

STUDIES ON THE DOUBLE MANNICH CONDENSATION
REACTION OF *o*-PHTHALALDEHYDE WITH *p*-SUBSTITUTED
ANILINES IN THE PRESENCE OF 1,2,3-1*H*-BENZOTRIAZOLE¹

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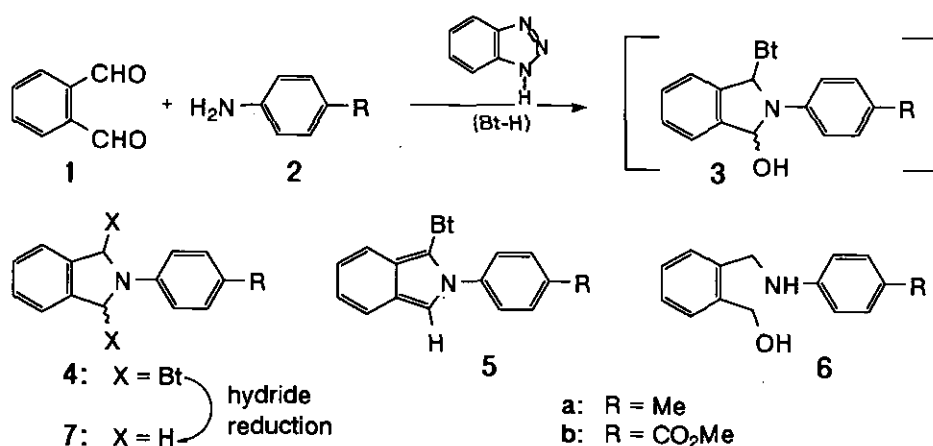
Abstract - The double Mannich condensation reaction in acetonitrile at room temperature has been investigated. In the condensation reaction of *o*-phthalaldehyde (1) with *p*-toluidine (2a; 1 equiv.) in the presence of 1,2,3-1*H*-benzotriazole (Bt-H), the use of 3 equiv. of Bt-H afforded Bt-substituted isoindoline derivative (4a) exclusively for 8 h, and the use of 4 equiv. of Bt-H did for 4 h; further increment of reaction time induced the dissociation of Bt-H from 4a to give 2*H*-isoindole derivative (5a). On the other hand, when methyl *p*-aminobenzoate (2b) was used instead of 2a, the rate of the formation of isoindoline (4b) increased as the amount used of Bt-H was large (2 → 3 → 4 equiv.). Different from the 2-(*p*-tolyl) counterpart, the increment of the reaction time did not induce the dissociation of Bt-H to afford 2*H*-isoindole derivative (5b).

The utility of 1,2,3-1*H*-benzotriazole (Bt-H) as the synthetic auxiliary to Mannich type condensation

This paper is dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

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 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 However, past research works were limited to the uses of monoaldehydes as substrates, and were done but without the aim of constructing practically useful materials.

Focusing on this point, we came to investigate on the "double" Mannich type condensation reaction of *o*-phthalaldehyde (a representative dialdehyde) with amines in the presence of $Bt-H$ to form Bt -substituted isoindoline (dihydroisoindole) derivatives, of which skeletons have been evaluated as the antihypertensives/antihyperglycemics³ and as the unit compounds for electrically conductive polymers.⁴ Our preliminary experiments showed that 2-anilinomethylbenzyl alcohols (**6**) and 2-arylisoindolines (**7**) were obtained from the products by reactions of *o*-phthalaldehyde (**1**) with anilines (**2**; 1 equiv.) in the presence of $Bt-H$ (2 equiv.) in ether, upon a hydride reduction with $NaBH_4$ (Scheme 1).^{5,6} The precursors assumed were 1-benzotriazolyl-3-hydroxy- (**3**) and 1,3-bis(benzotriazolyl)isoindolines (**4**). Compounds **6** have been prepared from phthalide but in a multi-step procedure.⁷ Meanwhile, compounds **4** are expected to be the versatile intermediates to 1,3-disubstituted (or unsubstituted) isoindolines and 2*H*-isoindoles, the latter of which are the important reaction intermediates equivalent to isobenzofurans.⁸



Scheme 1

It is desirable to find out some strategy to produce some two useful independent species from a single reaction system. Our further study using acetonitrile as reaction solvent proved, different from preliminary runs in ether, that Bt-substituted compounds obtained were **4** and 1-benzotriazolyl-2*H*-isoindoles (**5**), but none of **3**.⁶ In this paper, we wish to report on the distribution and its dependency of the products to reaction time and amount (equiv.) of Bt-H, from the reaction system of **1** with *p*-toluidine (**2a**; R = Me) or methyl *p*-aminobenzoate (**2b**; R = CO₂Me) in acetonitrile.

We adopted the following reaction/work-up procedure in order to eliminate the concomitant polymeric materials (red oil). Thus, *o*-phthalaldehyde (**1**) was added portionwise to a solution of aniline (**2a(b)**; 1 equiv.) and benzotriazole (appropriate amount) in acetonitrile, and the mixture was stirred for appropriate reaction time at room temperature. After the filtration of precipitates (if any; sample A), the filtrate was evaporated and the residue was triturated with ether to give another crop of precipitates (sample B). Similar treatments were repeated until no more precipitates were formed. Amounts of **4a(b)** and **5a(b)** in mixtures were each determined by ¹H nmr spectra, which were summed to give a product distribution data of a single entry. In general, the first precipitates were formed for *ca.* 12 h, and therefore, the reaction system underwent heterogeneous afterwards. For this reason, the product distribution data were obtained from a series of independent experiments. These data are plotted along reaction time in Figure 1 (a) through (f).

The following tendencies were observed as to this reaction system when *p*-toluidine (**2a**; R = Me) was used as aniline.

(i) When 2 equiv. of Bt-H was used (a), **4a** showed a maximum (48% yield) for 4 h, a small maximum (30% yield) for 48 h, and then gradually decreased afterwards to reach 0% yield for 336 h (2 weeks). On the other hand, **5a** gradually increased from the beginning, and reached constant (~40% yield) after 96 h.

(ii) When 3 equiv. of Bt-H was used (b), **4a** was formed in 83% yield for 8 h, and gradually fell off afterwards. On the contrary, **5a** gradually rose from the beginning. Amounts of both **4a** and **5a** reached almost constant (~50% and 20% yields, respectively) after 48 h. Furthermore, **4a** exhibited a sharp minimum (42% yield for 13.5 h) and **5a** did a sharp maximum (14% yield for 12 h). These

facts may possibly be effected by the "coalescent" reaction mixtures, which were about to precipitate.

(iii) When 4 equiv. of Bt-H was used (c), **4a** was formed in 88% yield for 4 h, and rapidly decreased afterwards. On the contrary, **5a** rapidly increased from the beginning. As the results, both graphs clearly intersect between 24 h and 48 h.

(iv) When 10 equiv. of Bt-H was used (not plotted), the product distribution for 8 h was **4a**(%)/**5a**(%) = 83/10, indicating the similar composition to those in (ii) and (iii). When 1 equiv. of Bt-H was used (not plotted), the reaction did not take place at all.

From these results, the excessive amount of Bt-H over stoichiometry (2 equiv.) appeared to be important. It promoted the formation of **4a** in the beginning, and then did the dissociation of Bt-H to afford **5a**. Considering that Bt-H dissociated the proton at neutral *pH* region ($pK_a \sim 8$),² Bt-H worked as a mild base catalyst, and probably also as a surfactant, which decreased the nucleophilicity of water molecules (from the condensation reaction) to avoid the reaction in reverse.⁹ When 3 equiv. of Bt-H was used, excess 1 equiv. of Bt-H appeared to be intact as the promotor of dissociation; Bt-H may be "bound" to 2 equiv. of water. As the results, pure **4a** was readily available from the products from 8 h reaction using 3 equiv. of Bt-H or 4 h reaction using 4 equiv. of Bt-H, through a simple washing with acetonitrile (>85% recovery).

In turn, the following tendencies were observed as to this reaction system when methyl *p*-amino-benzoate (**2b**; R = CO₂Me) was used as aniline.

(v) When 2 equiv. of Bt-H was used (d), **4b** gradually increased from the beginning to reach 77% yield for 168 h.

(vi) When 3 equiv. of Bt-H was used (e), **4b** was formed in 84% yield for 20 h, and gradually decreased afterwards (72% for 168 h). In addition, yield of **4b** showed sharp minima (28% for 6 h and 65% for 16 h). The latter facts, observed also in (ii), may possibly be effected by the "coalescent" reaction mixtures, which were about to precipitate. The rate of the formation of **4b** was larger than in (v).

(vii) When 4 equiv. of Bt-H was used (f), **4b** was formed in 89% yield for 16 h, and remained constant afterwards (92% for 168 h). Different from (vi), a zigzag in yields was not found.

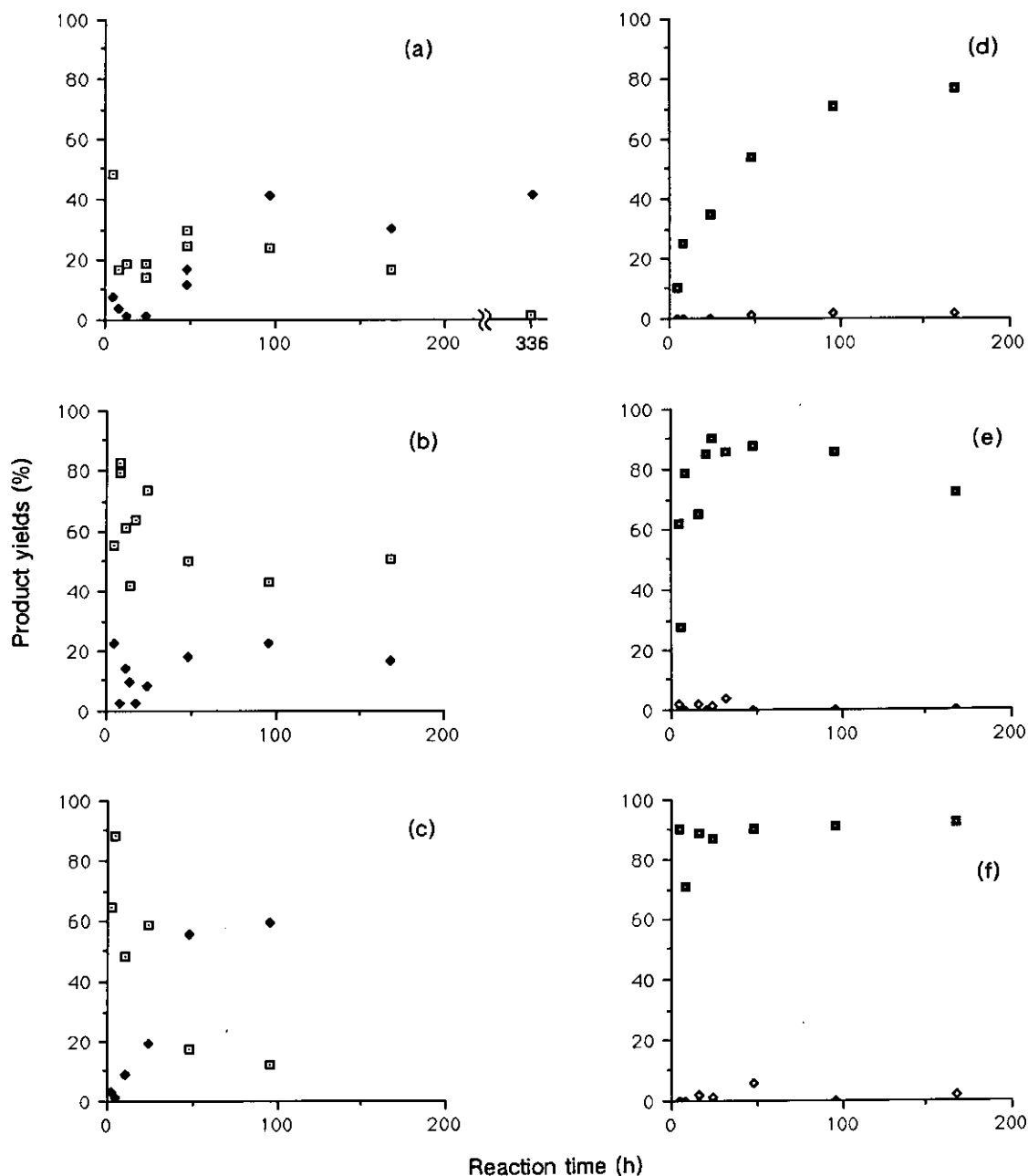


Figure 1. Time dependency of the product distribution in the condensation reaction of *o*-phthalaldehyde (1) with *p*-substituted anilines (2a-b) in the presence of Bt-H.

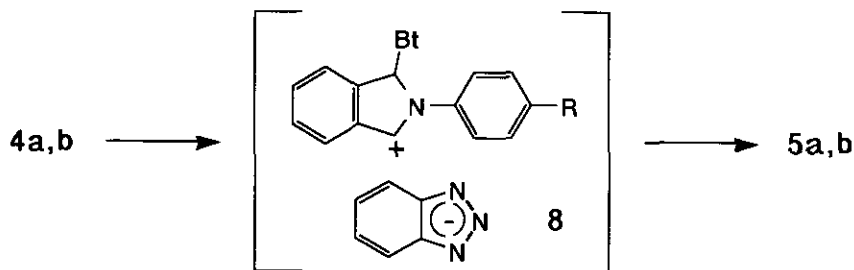
Yields of isoindolines (4a, □; 4b, ■) and 2H-isoindoles (5a, ◆; 5b, ●) depending on reaction times. *p*-Substituted anilines and equiv. of Bt-H are as follows: *p*-toluidine (2a), 2 equiv. (a); 2a, 3 equiv. (b); 2a, 4 equiv. (c); methyl *p*-aminobenzoate (2b), 2 equiv. (d); 2b, 3 equiv. (e); 2b, 4 equiv. (f).

(viii) The formation of **4b** appeared to follow a typical kinetic saturation curve having a maximum of ~80% (d) or ~90% (e and f) yield.

(ix) Throughout all entries examined, **5b** could often be detected, but in trace amounts.

Here again, from these results, the excessive amount of Bt-H over stoichiometry was found to be important. Bt-H worked as a mild base catalyst to promote the formation of **4b**. However, different from the system using *p*-toluidine (**2a**; R = Me) as aniline, Bt-H did not appear to promote the formation of **5b** out of **4b**. As the results, pure **4b** was available from almost all entries through a simple washing with acetonitrile (>85% recovery).

Our working hypothesis of this point on the formation of 2*H*-isoindoles (**5**) from isoindolines (**4**) is as follows. Whenever Bt-substituted mixed aminals (**4** is the one) are about to react, they are expected to exist in the character of the ion-pair (**8**) to a certain extent,² as shown in Scheme 2. In other words, in our reaction system, Bt-H is eliminated from the intermediate **8** to form 2*H*-isoindole (**5**). The presence of electron-withdrawing substituent (R = CO₂Me in **b**; $\sigma_p = +0.52$) more destabilizes the cation species than that of electron-donating substituent (R = Me in **a**; $\sigma_p = -0.17$). Therefore, **4b** is better to possess the character of covalently-bonded **4** rather than the ion-pair (**8**).



Scheme 2

In conclusion, we have described the investigation on the double Mannich condensation reaction of *o*-phthalaldehyde with *p*-substituted anilines (**2**; 1 equiv.) in the presence of 1,2,3-1*H*-benzotriazole (Bt-H) in acetonitrile at room temperature. As the results, pure 1,3-bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-substituted phenyl)isoindolines (**4**) are found to be available from compound **4**-rich samples through a simple washing with acetonitrile in good recovery yields. On the contrary, pure 1-(1,2,3-

1*H*-benzotriazol-1-yl)-2-(*p*-tolyl)-2*H*-isoindole (**5a**) is available arbitrarily but without convenience (336 h reaction using 2 equiv. of Bt-H). Obtention of the corresponding 2-(*p*-methoxycarbonylphenyl) counterpart (**5b**) remains to be seen. Further exploitation on this series of reaction system is now in progress in our laboratory.

EXPERIMENTAL SECTION

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 and ¹³C Nuclear magnetic resonance (nmr) spectral measurements were carried out with a JEOL JNM-GX200 Fourier transform nmr spectrometer (270 MHz). All signals are expressed as ppm downfield from tetramethylsilane (TMS) used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), multiplet (m). Positional numbers are assembled as follows: no prime, isoindole ring; single prime, benzotriazole ring; double prime, phenyl substituent. Mass spectra (ms; mode: EI and FAB) were taken with a JEOL JMS-DX300 mass spectrometer. In measurements of FABms, *m*-nitrobenzyl alcohol (MNBA) was used as a matrix. Chloroform-*d* in nmr measurements was purchased from ISOTEC through Nippon Oxygen Co. Ltd.¹⁰

1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-tolyl)isoindoline (4a). To a solution of 1,2,3-1*H*-benzotriazole (1.79 g, 15.0 mmol) and *p*-toluidine (**2a**; 0.535 g, 5.0 mmol) in acetonitrile (30 ml) was added *o*-phthalaldehyde (**1**; 0.671 g, 5.0 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. Acetonitrile was evaporated *in vacuo*, and the residue was triturated with ether (30 ml) for 30 min, then filtered. Filter cakes were successively washed with ether and acetonitrile for several times, then dried *in vacuo*. Based on the intensity ratio of Ar-CH₃ signals in ¹H nmr, dried crude material (white solid, 1.878 g) proved to be a 97:3 mixture of isoindoline **4a** (1.836 g, 82.8%) and 2*H*-isoindole **4b** (0.042 g, 2.6%; 85.4% yield in total). This sample was further washed with acetonitrile to give analytically pure **4a** in >80% yield. Physical data of **4a** are as follows: white powder, mp 139.5-141 °C (decomp.). ¹H Nmr (CDCl₃) δ 8.43 (2H, s, H-1 and H-3), 8.02-7.99 (2H,

m, H-4'), 7.50-7.40 (4H, m, H-5' and H-6'), 7.32-7.22 (4H, m, H-4, 5, 6, and 7), 7.02 (2H, $J = 9$ Hz, H-2" and 6"), 6.90-6.87 (2H, m, H-7'), 6.82 (2H, d, $J = 9$ Hz, H-3" and 5"), 2.02 (3H, s, CH_3). ^{13}C Nmr (CDCl_3) δ 146.8 (C-1'), 136.8 (C-7'a), 135.5 (C-3a and 3'a), 131.2 (C-4), 130.3 (C-4'), 129.9 (C-3"), 128.0 (C-6'), 124.2 (C-5), 123.6 (C-5'), 120.3 (C-4'), 115.1 (C-2"), 109.5 (C-7'), 76.8 (C-1), 20.3 (CH_3). Ir (KBr) ν 1522 cm^{-1} . Elms m/z (rel. intensities) 324 ($M^+ - \text{Bt}$, 12), 295 ($M^+ - \text{Bt} - \text{N}_2 - 1$, 100), 281 (11), 268 (15), 254 (11), 205 (8), 180 (10), 140 (7), 119 (18), 91 (28), 76 (7), 65 (16). FABms m/z (rel. intensities) 446 ($M^{++} + 3$, 9), 443 (M^+ , 9), 325 ($M^+ - \text{Bt} + 1$, 100), 296 ($M^+ - \text{Bt} - \text{N}_2$, 99). *Anal.* Calcd for $\text{C}_{27}\text{H}_{21}\text{N}_7$: C, 73.12; H, 4.77; N, 22.11. Found: C, 73.28; H, 4.77; N, 22.15. ^1H Nmr spectral pattern of **4a** is not at all analogous to that of 2-phenyl derivative reported previously.¹¹

1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(*p*-tolyl)isoindole (5a). A 336 h reaction with 2 equiv. of Bt-H gave crude product (**4a**/**5a** = 4/96) in 43.2% yield, which was recrystallized from EtOH to give analytically pure **5a** in >30% yield. Physical data of **5a** are as follows: pale-orange prisms, mp 164-166 °C (decomp.). ^1H 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, CH_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', C-7), 117.0 (C-2"), 113.1 (C-3), 111.6 (C-7a), 109.9 (C-7'), 20.9 (CH_3). Ir (KBr) ν 3123, 3063, 2917, 1514, 1493 cm^{-1} . Elms m/z (rel. intensities) 324 (M^+ , 2), 296 ($M^+ - \text{N}_2$, 100), 295 ($M^+ - \text{N}_2 - 1$, 99), 281 (31), 268 (46), 254 (30), 205 (15), 194 (13), 180 (26), 165 (15), 152 (18), 140 (15), 127 (9), 91 (36), 77 (10), 65 (31), 51 (9). *Anal.* Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.91; H, 4.99; N, 17.54.

1,3-Bis(1,2,3-1*H*-benzotriazol-1-yl)-2-(*p*-methoxycarbonylphenyl)isoindoline (4b). To a solution of 1,2,3-1*H*-benzotriazole (1.79 g, 15.0 mmol) and methyl *p*-aminobenzoate (**2b**; 0.755 g, 5.0 mmol) in acetonitrile (30 ml) was added *o*-phthalaldehyde (**1**; 0.671 g, 5.0 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. Precipitates were filtered, washed with ice-

cooled acetonitrile, then dried *in vacuo* (sample A; white solid, 0.715 g). The filtrate was evaporated *in vacuo*, and the residue was triturated with ether (10 ml) for 30 min, then filtered. Filter cakes were successively washed with ether and acetonitrile for several times, then dried *in vacuo* (sample B; white solid, 1.207 g). Both samples proved to be isoindoline (**4b**) from ^1H Nmr (78.9% yield in total). The combined samples were further washed with acetonitrile to give analytically pure **4b** in >70% yield. Physical data of **4b** are as follows: white powder, mp 173-174 °C (decomp.). ^1H Nmr (CDCl_3) δ 8.49 (2H, s, H-1 and 3), 8.04-8.00 (2H, m, H-4'), 7.70 (2H, d, $J = 9$ Hz, H-2' and 6'), 7.51-7.42 (4H, m, H-5' and 6'), 7.31-7.27 (4H, m, H-4, 5, 6, and 7), 7.16 (2H, d, $J = 9$ Hz, H-3' and 5'), 6.89-6.85 (2H, m, H-7'), 3.72 (3H, s, CO_2CH_3). ^{13}C Nmr (CDCl_3) δ 166.4 ($\text{C}=\text{O}$), 146.9 ($\text{C}-1'$), 143.3 ($\text{C}-7'a$), 134.8 ($\text{C}-3a$ and $3'a$), 131.6 ($\text{C}-3''$), 131.2 ($\text{C}-4$), 128.3 ($\text{C}-6'$), 124.5 ($\text{C}-5$), 123.8 ($\text{C}-5'$), 122.6 ($\text{C}-4'$), 120.6 ($\text{C}-4''$), 114.3 ($\text{C}-2''$), 109.1 ($\text{C}-7'$), 76.5 ($\text{C}-1$), 51.7 (CH_3). Ir (KBr) ν 1710, 1610 cm^{-1} . Elms m/z (rel. intensities) 368 ($M^+ - \text{Bt}$, 10), 340 ($M^+ - \text{Bt} - \text{N}_2$, 100), 282 (30), 255 (15), 180 (10), 141 (11), 120 (20), 92 (14), 64 (10). FABms m/z (rel. intensities) 490 ($M^{++} + 3$, 3), 487 (M^+ , 2), 369 ($M^+ - \text{Bt} + 1$, 27), 340 ($M^+ - \text{Bt} - \text{N}_2$, 12). Anal. Calcd for $\text{C}_{28}\text{H}_{21}\text{N}_7\text{O}_2$: C, 68.98; H, 4.34; N, 20.11. Found: C, 69.08; H, 4.31; N, 20.40.

If 2*H*-isoindole (**5b**) is present, amounts of compounds (**4b/5b**) were determined by relative intensities of $-\text{CO}_2\text{CH}_3$ signals in ^1H Nmr; 3.72 ppm in **4b** and 3.87 ppm in **5b**. The latter value was obtained from a sample of **4b** (minor) + **5b** (major), which was available through the treatment of a sample of **4b** (major) + **5b** (minor) with boiling EtOH.

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