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A practical and efficient synthesis of (*E*)-β-aryl-α,β-unsaturated amides

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ABSTRACT

In this paper, we report a one-step convergent synthesis of (*E*)-β-monosubstituted α,β-unsaturated amides **3** from α-sulfonyl acetamide **1** and benzyl bromide derivatives **2**.

1. Introduction

The development of methodologies for the formation of carbon–carbon double bonds could be considered one of the most important challenges in organic synthesis.[1] α,β-Unsaturated amides are an important class of compounds because of their presence in the structure of natural products[2] and their role as a reaction partner in many useful reactions such as conjugate addition of copper[3] and Grignard[4] reagents and other reactions.[5] They are often employed as starting materials to obtain many natural products[6] as exemplified by the recent syntheses of deplancheine, tacamonine, and paroxetine.[6e] Furthermore, a number of non-natural acrylamide derivatives have also shown both important biological and insecticidal activities.[1,7]

Although many methods have been developed for the synthesis of α,β-unsaturated amides,[3d,7c,8] the development of simple and efficient routes toward their synthesis remains an area of research interest. However, to the best of our knowledge, no synthetic method for (*E*)-β-monosubstituted α,β-unsaturated amides from benzyl halide derivatives and α-sulfonyl acetamides has been reported.

Recently, we have been interested in the chemistry of α-sulfonyl acetamides and successfully applied them to the synthesis of glutarimide and pyroglutamate skeletons via Michael addition and substitution reactions (Fig. 1).[9]

In this paper, we report a new approach to (*E*)-β-aryl-α,β-unsaturated amides. Instead of using aldehydes, phosphorus, silicon containing compounds, and metal catalysts for the synthesis of double bonds, α-sulfonyl acetamide **1** and various benzyl bromides **2** were used as starting materials (Fig. 2).

2. Results and discussion

2.1. Synthesis of (*E*)-β-aryl-α,β-unsaturated amides (3a)

The procedure used for this approach is exemplified by the reaction of α-toluenesulfonyl acetamide **1a** with 4-nitrobenzyl bromide **2a**. After the reaction of **1** in THF with 2.2 equiv of sodium hydride, the resulting anion was reacted with 4-nitrobenzyl bromide to afford the corresponding (*E*)-β-aryl acrylamide derivative **3aa** in 90% yield.

As shown in Table 1, reactions of **1a** with benzyl bromide bearing strong electron-withdrawing substituents (such as nitro and cyano groups) furnished the corresponding (*E*)-β-aryl-α,β-unsaturated acetamides at room temperature in a short period of time (entries 1–6). Apparently, the strong electron-withdrawing groups activate the substitution–elimination process. When **1a** was reacted with halogen substituted benzyl bromides, higher temperature and longer reaction times were required to yield the desired products (entries 7–11).

It is interesting to note that besides entry 2,[10] all of the benzyl halides afforded β-aryl-α,β-unsaturated amides in moderate to high yields and with (*E*)-selectivity. The geometry of the products was determined by the characteristic coupling constants between the two olefinic protons from ^{1}H NMR.

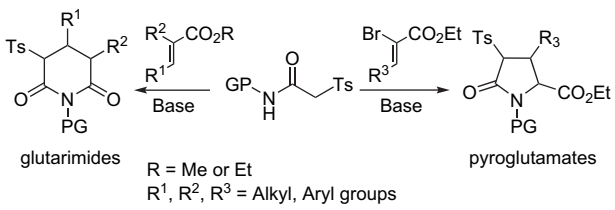

Figure 1. The application of α-sulfonyl acetamides to glutarimide and pyroglutamate skeletons.

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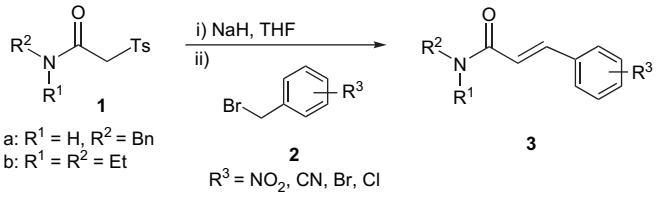
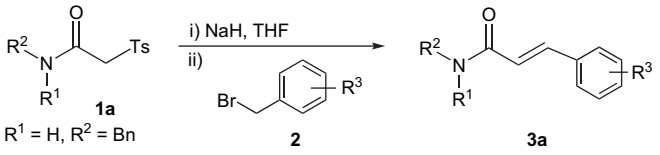


Figure 2. The application of α-sulfonyl acetamides to α,β-unsaturated amides.

The scope of the reaction appears to be limited to benzyl bromides with electron-withdrawing substituent at the benzene ring. In the reaction of benzyl bromides bearing no substituents or electron-donating groups, the major products obtained are *C*-alkylated amides, in which the tosyl group is retained. Using

Table 1
Reaction of α-sulfonyl acetamide **1a** with benzyl halide derivatives **2**[a]



Entry	3a	R^3	Temp (°C)	Rxn time (min)	*E*/*Z*[b]	Yield[c] (%)
1	**3aa**	*p*-NO_2	rt	10	100:0	90
2	**3ab**	*m*-NO_2	rt	20	82:18	82
3	**3ac**	*o*-NO_2	rt	15	100:0	88
4	**3ad**	*p*-CN	rt	30	100:0	74
5	**3ae**	*m*-CN	rt	40	100:0	66
6	**3af**	*o*-CN	rt	30	100:0	43
7	**3ag**	*p*-Br	Reflux	120	100:0	85
8	**3ah**	*o*-Br	Reflux	120	100:0	76
9	**3ai**	*p*-Cl	Reflux	120	100:0	53
10	**3aj**	*m*-Cl	Reflux	150	100:0	72
11	**3ak**	*o*-Cl	Reflux	120	100:0	79

[a] THF was used as solvent.
[b] Determined by ^{1}H NMR spectra.
[c] The yield of (*E*)-olefins was based on **1a**.

1 equiv of sodium hydride affords complicated result. Replacing sodium hydride with stronger bases, such as LDA or LHMDS, gave no desired β-substituted acrylamides under various reaction conditions and the reason still remains unclear.

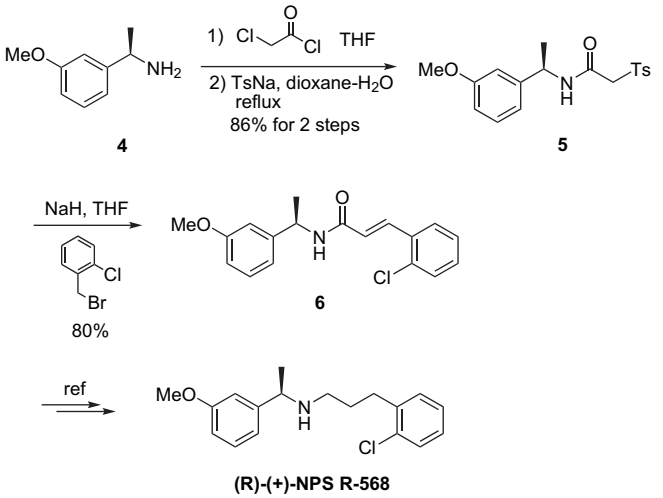
2.2. Formal synthesis of the calcimimetic (+)-NPS R-568

To demonstrate the synthetic applications of our approach, we then applied it to the formal synthesis of the calcimimetic (+)-NPS R-568, which has shown great potential as an innovative medical approach for the treatment of primary and secondary hyperparathyroidisms.[11] As shown in Scheme 1, (*R*)-sulfonyl acetamide **5** can be obtained in two steps from the commercially available (*R*)-(+)-1-(3-methoxyphenyl)-ethylamine **4**. Similar to **1a**, treatment of **5** with sodium hydride and 2-chlorobenzyl bromide provided the corresponding (*E*)-β-aryl acrylamide derivative **6** in 80% yield, which has previously been further transformed into the calcimimetic (+)-NPS R-568.[12]

2.3. Synthesis of *N*,*N*-disubstituted (*E*)-acrylamides (3b)

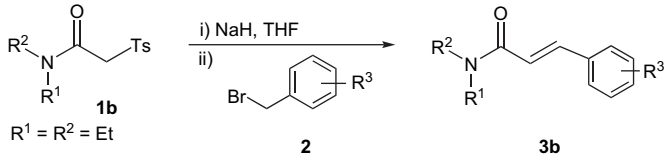
We next focused our attention on the reaction of *N*,*N*-diethyl acetamide **1b**, which was needed as a starting material (Table 2).

The corresponding *N*,*N*-disubstituted (*E*)-α,β-unsaturated amides **3ba**–**3bc** were obtained exclusively and with good yields. Besides, all of the reactions could be carried out at room temperature.



Scheme 1. Formal synthesis of (+)-NPS R-568.

Table 2
Reaction of *N*,*N*-diethyl acetamide **1b** with benzyl halide derivatives **2**[a]



Entry	3b	R^3	Temp (°C)	Rxn time (h)	*E*/*Z*[b]	Yield[c] (%)
1	**3ba**	*p*-NO_2	rt	12	100:0	85
2	**3bb**	*o*-CN	rt	12	100:0	81
3	**3bc**	*m*-Cl	rt	12	100:0	79

[a] THF was used as solvent.
[b] Determined by ^{1}H NMR spectra.
[c] The yield of (*E*)-olefins was based on **1b**.

3. Conclusion

In summary, a sequential substitution–elimination reaction involving readily available α-sulfonyl acetamide and substituted benzyl bromides to afford (*E*)-β-aryl-α,β-unsaturated amides has been developed. This practical and efficient process is highly stereoselective. There is no limitation in the position of the substituent on the benzene ring of the benzyl bromide as long as it is electron withdrawing. We also applied this methodology to the formal synthesis of (+)-NPS R-568. Further studies directed toward the development of synthetic applications of this method are currently under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were determined with Fargo micro-melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VRX 500 spectrometer. NMR spectra were recorded in $CDCl_3$ (^{1}H at 500 MHz and ^{13}C at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. HRMS was recorded on a BRUKER DALTONICS APEX II30e spectrometer. Infrared spectra were recorded on a Perkin–Elmer Spectrum 100 FTIR spectrometer as KBr plates and peaks are reported in cm^{-1}.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried over anhydrous magnesium sulfate before concentration under vacuum.

(*R*)-(+)-1-(3-Methoxyphenyl)ethylamine **4** was purchased from Lancaster (ChiPros 99+%, ee 98%). Compounds **5** and **1b** were synthesized according to the reported procedures[9b] and their spectral data are described below:

*4.1.1. N-[1-(3-Methoxyphenyl)ethyl]-2-(toluene-4-sulfonyl)acetamide (**5**)*

Yield 86%; colorless oil; IR (CH_2Cl_2, cm^{-1}): 3328, 2976, 2932, 1660, 1598, 1534; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J=8.0 Hz, 2H), 7.27 (d, J=8.0 Hz, 1H), 7.23 (d, J=9.0 Hz, 2H), 7.21 (d, J=9.0 Hz, 1H), 6.88–6.87 (m, 2H), 6.79 (dd, J=8.0, 2.5 Hz, 1H), 4.98 (m, 1H), 4.02 (d of a pair of ABq type, J=14.0 Hz, 1H), 3.96 (d of a pair of ABq type, J=14.0 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H), 1.42 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.5, 145.1, 144.0, 134.9, 129.6 (2C), 129.4, 128.0 (2C), 118.2, 112.6, 111.8, 61.9, 55.0, 49.2, 21.40, 21.38; HRMS m/z (ESI, M^++Na) calcd for $C_{18}H_{21}NO_4SNa$ 370.1089, found 370.1091.

*4.1.2. N,N-Diethyl-2-(toluene-4-sulfonyl)acetamide (**1b**)*

Yield 90%; white solid; mp=87–88 °C; IR (CH_2Cl_2, cm^{-1}): 2976, 1648, 1452; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 4.18 (s, 2H), 3.50 (q, J=7.0 Hz, 2H), 3.34 (q, J=7.0 Hz, 2H), 2.44 (s, 3H), 1.22 (t, J=7.0 Hz, 3H), 1.10 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 145.2, 135.8, 129.7 (2C), 128.6 (2C), 59.9, 43.1, 40.8, 21.7, 14.2, 12.7; HRMS m/z (ESI, M^++Na) calcd for $C_{13}H_{19}NO_3SNa$ 292.0983, found 292.0981. Compound **1b** was recrystallized from ethyl acetate as a colorless prism.

4.2. General procedure for the preparation of (*E*)-β-aryl-α,β-unsaturated amides (3a)

A solution of α-toluenesulfonyl acetamide **1a** (303 mg, 1.0 mmol) in dry THF (5.0 mL) was added to a rapidly stirred suspension of sodium hydride (88 mg, 2.2 mmol, 60%) in dry THF (10 mL). After the reaction mixture was stirred at room temperature for 30 min, the benzyl bromide derivative **2** (1.0 mmol) was added to the solution. The resulting mixture was stirred at room temperature (for **3aa**–**3af**) for 10–40 min or refluxed (for **3ag**–**3ak**) for 120–150 min (as show in Table 1). After the reaction was complete (as indicated by TLC), the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL) and the solvent was removed with a rotary evaporator under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford amides **3**.

*4.2.1. (E)-N-Benzyl-3-(4-nitrophenyl)acrylamide (**3aa**)*

Yield 90%; yellow solid; mp=185–186 °C; IR (CH_2Cl_2, cm^{-1}): 3445, 3058, 1682; ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J=8.5 Hz, 2H), 7.72 (d, J=15.5 Hz, 1H), 7.64 (d, J=8.5 Hz, 2H), 7.38–7.29 (m, 5H), 6.53 (d, J=15.5 Hz, 1H), 6.0 (br s, 1H), 4.60 (d, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 148.2, 141.0, 138.9, 137.7, 128.9 (2C), 128.4 (2C), 128.0 (2C), 127.8, 124.5, 124.2 (2C), 44.1; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}N_2O_3$ 283.1083, found 283.1082.

*4.2.2. (E)-N-Benzyl-3-(3-nitrophenyl)acrylamide (**3ab**)*

Yield 67%; yellow solid; mp=133–134 °C; IR (CH_2Cl_2, cm^{-1}): 3473, 1645; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J=2.0 Hz, 1H), 8.17 (ddd, J=8.5, 2.0, 1.0 Hz, 1H), 7.74 (d, J=15.5 Hz, 1H), 7.69 (d, J=15.5 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.36–7.26 (m, 5H), 6.57 (d, J=15.5 Hz, 1H), 6.25 (br s, 1H), 4.58 (d, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 148.6, 138.7, 137.8, 136.5, 133.9, 129.9, 128.8 (2C), 127.9 (2C), 127.7, 124.0, 123.5, 121.7, 44.0; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}N_2O_3$ 283.1083, found 283.1082.

*4.2.3. (Z)-N-Benzyl-3-(3-nitrophenyl)acrylamide (**3ab**-Z)*

Yield 15%; yellow solid; IR (CH_2Cl_2, cm^{-1}): 3349, 1678; ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, J=2.5 Hz, 1H), 8.25 (dd, J=9.5, 2.5 Hz, 1H), 7.83 (d, J=10.0 Hz, 1H), 7.36–7.31 (m, 5H), 7.19 (d, J=6.5 Hz, 2H), 6.93 (d, J=10.0 Hz, 1H), 5.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 143.5, 142.2, 139.1, 135.2, 129.2, 129.1 (2C), 127.8, 126.4 (2C), 125.2, 124.6, 123.86, 120.4, 115.7, 46.4.

*4.2.4. (E)-N-Benzyl-3-(2-nitrophenyl)acrylamide (**3ac**)*

Yield 88%; yellow solid; mp=184–185 °C; IR (CH_2Cl_2, cm^{-1}): 3452, 1685; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J=8.0 Hz, 1H), 8.01 (d, J=15.5 Hz, 1H), 7.62–7.54 (m, 2H), 7.52–7.49 (m, 2H), 7.38–7.26 (m, 4H), 6.33 (d, J=15.5 Hz, 1H), 5.96 (br s, 1H), 4.58 (d, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 148.3, 137.8, 136.5, 133.4, 131.1, 129.8, 129.1, 128.8 (2C), 128.0 (2C), 127.7, 125.8, 124.9, 44.0; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}N_2O_3$ 283.1083, found 283.1082.

*4.2.5. (E)-N-Benzyl-3-(4-cyanophenyl)acrylamide (**3ad**)*

Yield 74%; white solid; mp=173–174 °C; IR (CH_2Cl_2, cm^{-1}): 3426, 2230, 1664; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J=15.5 Hz, 1H), 7.66 (d, J=8.5 Hz, 2H), 7.58 (d, J=8.5 Hz, 2H), 7.38–7.30 (m, 5H), 6.49 (d, J=15.5 Hz, 1H), 5.94 (br s, 1H), 4.6 (d, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 139.4, 139.1, 137.8, 132.6 (2C), 128.8 (2C), 128.2 (2C), 128.0 (2C), 127.8, 123.8, 118.4, 112.9, 44.0; HRMS m/z (ESI, M^++1) calcd for $C_{17}H_{15}N_2O$ 263.1184, found 263.1183.

*4.2.6. (E)-N-Benzyl-3-(3-cyanophenyl)acrylamide (**3ae**)*

Yield 66%; white solid; mp=140–141 °C; IR (CH_2Cl_2, cm^{-1}): 3428, 3274, 2232, 1666; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.65 (d, J=15.5 Hz, 1H), 7.63 (d, J=9.0 Hz, 1H), 7.49 (dd, J=8.5, 8.0 Hz, 1H), 7.38–7.29 (m, 5H), 6.46 (d, J=15.5 Hz, 1H), 5.99 (br s, 1H), 4.59 (d, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 139.0, 137.8, 136.4, 132.7, 132.0, 130.8, 129.8, 128.8 (2C), 127.9 (2C), 127.8, 122.9, 118.3, 113.2, 44.0; HRMS m/z (ESI, M^++1) calcd for $C_{17}H_{15}N_2O$ 263.1184, found 263.1185.

*4.2.7. (E)-N-Benzyl-3-(2-cyanophenyl)acrylamide (**3af**)*

Yield 43%; white solid; mp=150–151 °C; IR (CH_2Cl_2, cm^{-1}): 3262, 2226, 1652; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J=15.5 Hz, 1H), 7.70 (d, J=8.5 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.60 (dd, J=8.0, 7.5 Hz, 1H), 7.45 (dd, J=8.0, 7.5 Hz, 1H), 7.38–7.28 (m, 5H), 6.70 (d, J=155 Hz, 1H), 6.02 (br s, 1H), 4.60 (d, J=6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 137.8, 137.6, 136.5, 133.8, 133.0, 129.5, 128.8 (2C), 128.1, 128.0 (2C), 127.7, 125.6, 117.6, 117.7, 44.0; HRMS m/z (ESI, M^++1) calcd for $C_{17}H_{15}N_2O$ 263.1184, found 263.1186.

*4.2.8. (E)-N-Benzyl-3-(4-bromophenyl)acrylamide (**3ag**)*

Yield 85%; white solid; mp=173–174 °C; IR (CH_2Cl_2, cm^{-1}): 3280, 1654, 1620; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J=15.5 Hz, 1H), 7.50 (d, J=8.5 Hz, 2H), 7.38–7.30 (m, 7H), 6.39 (d, J=15.5 Hz, 1H), 5.88 (br s, 1H), 4.59 (d, J=6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 140.2, 138.0, 133.7, 132.1 (2C), 129.2 (2C), 128.8 (2C), 127.9 (2C), 127.7, 123.9, 121.0, 43.9; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}NOBr$ 316.0337, found 316.0337.

*4.2.9. (E)-N-Benzyl-3-(2-bromophenyl)acrylamide (**3ah**)*

Yield 76%; white solid; mp=142–143 °C; IR (CH_2Cl_2, cm^{-1}): 3276, 1650, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 8.0 (d, J=16.0 Hz, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.38–7.29 (m, 6H), 7.20 (dd, J=9.0, 7.5 Hz, 1H), 6.37 (d, J=16.0 Hz, 1H), 5.92 (br s, 1H), 4.60 (d, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 139.9, 138.0, 135.0, 133.4, 130.7, 128.8 (2C), 128.0 (2C), 127.7, 127.59, 127.57, 125.1, 123.5, 43.9; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}NOBr$ 316.0337, found 316.0338.

*4.2.10. (E)-N-Benzyl-3-(4-chlorophenyl)acrylamide (**3ai**)*

Yield 53%; white solid; mp=136–137 °C; IR (CH_2Cl_2, cm^{-1}): 3430, 3278, 1666, 1626, 1512; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J=15.5 Hz, 1H), 7.42 (d, J=8.0 Hz, 2H), 7.37–7.28 (m, 7H), 6.38 (d, J=15.5 Hz, 1H), 5.92 (br s, 1H), 4.58 (d, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 140.1, 138.0, 135.6, 133.2, 129.1 (2C), 129.0 (2C), 128.8 (2C), 127.9 (2C), 127.7, 120.9, 43.9; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}NOCl$ 272.0842, found 272.0840.

*4.2.11. (E)-N-Benzyl-3-(3-chlorophenyl)acrylamide (**3aj**)*

Yield 72%; white solid; mp=108–109 °C; IR (CH_2Cl_2, cm^{-1}): 3430, 3286, 1664, 1512; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J=15.5 Hz, 1H), 7.49 (s, 1H), 7.38–7.29 (m, 8H), 6.41 (d, J=15.5 Hz, 1H), 5.91 (br s, 1H), 4.59 (d, J=5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 140.0, 138.0, 136.6, 134.8, 130.1, 129.6, 128.8 (2C), 127.9 (2C), 127.7, 127.4, 126.2, 121.7, 43.9; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}NOCl$ 272.0842, found 272.0840.

*4.2.12. (E)-N-Benzyl-3-(2-chlorophenyl)acrylamide (**3ak**)*

Yield 79%; white solid; mp=158–159 °C; IR (CH_2Cl_2, cm^{-1}): 3268, 1650; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J=16.0 Hz, 1H), 7.56 (d, J=7.5 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.38–7.24 (m, 7H), 6.42 (d, J=16.0 Hz, 1H), 5.96 (br s, 1H), 4.59 (d, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 138.1, 137.3, 134.8, 133.1, 130.5, 130.2, 128.8 (2C), 128.0 (2C), 127.7, 127.5, 126.9, 123.3, 43.9; HRMS m/z (ESI, M^++1) calcd for $C_{16}H_{15}NOCl$ 272.0842, found 272.0840.

*4.2.13. Synthesis of 3-(2-chlorophenyl)-N-[1-(3-methoxyphenyl)ethyl] acrylamide (**6**)*

A solution of α-toluenesulfonyl acetamide **5** (347 mg, 1.0 mmol) in dry THF (5.0 mL) was added to a rapidly stirred suspension of sodium hydride (88 mg, 2.2 mmol, 60%) in dry THF (10 mL). After the reaction mixture was stirred at room temperature for 30 min, 2-chlorobenzyl bromide **2k** (1.0 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 12 h. After the reaction was complete (as indicated by TLC), the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL) and the solvent was removed with a rotary evaporator under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford amides **6** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J=15.5 Hz, 1H), 7.53 (dd, J=7.5, 1.5 Hz, 1H), 7.39 (dd, J=7.5, 1.0 Hz, 1H), 7.28–7.21 (m, 3H), 6.95 (d, J=7.5 Hz, 1H), 6.91–6.90 (m, 1H), 6.81 (dd, J=8.5, 2.5 Hz, 1H), 6.40 (d, J=15.5 Hz, 1H), 6.02 (br d, 1H), 5.24 (m, 1H), 3.80 (s, 3H), 1.55 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 159.8, 144.7, 137.1, 134.7, 133.1, 130.4, 130.1, 129.8, 127.5, 126.9, 123.5, 118.5, 112.6, 112.3, 55.2, 49.0, 21.6; HRMS m/z (ESI, M^++1) calcd for $C_{18}H_{19}Cl\ NO_2$ 316.1104, found 316.1106.

4.3. General procedure for the preparation of *N,N*-disubstituted (*E*)-acrylamides (3b)

A solution of α-toluenesulfonyl acetamide **1b** (269 mg, 1.0 mmol) in dry THF (5.0 mL) was added to a rapidly stirred suspension of sodium hydride (88 mg, 2.2 mmol, 60%) in dry THF (10 mL). After the reaction mixture was stirred at room temperature for 30 min, the benzyl bromide derivative **2** (1.0 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 12 h. After the reaction was complete (as indicated by TLC), the reaction mixture was quenched with a saturated ammonium chloride solution (1 mL) and the solvent was removed with a rotary evaporator under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1 to 2:1) to afford amides **3b**.

*4.3.1. N,N-Diethyl-3-(4-nitrophenyl)acrylamide (**3ba**)*

Yield 85%; pale yellow solid; mp=156–157 °C; IR (CH_2Cl_2, cm^{-1}): 2978, 1650, 1608, 1520; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J=9.0 Hz, 2H), 7.73 (d, J=15.5 Hz, 1H), 7.66 (d, J=9.0 Hz, 2H), 6.96 (d, J=15.5 Hz, 1H), 3.54–3.48 (m, 4H), 1.29 (t, J=7.0 Hz, 3H), 1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 148.0, 141.7, 139.6, 128.3 (2C), 124.1 (2C), 122.1, 42.4, 41.2, 15.2, 13.1; HRMS m/z (ESI, M^++Na) calcd for $C_{13}H_{16}N_2O_3Na$ 271.1059, found 271.1057.

*4.3.2. N,N-Diethyl-3-(2-cyanophenyl)acrylamide (**3bb**)*

Yield 81%; yellowish oil; IR (CH_2Cl_2, cm^{-1}): 3430, 2226, 1650, 1608; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=16.0 Hz, 1H), 7.70 (d, J=8.5 Hz, 1H), 7.64–7.59 (m, 2H), 7.43 (td, J=7.5, 1.5 Hz, 1H), 7.17 (d, J=16.0 Hz, 1H), 3.53–3.47 (m, 4H), 1.28 (t, J=7.0 Hz, 3H), 1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 138.4, 137.2, 133.8, 132.8, 129.0, 128.6, 123.5, 117.9, 111.2, 42.4, 41.1, 15.0, 13.1; HRMS m/z (ESI, M^++Na) calcd for $C_{14}H_{16}N_2ONa$ 251.1160, found 251.1158.

*4.3.3. N,N-Diethyl-3-(3-chlorophenyl)acrylamide (**3bc**)*

Yield 79%; pale yellow oil; IR (CH_2Cl_2, cm^{-1}): 3412, 2976, 1650; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J=15.5 Hz, 1H), 7.51 (s, 1H), 7.39–7.30 (m, 3H), 6.82 (d, J=15.5 Hz, 1H), 3.52–3.46 (m, 4H), 1.27 (t, J=7.0 Hz, 3H), 1.19 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 140.7, 137.3, 134.7, 130.0, 129.3, 127.1, 126.2, 119.2, 42.3, 41.1, 15.1, 13.1; HRMS m/z (ESI, M^++Na) calcd for $C_{13}H_{16}ClNONa$ 260.0818, found 260.0819.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.057.

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