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NEW SYNTHESSES OF 1-BENZOYL-TETRAHYDRO-ISOQUINOLINE DERIVATIVES USING POLYMER-SUPPORTED BIS(TRIFLUOROACETOXYIODO)BENZENE

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Abstract—The reaction of *N*-benzenesulfonyl- β -phenethylamines with α -benzoyl sulfides using polymer-supported bis(trifluoroacetoxyiodo)benzene (PSBTI) gives moderate to good yields of the corresponding 1-benzoyltetrahydroisoquinoline derivatives.

Pictet-Spengler reaction is one of the fundamental reaction for the preparation of 1,2,3,4-tetrahydroisoquinolines.¹ This reaction occurs only when the ring-closure position is activated by electron donating substituents. However, β -phenethylamines bearing an electron withdrawing substituent on the benzene ring afford 1,2,3,4-tetrahydroisoquinoline derivatives in poor yields or do not give any cyclized product. Modifications of the original strategy to increase the electrophilicity of the iminium intermediate, which employ electron withdrawing groups on the nitrogen such as acyl² or sulfonyl³ moieties, are known.

In recent years, hypervalent iodine(III) reagents have been used extensively in organic syntheses due to their low toxicity, ready availability, and easy handling.⁴ As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have reported a modified Pictet-Spengler reaction of *N*-benzenesulfonyl- β -phenethylamines with ethyl methylthioacetate using bis(trifluoroacetoxyiodo)-benzene (BTI) to afford ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.⁵ Recently, Togo *et al.*,⁶ Ley *et al.*⁷ and Kita *et al.*⁸ demonstrated that polymer-supported bis(trifluoroacetoxyiodo)benzene (PSBTI) shows similar reactivity to BTI and have utilized it as a replacement for previously reported iodine(III) reagents. In this work, Pummerer-type reaction of α -benzoyl sulfides using PSBTI was applied to prepare 1-benzoyltetrahydroisoquinoline derivatives by means of Pictet-Spengler reaction.

As shown in Table 1, the reaction of α -benzoyl sulfides (**1**) with *N*-benzenesulfonyl- β -phenethylamines

(**2a**, **b**, **c** and **d**) in the presence of PSBTI gave the cyclized products (**3a**, **b**, **c** and **d**) in moderate yields, respectively (Entries 1, 2, 3 and 4). On the other hand, the 3,4-dimethoxy derivative (**2e**), carrying activating substituent *para* to the ring closure position afforded the expected product (**3e**) in 80% yield (Entry 5). However, *N*-benzenesulfonyl derivatives (**2f**, **2g**, and **2h**) containing deactivated aromatic rings also furnished the corresponding cyclized products in reasonable yields (Entries 6, 7 and 8). Interestingly, unlike the case of the sulfur-based reagent employed by Kohno,⁹ no Friedel-Crafts reaction products were detected when activated phenethylamines were cyclized.¹⁰

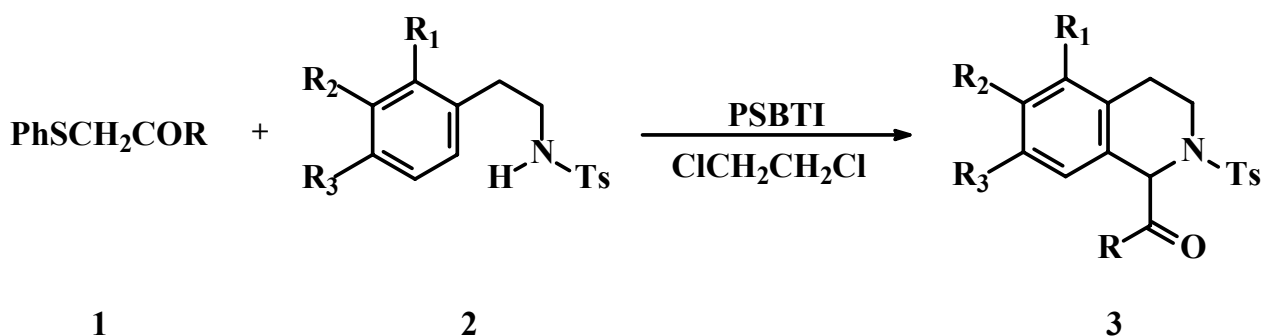
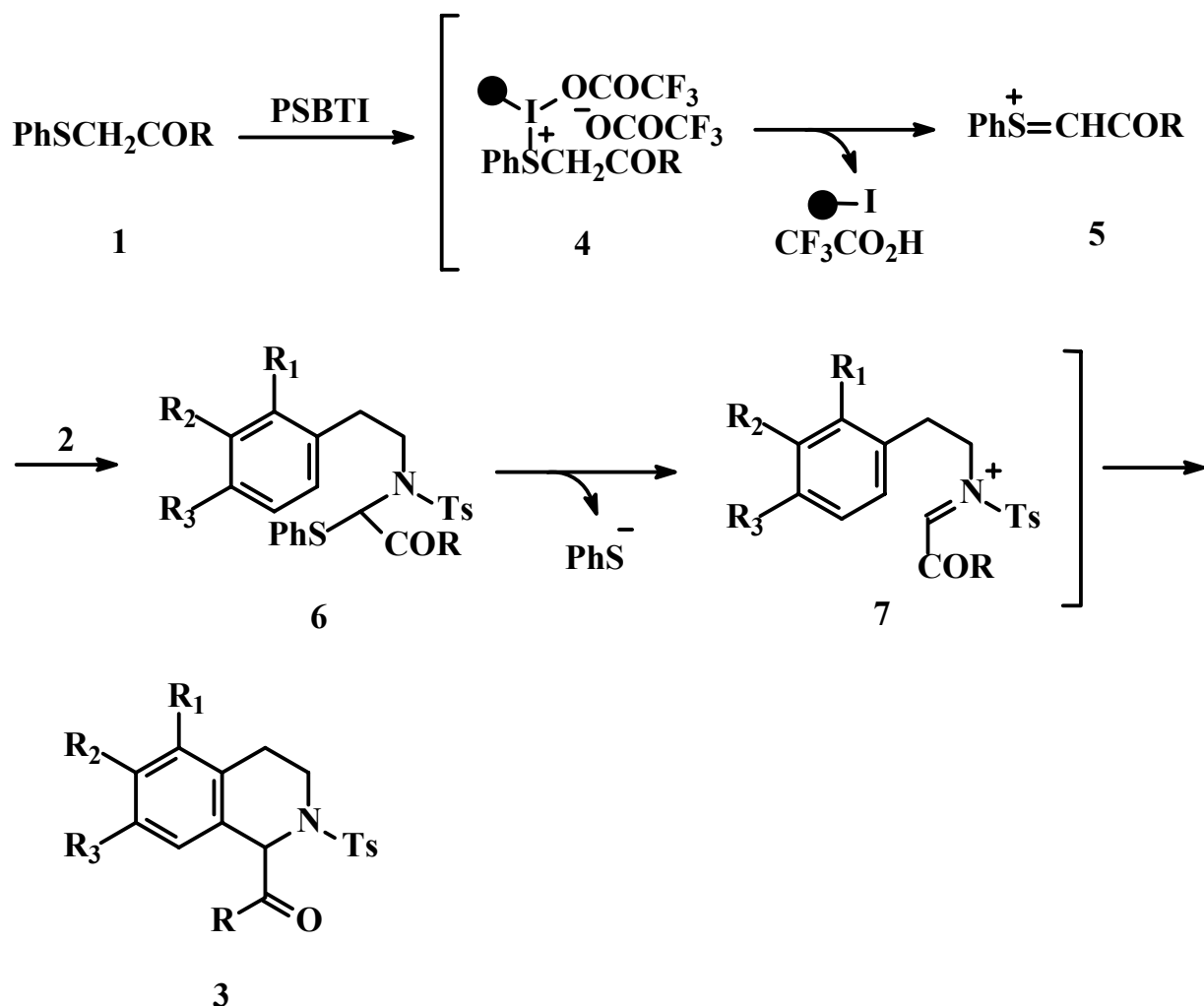


Table 1. The reaction *N*-benzenesulfonyl- β -phenethylamines with α -benzoyl sulfides (**1**) using PSBTI

Entry	Compd	R	R ₁	R ₂	R ₃	Product	Yield (%)
1	2a	Ph	H	H	H	3a	73
2	2b	Ph	H	H	OMe	3b	70
3	2c	<i>p</i> -MeOC ₆ H ₄	H	H	H	3c	72
4	2d	<i>p</i> -MeOC ₆ H ₄	H	H	OMe	3d	68
5	2e	<i>p</i> -MeOC ₆ H ₄	H	OMe	OMe	3e	80
6	2f	<i>p</i> -MeOC ₆ H ₄	Cl	H	H	3f	50
7	2g	<i>p</i> -MeOC ₆ H ₄	H	Cl	H	3g	53
8	2h	<i>p</i> -MeOC ₆ H ₄	H	H	Cl	3h	51

The recovery and recycling of the resin (polyiodostyrene) are easy. After quenching with saturated aqueous NaHCO₃, the resin was recovered nearly quantitatively by filtering the resulting mixture. The recovered resin was easily reoxidized to PSBTI *via* polymer-supported (diacetoxyiodo)benzene (PSDIB)¹¹ by heating in CF₃CO₂H at 70 °C, followed by precipitation by Et₂O. Thus, PSBTI can be used repeatedly without loss of activity. A reasonable pathway of the cyclization is assumed to proceed through the Pummerer-type reaction intermediate (**5**) which would be formed by attack of PSBTI on the sulfur atom of **1**, followed by simultaneous elimination of the polyiodobenzene and trifluoroacetic acid from the resultant sulfonium salt (**4**). Alkylation of *N*-benzenesulfonyl- β -phenethylamines (**2**) gave the

Pummerer reaction products (6). Step 6 to cyclized products (3) can occur through iminium cation (7) formation as shown in Scheme I.



Scheme I

In this reaction, we speculate that cyclization of iminium cation intermediate (7) to tetrahydroisoquinoline (3) was accelerated by two electron withdrawing groups, *N*-benzenesulfonyl group and benzoyl group.

Our results herein that the modified Pictet-Spengler reaction of *N*-sulfonyl- β -phenethylamines with α -benzoyl sulfides using PSBTI provides moderate to good yields of 1-benzoyltetrahydroisoquinolines.

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EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

1-Benzoyl-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3a); Typical procedure

To a solution of the α -benzoyl sulfide (**1a**) (228 mg, 1.0 mmol) in 1,2-dichloroethane (10 mL) was added PSBTI (571 mg, 1.2 mmol), and the mixture was stirred at rt for 1 h. Then *N*-sulfonyl- β -phenethylamine (**2a**) (275 mg, 1.0 mmol) was added and the mixture was refluxed for 4 h to complete the reaction. The resultant mixture was quenched with water and extracted with dichloromethane. The extract was dried (MgSO_4) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column with hexane-ethyl acetate (5:1) to give **3a**. mp 94-96 °C (AcOEt-*n*-hexane), yield 285 mg (73 %). IR (KBr) ν : 1690, 1326, 1153 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.34 (s, 3H), 2.76-3.01 (m, 2H), 3.54-3.93 (m, 2H), 6.34 (s, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 2H), 7.13 (d, $J = 7.6$ Hz, 1H), 7.16-7.18 (m, 2H), 7.47-7.50 (m, 2H), 7.57-7.63 (m, 3H), 8.06-8.08 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.4, 27.6, 41.5, 59.7, 126.3, 126.9, 127.4, 127.5, 128.0, 128.2, 128.4, 128.4, 128.6, 128.6, 129.1, 129.4, 130.1, 133.2, 134.0, 135.3, 135.9, 143.6, 197.3; MS (EI) m/z : 391 (M^+), 286, 155, 130, 105, 91, 77, 65, 51. Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_3\text{S}$: C, 70.57; H, 5.41; N, 3.58. Found : C, 70.35; H, 5.62; N, 3.36.

1-Benzoyl -7-methoxy-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3b)

mp 146-147 °C (AcOEt-*n*-hexane), yield 295 mg (70 %). IR (neat) ν : 1688, 1338, 1160 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.36 (s, 3H), 2.68-2.91 (m, 2H), 3.49-3.89 (m, 2H), 3.61 (s, 3H), 6.23 (s, 1H), 6.49 (d, $J = 2.8$ Hz, 1H), 6.71 (dd, $J = 2.8, 8.8$ Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 1H), 7.17-7.19 (m, 2H), 7.46-7.50 (m, 2H), 7.57-7.62 (m, 3H), 8.05-8.07 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.4, 26.8, 41.8, 55.1, 60.2, 111.8, 113.9, 125.9, 125.9, 127.5, 127.5, 128.7, 128.7, 129.2, 129.5, 129.5, 130.2, 131.0, 133.2, 135.2, 135.9, 143.6, 157.8, 197.2; MS (EI) m/z : 421 (M^+), 316, 160, 155, 105, 91, 77, 51. Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_4\text{S}$: C, 68.39; H, 5.50; N, 3.32. Found : C, 68.47; H, 5.37; N, 3.46.

1-(*p*-Methoxybenzoyl)-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3c)

mp 134-136 °C (AcOEt-*n*-hexane), yield 303 mg (72 %). IR (KBr) ν : 1681, 1320, 1155 cm^{-1} ; ^1H NMR

(CDCl₃) δ : 2.34 (s, 3H), 2.90-3.24 (m, 2H), 3.59-3.95 (m, 2H), 3.89 (s, 3H), 6.35 (s, 1H), 6.97-7.11 (m, 4H), 7.14-7.16 (m, 2H), 7.57-7.63 (m, 2H), 7.67-7.70 (m, 2H), 8.10-8.12 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ : 21.4, 35.7, 44.1, 55.4, 58.8, 113.9, 113.9, 126.3, 126.7, 126.8, 127.0, 128.6, 128.6, 129.2, 129.4, 129.6, 130.7, 131.7, 134.0, 135.6, 143.3, 143.5, 163.8, 195.6; MS (EI) m/z : 421 (M⁺), 286, 155, 135, 130, 107, 92, 91, 77, 65. Anal. Calcd for C₂₄H₂₃NO₄S: C, 68.39; H, 5.50; N, 3.32. Found : C, 68.23; H, 5.65; N, 3.24.

1-(*p*-Methoxybenzoyl)-7-methoxy-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3d)

Pale yellow oil, yield 307 mg (68 %). IR (KBr) ν : 1672, 1323, 1162 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.37 (s, 3H), 2.55-2.58 (m, 2H), 3.04-3.09 (m, 2H), 3.66 (s, 3H), 3.75 (s, 3H), 6.37 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.81-6.83 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.25-7.27 (m, 2H), 7.65-7.68 (m, 2H), 7.92-7.94 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ : 21.3, 34.6, 44.0, 55.2, 55.3, 55.6, 111.0, 113.6, 113.7, 113.8, 125.4, 126.8, 129.3, 129.5, 129.6, 130.2, 130.9, 132.1, 132.4, 134.4, 136.8, 143.1, 154.5, 163.5, 193.6; MS (EI) m/z : 451 (M⁺), 155, 135, 109, 91, 77, 65. HRMS (EI) Calcd for C₂₅H₂₅NO₅S: 451.1453. Found: 451.1456.

1-(*p*-Methoxybenzoyl)-6,7-dimethoxy-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3e)

Pale yellow oil, yield 385 mg (80 %). IR (neat) ν : 1676, 1334, 1164 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.26 (s, 3H), 2.58-2.80 (m, 2H), 3.46-3.82 (m, 2H), 3.58 (s, 3H), 3.71 (s, 3H), 3.77 (s, 3H), 6.13 (s, 1H), 6.42 (s, 1H), 6.45 (s, 1H), 6.88-6.91 (m, 2H), 7.09-7.11 (m, 2H), 7.55-7.57 (m, 2H), 8.07-8.09 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ : 21.1, 26.5, 41.2, 55.1, 55.4, 59.1, 109.2, 111.3, 111.3, 113.6, 113.6, 121.9, 125.8, 127.1, 128.3, 129.1, 129.1, 129.1, 131.3, 131.3, 135.0, 143.3, 147.2, 148.0, 163.4, 195.2; MS (EI) m/z : 481 (M⁺), 191, 176, 135, 107, 92, 91, 77, 76. HRMS (EI) Calcd for C₂₆H₂₇NO₆S: 481.1559. Found: 481.1557.

1-(*p*-Methoxybenzoyl)-5-chloro-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3f)

mp 58-60 °C (AcOEt-*n*-hexane), yield 227 mg (50 %). IR (neat) ν : 1684, 1333, 1159 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.30 (s, 3H), 2.53-2.78 (m, 2H), 3.65-3.85 (m, 2H), 3.87 (s, 3H), 6.41 (s, 1H), 6.96-6.98 (m, 2H), 7.01 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.50-7.53 (m, 2H), 7.66-7.70 (m, 2H), 8.16-8.18 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ : 21.3, 24.3, 42.3, 55.4, 58.4, 114.0, 114.0, 125.5, 126.8, 126.9, 126.9, 127.2, 128.1, 128.1, 129.2, 129.5, 129.5, 132.0, 134.5, 135.4, 143.2, 143.8, 164.0, 194.6; MS (EI) m/z : 457 (M⁺+2), 455 (M⁺), 184, 155, 125, 91, 89, 65, 63. Anal. Calcd for C₂₄H₂₂NO₄ClS: C, 63.22; H, 4.86; N, 3.07. Found : C, 63.43; H, 4.76; N, 3.25.

1-(*p*-Methoxybenzoyl)-6-chloro-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3g)

mp 68-70 °C (AcOEt-*n*-hexane), yield 241 mg (53 %). IR (neat) ν : 1675, 1324, 1159 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.35 (s, 3H), 2.53-2.78 (m, 2H), 3.65-3.85 (m, 2H), 3.90 (s, 3H), 6.36 (s, 1H), 6.97-6.99 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.26 (s, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.55-7.57 (m, 2H), 7.67-7.69 (m, 2H), 8.10-8.13 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.5, 27.0, 40.7, 55.5, 58.2, 114.1, 114.1, 126.5, 126.9, 127.0, 127.2, 128.2, 129.3, 129.4, 129.7, 129.7, 129.9, 131.7, 135.6, 136.7, 139.7, 143.5, 164.0, 195.1; MS (EI) m/z : 457 ($\text{M}^+ + 2$), 455 (M^+), 366, 231, 229, 135, 121, 109, 77, 51. Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_4\text{Cl}$: C, 63.22; H, 4.86; N, 3.07. Found : C, 63.38; H, 4.72; N, 3.21.

1-(*p*-Methoxybenzoyl)-7-chloro-2-(*p*-tosyl)-1,2,3,4-tetrahydroisoquinoline (3h)

mp 108-110 °C (AcOEt-*n*-hexane), yield 232 mg (51 %). IR (neat) ν : 1679, 1315, 1157 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.35 (s, 3H), 2.66-2.84 (m, 2H), 3.65-3.82 (m, 2H), 3.91 (s, 3H), 6.35 (s, 1H), 6.99-7.01 (m, 2H), 7.12-7.29 (m, 3H), 7.54-7.56 (m, 2H), 7.66-7.68 (m, 2H), 8.12-8.14 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.4, 35.1, 44.0, 55.5, 58.0, 114.1, 114.1, 126.7, 127.0, 127.3, 127.7, 128.2, 128.7, 129.4, 129.6, 130.0, 130.5, 131.8, 132.5, 136.7, 137.4, 143.4, 164.1, 194.8; MS (EI) m/z : 457 ($\text{M}^+ + 2$), 455 (M^+), 184, 155, 127, 125, 91, 89, 65. Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_4\text{Cl}$: C, 63.22; H, 4.86; N, 3.07. Found : C, 63.35; H, 4.67; N, 3.16.

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