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Chemo, Regio, and Stereoselectivity in the Olefination of Hydrazone 1,4-Adducts Between Conjugated Azoalkenes and Sulphur Co-activated Methylene Compounds

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Abstract. In the presence of sodium methoxide in catalytic amount, conjugated azoalkenes smoothly add at room temperature (phenylsulphonyl)acetamide, methyl (phenylsulphonyl)acetate, methyl (phenylsulphinyl)acetate, (arylsulphonyl)acetonitriles, bis(phenylsulphonyl)methane, and (arylsulphonyl)nitromethane to yield the corresponding α-functionalized hydrazone derivatives by 1,4-addition. In some cases these hydrazones were isolated, while in others their formation is accompanied by olefination products. Under the same reaction conditions and/or in methanol by means of gentle heating, several of these adducts give rise to the related α,β-olefinated hydrazone derivatives as pure isomeric forms or as *EE/EZ* mixtures by loss of the nitro, sulphonyl or sulphinyl group. It is noteworthy that for β-cyano-β-arylsulphonyl adducts it was mainly detected the elimination of the arylsulphonyl group affording β-cyano-α,β-olefinated hydrazones, while for analogous β-nitro-β-arylsulphonyl adducts it was principally observed the loss of the nitro moiety producing β-arylsulphonyl-α,β-olefinated hydrazones.

INTRODUCTION

In previous papers, we reported some olefination processes occasionally observed in α-functionalized hydrazone derivatives obtained by 1,4-addition (Michael-type) of nucleophilic reagents to the azo-ene system of conjugated azoalkenes.[1-4] In these occasions, however, the regio- and stereochemical aspects of these reactions were not studied in detail.

Indeed, α,β-olefinated hydrazone derivatives are valuable tools in organic synthesis. In fact, they permit not only an efficient entry to widely functionalized α,β-unsaturated carbonyl compounds after cleavage of the protective hydrazono group,[5,6] but also allow an expeditious access to conjugated heterodiene systems useful for further Michael-like additions[7] as well as for [4+2] cycloadditions of the hetero Diels-Alder type.[8]

In consideration of these facts and in connection with our ongoing activity aimed at exploring the synthetic potentialities of conjugated azoalkenes,[9,10] we decided to investigate systematically the different addition-elimination behaviours of some sulphur co-activated methylene compounds on azoalkene substrates.

RESULTS AND DISCUSSION

Conjugated azoalkenes **1a-g** in tetrahydrofuran in the presence of sodium methoxide in catalytic amount smoothly add at room temperature (phenylsulphonyl)acetamide (**2a**), methyl (phenylsulphonyl)acetate (**2b**),

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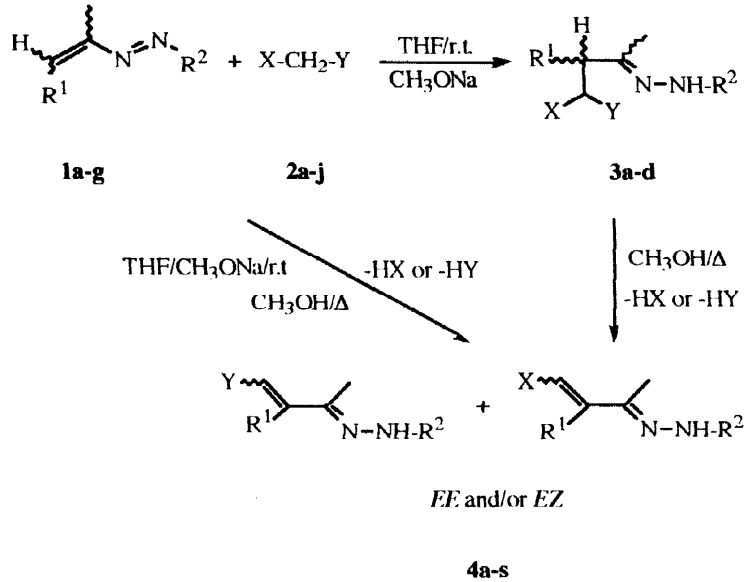
methyl (phenylsulphinyl)acetate (**2c**), (phenylsulphonyl)acetonitrile (**2d**), (4-toluensulphonyl)acetonitrile (**2e**), (4-chlorophenylsulphonyl)acetonitrile (**2f**), bis(phenylsulphonyl)methane (**2g**), (phenylsulphonyl)nitromethane (**2h**), (4-toluenesulphonyl)nitromethane (**2i**), and (4-chlorobenzenesulphonyl)nitromethane (**2j**). However, only in the case of **2a-b** the corresponding α-functionalized hydrazone derivatives (**3a-d**) coming by 1,4-addition are clearly obtained as the main reaction products, showing good stability and resistance to the olefination process by elimination of a leaving group under the experimental conditions used in this work (see Scheme 1 and Table 1).



1a-g **2a-j** **3a-d**

4a-s

R^1 = CO_2Me, CO_2Et.

R^2 = CO_2Me, CO_2t-Bu, $CONH_2$, CONHPh.

X = $PhSO_2$, 4-$MeC_6H_4SO_2$, 4-$ClC_6H_4SO_2$.

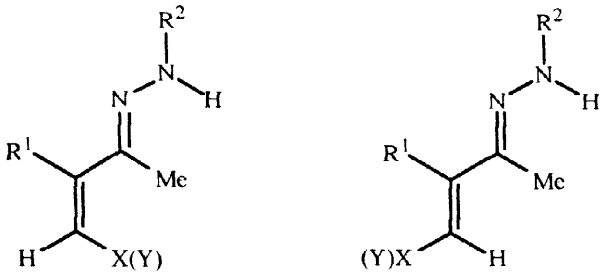
Y = $CONH_2$, CO_2Me, CN, $PhSO_2$, NO_2.

Scheme 1

Table 1. Preparation of α-functionalized hydrazones **3a-d**.

Azoalkenes			Methylene Compounds			Products	Yield	Time
1	R^1	R^2	**2**	X	Y	**3**	(%)	(h)
1d	CO_2Me	$CONH_2$	**2a**	$PhSO_2$	$CONH_2$	**3a**	76	5.0
1f	CO_2Et	CO_2Me	**2a**	$PhSO_2$	$CONH_2$	**3b**	66	1.5
1a	CO_2Et	$CONH_2$	**2b**	$PhSO_2$	CO_2Me	**3c**	72	0.1
1f	CO_2Et	CONHPh	**2b**	$PhSO_2$	CO_2Me	**3d**	74	0.5

Probably, the elimination of the sulphonyl group should require more drastic conditions.[11] In the other cases (**2c-j**) the formation of the adducts (**3**) is concomitant with their transformation into the corresponding α,β-olefinated hydrazones (**4a-s**). In such circumstances, the conversion of the adduct intermediates into α,β-olefinated hydrazone derivatives is more satisfactorily completed in methanol under reflux. Compounds **4a-s**, due to the presence of two stereogenic centres, can in principle exist as four different stereoisomers *EE*, *EZ*, *ZE*, *EE*, where the first letter refers to the C=N configuration, and the second letter to the C=C configuration, respectively (see Figure 1).



EE *EZ*

Figure 1

Actually, only two isomers were detected, and their configurations were determined by NOE experiments to be *EE* and *EZ* on the basis of the following criteria. Both isomers showed considerable NOE enhancement of NH by irradiation of CH_3, and *viceversa*: this evidence suggests the proximity of these two groups in both cases, in agreement with the *E* configuration of the C=N centre. On the contrary, irradiation of CH_3 resulted in NOE enhancement of CH and *viceversa* only in one isomer: therefore to this isomer the *Z* configuration of the C=C centre was assigned. As a check, the *E* isomer did not show any CH_3/CH NOE effect.

Only in a few cases was a pure isomer: for **4d** the only observed product was *EE*, whereas in **4i-k** only *EZ* was detected. In the remaining cases a mixture of both isomers was obtained, from which either the predominant isomer (**4a, b, l, n**) or both isomers (**4a,e, o, q, r**) were isolated. When the separation of the isomers proved difficult, the ratio between the two isomers was determined by ^1H NMR spectroscopy (see Table 2).

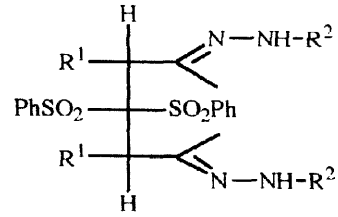
It is worth emphasising that for the adducts between conjugated azoalkenes (**1a-g**) and methyl (phenylsulphinyl)acetate (**2c**), (phenylsulphonyl)acetonitrile (**2d**), (4-toluensulphonyl)acetonitrile (**2e**), (4-chlorophenylsulphonyl)acetonitrile (**2f**) and bis(phenylsulphonyl)methane (**2g**) the main product resulted from the smooth elimination of the phenylsulphinyl or arylsulphonyl group[12,13] affording β-methoxycarbonyl- (**4a-d**) or β-cyano-α,β-olefinated hydrazones (**4e-h**). In a different way, for the adducts between conjugated azoalkenes (**1d-g**) and (phenylsulphonyl)nitromethane (**2h**), (4-toluenesulphonyl)nitromethane (**2i**), and (4-chlorobenzenesulphonyl)nitromethane (**2j**) the principal pathway was the easy loss of the nitro moiety producing β-arylsulphonyl-α,β-olefinated hydrazones (**4i-s**). For this reason, it is possible to obtain by this reaction two families of compounds bearing a different substituent group on the olefinic function (see Table 2). Both these behaviours are in good agreement with some our previous findings leading to the formation of

Table 2. Preparation of α,β-olefinated hydrazones **4a-s**.

Azoalkenes			Methylene Compounds			Products					Yield(%)		Time (h)	
1	R^1	R^2	**2**	X	Y	**4**	R^1	R^2	X	Y	*EE*	*EZ*	*a*	*b*
1a	CO_2Me	CO_2Me	**2c**	PhSO	CO_2Me	**4a**	CO_2Me	CO_2Me		CO_2Me	29	40	0.1	6.0
1b	CO_2Et	CO_2Me	**2c**	PhSO	CO_2Me	**4b**	CO_2Et	CO_2Me		CO_2Me	36	44	0.1	1.5
1e	CO_2Et	$CONH_2$	**2c**	PhSO	CO_2Me	**4c**	CO_2Et	$CONH_2$		CO_2Me	41	31	1.5	2.0
1g	CO_2Et	CONHPh	**2c**	PhSO	CO_2Me	**4d**	CO_2Et	CONHPh		CO_2Me	75	----	0.1	3.5
1e	CO_2Et	$CONH_2$	**2d**	$PhSO_2$	CN	**4e**	CO_2Et	$CONH_2$		CN	20	66	0.2	2.0
1e	CO_2Et	$CONH_2$	**2e**	$4\text{-}MeC_6H_4SO_2$	CN	**4e**	CO_2Et	$CONH_2$		CN	15	78	0.1	0.5
1f	CO_2Me	CONHPh	**2d**	$PhSO_2$	CN	**4f**	CO_2Me	CONHPh		CN	40	30	0.5	1.5
1d	CO_2Me	$CONH_2$	**2e**	$4\text{-}MeC_6H_4SO_2$	CN	**4g**	CO_2Me	$CONH_2$		CN	30	63	0.1	0.5
1d	CO_2Me	$CONH_2$	**2f**	$4\text{-}ClC_6H_4SO_2$	CN	**4g**	CO_2Me	$CONH_2$		CN	17	61	0.25	1.0
1g	CO_2Et	CONHPh	**2e**	$4\text{-}MeC_6H_4SO_2$	CN	**4h**	CO_2Et	CONHPh		CN	8	43	0.1	0.5
1a	CO_2Me	CO_2Me	**2g**	$PhSO_2$	$PhSO_2$	**4i**	CO_2Me	CO_2Me	$PhSO_2$		----	54	----	0.3
1b	CO_2Et	CO_2Me	**2g**	$PhSO_2$	$PhSO_2$	**4j**	CO_2Et	CO_2Me	$PhSO_2$		----	66	----	0.5
1c	CO_2Me	CO_2t-Bu	**2g**	$PhSO_2$	$PhSO_2$	**4k**	CO_2Me	CO_2t-Bu	$PhSO_2$		----	41	----	1.5
1d	CO_2Me	$CONH_2$	**2g**	$PhSO_2$	$PhSO_2$	**4l**	CO_2Me	$CONH_2$	$PhSO_2$		57	3	----	72.0
1d	CO_2Me	$CONH_2$	**2h**	$PhSO_2$	NO_2	**4l**	CO_2Me	$CONH_2$	$PhSO_2$		30	57	4.0	2.5
1e	CO_2Et	$CONH_2$	**2g**	$PhSO_2$	$PhSO_2$	**4m**	CO_2Et	$CONH_2$	$PhSO_2$		37	31	----	72.0
1f	CO_2Me	CONHPh	**2h**	$PhSO_2$	NO_2	**4n**	CO_2Me	CONHPh	$PhSO_2$		55	15	1.0	2.0
1g	CO_2Et	CONHPh	**2h**	$PhSO_2$	NO_2	**4o**	CO_2Et	CONHPh	$PhSO_2$		61	12	1.5	4.0
1e	CO_2Et	$CONH_2$	**2i**	$4\text{-}MeC_6H_4SO_2$	NO_2	**4p**	CO_2Et	$CONH_2$	$4\text{-}MeC_6H_4SO_2$		45	26	2.0	1.5
1g	CO_2Et	CONHPh	**2i**	$4\text{-}MeC_6H_4SO_2$	NO_2	**4q**	CO_2Et	CONHPh	$4\text{-}MeC_6H_4SO_2$		59	18	0.5	2.5
1d	CO_2Me	$CONH_2$	**2j**	$4\text{-}ClC_6H_4SO_2$	NO_2	**4r**	CO_2Me	$CONH_2$	$4\text{-}ClC_6H_4SO_2$		42	19	2.0	2.5
1f	CO_2Me	CONHPh	**2j**	$4\text{-}ClC_6H_4SO_2$	NO_2	**4s**	CO_2Me	CONHPh	$4\text{-}ClC_6H_4SO_2$		55	25	0.5	1.5

[a] Time of disappearance of reagents **1** and **2**. [b] Time to produce compounds **4a-s**.

carbon-carbon or carbon-heteroatom double bonds.[4,14,15] Indeed, in the reactions of conjugated azoalkenes (**1b,c**) with bis(phenylsulphonyl)methane (**2g**) the corresponding bis-1,4-adducts **5a** and **5b** in yields of 16% and 15%, respectively have been isolated (see Figure 2). Any attempt to minimize the formation of this by-product failed. However, similar compounds have been reported in our previous investigations and demonstrated to be useful for further interesting chemical transformations.[16]



5a R^1=CO_2Et R^2=CO_2Me
5b R^1=CO_2Me R^2=CO_2*t*-Bu

Figure 2

It is noteworthy that β-keto equivalents of **2** by reaction with conjugated azoalkenes **1** under the same experimental conditions provided exclusively 1-aminopyrroles according to our previous findings,[17] while thio homologous of **2** did not add to the azo-ene system.

The present investigation confirms once again the utility of conjugated azoalkenes in organic synthesis.[9,10]

EXPERIMENTAL

(Alkoxycarbonyl)azoalkenes **1a-c**, (aminocarbonyl)azoalkenes **1d,e**, and (anilinocarbonyl)azoalkenes **1f,g** were synthesized as standard isomer mixtures according to previously reported procedures.[18,19] Starting materials of the above-mentioned reagents, as well as (phenylsulphonyl)acetamide (**2a**), methyl (phenylsulphonyl)acetate (**2b**), methyl (phenylsulphinyl)acetate (**2c**), (phenylsulphonyl)acetonitrile (**2d**), (4-toluensulphonyl)acetonitrile (**2e**), (4-chlorophenylsulphonyl)acetonitrile (**2f**), bis(phenylsulphonyl)methane (**2g**), (phenylsulphonyl)nitromethane (**2h**), (4-toluenesulphonyl)nitromethane (**2i**), and (4-chlorobenzenesulphonyl)nitromethane (**2j**), sodium methoxide and solvents are commercially available materials (Aldrich, Acros, Lancaster, Avocado or Menai) and were used without further purification. Melting points were determined in open capillary tubes with a Büchi (Tottoli) or Gallenkamp apparatus and are uncorrected. The products often decompose at melting point. IR spectra were obtained as liquid film or Nujol mull with a Perkin-Elmer 298 spectrophotometer. IR-FT spectra were performed with a Nicolet Impact 400 spectrophotometer. MS spectra were made with a Hewlett Packard 5995 C spectrometer. Elemental analyses were performed with a Fisons EA 1108 instrument. ^{1}H-NMR spectra at 60 MHz were recorded on Varian EM 360 L, while ^{1}H- (200 MHz) and ^{13}C-NMR (50.32 MHz) spectra were recorded on Bruker AC 200 spectrometers and performed in

DMSO-d_6 unless otherwise stated. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (*J*) in Hz. The abbreviations used are as follows: s, singlet; d, doublet, dd, doublet-doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O exch, D_2O exchange. NOE enhancement factors were determined on degassed DMSO 0.01 M solutions at 300 K, using NOEDIFF pulse program of Bruker. Generally, irradiation time was 2 sec, with a power level of 31 low. The NOE experiments were performed after separation of pure isolated isomers in the case of **4d** (only *EE* isomer), **4l** (both *EE* and *EZ* isomers), and **4j** (only *EZ* isomer). In the other cases **4a**, **4f**, **4l** and **4n**) we used mixtures of the two isomers and one of them, when the separation was successful: *EZ* isomer in the case of **4a** and **4l** and *EE* isomer in the case of **4n**. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (TLC) and silica gel Amicon LC 60 Å (35-70 mμ) for column chromatography. All new compounds showed satisfactory elemental analysis (C ±0.35, H ±0.30, N ±0.30).

Preparation of α-Functionalized Hydrazones 3a-d. To a magnetically stirred solution of azoalkene **1a,d,f** (1 mmol) in tetrahydrofuran (3 mL) was added dropwise a solution of phenylsulphonylacetamide (**2a**) or methylphenylsulphonylacetate (**2b**) (1 mmol) and sodium methoxide (0.1 mmol) in tetrahydrofuran (3 mL). The reaction was stirred at room temperature until azoalkene **1** disappeared (checked by TLC). After partial evaporation of the solvent under reduced pressure and subsequent addition of *n*-pentane, the products **3a-b** were collected by filtration as white powder in satisfactory purity. In the case of products **3c-d**, after total evaporation of solvent under reduced pressure, a white powder was obtained on addition of ethyl acetate/petroleum ether (40-60 °C).

Compound (3a).
Mp 161-163 °C; IR ν_{max} 3485, 3420, 3390, 3120, 1730, 1715, 1690, 1680, 1575, 1560 cm^{-1}; ^{1}H NMR δ 1.66 and 1.78 (2 s, 3 H, Me), 3.54 and 3.63 (2 s, 3 H, CO_2Me), 3.70 and 3.80 (2 d, 1 H, J = 12 Hz, CH), 5.09 and 5.12 (2 d, 1 H, J = 12 Hz, CH), 6.36 (br s, 2 H, NH_2, D_2O-exch), 7.47-7.80 (m, 7 H, Ph and NH_2, D_2O-exch), 9.12 and 9.23 (2 s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_{14}H_{18}N_4O_6S$: C, 45.39; H, 4.90; N, 15.13. Found: C, 45.65; H, 4.79; N, 15.18.

Compound (3b).
Mp 156-157 °C; IR ν_{max} 3440, 3400, 3330, 3180, 1715, 1695, 1670, 1595, 1585, 1525 cm^{-1}; ^{1}H NMR δ 1.86 (s, 3 H, Me), 3.64 (s, 3 H, CO_2Me), 3.84 (d, 1 H, J = 12 Hz, CH), 5.20 (d, 1 H, J = 12 Hz, CH), 6.99-7.84 (m, 12 H, 2 Ph and NH_2, D_2O-exch), 8.39 (s, 1 H, NH, D_2O-exch), 9.77 (s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_{20}H_{22}N_4O_6S$: C, 53.80; H, 4.97; N, 12.55. Found: C, 53.71; H, 4.84; N, 12.46.

Compound (3c).
Mp 125-127 °C; IR ν_{max} 3450, 3220, 3150, 3100, 1745, 1730, 1700, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3 H, Me), 3.67 (s, 3 H, CO_2Me), 3.73 (s, 3 H, CO_2Me), 3.78 (s, 3 H, CO_2Me), 4.18 (d, 1 H, J = 12 Hz, CH), 5.12 (d, 1 H, J = 12 Hz, CH), 7.52-7.89 (m, 6 H, Ph and NH, D_2O-exch). Anal. Calcd for $C_{16}H_{20}N_2O_8S$: C, 48.0; H, 5.03; N, 7.0. Found: C, 48.21; H, 5.16; N, 7.11.

Compound (3d).

Mp 138-139 °C; IR ν_{max} 3440, 3360, 3180, 3080, 1725, 1680, 1585, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H, Me), 3.61 (s, 3 H, CO_2Me), 3.81 (s, 3 H, CO_2Me), 4.14 (d, 1 H, J = 12 Hz, CH), 5.00 (d, 1 H, J = 12 Hz, CH), 7.03-7.96 (m, 11 H, 2 Ph and NH, D_2O-exch), 9.19 (s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_{21}H_{23}N_3O_7S$: C, 54.66; H, 5.02; N, 9.11. Found: C, 54.41; H, 5.16; N, 9.29.

Procedure for the Synthesis of α,β-Olefinated Hydrazones 4a-s. To a magnetically stirred solution of azoalkene **1a-g** (1 mmol) in tetrahydrofuran (3 mL) was added dropwise a solution of methyl (phenylsulphinyl)acetate (**2c**), (phenylsulphonyl)acetonitrile (**2d**), (4-toluensulphonyl)acetonitrile (**2e**), (4-chlorophenylsulphonyl)acetonitrile (**2f**), bis(phenylsulphonyl)methane (**2g**), (phenylsulphonyl)nitromethane (**2h**), (4-toluenesulphonyl)nitromethane (**2i**), and (4-chlorobenzenesulphonyl)nitromethane (**2j**) (1 mmol) and sodium methoxide (0.1 mmol) in tetrahydrofuran (3 mL). The reaction was stirred at room temperature until the azoalkene **1** disappeared (checked by TLC). Only in the case of the reactions between azoalkenes **1a-e** and **2g**, the products **4i-m** were directly formed, while in the other cases the reaction shown mixtures of the products **3** and **4** as a mixture of isomers. The complete conversion of hydrazone intermediates **3** into the pertinent products **4a-g,l-s** occurred under reflux, using methanol, after total evaporation of the reaction solvent, under reduced pressure. The α,β-olefinated hydrazones **4a-s** were purified by chromatography on a silica gel column (elution with cyclohexane-ethyl acetate mixtures), and then crystallized as follows.

Compound (4a).

EE+EZ isomers: mp 130-146 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3420, 3350, 3210, 1750, 1720, 1710, 1625 cm^{-1}; ^1H NMR δ 1.98 and 2.02 (2 s, 3 H, Me), 3.66-3.78 (m, 9 H, 3 CO_2Me), 6.30 and 6.79 (2 s, 1 H, CH), 10.25 and 10.60 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.89 (q), 16.77 (q), 51.83 (q), 51.97 (q), 52.32 (q), 52.90 (q), 118.16 (d), 129.80 (d), 142.33 (s), 145.74 (s), 146.34 (s), 146.97 (s), 153.85 (s), 154.40 (s), 164.71 (s), 164.80 (s), 166.24 (s); MS *m/z* (M^+) calcd 258.2, obsd 258.1. Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.31; H, 5.57; N, 10.61.

EZ isomer: mp 168-169 °C (methanol); IR ν_{max} 3420, 3350, 1745, 1720, 1635 cm^{-1}; ^1H NMR δ 2.02 (s, 3 H, Me), 3.69 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 6.30 (s, 1 H, CH), 10.60 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.89 (q), 51.83 (q), 52.32 (q), 118.16 (d), 145.74 (s), 148.95 (s), 153.85 (s), 164.80 (s), 166.24 (s); MS *m/z* (M^+) calcd 258.2, obsd 258.4.Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.36; H, 5.62; N, 10.59.

NOE enhancement factors: *EE* isomer: $CH_3\{NH\}$ 19%; $NH\{CH_3\}$ 7%; *EZ* isomer: $CH\{CH_3\}$ 9%; $CH_3\{NH\}$ 18%; $CH_3\{CH\}$ 17%; $NH\{CH_3\}$ 6%.

Compound (4b).

EE+EZ isomers: mp 97-100 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3440, 3240, 1755, 1720, 1700, 1640 cm^{-1}; ^1H NMR δ 1.23 (t, 3 H, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 1.96 and 2.01 (2 s, 3 H, Me), 3.65-3.68 (m, 6 H, 2 CO_2Me), 4.20 (q, 2 H, J = 7 Hz, $CO_2\mathit{CH_2}Me$), 6.25 and 6.76 (2 s, 1 H, CH), 10.20 and 10.55 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.86 (q), 13.83 (q), 16.74 (q), 51.80 (q), 51.92 (q), 52.26 (q), 60.55 (t), 61.71 (t), 117.93 (d), 129.39 (d), 142.56 (s), 145.74 (s), 149.00 (s), 153.91 (s), 154.40 (s), 162.57 (s),

164.33 (s), 166.77 (s); MS *m/z* (M^+) calcd 272.2, obsd 272.4. Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.28; H, 6.11; N, 10.35.

EZ isomer: mp 127-129 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3440, 3340, 1755, 1720, 1615 cm^{-1}; ^1H NMR δ 1.24 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 2.01 (s, 3 H, Me), 3.68 (s, 3 H, CO_2Me), 3.69 (s, 3 H, CO_2Me), 4.20 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.26 (s, 1 H, CH), 10.55 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.86 (q), 13.83 (q), 51.80 (q), 52.26 (q), 60.55 (t), 117.93 (d), 145.74 (s), 149.00 (s), 153.91 (s), 162.57 (s), 164.77 (s); MS *m/z* (M^+) calcd 272.2, obsd 272.3. Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.31; H, 5.81; N, 10.48.

Compound (4c).

EE+EZ isomers: mp 143-146 °C (ethyl acetate/cyclohexane); IR ν_{max} 3490, 3480, 3340, 3250, 3190, 1730, 1710, 1690, 1645, 1515 cm^{-1}; ^1H NMR δ 1.23 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 1.94 and 2.01 (2 s, 3 H, Me), 3.65 and 3.68 (2 s, 3 H, CO_2Me), 4.21 and 4.32 (2 q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.17 (br s, 2 H, NH_2, D_2O-exch), 6.25 and 6.77 (2 s, 1 H, CH), 9.53 and 10.04 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.66 (q), 13.86 (q), 13.94 (q), 16.28 (q), 51.83 (q), 51.92 (q), 60.84 (t), 61.65 (t), 117.24 (d), 122.26 (s), 129.45 (d), 141.41 (s), 141.64 (s), 148.74 (s), 156.08 (s), 156.77 (s), 164.63 (s), 164.91 (s), 165.49 (s), 166.04 (s); MS *m/z* (M^+) calcd 257.2, obsd 257.0. Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.48; H, 5.91; N, 16.48.

Compound (4d).

EE isomer: mp 173-175 °C (ethyl acetate/cyclohexane); IR ν_{max} 3250, 3190, 1715, 1660, 1610, 1555 cm^{-1}; ^1H NMR δ 1.25 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 2.03 (s, 3 H, Me), 3.64 (s, 3 H, CO_2Me), 4.23 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.85 (s, 1 H, CH), 6.96-7.56 (m, 5 H, Ph), 8.48 (s, 1 H, NH, D_2O-exch), 9.98 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 13.85 (q), 16.54 (q), 51.97 (q), 61.68 (t), 118.85 (d), 122.29 (d), 128.62 (d), 129.68 (d), 139.01 (s), 141.47 (s), 142.88 (s), 152.87 (s), 164.48 (s), 165.58 (s); MS *m/z* (M^+) calcd 333.3, obsd 333.5. Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.42; H, 5.69; N, 12.82. NOE enhancement factors: *EE* isomer: $CH_3\{NH\}$ 9%; $NH\{CH_3\}$ 2%.

Compound (4e).

EE isomer: mp 139-141 °C (ethyl acetate/cyclohexane); IR ν_{max} 3430, 3210, 3070, 2220, 1720, 1710, 1680, 1575 cm^{-1}; ^1H NMR δ 1.24 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 2.00 (s, 3 H, Me), 4.24 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.47 (br s, 2 H, NH_2, D_2O-exch), 6.50 (s, 1 H, CH), 9.92 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 13.77 (q), 15.27 (q), 62.14 (t), 104.79 (d), 116.75 (s), 139.01 (s), 149.64 (s), 156.45 (s), 164.02 (s); MS *m/z* (M^+) calcd 224.2, obsd 224.1. Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.10; H, 5.58; N, 25.11.

EZ isomer: mp 175-177 °C (ethyl acetate/cyclohexane); IR ν_{max} 3475, 3370, 3210, 3110, 3070, 2220, 1720, 1700, 1580 cm^{-1}; ^1H NMR δ 1.26 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 1.98 (s, 3 H, Me), 4.33 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.31 (br s, 2 H, NH_2, D_2O-exch), 6.35 (s, 1 H, CH), 10.04 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.63 (q), 13.89 (q), 61.87 (t), 98.28 (d), 116.14 (s), 140.37 (s), 153.54 (s), 155.82 (s), 164.94 (s); MS *m/z* (M^+) calcd 224.2, obsd 224.4. Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.44; H, 5.71; N, 25.31.

NOE enhancement factors: *EE* isomer: CH_3{NH} 24%; NH{CH_3} 5%; *EZ* isomer: CH{CH_3} 9%; CH_3{NH} 21%; CH_3{CH} 11%; NH{CH_3} 5%.

Compound (4f).

EE+EZ isomers: mp 158-160 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3420, 3350, 3140, 3080, 2220, 1740, 1730, 1685, 1590, 1575 cm^{-1}; ^1H NMR δ 2.05 and 2.07 (2 s, 3 H, Me), 3.81 and 3.89 (2 s, 3 H, CO_2Me), 6.49 and 6.62 (2 s, 1 H, CH), 7.02-7.57 (m, 5 H, Ph), 8.50 and 8.71 (2 s, 1 H, NH, D_2O-exch), 10.40 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.07 (q), 15.62 (q), 53.01 (q), 53.19 (q), 99.85 (d), 105.86 (d), 116.11 (d), 119.03 (d), 122.75 (d), 122.95 (d), 128.73 (d), 128.87 (d), 132.60 (s), 138.23 (s), 138.52 (s), 140.48 (s), 141.81 (s), 148.86 (s), 149.06 (s), 151.95 (s), 152.70 (s), 152.90 (s), 164.34 (s), 165.20 (s); MS *m/z* (M^+) calcd 286.3, obsd 286.5. Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.61; H, 4.72; N, 19.71.

NOE enhancement factors: *EE* isomer: CH_3{NH} 9%; NH{CH_3} 3%; *EZ* isomer: CH{CH_3} 2%; CH_3{NH} 10%; CH_3{CH} 10%; NH{CH_3} 2%.

Compound (4g).

EE+EZ isomers: mp 182-185 °C (methanol); IR ν_{max} 3510, 3490, 3400, 3370, 3200, 3100, 3050, 2225, 1745, 1710, 1580 cm^{-1}; ^1H NMR δ 1.98 and 2.00 (2 s, 3 H, Me), 3.79 and 3.84 (2 s, 3 H, CO_2Me), 6.36 and 6.51 (2 s, 1 H, CH), 6.43 (br s, 2 H, NH_2, D_2O-exch), 9.89 and 10.02 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.84 (q), 15.25 (q), 52.96 (q), 53.10 (q), 96.52 (d), 105.07 (d), 118.18 (s), 118.70 (s), 139.05 (s), 140.39 (s), 149.34 (s), 153.51 (s), 155.82 (s), 156.49 (s), 164.48 (s), 165.35 (s); MS *m/z* (M^+) calcd 210.2, obsd 210.1. Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.8; N, 26.66. Found: C, 45.69; H, 4.97; N, 26.43.

Compound (4h).

EE+EZ isomers: mp 159-160 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3375, 3200, 3100, 3070, 2220, 1735, 1695, 1600, 1580, 1540 cm^{-1}; ^1H NMR δ 1.23 and 1.33 (m, 3 H, CO_2CH_2*Me*), 2.05 and 2.07 (2 s, 3 H, Me), 4.28 and 4.37 (2 q, 2 H, J = 7 Hz, CO_2*CH_2*Me), 6.49 and 6.62 (2 s, 1 H, CH), 7.01-7.57 (m, 5 H, Ph), 8.47 and 8.71 (2 s, 1 H, NH, D_2O-exch), 10.40 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 13.65 (q), 13.74 (q), 14.89 (q), 15.59 (q), 62.06 (t), 62.21 (t), 105.52 (d), 117.07 (s), 118.83 (d), 119.03 (d), 122.70 (d), 128.59 (d), 128.68 (d), 129.48 (d), 134.69 (s), 137.68 (s), 138.52 (s), 140.37 (s), 145.19 (s), 149.09 (s), 152.67 (s), 163.30 (s), 163.82 (s); MS *m/z* (M^+) calcd 300.3, obsd 300.5. Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 60.29; H, 5.51; N, 18.41.

Compound (4i).

EZ isomer: mp 133-135 °C (dichloromethane/petroleum ether 40-60 °C); IR ν_{max} 3330, 1780, 1700, 1570 cm^{-1}; ^1H NMR δ 1.96 (s, 3 H, Me), 3.79 (s, 3 H, CO_2Me), 4.05 (s, 3 H, CO_2Me), 7.17 (s, 1 H, CH), 7.65-7.94 (m, 5 H, Ph), 10.67 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.15 (q), 52.26 (q), 52.41 (q), 127.43 (d), 127.94 (d), 129.63 (d), 134.17 (d), 139.99 (s), 144.79 (s), 145.78 (s), 153.77 (s), 164.71 (s); MS *m/z* (M^+) calcd 340.3, obsd 340.0. Anal. Calcd for $C_{14}H_{16}N_2O_6S$: C, 49.41; H, 4.74; N, 8.23. Found: C, 49.58; H, 4.51; N, 8.11.

Compound (4j).

EZ isomer: mp 128-129 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3320, 1740, 1725, 1560, 1510 cm^{-1}; ^1H NMR δ 1.31 (t, 3 H, $J = 7$ Hz, CO_2CH_2Me), 1.96 (s, 3 H, Me), 3.70 (s, 3 H, CO_2Me), 4.29 (q, 2 H, $J = 7$ Hz, CO_2CH_2Me), 7.14 (s, 1 H, CH), 7.65-7.95 (m, 5 H, Ph), 10.66 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.15 (q), 13.80 (q), 52.38 (q), 61.24 (t), 127.43 (d), 127.66 (d), 129.60 (d), 134.16 (d), 140.08 (s), 144.81 (s), 145.88 (s), 153.82 (s), 164.11 (s); MS *m/z* (M^+) calcd 354.4, obsd 354.2. Anal. Calcd for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.9. Found: C, 50.61; H, 5.01; N, 8.01.

NOE enhancement factors: *EZ* isomer: CH{CH_3} 9%; CH_3{NH} 17%; CH_3{CH} 17%; NH{CH_3} 5%.

Compound (4k).

EZ isomer: mp 139-140 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3360, 1740, 1700, 1570, 1500 cm^{-1}; ^1H NMR δ 1.44 (s, 9 H, CO_2t-Bu), 1.94 (s, 3 H, Me), 3.78 (s, 3 H, CO_2Me), 7.12 (s, 1 H, CH), 7.64-7.93 (m, 5 H, Ph), 10.35 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.05 (q), 27.66 (q), 52.21 (q), 80.42 (s), 127.41 (d), 129.60 (d), 134.13 (d), 135.44 (s), 140.07 (s), 143.64 (s), 146.06 (s), 152.05 (s), 164.78 (s); MS *m/z* (M^+) calcd 382.4, obsd 382.5. Anal. Calcd for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.8; N, 7.33. Found: C, 53.47; H, 5.61; N, 7.09.

Compund (4l).

EE+EZ isomers: mp 187-190 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3500, 3450, 3370, 3210, 1750, 1700, 1680, 1570 cm^{-1}; ^1H NMR δ 1.85 and 1.95 (2 s, 3 H, Me), 3.75 and 3.82 (2 s, 3 H, CO_2Me), 6.39 (br s, 2 H, NH_2, D_2O-exch), 7.18 and 7.45 (2 s, 1 H, CH), 7.64-7.93 (m, 5 H, Ph), 9.67 and 10.09 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.95 (q), 16.37 (q), 52.55 (q), 53.30 (q), 127.03 (d), 127.37 (d), 127.78 (d), 129.65 (d), 134.19 (d), 139.07 (d), 139.30 (s), 139.44 (s), 140.05 (s), 140.43 (s), 141.12 (s), 145.39 (s), 155.76 (s), 156.63 (s), 164.01 (s), 165.06 (s); MS *m/z* (M^+) calcd 325.3, obsd 325.1. Anal. Calcd for $C_{13}H_{15}N_3O_5S$: C, 47.99; H, 4.65; N, 12.92. Found: C, 48.11; H, 4.42; N, 12.71.

EZ isomer: mp 162-165 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3620, 3540, 3510, 3370, 3210, 1750, 1700, 1680, 1620, 1570 cm^{-1}; ^1H NMR δ 1.95 (s, 3 H, Me), 3.82 (s, 3 H, CO_2Me), 5.86 and 6.69 (2 br s, 2 H, NH_2, D_2O-exch), 7.18 (s, 1 H, CH), 7.68-7.92 (m, 5 H, Ph), 10.09 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.95 (q), 52.55 (q), 127.03 (d), 127.37 (d), 129.65 (d), 134.19 (d), 140.05 (s), 140.43 (s), 145.39 (s), 155.76 (s), 165.06 (s); MS *m/z* (M^+) calcd 325.3, obsd 325.5. Anal. Calcd for $C_{13}H_{15}N_3O_5S$: C, 47.99; H, 4.65; N, 12.92. Found: C, 47.71; H, 4.81; N, 12.82.

NOE enhancement factors: *EE* isomer: CH_3{NH} 16%; NH{CH_3} 5%; *EZ* isomer: CH{CH_3} 8%; CH_3{NH} 16%; CH_3{CH} 13%; NH{CH_3} 5%.

Compound (4m).

EE+EZ isomers: mp 115-118 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3440, 3280, 3170, 1720, 1685, 1575 cm^{-1}; ^1H NMR δ 1.18-1.33 (m, 3 H, CO_2CH_2Me), 1.84 and 1.95 (2 s, 3 H, Me), 4.12-4.36 (m, 2 H, CO_2CH_2Me), 6.29 (br s, 2 H, NH_2, D_2O-exch), 7.15 and 7.43 (2 s, 1 H, CH), 7.59-7.93 (m, 5 H, Ph), 9.63 and 10.08 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.96 (q), 13.75 (q), 14.92 (q), 16.34 (q), 61.46 (t), 62.34 (t), 127.34 (d), 127.57 (d), 127.76 (d), 129.60 (d), 134.11 (d), 139.31 (d), 139.52 (s), 139.73 (s), 140.17 (s), 140.48 (s), 141.46 (s), 145.51 (s), 155.81 (s), 156.55 (s), 163.45 (s), 164.45 (s); MS *m/z* (M^+)

calcd 339.4, obsd 339.6. Anal. Calcd for $C_{14}H_{17}N_3O_5S$: C, 49.55; H, 5.05; N, 12.38. Found: C, 49.31; H, 5.31; N, 12.19.

Compound (4n).

EE+EZ isomers: mp 109-115 °C (methanol); IR ν_{max} 3380, 3320, 3200, 3090, 1730, 1715, 1600, 1540 cm^{-1}; ^1H NMR δ 1.92 and 2.03 (2 s, 3 H, Me), 3.76 and 3.91 (2 s, 3 H, CO_2Me), 6.98-7.96 (m, 10 H, 2 Ph), 7.26 and 7.50 (2 s, 1 H, CH), 8.33 and 8.75 (2 s, 1 H, NH, D_2O-exch), 10.19 and 10.54 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.18 (q), 16.37 (q), 52.64 (q), 53.33 (q), 118.59 (d), 118.77 (d), 122.49 (d), 122.98 (d), 127.46 (d), 127.69 (d), 128.73 (d), 129.05 (d), 129.60 (d), 134.28 (d), 134.39 (d), 138.08 (s), 138.81 (s), 139.42 (d), 139.94 (s), 140.63 (s), 140.97 (s), 141.23 (s), 141.99 (s), 145.13 (s), 150.70 (s), 151.80 (s), 152.81 (s), 163.85 (s), 165.17 (s); MS *m/z* (M^+) calcd 401.1, obsd 401.2. Anal. Calcd for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.57; H, 4.61; N, 10.31.

EE isomer: mp 116-119 °C (methanol); IR ν_{max} 3330, 3190, 3140, 1730, 1695, 1600, 1540 cm^{-1}; ^1H NMR δ 1.92 (s, 3 H, Me), 3.76 (s, 3 H, CO_2Me), 6.98-7.95 (m, 10 H, 2 Ph), 7.52 (s, 1 H, CH), 8.57 (s, 1 H, NH, D_2O-exch), 10.19 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 16.37 (q), 53.33 (q), 118.77 (d), 122.49 (d), 127.69 (d), 128.73 (d), 128.96 (s), 129.60 (d), 134.39 (d), 138.81 (s), 139.42 (d), 140.63 (s), 140.97 (s), 152.81 (s), 163.85 (s); MS *m/z* (M^+) calcd 401.1, obsd 401.4. Anal. Calcd for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.91; H, 4.81; N, 10.39.

NOE enhancement factors: *EE* isomer: $CH_3\{NH\}$ 17%; $NH\{CH_3\}$ 3%; *EZ* isomer: $CH\{CH_3\}$ 7%; $CH_3\{NH\}$ 16%; $CH_3\{CH\}$ 13%; $NH\{CH_3\}$ 1%.

Compound (4o).

EE isomer: mp 116-118 °C (ethyl ether/petroleum ether 40-60 °C); IR ν_{max} 3360, 3200, 3070, 1730, 1710, 1690, 1600, 1540 cm^{-1}; ^1H NMR δ 1.23 (t, 3 H, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 1.92 (s, 3 H, Me), 4.22 (q, 2 H, J = 7 Hz, $CO_2\mathit{CH_2}Me$), 6.98-7.95 (m, 10 H, 2 Ph), 7.50 (s, 1 H, CH), 8.77 (s, 1 H, NH, D_2O-exch), 10.17 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 13.76 (q), 16.37 (q), 62.41 (t), 118.74 (d), 122.49 (d), 127.71 (d), 128.73 (d), 129.59 (d), 134.37 (s), 138.84 (s), 139.24 (d), 139.45 (s), 140.68 (s), 141.29 (s), 152.78 (s), 163.32 (s); MS *m/z* (M^+) calcd 414.4, obsd 414.6. Anal. Calcd for $C_{20}H_{20}N_3O_5S$: C, 57.96; H, 4.86; N, 10.14. Found: C, 57.81; H, 4.73; N, 10.38.

EZ isomer: mp 129-131 °C (methanol); IR ν_{max} 3350, 3200, 3050, 1760, 1700, 1600, 1580, 1550 cm^{-1}; ^1H NMR δ 1.33 (t, 3 H, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 2.02 (s, 3 H, Me), 4.37 (q, 2 H, J = 7 Hz, $CO_2\mathit{CH_2}Me$), 7.01-7.95 (m, 10 H, 2 Ph), 7.24 (s, 1 H, CH), 8.30 (s, 1 H, NH, D_2O-exch), 10.48 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.20 (q), 13.88 (q), 61.59 (t), 118.66 (d), 123.01 (d), 127.40 (d), 127.66 (d), 129.02 (d), 129.64 (d), 134.19 (s), 138.06 (s), 140.05 (s), 142.07 (s), 145.20 (s), 151.83 (s), 164.50 (s); MS *m/z* (M^+) calcd 414.4, obsd 414.1. Anal. Calcd for $C_{20}H_{20}N_3O_5S$: C, 57.96; H, 4.86; N, 10.14. Found: C, 58.04; H, 4.92; N, 10.51.

Compound (4p).

EE+EZ isomers: mp 133-135 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3460, 3430, 3270, 3250, 1730, 1710, 1690, 1665, 1570 cm^{-1}; ^1H NMR δ 1.16-1.32 (m, 3 H, $CO_2CH_2\mathit{Me}$), 1.85 and 1.94 (2 s, 3 H, Me), 2.41 (s, 3 H, Me), 4.14-4.31 (m, 2 H, $CO_2\mathit{CH_2}Me$), 6.30 (br s, 2 H, NH_2, D_2O-exch), 7.10 and 7.39 (2

s, 1 H, CH), 7.42-7.49 (m, 2 H, Ph), 7.75 and 7.79 (2 d, 2 H, J = 8 Hz, Ph), 9.64 and 10.08 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.93 (q), 13.74 (q), 13.86 (q), 16.43 (q), 21.13 (q), 61.44 (t), 62.31 (t), 127.17 (d), 127.42 (d), 127.66 (d), 130.03 (d), 136.83 (s), 137.28 (s), 139.16 (d), 139.36 (s), 140.51 (s), 141.05 (s), 144.82 (s), 144.99 (s), 145.10 (s), 155.87 (s), 156.62 (s), 163.50 (s), 164.50 (s); MS m/z (M^+) calcd 353.4, obsd 353.5. Anal. Calcd for $C_{15}H_{19}N_3O_5S$: C, 50.98; H, 5.42; N, 11.89. Found: C, 51.11; H, 5.31; N, 12.01.

Compound (4q).

EE isomer: mp 141-143 °C (methanol); IR ν_{max} 3370, 3200, 3100, 1725, 1705, 1600, 1540 cm^{-1}; ^1H NMR δ 1.23 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 1.92 (s, 3 H, Me), 2.31 (s, 3 H, Me), 4.22 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 6.98-7.39 (m, 5 H, Ph), 7.48 (s, 1 H, CH), 7.53 (d, 2 H, J = 8 Hz, Ph), 7.79 (d, 2 H, J = 8 Hz, Ph), 8.84 (s, 1 H, NH, D_2O-exch), 10.15 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 13.74 (q), 16.45 (q), 21.02 (q), 62.38 (t), 118.88 (d), 122.43 (d), 127.72 (d), 128.67 (d), 130.00 (d), 136.67 (s), 138.79 (s), 139.67 (d), 140.73 (s), 141.09 (s), 145.07 (s), 152.76 (s), 163.32 (s); MS m/z (M^+) calcd 429.5, obsd 429.6. Anal. Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.4; N, 9.78. Found: C, 58.61; H, 5.62; N, 9.51.

EZ isomer: mp 148-149 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3450, 3320, 3170, 1740, 1685, 1675, 1585, 1570 cm^{-1}; ^1H NMR δ 1.34 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 2.03 (s, 3 H, Me), 2.43 (s, 3 H, Me), 4.38 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 7.03-7.53 (m, 5 H, Ph), 7.22 (s, 1 H, CH), 7.51 (d, 2 H, J = 8 Hz, Ph), 7.83 (d, 2 H, J = 8 Hz, Ph), 8.31 (s, 1 H, NH, D_2O-exch), 10.51 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.19 (q), 13.90 (q), 21.13 (q), 61.59 (t), 118.66 (d), 123.02 (d), 127.51 (d), 128.01 (d), 129.04 (d), 130.09 (d), 137.17 (s), 138.05 (s), 142.10 (s), 144.71 (s), 144.96 (s), 151.88 (s), 164.58 (s); MS m/z (M^+) calcd 429.5, obsd 429.3. Anal. Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.73; H, 5.4; N, 9.78. Found: C, 58.89; H, 5.11; N, 9.81.

Compound (4r).

EE isomer: mp 248-250 °C (methanol); IR ν_{max} 3510, 3440, 3380, 3180, 1730, 1705, 1680, 1600, cm^{-1}; ^1H NMR δ 1.88 (s, 3 H, Me), 3.76 (s, 3 H, CO_2Me), 6.32 (br s, 2 H, NH_2, D_2O-exch), 7.50 (s, 1 H, CH), 7.72 (d, 2 H, J = 8.5 Hz, Ph), 7.91 (d, 2 H, J = 8.5 Hz, Ph), 9.86 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 16.37 (q), 53.32 (q), 129.36 (d), 129.63 (d), 138.32 (s), 138.93 (d), 139.48 (s), 141.50 (s), 145.86 (s), 156.51 (s), 163.92 (s); MS m/z (M^+) calcd 359.8, obsd 360.0. Anal. Calcd for $C_{13}H_{14}ClN_3O_5S$: C, 43.4; H, 3.92; N, 11.68. Found: C, 43.11; H, 3.71; N, 11.81.

EZ isomer: mp 193-195 °C (methanol); IR ν_{max} 3510, 3380, 3220, 3120, 1750, 1710, 1690, 1580, cm^{-1}; ^1H NMR δ 1.95 (s, 3 H, Me), 3.83 (s, 3 H, CO_2Me), 5.96 and 6.68 (2 br s, 2 H, NH_2, D_2O-exch), 7.20 (s, 1 H, CH), 7.78 (d, 2 H, J = 8.5 Hz, Ph), 7.90 (d, 2 H, J = 8.5 Hz, Ph), 10.10 (s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.69 (q), 52.55 (q), 126.61 (d), 129.32 (d), 129.80 (d), 138.70 (s), 139.21 (s), 140.31 (s), 145.83 (s), 155.67 (s), 164.94 (s); MS m/z (M^+) calcd 359.8, obsd 360.0. Anal. Calcd for $C_{13}H_{14}ClN_3O_5S$: C, 43.4; H, 3.92; N, 11.68. Found: C, 43.71; H, 3.77; N, 11.58.

Compound (4s).

EE+EZ isomers: mp 145-147 °C (methanol); IR ν_{max} 3440, 3340, 3180, 3080, 1720, 1700, 1685, 1675, 1585 cm^{-1}; ^1H NMR δ 1.96 and 2.03 (2 s, 3 H, Me), 3.78 and 3.90 (2 s, 3 H, CO_2Me), 6.98-7.99 (m, 11 H, 2 Ph

and CH), 8.33 and 8.71 (2 s, 1 H, NH, D_2O-exch), 10.20 and 10.54 (2 s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.15 (q), 16.40 (q), 52.64 (q), 53.33 (q), 118.61 (d), 118.77 (d), 122.49 (d), 122.99 (s), 127.46 (d), 127.65 (d), 128.71 (d), 129.01 (d), 129.42 (d), 129.70 (d), 129.85 (d), 137.05 (s), 138.08 (s), 138.35 (s), 138.78 (s), 139.13 (d), 139.50 (s), 140.22 (s), 140.63 (s), 141.44 (s), 145.57 (s), 151.57 (s), 151.76 (s), 152.73 (s), 163.77 (s), 165.06 (s); MS *m/z* (M^+) calcd 435.9, obsd 436.0. Anal. Calcd for $C_{19}H_{18}ClN_3O_5S$: C, 52.36; H, 4.16; N, 9.64. Found: C, 52.21; H, 4.31; N, 9.78.

Compound (5a).

Mp 110-111 °C (ethyl acetate/petroleum ether 40-60 °C); IR ν_{max} 3420, 3180, 1725, 1710, 1520 cm^{-1}; ^1H NMR δ 1.07 (t, 6 H, J = 7 Hz, 2 CO_2CH_2*Me*), 2.04 (s, 6 H, 2 Me), 3.64 (s, 6 H, 2 CO_2Me), 4.08 (q, 4 H, J = 7 Hz, 2 CO_2*C*H_2Me), 5.34 (s, 2 H, 2 CH), 7.61-7.92 (m, 10 H, 2 Ph), 10.29 (s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 13.60 (q), 15.41 (q), 52.03 (q), 61.99 (t), 76.06 (d), 126.36 (s), 128.93 (d), 129.16 (d), 134.48 (d), 138.00 (s), 142.01 (s), 151.14 (s), 163.18 (s). Anal. Calcd for $C_{29}H_{36}N_4O_{12}S_2$: C 49.99; H, 5.21; N, 8.04. Found: C, 50.01; H, 5.24; N, 8.02.

Compound (5b).

Mp 112-114 °C (dichloromethane/petroleum ether 40-60 °C); IR ν_{max} 3460, 3220, 1745, 1720, 1550 cm^{-1}; ^1H NMR δ 1.42 (s, 18 H, 2 CO_2t-Bu), 2.01 (s, 6 H, 2 Me), 3.63 (s, 6 H, 2 CO_2Me), 5.34 (s, 2 H, 2 CH), 7.61-7.90 (m, 10 H, 2 Ph), 9.96 (s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 15.39 (q), 27.92 (q), 52.84 (q), 76.14 (d), 79.75 (s), 126.28 (s), 128.93 (d), 129.11 (d), 134.45 (d), 137.88 (s), 141.06 (s), 152.38 (s), 163.76 (s). Anal. Calcd for $C_{33}H_{44}N_4O_{12}S_2$: C, 52.65; H, 5.89; N, 7.44. Found: C, 52.66; H, 5.87; N, 7.41.

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