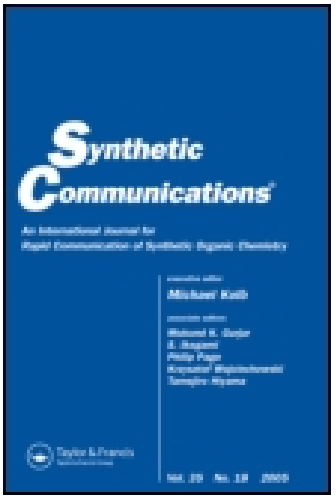

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Efficient Synthesis of α,β-Diamino Acid Derivatives by In(III)-Catalyzed Regioselective Addition of Amines to Aziridines

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EFFICIENT SYNTHESIS OF α,β-DIAMINO ACID DERIVATIVES BY In(III)-CATALYZED REGIOSELECTIVE ADDITION OF AMINES TO AZIRIDINES

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GRAPHICAL ABSTRACT

Abstract *An efficient catalytic method for the synthesis of α, β-diamino acid derivatives has been developed via regioselective ring opening of aziridines by amines in the presence of indium(III) salt under very mild reaction conditions.*

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Keywords Amines; aziridines; catalytic synthesis; α,β-diamino acid; indium(III) salt

INTRUCTION

α,β-Diamino acid derivatives, a special class of non-proteinogenic amino acids, have increasingly attracted attention for their great importance as key structural motifs in the synthesis of various biologically active compounds and therapeutic agents.[1] For example, α, β-diamino acid derivatives **I, II**, and **III** are used as crucial intermediates in the synthesis of G protein-coupled receptor kinase (GRK) inhibitors, which are applied in therapy of circulatory diseases such as heart failure, hypertension, and arteriosclerosis.[2] Compound **IV** and its derivatives can be used to construct vanadium pharmaceutical agents (Fig. 1).[3]

Because of the biological and chemical significance of α, β-diamino acid derivatives, a variety of synthetic approaches have been developed,[4] such as nucleophilic addition of glycinates to imines and related compounds,[5] electrophilic

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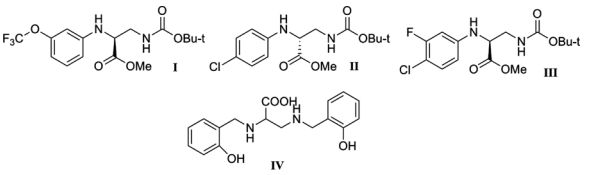


Figure 1. Biologically active α,β-diamino acid derivatives.

amination of β-amino enolates,[6] and introduction of the nitrogen atoms to amino acids, α, β-unsaturated alkenoates, or β-keto esters.[7] Nevertheless, most of these methods usually need relatively severe or cumbersome reaction conditions. Therefore, both for scientific interest and practical applications, it is highly desirable to develop simple, mild, and efficient catalytic methods for the preparation of α, β-diamino acid derivatives. Herein, we report an $In(OTf)_3$-catalyzed efficient method for the synthesis of α, β-diamino acid derivatives via regioselective ring opening of 2-carboxylate aziridines by amines under very mild conditions.

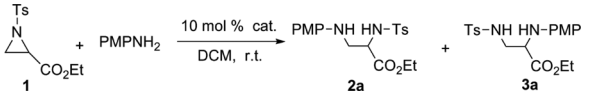
Catalytic methods for the ring opening of aziridines with amines usually generated simple 1,2-diamines.[8] So far, only a few noncatalytic approaches have been available for the synthesis of α, β-diamino acid derivatives, but such processes were only compatible with aliphatic primary amines and usually required much excess of amines.[9] To the best of our knowledge, the present method is the first example of catalytic synthesis of α,β-diamino acid derivatives via regioselective ring opening of N-tosylaziridine-2-carboxylate (**1**)[10] by aromatic and aliphatic amines.

RESULTS AND DISCUSSION

Initial attempts to achieve the regioselective ring opening of N-tosylaziridine -2-carboxylate **1** with *p*-methoxyaniline in the presence of silver(I) catalyst were encouraging, providing the C-3 regioselective ring-opening product **2a** in 65% yield along with another component **3a** (only 5%), which was a C-2 ring-opening product (Table 1, entry 1), indicating that the steric effect of carbonyl group in substrate **1** determined the regioselectivity. This result was further confirmed by the x-ray crystal diffraction of product **2g** when *p*-nitroaniline was used as substrate; see Fig. 2. We then switched our efforts to other transition-metal catalysts, such as Au(III), In(III), Zn(II), and Cu(I)/(II) salts (Table 1). Among those catalysts examined, $In(OTf)_3$ exhibited the best catalytic activity and regioselectivity (entry 5). $AuBr_3$, $AuCl_3$, and $Zn(OTf)_2$ could also give the desired product in moderate yields (entries 3, 4, and 6). However, $AgNO_3$, $Cu(OTf)_2$, and $CuOTf \cdot 0.5C_6H_5CH_3$ showed much less efficiency for this transformation (entries 2, 7, and 8).

Next, other factors (solvent and temperature) were examined using $In(OTf)_3$ as catalyst (Table 2). The screening of a range of solvents showed that dichloromethane (DCM) was the optimal reaction medium in terms of yield and regioselectivity (entries 1–4). The preferred temperature for the reaction was 25 °C (rt), with lower temperatures resulting in poor yields, and higher temperatures leading to less regioselectivity (entries 5–7).

Table 1. Effect of catalyst variations on the reaction of **1** and $PMPNH_2$[a]



Entry	Catalyst	Yield (%)[b]	Ratio (**2a**:**3a**)[c]
1	AgOTf	70	13:1
2	$AgNO_3$	<10	only **2a**
3	$AuBr_3$	62	14:1
4	$AuCl_3$	58	14:1
5	**$In(OTf)_3$**	**88**	**20:1**
6	$Zn(OTf)_2$	65	12:1
7	$Cu(OTf)_2$	32	only **2a**
8	$CuOTf \cdot 0.5C_6H_5CH_3$	38	only **2a**
9	—	0	—

[a]Reaction conditions: compound **1** (0.4 mmol) and $PMPNH_2$ (0.6 mmol) in DCM (1 mL), time (24 h).
[b]Isolated yields based on substrate **1**.
[c]The ratio of **2a:3a** refers to isolated yields.

To establish the general utility of this methodology, $In(OTf)_3$-catalyzed regioselective ring opening of 2-carboxylate aziridine **1** with various aromatic and aliphatic amines were performed under the optimized conditions, and the results are summarized in Table 3. The electronic effect on the aromatic ring of amines showed significant influence on this process. Those containing electron-donating groups, such as *p*-methoxyaniline, and *p*-methylaniline, gave the desired products in good yields (entries 1 and 5). However, amines bearing electron-withdrawing groups generated comparatively lower yields of the targets even with prolonged reaction times (entries 3, 6, and 7). Ortho-substituted amines also gave relatively lower yields, because of the steric effect (entries 4 and 8). With respect to aliphatic amines such as benzylamine

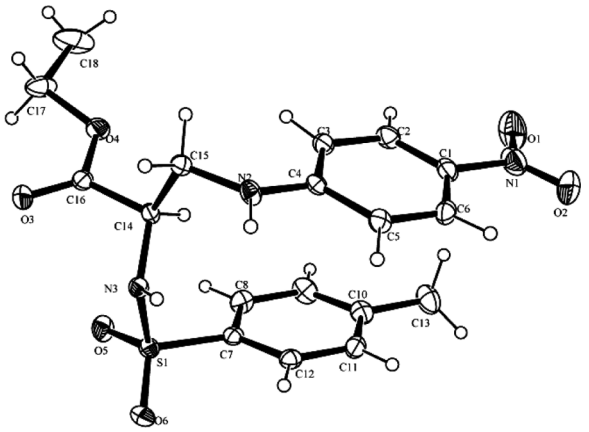
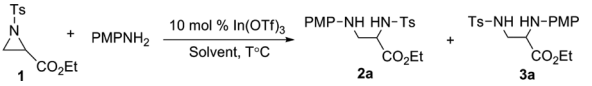


Figure 2. X-ray crystal diffraction of product **2g**.

Table 2. Effect of reaction condition variations on the reaction of compound **1** and $PMPNH_2$[a]



Entry	Solvent	T (°C)	Yield (%)[b]	Ratio (**2a**:**3a**)[c]
1	DCM	25	88	20:1
2	THF	25	68	10:1
3	toluene	25	32	15:1
4	hexane	25	<5	only **2a**
5	DCM	0	22	19:1
6	DCM	40	86	7:1
7	DCM	60	87	8:1

[a]Reaction conditions: $In(OTf)_3$ (10 mol %), compound **1** (0.4 mmol), $PMPNH_2$ (0.6 mmol), solvent (1 mL), time (24 h).
[b]Isolated yields based on substrate **1**.
[c]The ratio of **2a:3a** refers to isolated yields.

and morpholine, the reaction proceeded smoothly with good regioselectivity, and the desired products were obtained in moderate to excellent yields (entries 9 and 10).

It is worth mentioning that when *p*-methoxyaniline and benzylamine were used as substrates (Table 3, entries 1 and 9), the produced N-PMP- and N-Bn-protected α,β-diamino acid derivatives (Scheme 1) provide convenience and flexibility for further structure elaboration, which is attractive in synthetic chemistry.

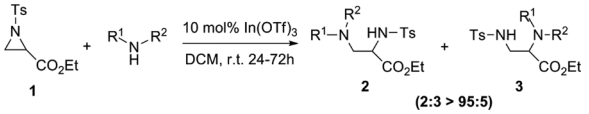
CONCLUSIONS

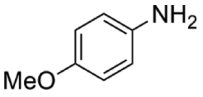
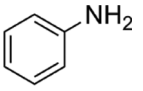
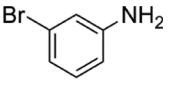
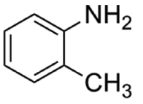
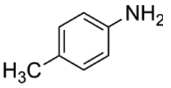
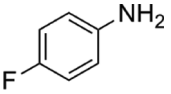
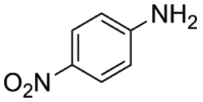
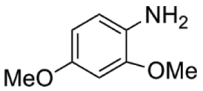
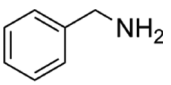
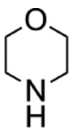
In summary, we have developed a simple and effective catalytic method for the synthesis of α, β-diamino acid derivatives via $In(OTf)_3$-catalyzed regioselective ring opening of 2-carboxylate aziridines with aromatic and aliphatic amines under very mild reaction conditions. This methodology provides a novel strategy for the construction of dual protected α, β-diamino acid derivatives, which can be used for further structural elaboration. Taking into account the desirable features, such as atom efficiency, operation simplicity, and high regioselectivity, this catalytic system is expected to provide a convenient method to construct versatile building blocks for applications in increasingly important protein engineering and peptide-based pharmaceutical research. The asymmetric version and synthetic application of this reaction are under investigation.

EXPERIMENTAL

All experiments were carried out under an inert atmosphere of nitrogen. All reagents and solvents were purchased and used without prior purification unless otherwise stated. Dichlormethane (DCM) was distilled from CaH_2 and kept over 4-Å molecular sieves. NMR spectra were recorded in $CDCl_3$ on a Bruker Avance

Table 3. $In(OTf)_3$-catalyzed regioselective addition of amines to N-tosylaziridine-2-carboxylate **1**[a]



Entry	Amine	Yield (%)[b]	Ratio (**2**:**3**)[c]
1		88	20:1 (**2a**:**3a**)
2		72	18:1 (**2b**:**3b**)
3		50	only **2c**
4		48	only **2d**
5		75	22:1 (**2e**:**3e**)
6		42	only **2f**
7		30	only **2g**
8		46	25:1 (**2h**:**3h**)
9		62	only **2i**
10		92	16:1 (**2j**:**3j**)

[a]Reaction conditions: compound **1** (0.4 mmol), amine (0.6 mmol), $In(OTf)_3$ (10 mol %), DCM (1 mL).
[b]Isolated yields based on substrate **1**.
[c]The ratio of **2:3** refers to isolated yields.

Scheme 1. N-PMP and N-Bn protected α,β-diamino acid derivatives.

600 spectrometer with tetramethylsilane (TMS) as internal standard (600 MHz ^{1}H, 150 MHz ^{13}C) at room temperature, and the chemical shifts (δ) were expressed in parts per million (ppm) and J values were given in hertz (Hz). The following abbreviations are used to indicate the multiplicity: s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Mass analyses and high-resolution mass spectra (HRMS) were obtained on a Finnigan-LCQ^{DECA} mass spectrometer and a Bruker Daltonics Bio-TOF-Q mass spectrometer by the elecrospray ionization (ESI) method, respectively. Column chromatography was performed on silica gel (200–300 mesh).

General Procedure for Regioselective Ring Opening of Aziridine

The N-Ts-protected aziridine **1** (0.4 mmol) was added to a stirred mixture of amine (0.6 mmol) and $In(OTf)_3$ (0.04 mmol) in DCM (1 mL). The reaction mixture was stirred at room temperature (25 °C) for the indicated time until complete consumption of starting material, and then the suspension was filtered through silica gel and washed with EtOAc (10 mL) to give a brown solution. The solution was concentrated in vacuum, and the affording residue was purified with flash chromatography (petroleum ether / EtOAc, 6:1) to give the desired addition products as light-yellow oils.

Spectral Data for All Compounds

Ethyl 1-tosylaziridine-2-carboxylate (1). Light-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 2.55 (d, J = 4.1 Hz, 1H), 2.75 (d, J = 7.1 Hz, 1H), 3.32 (dd, J_1 = 7.1 Hz, J_2 = 4.1 Hz, 1H), 4.14–4.19 (m, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H); ESIMS (positive mode) m/z: 270 $[M + H]^+$, 292 $[M + Na]^+$.

Ethyl 2-(4-methoxyphenylamino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 1 and 2a). Light-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.38 (dd, J_1 = 13.3 Hz, J_2 = 5.8 Hz, 1H), 3.47 (dd, J_1 = 13.3 Hz, J_2 = 4.5 Hz, 1H), 3.74 (s, 3H), 3.98–4.01 (m, 2H), 4.04–4.06 (m, 1H), 5.47 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 21.5, 47.7, 55.4, 55.7, 62.2, 114.9, 115.2, 127.3, 129.7, 136.4, 141.0, 143.9, 152.9, 170.3; ESIMS (positive mode) m/z: 393 $[M + H]^+$, 415 $[M + Na]^+$; HRESIMS (positive ion) m/z: 415.1284 $[M + Na]^+$ (calcd. for $C_{19}H_{24}N_2Na_1O_5S_1$, 415.1298).

Ethyl 3-(4-methoxyphenylamino)-2-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 1 and 3a). Light-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.2$ Hz, 3H), 2.43 (s, 3H), 3.21–3.26 (m, 1H), 3.36–3.40 (m, 1H), 3.74 (s, 3H), 4.03 (t, $J = 5.3$, 1H), 4.14–4.19 (m, 2H), 5.01 (t, $J = 6.2$ Hz, 1H), 6.54 (d, $J = 8.8$ Hz, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.73 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.1$, 21.5, 44.6, 55.7, 57.8, 62.0, 114.9, 116.0, 127.1, 129.8, 136.7, 139.8, 143.7, 153.5, 171.7; ESIMS (positive mode) m/z: 393 $[M + H]^+$, 415 $[M + Na]^+$; HRESIMS (positive ion) m/z: 415.1283 $[M + Na]^+$ (calcd. for $C_{19}H_{24}N_2Na_1O_5S_1$, 415.1298).

Ethyl 3-(4-methylphenylsulfonamido)-2-(phenylamino)propanoate (Table 3, Entries 2 and 2b). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.2$ Hz, 3H), 2.39 (s, 3H), 3.43 (dd, $J_1 = 13.4$ Hz, $J_2 = 6.0$ Hz, 1H), 3.52 (dd, $J_1 = 13.4$ Hz, $J_2 = 4.6$ Hz, 1H), 3.97–4.02 (m, 2H), 4.06–4.09 (m, 1H), 5.54 (d, $J = 8.0$ Hz, 1H), 6.57 (d, $J = 8.0$ Hz, 2H), 6.72 (t, $J = 7.3$ Hz, 1H), 7.14 (t, $J = 8.0$ Hz, Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 21.5, 46.6, 55.4, 62.2, 113.5, 118.4, 127.3, 129.3, 129.7, 136.4, 143.9, 147.0, 170.3; ESIMS (positive mode) m/z: 385 $[M + Na]^+$, HRESIMS (positive ion) m/z: 385.1181 $[M + Na]^+$ (calcd. for $C_{18}H_{22}N_2Na_1O_4S_1$, 355.1192).

Ethyl 2-(4-methylphenylsulfonamido)-3-(phenylamino)propanoate (Table 3, Entries 2 and 3b). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 6.8$ Hz, 3H), 2.42 (s, 3H), 3.29–3.33 (m, 1H), 3.36–3.40 (m, 1H), 4.14 (t, $J = 5.3$ Hz, 1H), 4.16–4.21 (m, 2H), 4.94 (t, $J = 6.2$ Hz, 1H), 6.56 (d, $J = 8.2$ Hz, 2H), 6.78 (t, $J = 7.5$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 11.4$, 21.5, 44.4, 56.4, 62.1, 113.9, 119.2, 127.1, 129.4, 129.8, 136.7, 143.7, 145.9, 171.4; ESIMS (positive mode) m/z: 363 $[M + H]^+$, 385 $[M + Na]^+$; HRESIMS (positive ion) m/z: 385.1194 $[M + Na]^+$ (calcd. for $C_{18}H_{22}N_2Na_1O_4S_1$, 355.1192).

Ethyl 2-(3-bromophenylamino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 3 and 2c). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.3$ Hz, 3H), 2.41 (s, 3H), 3.41 (dd, $J_1 = 13.0$ Hz, $J_2 = 5.7$ Hz, 1H), 3.50 (br d, $J = 13.0$ Hz, 1H), 4.00–4.05 (m, 3H), 4.11 (br s, 1H), 5.53 (d, $J = 7.6$ Hz, 1H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.68 (s, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.99 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 21.5, 46.2, 55.3, 62.5, 112.2, 115.9, 121.1, 123.2, 127.3, 129.8, 130.5, 136.2, 144.0, 148.3, 170.0; ESIMS (positive mode) m/z: 463 $[M + Na]^+$; HRESIMS (positive ion) m/z: 463.0274 $[M + Na]^+$ (calcd. for $C_{18}H_{21}Br_1N_2Na_1O_4S_1$, 463.0298).

Ethyl 2-(*o*-toluidino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 4 and 2d). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.1$ Hz, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 3.42–3.44 (m, 1H), 3.55–3.57 (m, 1H), 3.94 (br s, 1H), 3.99–4.03 (m, 2H), 4.10–4.13 (m, 1H), 5.59 (d, $J = 8.0$ Hz, 1H), 6.55 (d, $J = 8.0$ Hz, 1H), 6.67 (t, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 7.1$ Hz, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 17.3, 21.5, 46.3, 55.3, 62.3, 110.1, 117.9, 122.9, 127.0, 127.2, 129.7, 130.3, 136.4, 143.9, 144.9, 170.4; ESIMS (positive mode) m/z: 399

$[M + Na]^+$; HRESIMS (positive ion) m/z: 399.1366 $[M + Na]^+$ (calcd. for $C_{19}H_{24}N_2Na_1O_4S_1$, 399.1349).

Ethyl 3-(*p*-toluidino)-2-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 5 and 2e). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.0$ Hz, 3H), 2.23 (s, 3H), 2.40 (s, 3H), 3.40 (dd, $J_1 = 13.4$ Hz, $J_2 = 5.8$ Hz, 1H), 3.50 (dd, $J_1 = 13.4$ Hz, $J_2 = 4.7$ Hz, 1H), 3.97–4.02 (m, 2H), 4.05–4.08 (m, 1H), 5.45 (d, $J = 7.8$ Hz, 1H), 6.50 (d, $J = 8.2$ Hz, 2H), 6.92 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 20.4, 21.5, 47.0, 55.4, 62.2, 113.8, 127.3, 127.7, 129.7, 129.8, 136.5, 143.9, 144.6, 170.3; ESIMS (positive mode) m/z: 377 $[M + H]^+$, 399 $[M + Na]^+$; HRESIMS (positive ion) m/z: 399.1348 $[M + Na]^+$ (calcd. for $C_{19}H_{24}N_2Na_1O_4S_1$, 399.1349).

Ethyl 2-(*p*-toluidino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 5 and 3e). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.3$ Hz, 3H), 2.23 (s, 3H), 2.43 (s, 3H), 3.25–3.29 (m, 1H), 3.36–3.40 (m, 1H), 4.08–4.10 (m, 1H), 4.16–4.18 (m, 2H), 4.89 (t, $J = 6.0$ Hz, 1H), 6.48 (d, $J = 7.9$ Hz, 2H), 6.96 (d, $J = 7.9$ Hz, 2H), 7.29 (d, $J = 7.9$ Hz, 2H), 7.72 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.1$, 20.4, 21.5, 44.5, 56.9, 62.0, 114.3, 127.1, 128.7, 129.8, 129.9, 136.7, 143.6, 143.7, 171.5; ESIMS (positive mode) m/z: 377 $[M + H]^+$, 399 $[M + Na]^+$; HRESIMS (positive ion) m/z: 399.1358 $[M + Na]^+$ (calcd. for $C_{19}H_{24}N_2Na_1O_4S_1$, 399.1349).

Ethyl 2-(4-fluorophenylamino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 6 and 2f). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.1$ Hz, 3H), 2.40 (s, 3H), 3.38 (dd, $J_1 = 13.3$ Hz, $J_2 = 6.0$ Hz, 1H), 3.49 (dd, $J_1 = 13.3$ Hz, $J_2 = 4.4$ Hz, 1H), 3.99–4.05 (m, 3H), 5.47 (d, $J = 7.6$ Hz, 1H), 6.51–6.53 (m, 2H), 6.86 (t, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 7.9$ Hz, 2H), 7.69 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 21.5, 47.3, 55.3, 62.2, 114.5, 114.6, 115.6, 115.8, 127.3, 129.8, 136.3, 143.3, 144.0, 155.5, 170.2; ESIMS (positive mode) m/z: 381 $[M + H]^+$, 403 $[M + Na]^+$; HRESIMS (positive ion) m/z: 403.1116 $[M + Na]^+$ (calcd. for $C_{18}H_{21}F_1N_2Na_1O_4S_1$, 403.1098).

Ethyl 3-(4-methylphenylsulfonamido)-2-(4-nitrophenylamino) propanoate (Table 3, Entries 7 and 2g). Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 3.50–3.54 (m, 1H), 3.65–3.69 (m, 1H), 4.03–4.08 (m, 3H), 4.92 (br s, 1H), 5.49 (d, $J = 7.2$ Hz, 1H), 6.56 (d, $J = 9.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 8.08 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.9$, 21.5, 45.7, 55.1, 62.8, 111.7, 126.3, 127.3, 129.9, 135.8, 139.0, 144.4, 152.3, 169.4; ESIMS (positive mode) m/z: 408 $[M + H]^+$, 430 $[M + Na]^+$; HRESIMS (positive ion) m/z: 408.1210 $[M + H]^+$ (calcd. for $C_{18}H_{22}N_3Na_1O_6S_1$, 408.1224).

Ethyl 2-(2,4-dimethoxyphenylamino)-3-(4-methylphenylsulfonamido)-propanoate (Table 3, Entries 8 and 2h). Light-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.1$ Hz, 3H), 2.40 (s, 3H), 3.45 (d, $J = 4.8$ Hz, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 3.96–4.00 (m, 2H), 4.07–4.11 (m, 1H), 4.17 (br s, 1H), 5.42 (d, $J = 8.3$ Hz, 1H), 6.36 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.5$ Hz, 1H), 6.42 (d, $J = 2.5$ Hz, 1H), 6.50 (d, $J = 8.6$ Hz, 1H), 7.25 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H);

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 21.5, 47.3, 55.3, 55.5, 55.8, 62.0, 99.3, 103.8, 111.3, 127.3, 129.6, 131.0, 136.6, 143.7, 148.4, 152.7, 170.5; ESIMS (positive mode) m/z: 445 $[M + Na]^+$; HRESIMS (positive ion) m/z: 445.1388 $[M + Na]^+$ (calcd. for $C_{20}H_{26}N_2Na_1O_6S_1$, 445.1404).

Ethyl 3-(2,4-dimethoxyphenylamino)-2-(4-methylphenylsulfonamido)-propanoate (Table 3, Entries 8 and 3h). Light-yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.0 Hz, 3H), 2.42 (s, 3H), 3.23–3.27 (m, 1H), 3.36–3.40 (m, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.05 (t, J = 5.3, 1H), 4.12–4.17 (m, 2H), 5.01 (t, J = 6.2 Hz, 1H), 6.31 (dd, J_1 = 8.6 Hz, J_2 = 2.6 Hz, 1H), 6.41 (d, J = 8.6 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.1, 21.5, 44.6, 55.6, 55.7, 57.2, 61.8, 99.4, 103.8, 112.5, 127.1, 129.7, 129.8, 136.8, 143.5, 148.9, 153.5, 171.6; ESIMS (positive mode) m/z: 445 $[M + Na]^+$; HRESIMS (positive ion) m/z: 445.1381 $[M + Na]^+$ (calcd. for $C_{20}H_{26}N_2Na_1O_6S_1$, 445.1404).

Ethyl 2-(benzylamino)-3-(4-methylphenylsulfonamido)propanoate (Table 3, Entries 9 and 2i). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.2 Hz, 3H), 2.40 (s, 3H), 2.87–2.93 (m, 2H), 3.66 (d, J = 13.3 Hz, 1H), 3.75 (d, J = 13.3 Hz, 1H), 3.96–4.02 (m, 3H), 7.23–7.32 (m, 7H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 21.5, 50.5, 53.1, 55.6, 61.8, 127.1, 127.3, 128.1, 128.4, 129.7, 136.8, 139.7, 143.6, 170.7; ESIMS (positive mode) m/z: 377 $[M + H]^+$, 399 $[M + Na]^+$; HRESIMS (positive ion) m/z: 377.1516 $[M + H]^+$ (calcd. for $C_{19}H_{25}N_2O_4S_1$, 399.1530).

Ethyl 3-(4-methylphenylsulfonamido)-2-morpholinopropanoate (Table 3, Entries 10 and 2j). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.0 Hz, 3H), 2.32–2.39 (m, 4H), 2.42 (s, 3H), 2.60 (dd, J_1 = 12.8 Hz, J_2 = 5.5 Hz, 1H), 2.66 (dd, J_1 = 12.8 Hz, J_2 = 7.3 Hz, 1H), 3.57 (br t, J = 4.4 Hz, 4H), 3.95 (br s, 1H), 3.99–4.07 (m, 2H), 5.51 (br s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 21.5, 53.5, 53.9, 59.3, 61.6, 66.8, 127.3, 129.6, 136.8, 143.7, 170.7; ESIMS (positive mode) m/z: 357 $[M + H]^+$, 379 $[M + Na]^+$; HRESIMS (positive ion) m/z: 357.1487 $[M + H]^+$ (calcd. for $C_{16}H_{25}N_2O_5S_1$, 357.1479).

Ethyl 2-(4-methylphenylsulfonamido)-3-morpholinopropanoate (Table 3, Entries 10 and 3j). Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.3 Hz, 3H), 2.38–2.41 (m, 2H), 2.43 (s, 3H), 2.60 (br s, 2H), 3.04–3.08 (m, 1H), 3.22–3.26 (m, 2H), 3.57-3.65 (m, 4H), 4.11–4.22 (m, 2H), 5.07 (br d, J = 5.5 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.5, 40.3, 49.5, 60.9, 65.6, 67.2, 127.1, 129.8, 136.8, 143.7, 169.4; ESIMS (positive mode) m/z: 357 $[M + H]^+$, 379 $[M + Na]^+$; HRESIMS (positive ion) m/z: 357.1483 $[M + H]^+$ (calcd. for $C_{16}H_{25}N_2O_5S_1$, 357.1479).

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