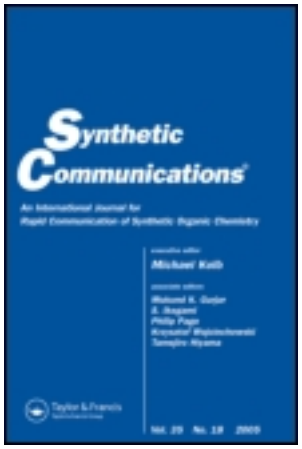

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Mild and Efficient Syntheses of 1-Aryl-3,4-dihydroisoquinolines and 1-Aryl-3,4-dihydro-β-carbolines via Regiospecific β-Eliminations of the Corresponding N-Tosyl-1,2,3,4-tetrahydroisoquinolines and N-Tosyl-1,2,3,4-tetrahydro-β-carbolines

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MILD AND EFFICIENT SYNTHESES OF 1-ARYL-3,4-DIHYDROISOQUINOLINES AND 1-ARYL-3,4-DIHYDRO-β-CARBOLINES VIA REGIOSPECIFIC β-ELIMINATIONS OF THE CORRESPONDING *N*-TOSYL-1,2,3,4-TETRAHYDROISOQUINOLINES AND *N*-TOSYL-1,2,3,4-TETRAHYDRO-β-CARBOLINES

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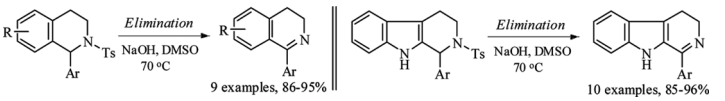
Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *Treatment of* N*-tosyl-1-aryl-1,2,3,4-tetrahydro-isoquinolines or* N*-tosyl-1-aryl-1,2,3,4-tetrahydro-*β*-carbolines with a strong base such as NaOH or KOH at 70 °C in dimethylsulfoxide (DMSO) produced 1-aryl-3,4-dihydroisoquinolines or 1-aryl-3,4-dihydro-*β*-carbolines in good yields via mild and regiospecific* β*-eliminations. A dramatic solvent effect was observed, DMSO was crucial for the reactions. The temperature is also crucial for the reactions and should be kept between 60 and 80 °C.*

Keywords 3,4-Dihydro-*β*-carboline; 3,4-dihydroisoquinoline; synthesis; 1,2,3,4-tetrahydro-*β*-carboline; 1,2,3,4-tetrahydroisoquinoline

INTRODUCTION

1-Substituted 3,4-dihydroisoquinolines (3,4-DHIQs) and 3,4-dihydro-β-carbolines (3,4-DHBCs) are important compounds because they not only have exhibited various biological activities[1,2] but also can be reduced to produce 1-substituted 1,2,3,4-tetrahydroisoquinolines (THIQs)[3] and 1,2,3,4-tetrahydro-β-carbolines (THBCs)[3c–3e,4] or oxidized to afford fully aromatized 1-substituted isoquinolines[1b,1c,5] and β-carbolines.[6]

1-Substituted 3,4-DHIQs and 3,4-DHBCs normally can be obtained via Bischler–Napieralski cyclization of *N*-2-aryl/indolyl ethyl amides[7] or the oxidation

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of 1-substituted THIQs and THBCs.[8] However, Bischler–Napieralski cyclization may suffer from poor yields and use of hazardous,[7b] toxic,[7d] strongly acidic,[7e] or expensive[7f] reagents, whereas the oxidation of 1-substituted THIQs and THBCs needs strong oxidants that may lead to overoxidation.[8b,8c] Therefore, mild and efficient methods for the syntheses of 1-substituted 3,4-DHIQs and 3,4-DHBCs should be highly desirable. Herein we report a novel method for the syntheses of 1-substituted 3,4-DHIQs and 3,4-DHBCs via regiospecific β-eliminations of the readily available 1-substituted *N*-tosyl-THIQs and *N*-tosyl-THBCs.

RESULTS AND DISCUSSION

1-Substituted *N*-tosyl-THIQs **1** were directly obtained from *N*-sulfonyl Pictet–Spengler reaction[9] of *N*-2-arylethyl *p*-toluenesulfonamides with aldehydes. 1-Substituted *N*-tosyl-THBCs **2** were obtained in a two-step fashion: Pictet–Spengler reaction of tryptamine hydrochloride with aldehydes[10] first gave 1-substituted THBCs, which were then transformed into the compound **2** in almost quantitative yields by exposure to *p*-toluenesulfonyl chloride in the presence of excess powdered potassium carbonate and a catalytic amount of pyridine.

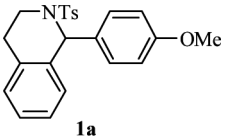
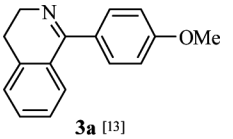
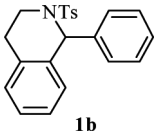
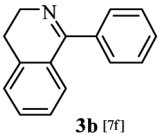
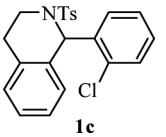
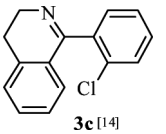
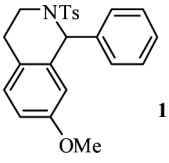
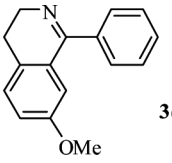
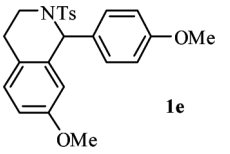
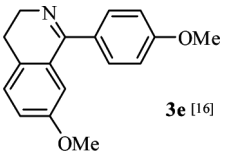
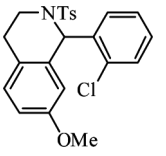
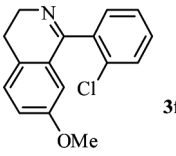
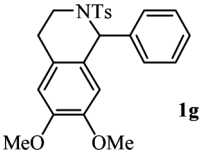
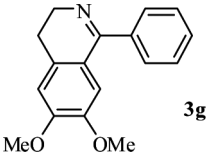
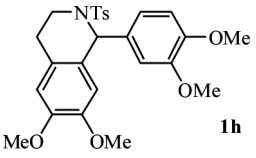
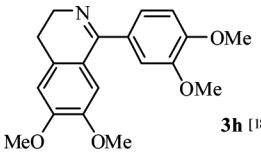
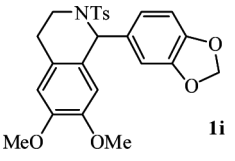
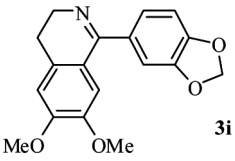
With 1-substituted *N*-tosyl-THIQs **1a–i** and *N*-tosyl-THBCs **2a–j** to hand, we then attempted the conversions of compound **1** into 1-substituted 3,4-DHIQs **3** and compound **2** into 1-substituted 3,4-DHBCs **4** under various conditions. The results are summarized in Tables 1 and 2, respectively.

As can be seen from Table 1, 1-substituted *N*-tosyl-THIQs **1a–i** were treated with 3 molar equivalents of NaOH at 70 °C in dimethylsulfoxide (DMSO). β-Elimination[11] of *p*-toluenesulfinic acid (p-$CH_3C_6H_4SO_2H$) took place rapidly (1.5–2.5 h), affording 1-substituted 3,4-DHIQs **3a–i** in 86–95% yields. DMSO was crucial for the reaction: when other solvents such as ethanol, isopropanol, octanol, 1,4-dioxane, and *N,N*-dimethylformamide were used instead of DMSO, the β-elimination was sluggish and 3,4-DHIQs were obtained only in poor yields after the reaction mixtures were stirred at 70 °C for 12 h. Other bases have also been tried: Strong bases such as KOH, $NaOCH_3$, and NaOEt also worked well, whereas weak bases such as Na_2CO_3, K_2CO_3, and Na_3PO_4 could not be used for the reaction.

As can be seen from Table 2, 1-substituted *N*-tosyl-THBCs **2a–j** were treated with 3 molar equivalents of NaOH at 70 °C in DMSO. β-Elimination also took place quickly, and 1-substituted 3,4-THBCs **4a–j** were obtained in 85–96% yields. A dramatic solvent effect was also observed here, and DMSO was found to be the best solvent for the reaction. Strong bases such as NaOH, KOH, $NaOCH_3$, and NaOEt were appropriate to the reaction, among which NaOH gave the best yields.

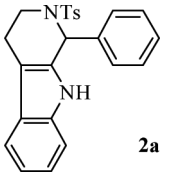
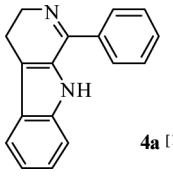
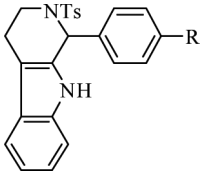
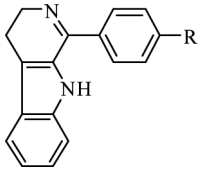
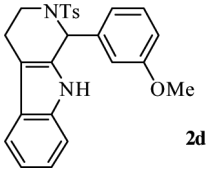
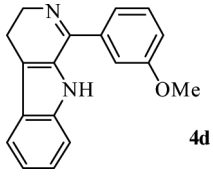
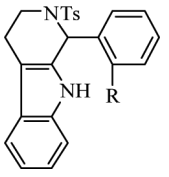
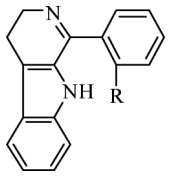
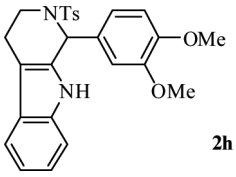
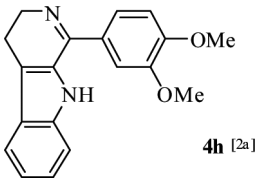
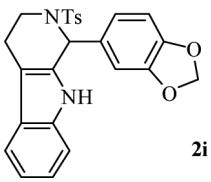
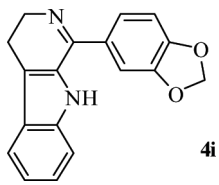
For both β-eliminations, the reaction temperatures should be kept between 60 and 80 °C (70 ± 10 °C); otherwise the reactions would be too slow (<60 °C) or yields would be diminished by formation of by-products (>80 °C). Moreover, substituents at the C-1 position were limited to only aryl groups. When substituents were changed to alkyl groups such as methyl, hexyl, and isopropyl groups, the β-eliminations were sluggish even at 100 °C. If the reaction temperature was raised up to 125 °C, tandem β-elimination and aromatization would occur to afford fully aromatized 1-alkyl-isoquinolines or 1-alkyl-β-carbolines as described in our previous article.[12]

Table 1. Synthesis of 1-aryl-3,4-DHIQs **3** via highly selective β-elimination of *N*-tosyl-1-aryl-THIQs **1** by treatment with 3 molar equivalents of NaOH at 70 °C in DMSO

Entry	*N*-Tosyl-THIQs **1**	Time (h)	3,4-DHIQs **3**[lit.]	Yield (%)[a]
1	 **1a**	2	 **3a** [13]	93
2	 **1b**	1.5	 **3b** [7f]	91
3	 **1c**	1.5	 **3c** [14]	95
4	 **1d**	1.5	 **3d** [15]	92
5	 **1e**	2	 **3e** [16]	90
6	 **1f**	1.5	 **3f**	89
7	 **1g**	2	 **3g** [17]	90
8	 **1h**	2.5	 **3h** [18]	88
9	 **1i**	2.5	 **3i** [18]	86

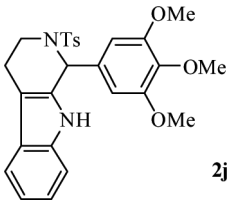
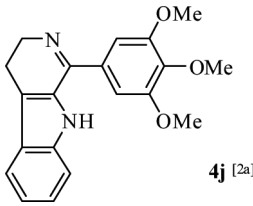
[a]Isolated yield.

Table 2. Synthesis of 1-aryl-3,4-DHBCs **4** via β-elimination of *N*-tosyl-1-aryl-THBCs **2** by treatment of 3 molar equivalents of NaOH at 70 °C in DMSO

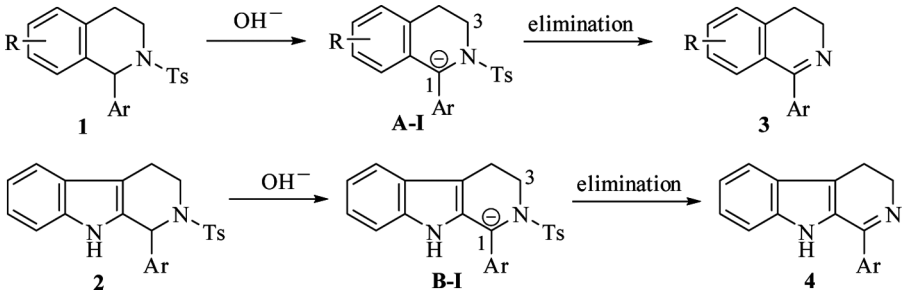
Entry	*N*-Tosyl-THBCs **2**	Time (h)	3,4-DHBCs **4**[lit.]	Yield (%)[a]
1	 **2a**	0.5	 **4a** [19]	95
2	 R=OMe **2b**	0.5	 R=OMe **4b**	90
3	R=OEt **2c**	1	R=OEt **4c**	85
4	 **2d**	0.5	 **4d**	93
5	 R=OMe **2e**	0.5	 R=OMe **4e**	94
6	R=OEt **2f**	1	R=OEt **4f**	90
7	R=Cl **2g**	1	R=Cl **4g**	87
8	 **2h**	0.5	 **4h** [2a]	91
9	 **2i**	0.5	 **4i**	96

(*Continued*)

Table 2. Continued

Entry	*N*-Tosyl-THBCs **2**	Time (h)	3,4-DHBCs **4**[lit.]	Yield (%)[a]
10	 **2j**	0.5	 **4j** [2a]	91

[a]Isolated yield.



Scheme 1. A plausible mechanism for both β-eliminations from compounds **1** to **3** and from compounds **2** to **4**.

A plausible mechanism is proposed in Scheme 1. *N*-Tosyl-1-aryl-THIQs **1** or *N*-tosyl-1-aryl-THBCs **2** first reacts with a strong base to form an anion, **A-I** or **B-I**, which then immediately undergoes β-elimination with Ts^- (p-$CH_3C_6H_4SOO^-$) as a leaving group to afford 1-aryl-3,4-DHIQs **3** or 1-aryl-3,4-DHBCs **4**. Regioslectivities of the β-eliminations from compounds **1** to **3** and from compounds **2** to **4** are actually very high; almost none of 1-aryl-1,4-DHIQs or 1-aryl-1,4-DHBCs could be detected. It is probably because the protons at the bis-allylic C-1 positions of compounds **1** and **2** are much more acidic than the protons at C-3 positions.

CONCLUSION

A mild and efficient method for the transformations from *N*-tosyl-1-aryl-THIQs **1** to 1-aryl-3,4-DHIQs **3** and from *N*-tosyl-1-aryl-THBCs **2** to 1-aryl-3,4-DHBCs **4** has been developed. Reaction conditions were optimized, DMSO was found to be the best solvent, and the most appropriate temperature was around 70 °C. Considering that *N*-tosyl-1-aryl-THIQs **1** and *N*-tosyl-1-aryl-THBCs **2** could be readily prepared via Pictet–Spengler reactions,[9,10] the work described herein might provide an efficient, mild, and practical approach to the syntheses of 1-aryl-3, 4-DHIQs **3** and 1-aryl-3,4-DHBCs **4**.

EXPERIMENTAL

All chemicals were analytically pure and were used as such from commercial suppliers. ^{1}H NMR spectra were acquired on a Bruker AM-500 instrument. Chemical shifts were given on the δ scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a Nicolet Magna IR-550 instrument. Mass spectra were recorded on a HP5989A device. High-performance liquid chromatographic (HPLC) analysis was performed with an Agilent/HP 1200 series instrument equipped with a variable wavelength detector (VWD). Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.). 1-Substituted *N*-tosyl-THIQs **1** were directly obtained from *N*-sulfonyl Pictet–Spengler reaction according to a known procedure.[9] 1-Substituted *N*-tosyl-THBCs **2** were obtained via Pictet–Spengler reaction of tryptamine hydrochloride with aldehydes[10] and the subsequent *N*-tosylation of the resulting 1-substituted THBCs according to our previous report.[12]

Typical Procedure for the Preparation of 1-Aryl-3,4-DHIQs 3 from *N*-Tosyl-1-aryl-THIQs 1

A freshly prepared aqueous solution of NaOH (1.20 g, 30.00 mmol) in water (3 mL) was dropwise added at 70 °C over 5 min to a well-stirred solution of compound **1a** (3.93 g, 9.99 mmol) in DMSO (20 mL). After addition was finished, stirring was continued at 70 °C, and the reaction was traced by thin-layer chromatography (TLC, EtOAc/hexane = 1:3). When the reaction was complete, the mixture was immediately cooled down to room temperature. The reaction mixture was diluted with water (90 mL), and then the aqueous solution was extracted twice with ethyl acetate (80 mL × 2). The extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude oil, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to afford compound **3a** (2.21 g, 9.32 mmol) in 93% yield. Compounds **3b–i** were obtained from the same procedure in the yields indicated in Table 1. HPLC analysis (column: C18 4.6 × 250 mm; mobile phase: 10% IPA in hexane; wavelength: 230 nm; flow rate: 2.5 mL/min) showed that the purity of the compounds **3a–i** was greater than 99%.

Characterization Data of Compounds 3a–3i

Compound 3a. Mp 212–213 °C (lit.[13] 212–214 °C). ^{1}H NMR ($CDCl_3$) $\delta = 2.79$ (t, $J = 7.2$ Hz, 2H), 3.81 (t, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 6.95 (d, $J = 8.6$ Hz, Hz, 2H), 7.22–7.29 (m, 2H), 7.31 (d, $J = 7.4$ Hz, 1H), 7.38 (t, $J = 7.4$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 2H). MS m/z (%) 237 (M^+, 48), 236 (100), 221 (9), 206 (17), 193 (7), 178 (6), 165 (7), 71 (7), 57 (8). IR (KBr) $\nu = 3065$, 2930, 2840, 1610, 1515, 1450, 1250, 1175, 1040, 840, 750 cm^{-1}.

Compound 3b[7f]. Mp 174–175 °C. ^{1}H NMR ($CDCl_3$) $\delta = 2.72$ (t, $J = 7.3$ Hz, 2H), 3.77 (t, $J = 7.3$ Hz, 2H), 7.12–7.21 (m, 3H), 7.27–7.38 (m, 4H), 7.48–7.55 (m, 2H). MS m/z (%) 207 (M^+, 51), 206 (100), 204 (23), 178 (22), 165 (3), 152 (3), 102 (4), 77 (4). IR (KBr) $\nu = 3060$, 2930, 2790, 1610, 1560, 1440, 1320, 1310, 1020, 760, 750, 700, 680, 650 cm^{-1}.

Compound 3c[14]. Mp 185–186 °C. ^{1}H NMR ($CDCl_3$) δ = 2.74–3.00 (m, 2H), 3.63–4.33 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 7.18 (dd, J_1 = 7.6 Hz, J_2 = 7.5 Hz, 1H), 7.25 (d, J = 6.4 Hz, 1H), 7.33–7.39 (m, 3H), 7.39–7.45 (m, 2H); MS m/z (%) 243 (20), 241 (M^+, 68), 206 (100), 178 (33), 151 (4), 102 (8), 77 (4). IR (KBr) ν = 3020, 2958, 2898, 2848, 1615, 1569, 1471, 1429, 1312, 1059, 1020, 761, 746 cm^{-1}.

Compound 3d. Mp 205–206 °C (lit.[15] 251–253 °C). ^{1}H NMR ($CDCl_3$) δ = 2.74 (t, J = 7.2 Hz, 2H), 3.72 (s, 3H), 3.84 (t, J = 7.2 Hz, 2H), 6.82 (d, J = 2.4 Hz, Hz, 1H), 6.95 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.47–7.39 (m, 3H), 7.53–7.65 (m, 2H). MS m/z (%) 237 (M^+, 44), 236 (100), 221 (7), 206 (7), 193 (5), 165 (6), 152 (1), 91 (1). IR (KBr) ν = 3050, 2940, 2930, 1600, 1570, 1495, 1320, 1275, 1220, 1040, 700 cm^{-1}. Anal. calcd for $C_{16}H_{15}NO$ (%): C, 80.98; H, 6.37; N, 5.90; Found: C, 80.80; H, 6.63; N, 5.80.

Compound 3e[16]. Mp 231–232. ^{1}H NMR ($CDCl_3$) δ = 2.73 (t, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.80 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 6.87 (d, J = 2.5 Hz, 1H), 6.93–6.99 (m, 3H), 7.20 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H). MS m/z (%) 267 (M^+, 46), 266 (100), 251 (7), 236 (17), 223 (4), 208 (5), 195 (2), 181 (2), 149 (2), 91 (1). HRMS calcd for $C_{17}H_{17}NO_2$: 267.1259; found: 267.1258. IR (KBr) ν = 3000, 2940, 2830, 1610, 1560, 1510, 1495, 1460, 1300, 1250, 1220, 1165, 1040, 840, 570 cm^{-1}.

Compound 3f. Mp 73–74 °C. ^{1}H NMR ($CDCl_3$) δ = 2.76–2.84 (m, 2H), 3.69 (s, 3H), 3.68–3.76 (m, 1H), 4.00–4.09 (m, 1H), 6.46 (s, 1H), 6.92 (d, J = 8.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.32–7.39 (m, 2H), 7.39–7.46 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 166.14, 158.41, 138.18, 132.57, 130.40, 129.93, 129.71, 129.67, 129.30, 128.27, 126.99, 115.82, 113.00, 55.41, 48.22, 25.03. MS m/z (%) 273 (21), 271 (M^+, 68), 236 (100), 221 (10), 205 (12), 165 (12), 118 (3), 91 (3). HRMS calcd for $C_{16}H_{14}ClNO$: 271.0764; found: 271.0765. IR (KBr) ν = 2939, 2831, 1608, 1577, 1316, 1302, 1279, 1217, 1050, 767, 750 cm^{-1}.

Compound 3g. Mp 118–119 °C (lit.[17] 120–121 °C). ^{1}H NMR ($CDCl_3$) δ = 2.74 (t, J = 7.3 Hz, 2H), 3.73 (s, 3H), 3.82 (t, J = 7.3 Hz, 2H), 3.95 (s, 3H), 6.79 (d, J = 6.4 Hz, 2H), 7.39–7.48 (m, 3H), 7.57–7.64 (m, 2H). MS m/z (%) 267 (M^+, 58), 266 (100), 250 (14), 236 (10), 222 (6), 180 (3), 152 (3), 115 (1), 77 (1). IR (KBr) ν = 2925, 1606, 1562, 1515, 1280, 1357, 1210, 1116, 712 cm^{-1}.

Compound 3h. Mp 169–170 °C (lit.[18] 168–169 °C). ^{1}H NMR ($CDCl_3$) δ = 2.73 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.79 (t, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.79 (s, 1H), 6.88 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.24 (s, 1H). MS m/z (%) 327 (M^+, 88), 326 (100), 312 (39), 296 (64), 281 (11), 268 (7), 252 (5), 238 (4), 226 (3), 195 (2), 140 (2), 77 (1). IR (KBr) ν = 2941, 2839, 1603, 1563, 1516, 1356, 1280, 1257, 1611, 1132, 1114, 1018, 870, 805 cm^{-1}.

Compound 3i. Mp 109–110 °C (lit.[18] 110–111 °C). ^{1}H NMR ($CDCl_3$) δ = 2.71 (t, J = 7.4 Hz, 2H), 3.76 (s, 3H), 3.77 (t, J = 7.4 Hz, 2H), 3.95 (s, 3H), 6.02 (s, 2H), 6.78 (s, 1H), 6.85 (s, 1H), 6.86 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 7.9 Hz, 1H), 7.14 (s, 1H). MS m/z (%) 311 (M^+, 59), 310 (100), 294 (12), 280 (16), 266

(6), 252 (3), 167 (1), 139 (2), 89 (1). IR (KBr) $\nu = 2958$, 2829, 1604, 1558, 1512, 1489, 1358, 1278, 1238, 1115, 1034, 924, 864, 800 cm^{-1}.

Typical Procedure for the Preparation of 1-Aryl-3,4-DHBCs 4 from *N*-Tosyl-1-aryl-THBCs 2

A freshly prepared aqueous solution of NaOH (1.20 g, 30.00 mmol) in water (3 mL) was dropwise added at 70 °C over 5 min to a well-stirred solution of compound **2a** (4.03 g, 10.01 mmol) in DMSO (20 mL). After addition was finished, stirring was continued at 70 °C, and the reaction was traced by TLC (EtOAc/hexane = 1:3). When the reaction was complete, the mixture was immediately cooled down to room temperature. Water (120 mL) was then slowly added while vigorous stirring was continued, and a pale yellow solid precipitated. The solid was collected on a Buchner funnel and rinsed with water. After drying in warm air, the crude product could be purified by recrystallization in aqueous isopropanol (*i*-PrOH/H_2O = 90:10) or by flash chromatography (eluent: EtOAc/CH_2Cl_2 = 1:5) to afford compound **4a** (2.34 g, 9.50 mmol) in 95% yield. Compounds **4b–j** were obtained from the same procedure in the yields as indicated in Table 2. HPLC analysis (Column: C18 4.6 × 250 mm; mobile phase: 5% IPA in dichloromethane; wavelength: 230 nm; flow rate: 1.0 mL/min) showed that the purity of the compounds **4a–j** was greater than 99%.

Characterization Data of Compounds 4a–4j

Compound 4a. Mp 221–222 °C (lit.[19] 218–220 °C). ^1H NMR ($CDCl_3$) $\delta = 2.97$ (t, $J = 8.3$ Hz, 2H), 4.03 (t, $J = 8.3$ Hz, 2H), 7.18 (t, $J = 7.9$ Hz, 1H), 7.28 (t, $J = 7.8$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.42-7.54 (m, 3H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.68–7.78 (m, 2H), 8.28 (s, 1H). MS m/z (%) 246 (M^+, 87), 245 (100), 217 (29), 189 (3), 173 (21), 165 (2), 143 (4), 115 (5), 97 (3). IR (KBr) $\nu = 3060$, 2937, 2836, 1540, 1323, 1306, 1290, 1237, 1153, 1012, 776, 741, 717 cm^{-1}.

Compound 4b. Mp 186–187 °C. ^1H NMR ($CDCl_3$) $\delta = 2.97$ (t, $J = 8.3$ Hz, 2H), 3.87 (s, 3H), 4.02 (t, $J = 8.3$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 7.18 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.0$ Hz, 1H), 7.29 (dd, $J_1 = 7.1$ Hz, $J_2 = 8.0$ Hz, 1H), 7.38 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.8$ Hz, 2H), 8.14 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 161.03$, 159.03, 136.72, 129.98, 129.48, 128.05, 125.51, 124.45, 102.28, 119.96, 117.89, 114.05, 112.16, 55.39, 48.39, 19.33. MS m/z (%) 276 (M^+, 100), 260 (7), 248 (11), 232 (8), 204 (7), 143 (3), 130 (4), 115 (1), 91 (1). HRMS calcd for $C_{18}H_{16}N_2O$: 276.1263; found: 276.1264. IR (KBr) $\nu = 2949$, 2825, 1610, 1539, 1319, 1257, 1174, 1034, 847, 740, 594 cm^{-1}.

Compound 4c. Mp 211–212 °C. ^1H NMR ($CDCl_3$) $\delta = 1.42$ (t, $J = 7.0$ Hz, 3H), 2.93 (t, $J = 8.2$ Hz, 2H), 3.97 (t, $J = 8.2$ Hz, 2H), 4.05 (q, $J = 7.0$ Hz, 2H), 6.95 (d, $J = 7.9$ Hz, 2H), 7.16 (dd, $J_1 = 7.0$ Hz, $J_2 = 8.0$ Hz, 1H), 7.27 (dd, $J_1 = 7.0$ Hz, $J_2 = 8.0$ Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.60–7.71 (m, 3H), 8.41 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 160.46$, 158.88, 136.52, 129.92, 129.36, 128.00, 125.59, 124.45, 120.33, 119.96, 117.86, 114.65, 112.03, 63.61, 48.58, 19.29, 14.77. MS m/z (%) 290 (M^+, 100), 261 (21), 245 (9), 233 (13), 217 (7), 204 (12), 143 (5), 115 (3), 102 (1).

IR (KBr) $\nu = 3061$, 2978, 2931, 1608, 1542, 1321, 1246, 1177, 842, 742 cm^{-1}. Anal. calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65; Found: C, 78.57; H, 6.43; N, 9.81.

Compound 4d. Mp 191–192 °C. ^1H NMR ($CDCl_3$) $\delta = 2.96$ (t, $J = 8.3$ Hz, 2H), 3.82 (s, 3H), 4.02 (t, $J = 8.3$ Hz, 2H), 6.97–7.04 (m, 1H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.30–7.21 (m, 3H), 7.42–7.30 (m, 2H), 7.64 (d, $J = 8.0$ Hz, 1H), 8.41 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 159.95$, 159.38, 138.86, 136.61, 129.77, 127.81, 125.51, 124.57, 120.36, 120.31, 120.00, 117.83, 116.15, 112.85, 112.10, 55.41, 48.75, 19.26. MS m/z (%) 276 (M^+, 87), 275 (100), 260 (5), 245 (7), 232 (7), 217 (10), 204 (11), 143 (3), 115 (4), 102 (2), 77 (1). IR (KBr) $\nu = 3060$, 2940, 2830, 1579, 1542, 1321, 1288, 1215, 1055, 1018, 750 cm^{-1}. Anal. calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14; Found: C, 78.14; H, 5.93; N, 10.06.

Compound 4e. Mp 167–168 °C. ^1H NMR ($CDCl_3$) $\delta = 2.97$ (t, $J = 8.5$ Hz, 2H), 3.85 (s, 3H), 4.10 (t, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 1H), 7.08 (dd, $J_1 = 7.4$ Hz, $J_2 = 7.5$ Hz, 1H), 7.14 (dd, $J_1 = 7.1$ Hz, $J_2 = 7.2$ Hz, 1H), 7.24 (d, $J = 8.1$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.44 (dd, $J_1 = 8.2$ Hz, $J_2 = 8.3$ Hz, 1H), 7.48 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.6$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 158.84$, 156.70, 136.57, 130.93, 130.56, 129.34, 127.73, 125.53, 124.42, 121.69, 120.13, 120.03, 116.68, 111.92, 111.77, 56.19, 49.02, 19.28. MS m/z (%) 276 (M^+, 100), 259 (45), 247 (60), 232 (11), 218 (23), 204 (13), 171 (5), 143 (5), 115 (4), 102 (2). IR (KBr) $\nu = 2938$, 2837, 1600, 1543, 1491, 1464, 1320, 1300, 1246, 1012, 747 cm^{-1}. Anal. calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14; Found: C, 77.91; H, 5.85; N, 10.13.

Compound 4f. Mp 123–124 °C. ^1H NMR ($CDCl_3$) $\delta = 1.25$ (t, $J = 7.0$ Hz, 3H), 2.96 (t, $J = 8.5$ Hz, 2H), 4.09 (t, $J = 8.5$ Hz, 2H), 4.13 (q, $J = 7.0$ Hz, 2H), 7.04 (d, $J = 8.2$ Hz, 1H), 7.07 (dd, $J_1 = 7.4$ Hz, $J_2 = 7.5$ Hz, 1H), 7.14 (dd, $J_1 = 7.1$ Hz, $J_2 = 7.2$ Hz, 1H), 7.22–7.24 (m, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.42 (dd, $J_1 = 8.2$ Hz, $J_2 = 8.3$ Hz, 1H), 7.52 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.6$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 8.53 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 159.16$, 155.96, 136.61, 130.92, 130.71, 129.55, 128.33, 125.44, 124.34, 121.81, 120.03, 120.00, 116.68, 113.24, 111.89, 64.90, 48.95, 19.33, 14.81. MS m/z (%) 290 (M^+, 57), 275 (100), 261 (22), 245 (47), 233 (7), 217 (13), 144 (6), 115 (3), 102 (1). HRMS calcd. for $C_{19}H_{18}N_2O$: 290.1419; found: 290.1420. IR (KBr) $\nu = 3060$, 2980, 2943, 2891, 1601, 1538, 1493, 1453, 1319, 1306, 1244, 1154, 1123, 1042, 744 cm^{-1}.

Compound 4g. Mp 192–193 °C. ^1H NMR ($CDCl_3$) $\delta = 2.99$ (t, $J = 8.6$ Hz, 2H), 4.06 (t, $J = 8.6$ Hz, 2H), 7.09–7.17 (m, 1H), 7.19–7.28 (m, 2H), 7.30–7.43 (m, 3H), 7.45 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 8.30 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 158.82$, 137.00, 136.76, 132.38, 130.56, 130.41, 130.00, 128.34, 127.27, 125.43, 124.65, 120.29, 120.08, 116.86, 112.16, 48.96, 19.32. MS m/z (%) 280 (M^+, 69), 279 (100), 243 (12), 217 (33), 189 (3), 143 (4), 122 (5), 115 (4), 89 (2). IR (KBr) $\nu = 2942$, 2875, 1590, 1543, 1433, 1320, 1294, 1062, 750 cm^{-1}. Anal. calcd. for $C_{17}H_{13}ClN_2$ (%): C, 72.73; H, 4.67; N, 9.98; Found: C, 72.81; H, 4.63; N, 9.89.

Compound 4h. Mp 289–290 °C (lit.[2a] 288–290 °C). ^1H NMR ($CDCl_3$) $\delta = 2.99$ (t, $J = 8.3$ Hz, 2H), 3.95 (s, 3H), 3.96 (s, 3H), 4.03 (t, $J = 8.3$ Hz, 2H), 6.96

(d, $J = 8.2$ Hz, 1H), 7.20 (dd, $J_1 = 7.2$ Hz, $J_2 = 7.7$ Hz, 1H), 7.31 (dd, $J_1 = 8.0$ Hz, $J_2 = 8.3$ Hz, 2H), 7.35–7.42 (m, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 8.18 (s, 1H). MS m/z (%) 306 (M^+, 100), 289 (13), 275 (14), 247 (14), 232 (3), 204 (4), 137 (1), 115 (1), 102 (1). IR (KBr) $\nu = 3057$, 2921, 1542, 1515, 1468, 1420, 1336, 1302, 1273, 1251, 1147, 1027, 747 cm^{-1}.

Compound 4i. Mp 177–178 °C. ^1H NMR ($CDCl_3$) $\delta = 2.97$ (t, $J = 8.3$ Hz, 2H), 4.02 (t, $J = 8.3$ Hz, 2H), 6.05 (s, 2H), 6.93 (d, $J = 8.1$ Hz, 1H), 7.19 (dd, $J_1 = 7.6$ Hz, $J_2 = 7.3$ Hz, 1H), 7.27–7.33 (m, 3H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 8.12 (s, 1H). ^{13}C NMR ($CDCl_3$) $\delta = 158.99$, 149.05, 147.88, 136.83, 131.59, 127.92, 125.44, 124.45, 122.42, 120.24, 119.95, 117.91, 112.22, 108.40, 108.26, 101.41, 48.38, 19.35. MS m/z (%) 290 (M^+, 100), 275 (2), 261 (11), 233 (4), 204 (11), 176 (2), 143 (3), 115 (2). HRMS calcd for $C_{18}H_{14}N_2O_2$: 290.1055; found: 290.1045. IR (KBr) $\nu = 3060$, 2937, 1541, 1503, 1490, 1444, 1291, 1248, 1039, 740 cm^{-1}.

Compound 4j. Mp 173–174 °C (lit.[2a] 251 °C). ^1H NMR ($CDCl_3$) $\delta = 2.96$ (t, $J = 8.2$ Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.00 (t, $J = 8.2$ Hz, 2H), 6.88 (s, 1H), 6.89 (s, 1H), 7.18 (dd, $J_1 = 7.9$ Hz, $J_2 = 7.2$ Hz, 1H), 7.30 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.3$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 7.9$ Hz, 1H), 9.04 (s, 1H). MS m/z (%) 336 (M^+, 100), 321 (15), 305 (17), 290 (9), 277 (18), 262 (5), 206 (5), 152 (3), 115 (2), 102 (1). IR (KBr) $\nu = 2938$, 2834, 1580, 1539, 1506, 1413, 1372, 1342, 1127, 1005, 739 cm^{-1}. Anal. calcd. for $C_{20}H_{20}N_2O_3$ (%): C, 71.41; H, 5.99; N, 8.33; Found: C, 71.61; H, 5.63; N, 8.38.

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