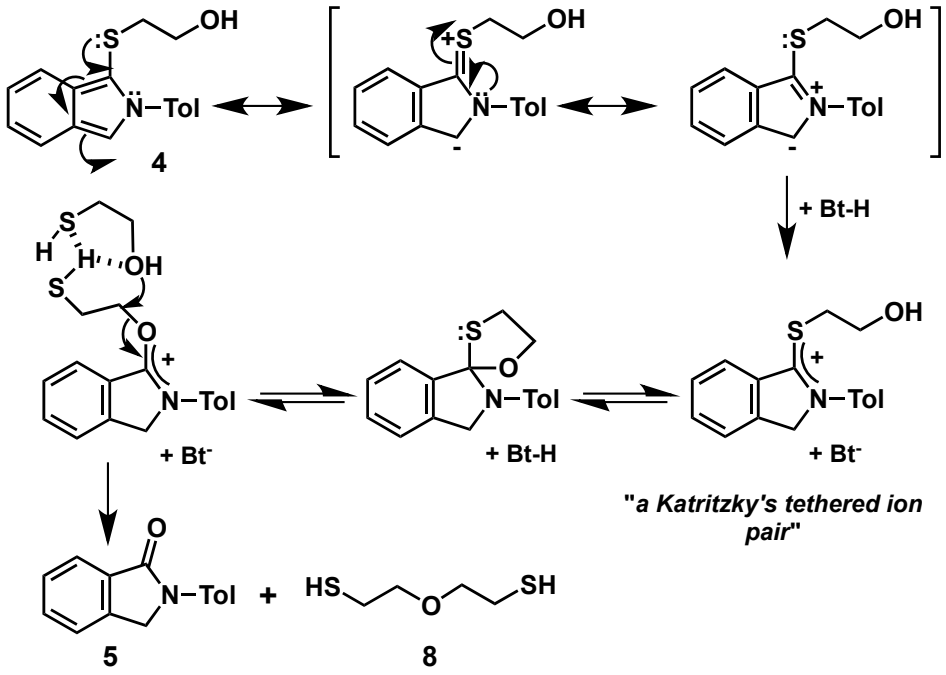
results and authors' experiences on the Mannich-type condensation reactions in the past, plausible reaction mechanisms are postulated as follows (Schemes 3 and 4).



Scheme 3. A Plausible Reaction Mechanism (part 1)

When we examined the reaction system containing OPT, primary amine, and Bt-H in a ratio of 1:1:1,[12] reactions proceeded so as to form isoindolinol **I** but not to drive to 2*H*-isoindole **III** *via* isoindoline **II**; it was probably because the conversion from **I** to **II** would require first the ejection of OH^- *via* an S_N1-like slow mode, for which sufficient amount of proton source like Bt-H (or MET in the present study) was needed, as reported by Katritzky and co-workers.[10] During our present study, the amount of Bt-H was fixed at 1 equiv. at most entries, and therefore, the path of OPT → **I** → **II** → **III** would not go forth either. Reactions in the presence of excessive amount of MET is believed to proceed in a similar manner to those in the presence of excessive amount of Bt-H examined by us in the past.[12] No rumor was observed in which phthalimidine **5** was formed at once with 2*H*-isoindole **4**, and therefore, the main path of generating **5** from isoindoline **6** through the elimination of MET did not work. Reasonable thought at this point is the formation of bis-MET-substituted isoindoline **7** like bis-Bt-substituted one **II** as before,[15] which is followed by the elimination of MET to afford 2*H*-isoindole intermediate **4**. To be

exact, up to the point where 2*H*-isoindole **4** was formed, both Bt-H and buffer solution did not appear to contribute the reaction path at all (Scheme 3).[18]



Scheme 4. A Plausible Reaction Mechanism (part 2)

In the latter half of the plausible reaction mechanism, we took the following points into consideration: reports on the immonium salts out of Katritzky's group and researches out of Simons and Stobaugh groups.[10,11] Thus, as the result of protonation on the benzyl anion (a resonance contributor of 2*H*-isoindole **4** an ion pair involving *hard* carbocation and *soft* Bt anion would be formed. As a matter of fact, such an ion pair is well known as a "Katritzky's tethered ion pair," of which existence has been ascertained from cumulative circumstantial evidences in solution from spectral measurements, and therefore, we assume this sort of ion pair is also to be formed in our reaction system. Once the tethered ion pair is formed, as reported by groups of Simons and Stobaugh, formation of spiro intermediate by the nucleophilic attack by OH group is enabled, which is followed by C-S bond cleavage to give another tethered ion pair; nucleophilic attack of excessive amount of free MET would afford bis(mercaptoethyl) ether (**8**) in an amount stoichiometric to the formation of phthalimidine **5**.[19] The nucleophile at the final stage may be played by water molecule instead. However, far excessive amount of MET could tangle with the side chain to form a cluster intermediate, and therefore, the formation of ether **8** would be exclusive. Practically, the formation of **8** was found as equimolar as that of **5**. Therefore, probability of the reaction path in which the direct hydrolysis of tethered ion pair to give phthalimidine **5** is considered to be negligible. Anyway, the formation of ether **8** apparently supports the formation of a tethered ion pair intermediate or some kind of its relatives (Scheme 4).

CONCLUSION

As an extension of our benzotriazole (Bt-H)-mediated Mannich-type condensation reactions, we set out for targetting phthalimidine, which has been a minor product during our past expeditions. Utility of dual synthetic auxiliaries (Bt-H by us and MET by Simons and Stobaugh) at once brought about the first striking improvement of mild-condition phthalimidine synthesis which was originally exposed by Thiele and co-workers some 100 years ago! Application of this interesting/promising reaction system to primary amines other than *p*-toluidine is to be reported in the following article.

EXPERIMENTAL

General Information. All melting points are uncorrected. Infrared (ir) spectra were measured with a Shimadzu IR-430 grating infrared spectrophotometer and a JASCO FT/IR-8000 Fourier transform infrared spectrometer. ^{1}H (270 MHz) and ^{13}C (67.5 MHz) nuclear magnetic resonance (nmr) spectral measurements were carried out with a JEOL JNM-GX200 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 ring; single prime, substituent at 2-position. Mass spectra (ms; EI and FAB modes) were taken with a JEOL JMS DX-303 mass spectrometer, where mass numbers of local maxima (relative intensities in parentheses) are recorded.

All chemicals and solvents were commercially purchased in the purest grade and used without further purifications. The following materials were utilized to settle appropriate pH values: oxalate pH standard solution (Wako) for pH 1.7; phthalate pH standard solution (Wako) for pH 4; 0.05 *M* H_3BO_3-KCl-NaOH (TCI) for pH 9.6; 0.05 *M* Na_2HPO_4-NaOH (TCI) for pH 11; 0.05 *M* NaOH (TCI) for pH 14.

General procedure for the determination of the product distribution patterns. To a solution of *o*-phthalaldehyde (OPT, 1.341 g, 10 mmol) in an organic solvent (30 mL of Et_2O or EtOH or MeCN in the present work) was added successively (i) a solution of 2-mercaptoethanol (MET; variable amount between 3 and 86 mmol) in the organic solvent (as above, 10 mL) over 1 min, (ii) a solution of *p*-toluidine (1.072 g, 10 mmol) in the organic solvent (as above, 5 mL) over 1 min, (iii) 1,2,3-1*H*-benzotriazole (variable amount between 0 and 20 mmol) portionwise over 2 min, and (iv) 5 mL of water or a buffer solution (variable values between 1.7 and 11) over 2 min with stirring at room temperature. After the additions were complete, the mixture was further stirred at room temperature for a variable reaction time (0.5 and 49 h) under N_2, and then evaporated.[20] After storage in refrigerator for 1 h, the resulting solids were filtered, washed successively with ice-cold Et_2O and water, and then dried *in*

vacuo to give the mixture of 2*H*-isoindole **4** and phthalimidine **5** as a crude product. As we have reported previously,[12-14] 2*H*-isoindole derivatives are in general unstable in organic solvent systems and tend to decompose during chromatographic purifications, and therefore, in the present study, we adopted the method with which solid samples are available quickly. Product distribution patterns in crude products were determined by ^{1}H NMR spectral measurements, out of which the yields of 2*H*-isoindole **4** and phthalimidine **5** were calculated. For characterization, compounds **4** and **5** were isolated from such reaction entries as to form these compounds as sole products.

2-(*p*-Methylphenyl)-3-(2-hydroxyethylthio)-2*H*-isoindole (4). Beige cotton-like solids from ice-cold Et_2O washing; mp 119-125 °C (dec.). ^{1}H NMR ($CDCl_3$) δ 7.72 (1H, d, *J* = 8 Hz, H-7), 7.58 (1H, d, *J* = 8 Hz, H-4), 7.45 (1H, s, H-3), 7.34 (4H, bs, H-2', 3', 5', and 6'), 7.11 (1H, dd, *J* = 7 Hz and 6 Hz, H-5), 7.03 (1H, dd, *J* = 8 Hz and 7 Hz, H-6), 3.32 (2H, t, *J* = 6 Hz, C$\underline{H}_2$O), 2.57 (2H, t, *J* = 6 Hz, C$\underline{H}_2$S), 2.45 (3H, s, ArC$\underline{H}_3$), 1.68 (1H, bs, O$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ 138.5 (C-1'), 136.9 (C-3a), 130.6 (C-4'), 129.5 (C-3'), 126.9 (C-2'), 124.3 (C-7a), 123.0 (C-7), 122.0 (C-5), 120.2 (C-6), 119.2 (C-4), 116.9 (C-3), 109.5 (C-1), 60.4 ($\underline{C}H_2$O), 41.0 ($\underline{C}H_2$S), 21.2 (Ar$\underline{C}H_3$). IR (KBr): ν_{max} (cm^{-1}) 3302 (OH), 1070, 1044, 1013 (C-O), 822, 765, 754 (arom). MS (EI): *m/z* (rel. intensities) 284 [(*M*+1)$^+$, 52], 239 (100), 224 (38), 208 (10), 195 (7), 166 (4), 147 (7), 112 (4), 91 (14), 77 (6), 65 (8), 60 (7), 45 (7). *Anal.* Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.12; N, 4.75.

2-(*p*-Methylphenyl)-phthalimidine (5). White crystalline solids from MeOH; mp 140-141.5 °C (lit.,[12] 139-140 °C). ^{1}H NMR ($CDCl_3$) δ 7.92 (1H, dd, *J* = 8 Hz and 1 Hz, H-7), 7.73 (2H, d, *J* = 8 Hz, H-2' and 6'), 7.58 (1H, ddd, *J* = 7 Hz, 7 Hz, and 1 Hz, H-5), 7.50 (1H, d, *J* = 7 Hz, H-4), 7.49 (1H, dd, *J* = 7 Hz and 7 Hz, H-6), 7.22 (2H, d, *J* = 8 Hz, H-3' and 5'), 4.82 (2H, s, H-3), 2.35 (3H, s, ArC$\underline{H}_3$). ^{13}C NMR ($CDCl_3$) δ 167.0 (C=O), 139.9 (C-3a), 136.7 (C-1'), 133.6 (C-4'), 133.0 (C-7a), 131.6 (C-5), 129.3 (C-3' and 5'), 127.9 (C-7), 123.5 (C-4), 122.3 (C-6), 119.0 (C-2' and 6'), 50.4 (C-3), and 20.5 (Ar$\underline{C}H_3$). IR (KBr): ν_{max} (cm^{-1}) 1680 (C=O), 1599, 810, 729 (arom). MS (EI): *m/z* (rel. intensities) 223 (*M*$^+$, 100), 194 (19), 165 (5), 110 (9), 91 (7), 77 (5), 65 (7), 51 (3), 39 (4).

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16. Preliminary discussion on this point was exposed at ref. 9 (authors' review).
17. Although a small amount of phthalimidine was formed in DME in our expedition (ref. 12), this solvent was omitted because of a huge amount of concomitant unidentifiable byproducts.
18. When simple thiol such as 3-propanethiol was used instead of MET, different from the report in ref. 11, we did not succeed in the isolation of the corresponding 2*H*-isoindole due to its instability. However, from our past experiences, polymeric red materials were considered to be formed from the quick polymerization of *in situ* formed 2*H*-isoindoles. Therefore, the mercapto groups of synthetic auxiliaries such as MET and 3-propanethiol would be helpful to form 2*H*-isoindoles. In turn, no phthalimidines were detected at all throughout experiments using 3-propanethiol, indicating that the existence of the hydroxy group of MET-derived moiety is indispensable to form phthalimidines. These results are considered to support our plausible reaction mechanisms.
19. Treatment of 2*H*-isoindole **4** under our optimized reaction condition (Scheme 2, for 16 h) gave phthalimidine **5** as a sole product but in 39% yield, concomitant with polymeric red materials. We suppose that the yield of **5** lower than the result in Scheme 2 (68%) was due to the instability of **4**, since the treatment of **4** in MeCN-buffer at room temperature for 16 h gave **4** (recovery) in 70% only. We thus consider the conversion from **4** to **5** *must be* the main path of the phthalimidine-forming reaction.
20. Bis(2-mercaptoethyl) ether (**8**) was able to be isolated from the crude product shortly after evaporation by column chromatography (silica gel, eluted with benzene-EtOAc), whenever phthalimidine **5** was formed. Obtained **8** in our present study was identical with the sample commercially available from TCI.