Pergamon

Tetrahedron 54 (1998) 3589–3606

TETRAHEDRON

Synthesis and Reactivity of N-Alkyl-2-oxoalkanesulfonamides[1]

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Received 17 December 1997; revised 26 January 1998; accepted 29 January 1998

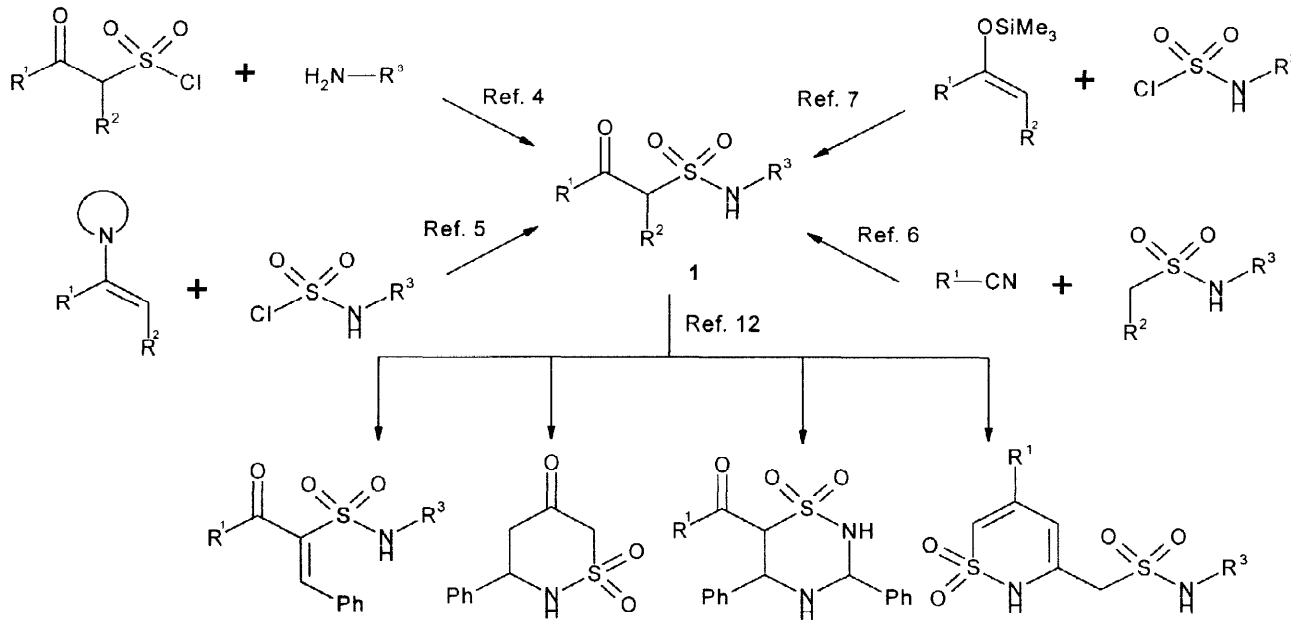
Abstract: A series of N-alkyl-2-oxoalkanesulfonamides have been synthesized by reacting silyl enol ethers with N-alkyl-sulfamoyl chlorides. Their reactivity towards electrophiles was investigated in order to explore the regio- and stereoselectivity of the process. 2-Oxoalkanesulfonamides were used to prepare 5-(methylsulfamoyl)-1,4-dihydropyridines derivatives.

INTRODUCTION

The sulfonamide group forms the bioactive moiety of many compounds with therapeutical interest, such as antibacterials, diuretics, oral antidiabetics and antibiotics.[2] Our interest in calcium modulators[3] prompted us to explore the synthesis of 2-oxoalkanesulfonamide derivatives for the preparation of new potential 5-(methylsulfamoyl)-1,4-dihydropyridine derivatives as potential calcium antagonists.

The synthesis of N-alkyl-2-oxoalkanesulfonamides **1** was first reported by Hendrickson and Bergeron.[4] The reaction of benzoylmethylsulfonyl chloride with primary amines yielded N-benzoylmethylsulfonyl derivatives from which amines can be regenerated by reductive treatment. A different approach was carried out by Bender *et al.*[5] The reaction of enamines with N-alkyl-sulfamoyl chlorides at low temperature led, after hydrolysis, to 2-oxoalkanesulfonamides **1**. The treatment of N-alkyl-alkanesulfonamides with two equivalents of strong base and further reaction with nitriles has also led, after hydrolysis, to N-alkyl-2-oxoalkanesulfonamides **1**.[6] Recently, our group reported a new procedure which improves on Bender's method[5] using a related strategy.[7] Thus, by reacting silyl enol ethers[8,9] with N-methyl-sulfamoyl imine, generated *in situ* from N-methyl-sulfamoyl chloride,[10,11] good yields of N-methyl-2-oxoalkanesulfonamides were obtained (Scheme 1).

0040-4020/98/$19.00
PII: S0040-4020(98)00093-3



Scheme 1

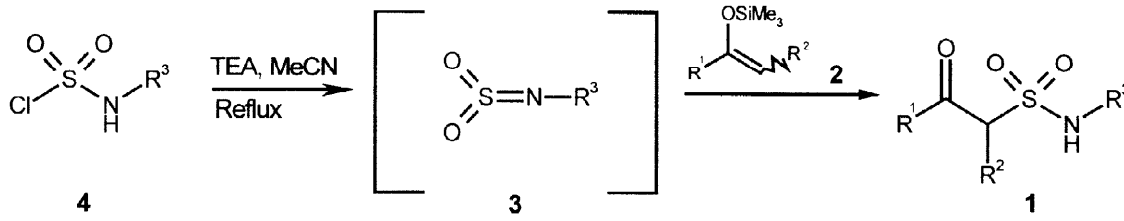
The reactivity of 2-oxoalkanesulfonamides has been scantily investigated. To our knowledge, only two reports describe the chemistry of 2-oxoalkanesulfonamides: the above mentioned work of Hendricson *et al*[4] where N-alkyl-benzoylmethylsulfonamides are C- and N- alkylated (apparently monoalkylation of the methylene always occurs faster than N-alkylation) and the report of Bender *et al*[12] which studies their reactions with carbonyl compounds which were found to behave as monofunctional ketones, active-hydrogen compounds or sulfonamides, and often as bifunctional compounds with formation of cyclic products (Scheme 1).

We report here the synthesis of N-alkyl-2-oxoalkanesulfonamides, and their chiral derivatives, using our previously reported procedure, as well as a study of their regio- and stereoselective reactions with methyl iodide and acyl chlorides. We also report the synthesis of 5-(methylsulfamoyl)-1,4-dihydropyridine derivatives from N-methyl-2-oxoalkanesulfonamides in order to test their calcium antagonist activity.

RESULTS AND DISCUSION

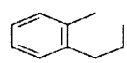
Synthesis of N-alkyl-2-oxoalkanesulfonamides 1

We extended our previously reported procedure[7] to the synthesis of a range of silyl enol ethers and sulfamoyl chlorides (Scheme 2). Thus, by reacting silyl enol ethers **2** with N-alkyl-sulfonyl imines **3**, generated *in situ* from N-alkyl-sulfamoyl chlorides **4**, good to moderate yields of N-alkyl -2-oxoalkanesulfonamides **1** were obtained (Table 1). Silyl enol ethers **2** were prepared using the procedure reported by Walse and Woodward[9] which led to better yields than the procedures reported by Chu *et al*[13] and Dubois *et al.*[14] N-Alkyl-sulfamoyl chlorides **4** were obtained using the procedure reported by Günter and Schulze,[15] which uses Lewis acid catalysts such as $SbCl_5$ or PCl_5 to accelerate the reaction rate.



Scheme 2

Table 1. Synthesis of N-alkyl-2-oxoalkanesulfonamides **1**.

Entry	Compound	R^1	R^2	R^3	Time (h)	Yield (%)
1	**1a**	Me	H	Me	5	81[a]
2	**1b**	Et	Me	Me	20	65[a]
3	**1c**	$-(CH_2)_3-$		Me	6	67[a]
4	**1d**	$-(CH_2)_4-$		Me	24	85[a]
5	**1e**	$-(CH_2)_5-$		Me	20	61[a]
6	**1f**	$-(CH_2)_6-$		Me	26	60[a]
7	**1g**	$-(CH_2)_9-$		Me	24	28[a]
8	**1h**	Ph	H	Me	5	50[a]
9	**1i**	2-Thiophenyl	H	Me	2	60[a]
10	**1j**			Me	9	75[a]
11	**1k**	Me	H	Cyclohexyl	4	47
12	**1l**	Ph	H	Cyclohexyl	5	54
13	**1m**	$-(CH_2)_3-$		Cyclohexyl	10	36
14	**1n**	Me	H	Benzyl	18	50
15	**1o**	Ph	H	Benzyl	4	57
16	**1p**	$-(CH_2)_3-$		Benzyl	12	47
17	**1q**	Me	H	1-phenylethyl[b]	6	58
18	**1r**	Ph	H	1-phenylethyl[b]	1	60
19	**1s**	$-(CH_2)_3-$		1-phenylethyl[b]	6	58
20	**1t**	$-(CH_2)_4-$		1-phenylethyl[b]	10	50
21	**1u**	$-(CH_2)_5-$		1-phenylethyl[b]	3	40

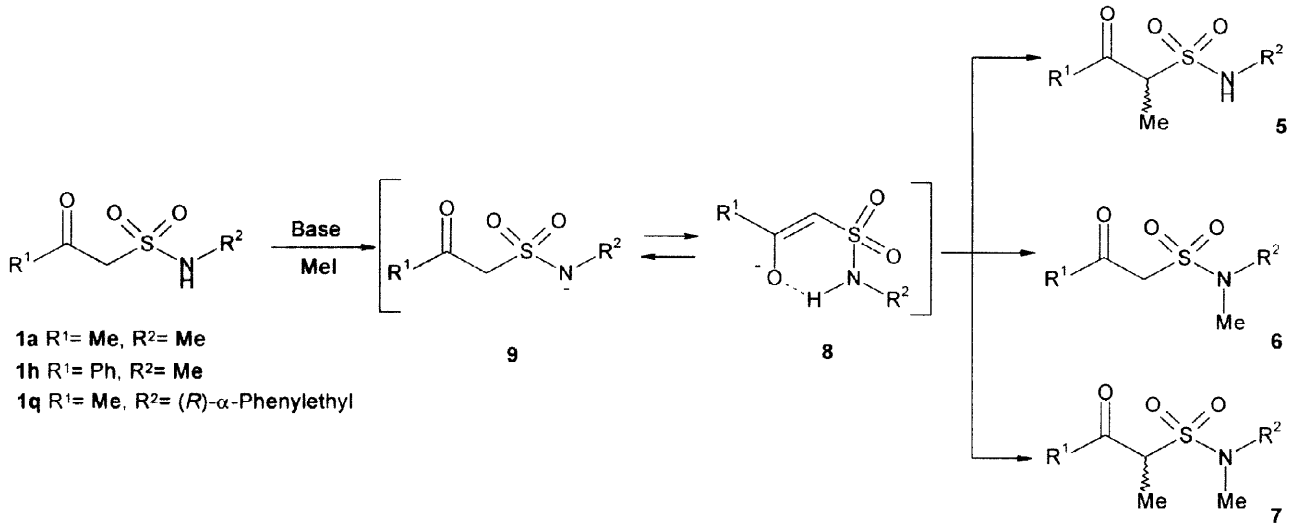
a) Reference 7. b) Pure (*R*)-enantiomer.

Chiral cyclic sulfonamides **1s-1u** were obtained as a mixture of diastereomers. Although diastereomeric

excess could not be determined for **1s** by ^{1}H-NMR, for **1t** d.e. was not observed and only 30% d.e. for compound **1u** was determined.

Alkylation of N-alkyl-2-oxoalkanesulfonamides

The alkylation of N-alkyl-2-oxoalkanesulfonamides **1** with MeI, using different bases and conditions, was investigated (Scheme 3). We were interested in developing not only a regioselective procedure, but also a stereoselective one by using a chiral auxiliary fragment ((*R*)-1-phenylethylamine) linked to the sulfonamide group.



Scheme 3

We tested compounds **1a** and **1h** for regioselectivity and **1q** for both regio- and stereoselectivity (Table 2). As expected, low temperatures and weaker bases gave better selectivities (entries 1 *vs* 2, 4 *vs* 5, 7 *vs* 9 and 2 *vs* 3, 5 *vs* 6 and 7 *vs* 9 respectively). Compound **1h** (R^1= Ph) gave better selectivities than compound **1a** (R^1= Me) at low temperatures (entries 4 and 1).

For the stereoselective process, using method C for compound **1q** (R^1= Me) gave better regioselectivity than method B for compound **1a** (R^1= Me) (entries 7 *vs* 3). However, although the regiochemistry for the reaction was complete, diastereoselectivity was poor (entry 7). The diastereomeric ratio was determined by ^{1}H-NMR since diastereomers could not be separated. When the reaction temperature was increased regioselectivity decreased (entries 7 *vs* 8). For compound **6q** diastereomeric excess could not be determined.

As previously pointed out by Hendrickson and Bergeron[4], we have found that C-alkylation (compound **5**) is faster than N-alkylation (compound **6**), which is to say, **5** is the kinetic product and **6** is the thermodynamic one. The C- and N-alkylation compound **7** is produced only when the temperature is raised or the enolate intermediate derived from compound **6** is stabilised by a phenyl group (entries 8 and 5-6 respectively). The absence of water in the reaction media (method C) drives the course of the reaction exclusively towards the formation of compound **5** by shifting the intermediate equilibrium towards the more stable anion enolate intermediate **8**. In the presence of

water (method B) the enolate anion **8** is partially protonated and the sulfonamidate anion **9** dominates (Scheme 3).

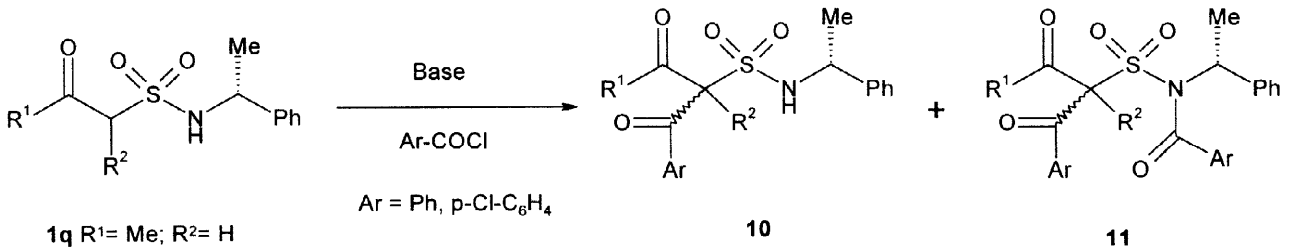
Table 2. Regioselective alkylation of N-alkyl-2-oxoalkanesulfonamides **1** with MeI.

Entry	Compound	R^1	R^2	Method[a]	T(°C)	Time	**7:6:5** ratio (d.e.)[b]
1	**1a**	Me	Me	A	-40	5	0:30:70
2	**1a**	Me	Me	A	20	2	0:50:50
3	**1a**	Me	Me	B	20	20	0:9:91
4	**1h**	Ph	Me	A	-40	10	0:1:99
5	**1h**	Ph	Me	A	20	18	44:18:38
6	**1h**	Ph	Me	B	20	20	8:1:91
7	**1q**	Me	1-phenylethyl[c]	C	20	20	0:0:100(60)
8	**1q**	Me	1-phenylethyl[c]	B	40	20	12(0):13:75(20)
9	**1q**	Me	1-phenylethyl[c]	A	20	14	0:11:89(60)

a) Method (base/solvent): A (LDA/THF); B (K_2CO_3/H_2O-DCM); C (K_2CO_3/DCM). b) For compound **6q** e.d. was not determined. c) Pure (*R*)-enantiomer.

Acylation of 2-oxoalkanesulfonamides 1

We have simultaneously investigated the regio- and stereoselective acylation of compounds **1q-1t** with benzoyl and *p*-chlorobenzoyl chloride, using several base systems (Scheme 4). The reaction gave mixtures of C-acylated compounds **10** and C- and N-acylated compounds **11**, but none of the N-acylated compound.



Scheme 4

As shown in Table 3, the steric hindrance of the base significantly affects the regioselectivity of the reaction. The bulkier the base, the higher is the regioselectivity ratio **10**:**11**. The base does not play such as important role in the diastereomeric excess of compounds **10** since switching TEA with Hünig base ($EtPr^i_2N$) did not lead to high diastereomeric excess differences. However, a bulkier base led to slightly better diastereomeric excess. By using K_2CO_3 instead of TEA or Hünig base we observed lower regio- and stereoselectivities for the reaction (entries 3 and

6) excepting when the sulfonamide is a cyclic one (entry 9).

Table 3. Acylation of chiral N-alkyl-2-oxoalkanesulfonamides **1q-t**.

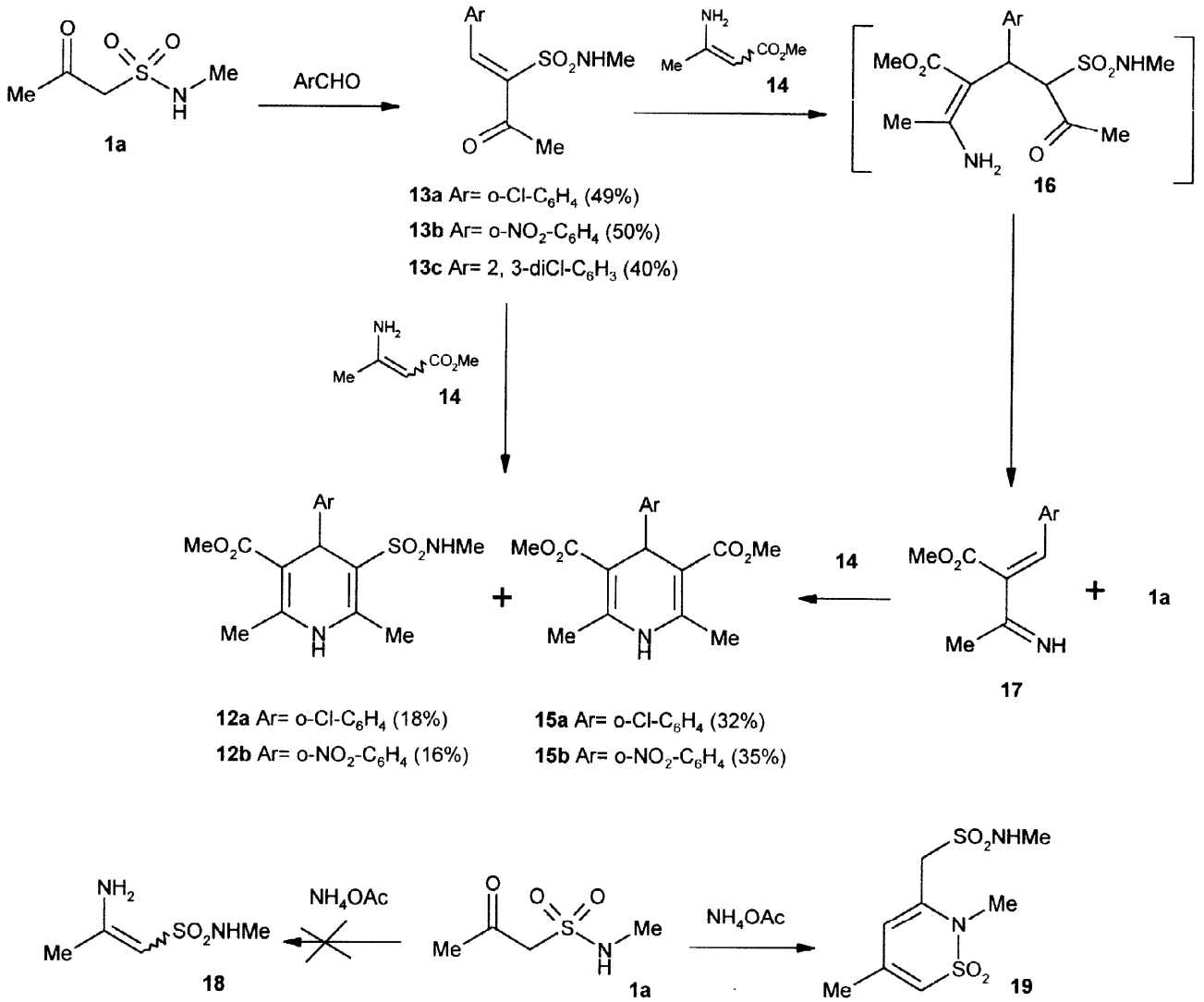
Entry	Compound	R^1	R^2	Ar	Method[a]	Time (h)	**10**:**11** ratio (d.e.)
1	**1q**	Me	H	p-Cl-C_6H_4	A	6	23(60):1(0)
2	**1q**	Me	H	p-Cl-C_6H_4	B	96	60(78):1(0)
3	**1q**	Me	H	p-Cl-C_6H_4	C	16	2(10):1(0)
4	**1r**	Ph	H	p-Cl-C_6H_4	A	1	7(50):1(0)
5	**1r**	Ph	H	p-Cl-C_6H_4	B	14	12(62):1(0)
6	**1r**	Ph	H	p-Cl-C_6H_4	C	23	5(20):1(0)
7	**1s**	-$(CH_2)_3$-		p-Cl-C_6H_4	A	2	2(60):1(0)
8	**1s**	-$(CH_2)_3$-		p-Cl-C_6H_4	B	10	27(68):1(0)
9	**1s**	-$(CH_2)_3$-		p-Cl-C_6H_4	C	20	9(60):1(0)
10	**1t**	-$(CH_2)_4$-		C_6H_4	A	2	4(24):1(0)
11	**1t**	-$(CH_2)_4$-		C_6H_4	B	10	24(50):1(0)

a) Method (base/solvent): A (Et_3N/DCM); B ($EtPr^i_2N$/DCM); C (K_2CO_3/MeCN).

Synthesis of 5-(methylsulfamoyl)-1,4-dihydropyridine derivatives 12

Our target dihydropyridine structures were asymmetrically substituted 1,4-dihydropyridine derivatives **12** since this structure retains all the features required for calcium antagonist activity,[16] and bears a sulfonamide group which could be an interesting isostere for the usual carboxylic ester group.

The synthesis of these derivatives was carried out using the traditional Hantzsch strategy (Scheme 2). Arylidenesulfonamides **13** were obtained in moderate yields using the same procedure reported for the preparation of arylideneacetoacetates.[17] These compounds were further reacted with methyl 2-aminocrotonate **14** to give a mixture of dihydropyridines **12** and **15**. These symmetrically substituted Hantzsch dihydropyridines **15** are produced as a consecuence of a retro-Michael process on the adduct intermediate **16**, which gives the imine **17** which then reacts with the aminocrotonate **14** to give Hantzsch dihydropyridines **15**. A side-product from this retro-Michael reaction, 2-oxoalkanesulfonamide **1a**, was also isolated from the reaction mixture. This undesirable pathway has been detected when unsymmetrical Hantzsch dihydropyridines are prepared, although only traces of the symmetrically substituted dihydropyridines are normally produced in such cases.[3] However, in our case this is the main reaction pathway probably because of the enhanced acidity of the hydrogen α to the sulfonamide group in the intermediate **16** over that of an acetate group.



Scheme 2

Dihydropyridines **12** were tested for calcium antagonist activity,[3] but no activity was detected. This result could be because of the acidity of the hydrogen in the sulfonamide group which resembles that of a carboxyl group in dihydropyridine carboxylic acids which have not shown activity.[16]

An alternative strategy[3] in which it was hoped to obtain the enamine **18** from **1a** by reacting with NH_4OAc, which could then be used to synthesize compounds **12** was examined. Unfortunately, the reaction did not yield **18** but rather compound **19** which arose through a self-condensation and subsequent cyclization. A similar compound to **19** have been reported when not N-methylated **1a** was treated with KOH/EtOH.[12]

EXPERIMENTAL

Instruments and Materials. Melting points were determined on a Buchi SMP-20 apparatus and are

uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity FT-80 or Varian Unity 300 spectrometer with TMS as internal standard. ^{13}C-NMR spectra were recorded on a Varian Unity 300 spectrometer. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on a Heraeus CHN Rapid analyzer. MS were obtained on a Hewlett-Packard 5988 A spectrometer.

All reagents were purchased from Aldrich Co. or Janssen Co. Flash chromatography was carried out on silica gel 60 (400-630 mesh). Reagents and solvents were purified and dried prior to use when neccesary according to stablished procedures.[18] NaI and K_2CO_3 were dried by irradiation in a domestic microwave oven for 15 min at 300 watt.

Synthesis of N-alkyl-2-oxoalkanesulfonamides 1. General procedure. To a mixture of silyl enol ether **2** and triethylamine dissolved in MeCN was added a solution of sulfamoyl chloride **3** at room temperature under an argon atmosphere. After the addition was complete the mixture was heated at reflux. The solvent was evaporated and the residual oil chromatographed on silica gel.

1a. Reaction of a solution of **2a** (0.43 g; 3.3 mmol) and TEA (0.41 g; 4.1 mmol) in MeCN (10 mL) with a solution of **4a** (0.51 g; 4.0 mmol) in MeCN (3 mL) for 5 h yields 0.40 g (81%) of **1a** after chromatography using n-hexane/ethyl acetate 1:1; bp 203-205 ^{0}C/0.8 mm Hg; IR ($CHBr_3$) 3370, 3021, 2476, 2258, 1725, 1467, 1317, 1248, 1137, 1041, 876, 808, 692, 641 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.69 (bs, 1H); 4.07 (s, 2H); 2.81 (d, 3H, J = 4.9 Hz); 2.39 (s, 3H) ppm; ms (EI) m/z 152 (M+1).

1b. Reaction of a solution of **2b** (0.94 g; 5.96 mmol) and TEA (0.72 g; 7.4 mmol) in MeCN (10 mL) with a solution of **4a** (1.30 g; 10 mmol) in MeCN (3 mL) for 24 h yields 0.69 g (65%) of **2a** after chromatography using toluene/ethanol 9:1; bp 128-130 °C/0.2 mm Hg; IR ($CHBr_3$) 3610, 3316, 2981, 2943, 1718, 1626, 1538, 1452, 1404, 1355, 1078, 996, 845, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 4,58 (s, 1H); 4.12 (q, 1H, J = 7.1 Hz); 2.82 (d, 3H, J = 5.1 Hz); 2.72 (c, 2H, J = 7.1 Hz); 1.55 (d, 3H, J = 7.1 Hz); 1.07 (t, 3H, J = 7.1 Hz) ppm; ms (EI) m/z 179 (M+1).

1c. Reaction of a solution of **3a** (0.25 g; 1.9 mmol) and TEA (0.23 g; 2.3 mmol) in MeCN (10 mL) with a solution of **4a** (0.29 g; 2.2 mmol) in MeCN (3 mL) for 4 h yields 0.22 g (67%) of **1c** after chromatography using n-hexane/ethyl acetate 8:2; bp 146-150 °C/0.1 mm Hg; IR ($CHBr_3$) 3344, 3021, 2974, 1738, 1403, 1327, 1247, 1140, 1074, 1044, 812, 692, 663 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 4.7 (bs, 1H); 3.7-3.65 (t, 1H, J = 8.4 Hz); 2.83 (d, 3H, J = 5.4 Hz); 2.6-2.4 (m, 4H); 2.3-2.2 (m, 1H); 2.0-1.0 (m, 1H) ppm; ms (EI) m/z 178 (M+1).

1d. Reaction of a solution of **2d** (0.51 g; 3.0 mmol) and TEA (0.66 g; 6.6 mmol) in MeCN (18 mL) with a solution of **4a** (0.77 g; 6 mmol) in MeCN (3 mL) for 24 h yields 0.50 g (87%) of **1d** after chromatography using n-hexane/ethyl acetate 8:2; bp 170-175 °C/0.1 mm Hg; IR ($CHBr_3$) 3362, 3020, 2948, 2658, 248, 2278, 2257, 1706, 1603, 1444, 1393, 1355, 1321, 1137, 1077, 812, 691, 693 cm-1; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 5.26 (m, 1H); 3.9-3.8

(t, 1H, J = 5.3 Hz); 3.49-3.31 (t, 2H, J = 5.3 Hz); 2.88-2.79 (d, 3H, J = 2.4 Hz); 2.61-1.72 (m, 6H) ppm; ms (EI) m/z 191 (M+1).

1e. Reaction of a solution of **2e** (0.69 g; 3.8 mmol) and TEA (0.61 g; 6.0 mmol) in MeCN (15 mL) with a solution of **4a** (0.53 g; 4.1 mmol) in MeCN (3 mL) for 20 h yields 0.48 g (61%) of **1e** after chromatography using n-hexane/ethyl acetate 4:6; bp 195-197 °C/0.4 mm Hg; IR ($CHBr_3$) 3549, 3308, 2934, 2860, 1704, 1452, 1316, 1237, 1148, 997, 970, 940, 907, 839, 675 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.52 (d, 1H, J = 4.8 Hz); 3.89-3.83 (dd, 1H, J = 4.6 and 11.7 Hz); 2.83-2.82 (d, 3H, J = 5.3 Hz); 2.62-2.40 (m, 2H); 2.2-1.18 (m, 4H); 1.55-1.25 (m, 4H) ppm; Anal. Calcd for $C_8H_{15}NO_3S$: C, 46.81; H, 7.36; N, 6.82. Found: C, 46.73; H, 7.39; N, 7.20.

1f. Reaction of a solution of **2f** (0.61 g; 3.1 mmol) and TEA (0.47 g; 4.7 mmol) in MeCN (10 mL) with a solution of **4a** (0.53 g; 4.1 mmol) in MeCN (3 mL) for 12 h yields 0.40 g (60%) of **1f** after chromatography using toluene/ethanol 9:1; bp 220 °C/0.1 mm Hg; IR ($CHBr_3$) 3550, 3300, 2910, 1703, 1460, 1304, 1220, 1150, 990, 840, 675 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.56 (bs, 1H); 4.04-4.0 (dd, 1H, J = 2.9 and 12.0 Hz); 2.85 (d, 3H, J = 5.3 Hz); 2.56-2.54 (m, 1H); 2.51-2.49 (m, 1H); 2.41-2.35 (m, 2H); 1.19-1.1 (m, 6H) ppm; ms (EI) m/z 219 (M+1).

1g. Reaction of a solution of **2g** (1.00 g; 4.3 mmol) and TEA (0.64 g; 6.3 mmol) in MeCN (15 mL) with a solution of **4a** (0.73 g; 5.6 mmol) in MeCN (3 mL) for 24 h yields 0.33 g (28%) of **1g** after chomatography using n-hexane/ethyl acetate 8:2; mp 129-131 °C (EtOH); IR (KBr) 2932, 2862, 1712, 1472, 1414, 1300, 1156, 1086, 864 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.37 (dd, 1H, J = 11.8 and 3.3 Hz); 3.30 (d, 3H, J = 5.3 Hz); 2.8 (m, 1H); 2.5 (m, 4H); 6.21 (m, 1H); 1.78 (m, 2H); 1.50 (m, 1H); 1.20 (m, 1H) ppm; Anal. Calcd for $C_{13}H_{25}NO_3S$: C, 56.69; H, 9.15; N, 5.08. Found: C, 56.94; H, 9.23; N, 5.46.

1h. Reaction of a solution of **2h** (0.33 g; 1.7 mmol) and TEA (0.38 g; 3.8 mmol) in MeCN (5 mL) with a solution of **4a** (0.39 g; 3.0 mmol) in MeCN (1 mL) for 5 h yields 0.18 g (50%) of **1h** after chromatography using n-hexane/ethyl acetate 7:3; mp 146-147 °C (EtOH); IR (KBr) 3330, 3018, 2961, 2595, 1680, 1595, 1471, 1451, 1399, 1369, 1330, 1213, 1141, 1062, 898, 859, 754, 650 cm-1; ^{1}H-NMR (DMSO-d_6, 300 Mhz) δ 7.89 (d, 2H, J = 8.3 Hz); 7.53 (t, 1H, J = 6.3 Hz); 7.41 (t, 2H, J = 7.1 Hz); 7.07 (s, 1H); 4.71 (s, 2H); 2.35 (d, 3H, J = 5.3 Hz) ppm; Anal. Calcd for $C_9H_1NO_3S$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.47; H, 5.40; N, 6.63.

1i. Reaction of a solution of **2i** (0.33 g; 1.7 mmol) and TEA (0.38 g; 3.8 mmol) in MeCN (5 mL) with a solution of **4a** (0.39 g; 3 mmol) in MeCN (1 mL) for 2 h yields 0.48 g (60%) of **1i** after chromatography using n-hexane/ethyl acetate 7:3; mp 119-120 °C (EtOH); IR (KBr) 3310, 2972, 1641, 1517, 1423, 1246, 1132, 856, 731 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.10 (m, 2H); 7.30 (dd, 1H, J = 4.9 and 4.0 Hz); 7.20 (d, 1H, J = 5.3 Hz); 4.57 (s, 2H); 2.56 (d, 3H, J = 5.3 Hz) ppm; Anal. Calcd for $C_7H_9NO_3S_2$: C, 38.84; H, 4.14; N, 6.39. Found: C, 39.11; H, 4.40; N, 6.77.

1j. Reaction of a solution of **2j** (0.74 g; 3.4 mmol) and TEA (0.51 g; 5.1 mmol) in MeCN (12 mL) with a solution of **4a** (0.60 g; 4.6 mmol) in MeCN (4 mL) for 9 h yields 0.61 g (75%) of **1j** after chromatography using

n-hexane/ethyl acetate 7:3; mp 141-143 °C (EtOH); IR (KBr) 3311, 2974, 2944, 1964, 1670,1597, 1452, 1404, 1321, 1236, 1147, 1055, 938, 835, 720, 678, 642 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.02 (d, 1H, *J* = 7.8 Hz); 7.53 (t, 1H, *J* = 7.52 Hz); 7.37-7.25 (m, 2H); 4.96 (d, 1H, *J* = 4.6 Hz); 4.05-4.02 (t, 1H, *J* = 6.3 Hz); 3.36-3.26 (m, 1H); 3.07-2.94 (m, 1H); 2.89 (d, 3H, *J* = 5.3 Hz); 2.73-2.64 (m, 2H) ppm; ms (EI) m/z 239 (M+1); Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85. Found: C, 54.99; H, 5.60; N, 5.99.

1k. Reaction of a solution of **2a** (0.33 g; 2.5 mmol) and TEA (0.26 g; 2.6 mmol) in MeCN (6 mL) with a solution of **4b** (0.50 g; 2.6 mmol) in MeCN (1 mL) for 4 h yields 0.26 g (47%) of **1k** after chromatography using n-hexane/ethyl acetate 8:2; bp 140-145 °C/0.5 mm Hg; IR ($CHBr_3$) 3278, 2933, 1710, 1446, 1333, 1158, 1076, 733 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.59 (d, 1H, J= 6.8 Hz); 3.25 (bs, 1H); 2.38 (s, 3H); 2.0 (m, 2H); 1.57 (m, 2H); 1.60 (m, 1H); 1.30 (m, 5H) ppm; ms (EI) m/z 219 (M+1).

1l. Reaction of a solution of **2h** (0.25 g; 1.2 mmol) and TEA (0.30 g; 2.9 mmol) in MeCN (10 mL) with a solution of **4b** (0.34 g; 1.7 mmol) in MeCN (1 mL) for 5 h yields 0.18 g (54%) of **1l** after chromatography using n-hexane/ethyl acetate 7:3; mp 137-138 °C (EtOH); IR (KBr) 3281, 3199, 2932, 1669, 1324, 1281, 1141, 741 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, 2H, *J* = 8.4 Hz); 7.63 (t, 1H, *J* = 6.9 Hz); 7.5 (t, 2H, *J* = 7.3 Hz); 4.84 (d, 1H, *J* = 7.3 Hz); 4.63 (s, 2H); 3.35 (bs, 1H); 2.0 (m, 2H); 1.70 (m, 2H); 1.55 (m, 1H); 1.4-1.05 (m, 5H) ppm; Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.50; H, 7.12; N, 4.81.

1m. Reaction of a solution of **2c** (0.20 g; 1.28 mmol) and TEA (0.30 g; 2.9 mmol) in MeCN (10 mL) with a solution of **4b** (0.33 g; 1.7 mmol) in MeCN (1 mL) for 10 h yields 0.11 g (36%) of **1m** after chromatography using n-hexane/ethyl acetate 8:2; mp 120-122 °C (EtOH); IR (KBr) 3259, 2857, 1742, 1323, 1158, 1083, 1000, 923, 694 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.70 (d, 1H, *J* = 7.0 Hz); 3.63 (t, 1H, *J* = 8.1 Hz); 3.3 (m, 1H); 2.6-2.3 (m, 4H); 2.25-2.15 (m, 1H); 2.1-1.95 (m, 2H); 1.9-1.85 (m, 1H); 1.8-1.65 (m, 2H); 1.6-1.15 (m, 1H); 0.9-0.1 (m, 5H) ppm; Anal. Calcd for $C_{11}H_{19}NO_3S$: C, 53.85; H, 7.80; N, 5.71. Found: C, 53.85; H, 8.01; N, 5.86.

1n. Reaction of a solution of **2a** (0.86 g; 6.6 mmol) and TEA (0.70 g; 7.1 mmol) in MeCN (20 mL) with a solution of **4c** (1.43 g; 7.0 mmol) in MeCN (7 mL) for 18 h yields 0.75 g (50%) of **1n** after chromatography using n-hexane/ethyl acetate 7:3; mp 140 °C (EtOH); IR (KBr) 3293, 2972, 1679, 1450, 1325, 1143, 840, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.9 (s, 1H); 7.3 (m, 5H); 4.2 (s, 2H); 4.16 (d, 2H, *J* = 5.8 Hz); 2.24 (s, 3H) ppm; Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H,5.77; N,6.16. Found: C, 52.57; H, 5.64; N, 6.10.

1o. Reaction of a solution of **2h** (0.25 g; 2.4 mmol) and TEA (0.30 g; 2.9 mmol) in MeCN (10 mL) with a solution of **4c** (0.35 g; 1.7 mmol) in MeCN (1 mL) for 4 h yields 0.40 g (57%) of **1o** after chromatography using n-hexane/ethyl acetate 7:3; mp 128-129 °C (EtOH); IR (KBr) 3291, 2921, 1678, 1450, 1332, 1143, 928, 693 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, 2H, *J* = 8.4 Hz); 7.62 (t, 1H, *J* = 8.4 Hz); 7.49 (t, 2H, *J* = 8.4 Hz); 5.25 (bs, 1H); 4.49 (s, 2H); 4.36 (d, 2H, *J* = 6.2 Hz) ppm; Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.22; N, 4.84. Found: C, 62.18; H, 5.27; N, 4.61.

1p. Reaction of a solution of **2c** (0.20 g; 1.3 mmol) and TEA (0.30 g; 2.9 mmol) in MeCN (10 mL) with a solution of **4c** (0.35 g; 1.7 mmol) in MeCN (1 mL) for 12 h yields 0.15 g (47%) of **1p** after chromatography using n-hexane/ethyl acetate 8:2; mp 114-117 °C (EtOH); IR (KBr) 3275, 2930, 1746, 1455, 1314, 1143, 908, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7,40-7,20 (m, 5H); 5,10 (bs, 1H); 4,60 (d, 2H, *J* = 6,1 Hz); 3,55-3,50 (m, 1H); 2,60-2,40 (m, 4H); 1,30-1,22 (m, 2H); Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.40; H, 6.10; N, 5.90.

1q. Reaction of a solution of **2a** (0.30 g; 1.2 mmol) and TEA (0.30 g; 2.9 mmol) in MeCN (10 mL) with a solution of **4d** (0.33 g; 2.9 mmol) in MeCN (1 mL) for 6 h yields 0.17 g (58%) of **1q** after chromatography using n-hexane/ethyl acetate 7:3; mp 63-65 °C (Et_2O); $[\alpha]^{25}_D$ = +27.7 (c 0.27, MeOH); IR (KBr) 3293, 2935, 1728, 1428, 1329, 1156, 1085, 763 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 Mhz) δ 7.3 (m, 5H); 5.2 (d, 1H, *J* = 7.7 Hz); 4.63 (m, 1H); 3.82 (d, 1H, *J* = 15.4 Hz); 3.35 (d, 1H, *J* = 15.4 Hz); 2.1 (s, 3H); 1.55 (d, 3H, *J* = 7.0 Hz) ppm;. Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.26; N, 5.80. Found: C, 54.50; H, 5.91; N, 5.73.

1r. Reaction of a solution of **2h** (0.61 g; 3.2 mmol) and TEA (0.80 g; 7.7 mmol) in MeCN (5 mL) with a solution of **4d** (0.60 g; 2.7 mmol) in MeCN (1 mL) for 1 h yields 0.58 g (60%) of **1r** after chromatography using n-hexane/ethyl acetate 7:3. M. p. 99-100 °C (EtOH).$[\alpha]_D$ = +44.2 (c = 0.29, MeOH). IR (KBr) 3307, 2978, 1672, 1448, 1327, 1153, 1083, 963 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 7.72 (d, 2H, J= 6.9 Hz); 7.61 (t, 1H, J= 4.4 Hz); 7.45 (d, 2H, J= 7.9 Hz); 7.3 -7.11 (m, 5H); 5.45 (d, 1H, J=8.2 Hz); 4.7 (t, 1H, J= 7.1 Hz); 4.4 (d, 1H, J= 7.2 Hz); 3.82 (d, 1H, J= 16 Hz); 1.58 (d, 3H, J= 6.9 Hz) ppm. ^{13}C-NMR ($CDCl_3$) 189.8, 141.4, 135.1, 134.0, 128.5, 128.4, 128.0, 127.6, 127.5, 127.0, 126.1, 125.8, 58.1, 54.0, 23.2 ppm. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.15; H, 5.75; N, 4.70.

1s. Reaction of a solution of **2c** (0.35 g; 2.3 mmol) and TEA (0.58 g; 5.6 mmol) in MeCN (10 mL) with a solution of **4d** (0.50 g; 237 mmol) in MeCN (1 mL) for 6 h yields 0.36 g (58%) of **1s** after chromatography using n-hexane/ethyl acetate 7:3; mp 136-137 °C (EtOH); $[\alpha]^{25}_D$ = +29.9 (c 0.55, MeOH); IR (KBr) 3352, 2974, 1742, 1452, 1398, 1142, 1044, 696 cm-1; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5H); 5.29 (d, 2H, *J* = 8.2 Hz); 4.7 (m, 1H); 2.82 (t, 1H, *J* = 9.0 Hz); 2.44-2.24 (m, 4H); 2.1 (m, 1H); 1.7 (m, 1H); 1.6 (d, 3H, *J* = 7.0 Hz) ppm; Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.28; H, 6.19; N, 4.98.

1t. Reaction of a solution of **2d** (0.66 g; 3.9 mmol) and TEA (0.98 g; 9.4 mmol) in MeCN (5 mL) with a solution of **4d** (0.60 g; 2.6 mmol) in MeCN (1 mL) for 10 h yields 0.55 g (50%) of **1t** after chromatography using n-hexane/ethyl acetate 7:3; bp 190 °C/0.4 mm Hg; $[\alpha]^{25}_D$ = +20.0 (c 0.24, MeOH); IR ($CHBr_3$) 3305, 1711, 1449, 1325, 1142, 869, 694, 651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.34-7.2 (m, 5H); 5.34 (d, 0.5 H, *J* = 9.8 Hz); 5.08 (d, 0.5 H, *J* = 7.7 Hz); 4.7-4.6 (m, 1H); 3.78-3.65 (m, 0.5H); 2.8-2.55 (m, 0.5H); 2.48-2.3 (m, 3H); 2.0-1.85 (m, 4H); 1.53 (d, 3H, *J* = 7.3 Hz); ms (EI) m/z 282 (M+1).

1u. Reaction of a solution of **2e** (1.34 g; 7.3 mmol) and TEA (1.80 g; 17.6 mmol) in MeCN (10 mL) with

a solution of **4d** (0.80 g; 3.6 mmol) in MeCN (1 mL) for 3 h yields 0.86 g (40%) of **1u** after chromatography using n-hexane/ethyl acetate 7:3; mp 68-69 °C (Et_2O-Hexanes); $[\alpha]^{25}_D$ = +83.6 (c 0.27, MeOH); IR ($CHBr_3$) 3296, 3022, 2859, 1703, 1453, 1318, 1142, 968, 694 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.2 (m, 5H); 5.16 (d, 0.66H, *J* = 8.9 Hz); 4.9 (d, 0.33H, *J* = 6.9 Hz); 4.65 (q, 1H, *J* = 6.2 Hz); 3.9-3.75 (dd, 0.66H, *J* = 4.2 and 11.5 Hz,); 3.3-3.1 (dd, 0.33H, *J* =7.7 and 5.9 Hz,); 2.8-2.4 (m, 1H); 2.4-2.2 (m, 1H); 2.0-17 (m, 4H); 1.6 (m, 3H); 1.5-1.2 (m, 4H) ppm; ms (EI) m/z 296 (M+1); Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 60.78; H, 7.14; N, 4.72. Found: C, 60.76; H, 6.97; N, 5.20.

Alkylation of 2-oxoalkanesulfonamides 1. Method A. A solution of **1** in THF was added over a 2M solution of LDA (2.2 equiv) in THF/hexanes at -78 °C and the mixture stirred for 1h. Then MeI (5 equiv) was added and the mixture was stirred for 1h. The temperature was raised and the reaction performed as indicated for each case. The reaction mixture was then quenched with 50% ammonium chloride solution and extracted with DCM. The organic extracts were dried and the solvent was removed under reduced pressure. The residue was cromatographed on silica gel using hexanes/ethyl acetate. **Method B.** A solution of compound **1** in DCM was treated with 50% potassium carbonate for 15 minutes and then MeI was added. The temperature and reaction time were kept as indicated for each case. Then the reaction mixture was extracted with DCM. The organic extracts were dried and the solvent removed under reduced pressure. The residue was cromatographed on silica gel using hexanes/ethyl acetate. **Method C.** To a solution of **1** in DCM solid potassium carbonate was added, the mixture stirred for 15 minutes and then MeI added. After the mixture was stirred at room temperature for the time indicated for each case the solid was filtered off and washed with DCM. The filtrate was evaporated and the residue chromatographed on silica gel using hexanes/ethyl acetate.

Methylation of 1a. Method A. The reaction of **1a** (0.10 g; 0.66 mmol) in THF for 5h at -40 °C yields **5a** (46 mg, 42%) and **6a** (20 mg, 18%) after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1a** (0.10 g; 0.66 mmol) for 20 h at room temperature yields **5a** (33 mg, 30%) and **6a** (10 mg, 9%) after chromatography using hexanes/ethyl acetate 8:2. **5a**: mp 50-51 °C (Et_2O-Hexanes); IR ($CHBr_3$) 3314, 1716, 1358, 1324, 1144, 842 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.32 (bs, 1H); 4.11 (q, 1H, *J* = 7.0 Hz); 2.84 (d, 3H, *J* = 5.3 Hz); 2.4 (s, 3H); 1.58 (d, 3H, *J* = 7.0 Hz) ppm; Anal. Calcd for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; N, 8.48. Found: C, 36.40; H, 6.89; N, 8.33. **6a**: mp 49-50 °C (Et_2O); IR ($CHBr_3$) 3306, 3026, 1716, 1418, 1142, 654 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.99 (s, 2H); 2.9 (s, 6H); 2.44 (s, 3H) ppm; Anal. Calcd for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; N, 8.48. Found: C, 36.80; H, 6.95; N, 8.10.

Methylation of 1h. Method A. The reaction of **1h** (0.10 g; 0.50 mmol) in THF (10 mL) for 20 h at room temperature yields **5h** (43 mg, 38%), **6h** (11 mg, 18%) and **7h** (51 mg, 42%) after chromatography using hexanes/ethyl acetate 8:2. The reaction of **1h** (0.10 g; 0.50 mmol) in THF (10 mL) for 10 h at -40 °C yields **5h** (94 mg, 83%) and **6h** (1 mg, 1%) after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1h** (0.10 g; 0.50 mmol) in DCM (5 mL) for 20h at room temperature yields **5h** (87 mg, 77%), **6h** (1 mg, 1%) and

7h (8mg, 7%) after chromatography using hexanes/ethyl acetate 8:2. **5h**: mp 73-74 °C (Et_2O); IR (KBr) 3294, 2975, 1678, 1449, 1307, 1150, 750 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, 2H, J = 7.1 Hz); 7.63 (m, 1H); 7.5 (t, 2H, J = 7.8 Hz); 5.2-5.1 (q, 1H, J = 7.1 Hz); 4.5 (m, 1H); 2.85 (d, 3H, J = 4.8 Hz); 1.7 (d, 3H, J = 7.1 Hz) ppm; Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.76; N, 6.16. Found: C, 52.79; H, 5.41; N, 6.49. **6h**: mp 71-72 °C (Et_2O); IR ($CHBr_3$) 2952, 1680, 1596, 1276, 1152, 964, 762 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 Mhz) δ 7.95 (d, 2H, J = 7.1 Hz); 7.55 (t, 1H, J = 7.3 Hz); 7.46 (t, 2H, J = 7.9) Hz; 4.5 (s, 2H); 2.9 (s, 6H) ppm; Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.76; N, 6.16. Found: C, 52.53; H, 5.79; N, 5.92. **7h**: mp 74-75 °C (Et_2O); IR ($CHBr_3$) 3024, 1678, 1595, 1448, 1333, 1143, 971, 750 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, 2H, J = 7.2 Hz); 7.59 (t, 1H, J = 6.9 Hz); 7.51 (t, 2H, J = 6.3 Hz); 5.13 (q, 1H, J = 7.1 Hz) ; 2.87 (s, 3H); 1.06 (d, 3H, J = 7.2 Hz) ppm; Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.26; N, 5.80. Found: C, 54.83; H, 6.21; N, 5.48.

Methylation of 1q. Method A. The reaction of **1q** (76 mg; 0.363 mmol) in THF (5.5 mL) for 14 h at room temperature yields **5q** (19.4 mg, 29%) and **6q** (2.3 mg, 3.5%) as yellowish oils after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1q** (0.20 g; 0.83 mmol) in DCM (5 mL) for 19h at reflux yields **5q** (59 mg; 28%), **6q** (17 mg, 8%) and**7q** (19%) as yellowish oils after chromatography using hexanes/ethyl acetate 8:2. **Method C.** The reaction of **1q** (0.20 g; 0.83 mmol) in DCM (56 mL) for 19h at reoom temperature yields **5q** (33 mg, 16%). **5q mixture of diastereomers (method C)**: IR ($CHBr_3$) 3290, 1720, 1430, 1329, 1157, 780 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.33-7.22 (m, 10H); 4.80 (d, 0.4H, J = 7.8 Hz); 4.74 (d, 1.6H, J = 7.8 Hz); 4.64-4.55 (m, 2H); 3.76 (q, 0.4H, J = 7.1 Hz); 3.74 (q, 1.6H, J = 7 Hz); 2.43 (s, 1.2H); 2.32 (s, 4.8H); 1.60-1.55 (m, 6H); 1.52 (d, 1.2H, J = 7 Hz); 1.36 (d, 4.8H, J = 7 Hz); ms (CI) m/z 256 (M-1). **6q**: IR ($CHBr_3$) 3290, 1720, 1430, 1329, 1157, 780 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.37-7.25 (m, 5H); 5.24 (q, 1H, J = 7.1 Hz); 4.00-3.70 (dd, 2H, J = 13, 4.2 Hz); 2.68 (s, 3H); 2.17 (s, 3H); 1.60 (d, 3H, J = 7.1 Hz); ms (CI) m/z 256 (M-1). **7q mixture of diastereomers (method B)**: IR ($CHBr_3$) 3180, 1730, 1328, 1114, 793 cm^{-1}. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.37-7.31 (m, 5H); 5.24 (q, 1H, J = 7.1 Hz); 4.10-4.05 (m, 1H); 2.61 (s, 1.5H); 2.59 (s, 1.5H); 2.38 (s, 3H); 1.60 (d, 3H, J = 7.2 Hz); 1.55 (d, 3H, J = 7.1 Hz); ms (CI) m/z 270 (M-1).

Acylation of 2-oxoalkanesulfonamides 1. General procedure. Method A and B. To a solution of 2-oxoalkanesulfonamide **1** in DCM, base (1.1 equiv) was added. After 5 minutes stirring, a solution of acylating reagent in DCM was added. The reaction time were kept as indicated in each case. The solvent was removed under reduced pressure and the residue chromatographed on silica gel with hexanes/ethyl acetate. **Method C.** To a solution of 2-oxoalkanesulfonamide **1** in MeCN, base (1.1 equiv) was added. After 1 minute stirring, a solution of acylating reagent in MeCN was added, and then the mixture heated at 50° C. The reaction time were kept as indicated in each case. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using hexanes/ethyl acetate

Acylation of 1q. Method A The reaction of **1q** (0.10 g; 0.41 mmol) and TEA (60 μL; 0.45 mmol) in DCM

(10 mL) and 4-chlorobenzoyl chloride (72 mg; 0.41 mmol) dissolved in DCM (2 mL) for 5h at room temperature yields **10q** (70 mg, 45%) and **11q** (5 mg, 2%) after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1q** (0.10g; 0.41 mmol) and Hünig base (0.057g; 77 μL; 0.442 mmol) in DCM (10 mL) and 4-chlorobenzoyl chloride (72 mg; 0.41mmol) dissolved in DCM (2 mL) for 96h at room temperature yields **10q** (84 mg, 40%) and **11q** (1.4 mg; 0.7%) after chromatography using hexanes/ethyl acetate 8:2. **Method C.** The reaction of **1q** (0.10g; 0.41 mmol) and K_2CO_3 (0.041g; 0.42 mmol) in acetonitrile (10 mL) and 4-chlorobenzoyl chloride (72 mg; 0.41mmol) dissolved in acetonitrile (2 mL) for 16h at 50° C yields **10q** (46.5 mg, 31%) and **11q** (31 mg; 16%) after chromatography using hexanes/ethyl acetate 8:2. **10q mixture of diastereomers (method B)**: mp 62-63 °C (Et_2O-hex); IR (KBr) 3298, 2978, 2676, 1724, 1689, 1591, 1423, 1281, 1091 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300MHz) δ 8.03-8.00 (m, 2H); 7.97-7.95 (m, 2 H); 7.46-7.27 (m, 5H); 5.71 (s, 0.12H); 5.66 (s, 0.88H); 4.92 (d, 1H , J = 7.3 Hz); 4.89-4.57 (q, 1H, J = 6.9 Hz); 2.03 (s, 0.36H); 1.98 (s, 2.64H); 1.54 (d, 3H, J = 6.9 Hz). Calcd for $C_{18}H_{18}ClO_4NS$: C, 56.92; H, 4.78; N, 3.69; Found: C, 56.98; H, 4.92; N, 3.78. **11q mixture of diastereomers (method B)**: mp 64-65 °C (Et_2O-hex); IR ($CHBr_3$) 2976, 2555, 1739, 1687, 1591, 1423, 1281, 1091, 851 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H); 7.42 (m, 2H); 7.42-7.39 (m, 9H); 6.09 (s, 0.5H); 6.06 (s, 0.5H); 5.35 (q, 0.5H, J = 6.9 Hz); 5.3 (q, 0.5H, J = 6.9 Hz); 2,18 (s, 1.5H); 2.16 (s, 1.5H); 1.86 (d, 1.5H, J = 6.9 Hz); 1.84 (d, 1.5H, J = 6.6 Hz); Calcd for $C_{25}H_{21}Cl_2NO_5S$: C, 57.92; H, 4.08; N, 2.70; Found: C, 58.11; H, 4.05; N, 2.25.

Acylation of 1r. Method A. The reaction of **1r** (0.10 g; 0.33 mmol) and TEA (47 μL; 0.34 mmol) dissolved in DCM (10 mL) and 4-chlorobenzoyl chloride (58 mg; 0.41 mmol) dissolved in DCM (2 mL) for 1h at room temperature yields **10r** (100 mg, 69%) and **11r** (19 mg; 10%) after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1r** (0.10g; 0.33 mmol) and Hünig base (0.043g; 58μL; 0.34 mmol) in DCM (10 mL) and 4-chlorobenzoyl chloride (58 mg; 0.33 mmol) dissolved in DCM (2 mL) for 14h at room temperature yields **10r** (52 mg, 34%) and **11r** (6.1 mg; 3%) after chromatography using hexanes/ethyl acetate 8:2. **Method C.** The reaction of **1r** (0.10g; 0.33 mmol) and K_2CO_3 (0.0323g; 0.33 mmol) in acetonitrile (10 mL) and 4-chlorobenzoyl chloride (58 mg; 0.33 mmol) dissolved in acetonitrile (2 mL) for 23h at 50° C yields **10r** (72.5 mg, 50%) and **11r** (19 mg; 10%) after chromatography using hexanes/ethyl acetate 8:2. **10r mixture of diastereomers (method B)**: mp 65-80 °C (Et_2O-hex). IR ($CHBr_3$) 3290, 3024, 1740, 1698, 1450, 1144, 696 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 500MHz) δ 8.11 (d, 1.5H, J = 8.5 Hz); 8.10 (d, 0.5H, J = 8.2 Hz); 7.50 (d, 2H, J = 8.5 Hz); 7.40-7.25 (m, 10H); 6.20 (s, 0.75H); 6.19 (s, 0.25H); 5.36 (d, 0.25H, J = 8.2 Hz); 4.75-4.70 (m, 0.25H;) 4.57 (d, 0.75H, J = 6.2 Hz); 4.43 (q, 0.75H, J = 6.7 Hz); 1.59 (d, 0.75H, J = 6.9 Hz); 1.49 (d, 2.25H, J = 6.7 Hz); Anal. Calcd for $C_{23}H_{20}ClNO_4S$: C, 62.51; H, 4.56; N, 3.17. Found: C, 62.10; H, 4.93; N, 3.50. **11r mixture of diastereomers (method B)**: mp 65-80 °C (Et_2O-hex); IR ($CHBr_3$) 2980, 1746, 1688, 1620, 1446, 1376, 1158, 1068, 754 cm^{-1} ; ^{1}H-RMN ($CDCl_3$, 300MHz) δ 7.99 (d, 2H, J = 8.4 Hz); 7.49-7.28 (m, 16H); 6.58 (s, 0.5H); 6.54 (s, 0.5H); 5.50-

5.37 (m, 1H); 1.90 (d, 3H, J = 7.0 Hz). Anal. Calcd for $C_{30}H_{23}Cl_2NO_5S$: C, 62.07; H, 3.99; N, 2.41. Found: C, 61.89; H, 4.25; N, 2.25.

Acylation of 1s. Method A. The reaction of **1s** (0.05 g; 0.19 mmol) and TEA (30 μL; 0.20 mmol) dissolved in DCM (5 mL) and 4-chlorobenzoyl chloride (33 mg; 0.19 mmol) dissolved in DCM (2 mL) for 2h at room temperature yields **10s** (45 mg, 59%) and **11s** (27 mg, 26%) after chromatography M. P. 138-148 °C using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1s** (0.10g; 0.37 mmol) and Hünig base (0.048g; 65μL; 0.376 mmol) in DCM (10 mL) and 4-chlorobenzoyl chloride (64 mg; 0.37 mmol) dissolved in DCM (2 mL) for 10h at room temperature yields **10s** (80 mg, 53%) and **11s** (4 mg; 2%) after chromatography using hexanes/ethyl acetate 8:2. **Method C.** The reaction of **1s** (0.10g; 0.37 mmol) and K_2CO_3 (0.0372g; 0.38 mmol) in acetonitrile (10 mL) and 4-chlorobenzoyl chloride (64 mg; 0.37 mmol) dissolved in acetonitrile (2 mL) for 23h at 50° C yields **10s** (60 mg, 40.5%) and **11s** (9 mg; 4.5%) after chromatography using hexanes/ethyl acetate 8:2. **10s mixture of diastereomers (method B)**: mp 138-148 °C (Et_2O-hex); IR (KBr) 3278, 1738, 1659, 1594, 1428, 1334, 1148, 1066, 980, 706 cm-1;. ^{1}H-RMN ($CDCl_3$, 500MHz) δ 8.00 (m, 2H); 7.46 (m, 2H); 7.32-7.28 (m, 5H); 4.98 (d, 0.2H, J = 5.5 Hz); 4.94 (d, 0.8H, J = 5.5 Hz); 4.64-4.56 (m, 1H); 2.75-2.70 (m, 2H); 2.44-2.40 (m, 2H); 2.38-2.33 (m, 2H); 1.50 (d, 2.4H, J = 6.9 Hz); 1.50 (d, 0.6H, J = 6.8 Hz). Anal. Calcd for $C_{20}H_{20}ClNO_4S$: C, 59.18; H, 4.96; N, 3.45. Found: C, 59.55; H, 4.83; N, 3.10. **11s mixture of diastereomers (method B)**: mp 60-80 °C (Et_2O-hex). IR ($CHBr_3$) 2978, 1730, 1656, 1590, 1428, 1331, 1022, 704 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300MHz) δ 8.00-7.98 (m , 2H); 7.50-7.23 (m, 11H); 5.49-5.90 (m, 1H); 2.92-2.89 (m, 2H); 2.66-2.63 (m, 2H); 2.01-1.99 (m, 2H); 1.90 (d, 1.5H, J = 7.0 Hz); 1.84 (d, 1.5H, J = 7.0 Hz). Anal. Calcd for $C_{27}H_{23}Cl_2O_5NS$: C, 59.56; H, 4.26; N, 2.57. Found: C, 59.80; H, 3.40; N, 2.90.

Acylation of 1t.Method A. The reaction of **1t** (0.05 g; 0.19 mmol) and TEA (27 μL; 0.19 mmol) dissolved in DCM (10 mL) and 4-chlorobenzoyl chloride (26 mg; 0.19 mmol) dissolved in DCM (2 mL) for 2h at room temperature yields **18t** (41 mg, 56%) and **19t** (13 mg, 14%) after chromatography using hexanes/ethyl acetate 8:2. **Method B.** The reaction of **1t** (0.10g; 0.356 mmol) and Hünig base (0.047g; 63μL; 0.36 mmol) in DCM (10 mL) and 4-chlorobenzoyl chloride (61 mg; 0.35 mmol) dissolved in DCM (2 mL) for 10h at room temperature yields **10t** (53 mg, 36%) and **11t** (3 mg; 1.5 %) after chromatography using hexanes/ethyl acetate 8:2. **10t mixture of diastereomers (method B)**: bp 205-203 °C/0,4 mmHg; IR ($CHBr_3$) 3372, 3278, 1736, 1660, 1450, 1142, 1022, 960, 698 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300MHz) δ 8,06 (d, 2H, J = 6.9 Hz); 7.93-7.91 (m, 1H); 7,5 (d, 2H, J = 8.1 Hz); 7.36-7.29 (m, 5H); 4.82 (d, 1H, J = 8.1 Hz); 4.57-4.45 (m, 1H); 2.30-2.20 (m, 4H); 1.70-1.55 (m, 4H); 1.51 (d, 2.25H, J = 6.9 Hz); 147 (d, 0.75H, J = 6.9 Hz). ms (CI) m/z 386 (M-1). **11t mixture of diastereomers (method B)**: mp 70-80 °C (Et_2O-hex);. IR ($CHBr_3$) 2980, 1730, 1662, 1140, 1009, 980 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300MHz) δ 8.00-7.98 (m, 2H); 7.92-7.22 (m, 13H); 5.40-5.35 (m, 1H); 2.40-2.30 (m, 4H); 1.66-1.50 (m, 4H); 1.54 (d, 1.5H, J = 7.1 Hz); 1.53 (d, 1.5H, J = 7.1 Hz). Anal. Calcd for $C_{28}H_{27}NO_5S$: C, 68.69; H, 5.56;

N, 2.86. Found: C, 68.42; H, 5.22; N, 2.77.

Synthesis of arylidenesulfonamides 13. General Procedure. A solution of **1a**, benzaldehyde derivative, piperidine and acetic acid in isopropanol was heated at 70 °C for 24 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel with toluene/ethyl acetate 9:1.

13a. Reaction of **1a** (0.20 g; 1.3 mmol), 2-chlorobenzaldehyde (0.36 g; 1.3 mmol), piperidine (0.7 μL), acetic acid (1.6 μL) and isopropanol (1 mL) yields 0.18 g (50%) of **13a**; mp 63-64 °C (Et_2O-Hexanes); IR ($CHBr_3$) 3301, 2921, 1695, 1417, 1328, 1188, 768 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 7.92 (s, 1H); 7.5-7.2 (m, 4H); 4.79 (m, 1H); 2.72 (d, 3H, J = 5.4 Hz); 2.15 (s, 3H) ppm; Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.35; H, 4.43; N, 5.13. Found: C, 48.00; H, 4.74; N, 5.08.

13b. Reaction of **1a** (0.50 g; 3.3 mmol), 2-nitrobenzaldehyde (0.94 g; 3.3 mmol), piperidine (1.8 μL), acetic acid (4.4 μL) and isopropanol (2 mL) yields 0.47 g (49%) of **13b**; mp 90-92 °C (Et_2O); IR (KBr) 3105, 2943, 1673, 1523, 1339, 1153, 1074, 867, 707 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.30 (d, 1H, J = 7.8 Hz); 7.93 (s, 1H); 7.78 (t, 1H, J = 6.8 Hz); 7.72 (t, 1H, J = 7.3 Hz); 7.39 (d, 1H, J = 7.6 Hz); 2.62 (s, 3H); 2.20(s, 3H) ppm; ms (EI) m/z 289 (M+1).

13c. Reaction of **1a** (0.50 g; 3.3 mmol), 2,3-dichlorobenzaldehyde (1.02 g; 3.3 mmol), piperidine (1.8 μL), acetic acid (4.4 μL) and isopropanol (2 mL) yields 0.41 g (40%) of **13c**; mp 164-166 °C (EtOH); IR (KBr) 3302, 2980, 2825, 1695, 1412, 1328, 1168, 877, 653 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.80 (s, 1H); 7.50 (m, 1H); 7.10 (m, 2H); 4.70 (m, 1H); 2.70 (d, 3H, J = 5.4 Hz); 2.10 (s, 3H); Anal. Calcd for $C_{11}H_{11}Cl_2NO_3S$: C, 42.87; H, 3.60; N, 4.54. Found: C, 43.00; H, 3.99; N, 4.13.

Synthesis of dihydropyridines 12. General procedure. A mixture of compounds **13** and **14** (1 equiv each) in ethanol (for **13a**) or isopropanol (for **13b**) was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with hexanes/ethyl acetate (**13a**) or toluene/ethanol (**13b**).

12a. A mixture of compounds **13a** (0.15 g; 0.6 mmol) and **14** (0.06 g; 0.6 mmol) was dissolved in ethanol (0.6 mL) and refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with toluene/ethanol 9:1 yielding **12a** (40 mg; 18%) and **15a** (32%) as yellowish oils. Spectroscopic data for **12a**: IR ($CHBr_3$) 3341, 1699, 1607, 1434, 1305, 1094, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, 1H, J = 8.0 Hz); 7.23 (d, 1H, J = 7.8 Hz); 7.13 (t, 1H, J = 7.6 Hz); 7.03 (t, 1H, J = 7.3 Hz); 5.6 (bs, 1H); 5.39 (s, 1H); 4.35 (bs, 1H); 3.6 (s, 3H); 2.81 (d, 3H, J = 5.3 Hz); 2.31 (s, 3H); 1.24 (s, 3H) ppm. ms (EI) m/z 370 (M+1). For compound **15a** the spectroscopic data are identical to those of an authentical sample.[19]

12b. A mixture of compounds **13b** (0.17 g; 0.6 mmol) and **14** (0.06 g; 0.6 mmol) was dissolved in isopropanol (0.5 mL) and refluxed for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with n-hexane/ethyl acetate 1:1 yielding **12b** (37 mg; 16%) and **15b** (35%) as yellowish oils. Spectroscopic data for **12b**: IR ($CHBr_3$) 3343, 1700, 1646, 1526, 1355, 1157, 148 cm^{-1}; ^{1}H-NMR

($CDCl_3$, 300 MHz) δ 7.8-7.2 (m, 4H); 5.9 (s, 1H); 5.45 (s, 1H); 5.05 (s, 1H); 3.53 (s, 3H); 2.31 (s, 3H); 2.27 (d, 3H, J = 5.1 Hz); 1.24 (s, 3H) ppm; ms (EI) m/z 381 (M+1). For compound **15b** the spectroscopic data are identical to those of an authentical sample.[19]

Preparation of 19. A mixture of compound **1a** (0.5 g; 3.3 mmol) and ammonium acetate (3.5 g; 45.5 mmol) dissolved in absolute ethanol (2.5 ml) was heated at reflux for 24 h. The solvent was evaporated and the residue chromatographed with hexanes/ethyl acetate 1:1. After the solvent was removed the residual oil was crystallised (0.45 g, 51%); mp 136-137 °C (EtOH); IR (KBr) 3070, 1620, 1320, 1128, 844 cm-1; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.30 (s, 1H); 5.30 (s, 1H); 4.65 (m, 1H); 4.10 (s, 2H); 3.38 (s, 3H); 2.82 (d, 3H, J = Hz, J= Hz); 2.10 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.7, 135.4, 116.5, 115.0, 54.5, 30.3, 28.6, 20.2 ppm; ms (EI) m/z 266 (M+1); Anal. Calcd for $C_8H_{14}N_2O_4S_2$: C, 30.08; H, 5.30; N, 10.51. Found: C, 29.88; H, 5.23; N, 10.13.

ACKNOWLEDGMENTS

We thank ALTER S. A. (Madrid, Spain) for financial support. J. A. V. also thanks ALTER S. A. for a fellowship.

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19. We thank Dr. M. Fau de Casa-Juana for the generous gift of compounds **15a** and **15b**.