Synthesis of 3-Arylpropylamine Derivatives from Aryl Halides Using Heck Reaction

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As a part of our research directed toward the development of new capsaicinoids as analgesics, we found that N-(3-phenylalkyl)-homovanillic amide 1 has excellent in vivo analgesic activity in mice model test and the results of our study were published. In the reports, we emphasized that the chain length of phenylalkyl part of 1 is critical to provide high analgesic activity and three-carbon length (n = 1) is optimal. In the continuing our efforts to investigate further structural requirements, we have focused on the synthesis of 3-arylpropylamine derivative 2, which is a key intermediate for synthesis of 1.

Our initial attempt to synthesize 2 began with two-carbon homologation of substituted benzylchloride 3 using malonate chemistry to give 3-arylpionic acid 6, which was converted to corresponding amine 8 (eq 1).3 Palladium-catalyzed hydrogenation of substituted cinnamic acid 4 also gave 3-arylpionic acid 6, but the commercially available 4 is limited (eq 2).3 Meerwein reactions of arylamine 5 with acrylonitrile in the presence of copper halide (I) or (II) catalyst gave α-halo-β-arylpionitrile 7 and then LiAlH4 reduction of 7 provided corresponding amine 8. However, apparance of Sandmeyer reaction type product and removal of the undesired halogen group of 7 were problematic (eq. 3).4

The palladium-catalyzed coupling of aryl or vinyl halide with olefin, which was discovered by R. F. Heck in the late sixties, has been a convenient method for forming carbon-carbon bonds in organic synthesis. The direction of addition of aryl halide to olefin appears to be sterically controlled.

However, in the case of α,β-unsaturated carbonyl, addition of aryl halide generally takes place predominantly on the electronically demanding β-carbon. Even in the literature, many reaction examples of aryl halide with variety of olefins are reported, but reactions of aryl halide with acrylamide and their further reactions to 3-arylacrylamide are rare.6 Herein, we report a facile synthesis of 2 through three consequent steps; (1) Heck reactions of aryl halide and acrylamide, (2) palladium-catalyzed hydrogenation of 3-arylacrylamide, and (3) LiAlH4 reduction of 3-arylpionamide.

3-Arylacrylamide 11a, 11b, 11e were obtained in high yields from either aryl iodide 9 or bromide 10 under typical Heck reaction condition using Pd(OAc)2, tri-o-tolysolphine, and Et3N in MeCN. However, reaction of sterically bulky aryl bromide 10 having methyl substituent at C-2 or C-6 position (11c, 11d) was not completed within 2 days and gave low yields (Table 1). 3-Arylpionylamine 8 was obtained from 11 through conventional palladium-catalyzed hydrogenation followed by LiAlH4 reduction. Even though LiAlH4 reduction of 11a could give 8a directly, the yield was lower (56%) than the combined yields (90%, 86%) of two separated steps. Table 2 shows the synthesis of 3,3-diaarylpropylamine 13. The introduction of second aryl group to 11 was also done by Heck reaction conditions to provide 3,3-diarly substituted acrylamides 12. The Heck reactions were slowly occurred at reflux condition in DMF or ODCB as moderate yields. Even though 12 might exist as regioisomeric mixture (E vs. Z), we could not distinguish clearly whether 12 was isomeric mixture or not by 1H NMR. 12 gave 3,3-diarylpionylamine 13 as described for 8. Finally, 3-arylpionylamine 16 or 20 which has methyl group on aliphatic chain was provided from 14 or 17 (Scheme 1).

Table 1. Synthesis of 3-Arylpropionylamines 8 from Arylhalides and Acrylamide

<table>
<thead>
<tr>
<th>9 or 10</th>
<th>11 (time, yield)</th>
<th>11 to 8 (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-Me3-PhI 11a</td>
<td>1h, 92%</td>
<td>90% 86%</td>
</tr>
<tr>
<td>3-Me,4-F-PhBr</td>
<td>11b</td>
<td>24h, 92%</td>
</tr>
<tr>
<td>2,4,5-Me3-PhBr</td>
<td>11c</td>
<td>2days, 63%</td>
</tr>
<tr>
<td>2,3,5,6-Me3-PhBr</td>
<td>11d</td>
<td>2days, 25%</td>
</tr>
<tr>
<td>1-Bromonaphthalene 11e</td>
<td>6h, 89%</td>
<td>96% 61%</td>
</tr>
</tbody>
</table>
Table 2. Synthesis of 3,3-Diarylpropylamine 13 from 3-Arylacrylamide 11 and Aryl iodide 9

<table>
<thead>
<tr>
<th>Ar (R)</th>
<th>(Ar')</th>
<th>Condition, Yield</th>
<th>Step (i)</th>
<th>Step (ii)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>3-Me-Ph</td>
<td>12a ODCB, 24h, 75%</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>Ph</td>
<td>2,3-Me₂-Ph</td>
<td>12b ODCB, 2day, 55%</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td>3-Me-4-F-Ph</td>
<td>3,4-Me₂-Ph</td>
<td>12c DMF, 3days, 95%</td>
<td>90%</td>
<td>83%</td>
</tr>
<tr>
<td>3-Thionyl</td>
<td>Ph</td>
<td>12d DMF, 3days, 51%</td>
<td>75%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Scheme 1. (a) Pd(OAc)₂, Tri-o-tolylphosphine, Et₃N, CH₃CN, reflux. (b) H₂/10% Pd-C, MeOH. (c) LiAlH₄, THF, r.t. (d) NH₂OH-amide through three consequent steps including Heck reaction. Column chromatography was performed with Merck-EM

In summary, we could obtain 3-arylpolyamine 8, 16, 20 and 3,3-diarylpolyamine 13 from aryl halide 9, 10 or 11 through three consequent steps including Heck reaction.

**Experimental Section**

All reactions were carried out under N₂ atmosphere unless otherwise noted. MeCN was distilled from CaH₂ prior to use. Organic extracts or filtrates were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude was recrystallized from EtOAc/n-hexane to give 11a (20.87 g, 92%) as a white solid: mp 136-138 °C; ¹H NMR (CDCl₃) δ 2.23 (s, 3H, CH₃), 2.24 (s, 3H, CH₃), 5.85 (br s, 1H, NH), 6.05 (br s, 1H, NH), 6.41 (d, J=15.7 Hz, 1H, CH), 7.09 (d, J=7.7 Hz, 1H, ArH), 7.20 (d, J=7.7 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 7.56 (d, J=15.7 Hz, 1H, CH); EIMS m/z 175 (M⁺), 160, 129, 115.

3-(4-Fuoro-3-methylphenyl)acrylamide 11b. Reaction of 5-Bromo-2-fluorotoluene (2.27 g, 14.4 mmol), Pd(OAc)₂ (54 mg, 0.24 mmol), tri-o-tolylphosphine (1.18 g, 16.5 mmol), Et₃N (2.0 mL, 14.4 mmol) in CH₃CN (10 mL) was carried out for 24 h as described for 11a. The crude solid was recrystallized from EtOAc/n-hexane to give 11b (2.0 g, 92%) as a white solid: mp 130-131 °C; ¹H NMR (DMSO-d₆) δ 2.34 (s, 3H, CH₃), 6.58 (d, J=16.1 Hz, 1H, CH), 7.47 (d, J=16.1 Hz, 1H, CH), 7.18-7.59 (m, 3H, ArH); EIMS m/z (rel. intensity) 179 (M⁺), 178 (100), 164 (62), 163 (63), 135 (60), 133 (87), 115 (77).

3-(2,4,5-Trialkylphenyl)acrylamide 11c. Reaction of 5-Bromo-1,2,4-trimethylbenzene (3.0 g, 15.1 mmol), acrylamide (1.18 g, 16.5 mmol), Pd(OAc)₂ (68 mg, 0.3 mmol), tri-o-tolylphosphine (275 mg, 0.9 mmol), Et₃N (1.83 g, 18.1 mmol) in DMF (15 mL) was heated at 140-150 °C for 2 days. The reaction mixture was passed through a celite pad and the filtrate was concentrated by vacuum distillation. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a crude solid which was recrystallized from EtOAc/n-hexane to give 11c (1.02 g, 14.4 mmol), Pd(OAc)₂ (54 mg, 0.24 mmol), tri-o-tolylphosphine (275 mg, 0.9 mmol), Et₃N (1.83 g, 18.1 mmol) in DMF (15 mL) was carried out for 24 h as described for 11a. The crude solid was recrystallized from EtOAc/n-hexane to give 11c (1.8 g, 63%) as a white solid: mp 118-120.5 °C; ¹H NMR (CDCl₃) δ 1.95 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 3.00 (s, 3H, CH₃), 5.85 (br s, 1H, ArH), 6.32 (d, J=15.5 Hz, 1H, CH), 6.67 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.82 (d, J=15.5 Hz, 1H, CH); EIMS m/z 179 (M⁺), 178 (100), 164 (62), 163 (63), 135 (60), 133 (87), 115 (77).

3-(2,4,5-Tetramethylphenyl)acrylamide 11d. Reaction of 5-Bromo-2,4,5-tetramethylbenzene (3.0 g, 15.1 mmol), acrylamide (1.8 g, 16.5 mmol), Pd(OAc)₂ (68 mg, 0.3 mmol), tri-o-tolylphosphine (275 mg, 0.9 mmol), Et₃N (1.83 g, 18.1 mmol) in DMF (15 mL) was heated at 140-150 °C for 2 days as described for 11c. The crude solid was recrystallized from EtOAc/n-hexane to give 11d (0.68 g, 25%) as a white solid: mp 216-217 °C; ¹H NMR (CDCl₃) δ 1.98 (s, 3H, CH₃), 2.20 (d, J=16.1 Hz, 1H, CH), 6.97 (s, 1H, ArH), 7.82 (d, J=16.1 Hz, ArH); EIMS m/z 179 (M⁺), 178 (100), 164 (62), 163 (63), 135 (60), 133 (87), 115 (77).

3-(2,3,5,6-Tetramethylphenyl)acrylamide 11e. Reaction of 1-bromo-2,3,5,6-tetramethylbenzene (3.0 g, 14 mmol), acrylamide (1.10 g, 15.5 mmol), Pd(OAc)₂ (63 mg, 0.28 mmol), tri-o-tolylphosphine (0.26 g, 0.85 mmol), Et₃N (1.71 g, 17 mmol) in DMF (10 mL) was heated at 140-150 °C for 2 days as described for 11c. The crude solid was recrystallized from EtOAc/n-hexane to give 11e (0.68 g, 25%) as a white solid: mp 216-217 °C; ¹H NMR (CDCl₃) δ 1.95 (s, 3H, CH₃), 2.26 (s, 6H, 2CH₃), 5.56 (br s, 2H, NH), 6.53 (d, J=15.5 Hz, 1H, CH), 7.03 (d, J=15.5 Hz, 1H, ArH); EIMS m/z 179 (M⁺), 178 (100), 164 (62), 163 (63), 135 (60), 133 (87), 115 (77).

3-Naphthalen-1-ylacrylamide 11f. Reaction of 1-bromonaphthalene (2.0 g, 9.7 mmol), acrylamide (0.75 g, 10.6 mmol), Pd(OAc)₂ (44 mg, 0.19 mmol), tri-o-tolylphosphine (176 mg, 0.58 mmol), and Et₃N (1.72 g, 11.6 mmol) in CH₃CN (25 mL) was carried out for 6 h as described for
11a. The crude solid was recrystallized from CHCl3/n-hexane to give 11e (1.69 g, 89%) as a white solid; mp 177-178.5 °C; 1H NMR (DMSO-d6) δ 6.65 (d, J=15.7 Hz, 1H, CH), 7.20 (br s, 1H, NH2), 7.51-7.61 (m, 3H, ArH), 7.65 (br s, 1H, NH2), 7.76-7.79 (m, 1H, ArH), 7.95-7.99 (m, 2H, ArH), 8.18-8.23 (m, 1H, NH), 8.20 (d, J=15.7 Hz, 1H, CH); EIMS m/z (rel. intensity) 197 (M+, 19), 155 (67), 154 (quint, J=7 Hz, ArH), 7.79-7.85 (m, 1H, ArH), 8.02-8.08 (m, 1H, ArH).

General Method of Hydrogenation Reaction of Acrylamide. A mixture of acrylamide and 10% Pd/C (10 wt % of acrylamide) in MeOH was stirred under H2. The reaction mixture was passed through a celite pad and the filtrate was concentrated to give a crude propionamide which was recrystallized from EtOAc/n-hexane.

General Method of LiAlH4 Reduction of Propionamide. To a mixture of LiAlH4 in THF was added a solution of propionamide in THF, and the mixture was stirred at r.t. or heated at reflux temperature. MeOH, H2O followed by 1N NaOH solutions were added and the resulting mixture was passed through a celite pad. The filtrate was concentrated under reduced pressure and purified by vacuum distillation.

3-(3,4-Dimethylphenyl)propionamide 8a. A mixture of 11a (0.11 g, 0.63 mmol) and 10% Pd/C (0.02 g) in MeOH (5 mL) was stirred under H2 balloon for 2 h. The reaction mixture was passed through a celite pad and the filtrate was concentrated to give a crude 3-(3,4-dimethylphenyl)propionamide (0.10 g, 90%) as a white solid; mp 115-117 °C; 1H NMR (CDCl3) δ 2.21 (s, 6H, 2ArCH3), 2.49 (t, J=7 Hz, 2H, CH2), 2.88 (t, J=7 Hz, 2H, CH2), 5.60 (br s, 1H, NH), 6.02 (br s, 1H, NH), 6.89-7.25 (m, 3H, ArH).

To a mixture of LiAlH4 (10.17 g, 0.268 mol) in THF (290 mL) was added a solution of 3-(3,4-dimethylphenyl)propionamide (19.3 g, 0.109 mol) in THF (160 mL), and the mixture was heated at reflux temperature for 5 h. MeOH, H2O followed by 1N NaOH solutions were added and the resulting mixture was passed through a celite pad. The filtrate was concentrated under reduced pressure and purified by vacuum distillation to give 8a (15.3 g, 86%); bp 140-150 °C (0.5 mmHg); 1H NMR (CDCl3) δ 1.32 (br s, 2H, NH2), 1.74 (quint, J=7 Hz, 2H, CH2), 2.23 (s, 3H, CH3), 2.24 (s, 3H, CH3), 2.59 (t, J=7 Hz, 2H, CH2), 2.72 (t, J=7 Hz, 2H, CH2), 6.91-7.06 (m, 3H, ArH).

3-(4-Fuoro-3-methylphenyl)propionamide 11a. The crude solid was recrystallized from CHCl3/n-hexane to give 11e (1.79 g, 9.47 mmol) and 10% Pd/C (0.18 g) in MeOH (20 mL) was carried out for 24 h as described for 8a to give 3-(4,5-trimethylphenyl)propionamide (1.68 g, 93%) as a white solid; mp 143-147 °C; 1H NMR (CDCl3) δ 2.18 (s, 6H, 2CH3), 2.24 (s, 3H, CH3), 2.49 (t, J=7.3 Hz, 2H, CH2), 2.90 (t, J=7.3 Hz, 2H, CH2), 5.34 (br s, 2H, NH2), 6.90 (s, 2H, ArH); EIMS m/z (rel. intensity) 191 (M+, 19), 174 (45), 146 (29), 133 (100).

Reaction of 3-(4,5-trimethylphenyl)propionamide (1.63 g, 8.63 mmol) and LiAlH4 was carried out as described for 8a, and the crude was purified by column chromatography to give 8e (1.24 g, 82%) as a colorless oil; 1H NMR (CDCl3) δ 1.69 (quint, J=7.3 Hz, 2H, CH2), 1.26 (s, 6H, 2CH3), 2.34 (s, 3H, CH3), 2.56 (t, J=7.0 Hz, 2H, CH2), 2.75 (t, J=7.0 Hz, 2H, CH2), 6.90 (s, 2H, ArH); EIMS m/z (rel. intensity) 177 (M+, 7), 160 (45), 147 (100), 133 (28).

3-(2,3,5,6-Tetramethylphenyl)propionamide 8d. A mixture of 11d (680 mg, 3.49 mmol) and 10% Pd/C (70 mg) in MeOH (20 mL) was carried out for 24 h as described for 8a to give 3-(2,3,5,6-tetramethylphenyl)propionamide (650 mg, 87%) which was used for next step without further purification: 1H NMR (CDCl3) δ 2.24 (s, 12H, 4CH3), 2.39 (t, J=8.6 Hz, 2H, CH2), 3.08 (t, J=8.6 Hz, 2H, CH2), 5.38 (br s, 2H, NH2), 6.89 (s, 2H, ArH).

Reaction of 3-(2,3,5,6-tetramethylphenyl)propionamide (650 mg, 3.38 mmol) and LiAlH4 was carried out as described for 8a, and the crude was purified by vacuum distillation using Kugelrohr apparatus to give 8d (850 mg, 90%) as a colorless oil; 1H NMR (CDCl3) δ 1.65 (quint, J=7.1 Hz, 2H, CH2), 2.20 (s, 6H, 2CH3), 2.22 (s, 2CH2), 2.69 (t, J=7.1 Hz, 2H, CH2), 2.83 (t, J=7.1 Hz, 2H, CH2), 6.84 (s, 1H, ArH).

3-Naphthalen-1-ylpropionamide 8e. A mixture of 11e (1.69 g, 8.48 mmol) and 10% Pd/C (160 mg) in MeOH (20 mL) was carried out for 24 h as described for 8a to give 3-naphthalen-1-ylpropionamide (650 mg, 87%) which was used for next step without further purification: mp 99-101 °C; 1H NMR (CDCl3) δ 2.48 (t, J=7.6 Hz, 2H, CH2), 3.29 (t, J=7.6 Hz, 2H, CH2), 6.83 (br s, 2H, NH2), 7.35-7.58 (m, 4H, ArH), 7.60-7.79 (m, 1H, ArH), 7.90-7.95 (m, 1H, ArH), 8.07-8.12 (m, 1H, NH), EIMS m/z 199 (M+, 32), 153 (79), 141 (100).

Reaction of 3-naphthalen-1-ylpropionamide (1.60 g, 8.04 mmol) and LiAlH4 (603 mg, 15.9 mmol) was carried out as described for 8a, and the crude was purified by column chromatography to give 8e (910 mg, 61%) as a colorless oil; 1H NMR (CDCl3) δ 1.88 (quint, J=7.6 Hz, 2H, CH2), 2.02 (br s, 2H, NH2), 2.80 (t, J=7.0 Hz, 2H, CH2), 3.10 (t, J=7.6 Hz, 2H, CH2), 7.30-7.54 (m, 4H, ArH), 7.67-7.71 (m, 1H, ArH), 7.79-7.85 (m, 1H, ArH), 8.02-8.08 (m, 1H, ArH).

3-Phenyl-3-m-tolylacrylamide 12a. Reaction of 3-phenylacrylamide (2.2 g, 14.7mmol) and iodobenzene in ODCB was carried out for 24 h as described for 11a to give 12a (2.6 g, 75%): 1H NMR (CDCl3) δ 2.33 (s, 3H, ArCH3), 5.14 (br s, 1H, ArH), 6.98-7.05 (m, 3H, ArH); EIMS m/z (rel. intensity) 197 (M+, 19), 174 (45), 146 (29), 133 (100).
1H, NH), 5.57 (br s, 1H, NH), 6.38 (s, 1H, ArCH), 7.04-7.48 (m, 9H, ArH). EIMS m/z (rel. intensity) 225 (M⁺, 9), 208 (51), 193 (100), 179 (72), 165 (87).

3-(2,3-Dimethylphenyl)-3-phenylacrylamide 12b. A solution of 3-phenylacrylamide (1.5 g, 10.1 mmol), tri-o-tolylphosphine (185 mg, 0.6 mmol), and Et₃N (1.2 g, 12.2 mmol) in ODCB (20 mL) was heated at reflux temperature for 2 days. The reaction mixture was passed through a pad of celite and the filtrate was concentrated in vacuo. Water was added and the mixture was extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and purified by column chromatography to give 12b (1.4 g, 55%) as a white solid: mp 131-133 °C; 1H NMR (CDCl₃) δ 8.07-8.15 (m, 9H, ArH); EIMS m/z (rel. intensity) 240 (M⁺, 18), 239 (24), 227 (39), 223 (40), 221 (22).

3-(3,4-Dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propylamine 13a. A mixture of 3-(3,4-dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propylamine (1.1 g, 51%) as a white solid: mp 99-100 °C; 1H NMR (DMSO-d₆) δ 2.20 (s, 3H, ArCH₃), 2.26 (s, 3H, ArCH₃), 5.75 (s, 1H, CH), 5.94 (br s, 2H, NH₂), 7.11-7.35 (m, 10H, ArH); EIMS m/z (rel. intensity) 284 (M⁺, 26), 283 (100), 282 (100), 286 (50), 267 (39), 239 (34), 133 (48).

3-Phenyl-3-thiophen-3-yl-acrylamide 13b. Reaction of 3-(3,4-dimethylphenyl)-2-methyl-2-propenamide 8a to give 13b (99%). 1H NMR (CDCl₃) δ 1.46 (br s, 2H, NH₂), 2.15 (s, 3H, CH₃), 2.20 (s, 6H, 2CH₃), 2.05-2.15 (m, 2H, CH₂), 2.62 (t, J=7.2 Hz, 2H, CH₂), 3.87 (t, J=7.0 Hz, 1H, CH), 6.87-7.04 (m, 6H, ArH). EIMS m/z (rel. intensity) 277 (M⁺, 6), 254 (24), 240 (20), 239 (100), 197 (39), 176 (21).

3-Phenyl-3-thiophen-3-yl-propionamide 13c. A mixture of 3-(3,4-dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propionamide (240 mg, 0.84 mmol) and LiAlH₄ was carried out as described for 8a to give 13c (200 mg, 83%). 1H NMR (CDCl₃) δ 2.38 (dd, J=14.5, 7.8 Hz, 1H, CH), 2.96 (dd, J=14.5, 7.4 Hz, 1H, CH), 4.59 (t, J=7.7 Hz, 1H, CH), 6.88-6.91 (m, 1H, ArH), 6.98-7.00 (m, 1H, ArH), 7.19-7.29 (m, 6H, ArH). Reaction of 3-phenyl-3-thiophen-3-yl-propionamide (320 mg, 1.38 mmol) and LiAlH₄ was carried out as described for 8a to give 13d (160 mg, 54%) as an oil: 1H NMR (CDCl₃) δ 2.15-2.25 (m, 2H, CH₂), 2.64-2.71 (m, 4H, CH₂ and NH₂), 4.09 (t, J=7.5 Hz, 1H, CH), 6.87-6.90 (m, 1H, ArH), 6.97-6.99 (m, 1H, ArH), 7.16-7.30 (m, 6H, ArH). EIMS m/z (rel. intensity) 217 (M⁺, 7), 200 (80), 185 (27), 173 (61), 71 (100).
mL) was carried out for 3 h as described for 8a to give 3-(3,4-dimethylphenyl)-2-methyl-2-propanamide (5.4 g, 99%) as a crude which was used for next step without further purification: mp 95-96 °C; 1H NMR (CDCl3) δ 1.18 (d, J=6.0 Hz, 3H, CH3), 2.22 (s, 6H, 2CH3), 2.46-2.65 (m, 2H, CH2), 2.88-2.94 (m, 1H, CH), 5.27 (br s, 1H, NH), 5.50 (br s, 1H, NH), 7.02-7.26 (m, 3H, ArH); EIMS m/z (rel. intensity) 191 (M+, 14), 174 (12), 159 (41), 133 (41), 119 (100), 115 (12), 91 (28).

Reaction of 3-(3,4-dimethylphenyl)-2-methyl-2-propanamide (5.4 g, 28 mmol) and LiAlH4 (2.0 g, 52.6 mmol) in THF was carried out as described for 8a to give 16 (4.5 g, 90%) as an oil: 1H NMR (CDCl3) δ 0.87 (d, J=6.0 Hz, 3H, CH3), 1.15 (d, J=6.9 Hz, 3H, CH3), 1.34 (br s, 2H, NH2), 1.67-1.78 (m, 1H, CH), 2.22 (s, 6H, 2CH3), 2.24-2.35 (m, 1H, CH), 2.44-2.69 (m, 2H, CH2), 6.85-7.24 (m, 3H, ArH).

4-(3,4-Dimethylphenyl)-3-buten-2-one 18. Reaction of 4-iodo-o-xylene (6.0 g, 25.9 mmol), methyl vinyl ketone (2.8 g, 40.0 mmol), Pd(OAc)2 (0.4 g, 1.8 mmol), tri-o-tolylphosphine (0.5 g, 1.8 mmol), and Et3N (15 mL, 107 mmol) in MeCN (15 mL) was carried out for 6 h as described for 11a. The crude was purified by column chromatography (EtOAc:n-hexane = 1:4) to give 18 as a white solid: mp 50-51 °C; 1H NMR (CDCl3) δ 0.87 (d, J=6.8 Hz, 3H, CH3), 1.15 (d, J=6.9 Hz, 3H, CH3), 1.34 (br s, 2H, NH2), 1.67-1.78 (m, 1H, CH), 2.22 (s, 6H, 2CH3), 2.46-2.65 (m, 2H, CH2), 6.91-7.08 (m, 3H, ArH); EIMS m/z (rel. intensity) 191 (M+, 14), 174 (12), 159 (41), 133 (41), 119 (100), 115 (12), 91 (28).

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References