Hydrazidohydroxylation of Styrenes with N-Acetylanminophthalimide Using Phenyliodine(III) Bis(trifluoroacetate) (PIFA)

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Abstract: Regioselective hydrazidohydroxylation of styrenes with N-acetylanminophthalimide using phenyliodine(III) bis(trifluoroacetate) was carried out to afford 1-aryl-2-(N-acetyl-N-phthalimido)aminoethyl trifluoroacetates in high yields. The procedure is operationally simple and removal of trifluoroacetyl and phthalimido groups was performed by treatment of the trifluoroacetate with hydrazine hydrate in good yield. A synthetic study and a mechanistic proposal for the hydrazidohydroxylation are presented.

Key words: hydrazidohydroxylation, styrene, N-acetylaminophthalimide, nitrenium ion, phenyliodine(III) bis(trifluoroacetate)

Divalent positively charged nitrogen species (nitrenium ions) which are stabilized by the neighboring groups have been widely applied in the field of synthetic organic chemistry.1 Previously, we have reported that nitrenium ions I (Figure 1) can be generated from the corresponding N-methoxy- or N-allyloxy-N-chloroamides by the action of silver2 or zinc3 ions or triethylamine4 or by direct oxidation of the corresponding amides with phenyliodine(III) bis(trifluoroacetate) (PIFA).5

Figure 1 Nitrenium ions I and II

More recently, hypervalent iodine compounds such as PIFA have been often utilized because these reagents have low toxicity, are readily available, are easy to handle, and are environmentally friendly.5 We recently reported a fundamentally new protocol for the construction of nitrogen heterocycles by the intramolecular electrophilic aromatic substitution with N-acyl-N-phthalimidonitrenium ions II generated from the corresponding N-acetylanminophthalimides using PIFA.7 In an extension of this work, we have investigated the reaction of olefins 1 with N-acylaminophthalimides 2.

Figure 2 Compounds 1–6
nophthalimide (2) using PIFA anticipating that hydrazide derivatives having a trifluoroacetoxy group on the adjacent carbon might be formed (Figure 2).

Initially, we examined the reaction of 4-chlorostyrene (1d) with 2 using PIFA in various solvents such as chloroform, acetonitrile, tetrahydrofuran, and 2,2,2-trifluoroethanol. Treatment of 1d and 2 (1.1 molar equiv) with PIFA (1.2 molar equiv) in chloroform at reflux for 30 minutes gave 2-(N-acetyl-N-phthalimido)-1-(4-chlorophenyl)aminoethyl trifluoroacetate (3d) in 85% yield. The structural determination of 3d was performed by the comparison of the chemical shifts of the benzylic proton of 3d and of the corresponding proton of the hydrolyzed 3d (5d). The signal of the benzylic proton of 5d apparently appeared at considerably higher field (1 ppm) compared with the benzylic proton of 3d, which indicates that the oxygen function attached to the benzylic position. In acetonitrile or tetrahydrofuran the reaction mixture contained several unidentifiable products (TLC) and 3d was obtained in poor yield. In 2,2,2-trifluoroethanol PIFA reacted with 2 for one hour in the presence of 1a at room temperature to form the adduct, the iodophenyl group of which rearranged to the amide nitrogen to give N-acetyl-N-(4-iodophenyl)aminoethyl trifluoroacetate (4) in 80% yield. A similar N-iodophenylation reaction of acetanilides using PIFA was reported previously. Accordingly, several styrenes reacted in chloroform, and the results are presented in Table 1.

Normally, the nitrenium ion IIa could attack both α- and β-carbons of styrenes to afford two regioisomers. In practice, however, HPLC analysis of the reaction mixture revealed that the reaction is extremely regioselective and one regioisomer alone is obtained in the case of unsubstituted and α-methyl substituted styrenes in high yield (Table 1, entries 1–9). For β-methyl-substituted styrenes, two regioisomers were obtained (entry 10).

Next, we tried the hydrolysis of 3. Initially the hydrolysis was performed in 10% aqueous sodium bicarbonate solution at room temperature. However, no products were extracted from the aqueous solution, probably because the phthalimido ring opened in addition to the hydrolysis of trifluoroacetate. Next, a weakly acidic solvent (AcOH–H2O = 2:1) was used for hydrolysis. To our surprise, the two corresponding regioisomeric alcohols were obtained from pure 3a, 3d and 3g. The results are presented in Table 2.

The described transformation can be rationalized as depicted in Scheme 1. Thus the trifluoroacetyl group of 3a is eliminated by the assistance of the adjacent acetamido nitrogen to form the aziridinium ion. The solvent water attacks both the α and β positions of this new intermediate to give the two regioisomers 5a and 5a’, respectively.

These regioisomers thus obtained were trifluoroacetylated with trifluoroacetic anhydride to give 3a’, 3d’, and 3g’ and

![Scheme 1](image-url)  
**Scheme 1** Probable reaction mechanism for the hydrolysis of 3a

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product (yield, %)<strong>b</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3a (90)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
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</tr>
<tr>
<td>3</td>
<td>1c</td>
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<tr>
<td>4</td>
<td>1d</td>
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<tr>
<td>5</td>
<td>1e</td>
<td>3e (82)</td>
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<tr>
<td>6</td>
<td>1f</td>
<td>3f (74)</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>3g (80)</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>3h (68), 5h (10)c</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>3i (90)</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>3j (32), 3j’ (44)</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product (yield, %)<strong>b</strong></th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>5a (68), 5a’ (22)</td>
</tr>
<tr>
<td>2</td>
<td>3d</td>
<td>5d (63), 5d’ (11)</td>
</tr>
<tr>
<td>3</td>
<td>3g</td>
<td>5g (61), 5g’ (29)</td>
</tr>
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<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions: A mixture of 3 (0.1 mmol) in AcOH–H2O (2:1, 9 mL) was heated at 70 °C for 0.5–1 h</th>
<th>Product (yield, %)<strong>b</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A mixture of 3 in 10% aqueous sodium bicarbonate solution at room temperature</td>
<td>5a (68), 5a’ (22)</td>
</tr>
<tr>
<td>2</td>
<td>A mixture of 3 in 2,2,2-trifluoroethanol with PIFA (1.2 mmol)</td>
<td>5d (63), 5d’ (11)</td>
</tr>
<tr>
<td>3</td>
<td>A mixture of 3 in AcOH–H2O (2:1)</td>
<td>5g (61), 5g’ (29)</td>
</tr>
</tbody>
</table>

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**Table 2** Hydrolysis of the Trifluoroacetates of 3 in Acidic Conditions

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**Table 1** Hydrotriazidohydroxylation of Styrenes with N-Acetylaminoethylphthalimide Using PIFA

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were used as authentic samples for the HPLC analysis. The phthaloyl and trifluoroacetyl groups of 3a were deprotected by the action of hydrazine hydrate as usual to give N-(2-hydroxy-2-phenylethyl)acetohydrazide (6) in 75% yield. Synthesis of hydrindanthrones is rarely reported\(^2\) and this method will offer an alternative for their synthesis.

Taking the above-mentioned mechanism of hydrolysis into consideration, a plausible pathway for the original reaction of the nitrenium ion IIa to the double bond, and subsequent without formation of aziridinium ions\(^1\), the created carbocationic species can be captured by a free trifluoroacetate anion or quenched by the elimination of an adjacent hydrogen (entry 9) to afford the products.

In conclusion, we have achieved highly regioselective vicinal difunctionalization in a simple single-step reaction. Thus, the reaction of the nitrenium ion IIa with styrenes gave hydrazide derivatives having a trifluoroacetyl group on the adjacent carbon in good yields. Further application of this methodology for the synthesis of lactams having a trifluoroacetoxy group in a molecule is underway.

All required fine chemicals were used directly without purification. CHCl\(_3\) and THF used for the reactions were of commercial anhydrous grade. Silica gel (230–400 mesh) was used for column chromatography, while 250 μm silica gel plates were used for TLC analysis. The purities of several compounds were analyzed by high-performance liquid chromatography using Shimpack C\(_18\) reverse phase column (4.6 mm × 150 mm), with flow rate 0.3 mL/min and a tunable UV detector set at 254 nm. A mixture of MeCN–H\(_2\)O (75:25) was used as mobile phase. \(^1\)H NMR spectra were recorded at 270 or 500 MHz using TMS as reference. \(^13\)C NMR spectra were recorded at 67.8 or 125.7 MHz. Mass spectra were measured with a Shimadzu GCMS-QP2010SE. HPLC (Shimpak C\(_18\) reverse phase column, MeCN–H\(_2\)O (75:25), 0.3 mL/min, \(\lambda = 254\) nm), \(t\)_R = 18.18.

IR (KBr): 1790, 1750, 1700, 1690, 1220, 1180 cm\(^{-1}\).

\(^1\)H NMR (270 MHz, CDCl\(_3\), rotamers): \(\delta = 1.98\) (s, 2.4 H), 2.37 (s, 0.9 H), 3.92–4.32 (m, 2 H), 6.37–6.55 (m, 1 H), 7.26–7.43 (m, 5 H), 7.8–8.01 (m, 4 H).

\(^13\)C NMR (125.7 MHz, DMSO-\(d_6\), rotamers): \(\delta = 19.6, 20.2, 50.0, 53.9, 77.3, 77.5, 114.2\) (q, \(J = 286.1\) Hz), 123.7, 123.90, 123.91, 124.1, 126.6, 126.9, 128.76, 128.79, 129.2, 129.3, 129.5, 129.60, 129.64, 129.7, 134.9, 135.2, 135.3, 155.52 (q, \(J = 41.7\) Hz), 155.54 (q, \(J = 41.7\) Hz), 164.7, 165.0, 165.1, 165.4, 168.5, 171.6.

FABMS (3-nitrobenzyl alcohol + NaI): \(m/z\) (%) = 443 (\(M^+ + Na\), 28.7).

Anal. Calcd for C\(_{20}\)H\(_{14}\)ClF\(_3\)N\(_2\)O\(_5\): C, 52.82; H, 3.10; N, 6.16. Found: C, 52.73; H, 3.48; N, 6.49.

1-(2-Chlorophenyl)-2-[N-(1,3-dioxoisooindolin-2-yl)acetamido]ethyl 2,2,2-Trifluoroacetate (3b)
White crystals; mp 127–130 °C (Et\(_2\)O–hexane).

IR (KBr): 1850, 1800, 1765 cm\(^{-1}\).

\(^1\)H NMR (270 MHz, CDCl\(_3\), rotamers): \(\delta = 1.98\) (s, 2.1 H), 2.37 (s, 0.9 H), 3.92–4.32 (m, 2 H), 6.37–6.55 (m, 1 H), 7.26–7.43 (m, 5 H), 7.8–8.01 (m, 4 H).

\(^13\)C NMR (125.7 MHz, DMSO-\(d_6\), rotamers): \(\delta = 19.6, 20.1, 50.0, 52.6, 74.8, 75.6, 115.0\) (q, \(J = 286.2\) Hz), 123.9, 124.0, 124.10, 124.13, 127.8, 128.0, 128.2, 128.7, 129.2, 129.6, 129.31, 129.8, 130.0, 131.0, 131.2, 131.5, 131.75, 131.82, 132.5, 135.4, 135.5, 135.6, 155.5 (q, \(J = 41.5\) Hz), 155.7 (q, \(J = 41.5\) Hz), 164.0, 164.7, 165.1, 165.4, 168.5, 171.9.

FABMS (3-nitrobenzyl alcohol): \(m/z\) (%) = 431 (\(M^+ + Na\), 0.9), 154 (100), 137 (72.5), 136 (84.6).

Anal. Calcd for C\(_{20}\)H\(_{14}\)ClF\(_3\)N\(_2\)O\(_5\): C, 52.82; H, 3.10; N, 6.16. Found: C, 52.65; H, 2.99; N, 6.02.

1-(3-Chlorophenyl)-2-[N-(1,3-dioxoisooindolin-2-yl)acetamido]ethyl 2,2,2-Trifluoroacetate (3c)
White crystals; mp 125–127 °C (Et\(_2\)O–hexane).

IR (KBr): 1850, 1800, 1765 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, DMSO-\(d_6\), rotamers): \(\delta = 1.91\) (s, 1.8 H), 2.34 (s, 1.2 H), 3.71 (dd, \(J = 14.8, 3.1\) Hz, 0.6 H), 3.82 (dd, \(J = 15.9, 2.9\) Hz, 0.4 H), 4.60–4.69 (m, 1 H), 6.09 (m, 1 H), 7.42–7.56 (m, 4 H), 7.97–8.09 (m, 4 H).

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1H NMR (270 MHz, CDCl3, rotamers): δ = 1.98 (s, 2.7 H), 2.30 (s, 0.3 H), 3.87 (dd, J = 15.4, 2.7 Hz, 1 H), 5.95 (dd, J = 9.5, 3.5 Hz, 0.1 H), 6.11 (dd, J = 9.5, 2.7 Hz, 0.9 H), 7.26–7.44 (m, 4 H), 7.81–8.01 (m, 4 H).

13C NMR (125.7 MHz, DMSO-d6, rotamers): δ = 123.7, 123.9, 124.1, 124.8, 125.1, 125.5, 126.8, 127.1, 128.8, 129.1, 129.3, 129.6, 129.7, 130.7, 130.8, 133.3, 133.4, 135.3, 136.2, 137.2, 137.5, 155.6 (q, J = 42.0 Hz), 155.8 (q, J = 42.0 Hz), 164.7, 165.1, 165.4, 168.5, 171.6.

FABMS (3-nitrobenzyl alcohol + NaI): m/z (%) = 477 (M⁺ + Na, 26%).


2-[(1,3-Dioxoisouindolin-2-yl)acetamido]-1-phenyl-2,2,2-Trifluoroacetate (3c)
White crystals; mp 95–97 °C (EtO₂-O-hexane).
MR (KBr): 1790, 1790, 1700, 1230, 1150 cm⁻¹.

1H NMR (500 MHz, DMSO-d6, rotamers): δ = 1.92 (s, 1.7 H), 2.30, 2.31, 2.34 (each, 4.3 H), 3.72 (dd, J = 14.8, 2.9 Hz, 0.5 H), 3.83 (dd, J = 15.9, 3.1 Hz, 0.5 H), 4.56–4.65 (m, 1 H), 6.06–6.11 (m, 1 H), 7.22 (dd, J = 10.0 Hz, 1 H), 7.25 (d, J = 10.0 Hz, 1 H), 7.34 (d, J = 10.0 Hz, 1 H), 7.45 (d, J = 10.0 Hz, 1 H) 7.95–8.08 (m, 4 H).

13C NMR (125.7 MHz, DMSO-d6, rotamers): δ = 19.6, 20.2, 20.69, 20.71, 49.9, 53.9, 64.7, 77.3, 77.5, 114.1 (q, J = 285.7 Hz), 123.7, 123.89, 123.9, 124.1, 124.7, 128.8, 128.8, 129.0, 129.5, 129.6, 129.7, 133.8, 133.9, 134.0, 134.1, 135.3, 135.5, 155.5 (q, J = 42.0 Hz), 155.8 (q, J = 41.4 Hz), 164.7, 165.0, 165.1, 165.4, 168.5, 171.6.

FABMS (3-nitrobenzyl alcohol + NaI): m/z (%) = 457 (M⁺ + Na, 19.8).


Methyl 4-[(2-[(1,3-Dioxoisouindolin-2-yl)acetamido]-1-hydroxyethyl}benzoate (5b)
White crystals; mp 155–156 °C (EtO₂-O-hexane).
MR (KBr): 1790, 1740, 1710, 1210, 1230, 1150 cm⁻¹.

1H NMR (270 MHz, CDCl3, rotamers): δ = 1.98 (s, 2.7 H), 2.29 (s, 0.3 H), 3.81–3.86 (m, 1 H), 3.91 (s, 1.7 H), 4.48 (dd, J = 15.4, 2.2 Hz, 1 H), 6.02 (d, J = 6.9 Hz, 0.1 H), 6.19 (d, J = 6.9 Hz, 0.9 H), 7.5 (d, J = 8.4 Hz, 2 H), 7.9 (d, J = 8.4 Hz, 2 H), 7.91–8.11 (m, 4 H).

13C NMR (67.8 MHz, DMSO-d6, rotamers): δ = 19.5, 20.2, 49.6, 52.18, 52.22, 53.6, 76.6, 76.9, 114.1 (q, J = 285.7 Hz), 123.7, 123.9, 124.1, 126.9, 127.1, 124.69, 126.9, 125.59, 125.99, 126.9, 130.2, 130.3, 135.3, 139.8, 140.1, 155.5 (q, J = 42.1 Hz), 155.8 (q, J = 41.7 Hz), 166.4, 165.0, 165.1, 165.4, 165.7, 168.5, 171.5.

FABMS (3-nitrobenzyl alcohol): m/z (%) = 479 (M⁺ + H, 42), 365 (100).


Methyl 4-[(2-[(1,3-Dioxoisouindolin-2-yl)acetamido]-1-hydroxyethyl}benzoate (5b)
White crystals; mp 136–138 °C (EtO₂-O-hexane).
MR (KBr): 3500, 1800, 1740, 1620, 1380, 1280 cm⁻¹.

1H NMR (500 MHz, DMSO-d6, rotamers): δ = 1.91 (s, 1.6 H), 2.15 (s, 1.4 H), 3.58–3.61 (m, 0.7 H), 3.72 (dd, J = 15.3, 5.0 Hz, 0.8 H), 3.84 (s, 3 H), 3.97 (dd, J = 15.3, 5.0 Hz, 0.5 H), 4.07 (dd, J = 14.4, 5.0 Hz, 0.5 H), 4.80 (dd, J = 8.0, 5.0 Hz, 0.5 H), 4.92 (dd, J = 8.0, 5.0 Hz, 0.5 H), 7.50 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 8.2 Hz, 1 H), 7.89 (d, J = 8.2 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 1 H), 7.95–8.01 (m, 4 H).

13C NMR (125.7 MHz, DMSO-d6, rotamers): δ = 19.9, 20.6, 52.0, 52.1, 52.2, 57.8, 70.5, 70.8, 123.67, 123.71, 123.9, 124.0, 126.4, 126.6, 128.5, 128.6, 129.00, 129.04, 129.52, 129.56, 129.64, 135.20, 135.21, 135.3, 148.29, 148.31, 164.5, 164.9, 165.1, 165.2, 167.06, 167.11, 169.1, 171.7.

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N-(1,3-Dioxoisindolin-2-yl)-N-(2-phenallyl)acetamide (3i)
White crystals; mp 112–115 °C (EtO<sub>O</sub>-hexane).

IR (KBr): 1800, 1740, 1690 cm<sup>-1</sup>.

1H NMR (500 MHz, DMSO-<sub>d<sub>6</sub></sub>, rotamers): δ = 1.91 (s, 2.1 H), 2.24 (s, 0.9 H), 4.73 (s, 1.4 H), 4.87 (s, 0.6 H), 5.28 (s, 0.7 H), 5.48 (s, 0.7 H), 5.55 (s, 0.3 H), 5.69 (s, 0.3 H), 7.23–7.57 (m, 5 H), 7.93–8.04 (m, 4 H).

13C NMR (125.7 MHz, DMSO-<sub>d<sub>6</sub></sub>, rotamers): δ = 15.4, 15.8, 20.1, 20.2, 20.3, 47.9, 54.3, 115.7, 117.5, 122.5, 123.7, 123.8, 123.9, 124.0, 124.1, 125.8, 125.9, 126.1, 126.23, 127.77, 127.84, 128.0, 128.2, 128.4, 128.4, 128.5, 129.0, 129.2, 129.3, 134.6, 135.3, 135.38, 135.42, 135.5, 138.0, 138.5, 138.9, 139.4, 141.4, 142.1, 164.3, 164.4, 164.5, 167.4, 169.0, 169.1, 170.2, 171.4.

FABMS (3-nitrobenzyl alcohol + Na<sup>+</sup>): m/z (%) = 321 (M<sup>+</sup> + H, 100).

Anal. Calcd for C<sub>35</sub>H<sub>34</sub>N<sub>2</sub>O<sub>7</sub>: C, 65.43; H, 4.58; N, 8.00. Found: C, 65.39; H, 4.57; N, 8.00.

5a
White crystals; mp 122–123 °C (EtOAc-hexane).

IR (KBr): 3420, 1800, 1740, 1660 cm<sup>-1</sup>.

1H NMR (270 MHz, CDCl<sub>3</sub> + D<sub>2</sub>O, rotamers): δ = 2.02 (s, 1.8 H), 2.38 (s, 1.2 H), 3.59–3.79 (m, 1 H), 3.95 (dd, J = 14.8, 9.7 H, 0.4 Hz), 4.13 (dd, J = 14.8, 2.1 Hz, 0.6 Hz), 4.84 (dd, J = 14.8, 2.7 Hz, 0.4 Hz), 5.02 (d, J = 9.4 Hz, 0.6 H), 7.19–7.42 (m, 5 H), 7.82–8.02 (m, 4 H).

13C NMR (125.7 MHz, DMSO-<sub>d<sub>6</sub></sub>, rotamers): δ = 19.9, 20.5, 52.3, 58.2, 70.7, 71.3, 123.6, 123.7, 123.9, 124.0, 124.3, 126.3, 126.7, 127.3, 127.32, 128.07, 128.11, 129.8, 129.1, 134.7, 135.1, 135.3, 135.38, 135.42, 135.5, 138.0, 138.5, 138.9, 139.4, 141.4, 142.1, 164.3, 164.4, 164.5, 167.4, 169.0, 169.1, 170.2, 171.4.

FABMS (3-nitrobenzyl alcohol + Na<sup>+</sup>): m/z (%) = 342 (M<sup>+</sup> + Na<sup>+</sup>, 100).

Anal. Calcd for C<sub>35</sub>H<sub>33</sub>N<sub>2</sub>O<sub>7</sub>: C, 65.24; H, 4.54; N, 7.96. Found: C, 65.20; H, 4.52; N, 7.92.

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Hydrazidohydroxylation of Styrenes

Typical Procedure

Trifluoroacetylation of 5a, 5d, 5g; 2-[N-(1,3-Dioxoisoindolin-2-yl)acetoamide]-2-phenylethyl 2,2,2-Trifluoroacetate (3a);

PAPER

Hydrazidohydroxylation of Styrenes

37

Anal. Calcd for C_{18}H_{15}ClN_{2}O_{4}: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.13; H, 4.07; N, 7.81.

Anal. Calcd for C_{20}H_{15}F_{3}N_{2}O_{5}: C, 57.15; H, 3.60; N, 6.66. Found: C, 56.99; H, 3.45; N, 6.58.

Anal. Calcd for C_{3}H_{2}ClN_{2}O_{5}C: C, 51.75; H, 3.60; N, 6.66. Found: C, 51.69; H, 3.45; N, 6.58.

Anal. Calcd for C_{3}H_{2}ClN_{2}O_{4}C: C, 63.79; H, 4.06; N, 7.78.

Anal. Calcd for C_{18}H_{15}ClN_{2}O_{4}: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.13; H, 4.07; N, 7.81.

Anal. Calcd for C_{20}H_{15}F_{3}N_{2}O_{5}: C, 57.15; H, 3.60; N, 6.66. Found: C, 56.99; H, 3.45; N, 6.58.

Anal. Calcd for C_{3}H_{2}ClN_{2}O_{5}C: C, 51.75; H, 3.60; N, 6.66. Found: C, 51.69; H, 3.45; N, 6.58.

Trifluoroacetylation of 5a, 5d, 5g; 2-[N-(1,3-Dioxoisoindolin-2-yl)acetoamide]-2-phenylethyl 2,2,2-Trifluoroacetate (3a);

Typical Procedure

Trifluoroacetic anhydride (0.1 mL, 0.525 mmol) was added to a solution of 5a (34 mg, 0.105 mmol) in pyridine (0.1 mL, 0.525 mmol) and THF (2.4 mL) at 0 °C. After stirring for 3 min, the reaction was quenched with 1% HCl (4 mL) and the mixture was extracted with EtO (2 × 20 mL). The combined organic solvents were washed with brine (15 mL), dried (Na_{2}SO_{4}), and concentrated. The residue was purified by short column chromatography on silica gel using 60% EtOAc–hexane to give the product 3a (31 mg, 70%); colorless crystals; mp 121–123 °C (EtOAc–hexane); HPLC: t_{R} = 21.08.

IR (KBr): 3450, 1790, 1750, 1720, 1400 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

IR (KBr): 1800, 1750, 1720, 1220 cm–1.

Anal. Calcd for C_{3}H_{2}ClN_{2}O_{5}C: C, 63.79; H, 4.06; N, 7.78.

Anal. Calcd for C_{18}H_{15}ClN_{2}O_{4}: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.13; H, 4.07; N, 7.81.

Anal. Calcd for C_{20}H_{15}F_{3}N_{2}O_{5}: C, 57.15; H, 3.60; N, 6.66. Found: C, 56.99; H, 3.45; N, 6.58.

Anal. Calcd for C_{3}H_{2}ClN_{2}O_{5}C: C, 51.75; H, 3.60; N, 6.66. Found: C, 51.69; H, 3.45; N, 6.58.

2-(4-Chlorophenyl)-2-hydroxyethyl-1-(N-(1,3-dioxoisoindolin-2-yl)acetamide) (5g)

White crystals; mp 126–127 °C (EtOAc–hexane).

IR (KBr): 3450, 1790, 1750, 1720, 1400 cm–1.

IR (KBr): 3450, 1790, 1750, 1720, 1400 cm–1.

IR (KBr): 3450, 1790, 1750, 1720, 1400 cm–1.

IR (KBr): 3450, 1790, 1750, 1720, 1400 cm–1.
1H NMR (500 MHz, DMSO-d6): δ = 2.0 (s, 3 H), 2.27 (s, 3 H), 3.88 (dd, J = 3.5, 14.5 Hz, 1 H), 4.39 (dd, J = 10.4, 14.3 Hz, 1 H), 5.87 (dd, J = 3.6, 10.2 Hz, 1 H), 7.17 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 8.01–8.11 (m, 4 H).

13C NMR (125.7 Hz, DMSO-d6): δ = 20.7, 53.3, 71.6, 115.2 (q, J = 297.7 Hz), 124.4, 124.5, 126.4, 129.0, 129.1, 129.2, 134.3, 135.8, 137.7, 157.3 (q, J = 36.2 Hz), 163.7, 163.9, 169.4.

FABMS (3-nitrobenzylalcohol + NaI): m/z (%) = 457 (M+ + Na, 100).

Anal. Calcd for C21H17F3N2O5: C, 58.07; H, 3.94; N, 6.45. Found: C, 58.16; H, 4.09; N, 6.46.

References

(3) Kikugawa, Y.; Shimada, M.; Matsumoto, K. Heterocycles 1994, 37, 293.
(11) In the intramolecular cyclization of an N-acylnitrenium ion and the olefin fragment in a molecule, Tellitu and Domínguez reported that the created carbocationic species are stabilized by the formation of aziridinium ion intermediates. See references 6j, 6l and 6m.