# PREPARATION OF 2-SUBSTITUTED 1,3-BIS(BENZOTRIAZOL-1-YL)ISOINDOLINES BY THE DOUBLE MANNICH CONDENSATION REACTION OF *o*-PHTHALALDEHYDE WITH PRIMARY AMINES IN THE PRESENCE OF 1,2,3-1*H*-BENZOTRIAZOLE[1]

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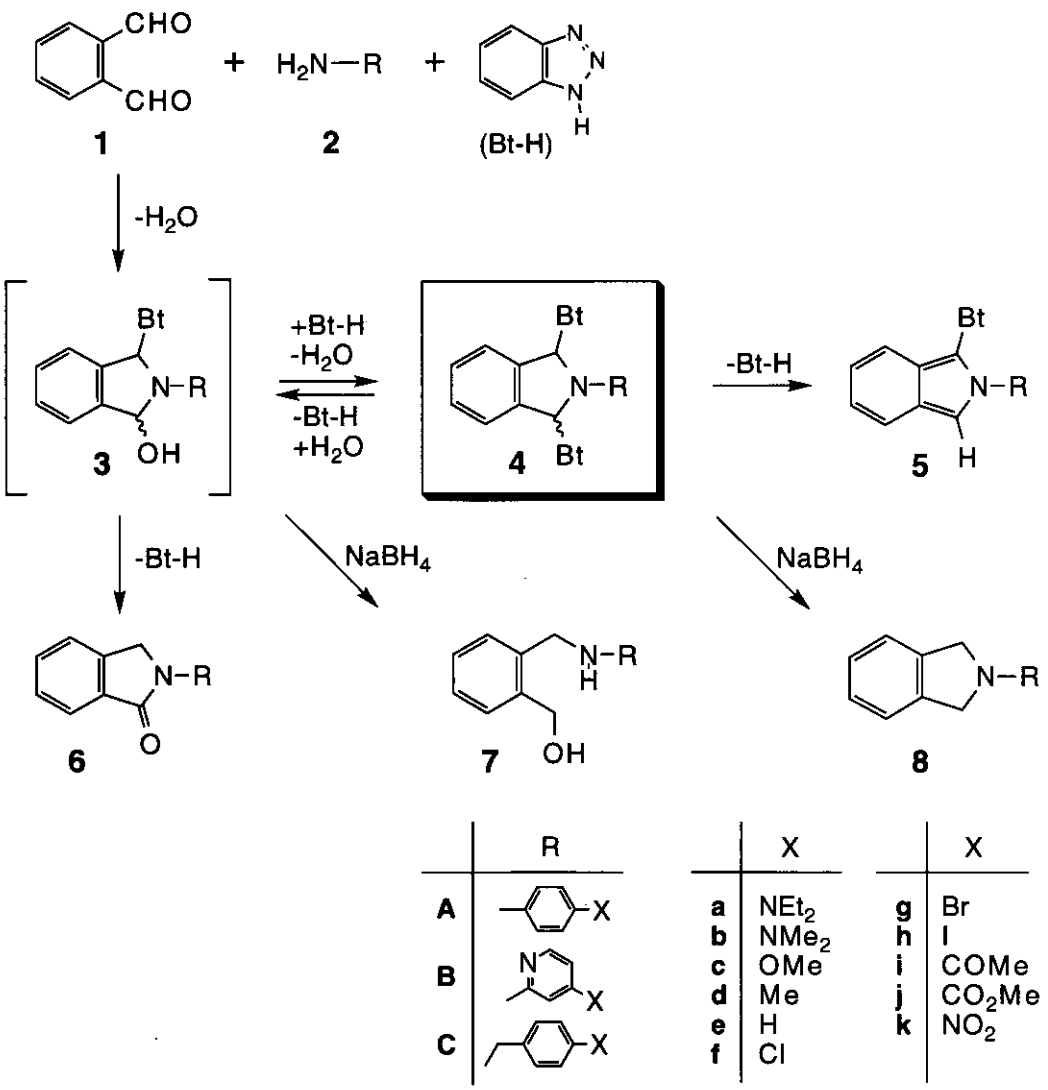
Abstract - The preparation of isoindolines (1,3-dihydro-2*H*-isoindoles) possessing two reactive centers as mixed aminals is investigated. In the double Mannich condensation reaction of *o*-phthalaldehyde with a variety of primary amines in the presence of 1,2,3-1*H*-benzotriazole (Bt-H) in MeCN, Bt-substituted isoindolines are obtained in fair to good yields when anilines are used as amines.

The utility of 1,2,3-1*H*-benzotriazole (Bt-H) as the synthetic auxiliary to the Mannich condensation reaction has attracted a considerable synthetic interest in recent years. Thus, the condensation reaction of aldehyde (RCHO), amine (R'R"NH), and Bt-H gives a mixed aminal [RCH(NR'R")Bt], which is readily converted into the corresponding RCH(NR'R")Nu, when attacked by a nucleophile ($Nu^-$). It is attributed to the dual character of Bt-H, performing first as a nucleophile and second as a leaving group ($Bt^-$).[2,3] As an extension of this strategy to polyfunctional substrates to produce practically useful materials, we investigated on the double Mannich condensation reaction of *o*-

phthalaldehyde (**1**; a representative dialdehyde) with amines (**2**) in the presence of Bt-H to form 2*H*-isoindole derivatives (**3**-**6**), of which skeletons have been evaluated as the antihypertensives/antihyperglycemics[4] and as the unit compounds for electrically conductive polymers.[5]




| | R |
|---|---|
| A |  |
| B |  |
| C |  |

| | X |
|---|---|
| a | $NEt_2$ |
| b | $NMe_2$ |
| c | OMe |
| d | Me |
| e | H |
| f | Cl |

| | X |
|---|---|
| g | Br |
| h | I |
| i | COMe |
| j | $CO_2Me$ |
| k | $NO_2$ |

**Scheme 1**

Previously we have reported the double Mannich condensation reaction of **1** with *p*-toluidine (**2Ad**, X = Me) in the presence of Bt-H to give mixtures of isoindoline (**4Ad**; 1,3-dihydro-2*H*-isoindole) and 2*H*-isoindole (**5Ad**) in varying amounts, which are dependent on reaction time, solvent, and amount of Bt-H (Scheme 1).[6-8] Both **4Ad** and **5Ad** are thermally stable enough to be isolated at room temperature, however, they easily undergo polymerization even under room light when dissolved in polar solvent systems.[9-11] They are the first successful examples of (doubly) Bt-containing reactive synthons, however, isomeric isoindoline **4Aj** (X = $CO_2Me$) is found too stable and inert.[8] In order to explore practically useful reactive synthons of this type, it is desirable to establish the "general" strategy to produce 1,3-bis(benzotriazolyl)isoindolines (**4**) having various 2-substituents. We wish to report it in this paper.

## RESULTS AND DISCUSSION

**Preparation of Bt-Substituted Isoindoline Derivatives.** The following reaction/work-up procedure (Method A) is adopted in order to eliminate the concomitant polymeric materials (usually red oils; their existence made the determination of product distribution patterns difficult in the past).[6-8] Thus, **1** (5 mmol) is added portionwise to a solution of amine (**2**; 5 mmol) and Bt-H (15 mmol) in MeCN (30 ml), and the mixture is stirred for 8 h at room temperature. Precipitates (if any) are filtered (sample A), and the filtrate is evaporated. The residue is treated with $Et_2O$ (30 ml) for 30 min to give another crop of precipitates (sample B). Since compounds **4** and **5** are found to undergo hydrolysis and/or polymerization upon purification such as recrystallization and chromatography, amounts of 2*H*-isoindole derivatives (**4**-**6**) in their mixtures are determined by $^1H$ nmr spectra, and are cumulated to afford the product distribution pattern of each Run. In principle, in order to determine **4Ad**/**5Ad**/**6Ad** ratios in crude samples for example, either of the following two sets of proton signal intensities in $^1H$ nmr are used (δ values in parentheses): (i) *p*-methyl protons of **4Ad** (2.02), **5Ad** (2.25), and **6Ad** (2.36); (ii) aromatic protons of **4Ad** (8.43, H-1), **5Ad** (*ca.* 8.10, H-4'), and **6Ad** (7.93, H-7).[6,8,12] Similar estimations are applied to samples bearing *p*-substituents other than Me. For comparison, two representative conditions in benzotriazole-assisted Mannich condensation reactions (Method B, **1**:**2**:Bt-H = 1:1:2 (neat), 120 °C, 15 min; Method C, **1**:**2**:Bt-H = 1:1:2 in $Et_2O$, room temperature, 24 h)[2,3,13] are examined. Results are summarized in Table 1.

**Table 1. Product distribution patterns in the condensation reaction of *o*-phthalaldehyde (1) with amines (2) in the presence of 1,2,3-1*H*-benzotriazole (Bt-H)**

| Run | Amine | | Product Yields (%)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Method A | | | Method B | | |
| | Compd. | X | 4 | 5 | 6 | 4 | 5 | 6 |
| 1 | **2Aa** | $NEt_2$ | 35.2 | 17.5 | 13.7 | -----[e] | -----[e] | -----[e] |
| 2 | **2Ab** | $NMe_2$ | 8.9 | 55.9 | 12.2 | -----[e] | -----[e] | -----[e] |
| 3 | **2Ac** | OMe | 74.8 | 11.2 | ------ | -----[e] | -----[e] | -----[e] |
| 4 | **2Ad** | Me | 82.8[b] | 2.6[b] | -----[b] | ------ | 9.8 | ------ |
| 5 | **2Ae** | H | 71.7 | 7.2 | ------ | 46.4 | trace | ------ |
| 6 | **2Af** | Cl | 26.6 | 1.1 | ------ | ------ | 11.6 | ------ |
| 7[c] | **2Ag** | Br | 21.6 | ------ | ------ | 8.6 | 16.8 | ------ |
| 8 | **2Ah** | I | 57.0 | 11.1 | ------ | -----[e] | -----[e] | -----[e] |
| 9 | **2Ai** | COMe | 23.6 | 5.2 | ------ | n.d.[f] | n.d.[f] | n.d.[f] |
| 10 | **2Aj** | $CO_2Me$ | 79.3[d] | trace | ------ | 14.5 | 1.0 | 2.3 |
| 11 | **2Ak** | $NO_2$ | 16.8 | ------ | ------ | 12.5 | trace | 25.6 |
| 12 | **2Bd** | Me | 4.2 | ------ | ------ | 53.4 | 8.7 | ------ |
| 13 | **2Be** | H | 6.8 | ------ | ------ | 73.4 | trace | ------ |
| 14 | **2Cc** | OMe | -----[e] | -----[e] | -----[e] | -----[e] | -----[e] | -----[e] |
| 15 | **2Ce** | H | ------ | 19.1 | ------ | -----[e] | -----[e] | -----[e] |

a) See text. b) Ref. 8. c) **4Ag** is specifically obtained in 55.9% yield with use of Method C. d) 24 h reaction raises the yield to 91.3 %. e) Complex mixtures. f) Containing polymeric materials.

Characteristics are as follows. First, Method A exhibits wider applicability and generality compared with Methods B and C, which have been traditionally in use. Thus, when 4-substituted anilines (**2Aa-k**) are used as amines, isoindolines (**4Ac-k**) are found as major products irrespective of 4-substituents (Runs 3-11); crude products are further washed with MeCN to give analytically pure isoindolines in >80% of yields in Table 1. The yield of **4Aj** (Run 10) is improved by the reaction for 24 h.[8] Formation of 2*H*-isoindoles (**5Aa-b**) and phthalimidines (**6Aa-b**) in large quantities from 4-(*N,N*-dialkylamino)anilines (**2Aa-b**; Runs 1-2) can be attributed to the easy elimination of Bt-H from the corresponding isoindolines (**4** and **3**, respectively), which are effected by the additional in-molecule base centers. This hypothesis is also supported by the specific formation of a 2*H*-isoindole derivative (**5Ce**) from aliphatic benzylamine (**2Ce**; Run 15), which is more basic than anilines. Attempts with use of aliphatic amines other than **2Ce** (only the results by **2Cc** are shown

in Table 1) have been unsuccessful. Low yields with use of 2-aminopyridine derivatives (**2Bd-e**; Runs 12-13) can be attributed to their less-nucleophilic amino groups.

Second, Method B exhibits some success in the preparation of 2-(2-pyridyl)isoindolines (**4Bd-e**; Runs 12-13), however, its utility is quite limited as a whole. It is because once formed "reactive isoindolines" must be lucky enough to solidify and then to survive the neat-heat condition, which was not well examined in the previous report.[14] Only **4Bd** is new to us.

Last, Method C (not in Table1 ; see footnote) miraculously affords the best result in the preparation of **4Ag** (Run 7), however, it is of little use to our *o*-phthalaldehyde system. In other Runs, low-yield mixtures of 2*H*-isoindole derivatives (**4-6**) are obtained throughout, which are even accompanied by some unidentifiable products (not polymeric). It is assumed that once eliminated water molecule kicks back **4** to regenerate **3**,[6,7] giving complicated product distribution patterns. This reversal process appears to be characteristic of our *o*-dialdehyde system, which has never been reported with use of monoaldehydes.[2]

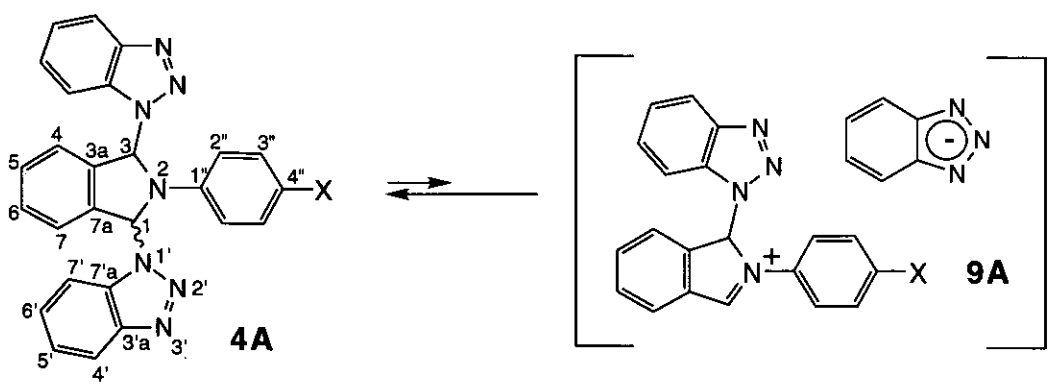
**Structural Determination of Bt-Substituted Isoindoline Derivatives.**

**General.** Obtained isoindoline derivatives (**4**), possessing two reactive centers as mixed aminals, have often been found difficult in determining their identities by combustion analyses (**4Ae** and **4Ak** in the present work). It is because these materials are likely to release Bt-H to afford the corresponding 2*H*-isoindoles (**5**) even under mild conditions,[9,11] which undergo polymerization. These characteristics, which are indispensable as reactive synthons, have inevitably limited the chance of their purification as well as the determination of their purities. For this reason, a series of derivatives, possessing molecular structures different only in substituents, must be determined as a whole by some indirect methods, *i.e.*, the cumulation of circumstantial evidences obtained from spectral measurements. In the present work, the structural determination of **4** based on nmr ($^1$H and $^{13}$C) and ms spectra are sought.

**$^1$H and $^{13}$C Nmr Spectra.** In the early stage of our study, no dependable spectral assignments of 2*H*-isoindoles were known on literature.[2,10,11,14] Therefore, we have referred to the spectral data of **7** (obtained by hydride reduction of **3** which has never successfully been isolated) and **8** (obtained similarly from **4**) in due course (Scheme 1).[15] Finally defined nmr spectral assignments

are assembled as Tables 2 and 3. Since compounds (**4Aa**) and (**4Ab**) have not been isolated, these spectral data in Table 2 are extracted from those of the corresponding reaction mixtures. Characteristic features are as follows. Aromatic rings of isoindoline moieties are observed as two multiplets with equal intensities ($^1$H) and three independent signals ($^{13}$C), indicating the existence of a symmetry. On the other hand, aromatic rings of benzotriazolyl moieties are observed as four multiplets with equal intensities ($^1$H) and six independent signals ($^{13}$C), indicating that both of these moieties exist as 1-benzotriazolyl (1-Bt) formats.[2] Chemical shifts of 2-(*p*-substituted phenyl) moieties are parallel with those of the corresponding *p*-substituted anilines.[16,17]

In $^1$H nmr spectra of 2-phenylisoindoline derivatives, 1- (or 3-) proton signals of isoindolines are found at δ 8.34 - 8.50 ppm, which are located downfield when compared with the corresponding benzylic methylene/methine protons in Bt-containing aminals (*e.g.*, Bt-C$\underline{H}_2$-$NMe_2$ appears at δ 5.41 (1-Bt) and δ 5.52 (2-Bt) ppm; Ph-C$\underline{H}$(Bt)-morpholino appears at δ 6.70 (1-Bt) and 6.78 (2-Bt) ppm, respectively).[11] These values are competitive to those of Schiff's bases such as benzal-*N*-methylamine (δ 8.19 ppm).[17] Since the existence of a positive charge on its nitrogen atom would induce the downfield shift of neighbouring protons (H-2 of thiazole and thiazolium appear at δ 8.69 and 9.97 ppm, respectively),[17] some contribution by a tethered (Katritzky) ion pair (*e.g.*, **9A** in Scheme 2) must be sought, which is formed by the dissociation of $Bt^-$ from the corresponding isoindoline (**4A**). Chemical shifts of methine protons in our present isoindoline systems are proportional to $\sigma_p$ values of *p*-substituents[18] and therefore, they are interpreted in terms of inductive effects.




**Scheme 2**

**Table 2. $^1$H Nmr Spectra of Isoindoline Derivatives 4[a]**

| Assignment | | Compound | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **4Aa[b]** | **4Ab[b]** | **4Ac** | **4Ad** | **4Ae** | **4Af** | **4Ag** | **4Ah** | **4Ai** | **4Aj** | **4Ak** | **4Bd** | **4Be** |
| Isoindoline | 1, 3 (2H, s) | 8.34 | 8.36 | 8.38 | 8.43 | 8.46 | 8.41 | 8.40 | 8.40 | 8.50 | 8.49 | 8.50 | 8.56 | 8.58 |
| | 4-7 (4H, m) | 7.30 -7.26 | 7.30 -(7.24)[c] | 7.29 -7.26 | 7.32 -7.22 | 7.29 -7.24 | 7.31 -7.27 | 7.31 -7.28 | 7.33 -7.26 | 7.31 -7.26 | 7.31 -7.27 | 7.34 -7.30 | 7.47 -7.28 | 7.38 -7.21 |
| *Benzotriazole* | 4' (2H, m) | 8.02 -7.98 | 8.02 -7.97 | 8.02 -7.98 | 8.02 -7.99 | 8.02 -7.99 | 8.04 -8.01 | 8.04 -8.01 | 8.04 -8.01 | 8.04 -8.01 | 8.04 -8.00 | 8.07 -8.03 | 8.01 d[d] | 8.02 d[e] |
| | 5', 6' (4H, m) | (7.50)[c] -(7.40)[c] | (7.45)[c] | 7.49 -7.40 | 7.50 -7.40 | 7.49 -7.40 | 7.51 -7.41 | 7.51 -7.41 | 7.50 -7.40 | 7.55 -7.43 | 7.51 -7.42 | 7.56 -7.44 | 7.47 -7.28 | 7.49 -7.38 |
| | 7' (2H, m) | 6.94 -6.90 | 6.93 -6.88 | 6.91 -6.88 | 6.90 -6.87 | 6.91 -6.88 | 6.88 -6.84 | 6.87 -6.84 | 6.86 -6.83 | 6.89 -6.86 | 6.89 -6.85 | 6.84 -6.81 | 7.23 d[e] | (7.38)[c] -(7.21)[c] |
| Aryl | 2", 6" (2H, d) | 6.95 | 6.99 | 7.04 | 7.02 | 7.05 -6.99 m | 7.06 | 7.01 | 6.90 | 7.18 | 7.16 | 7.23 | 7.76 d[f] (1H) | 7.91 d[f] (1H) |
| | 3", 5" (2H, d) | 6.34 | 6.41 | 6.56 | 6.82 | 7.12 dd[e] | 6.97 | 7.12 | 7.29 | 7.64 | 7.70 | 7.92 | g | h |
| | 4" (1H) | | | | | 6.66 t[e] | | | | | | | | (7.38)[c] -(7.21)[c] |
| Others | $CH_3$ | 0.94 t[d] (6H) | 2.67 s (6H) | 3.54 s (3H) | 2.02 s (3H) | | | | | 2.33 s (3H) | 3.72 s (3H) | | 2.06 s (3H) | |
| | $CH_2$ | 3.07 q[d] (4H) | | | | | | | | | | | | |

[a]Measured in $CDCl_3$/TMS. Unless otherwise stated, multiplicities are in parentheses and doublets are of $J$ = 9 Hz. [b]Values obtained from samples in which the corresponding 2*H*-isoindoles (**5**) are major components. [c]Uncertainties exist because of overlaps with other signals. [d]$J$ = 7 Hz. [e]$J$ = 8 Hz. [f]$J$ = 5 Hz. [g]$\delta$ = 6.72 (1H, s, H-3"), 6.35 (1H, d, $J$ = 5 Hz, H-5"). [h]$\delta$ = 6.90 (1H, d, $J$ = 8 Hz, H-3"), 6.52 (1H, dd, $J$ = 7 Hz and 5 Hz, H-5").

**Table 3. $^{13}C$ Nmr Spectra of Isoindoline Derivatives 4[a]**

| Assignment | | Compound | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **4Ac** | **4Ad** | **4Ae** | **4Af** | **4Ag** | **4Ah** | **4Ai** | **4Aj** | **4Ak** | **4Bd** | **4Be** |
| Isoindoline | 1 | 77.2 | 76.8 | 76.7 | 76.6 | 76.6 | 76.5 | 76.5 | 76.5 | 76.5 | 75.5 | 75.4 |
| | 3a | 135.8 | 136.8 | 140.0 | 137.9 | 138.4 | 139.1 | 143.5 | 143.3 | 145.0 | 147.7[b] | 148.2 |
| | 4 | 131.2 | 131.2 | 131.3 | 131.4 | 131.5 | 131.5 | 131.6 | 131.2 | 131.9 | 131.1 | 131.1 |
| | 5 | 124.3 | 124.2 | 124.2 | 124.4 | 124.5 | 124.4 | 124.5 | 124.5 | 124.7 | 124.1 | 124.1 |
| Benzotriazole | 3'a | 130.4 | 130.3 | 130.2 | 130.2 | 130.4 | 130.2 | 130.5 | 130.2 | 130.1 | 130.6 | 131.3 |
| | 4' | 120.4 | 120.3 | 120.4 | 120.5 | 120.6 | 120.6 | 120.6 | 120.6 | 120.8 | 120.2 | 120.2 |
| | 5' | 123.7 | 123.6 | 123.7 | 123.7 | 123.8 | 123.7 | 123.8 | 123.8 | 123.8 | 123.7 | 123.7 |
| | 6' | 128.0 | 128.0 | 128.4 | 128.2 | 128.2 | 128.6 | 128.3 | 128.3 | 128.6 | 127.7 | 127.8 |
| | 7' | 109.5 | 109.5 | 109.4 | 109.2 | 109.2 | 109.2 | 109.1 | 109.1 | 108.9 | 109.9 | 109.8 |
| | 7'a | 135.6 | 135.5 | 135.7 | 135.0 | 135.0 | 135.0 | 134.8 | 134.8 | 134.4 | 135.9 | 135.9 |
| Aryl | 1" | 146.8 | 146.8 | 146.8 | 146.8 | 146.9 | 146.9 | 146.9 | 146.9 | 146.9 | | |
| | 2" | 117.0 | 115.1 | 117.1 | 116.3 | 116.7 | 117.1 | 114.4 | 114.3 | 114.6 | 153.1 | 152.0 |
| | 3" | 114.8 | 129.9 | 129.2 | 129.4 | 132.3 | 138.2 | 130.2 | 131.6 | 125.6 | 112.6 | 108.9 |
| | 4" | 154.2 | 130.3 | 120.0 | 126.4 | 113.9 | 84.0 | 130.0 | 122.6 | 141.3 | 147.9[b] | 137.8 |
| | 5" | 114.8 | 129.9 | 129.2 | 129.4 | 132.3 | 138.2 | 130.2 | 131.6 | 125.6 | 119.5 | 116.3 |
| | 6" | 117.0 | 115.1 | 117.1 | 116.3 | 116.7 | 117.1 | 114.4 | 114.3 | 114.6 | 146.4 | 146.5 |
| Others | C=O | | | | | | | 196.4 | 166.4 | | | |
| | $CH_3$ | 55.2 | 20.3 | | | | | 26.0 | 51.7 | | 21.1 | |

[a]Measured in $CDCl_3$/TMS. [b]Assignments may be altered.

In $^{13}C$ nmr spectra of 2-phenylisoindoline derivatives, C-3'a (Bt-H) and C-4" (phenyl) of **4Ad** are located so close each other that they cannot be observed as two independent signals which are, for the present, defined as overlaps by chance in spectral assignments (δ 130.3 ppm). Except them, other carbon signals are observed independently and assigned properly. As the results, fundamental skeletons of compounds (**4A**) are proven as 1,3-bis(1-benzotriazolyl)-2-(*p*-substituted phenyl)isoindolines.

On the other hand, chemical shifts of C-3a (isoindoline) drift downfield as *p*-substituents of phenyl groups become more electron-withdrawing. Since C-4" (phenyl) is too far to effect on C-3a, the above fact may reflect the existence of a *cis/trans* isomerism as to C-1 and C-3 (aminal centers). In other words, C-3a signals in solution would be observed at weigh balanced positions between 1,3-*cis*- and 1,3-*trans*-isomers. However, we have never obtained any evidences supporting this hypothesis as yet; melting point isomers of **4Ag** exhibit identical $^{1}H$ nmr spectra; from MNDO calculations, 1,3-*trans*-isomers are energetically favored than the corresponding 1,3-*cis*-isomers by *ca.* 0.6 eV, irrespective of *p*-substituents (see Experimental Section). Further detailed examination by means of 2D nmr or other related techniques have thus far been unsuccessful, due to short lifetimes of the Bt-containing isoindoline derivatives.

**Mass Spectra.** In the electron ionization (EI) mode measurements, $M^{+}$'s have scarcely been found. In the fast atom bombardment (FAB) mode measurements using the ordinary *in-matrix* technique (a matrix solution of a sample is put on a target), $M^{+}$'s are not found either, and spectra themselves are not reproducible. It is attributed to the release of Bt-H from isoindolines in matrices (*m*-nitrobenzyl alcohol (MNBA), DMSO, ethylene glycol, *etc.*), which are proven as the rapid colorization of sample solutions.[9-11] When the *inverse-matrix* technique (a matrix is capsuled by a *sample* matrix, see Experimental Section) is used in FABms, all isolated isoindoline derivatives are found to exhibit their $M^{+}$'s with certain reproducibilities. Therefore, the inverse matrix technique possesses an advantage to elongate lifetimes of samples as isoindoline formats. In addition, fragment ions corresponding to $(M - BtH)^{+}$ and $(M - BtH - N_2)^{+}$ (trends of intensities of these fragment ions are inverse of those in EIms), characteristic of benzotriazole-containing compounds,[2,14] are observed to assure the original structures of Bt-substituted isoindolines.

Another remarkable feature of the spectra of isoindolines (**4**) is the presence of the fragment ions $(M - 220)^+$, which correspond to the structure of phthalimidines (**6**). These facts indicate the existence of the reversal reaction **4** → **3** induced by the attack of a water molecule, followed by the elimination of Bt-H from **3** to give **6**, which we have previously reported as a liquid phase reaction.[7] Water is expected to form from the dehydration of MNBA in the ion chamber of mass spectrometer, considering that the fragment ion of either m/z 154 (protonated MNBA) or m/z 136 (m/z 154 - $H_2O$) has often been observed as the base peak. Combining these results with other spectral data, a series of isoindolines are successfully proven as substituent isomers.

## CONCLUSION

In the preparation of isoindoline synthons possessing two reactive centers as aminals, after all, our new Method A (*o*-phthalaldehyde (**1**) : amine (**2**) : benzotriazole (Bt-H) = 1:1:3 in MeCN at room temperature for 8 h) is concluded as the only dependable strategy for the present, even though there has been a little success in the preparation of 2-alkylisoindolines (*e.g.*, **4Cc** and **4Ce**). In addition, a series of isoindolines (**4**) are identified through the cumulation of circumstantial evidences obtained from spectral measurements, including FABms data obtained with use of our new sample-sorting technique. On the whole, the first application of benzotriazole-assisted Mannich type condensation reaction to some practically useful materials is finely achieved. Further application of Bt-substituted reactive isoindolines are now underway in our laboratory.

## EXPERIMENTAL SECTION

**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. $^1H$ (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, benzotriazole ring; double prime, aryl substituent. 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. $CDCl_3$ in nmr measurements was purchased from ISOTEC through Nippon Oxygen Co. Ltd..[19]

**Typical Experimental Procedure in the Preparation of 2*H*-Isoindole Derivatives by the Benzotriazole-assisted Double Mannich Condensation Reaction. Preparation of 1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-methoxyphenyl)isoindoline (4Ac) in MeCN (Run 3; Method A).** To a solution of 1,2,3-1*H*-benzotriazole (Bt-H; 1.79 g, 15 mmol, 3 eq.) and *p*-anisidine (**2Ac**; 0.615 g, 5 mmol) in MeCN (30 ml) was added *o*-phthalaldehyde (**1**; 0.671 g, 5 mmol) portionwise at room temperature with stirring over 5 min. After the addition was complete, the mixture was further stirred at room temperature for 8 h. After the filtration of formed precipitates (sample A; white solid), MeCN was evaporated *in vacuo*, and the residue was triturated with $Et_2O$ (30 ml) for 30 min, then filtered (sample B; white solid). Filter cakes were successively washed with ice-cold $Et_2O$ and MeCN for several times, then dried *in vacuo* (samples weighed 0.287 g and 1.619 g, respectively). Based on the intensity ratio of Ar-O-C$\underline{H}_3$ signals in $^1$H nmr, dried crude material (1.906 g in total) proved to be an 87:13 mixture of isoindoline **4Ac** (1.716 g, 74.8%) and 2*H*-isoindole **5Ac** (0.190 g, 11.2%). This sample was further washed with MeCN to give analytically pure **4Ac** in >80% recovery. Similar procedures were used for all other Runs in Table 1, including a 24 h version of Run 10. Physical data of **4Ac** are as follows: beige powders, mp 123-124 °C (decomp.). Ir (KBr) *v* 1516, 1445, 1368, 1277, 1258, 1244, 1173, 1086, 1034, 828, 739 $cm^{-1}$. Elms (rel. intensities) m/z 340 ((M - BtH)$^+$, 5), 312 ((M - Bt - $N_2$)$^+$, 100), 297 (23), 281 (13), 268 (26), 254 (10), 224 (8), 196 (11), 178 (7), 140 (8), 119 (97). FABms (rel. intensities) m/z 462 ((M + 3)$^+$, 13), 459 (M$^+$, 6), 341 ((M - Bt)$^+$, 45), 312 ((M - BtH - $N_2$)$^+$, 100), 239 (M$^+$ of **6Ac**, 14). *Anal.* Calcd for $C_{27}H_{21}N_7O$: C, 70.57; H, 4.61; N, 21.34. Found: C, 70.27; H, 4.57; N, 21.30.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-methylphenyl)isoindoline (4Ad; Run 4; Method A).** Detailed preparation procedure has been reported previously.[8] Physical data of **4Ad** are as follows: white powders, mp 139.5-141 °C (decomp.). Ir (KBr) *v* 1522, 1372, 1323, 1275, 1240, 1186, 1130, 1109, 1090, 814, 770, 748, 737 $cm^{-1}$. Elms (rel. intensities) m/z 324 ((M - Bt)$^+$, 12), 295 ((M - Bt-$N_2$ -1)$^+$, 100), 281 (11), 268 (15), 254 (11), 205 (8), 180 (10), 140 (7), 119 (18). FABms (rel. intensities) m/z 446 ((M + 3)$^+$, 9), 443 (M$^+$, 9), 325 ((M - Bt)$^+$, 100), 296 ((M - BtH - $N_2$)$^+$,

99), 222 ((M - 1)+ of **6Ad**, 18). *Anal.* Calcd for $C_{27}H_{21}N_7$: C, 73.12; H, 4.77; N, 22.11. Found: C, 73.28; H, 4.77; N, 22.15.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-phenylisoindoline (4Ae; Run 5; Method A).** Determination of product distribution in crude sample was done by the intensity ratio between H-1 of **4Ae** and H-4 of **5Ae** (not isolated). MeCN-washed sample (with >80% recovery) was used for further data collections. Physical data of **4Ae** are as follows: beige powders, mp 133-139 °C (decomp.; lit.,[13] 158-160 °C). Ir (KBr) $\nu$ 3274, 1599, 1505, 1372, 1323, 1242, 1161, 1144, 1024, 750, 720 $cm^{-1}$. Elms (rel. intensities) m/z 429 ($M^+$, 0.4), 400 ((M - $N_2$ - 1)+, 0.8), 326 (3), 310 ((M - Bt)+, 1), 281 ((M - BtH - $N_2$ - 1)+, 8), 209 (62), 180 (100), 152 (10), 119 (68). FABms (rel. intensities) m/z 432 ((M + 3)+, 8), 429 ($M^+$, 3), 311 ((M - Bt)+, 47), 283 ((M - Bt - $N_2$)+, 34), 210 ((M + 1)+ of **6Ae**, 51). HRms (EI mode): Calcd for $C_{20}H_{14}N_4$ (M - BtH): 310.12184; Found: 310.12043. Calcd for $C_{20}H_{14}N_2$ (M - BtH - $N_2$): 282.11569; Found: 282.11542. $^1H$ Nmr spectral pattern of this compound is not at all analogous to that of **4Ae** reported previously.[13]

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-chlorophenyl)isoindoline (4Af; Run 6; Method A).** Analytically pure **4Af** was obtained as white powders after MeCN washing with >80% recovery, of which physical data are as follows: mp 124-126 °C (decomp.). Ir (KBr) $\nu$ 1501, 1370, 1323, 1275, 1237, 1109, 1090, 822, 770, 739 $cm^{-1}$. Elms (rel. intensities) m/z 344 ((M - BtH)+, 5), 315 ((M - BtH - $N_2$ -1)+, 83), 281 (37), 254 (16), 239 (9), 205 (10), 190 (4), 179 (10), 140 (10), 119 (100). FABms (rel. intensities) m/z 466 ((M + 3)+, 1), 465 ((M + 2)+, 6), 463 ($M^+$, 7), 345 ((M - Bt)+, 100), 316 ((M - BtH - $N_2$)+, 54), 242 ((M -1)+ of **6Af**, 28). *Anal.* Calcd for $C_{26}H_{18}N_7Cl$: C, 67.31; H, 3.91; N, 21.13. Found: C, 67.21; H, 3.89; 20.85.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-iodophenyl)isoindoline (4Ah; Run 8; Method A).** Analytically pure **4Ah** was obtained as white powders after MeCN washing with >80% recovery, of which physical data are as follows: mp 132-134 °C (decomp.). Ir (KBr) $\nu$ 1590, 1493, 1445, 1370, 1325, 1273, 1238, 1169, 1152, 1111, 1088, 814, 770, 739 $cm^{-1}$. Elms (rel. intensities) m/z 436 ((M - BtH)+, 5), 408 ((M - BtH - $N_2$)+, 100), 281 (73), 254 (30), 205 (23), 179 (20), 165 (10), 151 (16), 140 (26), 119 (88). FABms (rel. intensities) m/z 555 ($M^+$, 9), 437 ((M - Bt)+, 34),

408 ((M - BtH - $N_2$)$^+$, 39), 334 ((M - 1)$^+$ of **6Ah**, 17). *Anal.* Calcd for $C_{26}H_{18}N_7I$: C, 56.23; H, 3.27; N, 17.65. Found: C, 56.29; H, 3.19; N, 17.36.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-acetylphenyl)isoindoline (4Ai; Run 9; Method A).** Analytically pure **4Ai** was obtained as white powders with >80% recovery after MeCN washing, of which physical data are as follows: mp 170 °C (decomp.). Ir (KBr) $\nu$ 1676, 1597, 1518, 1368, 1323, 1267, 1237, 1186, 1154, 1088, 831, 812, 739 cm$^{-1}$. Elms (rel. intensities) m/z 352 ((M - BtH)$^+$, 12), 324 ((M - BtH - $N_2$)$^+$, 100), 309 (13), 281 (65), 254 (27), 236 (15), 223 (6), 208 (26), 179 (12), 152 (10), 119 (15). FABms (rel. intensities) m/z 471 (M$^+$, 5), 353 ((M - Bt)$^+$, 31), 325 ((M - Bt - $N_2$)$^+$, 9), 252 ((M + 1)$^+$ of **6Ai**, 6). *Anal.* Calcd for $C_{28}H_{21}N_7O$: C, 71.32; H, 4.49; N, 20.79. Found: C, 71.28; H, 4.52; N, 20.67.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-methoxycarbonylphenyl)isoindoline (4Aj; Run 10; Method A).** Detailed preparation procedure has been reported previously.[8] An 8 (or 24) h reaction using 3 eq. of Bt-H in MeCN gave crude **4Aj** containing trace amount of **5Aj** in 79.3% (or 91.3%) yield. Analytically pure **4Aj** was obtained as white powders after MeCN washing, of which physical data are as follows: mp 173-174 °C (decomp.). Ir (KBr) $\nu$ 1710, 1610, 1370, 1290, 735 cm$^{-1}$. Elms (rel. intensities) m/z 369 ((M - Bt)$^+$, 10), 341 ((M - Bt - $N_2$)$^+$, 100), 282 (30), 255 (15), 180 (10), 141 (11), 120 (20). FABms (rel. intensities) m/z 490 ((M + 3)$^+$, 3), 487 (M$^+$, 2), 369 ((M - Bt)$^+$, 27), 340 ((M - BtH - $N_2$)$^+$, 12), 266 ((M - 1)$^+$ of **6Aj**, 7). *Anal.* Calcd for $C_{28}H_{21}N_7O_2$: C, 68.98; H, 4.34; N, 20.11. Found: C, 69.08; H, 4.31; N, 20.40.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-nitrophenyl)isoindoline (4Ak; Run 11; Method A).** MeCN-washed sample (with >80% recovery) was used for further data collections. Physical data of **4Ak** are as follows: yellow powders, mp 142-145 °C (decomp.). Ir (KBr) $\nu$ 1597, 1507, 1372, 1321, 1275, 1157, 1113, 1082, 841, 808, 743 cm$^{-1}$. Elms (rel. intensities) m/z 355 ((M - BtH)$^+$, 2), 327 ((M - BtH - $N_2$)$^+$, 12), 280 (7), 254 (5), 225 (3), 140 (2), 119 (100). FABms (rel. intensities) m/z 474 (M$^+$, 5), 356 ((M - Bt)$^+$, 100), 328 ((M - Bt - $N_2$)$^+$, 13), 255 ((M + 1)$^+$ of **6Ak**, 10). HRms (EI mode): Calcd for $C_{20}H_{13}N_5O_2$ (M - BtH): 335.10692; Found: 335.10490. Calcd for $C_{20}H_{13}N_3O_2$ (M - BtH - $N_2$): 327.10077; Found: 327.09893.

**1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(*p*-(*N,N*-dimethylamino)phenyl)-2*H*-isoindole (5Ab; Run 2; Method A).** An 8 h reaction using 3 eq. of Bt-H gave crude product (**4Ab/5Ab/6Ab** = 12/73/15) in 77.0% yield, which was recrystallized from EtOH to give analytically pure **5Ab** in >80% recovery. Physical data of **5Ab** are as follows: golden yellow prisms, mp 168-171 °C (decomp.). $^1$H Nmr ($CDCl_3$) δ 8.09-8.07 (1H, m, H-4'), 7.68-7.65 (1H, m, H-7'), 7.47 (1H, s, H-3), 7.41-7.33 (2H, m, H-5' and 6'), 7.22-7.19 (1H, m, H-4), 7.16-7.02 (3H, m, H-5, 6, and 7), 7.09 (2H, d, $J$ = 9 Hz, H-2" and 6"), 6.48 (2H, d, $J$ = 9 Hz, H-3" and 5"), 2.87 (6H, s, $C\underline{H}_3$). $^{13}$C Nmr ($CDCl_3$) δ 150.1 (C-4"), 145.1 (C-1"), 135.8 (C-3'a), 128.3 (C-6'), 126.6 (C-7'a), 125.9 (C-6), 124.0 (C-5), 123.4 (C-5'), 122.7 (C-3a), 121.9 (C-4), 121.5 (C-1), 120.02, 119.97 (C-4' and 7), 116.9 (C-2"), 113.2 (C-3), 112.0 (C-3"), 111.6 (C-7a), 110.0 (C-7'), 40.2 ($N\underline{C}H_3$). Ir (KBr) $\nu$ 1611, 1524, 1445, 1362, 1352, 1337, 1231, 1210, 1042, 818, 748 cm$^{-1}$. Elms (rel. intensities) m/z 353 ($M^+$, 68), 326 (100), 325 ($(M - N_2)^+$, 53), 324 (34), 323 (94), 309 (33), 308 (54), 282 (29), 266 (31), 240 (15), 229 (25), 207 (93), 191 (62), 162 (95), 139 (29), 127 (38), 114 (15). *Anal.* Calcd for $C_{22}H_{19}N_5$: C, 74.77; H, 5.42; N, 19.82. Found: C, 74.87; H, 5.32; N, 19.77.

**1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(1-phenylmethyl)-2*H*-isoindole (5Ce; Run 15; Method A).** An 8 h reaction using 3 eq. of Bt-H in MeCN gave pure **5Ce** in 19.1% yield, which was subjected to elemental analysis immediately after washing with MeCN and drying *in vacuo*. Physical data of **5Ce** are as follows: pale-orange prisms, mp 154-155 °C (decomp.). $^1$H Nmr ($CDCl_3$) δ 8.13-8.11 (1H, m, H-4'), 7.64-7.61 (1H, m, H-7'), 7.37 (1H, s, H-3), 7.36-7.31 (2H, m, H-5' and 6'), 7.09-6.97 (7H, m), 6.87-6.84 (2H, m, H-3" and 5"), 5.25 (2H, d, $J$ = 4 Hz, benzylic H). $^{13}$C Nmr ($CDCl_3$) δ 145.1 (C-1"), 135.6, 135.2 (C-3'a and 7'a), 128.6 (C-3"), 128.3 (C-6'), 127.9 (C-4"), 127.2 (C-6), 124.2 (C-5), 123.3 (C-5'), 122.7 (C-3a), 121.7 (C-4), 120.7 (C-1), 120.09, 120.01 (C-4' and 7), 116.8 (C-2"), 112.4 (C-3), 111.6 (C-7a), 110.1 (C-7'), 51.9 (benzylic C). Ir (KBr) $\nu$ 3117, 3058, 3032, 1495, 1458, 1443, 1352, 1279, 1157, 1055, 764, 747, 702 cm$^{-1}$. Elms (rel. intensities) m/z 324 ($M^+$, 61), 295 ($(M - N_2 - 1)^+$, 95), 218 (34), 205 (42), 193 (100), 176 (20), 164 (33), 133 (20), 90 (12), 81 (27). *Anal.* Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.71; N, 4.97; N, 17.33.

**Preparation of 1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(4-methyl-2-pyridyl)isoindoline (4Bd) under Neat-heat Condition (Run 12; Method B).** A mixture of Bt-H (1.190 g, 10 mmol), 2-amino-4-picoline (**2Bd**; 0.540 g, 5 mmol), and **1** (0.670 g, 5 mmol) was heated at 120 °C for 15 min with stirring. After cooling, the reaction mixture was triturated with $Et_2O$ (10 ml) for 30 min, then filtered. Filter cakes were successively washed with ice-cold $Et_2O$ and MeCN for several times, then dried *in vacuo*. Based on the intensity ratio of PyC$\underline{H}_3$ signals in $^1$H nmr, dried crude material (1.327 g) proved to be an 86:14 mixture of isoindoline **4Bd** (1.186 g, 53.4%) and 2*H*-isoindole **5Bd** (0.141 g, 8.7%). This sample was further washed with MeCN to give analytically pure **4Bd** in >80% recovery. Physical data of **4Bd** are as follows: white powders, mp 209 °C (decomp.). Ir (KBr) $\nu$ 1611, 1485, 1443, 1410, 1360, 1316, 1275, 1235, 1109, 1088, 814, 743 cm$^{-1}$. Elms (rel. intensities) m/z 327 ((M - Bt + 1)$^+$, 88), 297 ((M - BtH - $N_2$)$^+$, 97), 271 (60), 205 (39), 191 (31), 110 (26). FABms (rel. intensities) m/z 444 (M$^+$, 3), 326 ((M - Bt)$^+$, 9), 298 ((M - Bt - $N_2$)$^+$, 8), 224 (M$^+$ of **6Bd**, 4). *Anal.* Calcd for $C_{26}H_{20}N_8$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.03; H, 4.52; N, 25.42.

**1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(2-pyridyl)isoindoline (4Be; Run 13; Method B).** MeCN-washed sample (with >80% recovery) was used for further data collections. Physical data of **4Be** are as follows: yellow powders, mp 208 °C (decomp.; lit.,[13] 217-218 °C). Ir (KBr) $\nu$ 1607, 1480, 1441, 1373, 1318, 1275, 1237, 1177, 1152, 1130, 1107, 1088, 928, 814, 772, 741 cm$^{-1}$. Elms (rel. intensities) m/z 411 (5), 370 (6), 343 (5), 316 (8), 312 ((M - Bt + 1)$^+$, 5), 284 ((M - Bt - $N_2$ + 1)$^+$, 23), 254 (24), 211 (20), 182 (11), 150 (17), 138 (16), 120 (33). FABms (rel. intensities) m/z 431 ((M + 1)$^+$, 7), 312 ((M - Bt)$^+$, 100), 284 ((M - Bt - $N_2$)$^+$, 18), 211 ((M + 1)$^+$ of **6Be**, 14). *Anal.* Calcd for $C_{25}H_{18}N_8$: C, 69.75; H, 4.21; N, 26.03. Found: C, 70.01; H, 3.85; N, 26.07. $^1$H Nmr spectral patterns of 2-(2-pyridyl) derivatives (**4Bd-e**) are not at all analogous to that of **4Be** reported previously.[13]

**1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(4-chlorophenyl)-2*H*-isoindole (5Af; Run 6; Method B).** MeCN-washed sample (with >80% recovery) was used for further data collections. Physical data of **5Af** are as follows: yellow powders, mp 184-186 °C (decomp.). $^1$H Nmr ($CDCl_3$) $\delta$ 8.14-8.08 (1H, m, H-4'), 7.70-7.64 (1H, m, H-7'), 7.50 (1H, s, H-3), 7.49-7.35 (2H, m, H-5' and 6'),

7.27-7.02 (4H, m, H-4, 5, 6, and 7), 7.24-7.16 (4H, m, H-2", 3", 5", and 6"). $^{13}C$ Nmr ($CDCl_3$) δ 145.0 (C-1"), 136.2 (C-7'a), 135.6 (C-4"), 134.5 (C-3'a), 129.5 (C-3"), 128.7 (C-6'), 126.4 (C-6), 124.4 (C-5), 124.1 (C-5'), 123.2 (C-3a), 122.6 (C-4), 121.8 (C-1), 120.3, 120.1 (C-4' and 7), 117.0 (C-2"), 113.0 (C-3), 111.6 (C-7a), 109.7 (C-7'). Ir (KBr) *v* 1593, 1493, 1410, 1379, 1337, 1281, 1235, 1206, 1179, 1121, 1092, 1038, 837, 750 $cm^{-1}$. Elms (rel. intensities) m/z 347 ($(M + 2)^+$, 5), 345 ($M^+$, 14), 319 ($(M + 2 - N_2)^+$, 57), 317 ($M - N_2)^+$, 100), 282 (80), 255 (37), 240 (14), 215 (11), 206 (22), 180 (24), 153 (29), 141 (52), 127 (22), 111 (51), 103 (8). *Anal.* Calcd for $C_{20}H_{13}N_4Cl$: C, 69.67; H, 3.80; N, 16.25. Found: C, 69.74; H, 3.41; N, 16.28.

**Preparation of 1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(*p*-bromophenyl)isoindoline (4Ag) in $Et_2O$ (Run 7; Method C[11]).** To a solution of Bt-H (1.190 g, 10 mmol) and *p*-bromoaniline (**2Ag**; 0.860 g, 5 mmol) in $Et_2O$ (30 ml) was added **1** (0.670 g, 5 mmol) portionwise over 5 min with stirring at room temperature. The reaction was slightly exothermic, and from the resulting yellow solution, white solid began to precipitate in 5 h. The whole mixture was stirred overnight at room temperature in order to terminate the precipitation. The resulting solid was filtered, washed with ice-cold $Et_2O$, then dried *in vacuo* to give **4Ag** as a sole product (white solid, 1.430 g, 55.9%; mp 152-155 °C (decomp.)). $Et_2O$-triturated sample (>80% recovery) was used for combustion analysis (mp unaltered). On the other hand, **4Ag** obtained in MeCN (Method A) showed mp 127-128 °C, however, the spectra of which were identical with those of the one obtained above. Physical data of **4Ag** are as follows: Ir (KBr) *v* 1593, 1499, 1447, 1368, 1323, 1275, 1238, 1167, 1152, 1111, 1084, 928, 816, 770, 739 $cm^{-1}$. Elms (rel. intensities) m/z 388 ($(M - BtH)^+$, 13), 361 ($(M - Bt - N_2)^+$, 100), 332 (12), 281 (84), 254 (33), 205 (23), 190 (12), 179 (21), 152 (21), 140 (28), 119 (36), 102 (10). FABms (rel. intensities) m/z 509 ($(M + 2)^+$, 10), 507 ($M^+$, 15), 389 ((M - Bt, 88), 361 ($(M - Bt - N_2)^+$, 53), 289 ($(M + 2)^+$ of **6Ag**, 31), 288 ($(M + 1)^+$ of **6Ag**, 21). *Anal.* Calcd for $C_{26}H_{18}N_7Br$: C, 61.43; H, 3.57; N, 19.29. Found: C, 61.39; H, 3.41; N, 18.97.

The following compounds possessing 2-(*p*-methylphenyl) substituents are also prepared, in order for the ease in determining product distribution patterns based on $^1H$ nmr spectra of this work.

**Preparation of 1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(*p*-methylphenyl)-2*H*-isoindole (5Ad).** A 168 h version of "Method A" reaction using 2 eq. of Bt-H gives crude product (**4Ad/5Ad** = <1/99) in 72.3% yield, which was recrystallized from EtOH to give analytically pure **5Ad** in >80% recovery.[8] Physical data of **5Ad** are as follows: pale-orange prisms, mp 164-166 °C (decomp.). $^1$H Nmr ($CDCl_3$) δ 8.10-8.07 (1H, m, H-4'), 7.70-7.66 (1H, m, H-7'), 7.50 (1H, s, H-3), 7.44-7.34 (2H, m, H-5' and 6'), 7.23-7.01 (8H, m), 2.25 (3H, s, $C\underline{H}_3$). $^{13}$C Nmr ($CDCl_3$) δ 145.0 (C-1"), 138.5 (C-7'a), 135.7 (C-4"), 135.3 (C-3'a), 129.8 (C-3"), 128.4 (C-6'), 124.9 (C-6), 124.2 (C-5), 123.7 (C-5'), 123.0 (C-3a), 122.2 (C-4), 121.7 (C-1), 120.14, 120.08 (C-4' and 7), 117.0 (C-2"), 113.1 (C-3), 111.6 (C-7a), 109.9 (C-7'), 20.9 ($\underline{C}H_3$). Ir (KBr) ν 3123, 3063, 2917, 1514, 1493, 1443, 1414, 1379, 1337, 1281, 1235, 1206, 1183, 1117, 1040, 820, 766, 748 cm$^{-1}$. Elms (rel. intensities) m/z 324 ($M^+$, 2), 296 ($(M - N_2)^+$, 100), 295 (99), 281 (31), 268 (46), 254 (30), 205 (15), 194 (13), 180 (26), 165 (15), 152 (18), 140 (15), 127 (9). *Anal.* Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.91; H, 4.99; N, 17.54.

**Preparation of 2-(*p*-Methylphenyl)phthalimidine (6Ad).[20]** A solution of **1** (0.500 g, 4 mmol) and *p*-toluidine (**2Ad**; 0.399 g, 4 mmol) in $Et_2O$ (10 ml) was stirred for 19 h at room temperature. The resulting solid was collected and subjected to column chromatography (silica gel; eluted with $C_6H_6$-EtOAc = 10:1) to give crude **6Ad** (0.155 g, 18.6%, mp 162-185 °C). Repeated recrystallizations of this sample from $C_6H_6$ gave pure **6Ad**. Physical data of **6Ad** are as follows: white thin needles, mp 140-141 °C (lit.,[20] 139-140 °C).

**Preparation of 2-((*N*-(*p*-methylphenyl)amino)methyl)benzenemethanol (7Ad) and 2-(*p*-methylphenyl)isoindoline (8Ad).[11,15]** To a solution of Bt-H (1.190 g, 10 mmol, 2 eq.) and *p*-toluidine (**2Ad**; 0.535 g, 5 mmol) in $Et_2O$ (30 ml) was added *o*-phthalaldehyde (**1**; 0.671 g, 5 mmol) portionwise at room temperature with stirring over 5 min. After the addition was complete, the mixture was further stirred at room temperature for 24 h. Precipitates were filtered and dried *in vacuo* to give the crude product as a white solid (0.991 g), which was immediately subjected to the following hydride reduction without further purification (from $^1$H nmr spectrum of this sample, **5Ad** was not detected). To a solution of the crude product obtained above (0.900 g) in THF (30 ml) was added $NaBH_4$ (0.27 g, 7 mmol) portionwise over 10 min, and the mixture was stirred at room

temperature for 2 days. After then, further amount of $NaBH_4$ (0.12 g, 3 mmol) was added, and the mixture was heated at reflux for 1.5 h. After cooling to room temperature, THF was evaporated, ice-cold water (30 ml) was added, and then the mixture was stirred at room temperature for overnight. The reaction mixture was extracted with $Et_2O$ for several times, and the combined organic extracts were washed with water, then dried over *anhyd.* $K_2CO_3$. Filtration followed by evaporation *in vacuo* gave the crude product as a white solid (0.506 g). Purification by column chromatography (silica gel; eluted with $C_6H_6$-EtOAc = 15:1) gave successively isoindoline (**8Ad**; white solid, 0.113 g, 11.9%, mp 175-181 °C) and benzenemethanol (**7Ad**; 0.310 g, 30.1%, mp 98-99 °C). Physical data are as follows.

**Compound 7Ad:** mp 98-99 °C (white needles from *n*-hexane). $^1$H Nmr ($CDCl_3$) δ 7.42-7.30 (4H, m, H-3, 4, 5, and 6), 7.04 (2H, d, *J* = 8 Hz, H-3" and 5"), 6.69 (2H, d, *J* = 8 Hz, H-2" and 6"), 4.72 (2H, s, C$\underline{H}_2$O), 4.33 (2H, s, C$\underline{H}_2$N), 3.66 (1H, bs, O$\underline{H}$ or N$\underline{H}$), 2.26 (3H, s, C$\underline{H}_3$). $^{13}$C Nmr ($CDCl_3$) δ 145.3 (C-1"), 140.1 (C-1), 137.3 (C-2), 129.9, 129.6 (C-3 and 6), 129.8 (C-3"), 128.8 (C-4"), 128.4, 128.3 (C-4 and 5), 114.7 (C-2"), 64.0 ($\underline{C}H_2$O), 48.2 ($\underline{C}H_2$N), 20.5 ($\underline{C}H_3$). Ir (KBr) *ν* 3237, 3065, 3027, 2967, 2909, 2863, 1520, 1005, 818, 741 cm$^{-1}$. Elms (rel. intensities) m/z 227 ($M^+$, 36), 208 (22), 120 (38), 108 (100). *Anal.* Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.28; H, 7.53; N, 6.19.

**Compound 8Ad:** mp 184-187 °C (white leaflets from EtOH; lit.,[21] 195 °C).

**FABms Measurements by the Inverse-Matrix Technique.** In measurements of FABms, *m*-nitrobenzyl alcohol (MNBA) was used as a matrix, which was put on a target (8 mm x 1 mm) as far as its surface tension allowed. Then an appropriate sample was immersed on it as much as possible, so as to adsorb the matrix in. The result of this sample-sorting is that an appropriate amount of a matrix is capsuled by a *sample-matrix*, which we name *inverse-matrix*, instead of a matrix solution of a sample (*in-matrix*). The gas for the fast atom gun is argon. The energy of the fast atoms is 4 keV and the tube current is 20 mA. It often happened either m/z 154 (protonated MNBA) or m/z 136 (m/z 154 - $H_2O$) to be found as base peaks.

**MNDO Calculations.** The MNDO calculations of 2-phenylisoindoline derivatives (**4A**) were made using the AMPAC-MNDO program by Dewar and collaborators.[22] All geometric parameters

(bond lengths, bond angles, and dihedral angles) were optimized without any specific assumptions. Results (total energies in eV) are as follows: 1,3-*trans*-**4Ad**, -5192.91518; 1,3-*cis*-**4Ad**, -5192.30431; 1,3-*trans*-**4Ae**, -5036.38529; 1,3-*cis*-**4Ae**, -5035.77193; 1,3-*trans*-**4Af**, -5376.88270; 1,3-*cis*-**4Af**, -5376.28337; 1,3-*trans*-**4Ak**, -5869.69831; 1,3-*cis*-**4Ak**, -5869.15854.

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phthalimides (δ 2.41 for 4-methyl) have never been found. Studies on the preparation of phthalimidines (**6**) will appear as a separate paper in a near future.

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