

Organic reactions in ionic liquids: MgO as efficient and reusable catalyst for the Michael addition of sulfonamides to α,β -unsaturated esters under microwave irradiation

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Abstract

The microwave-assisted Michael addition reaction of sulfonamides **1** to α,β -unsaturated esters **2** was carried out in the presence of a catalytic amount of magnesium oxide (MgO) and with the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) as a recyclable solvent affording *N*-alkyl sulfonamides **3** as well as *N,N*-dialkyl sulfonamides **4** in short reaction times.

Keywords: Michael addition, sulfonamide, α,β -unsaturated ester, ionic liquid, MgO, microwave

Introduction

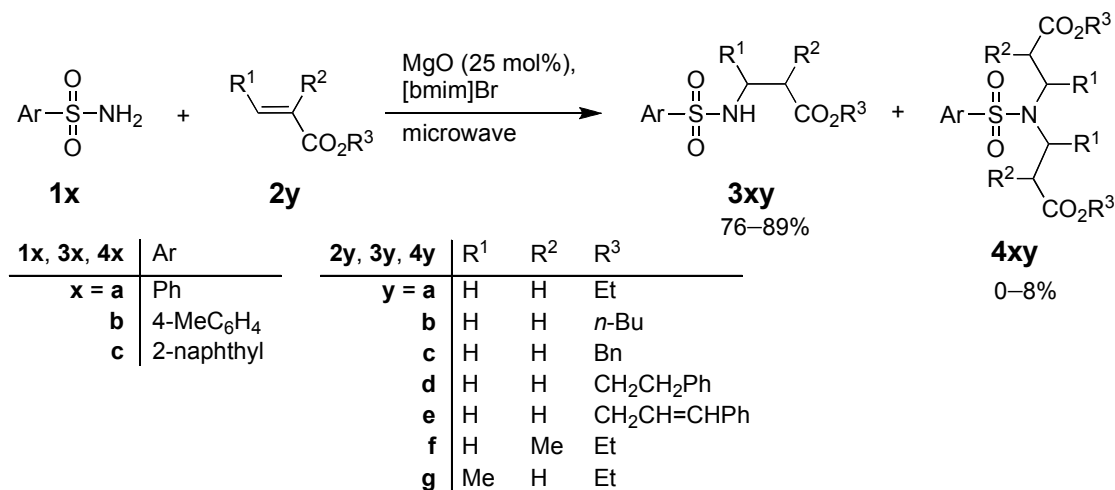
Room temperature ionic liquids have emerged as a new class of stable and inert solvents. This family of ionic compounds features interesting properties as compared to classical solvents: High thermal stability, high polarity due to their ionic nature, and the ability to dissolve polar and non-polar organic compounds.¹ Moreover, their immiscibility with some solvents and their very low vapor pressure make them very good solvents for both extraction and recyclability.² Some important reactions have been carried out and investigated in ionic liquids, for example, Biginelli's condensation,³ benzoin condensation,⁴ Michael addition,⁵ Heck reaction,⁶ oxidation,⁷ hydrogenation,⁸ Suzuki coupling,⁹ Pechmann condensation,¹⁰ diazotization reaction,¹¹ Friedel-Crafts reaction,¹² alkylation,¹³ Diels-Alder reaction,¹⁴ esterification,¹⁵ 1,3-dipolar cycloaddition reaction,¹⁶ aldol condensation reaction,¹⁷ Wittig reactions,¹⁸ etc. Moreover, non-conventional activation methods have been applied to decrease reaction times and to enhance reactivity, mainly microwave irradiation.¹⁹ Our recent interest is in the area of green synthesis under conventional heating as well as microwave conditions.²⁰ We were interested to achieve the Michael additions in ionic liquids. Michael reactions have been used in the formation of carbon-

nitrogen,²¹ carbon-oxygen,²² carbon-sulfur,²³ and carbon-carbon bonds.²⁴ The aza-Michael addition reaction of sulfonamides to α,β -unsaturated esters provides *N*-alkyl sulfonamides. Biological activities of these compounds include anti-inflammatory, antidepressant, psychostimulant, anti-ulcer, anti-emetic and analgesic properties.²⁵

Different substrates and catalysts have been used for aza-conjugate additions of amines,²¹ amides,²⁶ and imides^{20a,27} to α,β -unsaturated aldehydes, ketones, esters and imides, such as $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$,^{21a} aluminum dodecyl sulfate trihydrate,^{21b} micellar solution of sodium dodecyl sulfate,^{21c} polyacrylamide supported phenolate,^{21d} LiClO_4 ,^{21e} SmI_2 ,^{21f} kaolinitic clay,^{21g} β -cyclodextrin,^{21h} boric acid,²¹ⁱ bis(trifluoromethanesulfon)imide,^{21j} NaOH ,^{26a} *t*-BuOK,^{26b} $\text{Si}(\text{OEt})_4$ -CsF,^{26c} $\text{Pd}(\text{PhCN})_2\text{Cl}_2$,^{26d} ZnO ,^{20a} Na in absolute EtOH,^{27a} AlMe_2Cl ,^{27b} and K_2CO_3 .^{27c} However, the aza-Michael reaction of sulfonamides has been scarcely studied; Reitz et al. have used Al_2O_3 to achieve this reaction.²⁸

Magnesium oxide has been used for benzylation of aromatic compounds,²⁹ transesterification,³⁰ aldol reaction,³¹ intramolecular Tishchenko reaction,³² synthesis of chiral epoxy ketones, chiral nitro alcohols as well as Michael adducts,³³ etc.

With the above objects in mind and in continuation of our previous research on aza-Michael reactions,^{20a,20g} we report herein our results on the aza-conjugate addition of sulfonamides **1** to α,β -unsaturated esters **2** using MgO as catalyst in [bmim]Br (1-butyl-3-methylimidazolium bromide) under microwave irradiation. By this method, *N*-alkyl sulfonamides **3** were obtained and in very low yields *N,N*-dialkylated products **4** (Scheme 1).



Scheme 1. Michael addition of sulfonamides **1** to α,β -unsaturated esters **2**.

Results and Discussion

As a model reaction, the catalytic potential of some inorganic and organic bases was investigated for the Michael addition of benzenesulfonamide (**1a**) to *n*-butyl acrylate (**2b**) in [bmim]Br under microwave conditions (Table 1): Bu₃N and DABCO (1,4-diazabicyclo[2,2,2]octane) gave low yields of the *N*-substituted benzenesulfonamide **3ab**; CaO, Cs₂CO₃, *t*-BuOK and basic alumina afforded moderate to good yields of **3ab**; the most efficient catalyst was MgO. In all cases, the selectivity was high, the *N,N*-disubstituted Michael adduct **4ab** was obtained only in low yield. In another study, the reaction of benzenesulfonamide (**1a**) with *n*-butyl acrylate (**2b**) in the presence of MgO was examined at different microwave powers (100–600 W) with controlled temperature (max. 110 °C). The best results were observed at 300 W.

Table 1. Effect of catalysts (25 mol%) on the reaction of benzenesulfonamide (**1a**) with *n*-butyl acrylate (**2b**) in [bmim]Br (2 g) under microwave irradiation (300 W, max. 110 °C)

Entry	Catalyst	Time [min]	Yield ^a (%)	
			<i>N</i> -Alkylated Product 3ab	<i>N,N</i> -Dialkylated Product 4ab
1	MgO	5	89	7
2	CaO	5	67	10
3	Cs ₂ CO ₃	5	72	14
4	basic Al ₂ O ₃	7	58	9
5	<i>t</i> -BuOK	5	69	12
6	NBu ₃	8	22	<3
7	DABCO	8	17	<3

For the same reaction, various ionic liquids including [bmim]Br, [bmim]Cl, [bmim]BF₄ and [bmim]PF₆ were examined in the presence of MgO. The reactions were performed at 300 W of microwave power (max. 110 °C). All ionic liquids examined gave similar results; [bmim]Br was the solvent of choice, because of the facile preparation of this ionic liquid.

Table 2. Effect of conventional solvents (5 mL) vs. [bmim]Br (2 g) on the reaction of benzenesulfonamide (**1a**) with *n*-butyl acrylate (**2b**) in the presence of MgO under microwave irradiation

Entry	Solvent	Time [min]	Isolated Yield (%)	
			<i>N</i> -Alkylated Product 3ab	<i>N,N</i> -Dialkylated Product 4ab
1	—	25	23	4
2	DMSO	20	73	9
3	DMF	20	64	8
4	HMPTA	25	49	8
5	<i>o</i> -xylene	25	26	5
6	[bmim]Br	5	89	7

In order to determine if the ionic liquid was an essential factor to promote the Michael reaction, the model reaction was carried out using traditional solvents (Table 2): With classical solvents the reaction times were longer than those in ionic liquids. Also, the yields were lower than those in ionic liquids. Evidently, the ionic liquids accelerated the reaction.

To establish the generality and applicability of this method, some sulfonamides were added to structurally diverse α,β -unsaturated esters to furnish selectively the corresponding mono- and dialkylated Michael adducts in short reaction times. The results are listed in Table 3.

Table 3. Michael addition of sulfonamides **1** to α,β -unsaturated esters **2** in the presence of MgO in [bmim]Br under microwave conditions (300 W, max. 110 °C)

Entry	Starting Materials		Reaction Time [min]	Products			
	1	2		3	Yield (%) ^a	4	Yield (%) ^a
1 ^b	1a	2a	5	3aa	87	4aa	7
2	1a	2b	5	3ab	89	4ab	7
3	1a	2c	6	3ac	88	4ac	7
4	1a	2d	6	3ad	86	4ad	6
5	1a	2e	6	3ae	85	4ae	6
6	1a	2f	7	3af	82	4af	5
7 ^c	1a	2g	8	3ag	77	—	—
8	1b	2a	6	3bb	81	4bb	8
9 ^c	1c	2g	8	3cg	76	—	—

^a Isolated yield, ^b Ratio **1a/2a** 1:1.3, ^c Only monoadduct **3** was obtained.

Some structural effects of α,β -unsaturated esters on the Michael addition reaction were also studied. Lower yields of products and longer reaction times were obtained when benzenesulfonamide (**1a**) was added to sterically slightly more congested α,β -unsaturated esters

[ethyl methacrylate (**2f**) and ethyl crotonate (**2g**), Table 3, entries 6 and 7]. The reaction of benzenesulfonamide (**1a**) as well as of naphthalene-2-sulfonamide (**1c**) with ethyl crotonate (**2g**) afforded only monoadducts **3ag** and **3cg**, respectively (Table 3, entries 7 and 9).

Ease of recycling is a useful feature of ionic liquids: For the reaction **1a** + **2a** $\rightarrow$ **3aa** + **4aa** no significant loss of product yields was observed when [bmim]Br/MgO was used after three times recycling.

Conclusions

The Michael reaction between sulfonamides **1** and α,β -unsaturated esters **2** can be effectively performed in the ionic liquid [bmim]Br under microwave irradiation. This new method for the synthesis of *N*-alkyl sulfonamides has the advantage of high yield, high selectivity, short reaction time, ease of product isolation, potential for recycling of the ionic liquid and the catalyst as well as compliance with green chemistry protocols.

Experimental Section

General Procedures. All chemicals were obtained from Merck or Fluka. The ionic liquids were prepared according to reported methods.³⁴ All reactions were carried out in a CEM MARS 5TM microwave oven. Silica gel SILG/UV 254 plates were used for TLC. Spectra were recorded with the following apparatus: IR spectra with Shimadzu FTIR-8300 spectrophotometer; ¹H NMR (250 MHz) and ¹³C NMR (62.5 MHz) with Bruker Avanced DPX-250, FT-NMR spectrometer; mass spectra with Shimadzu GC MS-QP 1000 EX. Microanalyses were performed with a Perkin-Elmer 240-B microanalyzer. The refractive index was measured using a Schmidt Haensch apparatus. Melting points were recorded with a Büchi B-545 apparatus in open capillary tubes.

Michael addition of sulfonamides 1 to α,β -unsaturated esters 2. To a mixture of sulfonamide **1** (2 mmol), well-ground MgO (0.02 g, 0.5 mmol), and α,β -unsaturated ester **2** (2.2 mmol) in a microwave vessel was added [bmim]Br (2 g). Upon thorough mixing the mixture was irradiated in a microwave oven at 300 W at a maximum internal temperature of 110 °C for the time given in Table 3. Upon completion, the reaction mixture was cooled to room temperature and extracted with Et₂O (3×25 mL), and the organic extracts were combined. After removal of the solvent, the crude product was purified by column chromatography on silica gel with EtOAc/*n*-hexane (1:3). After extraction of the products, the remainder of the ionic liquid containing the catalyst MgO ([bmim]Br/MgO) was reused.

Ethyl 3-(phenylsulfonamido)propanoate (3aa). Colorless oil; n_D^{20} 1.4238; R_f 0.33 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3286, 3059, 2975, 1732, 1447, 1329 cm⁻¹; ¹H NMR (CDCl₃): δ 1.16 (3H, t, J = 7.0 Hz, CH₃), 2.48 (2H, t, J = 5.0 Hz, CH₂CO), 3.15 (2H, t, J = 5.0 Hz, CH₂N), 4.02 (2H, q, J = 7.0 Hz, CH₂O), 5.56 (1H, s, NH, D₂O exchangeable), 7.42–7.52 (3H, m, 3,4,5-H_{Ph}),

7.80 (2H, m, 2,6- H_{Ph}); ^{13}C NMR ($CDCl_3$): δ 14.0, 34.15, 38.7, 60.7, 127.0, 128.7, 132.6, 138.8, 171.7; MS: m/z (%) 257 (22.7, M^+); Anal. calcd. for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.52; H, 6.01; N, 5.30.

Diethyl 3,3'-(phenylsulfonylazanediyldipropanoate (4aa). Colorless oil; n_D^{20} 1.4326; R_f 0.43 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3028, 2984, 1733, 1447, 1317 cm^{-1} ; 1H NMR ($CDCl_3$): δ 1.22 (6H, t, $J = 7.1$ Hz, $2CH_3$), 2.59 (4H, t, $J = 5.0$ Hz, CH_2CO), 3.45 (4H, t, $J = 5.0$ Hz, CH_2NCH_2), 4.08 (4H, q, $J = 7.1$ Hz, $2CH_2O$), 7.46–7.57 (3H, m, 3,4,5- H_{Ph}), 7.87 (2H, m, 2,6- H_{Ph}); ^{13}C NMR ($CDCl_3$): δ 13.9, 32.8, 44.7, 60.4, 127.2, 129.1, 132.6, 138.9, 170.9; MS m/z (%): 357 (31.0, M^+); Anal. calcd. for $C_{16}H_{23}NO_6S$: C, 53.77; H, 6.49; N, 3.92. Found: C, 53.98; H, 6.33; N, 4.08.

Butyl 3-(phenylsulfonamido)propanoate (3ab). Colorless oil; n_D^{20} 1.4267; R_f 0.51 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3271, 3048, 2960, 1733, 1447, 1330 cm^{-1} ; 1H NMR ($CDCl_3$): δ 0.90 (3H, t, $J = 6.5$ Hz, CH_3), 1.34 (2H, m, CH_3CH_2), 1.56 (2H, m, $CH_3CH_2CH_2$), 2.51 (2H, t, $J = 5.0$ Hz, CH_2CO), 3.19 (2H, t, $J = 5.0$ Hz, CH_2N), 4.03 (2H, t, $J = 7.0$ Hz, CH_2O), 5.68 (1H, s, NH, D_2O exchangeable), 7.48–7.57 (3H, m, 3,4,5- H_{Ph}), 7.79 (2H, m, 2,6- H_{Ph}); ^{13}C NMR ($CDCl_3$): δ 13.5, 18.9, 30.4, 34.1, 38.7, 64.6, 126.8, 129.0, 132.5, 139.9, 172.7; MS: m/z (%) 285 (24.8, M^+); Anal. calcd. for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.48; H, 6.92; N, 5.06.

Dibutyl 3,3'-(phenylsulfonylazanediyldipropanoate (4ab). Colorless oil; n_D^{20} 1.4209; R_f 0.66 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3036, 2966, 1732, 1447, 1317 cm^{-1} ; 1H NMR ($CDCl_3$): δ 0.92 (6H, t, $J = 6.5$ Hz, $2CH_3$), 1.33 (4H, m, $2CH_3CH_2$), 1.56 (4H, m, $2CH_3CH_2CH_2$), 2.63 (4H, t, $J = 5.1$ Hz, $2CH_2CO$), 3.45 (4H, t, $J = 5.1$ Hz, CH_2NCH_2), 4.06 (4H, t, $J = 6.9$ Hz, $2CH_2O$), 7.51–7.60 (3H, m, 3,4,5- H_{Ph}), 7.82 (2H, m, 2,6- H_{Ph}); ^{13}C NMR ($CDCl_3$): δ 13.5, 18.9, 30.5, 34.2, 44.4, 64.2, 126.9, 129.0, 132.4, 138.9, 171.1; MS: m/z (%) 413 (17.6, M^+); Anal. calcd. for $C_{20}H_{31}NO_6S$: C, 58.09; H, 7.56; N, 3.39. Found: C, 58.20; H, 7.69; N, 3.25.

Benzyl 3-(phenylsulfonamido)propanoate (3ac). Pale yellow oil; n_D^{20} 1.4332; R_f 0.31 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3286, 3031, 2954, 1733, 1447, 1328 cm^{-1} ; 1H NMR ($CDCl_3$): δ 2.65 (2H, t, $J = 5.1$ Hz, CH_2CO), 3.17 (2H, t, $J = 5.1$ Hz, CH_2N), 5.00 (2H, s, CH_2O), 5.71 (1H, s, NH), 7.26–7.31 (5H, m, H_{PhC}), 7.45–7.51 (3H, m, 3,4,5- H_{PhS}), 7.82 (2H, m, 2,6- H_{PhS}); ^{13}C NMR ($CDCl_3$): δ 34.2, 38.7, 66.6, 126.9, 128.2, 128.4, 128.6, 129.2, 132.7, 135.4, 139.9, 171.7; MS: m/z (%) 319 (41.7, M^+); Anal. calcd. for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 59.94; H, 5.56; N, 4.26.

Benzyl 3,3'-(phenylsulfonylazanediyldipropanoate (4ac). Pale yellow oil; n_D^{20} 1.4430; R_f 0.51 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3051, 2965, 1734, 1447, 1316 cm^{-1} ; 1H NMR ($CDCl_3$): δ 2.58 (4H, t, $J = 5.0$ Hz, $2CH_2CO$), 3.36 (4H, t, $J = 5.0$ Hz, CH_2NCH_2), 5.00 (4H, s, $2CH_2O$), 7.22–7.25 (10H, m, H_{PhC}), 7.39–7.48 (3H, m, 3,4,5- H_{PhS}), 7.72 (2H, m, 2,6- H_{PhS}); ^{13}C NMR ($CDCl_3$): δ 33.3, 43.9, 65.5, 126.2, 127.7, 128.1, 128.9, 129.5, 131.8, 134.4, 137.8, 171.4; MS: m/z (%) 404 (3.7, $M-C_6H_5$), 374 (9.1, $M-C_7H_7O$), 340 (18.3, $M-C_6H_5SO_2$); Anal. calcd. for $C_{26}H_{27}NO_6S$: C, 64.85; H, 5.65; N, 2.91. Found: C, 65.04; H, 5.48; N, 2.80.

Phenethyl 3-(phenylsulfonamido)propanoate (3ad). Pale yellow oil; n_D^{20} 1.4535; R_f 0.45 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3285, 3063, 2957, 1732, 1447, 1329 cm^{-1} ; 1H NMR

(CDCl₃): δ 2.48 (2H, t, J = 5.2, CH₂CO), 2.88 (2H, t, J = 6.8 Hz, CH₂Ph), 3.14 (2H, t, J = 5.2 Hz, CH₂N), 4.24 (2H, t, J = 6.8 Hz, CH₂O), 5.43 (1H, s, NH), 7.15–7.28 (5H, m, H_{PhC}), 7.47–7.52 (3H, m, 3,4,5-H_{PhS}), 7.81–7.86 (2H, m, 2,6-H_{PhS}); ¹³C NMR (CDCl₃): δ 34.1, 34.9, 38.7, 65.2, 126.6, 126.9, 128.5, 128.8, 129.1, 132.7, 137.5, 139.9, 171.7; MS: m/z (%) 333 (37.2, M⁺); Anal. calcd. for C₁₇H₁₉NO₄S: C, 61.24; H, 5.74; N, 4.20. Found: C, 60.97; H, 5.89; N, 4.29.

Phenethyl 3,3'-(phenylsulfonylazanediyldipropionate (4ad). Pale yellow oil; n_D^{20} 1.4416; R_f 0.41 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3045, 2942, 1733, 1447, 1331 cm⁻¹; ¹H NMR (CDCl₃): δ 2.51 (4H, t, J = 5.2 Hz, 2CH₂CO), 2.82 (4H, t, J = 6.9 Hz, 2CH₂Ph), 3.30 (4H, t, J = 5.2 Hz, CH₂NCH₂), 4.19 (4H, t, J = 6.9 Hz, 2CH₂O), 7.10–7.19 (10H, m, H_{PhC}), 7.42–7.45 (3H, m, 3,4,5-H_{PhS}), 7.7–7.82 (2H, m, 2,6-H_{PhS}); ¹³C NMR (CDCl₃): δ 34.3, 34.9, 44.9, 65.2, 126.6, 126.7, 126.9, 128.6, 128.8, 129.2, 132.8, 137.5, 171.0; MS: m/z (%) 432 (2.3, M–C₆H₅), 388 (18.5, M–C₈H₉O), 368 (24.2, M–C₆H₅SO₂); Anal. calcd. for C₂₈H₃₁NO₆S: C, 65.99; H, 6.13; N, 2.75. Found: C, 65.87; H, 6.26; N, 2.89.

Cinnamyl 3-(phenylsulfonylamido)propanoate (3ae). Pale yellow oil; n_D^{20} 1.4296; R_f 0.38 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3287, 3059, 2964, 1732, 1447, 1329 cm⁻¹; ¹H NMR (CDCl₃): δ 2.55 (2H, t, J = 5.2 Hz, CH₂CO), 3.19 (2H, t, J = 5.2 Hz, CH₂N), 4.69 (2H, m, CH₂O), 5.50 (1H, s, NH), 6.23 (1H, m, =CHCH₂), 6.63 (1H, d, J = 15.7 Hz, =CHPh), 7.29–7.35 (5H, m, H_{PhC}), 7.45–7.50 (3H, m, 3,4,5-H_{PhS}), 7.95 (2H, m, 2,6-H_{PhS}); ¹³C NMR (CDCl₃): δ 34.2, 38.8, 65.8, 122.6, 122.9, 126.6, 126.9, 128.1, 128.6, 129.0, 132.7, 134.6, 139.9, 171.7; MS: m/z (%) 345 (26.5, M⁺); Anal. calcd. for C₁₈H₁₉NO₄S: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.82; H, 5.39; N, 4.21.

Cinnamyl 3,3'-(phenylsulfonylazanediyldipropionate (4ae). Pale yellow oil; n_D^{20} 1.4358; R_f 0.61 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3026, 2981, 1732, 1448, 1317 cm⁻¹; ¹H NMR (CDCl₃): δ 2.51 (4H, t, J = 5.1 Hz, 2CH₂CO), 3.41 (4H, t, J = 5.1 Hz, CH₂NCH₂), 4.73 (4H, m, 2CH₂O), 6.15 (2H, m, 2=CHCH₂), 6.54 (2H, d, J = 15.7 Hz, =CHPh), 7.28–7.36 (10H, m, H_{PhC}), 7.41–7.47 (3H, m, 3,4,5-H_{PhS}), 7.94 (2H, m, 2,6-H_{PhS}); ¹³C NMR (CDCl₃): δ 33.8, 43.2, 65.4, 122.4, 123.0, 126.7, 126.9, 127.9, 128.5, 129.4, 132.4, 134.1, 139.3, 171.5; MS: m/z (%) 400 (7.9, M–C₉H₉O), 392 (27.1, M–C₆H₅SO₂); Anal. calcd. for C₃₀H₃₁NO₆S: C, 67.52; H, 5.86; N, 2.62. Found: C, 67.40; H, 5.71; N, 2.78.

Ethyl 2-methyl-3-(phenylsulfonylamido)propanoate (3af). Pale yellow oil; n_D^{20} 1.4610; R_f 0.62 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3283, 3034, 2966, 1732, 1447, 1328 cm⁻¹; ¹H NMR (CDCl₃): δ 1.17–1.26 (6H, m, 2CH₃), 2.73 (1H, m, CHCO), 3.14–3.20 (2H, m, CH₂N), 4.12 (2H, q, J = 7.0 Hz, CH₂O), 5.65 (1H, s, NH), 7.55–7.64 (3H, m, 3,4,5-H_{Ph}), 7.93 (2H, m, 2,6-H_{Ph}); ¹³C NMR (CDCl₃): δ 14.0, 14.7, 39.6, 45.4, 60.8, 126.8, 129.1, 132.5, 139.9, 174.7; MS: m/z (%) 271 (36.4, M⁺); Anal. calcd. for C₁₂H₁₇NO₄S: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.31; H, 6.57; N, 5.01.

Diethyl 3,3'-(phenylsulfonylazanediyldi)bis(2-methylpropanoate) (4af). Pale yellow oil; n_D^{20} 1.4683; R_f 0.81 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3042, 2982, 1732, 1447, 1316 cm⁻¹; ¹H NMR (CDCl₃): δ 1.09–1.19 (12H, m, 4CH₃), 2.78 (2H, m, 2CHCO), 3.22–3.27 (4H, m, CH₂NCH₂), 4.03 (4H, q, J = 7.0 Hz, 2CH₂O), 7.44–7.53 (3H, m, 3,4,5-H_{Ph}), 7.75 (2H, m, 2,6-

H_{Ph}); ¹³C NMR (CDCl₃): δ 14.1, 15.3, 39.2, 52.4, 60.7, 127.3, 129.1, 132.7, 139.0, 174.7; MS: *m/z* (%) 385 (18.7, M⁺); Anal. calcd. for C₁₈H₂₇NO₆S: C, 56.08; H, 7.06; N, 3.63. Found: C, 55.80; H, 7.23; N, 3.77.

Ethyl 3-(phenylsulfonamido)butanoate (3ag). Pale yellow solid; mp 61.3 °C; R_f 0.54 (EtOAc/*n*-hexane, 1:3); IR (KBr): $\tilde{\nu}$ 3285, 3044, 2953, 1732, 1447, 1329 cm⁻¹; ¹H NMR (CDCl₃): δ 1.14–1.23 (6H, m, 2CH₃), 2.38–2.43 (2H, m, CH₂CO), 3.68 (1H, m, CHN), 4.04 (2H, q, *J* = 7.1 Hz, CH₂O), 5.39 (1H, s, NH), 7.49–7.59 (3H, m, 3,4,5-H_{Ph}), 7.89 (2H, m, 2,6-H_{Ph}); ¹³C NMR (CDCl₃): δ 14.0, 21.0, 40.7, 46.6, 60.7, 126.9, 129.0, 132.5, 140.9, 171.1; MS: *m/z* (%) 271 (44.2, M⁺); Anal. calcd. for C₁₂H₁₇NO₄S: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.30; H, 6.19; N, 5.31.

Butyl 3-(4-methylphenylsulfonamido)butanoate (3bb). Pale yellow oil; n_D²⁰ 1.4322; R_f 0.55 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3286, 3044, 2960, 1732, 1330 cm⁻¹; ¹H NMR (CDCl₃): δ 0.89 (3H, t, *J* = 6.8 Hz, CH₃CH₂), 1.33 (2H, m, CH₃CH₂), 1.56 (2H, m, CH₃CH₂CH₂), 2.40 (3H, s, CH₃Ar), 2.51 (2H, t, *J* = 5.3 Hz, CH₂CO), 3.16 (2H, t, *J* = 5.3 Hz, CH₂N), 4.04 (2H, t, *J* = 7.0 Hz, CH₂O), 5.76 (1H, s, NH), 7.31, 7.34 (2H, 3,5-H_{Ar}), 7.71, 7.74 (2H, 2,6-H_{Ar}); ¹³C NMR (CDCl₃): δ 13.5, 18.9, 21.3, 30.3, 34.1, 38.7, 64.5, 126.9, 129.6, 135.8, 143.2, 172.7; MS: *m/z* (%) 299 (28.1, M⁺); Anal. calcd. for C₁₄H₂₁NO₄S: C, 56.16; H, 7.07; N, 4.68. Found: C, 55.97; H, 7.18; N, 4.55.

Dibutyl 3,3'-(tosylazanediyl)bis(2-methylpropanoate) (4bb). Pale yellow oil; n_D²⁰ 1.4246; R_f 0.72 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3056, 2975, 1734, 1317 cm⁻¹; ¹H NMR (CDCl₃): δ 0.92 (6H, t, *J* = 6.9 Hz, 2CH₃CH₂), 1.32 (4H, m, 2CH₂CH₃), 1.57 (4H, m, 2CH₃CH₂CH₂), 2.42 (3H, s, CH₃Ar), 2.63 (4H, t, *J* = 5.2 Hz, 2CH₂CO), 3.43 (4H, t, *J* = 5.2 Hz, CH₂NCH₂), 4.02 (4H, t, *J* = 7.0 Hz, 2CH₂O), 7.30, 7.33 (2H, 3,5-H_{Ar}), 7.70, 7.74 (2H, 2,6-H_{Ar}); ¹³C NMR (CDCl₃): δ 13.6, 19.0, 21.4, 30.4, 33.9, 45.0, 64.5, 126.9, 129.5, 135.9, 143.5, 172.5; MS: *m/z* (%) 427 (9.2, M⁺); Anal. calcd. for C₂₁H₃₃NO₆S: C, 58.99; H, 7.78; N, 3.28. Found: C, 59.15; H, 7.68; N, 3.14.

Ethyl 3-(naphthalene-2-sulfonamido)butanoate (3ca). Buff oil; n_D²⁰ 1.4574; R_f 0.53 (EtOAc/*n*-hexane, 1:3); IR (neat): $\tilde{\nu}$ 3284, 3051, 2970, 1732, 1447, 1329 cm⁻¹; ¹H NMR (CDCl₃): δ 1.07–1.12 (6H, m, 2CH₃), 2.31–2.35 (2H, m, CH₂CO), 3.67 (1H, m, CHN), 3.99 (2H, q, *J* = 7.0 Hz, CH₂O), 5.38 (1H, s, NH), 7.52–7.57 (4H, m, H_{Ar}), 7.79–7.90 (3H, m, H_{Ar}); ¹³C NMR (CDCl₃): δ 14.0, 21.1, 40.6, 46.7, 60.7, 122.3, 127.5, 127.7, 127.9, 128.1, 128.3, 128.8, 129.2, 129.5, 132.1, 171.1; MS: *m/z* (%) 321 (20.9, M⁺); Anal. calcd. for C₁₆H₁₉NO₄S: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.90; H, 6.11; N, 4.51.

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