A Multicomponent Approach to the Synthesis of N-sulfonyl β²-³-Amino Esters

Erwan Le Gall,* Stéphane Sengmany, Issa Samb, Sabrina Benakrour, Christopher Colin, Antoine Pignon, Eric Léonel

Électrochimie et Synthèse Organique, Institut de Chimie et des Matériaux Paris Est, ICMPE, UMR 7182 CNRS
Université Paris Est Créteil Val-de-Marne, 2-8 rue Henri Dunant, 94320 Thiais, France

legall@icmpe.cnrs.fr

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General

All reactions were carried out under argon atmosphere. Reagents and solvents were obtained from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a 5 m BP1 column. Melting points (mp) were determined on a capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer in ATR mode. NMR spectra were recorded in CDCl$_3$ at 400 MHz ($^1$H), 100 MHz ($^{13}$C) and 376 MHz ($^{19}$F). Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signal. Coupling constant values (J) are given in Hertz (Hz) and refer to apparent multiplicities, indicated as follows: s (singlet); d (doublet); t (triplet); q (quadruplet); m (multiplet); dd (doublet of doublets), td (triplet of doublets). Flash chromatography was performed on silica gel (40 µm-centered particles). HRMS experiments were realized by an outside facility. Yields given below for β-amino esters 4 refer to mixtures of diastereoisomers. As far as possible, the NMR spectra of separated diastereoisomers are appended below, for more clarity. Unless otherwise stated, melting points are given for separated diastereoisomers. To the best of our knowledge, all β-amino esters 4 are new compounds.

Typical procedure for the synthesis of imines 1

Imines 1 were synthesized in 78-91% yield according to a procedure derived from that of Lu and Kwon (Org. Synth. 2009, 86, 212). In a typical procedure, methanesulfonamide (4.75 g, 50 mmol), benzaldehyde (7 mL, 70 mmol) and aluminum chloride (1.33 g, 10 mmol) were heated at reflux in toluene for 12 h using a Dean-Stark apparatus. Toluene was removed by evaporation then ethyl acetate (100 mL) was added to the remaining solid. The mixture was filtered and the solvent removed by evaporation. The solid was washed with a diethyl ether/pentane: 15/25 (2 × 40 mL) to afford the imine as off-white needles (8.40 g, 91%).

General procedure for the synthesis of β-amino esters 4a-t

A dried 50 mL round bottom flask surrounded by a reflux condenser was flushed with argon and charged with acetonitrile (10 mL). Dodecane (0.1 mL, internal standard), zinc dust (1.5 g, 23 mmol), organic bromide 3 (12 mmol), acrylate 2 (22.5 mmol), imine 1 (5 mmol), and cobalt bromide (300 mg, 1.35 mmol) were added under vigorous stirring (~500 rpm). Trifluoroacetic acid (0.1 mL, 1.3 mmol) was added to the mixture, which was stirred for 30 minutes at room temperature. The reaction mixture was poured into a sat. NH$_4$Cl solution (75 mL), extracted with ethyl acetate (2 × 50 mL). The organic fractions were dried over Na$_2$SO$_4$ and concentrated over silica gel. The crude reaction product was purified by flash column chromatography over silica gel using a petroleum ether 40-60°C / ethyl acetate mixture (4:1 to 0:1) as an eluent to afford the three-component coupling product 4 (in most cases, both diastereoisomers a and b were separated).
Characterization data

Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4a

Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound 4a was obtained as a mixture of diastereoisomers; white solid (mp = 83-85°C); yield: 1.89 g (81%);

$^1$H NMR (CDCl$_3$): δ 7.42 (dd, $J = 14.5, 8.2$ Hz, 2H$_a$+2H$_b$), 7.24 – 6.82 (m, 12H$_a$+12H$_b$), 6.21 (d, $J = 9.3$ Hz, 1H$_a$), 3.71 (t, $J = 6.5$ Hz, 2H$_a$), 3.55 (td, $J = 6.6, 2.3$ Hz, 2H$_b$), 3.07 – 2.65 (m, 3H$_a$+3H$_b$), 2.25 (s, 3H$_b$), 2.22 (s, 3H$_a$), 1.23 – 1.12 (m, 2H$_a$), 1.12 – 1.03 (m, 2H$_b$), 0.97 – 0.80 (m, 2H$_a$+2H$_b$), 0.70 – 0.59 (m, 3H$_a$+3H$_b$);

$^{13}$C NMR (CDCl$_3$): δ 173.85, 172.36, 143.13, 142.75, 138.90, 138.09, 138.05, 137.96, 137.29, 129.33, 129.14, 128.90, 128.81, 128.52, 128.41, 128.27, 127.74, 127.37, 127.15, 127.02, 126.90, 126.70, 126.43, 126.32, 64.67, 64.46, 59.41, 58.45, 54.16, 54.11, 36.49, 35.17, 30.30, 30.15, 21.40, 18.76, 18.74, 13.53;

IR (Neat): $\nu = 3279, 2956, 2932, 1718, 1709, 1329, 1159, 700, 664$ cm$^{-1}$; HRMS (ESI$^+$) m/z calcd. for C$_{27}$H$_{32}$NO$_4$S (M+H)$^+$: 466.2047; found: 466.2047.

Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4b

Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound 4b was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 141-142°C); yield: 1.51 g (61%);

$^1$H NMR (CDCl$_3$): δ 7.40 (d, $J = 8.3$ Hz, 2H), 7.08 – 6.90 (m, 7H), 6.85 (dd, $J = 7.5, 1.9$ Hz, 2H), 6.79 – 6.67 (m, 2H), 6.18 (d, $J = 9.2$ Hz, 1H), 4.55 (dd, $J = 9.2, 4.2$ Hz, 1H), 3.75 – 3.69 (m, 5H), 2.92 – 2.69 (m, 3H), 2.23 (s, 3H), 1.25 – 1.14 (m, 2H), 0.98 – 0.84 (m, 2H), 0.67 (t, $J = 7.3$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$): δ 173.99, 158.38, 142.75, 138.99, 138.09, 129.95, 129.91, 129.11, 128.27, 127.30, 126.88, 126.26, 113.91, 64.63, 58.14, 55.22, 54.29, 35.62, 30.23, 21.39, 18.75, 13.52; IR (Neat): $\nu = 3279, 2956, 2934, 1713, 1246, 1180, 1161, 1029, 817, 706, 665$ cm$^{-1}$; HRMS (ESI$^+$) m/z calcd. for C$_{28}$H$_{34}$NO$_5$S (M+H)$^+$: 496.2152; found: 496.2151.

Methyl 4-(3-butoxy-2-((4-methylphenylsulfonamido)(phenyl)methyl)-3-oxopropyl)benzoate 4c

Prepared following the general procedure, using methyl 4-bromobenzoate (2.6 g, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound 4c was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 129-132°C); yield: 1.49 g (57%);

$^1$H NMR (CDCl$_3$): δ 7.92 – 7.83 (m, 2H), 7.43 – 7.35 (m, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 7.07 – 6.91 (m, 5H), 6.85 (dd, $J = 7.6, 1.9$ Hz, 2H), 6.14 (d, $J = 9.4$ Hz, 1H), 4.56 (dd, $J = 9.3, 4.6$ Hz, 1H), 3.83 (s, 3H), 3.71 (t, $J = 6.5$ Hz, 2H), 3.09 – 2.78 (m, 3H), 2.23 (s, 3H), 1.24 – 1.11 (m, 2H), 0.96 – 0.79 (m, 2H), 0.65 (t, $J = 7.3$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$): δ 173.48, 166.94, 143.40, 142.88, 138.58, 137.92, 129.87, 129.15, 129.01, 128.70, 128.37, 127.48, 126.88, 126.26, 64.80, 58.40, 53.67, 52.08, 36.42, 30.18, 21.39, 18.72, 13.47; IR (Neat): $\nu = 3278, 2956, 2931, 1719, 1279, 1161, 704, 668$ cm$^{-1}$; HRMS (ESI$^+$) m/z calcd. for C$_{29}$H$_{34}$NO$_6$S (M+H)$^+$: 524.2101; found: 524.2100.
Ethyl 2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4d

Prepared following the general procedure, using 1-bromo-3,4-(methyleneedioxy)benzene (1.45 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and N-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound 4d was obtained as a mixture of diastereoisomers; off-white solid (mp = 122-124°C); yield: 1.59 g (66%); 1H NMR (CDCl3): δ 7.53 (d, J = 8.3 Hz, 2Hb), 7.48 (d, J = 8.3 Hz, 2Ha), 7.20 – 6.90 (m, 7Ha+7Hb), 6.77 – 6.47 (m, 3Ha+3Hb), 6.24 (d, J = 9.3 Hz, 1Ha), 5.93 (s, 2Ha), 5.91 (s, 2Hb), 5.66 (d, J = 8.9 Hz, 1Hb), 4.62 (dd, J = 9.3, 4.7 Hz, 1Ha), 4.53 – 4.45 (m, 1Hb), 3.96 – 3.85 (m, 2Ha), 3.76 (q, J = 7.1 Hz, 2Hb), 3.02 – 2.69 (m, 3Ha+3Hb), 2.35 (s, 3Hb), 2.31 (s, 3Ha), 0.98 (t, J = 7.1 Hz, 3Ha), 0.87 (s, J = 7.1 Hz, 3Hb); 13C NMR (CDCl3): δ 173.66, 173.12, 147.66, 147.57, 146.10, 146.21, 142.80, 138.85, 138.00, 137.22, 132.12, 131.63, 129.36, 129.13, 128.31, 128.30, 127.80, 127.38, 127.14, 126.98, 126.89, 126.33, 122.04, 121.83, 109.22, 109.20, 108.26, 108.19, 100.91, 100.84, 60.85, 60.65, 59.23, 58.22, 54.31, 36.08, 34.67, 21.44, 21.39, 13.89, 13.76; IR (Neat): ν = 3263, 3208, 2903, 1733, 1708, 1505, 1250, 1159, 1039, 813, 665 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C₂₆H₂₆NO₈S (M+H)⁺: 482.1632; found: 482.1629.

Ethyl 3-(4-methylphenylsulfonamido)-2-(3-(trifluoromethyl)benzyl)propanoate 4e

Prepared following the general procedure, using 3-bromobenzotrifluoride (1.65 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and N-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound 4e was obtained as a mixture of diastereoisomers; white solid (mp = 126-128°C); yield: 1.34 g (66%); 1H NMR (CDCl3): δ 7.46 – 7.20 (m, 6Ha+6Hb), 7.15 – 6.78 (m, 7Ha+7Hb), 6.11 (d, J = 9.3 Hz, 1Ha), 5.48 (d, J = 8.9 Hz, 1Hb), 4.57 (dd, J = 9.4, 4.9 Hz, 1Ha), 4.50 – 4.38 (m, 1Hb), 3.86 – 3.73 (m, 2Ha), 3.63 (q, J = 7.1 Hz, 2Hb), 3.19 – 2.76 (m, 3Ha+3Hb), 2.27 (s, 3Hb), 2.23 (s, 3Ha), 0.83 (t, J = 7.1 Hz, 3Ha), 0.72 (s, J = 7.1 Hz, 3Hb); 13C NMR (CDCl3): δ 173.27, 143.35, 142.56, 139.50, 138.95, 138.46, 138.74, 137.80, 137.11, 132.56, 132.32, 130.98, 130.66, 129.38, 129.17, 128.99, 128.87, 128.82, 128.42, 127.96, 127.57, 127.14, 126.88, 126.31, 125.59, 125.55, 125.51, 125.47, 123.66, 123.62, 122.70, 109.68, 109.74, 59.49, 58.56, 57.54, 54.01, 53.71, 36.18, 35.03, 33.59, 29.06, 26.92, 21.43, 21.39, 13.83, 13.72, 13.59 (C-F coupling constants are not indicated; most intense peaks are reported); 19F NMR (CDCl3): δ -62.63, -62.64; IR (Neat): ν = 3209, 2990, 1711, 1327, 1157, 1116, 702 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C₂₇H₂₇F₃NO₈S (M+H)⁺: 506.1607; found: 506.1608.

Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4f

Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-N-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound 4f was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 147-149°C); yield: 1.30 g (55%); 1H NMR (CDCl3): δ 7.49 (d, J = 8.3 Hz, 2H), 7.28 – 7.00 (m, 7H), 6.96 (dd, J = 5.1, 1.2 Hz, 1H), 6.64 (dd, J = 5.1, 3.6 Hz, 1H), 6.57 (d, J = 3.4 Hz, 1H), 6.10 (d, J = 9.3 Hz, 1H), 4.86 (dd, J = 9.3, 4.3 Hz, 1H), 3.79 (t, J = 6.6 Hz, 2H), 3.06 – 2.76 (m, 3H), 2.27 (s, 3H), 1.32 – 1.19 (m, 2H), 1.08 – 0.92 (m, 2H), 0.71 (t, J = 7.4 Hz, 3H); 13C NMR (CDCl3): δ 173.83, 143.06, 142.92, 138.12, 137.79, 129.23, 128.93, 128.56, 126.89, 126.77, 126.45, 125.36, 124.88, 64.88, 54.49, 54.16, 36.36, 30.24, 21.47, 18.81, 13.56; IR (Neat): ν = 3252, 2956, 2930, 1712, 1452, 1327, 1160, 700, 669 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C₂₅H₃₀NO₅S₂ (M+H)⁺: 472.1611; found: 472.1605.
Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4g

Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-N-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound 4g was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 93-96°C); yield: 1.41 g (56%); \( ^1H \) NMR (CDCl\(_3\)): \( \delta \) 7.45 (d, \( J = 8.2 \) Hz, 2H), 7.13 – 6.83 (m, 5H), 6.82 – 6.50 (m, 4H), 5.63 (d, \( J = 9.2 \) Hz, 1H), 4.72 (dd, \( J = 9.0, 6.8 \) Hz, 1H), 3.85 – 3.60 (m, 5H), 3.04 – 2.68 (m, 3H), 2.29 (s, 3H), 1.37 – 1.20 (m, 2H), 1.16 – 0.96 (m, 2H), 0.73 (t, \( J = 7.4 \) Hz, 3H); \( ^13C \) NMR (CDCl\(_3\)): \( \delta \) 172.42, 158.28, 143.20, 141.08, 137.39, 129.86, 129.41, 127.06, 126.46, 125.38, 113.91, 64.89, 55.24, 54.38, 53.99, 34.12, 30.30, 21.50, 18.95, 13.61; IR (Neat): \( \nu = 3235, 2954, 1729, 1512, 1249, 1157, 1034, 719, 668 \) cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{26}\)H\(_{32}\)NO\(_5\)S\(_2\) (M+H): 502.1716; found: 502.1712.

Butyl 2-(4-fluorobenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4h

Prepared following the general procedure, using 1-bromo-4-fluorobenzene (1.3 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-N-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound 4h was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 98-101°C); yield: 1.52 g (62%); \( ^1H \) NMR (CDCl\(_3\)): \( \delta \) 7.48 (d, \( J = 8.3 \) Hz, 2H), 7.16 – 6.83 (m, 7H), 6.68 – 6.50 (m, 2H), 6.08 (d, \( J = 9.4 \) Hz, 1H), 4.84 (dd, \( J = 9.4, 4.1 \) Hz, 1H), 3.80 (t, \( J = 6.6 \) Hz, 2H), 3.03 – 2.76 (m, 3H), 2.27 (s, 3H), 1.34 – 1.21 (m, 2H), 1.07 – 0.93 (m, 2H), 0.72 (t, \( J = 7.4 \) Hz, 3H); \( ^13C \) NMR (CDCl\(_3\)): \( \delta \) 172.62, 160.77 (d, \( 1J_{C-F} = 243.3 \) Hz), 141.94, 141.76, 137.00, 132.44 (d, \( 4J_{C-F} = 3.2 \) Hz), 129.45 (d, \( 3J_{C-F} = 7.9 \) Hz), 128.20, 125.84, 125.43, 125.38, 113.91, 64.89, 55.24, 54.38, 53.99, 34.12, 30.30, 21.50, 18.95, 13.61; \( ^19F \) NMR (CDCl\(_3\)): \( \delta \) -116.37; IR (Neat): \( \nu = 3257, 2960, 1709, 1509, 1327, 1221, 1157, 706, 664 \) cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{25}\)H\(_{29}\)FNO\(_4\)S\(_2\) (M+H): 490.1517; found: 490.1515.

Ethyl 3-(furan-3-yl)-2-(4-methylbenzyl)-3-(4-methylphenylsulfonamido)propanoate 4i

Prepared following the general procedure, using 4-bromotoluene (2.05 g, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and \( N \)-((furan-3-yl)methylene)-4-methylbenzenesulfonamide (1.25 g, 5 mmol). Compound 4i was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 121-123°C); yield: 1.15 g (52%); \( ^1H \) NMR (CDCl\(_3\)): \( \delta \) 7.51 (d, \( J = 8.3 \) Hz, 2H), 7.15 – 7.07 (m, 3H), 7.02 – 6.93 (m, 3H), 6.86 (d, \( J = 8.0 \) Hz, 2H), 6.05 – 5.96 (m, 1H), 5.58 (d, \( J = 9.3 \) Hz, 1H), 4.40 (dd, \( J = 9.3, 5.8 \) Hz, 1H), 3.86 (q, \( J = 7.2 \) Hz, 2H), 2.97 – 2.64 (m, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 0.96 (t, \( J = 7.1 \) Hz, 3H); \( ^13C \) NMR (CDCl\(_3\)): \( \delta \) 172.61, 143.32, 143.18, 140.29, 137.51, 136.03, 135.06, 129.45, 129.17, 128.68, 127.10, 122.71, 108.84, 60.87, 52.55, 50.78, 34.48, 29.23, 20.43, 17.79, 12.50; \( ^19F \) NMR (CDCl\(_3\)): \( \delta \) -116.37; IR (Neat): \( \nu = 3257, 2960, 1709, 1509, 1327, 1221, 1157, 706, 664 \) cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{28}\)H\(_{30}\)NO\(_5\)S (M+H): 442.1683; found: 442.1682.
(Z)-Ethyl 2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl)hex-4-enoate 4j

Prepared following the general procedure, using *cis*-1-bromo-1-propene (1.0 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (1.45 g, 5 mmol). Compound 4j was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 80-83°C); yield: 1.08 g (50%); 

\(^1\)H NMR (CDCl\(_3\)): \(\delta \) 7.39 (d, \(J = 8.3 \) Hz, 2H), 6.97 (d, \(J = 8.1 \) Hz, 2H), 6.86 – 6.78 (m, 2H), 6.59 – 6.51 (m, 2H), 6.01 (d, \(J = 9.1 \) Hz, 1H), 5.51 – 5.38 (m, 1H), 5.26 – 5.15 (m, 1H), 4.49 (dd, \(J = 9.0, 6.2 \) Hz, 1H), 3.99 – 3.88 (m, 2H), 3.65 (s, 3H), 2.65 – 2.52 (m, 1H), 2.38 – 2.28 (m, 1H), 2.24 (s, 3H), 2.11 – 1.99 (m, 1H), 1.50 – 1.43 (m, 3H), 1.04 (t, \(J = 7.1 \) Hz, 3H); 

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta \) 174.02, 158.85, 142.60, 138.14, 131.07, 129.08, 127.66, 127.09, 126.91, 125.63, 113.65, 60.87, 58.23, 55.23, 52.15, 27.73, 21.37, 14.07, 12.84; IR (Neat): \(\nu \) = 3246, 2962, 1728, 1515, 1156, 1031, 668 cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{23}\)H\(_{30}\)NO\(_5\)S (M+H): 432.1839; found: 432.1839.

Butyl 2-benzyl-3-(methylsulfonamido)-3-phenylpropanoate 4k

Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and \(N\)-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound 4k was obtained as a mixture of diastereoisomers; off-white solid (mp = 105-108°C); yield: 1.37 g (70%); 

\(^1\)H NMR (CDCl\(_3\)): \(\delta \) 7.38 – 6.97 (m, 10Ha+10Hb), 6.17 (d, \(J = 9.3 \) Hz, 1Ha), 5.58 (d, \(J = 9.1 \) Hz, 1Hb), 4.74 – 4.51 (m, 1Ha+1Hb), 3.81 (t, \(J = 6.1 \) Hz, 2Ha), 3.66 (t, \(J = 6.6 \) Hz, 2Hb), 3.16 – 2.80 (m, 3Ha+3Hb), 2.54 (s, 3Hb), 2.50 (s, 3Ha), 1.33 – 1.19 (m, 2Ha), 1.19 – 1.04 (m, 2Hb), 1.03 – 0.88 (m, 2Ha+2Hb), 0.75 – 0.60 (m, 3Ha+3Hb); 

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta \) 173.97, 172.24, 139.61, 138.68, 138.28, 137.81, 129.02, 128.94, 128.91, 128.82, 128.56, 128.53, 128.49, 128.25, 127.72, 126.79, 126.56, 126.46, 64.80, 64.59, 59.54, 58.42, 54.30, 54.00, 42.08, 41.78, 36.73, 35.44, 30.25, 30.21, 18.80, 18.77, 13.55; IR (Neat): \(\nu \) = 3296, 3264, 2957, 1726, 1706, 1319, 1156, 752, 701 cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{21}\)H\(_{28}\)NO\(_4\)S (M+H): 390.1733; found: 390.1734.

Butyl 2-(4-methylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4l

Prepared following the general procedure, using 4-bromotoluene (2.05 g, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound 4l was obtained as a mixture of diastereoisomers; white solid (mp = 99-102°C); yield: 1.33 g (66%); 

\(^1\)H NMR (CDCl\(_3\)): \(\delta \) 7.33 – 7.14 (m, 5Ha+5Hb), 7.06 – 6.89 (m, 4Ha+4Hb), 6.21 (d, \(J = 9.4 \) Hz, 1Ha), 5.76 (d, \(J = 9.2 \) Hz, 1Hb), 4.67 – 4.57 (m, 1Ha+1Hb), 3.89 – 3.75 (m, 1Hb), 3.64 (t, \(J = 6.6 \) Hz, 1Hb), 3.09 – 2.73 (m, 3Ha+3Hb), 2.52 (s, 3Hb), 2.48 (s, 3Ha), 2.22 (s, 3Hb), 2.20 (s, 3Ha), 1.31 – 1.21 (m, 2Ha), 1.20 – 1.08 (m, 2Hb), 1.03 – 0.82 (m, 2Ha+2Hb), 0.74 – 0.60 (m, 3Ha+3Hb); 

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta \) 174.00, 172.31, 139.67, 138.85, 136.26, 135.97, 135.19, 134.69, 129.23, 129.15, 129.01, 128.89, 128.77, 128.69, 128.44, 128.22, 127.27, 126.52, 64.78, 64.50, 59.59, 58.48, 54.46, 54.17, 42.03, 41.75, 36.25, 35.11, 30.31, 30.24, 21.05, 21.02, 18.82, 18.80, 13.57; IR (Neat): \(\nu \) = 3298, 3267, 2957, 1727, 1705, 1320, 1154, 765, 701 cm\(^{-1}\); HRMS (ESI\(^+\)) m/z calcd. for C\(_{22}\)H\(_{30}\)NO\(_4\)S (M+H): 404.1890; found: 404.1890.
Butyl 2-(4-isopropylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4m

Prepared following the general procedure, using 1-bromo-4-isopropylbenzene (1.85 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound 4m was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 121-124°C); yield: 1.41 g (65%); 1H NMR (CDCl3): δ 7.36 – 7.13 (m, 5H), 7.12 – 6.98 (m, 4H), 6.14 (d, J = 9.2 Hz, 1H), 4.63 (dd, J = 9.3, 4.8 Hz, 1H), 3.87 – 3.71 (m, 2H), 3.03 – 2.73 (m, 4H), 2.55 (s, 3H), 1.27 – 1.18 (m, 2H), 1.16 (s, J = 6.9 Hz, 6H), 1.01 – 0.89 (m, 2H), 0.69 (t, J = 7.3 Hz, 3H); 13C NMR (CDCl3): δ 174.12, 147.32, 139.75, 135.07, 128.96, 128.81, 128.18, 126.58, 126.42, 64.72, 58.32, 53.92, 42.11, 36.37, 33.71, 30.22, 24.01, 23.99, 18.75, 13.54; IR (Neat): v = 3279, 2959, 1716, 1324, 1152, 768, 709 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C24H34NO4S (M+H)⁺: 432.2203; found: 432.2218.

Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4n

Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound 4n was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 97-100°C); yield: 1.35 g (64%); 1H NMR (CDCl3): δ 7.35 – 7.11 (m, 5H), 7.04 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 6.14 (d, J = 9.2 Hz, 1H), 4.59 (dd, J = 9.2, 4.3 Hz, 1H), 3.80 (t, J = 6.5 Hz, 2H), 3.70 (s, 3H), 3.04 – 2.76 (m, 3H), 2.53 (s, 3H), 1.31 – 1.17 (m, 2H), 1.06 – 0.91 (m, 2H), 0.70 (t, J = 7.3 Hz, 3H); 13C NMR (CDCl3): δ 174.10, 158.44, 139.74, 129.98, 129.76, 128.97, 128.18, 126.38, 113.94, 64.75, 58.05, 55.21, 54.12, 42.13, 35.87, 30.28, 18.78, 13.54; IR (Neat): v = 3279, 2958, 1727, 1513, 1315, 1244, 1154, 752, 706 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C22H30NO5S (M+Na)⁺: 420.1839; found: 420.1837.

Butyl 2-benzyl-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4o

Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound 4o was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 131-134°C); yield: 1.25 g (63%); 1H NMR (CDCl3): δ 7.31 – 7.05 (m, 6H), 6.89 (dt, J = 4.9, 3.2 Hz, 2H), 6.06 (d, J = 9.3 Hz, 1H), 4.90 (dd, J = 9.3, 4.3 Hz, 1H), 3.88 (t, J = 6.6 Hz, 2H), 3.10 – 2.85 (m, 3H), 2.63 (s, 3H), 1.39 – 1.22 (m, 2H), 1.04 (dd, J = 15.1, 7.4 Hz, 2H), 0.83 – 0.66 (m, 3H); 13C NMR (CDCl3): δ 174.01, 143.54, 137.60, 128.97, 128.60, 127.05, 126.87, 125.81, 125.50, 65.04, 54.35, 54.02, 41.99, 36.63, 30.28, 18.84, 13.58; IR (Neat): v = 3249, 2955, 1712, 1322, 1149, 770, 700 cm⁻¹; HRMS (ESI⁺) m/z calcd. for C19H25NNaO3S2 (M+Na)⁺: 418.1117; found: 418.1115.
Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4p

Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound 4p was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 119-121°C); yield: 1.11 g (52%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ = 7.23 – 7.13 (m, 1H), 6.95 – 6.83 (m, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.07 (d, J = 9.3 Hz, 1H), 4.87 (dd, J = 9.3, 4.1 Hz, 1H), 3.90 (t, J = 6.6 Hz, 2H), 3.71 (s, 3H), 3.05 – 2.82 (m, 3H), 2.62 (s, 3H), 1.42 – 1.27 (m, 2H), 1.13 – 0.99 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 174.11, 158.50, 143.61, 130.00, 129.55, 127.02, 125.79, 125.47, 113.98, 65.02, 55.22, 54.25, 54.15, 41.97, 35.72, 30.33, 18.87, 13.58; IR (Neat): ν = 3251, 2954, 1711, 1513, 1320, 1247, 1151, 1038, 769, 707 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) m/z calcd. for C\textsubscript{20}H\textsubscript{27}NNaO\textsubscript{5}S\textsubscript{2} (M+Na\textsuperscript{+}): 448.1223; found: 448.1221.

Butyl 2-(4-fluorobenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4q

Prepared following the general procedure, using 1-bromo-4-fluorobenzene (1.3 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound 4q was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 78-80°C); yield: 1.24 g (60%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 7.36 – 7.23 (m, 1H), 7.20 – 7.06 (m, 2H), 7.07 – 6.88 (m, 4H), 5.64 (d, J = 9.4 Hz, 1H), 4.98 (dd, J = 9.4, 7.2 Hz, 1H), 3.93 (t, J = 6.6 Hz, 2H), 3.29 – 3.14 (m, 1H), 3.11 – 2.88 (m, 2H), 2.67 (s, 3H), 1.48 – 1.33 (m, 2H), 1.21 – 1.08 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 172.18, 161.70 (d, J\textsubscript{C-F} = 243.1 Hz), 141.50, 133.66 (d, J\textsubscript{C-F} = 3.2 Hz), 130.37 (d, J\textsubscript{C-F} = 7.9 Hz), 126.96, 126.94, 126.08, 115.35 (d, J\textsubscript{C-F} = 21.1 Hz), 65.04, 54.76, 54.20, 41.62, 34.49, 30.30, 18.91, 13.57; \textsuperscript{19}F NMR (CDCl\textsubscript{3}): δ -116.19; IR (Neat): ν = 3269, 2961, 1725, 1510, 1322, 1221, 1152, 731, 704 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) m/z calcd. for C\textsubscript{19}H\textsubscript{24}FNNaO\textsubscript{4}S\textsubscript{2} (M+Na\textsuperscript{+}): 436.1023; found: 436.1021.

Butyl 2-benzyl-3-(4-fluorophenyl)-3-(methylsulfonamido)propanoate 4r

Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-(4-fluorobenzylidene)methanesulfonamide (1.0 g, 5 mmol). Compound 4r was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 135-137°C); yield: 1.12 g (55%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 7.31 – 6.88 (m, 9H), 5.83 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 8.2 Hz, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.11 – 2.97 (m, 2H), 2.53 (s, 3H), 1.22 – 1.10 (m, 2H), 1.00 – 0.89 (m, 2H), 0.68 (t, J = 7.3 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 172.21, 161.49 (d, J\textsubscript{C-F} = 246.3 Hz), 138.06, 134.82 (d, J\textsubscript{C-F} = 3.3 Hz), 129.08 (d, J\textsubscript{C-F} = 8.1 Hz), 128.78, 128.51, 126.63, 115.86 (d, J\textsubscript{C-F} = 21.4 Hz), 64.62, 58.90, 54.40, 41.85, 35.61, 30.21, 18.78, 13.50; \textsuperscript{19}F NMR (CDCl\textsubscript{3}): δ -116.15; IR (Neat): ν = 3252, 2959, 1712, 1511, 1328, 1217, 1159, 707, 668 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) m/z calcd. for C\textsubscript{21}H\textsubscript{26}FNNaO\textsubscript{4}S (M+Na\textsuperscript{+}): 430.1464; found: 430.1461.
(Z)-Butyl 2-((4-fluorophenyl)(methylsulfonamido)methyl)hex-4-enoate 4s

Prepared following the general procedure, using cis-1-bromo-1-propene (1.0 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and N-(4-fluorobenzylidene)methanesulfonamide (1.0 g, 5 mmol). Compound 4s was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 58-60°C); yield: 1.04 g (56%); $^1$H NMR (CDCl$_3$): $\delta$ 7.32 – 7.13 (m, 2H), 6.97 (t, $J$ = 8.6 Hz, 2H), 5.75 (d, $J$ = 9.0 Hz, 1H), 5.59 – 5.41 (m, 1H), 5.36 – 5.16 (m, 1H), 4.61 (t, $J$ = 8.7 Hz, 1H), 3.82 (t, $J$ = 6.5 Hz, 2H), 2.87 – 2.69 (m, 1H), 2.51 (s, 3H), 2.48 – 2.30 (m, 2H), 1.50 (d, $J$ = 6.6 Hz, 3H), 1.40 – 1.26 (m, 2H), 1.18 – 1.05 (m, 2H), 0.77 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.44, 162.49 (d, $^{1}$J$_{C-F}$ = 246.1 Hz), 134.82 (d, $^{4}$J$_{C-F}$ = 3.3 Hz), 129.08 (d, $^{3}$J$_{C-F}$ = 8.1 Hz), 127.13, 125.83, 115.79 (d, $^{2}$J$_{C-F}$ = 21.5 Hz), 64.75, 58.42, 52.23, 41.83, 30.38, 26.80, 18.95, 13.56, 12.93; $^{19}$F NMR (CDCl$_3$): $\delta$ -113.15; IR (Neat): $\nu$ = 3277, 2961, 1722, 1510, 1318, 1226, 1151, 731 cm$^{-1}$; HRMS (ESI$^+$) m/z calcd. for C$_{18}$H$_{27}$FNO$_4$S (M+H)$^+$: 372.1639; found: 372.1638.

(Z)-Ethyl 2-((4-methoxyphenyl)(methylsulfonamido)methyl)hex-4-enoate 4t

Prepared following the general procedure, using cis-1-bromo-1-propene (1.0 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and N-(4-methoxybenzylidene)methanesulfonamide (1.05 g, 5 mmol). Compound 4t was obtained as a mixture of diastereoisomers; Thick pale yellow oil; yield: 0.96 g (54%); $^1$H NMR (CDCl$_3$): $\delta$ 7.14 (d, $J$ = 8.7 Hz, 2Ha+2Hb), 6.80 (d, $J$ = 8.6 Hz, 2Ha+2Hb), 5.92 (d, $J$ = 9.2 Hz, 1Ha), 5.58 – 5.39 (m, 1Ha+2Hb), 5.36 – 5.17 (m, 1Ha+1Hb), 4.63 – 4.49 (m, 1Ha+1Hb), 4.13 – 3.96 (m, 2Ha), 3.90 (q, $J$ = 7.1 Hz, 2Hb), 3.73 (s, 3Ha), 3.72 (s, 3Hb), 2.82 – 2.72 (m, 1Hb), 2.69 – 2.59 (m, 1Ha), 2.50 (s, 3Ha), 2.48 (s, 3Hb), 2.45 – 2.36 (m, 2Hb+Ha), 2.24 – 2.08 (m, 1Ha), 1.59 – 1.41 (m, 3Ha+3Hb), 1.12 (t, $J$ = 7.1 Hz, 3Ha), 1.01 (t, $J$ = 7.1 Hz, 3Hb); $^{13}$C NMR (CDCl$_3$): $\delta$ 174.09, 172.39, 159.48, 159.38, 131.61, 130.72, 128.50, 127.87, 127.26, 126.93, 126.12, 125.48, 114.31, 114.14, 61.02, 60.75, 58.62, 58.22, 55.28, 55.26, 52.26, 52.14, 41.95, 41.79, 27.82, 26.80, 14.13, 14.00, 12.94, 12.87; IR (Neat): $\nu$ = 3273, 2980, 1729, 1514, 1317, 1248, 1150, 1031, 834, 756 cm$^{-1}$; HRMS (ESI$^+$) m/z calcd. for C$_{17}$H$_{27}$NNaO$_4$S (M+Na)$^+$: 378.1346; found: 378.1345.
NMR Spectra

Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4a
Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4b
Methyl 4-(3-butoxy-2-((4-methylphenylsulfonamido)(phenyl)methyl)-3-oxopropyl)benzoate 4c

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\text{\includegraphics[width=\textwidth]{methyl Compound.png}}
\]
Ethyl 2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4d
Ethyl 3-(4-methylphenylsulfonamido)-3-phenyl-2-(3-(trifluoromethyl)benzyl)propanoate 4e
Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4f
Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonylamido)-3-(thiophen-2-yl)propanoate 4g
Butyl 2-(4-fluorobenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4h
Ethyl 3-(furan-3-yl)-2-(4-methylbenzyl)-3-(4-methylphenylsulfonamido)propanoate 4i
(Z)-Ethyl 2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl)hex-4-enoate 4j
Butyl 2-benzyl-3-(methylsulfonamido)-3-phenylpropanoate 4k
Butyl 2-(4-methylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4l
Butyl 2-(4-isopropylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4m
Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4n
Butyl 2-benzyl-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4o
Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4p
Butyl 2-(4-fluorobenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4q
Butyl 2-benzyl-3-(4-fluorophenyl)-3-(methylsulfonamido)propanoate 4r
(Z)-Butyl 2-((4-fluorophenyl)(methylsulfonamido)methyl)hex-4-enoate 4s
(Z)-Ethyl 2-((4-methoxyphenyl)(methylsulfonamido)methyl)hex-4-enoate 4t