A Convenient Synthesis of 1,4-Disubstituted Isoquinolines by Reactions of α-Substituted 2-Lithio-β-methoxystyrenes with Nitriles

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Received 13 April 2006; revised 19 May 2006

SYNTHESIS 2006, No. 17, pp 2934–2938
Advanced online publication: 15.08.2006
DOI: 10.1055/s-2006-950186; Art ID: F05706SS
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Abstract: It has been found that halogen–lithium exchange between α-substituted 2-bromo-β-methoxystyrene derivatives and n-butyllithium generates α-substituted 2-lithio-β-methoxystyrene derivatives, which successfully react with a range of nitriles to afford the corresponding 1,4-disubstituted isoquinolines in reasonable yields.

Key words: benzyl anion, isoquinoline, nitrile, organolithium, styrene

After our recent finding that the reaction of 2-(2-methoxyethenyl)benzonitrile derivatives with organolithiums affords isoquinoline derivatives,1 we wished to extend this study and investigate the possibility of reacting α-substituted 2-lithio-β-methoxystyrene derivatives 2 with nitriles, for the preparation of isoquinoline derivatives such as 3. This would constitute an improvement of the previous method, since the precursors of these lithium compounds, α-substituted 2-bromo-β-methoxystyrene derivatives 1, are simpler to prepare than the 2-(2-methoxyethenyl)benzonitrile derivatives, and a wider range of nitriles are available, compared to organolithiums. We now report a new synthesis of isoquinolines, which enabled us to prepare a range of 1,4-disubstituted derivatives. Since compounds based on the isoquinoline skeleton have received considerable attention because of their biological utilities,2 a number of approaches for the construction of this system have recently been developed.3

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Synthesis of 1,4-Disubstituted Isoquinolines

Table 1 Preparation of 1,4-Disubstituted Isoquinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>I</th>
<th>R^1 of R^3CN</th>
<th>3 (Yield/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ph</td>
<td>3a (73)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>o-Tol</td>
<td>3b (64)</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2-FC_6H_4</td>
<td>3c (68)</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>4-ClC_6H_4</td>
<td>3d (68)</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>4-CF_3C_6H_4</td>
<td>3e (66)</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>Naphthalen-1-yl</td>
<td>3f (52)</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>Pyridin-2-yl</td>
<td>3g (38)</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>(E)-PhCH=CH</td>
<td>3h (38)</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>i-Pr</td>
<td>3i (62)</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>Cy</td>
<td>3j (62)</td>
</tr>
<tr>
<td>11</td>
<td>1b</td>
<td>Ph</td>
<td>3k (71)</td>
</tr>
<tr>
<td>12</td>
<td>1b</td>
<td>Phenanthren-9-yl</td>
<td>3l (51)</td>
</tr>
<tr>
<td>13</td>
<td>1b</td>
<td>Et</td>
<td>3m (40)</td>
</tr>
<tr>
<td>14</td>
<td>1c</td>
<td>Ph</td>
<td>3n (43)</td>
</tr>
<tr>
<td>15</td>
<td>1c</td>
<td>4-CIC_6H_4</td>
<td>3o (45)</td>
</tr>
<tr>
<td>16</td>
<td>1c</td>
<td>4-FC_3C_6H_4</td>
<td>3p (44)</td>
</tr>
<tr>
<td>17</td>
<td>1c</td>
<td>r-Bu</td>
<td>3q (43)</td>
</tr>
<tr>
<td>18</td>
<td>1d</td>
<td>Ph</td>
<td>3r (36)</td>
</tr>
</tbody>
</table>

a Isolated yields.
b Reaction was allowed to come to room temperature after addition of PhCN.

temperature in order to allow the reaction to reach completion.

In the present work, we have demonstrated an efficient synthetic method that allows access to 1,4-disubstituted isoquinolines. The operational simplicity, together with the ready availability of the starting materials, makes this new procedure attractive. Work on investigating the possibility of preparing related heterocycles, using reactions of 2-lithio-β-methoxystyrene derivatives with other electrophiles, are currently in progress in our laboratory.

Methyl chlorophenyl)methanol, 2-bromophenyl(4-chlorophenyl)methanone, and 1-bromo-2-(2-methoxy-1-methylethenyl)benzene were prepared by literature methods. All other chemical used in this study were commercially available.

2-Bromophenyl(4-chlorophenyl)methanone

This compound was prepared by the oxidation of 2-bromophenyl(4-chlorophenyl)methanone with PCC at r.t. in DCE.

Yield: 89%; yellow oil; R_f = 0.42 (EtOAc–hexane, 1:5).

IR (neat): 1668 cm^{-1}.

1^H NMR (500 MHz, CDCl_3): δ = 7.3–7.5 (5 H, m), 7.65 (1 H, dd, J = 7.3, 1.3 Hz), 7.75 (2 H, d, J = 8.9 Hz).


Bromo-2-(2-methoxy-1-phenylethenyl)benzene (1a)

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (6.9 g, 20 mmol) in THF (40 mL) at 0 °C was added n-BuLi (1.6 M in hexane, 20 mmol) dropwise. After 15 min, a solution of 2-bromophenyl(4-chlorophenyl)methanone (2.1 g, 8.1 mmol) in THF (70 mL) was added and stirring was continued for an additional 30 min. The mixture was treated with H_2O (50 mL) and the organic materials were extracted with Et_2O (2 × 20 mL). The combined extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc–hexane, 1:20) to give 1a as a mixture of stereoisomers (E/Z = ca. 7:3). Yield: 1 g (75%); pale-yellow oil.

An analytical specimen of each isomer was obtained by fractional column chromatography.

E-Isomer

Pale-yellow oil; R_f = 0.45 (EtOAc–hexane, 1:20).

IR (neat): 1636 cm^{-1}.

1^H NMR (500 MHz, CDCl_3): δ = 3.81 (3 H, s), 6.25 (1 H, s), 7.14–7.19 (2 H, m), 7.26–7.34 (4 H, m), 7.37 (2 H, dd, J = 7.8, 0.9 Hz), 7.59 (1 H, dd, J = 8.2 Hz).

Anal. Calcd for C_{16}H_{14}Br: C, 52.83; H, 4.53. Found: C, 52.71; H, 4.50.

Z-Isomer

White solid; mp 80–82 °C (hexane–Et_2O).

IR (KBr): 1645 cm^{-1}.

1^H NMR (500 MHz, CDCl_3): δ = 3.74 (3 H, s), 6.67 (1 H, s), 7.12 (2 H, d, J = 7.8 Hz), 7.17 (2 H, dd, J = 7.8, 7.3 Hz), 7.23–7.26 (3 H, m), 7.33 (1 H, t, J = 7.3 Hz), 7.64 (1 H, d, J = 7.8 Hz).

Anal. Calcd for C_{16}H_{14}Br: C, 52.30; H, 4.53. Found: C, 61.94; H, 4.54.
1-Bromo-2-[2-methoxy-1-(4-chlorophenyl)ethyl]benzene (1b)
This compound was prepared from 2-bromophenyl(4-chlorophenyl)methane, in a manner similar to that described for the preparation of 1a, as a mixture of stereoisomers (E,Z = 7:3). Yield: 74%; colorless oil.

An analytical specimen of each isomer was obtained by fractional column chromatography.

E-Isomer
Colorless oil; \( R_f = 0.41 \) (CH\(_2\)Cl\(_2\)–hexane, 1:4).

IR (neat): 1634 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 3.82 \) (3 H, s), 6.26 (1 H, s), 7.19 (1 H, ddd, \( J = 9.2, 6.3, 2.4 \) Hz), 7.22 (2 H, d, \( J = 8.7 \) Hz), 7.29–7.34 (4 H, m), 7.59 (1 H, dd, \( J = 7.8, 1.4 \) Hz).

Anal. Calc'd for C\(_{16}\)H\(_{15}\)BrO\(_2\): C, 60.21; H, 4.74. Found: C, 59.98; H, 4.84.

IR (KBr): 1614 cm\(^{-1}\).

1-(2-Methylphenyl)-4-phenylisoquinoline (3b)
Pale-yellow oil; \( R_f = 0.17 \) (hexane–THF, 3:1).

IR (neat): 1614 cm\(^{-1}\).

1-[2-Fluorophenyl]-4-phenylisoquinoline (3e)
White solid: mp 116–118 °C (hexane–Et\(_2\)O).

IR (KBr): 1616 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 2.14 \) (3 H, s), 7.31–7.43 (4 H, m), 7.46–7.52 (2 H, m), 7.54–7.61 (4 H, m), 7.65 (1 H, ddd, \( J = 8.2, 6.9, 1.4 \) Hz), 7.73 (1 H, d, \( J = 8.2 \) Hz), 7.98 (1 H, d, \( J = 8.7 \) Hz), 8.57 (1 H, s).

MS (EI): \( m/\ell \) (%) = 294 (100) [M\(^+\)].

Anal. Calc'd for C\(_{22}\)H\(_{17}\)N: C, 90.60; H, 5.17; N, 4.23. Found: C, 89.39; H, 5.86; N, 4.68.

1-([Naphthalen-1-yl]-4-phenylisoquinoline (3f)
Colorless viscous oil; \( R_f = 0.12 \) (EtOAc–hexane, 1:2).

IR (neat): 1614 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.36 \) (1 H, ddd, \( J = 7.8, 7.3, 1.4 \) Hz), 7.42 (1 H, ddd, \( J = 8.2, 6.9, 1.4 \) Hz), 7.48–7.54 (3 H, m), 7.58 (2 H, dd, \( J = 7.8, 7.3 \) Hz), 7.62–7.67 (5 H, m), 7.69 (1 H, d, \( J = 8.2 \) Hz), 7.97 (1 H, dd, \( J = 7.8, 1.4 \) Hz), 8.01–8.03 (2 H, m), 8.66 (1 H, s).

MS (EI): \( m/\ell \) (%) = 331 (76) [M\(^+\)], 330 (100).


1-([Pyrindin-2-yl]-4-phenylisoquinoline (3g)
Yellow viscous oil; \( R_f = 0.23 \) (hexane–Et\(_2\)O, 1:2).

IR (neat): 1625 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.43 \) (1 H, ddd, \( J = 7.8, 7.3, 1.4 \) Hz), 7.49–7.57 (5 H, m), 7.61 (1 H, ddd, \( J = 8.2, 6.9, 1.4 \) Hz), 7.67 (1 H, ddd, \( J = 8.2, 6.9, 1.4 \) Hz), 7.94 (1 H, td, \( J = 7.3, 1.8 \) Hz), 7.97 (1 H, d, \( J = 8.7 \) Hz), 8.03 (1 H dd, \( J = 6.9, 0.9 \) Hz), 8.59 (1 H, s), 8.64 (1 H, dd, \( J = 9.1, 0.9 \) Hz), 8.81–8.84 (1 H, m).
MS (EI): m/z (%) = 282 (100) [M⁺].

4-Phenyl-1-[E]-2-phenylvinyl]isoquinoline (3h)
Pale-yellow oil; Rf = 0.31 (hexane–CH2Cl2, 1:1).
IR (neat): 1615 cm⁻¹.

4-Methyl-1-phenylisoquinoline (3r)¹¹
White solid; mp 71–74 °C (hexane–Et2O) (lit.¹¹ 75–76 °C). Spectral data (IR and 1H NMR) were identical to those reported previously.¹¹

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 142–145 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 107–108 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 117–120 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 117–120 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 142–145 °C (hexane–Et2O).
IR (KBr): 1620 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 107–108 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 117–120 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 107–108 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 117–120 °C (hexane–Et2O).
IR (KBr): 1618 cm⁻¹.
Acknowledgment

We thank Mrs. Miyuki Tanmatsu of this Department for determining mass spectra and performing combustion analyses.

References


(3) Compound 1d is a known compound, see: Wuensch, B.; Hoefner, G.; Bauschke, G. Arch. Pharm. 1993, 326, 513.


(7) A possibility of the formation of 3 via 6π electrocyclization of 4 followed by elimination of lithium methoxide cannot be excluded.

