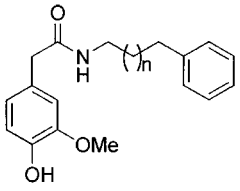
Synthesis of 3-Arylpropylamine Derivatives from Aryl Halides Using Heck Reaction

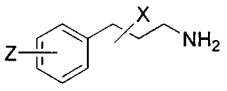
Gi Hyeon Baek, Sung Ju Cho, Young Sik Jung, Churl-Min Seong, Chang-Woo Lee, and No-Sang Park*

Bioorganic Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejon 305-606, Korea
Received November 27, 1998

As a part of our research directed toward the development of new capsaicinoids as analgesics,[1] 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.[2] 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**.

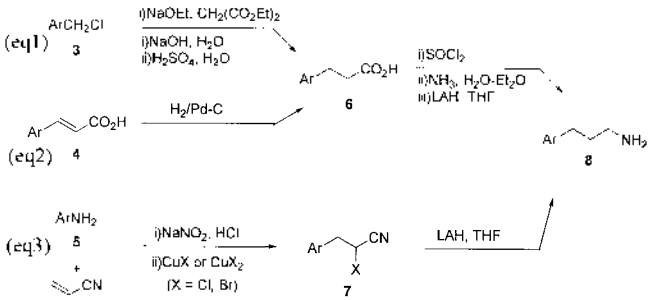


1



2

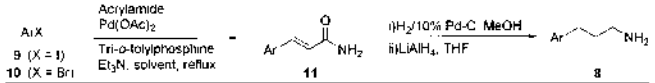
Our initial attempt to synthesize **2** began with two-carbon homologation of substituted benzylchloride **3** using malonate chemistry to give 3-arylpropionic acid **6**, which was converted to corresponding amine **8** (eq. 1).[3] Palladium-catalyzed hydrogenation of substituted cinnamic acid **4** also gave 3-arylpropionic 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-arylpropionitrile **7** and then $LiAlH_4$ reduction of **7** provided corresponding amine **8**. However, apperance 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.[5] 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-arylpropylamine 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) $LiAlH_4$ reduction of 3-arylpropionamide.

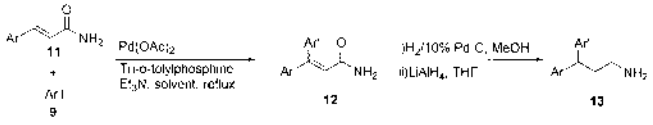
3-Arylacrylamide **11a**, **11b**, **11e** were obtained in high yields from either aryl iodide **9** or bromide **10** under typical Heck reaction condition using $Pd(OAc)_2$, tri-*o*-tolylphosphine, and Et_3N in MeCN.[5] However, reaction of sterically bulky aryl bromide **10** having methyl substituent at C-2 or C-6 position (**11c**, **11d**) was not completed within 2 days and gave low yields (Table 1). 3-Arylpropylamine **8** was obtained from **11** through conventional palladium-catalyzed hydrogenation followed by $LiAlH_4$ reduction. Even though $LiAlH_4$ 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-diarylpropylamine **13**. The introduction of second aryl group to **11** was also done by Heck reaction conditions to provide 3,3-diaryl 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-diarylpropylamine **13** as described for **8**. Finally, 3-arylpropylamine **16** or **20** which has methyl group on aliphatic chain was provided from **14** or **17** (Scheme 1).

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

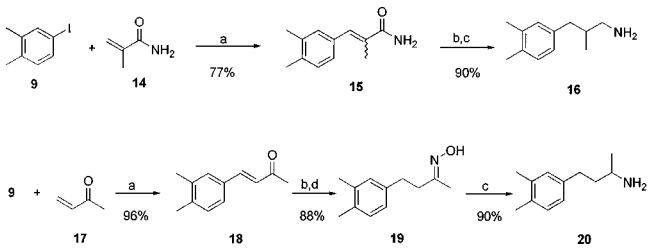


9 or 10	11	(time, yield)	11 to 8 (yield)	
			step (i)	step (ii)
3,4-Me_2-PhI	**11a**	1h, 92%	90%	86%
3-Me,4-F-PhBr	**11b**	24h, 92%	96%	79%
2,4,5-Me_3-PhBr	**11c**	2days, 63%	93%	82%
2,3,5,6-Me_4-PhBr	**11d**	2days, 25%	87%	90%
1-Bromonaphthalene	**11e**	6h, 89%	96%	61%

Table 2. Synthesis of 3,3-Diarylpropylamine **13** from 3-Arylacrylamide **11** and Aryl iodide **9**



11 (Ar)	**9** (Ar′)	**12**	(condition, yield)	**12** to **13** (yield)	
				step (i)	step (ii)
Ph	3-Me-Ph	**12a**	ODCB, 24h, 75%	91%	99%
Ph	2,3-Me_2-Ph	**12b**	ODCB, 2day, 55%	98%	90%
3-Me-4-F-Ph	3,4-Me_2-Ph	**12c**	DMF, 3days, 95%	90%	83%
3-Thionyl	Ph	**12d**	DMF, 3days, 51%	75%	54%



Scheme 1. (a) $Pd(OAc)_2$, Tri-o-tolylphosphine, Et_3N, CH_3CN, reflux. (b) H_2/10% Pd-C, MeOH. (c) $LiAlH_4$, THF, r.t. (d) NH_2OH-HCl, $NaHCO_3$.

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

Experimental Section

All reactions were carried out under N_2 atmosphere unless otherwise noted. MeCN was distilled from CaH_2 prior to use. Organic extracts or filtrates were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography was performed with Merck-EM Type 60 (230-400 mesh) silica gel (flash). ^1H NMR spectra were measured by Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS as internal standard. Mass spectrometric data determined by use of the electron impact (EIMS) method are reported as m/z (relative intensity). Melting points were uncorrected.

General method of Heck reaction. A mixture of aryl halide, acrylamide (1.1 equivalent of aryl halide), $Pd(OAc)_2$ (1 to 4 mol % of aryl halide), tri-*o*-tolylphosphine (4 to 10 mol % of aryl halide), and Et_3N (1.1 to 1.5 equivalent of aryl halide) in MeCN, DMF, or ODCB was heated at reflux temperature. The reaction was monitored by TLC. The mixture was passed through a celite pad. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude solid which was recrystallized from EtOAc/n-hexane.

3-(3,4-Dimethylphenyl)acrylamide 11a. A mixture of 4-iodo-*o*-xylene (30.21 g, 0.13 mol), acrylamide (11.54 g, 0.16 mol), $Pd(OAc)_2$ (0.29 g, 1.3 mmol), tri-*o*-tolylphosphine (1.58 g, 5.2 mmol), and Et_3N (23 mL, 0.16 mol) in MeCN (54 mL) was heated at 100-105 °C for 1 h. The mixture was passed through a celite pad. Water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude solid. 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 ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 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, 12 mmol), acrylamide (1.02 g, 14.4 mmol), $Pd(OAc)_2$ (54 mg, 0.24 mmol), tri-*o*-tolylphosphine (219 mg, 0.72 mmol), and Et_3N (2.0 mL, 14.4 mmol) in CH_3CN (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-d_6) δ 2.34 (s, 3H, CH_3), 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^+, 56), 178 (100), 164 (62), 163 (63), 135 (60), 133 (87), 115 (77).

3-(2,4,5-Trimethylphenyl)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), Et_3N (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 Na_2SO_4, and concentrated under reduced pressure. 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 ($CDCl_3$) δ 2.28 (s, 6H, $2CH_3$), 2.36 (s, 3H, CH_3), 5.53 (br s, 2H, NH_2), 6.32 (d, *J*=15.5 Hz, 1H, CH), 6.67 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.88 (d, *J*=15.5 Hz, 1H, CH).

3-(2,3,5,6-Tetramethylphenyl)acrylamide 11d. 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), Et_3N (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 **11d** (0.68 g, 25%) as a white solid: mp 216-217 °C; ^1H NMR ($CDCl_3$) δ 2.19 (s, 6H, $2CH_3$), 2.26 (s, 6H, $2CH_3$), 5.60 (br s, 2H, NH_2), 5.93 (d, *J*=16.1 Hz, 1H, CH), 6.97 (s, 1H, ArH), 7.82 (d, *J*=16.1 Hz, ArCH).

3-Naphthalen-1-ylacrylamide 11e. 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 Et_3N (1.72 g, 11.6 mmol) in CH_3CN (25 mL) was carried out for 6 h as described for

11a. The crude solid was recrystallized from CH_2Cl_2/n-hexane to give **11c** (1.69 g, 89%) as a white soild: mp 177-178.5 °C; ^{1}H NMR (DMSO-d_6) δ 6.65 (d, *J* 15.7 Hz, 1H, CH), 7.20 (br s, 1H, NH_2), 7.51-7.61 (m, 3H, ArH), 7.65 (br s, 1H, NH_2), 7.76-7.79 (m, 1H, ArH), 7.95-7.99 (m, 2H, ArH), 8.18-8.23 (m, 1H, ArH), 8.20 (d, *J* 15.7 Hz, 1H, CH); EIMS m/z (rel. intensity) 197 (M^+, 19), 155 (67), 154 (100).

General Method of Hydrgenation Reaction of Acrylamide. A mixture of acrylamide and 10% Pd/C (10 wt % of acrylamide) in MeOH was stirred under H_2. 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 $LiAlH_4$ Reduction of Propionamide. To a mixture of $LiAlH_4$ in THF was added a solution of propionamide in THF, and the mixture was stirred at *r.t.* or heated at reflux temperature. MeOH, H_2O 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)propylamine 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 H_2 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; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6H, $2ArCH_3$), 2.49 (t, *J* 7 Hz, 2H, CH_2), 2.88 (t, *J* 7 Hz, 2H, CH_2), 5.60 (br s, 1H, NH), 6.02 (br s, 1H, NH), 6.89-7.25 (m, 3H, ArH).

To a mixture of $LiAlH_4$ (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, H_2O 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); ^{1}H NMR ($CDCl_3$) δ 1.32 (br s, 2H, NH_2), 1.74 (quint, *J* 7 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.59 (t, *J* 7 Hz, 2H, CH_2), 2.72 (t, *J* 7 Hz, 2H, CH_2), 6.91-7.06 (m, 3H, ArH).

3-(4-Fuoro-3-methylphenyl)propylamine 8b. A mixture of **11b** (1.4 g, 7.8 mmol) and 10% Pd/C (0.14 g) in MeOH (20 mL) was carried out for 24 h as described for **8a** to give 3-(4-fuoro-3-methylphenyl)propionamide (1.36 g, 96%) as a white solid: mp 93-94 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 2.48 (t, *J* 7.5 Hz, 2H, CH_2), 2.89 (t, *J* 7.5 Hz, 2H, CH_2), 5.40 (br s, 2H, NH_2), 6.84-7.01 (m, 3H, ArH); EIMS m/z (rel. intensity) 181 (M^+, 37), 136 (54), 123 (100).

Reaction of 3-(4-fuoro-3-methylphenyl)propionamide (1.21 g, 6.2 mmol) and $LiAlH_4$ (47 mg, 12.4 mmol) was carried out as described for **8a**, and the crude was purified by vacuum distillation to give **8b** (820 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 1.35 (br s, 2H, NH_2), 1.71 (quint, *J* 7.3 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.58 (t, *J* 7.3 Hz, 2H, CH_2), 2.69 (t, *J* 7.3 Hz, 2H, CH_2), 6.83-7.00 (m, 3H, ArH); EIMS m/z (rel. intensity) 167 (M^+, 4), 166 (18), 150 (23), 135 (19).

3-(2,4,5-Trimethylphenyl)propylamine 8c. A mixture of **11c** (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-(2,4,5-trimethylphenyl)propionamide (1.68 g, 93%) as a white solid: mp 143-147 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6H, $2CH_3$), 2.24 (s, 3H, CH_3), 2.49 (t, *J* 7.3 Hz, 2H, CH_2), 2.90 (t, *J* 7.3 Hz, 2H, CH_2), 5.34 (br s, 2H, NH_2), 6.90 (s, 2H, ArH); EIMS m/z (rel. intensity) 191 (M^+, 74), 174 (45), 146 (29), 133 (100).

Reaction of 3-(2,4,5-trimethylphenyl)propionamide (1.63 g, 8.63 mmol) and $LiAlH_4$ was carried out as described for **8a**, and the crude was purified by column chromatography to give **8c** (1.24 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.69 (quint, *J* 7.3 Hz, 2H, CH_2), 2.16 (s, 6H, $2CH_3$), 2.34 (s, 3H, CH_3), 2.56 (t, *J* 7.0 Hz, 2H, CH_2), 2.75 (t, *J* 7.0 Hz, 2H, CH_2), 6.90 (s, 2H, ArH); EIMS m/z (rel. intensity) 177 (M^+, 7), 160 (47), 145 (100), 133 (28).

3-(2,3,5,6-Tetramethylphenyl)propylamine 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: ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 12H, $4CH_3$), 2.39 (t, *J* 8.6 Hz, 2H, CH_2), 3.08 (t, *J* 8.6 Hz, 2H, CH_2), 5.38 (br s, 2H, NH_2), 6.89 (s, 2H, ArH).

Reaction of 3-(2,3,5,6-tetramethylphenyl)propionamide (650 mg, 3.38 mmol) and $LiAlH_4$ was carried out as described for **8a**, and the crude was purified by vacuum distillation using Kugelrohr apparatus to give **8d** (580 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.65 (quint, *J* 7.1 Hz, 2H, CH_2), 2.20 (s, 6H, $2CH_3$), 2.22 (s, $2CH_3$), 2.69 (t, *J* 7.1 Hz, 2H, CH_2), 2.83 (t, *J* 7.1 Hz, 2H, CH_2), 6.84 (s, 1H, ArH).

3-Naphthalen-1-ylpropylamine 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; ^{1}H NMR ($CDCl_3$) δ 2.48 (t, *J* 7.6 Hz, 2H, CH_2), 3.29 (t, *J* 7.6 Hz, 2H, CH_2), 6.83 (br s, 2H, NH_2), 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, ArH); EIMS m/z 199 (M^+, 32), 153 (79), 141 (100).

Reaction of 3-naphthalen-1-ylpropionamide (1.60 g, 8.04 mmol) and $LiAlH_4$ (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: ^{1}H NMR ($CDCl_3$) δ 1.88 (quint, *J* 7.6 Hz, 2H, CH_2), 2.02 (br s, 2H, NH_2), 2.80 (t, *J* 7.0 Hz, 2H, CH_2), 3.10 (t, *J* 7.6 Hz, 2H, CH_2), 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%): ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H, $ArCH_3$), 5.14 (br s,

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) 237 (M^+, 63), 236 (100), 178 (56), 115 (33).

3-(2,3-Dimethylphenyl)-3-phenylacrylamide 12b. A solution of 3-phenylacrylamide (1.5 g, 10.1 mmol), 3-iodo-*o*-xylene (2.8 g, 12.1 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol), tri-*o*-tolylphosphine (185 mg, 0.6 mmol), and Et_3N (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 CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography to give **12b** (1.4 g, 55%) as a white solid: mp 138-140 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 6H, CH_3), 6.01 (s, 1H, CH), 7.07-7.37 (m, 10H, NH_2, ArH); EIMS m/z (rel. intensity) 251 (M^+, 22), 236 (90), 206 (100).

3-(3,4-Dimethylphenyl)-3-(4-fluoro-3-methylphenyl)acrylamide 12c. Reaction of 3-(4-fluoro-3-methylphenyl)acrylamide **11b** (180 mg, 1.00 mmol), 4-iodo-*o*-xylene (280 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), tri-*o*-tolylphosphine (18.3 mg, 0.06 mmol), and Et_3N (122 mg, 1.2 mmol) in DMF (10 mL) was carried out for 3 days as described for **12b** to give **12c** (270 mg, 95%) as a white solid: mp 99-100 °C; ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 9H, $3CH_3$), 6.43 (s, 1H, CH), 6.94-7.22 (m, 8H, NH_2, 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 12d. Reaction of 3-thiophen-3-yl-acrylamide (1.46 g, 9.5 mmol) and iodobenzene was carried out in DMF for 3 days as described for **11b** to give **12d** (1.1 g, 51%) as a white solid: mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 5.30 (br s, 2H, NH_2), 6.42 (s, 1H, CH), 6.88-7.50 (m, 8H, ArH); EIMS m/z (rel. intensity) 229 (M^+, 95), 184 (100), 152 (37), 139 (26).

3-Phenyl-3-*m*-tolylpropylamine 13a. A mixture of **12a** (2.6 g, 11 mmol) and 10% Pd/C in MeOH was carried out for 17 h as described for **8a** to give 3-phenyl-3-*m*-tolylpropionamide (2.4 g, 91%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 2.91 (d, 2H, *J* 7.7 Hz, CH_2), 4.48 (t, 1H, *J* 7.7 Hz, CH), 5.29 (br s, 2H, NH_2), 6.96-7.31 (m, 9H, ArH); EIMS m/z (rel. intensity) 239 (M^+, 54), 194 (49), 181 (100), 167 (65), 166 (70), 165 (73).

Reaction of 3-phenyl-3-*m*-tolylpropionamide (2.4 g, 10 mmol) and $LiAlH_4$ was carried out as described for **8a** to give **13a** (2.24 g, 99%): ^{1}H NMR ($CDCl_3$) δ 1.20 (br s, 2H, NH_2), 2.10-2.21 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.63 (t, *J* 7.0 Hz, 2H, NCH_2), 3.95 (t, *J* 7.8 Hz, 1H, CH), 6.94-7.25 (m, 9H, ArH); EIMS m/z (rel. intensity) 225 (M^+, 9), 208 (51), 193 (100), 166 (72), 165 (75).

3-(2,3-Dimethylphenyl)-3-phenylpropylamine 13b. A mixture of **12b** (800 mg, 3.2 mmol) and 10% Pd/C in MeOH was carried out for 22 h as described for **8a** to give 3-(2,3-dimethylphenyl)-3-phenylpropionamide (800 mg, 98%) as crude which was used for next step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6H, CH_3), 2.90 (d, *J* 7.6 Hz, 2H, CH_2), 4.82 (t, *J* 7.6 Hz, 1H, CH), 5.35 (br s, 2H, NH_2), 7.03-7.29 (m, 8H, ArH); EIMS m/z (rel. intensity) 253 (M^+, 56), 195 (99), 180 (100), 179 (94), 165 (68).

Reaction of 3-(2,3-dimethylphenyl)-3-phenylpropionamide (830 mg, 3.3 mmol) and $LiAlH_4$ was carried out as described for **8a** to give **13b** (800 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 1.84 (br s, 2H, NH_2), 2.10-2.28 (m, 2H, CH_2), 2.18 (s, 3H, $ArCH_3$), 2.26 (s, 3H, $ArCH_3$), 2.70 (t, *J* 7.3 Hz, 2H, CH_2), 4.29 (t, *J* 7.5 Hz, 1H, CH), 7.02-7.33 (m, 8H, ArH); EIMS m/z (rel. intensity) 240 (M^+, 18), 208 (59), 207 (100), 179 (72), 165 (87).

3-(3,4-Dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propylamine 13c. A mixture of **12c** (250 mg, 0.9 mmol) and 10% Pd/C in MeOH was carried out for 20 h as described for **8a** to give 3-(3,4-dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propionamide (240 mg, 96%) as a white solid: mp 100-101 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 9H, $3CH_3$), 2.89 (d, *J* 7.6 Hz, 2H, CH_2), 4.42 (t, *J* 7.6 Hz, 1H, CH), 5.25 (br s, 2H, NH_2), 6.85-7.08 (m, 6H, ArH); EIMS m/z (rel. intensity) 285 (M^+, 42), 240 (36), 228 (39), 227 (100), 225 (21), 212 (32), 221 (22).

Reaction of 3-(3,4-dimethylphenyl)-3-(4-fluoro-3-methylphenyl)propionamide (240 mg, 0.84 mmol) and $LiAlH_4$ was carried out as described for **8a** to give **13c** (190 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 1.46 (br s, 2H, NH_2), 2.15 (s, 3H, CH_3), 2.20 (s, 6H, $2CH_3$), 2.05-2.15 (m, 2H, CH_2), 2.62 (t, *J* 7.2 Hz, 2H, CH_2), 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-propionamine 13d. A mixture of **12d** (400 mg, 1.92 mmol) and 10% Pd/C (50 mg) in MeOH (50 mL) was carried out for 24 h as described for **8a** to give 3-phenyl-3-thiophen-3-yl-propionamide (330 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 2.83 (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 $LiAlH_4$ was carried out as described for **8a** to give **13d** (160 mg, 54%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.15-2.25 (m, 2H, CH_2), 2.64-2.71 (m, 4H, CH_2 and NH_2), 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 217 (M^+, 7), 200 (80), 185 (27), 173 (61), 71 (100).

3-(3,4-Dimethylphenyl)-2-methyl-2-propenamide 15. Reaction of 4-iodo-*o*-xylene **9** (10.0 g, 43.1 mmol), methacrylamide **14** (9.0 g, 107 mmol), $Pd(OAc)_2$ (0.4 g, 1.8 mmol), tri-*o*-tolylphosphine (1.0g, 3.3 mmol), and Et_3N (15 mL, 107 mmol) in MeCN (15 mL) was carried out for 15 h as described for **11a**. The crude was recrystallized (EtOAc/n-hexane) to give **15** (6.3 g, 77%) as a white solid: mp 84-86 °C; ^{1}H-NMR ($CDCl_3$) δ 2.11 (s, 3H, CH_3), 2.26 (s, 6H, $2CH_3$), 5.75 (s, 1H, CH), 5.94 (br s, 2H, NH_2), 7.11-7.35 (m, 3H, ArH); EIMS m/z (rel. intensity) 189 (M^+, 56), 188 (50), 174 (87), 144 (66), 128 (100), 115 (55), 91 (35), 77 (37).

3-(3,4-Dimethylphenyl)-2-methyl-2-propanamine 16. Reaction of 3-(3,4-dimethylphenyl)-2-methyl-2-propenamide **15** (5.4 g, 28.6 mmol) and Pd/C (10%) in MeOH (160

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; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, *J* 6.0 Hz, 3H, CH_3), 2.22 (s, 6H, $2CH_3$), 2.46-2.65 (m, 2H, CH_2), 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^+, 73), 190 (39), 176 (26), 159 (27), 146 (52), 119 (100).

Reaction of 3-(3,4-dimethylphenyl)-2-methyl-2-propanamide (5.4 g, 28 mmol) and $LiAlH_4$ (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: ^{1}H NMR ($CDCl_3$) δ 0.87 (d, *J* 6.8 Hz, 3H, CH_3), 1.34 (br s, 2H, NH_2), 1.67-1.78 (m, 1H, CH), 2.22 (s, 6H, $2CH_3$), 2.24-2.35 (m, 1H, CH), 2.44-2.69 (m, 3H, $C\underline{H}_2CH(CH_3)C\underline{H}_2$), 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 Et_3N (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** (4.3 g, 96%) as a white solid: mp 50-51 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H, $2CH_3$), 2.38 (s, 3H, $COCH_3$), 6.68 (d, *J* 16.4 Hz, 1H, CH), 7.15-7.33 (m, 3H, ArH), 7.48 (d, *J* 16.4 Hz, 1H, CH); EIMS m/z (rel. intensity) 174 (M^+, 14), 159 (100), 131 (28), 115 (37), 91 (42), 77 (19).

4-(3,4-Dimethylphenyl)-3-butanone oxime 19. Reaction of 4-(3,4-dimethylphenyl)-3-buten-2-one **18** (4.0 g, 23.0 mmol) and Pd/C (10%) in EtOAc (60 mL) was carried out for 3 h as described for **8a** to give 4-(3,4-dimethylphenyl)-3-butanone (3.9 g, 96%): ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, $COCH_3$), 2.24 (s, 3H, CH3), 2.25 (s, 3H, CH_3), 2.71-2.89 (m, 4H, CH_2CH_2), 6.91-7.08 (m, 3H, ArH); EIMS m/z (rel. intensity) 176 (M^+, 40), 133 (84), 119 (100), 105 (20), 84 (24), 77 (20).

A mixture of 4-(3,4-dimethylphenyl)-3-butanone (3.9 g, 22.1 mmol), hydroxylamine hydrochloride (3.1 g, 44.6 mmol), and $NaHCO_3$ (3.7 g, 44.2 mmol) in a mixture solvent of MeOH/H_2O (25 mL/45 mL) was stirred for 17 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give **19** (3.9 g, 92%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, $COCH_3$), 2.22 (s, 3H, CH_3), 2.23 (s, 3H, $2CH_3$), 2.48 (t, *J* 7.8 Hz, 2H, $C\underline{H}_2CH_2C(NOH)$), 2.76 (t, *J* 7.5 Hz, 2H, $CH_2C\underline{H}_2C(NOH)$), 6.92-7.06 (m, 3H, ArH); EIMS m/z (rel. intensity) 191 (M^+, 14), 174 (12), 159 (14), 133 (41), 119 (100), 115 (12), 91 (28).

3-(3,4-Dimethylphenyl)-1-methylpropylamine 20. To a solution of 4-(3,4-dimethylphenyl)-3-butanone oxime **19** (3.9 g, 20.4 mmol) in THF (80 mL) was added $LiAlH_4$ (1.5 g, 40.0 mmol) and stirred at *r.t.* for 12 h. Normal workup as described for **8a** gave **20** (3.2 g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.15 (d, *J* 6.3 Hz, 3H, CH_3), 1.68 (q, *J* 7.7 Hz, 2H, $CH_2C\underline{H}_2CH(CH_3)NH_2$), 2.22 (s, 6H, $2CH_3$), 2.56-2.63 (m, 2H, $C\underline{H}_2CH_2CH(CH_3)NH_2$), 2.89-3.02 (m, 1H, CH), 6.92-7.05 (m, 3H, ArH); EIMS m/z (rel. intensity) 177 (M^+, 5), 160 (48), 145 (54), 119 (51), 105 (16), 91 (26), 85 (37), 77 (21).

Acknowledgment. This work was financially supported by the Korea Ministry of Science and Technology.

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