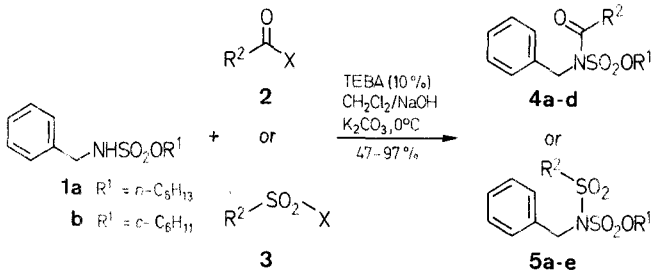
Acylation and Sulfonylation of Sulfamate Esters; Synthesis of an Acesulfam K Precursor

William J. Spillane*, Padraig O. Burke

Chemistry Department, University College, Galway, Ireland.

Convenient, high-yield procedures for the acylation and sulfonylation of sulfamate esters are described. These procedures yield the *N*-acylsulfamate ester and the *N*-sulfonylsulfamate ester functionalities, respectively. The alkylating ability of one of the *N*-acylated sulfamate esters prepared has been demonstrated. 4-Chlorophenyl *N*-acetoacetylsulfamate, an immediate precursor to the commercial cyclic sweetener Acesulfam K, has been prepared from 4-chlorophenyl sulfamate and diketene.

Recently we reported a useful method for the *N*-alkylation of sulfamate esters **1**[1]. In this paper we describe equally efficient methods for the acetylation, benzoylation and sulfonylation of sulfamate esters. The new materials formed are of types **4a–d** and **5a–e** (Scheme **A**). The functionality formed on acetylation and benzoylation of sulfamates, $-CONHSO_3-$ is well known when the sulfamate carries a negative charge[2–4] or when it occurs in a ring system, as in the oxathiazinone dioxide (acesulfam) sweeteners[5,6]. This functionality also occurs in the ester form; i.e., $-CONHSO_3R^7$.

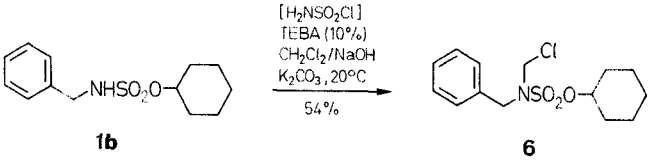


TEBA = benzyltriethylammoniumchloride

Scheme **A**

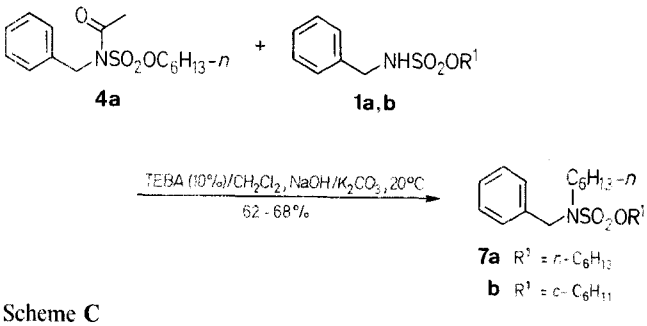
In previous syntheses of *N*-acylsulfamates[2–4] and *N*-sulfonylsulfamates[3], the carbonyl and sulfonyl groups were already present in the reactant(s) prior to sulfamation. In the present work the approach has been different in that we have been able to introduce carbonyl and sulfonyl groupings into the preformed sulfamate esters **1**. The yields of acylated and sulfonylated sulfamate esters (**4** and **5**) are good (Table 1) (Scheme **A**) and the reaction procedures described below are convenient and reproducible. The present methods thus offer a useful new, general synthesis of these types of esters.

Although the phase transfer catalyst triethylbenzylammonium chloride (TEBA) has been used, the mechanism of reaction is not substantially, and possibly not at all, a phase-transfer process. This is evident from runs in which the TEBA was omitted (see Table 1, footnotes e, f and g). TEBA, however, was used in most experiments since greater reproducibility could be attained when it was present.



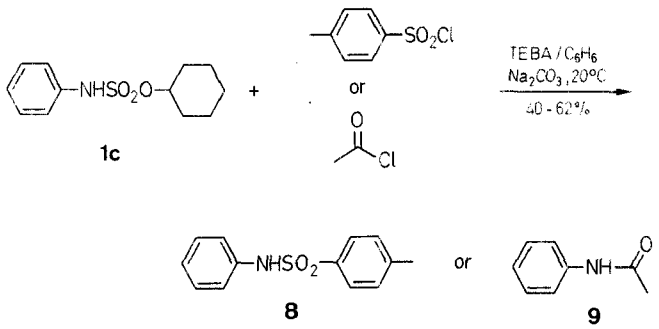
Scheme **B**

Attempts to achieve *N*-sulfamoylation of compounds **1**, using either *N,N*-dimethylsulfamoyl chloride or sulfamoyl chloride did not succeed (Scheme **B** and experimental). In the case of the reaction of **1b** with sulfamoyl chloride the chloride is hydrolysed and dichloromethane acts as alkylating agent yielding **6**.



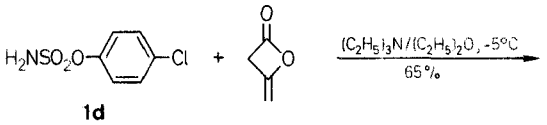
Scheme **C**

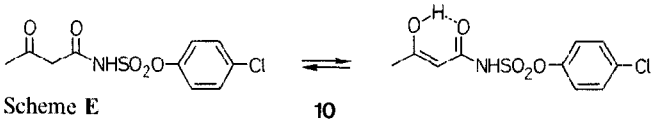
The presence of an acetyl group on the nitrogen atom in **4a** enhances its effectiveness as an alkylating agent, and it has been used to *N*-alkylate both **1a** and **1b** in separate experiments (Scheme **C**). However, when it is used to *N*-alkylate **1b** formation of the desired product **7b** is accompanied by formation of **7a**. This is accounted for by a process involving *N*-deacetylation of **4a** yielding **1a** followed by *N*-alkylation of **1a** by **4a**. Sulfonylation and acetylation reactions on **1c** yield the sulfonamide **8** and acetanilide **9**, respectively (Scheme **D**). Both of these reactions involve *N*-substitution followed by cleavage of the sulfamate N–S bond, a cleavage observed previously when **1c** was reacted with 2,4-dinitrofluorobenzene[1]. Thus, sulfonylation and acetylation of **1c** yield products which are unstable under our conditions, whereas with **1a** or **1b** (where R = aliphatic), the *N*-substituted products are stable.



Scheme **D**

It proved possible to extend our acylation procedures to synthesize the precursor, **10**, of the cyclic sweetener acesulfam K[8]. *N*-Acetoacetylation of 4-chlorophenylsulfamate (**1d**) was achieved using diketene (Scheme **E**). Analogs of the *N*-acetoacetylated product **10** have been prepared previously by a different route involving reaction of aryloxysulfonylisocyanates with butanone[9], and a procedure similar to the present one has been used to prepare acesulfam K in 91% yield by reaction of sulfamoyl fluoride (NH_2SO_2F) and diketene[10].





Scheme **E**

Propionic anhydride, the acyl and sulphonyl chlorides and N,N-dimethylsulfamoyl chloride (Merck) were commercially available and were used as obtained. Sulfamoyl chloride (m.p. 32–36°C, Lit.[11] m.p. 40°C, b.p. 87–88°C/2 torr.) was prepared according to the procedure of Appel and Berger[11]. Diketene (B.D.H.) and reaction solvents were distilled prior to use.

N-Substituted Sulfamic Acid Esters 1:

N-substituted sulfamic acid esters (**1**) were prepared and purified as reported previously[1].

n-*Hexyl* N-*Benzylsulfamate* (**1a**): yield: 65%; m.p. 34–35°C.

IR (Nujol mull): ν = 3307 (N—H), 1352 (SO_{2asym}), 1175 cm^{-1} (SO_{2sym}).

Table 1. *N*-Alkyl-*N*-acyl- and *N*-Alkyl-*N*-sulphonylsulfamic Esters

Substrate	Acylating Agent	Reaction Solvent	Addition Time[a]	Total Reaction Time [min]	Product	Yield[b]	m.p.[c] [°C]
1a	CH_3COCl	CCl_4	10	12	**4a**	97[d] (97)	oil
1b	CH_3COCl	CCl_4	10	20	**4b**	71[e] (80)	58–60
1b	C_6H_5COCl	CH_2Cl_2	12	14	**4c**	86 (98)	73–74
1b	$C_2H_5COOCOC_2H_5$	CH_2Cl_2	9	10	**4d**	70[f] (86)	46.5–47.5
1b	CH_3SO_2Cl	CH_2Cl_2	15	20	**5a**	48 (63)	75–77[h]
1b	$4\text{-}CH_3C_6H_4SO_2Cl$	CH_2Cl_2	10	12	**5b**	83 (92)	79–82
1b	$C_6H_5SO_2Cl$	CH_2Cl_2	8	11	**5d**	67 (98)	73–75
1b	$4\text{-}ClC_6H_4SO_2Cl$	CH_2Cl_2	8	14	**5d**	47 (60)	78–80[h]
1b	$4\text{-}BrC_6H_4SO_2Cl$	CH_2Cl_2	12	15	**5e**	64[g] (86)	83–85

[a] Time of addition of the acylating agent **2** or **3**.
[b] Yield of recrystallized, analytically pure product. Crude yield in brackets.
[c] Uncorrected.
[d] When this reaction was carried out at 20°C an overall yield of 0.54 g was obtained. This was shown by ^{1}H-NMR to consist of a 2 : 1 mixture of *n*-hexyl *N*-benzyl-*N*-acetylsulfamate (**4a**) and *n*-hexyl *N*-*n*-hexyl-*N*-benzylsulfamate (**7a**).
[e] 80% crude yield obtained after 15 min in absence of TEBA.
[f] 78% crude yield obtained after 15 min in absence of TEBA.
[g] 94% crude yield obtained after 40 min in absence of TEBA.
[h] Partial decomposition and purple colour obtained on melting.

Table 2. Spectroscopic Data for Products **4**, **5** and **6**

Product	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS_{int})[b] δ [ppm]	^{13}C-NMR ($CDCl_3$/TMS_{int})[c] δ [ppm]	IR[d] $\nu_{C=O}$ [cm^{-1}]
4a	$C_{15}H_{23}NO_4S$ (313.4)	0.76–1.08 (t, 3H); 1.08–1.72 (m, 8H); 2.45 (s, 3H); 3.86 (t, 2H); 4.94 (s, 2H); 7.16–7.44 (m, 5H)	13.90, 22.35, 24.30, 24.95, 28.46, 31.06, 50.16, 72.77, 128.00, 128.52, 136.71, 170.10	1710
4b	$C_{15}H_{21}NO_4S$ (311.4)	1.00–2.00 (m, 10H); 2.52 (s, 3H); 3.98–4.38 (m, 1H); 4.97 (s, 2H); 7.20–7.52 (m, 5H)	23.39, 24.30, 24.56, 31.97, 49.90, 84.34, 128.00, 128.52, 128.78, 136.84, 170.36	1703
4c	$C_{19}H_{23}NO_4S$ (373.5)	1.08–2.00 (m, 10H); 4.50–4.86 (m, 1H); 5.04 (s, 2H); 7.20–7.72 (m, 10H)	23.26, 24.82, 32.10, 51.85, 85.25, 128.26, 131.90, 134.89, 136.06, 170.88	1691
4d	$C_{16}H_{23}NO_4S$ (325.44)	1.00–1.92 (m, 13H); 2.84 (q, 2H); 4.02–4.42 (m, 1H); 5.00 (s, 2H); 7.18–7.46 (m, 5H)	8.97, 23.39, 24.69, 29.24, 31.97, 50.16, 84.21, 127.87, 128.65, 136.97, 174.13	1701
5a	$C_{14}H_{21}NO_5S_2$ (347.5)	1.08–2.08 (m, 10H); 3.04 (s, 3H); 4.44–4.76 (m, 1H); 4.89 (s, 2H); 7.20–7.64 (m, 5H)	23.13, 24.69, 31.84, 42.62, 53.28, 86.03, 128.65, 129.43, 135.02	
5b	$C_{20}H_{25}NO_5S_2$ (423.6)	1.16–2.04 (m, 10H); 2.40 (s, 3H); 4.40–4.80 (m, 1H); 4.88 (s, 2H); 7.20–7.80 (m, 9H)	21.57, 23.26, 24.82, 31.84, 53.41, 85.25, 128.39, 129.43, 135.15, 136.06, 145.02	
5c	$C_{19}H_{23}NO_5S_2$ (409.5)	1.12–2.08 (m, 10H); 4.48–4.76 (m, 1H); 4.94 (s, 2H); 7.30–8.00 (m, 10H)	23.26, 24.82, 31.97, 53.54, 85.51, 128.39, 128.91, 129.43, 133.85, 135.02, 139.04	
5d	$C_{19}H_{22}NClO_5S_2$ (443.9)	1.16–2.08 (m, 10H); 4.48–4.84 (m, 1H); 4.96 (s, 2H); 7.24–7.88 (m, 9H)	23.26, 24.69, 31.97, 53.54, 85.77, 128.52, 129.17, 129.43, 129.82, 134.76, 137.49, 140.64	
5e	$C_{19}H_{22}NBrO_5S_2$ (488.4)	1.08–2.08 (m, 10H); 4.52–4.84 (m, 1H); 4.97 (s, 2H); 7.28–7.80 (m, 9H)	23.26, 24.82, 31.97, 53.67, 85.77, 128.52, 129.56, 129.82, 132.16, 134.76, 138.00	
6	$C_{14}H_{20}NClO_3S$ (282.4)	1.12–2.28 (m, 10H); 4.52–4.80 (m, 3H); 4.83 (s, 2H); 7.36–7.80 (m, 5H)	23.26, 24.95, 32.23, 50.42, 59.78, 81.87, 128.00, 128.39, 129.17, 135.54	

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.33, N ±0.36; except **4b** (N +0.55) and **5e** (C +0.42).
[b] Recorded on a Jeol JNM-100 spectrometer.
[c] Recorded on a Jeol FX-60 spectrometer. (Broad-Band ^{1}H-decoupled).
[d] Recorded (neat or nujol mull) on a Perkin-Elmer 983G spectrophotometer. All products showed strong absorptions in the regions 1360–1398 c.m.$^{-1}$ and 1160–1192 c.m.$^{-1}$. These were complex for compounds **5a–e** due to the presence of two $-SO_2-$ moieties.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.75–1.00 (t, 3H); 1.14–1.80 (m, 8H); 4.03 (t, 2H); 4.25 (d, 2H); 4.76–5.00 (m, 1H), 7.24–7.48 ppm (m, 5H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.90, 22.48, 25.21, 28.72, 31.19, 47.82, 70.82, 128.13, 128.78, 136.32 ppm.

$C_{13}H_{21}NO_3S$	calc.	C 57.53	H 7.80	N 5.16
(271.37)	found	57.81	7.68	4.78

Cyclohexyl N-*Benzylsulfamate* **(1b)**; yield: 64%; m.p. 78–79°C.

IR (Nujol mulls): ν = 3226 (N–H), 1338 (SO_{2assym}), 1160 cm^{-1} (SO_{2sym}).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.16–2.12 (m, 10H); 4.22 (d, 2H); 4.36–4.60 (m, 1H); 4.84–5.12 (m, 1H); 7.24–7.44 ppm (m, 5H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 23.39, 24.95, 32.23, 47.69, 81.74, 128.00, 128.78, 136.58 ppm.

$C_{13}H_{19}NO_3S$	calc.	C 57.97	H 7.11	N 5.20
(251.21)	found	58.23	7.06	5.58

Cyclohexyl N-*Phenylsulfamate* **(1c)**; yield: 74%; m.p. 39–41°C. **1c** is prepared by our previously published procedure[1].

N-Alkyl-N-Acyl- and N-Alkyl-N-Sulphonylsulfamic Esters (4 and 5); General Procedure:

A suspension of compound **1** (2 mmol), anhydrous potassium carbonate (1 g), finely-powdered sodium hydroxide (0.13 g) and benzyltriethylammonium chloride (TEBA) (0.2 mmol) in solvent (6 ml, see Table 1) is cooled to ~0°C. A solution of **2** or **3** (2.2 mmol) in solvent (3 ml) is added dropwise to the vigorously stirred suspension over 8–15 min. The reaction is monitored by TLC (*n*-hexane/ethyl acetate, 4:1). At completion of the reaction *n*-hexane (25 ml) is added, and the mixture stirred and filtered. Removal of solvent from the filtrate (at 40°C/1 torr) yields crude products (**4** or **5**). In the case of solid products crystallization is brought about by cooling and scratching. The resulting solids are pulverized and recrystallized from ethyl acetate/*n*-hexane (1:4) or ethyl acetate/*n*-pentane (1:4) at −15°C. Concentration of the filtrate followed by further cooling at −15°C affords a second crop of product. The purity of the products is confirmed by TLC, IR, ^{1}H- and ^{13}C-NMR (Table 2) and by elemental analysis.

Reaction of 1b and sulfamoyl chloride:

Reaction conditions are similar to those used for the preparation of *N*-alkyl-*N*-acyl- and *N*-alkyl-*N*-sulfonylsulfamic esters (**4** and **5**) above. After a reaction time of 8 days work-up is as for **4** and **5**, followed by recrystallization from dichloromethane/*n*-hexane (1:4), to give analytically pure **6**; yield: 0.34 g (54%) (see Table 2).

Reaction of 4a with Esters 1a and 1b:

4a and 1a: To a vigorously stirred suspension of *n*-hexyl *N*-benzylsulfamate **(1a)** (542 mg, 2.0 mmol), benzyltriethylammonium chloride (45.5 mg, 0.2 mmol), powdered sodium hydroxide (0.13 g) and anhydrous potassium carbonate (1.0 g) in dichloromethane (8 ml) at 20°C is added dropwise to a solution of *n*-hexyl *N*-acetyl-*N*-benzylsulfamate **(4a)** (2.2 mmol) in dichloromethane (4 ml). Reaction is allowed to proceed for 2.5 h before work-up as for **4** and **5** above. The resultant crude product is purified by flash chromatography (eluant, *n*-hexane/ethyl acetate, 18:1) thus giving n-*hexyl* N-n-*hexyl*-N-*benzylsulfamate* **(7a)** as an oil; yield: 0.44 g (62% based on **1a**).

IR (Nujol mulls): ν = 1363 (SO_{2assym}), 1172 cm^{-1} (SO_{2sym}).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.72–1.04 (m, 6H); 1.04–1.90 (m, 16H); 3.13 (t, 2H); 4.08 (t, 2H); 4.37 (s, 2H); 7.16–7.40 ppm (m, 5H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.90, 22.48, 25.21, 26.25, 27.16, 28.98, 31.32, 48.08, 51.85, 70.30, 128.00, 128.52, 136.06 ppm.

$C_{19}H_{33}NO_3S$	calc.	C 64.19	H 9.36	N 3.94
(355.54)	found	64.00	9.30	4.11

4a and **1b**: Reaction conditions and isolation procedure are as for reaction of **4a** and **1a** above, but using 3.0 mmol. of **4a**. Oily material is obtained (0.58 g). From examination of the ^{13}C- and ^{1}H-NMR spectra, this material is clearly seen to be a mixture of *cyclohexyl* N-n-*hexyl*-N-*benzylsulfamate* **(7b)** and n-*hexyl*-N-n-*hexyl*-N-*benzylsulfamate* **(7a)** in 5:1 ratio. This represents a 68% yield of **6b** (based on **1b**).

Reaction of (1c) and p-Toluenesulfonyl Chloride:

To a vigorously stirred suspension of TEBA (455 mg, 2 mmol), cyclohexyl *N*-phenylsulfamate (**1c**; 510 mg, 2 mmol) and anhydrous sodium carbonate (2.0 g) in benzene (8 ml) is added dropwise, over 30 min, a solution of *p*-toluenesulphonyl chloride (381 mg, 2 mmol) in benzene (4 ml). The mixture is stirred at room temperature for 7 h. Ether (20 ml) is then added and the mixture stirred and filtered. Removal of solvent from the filtrate yields an oil which is purified by flash chromatography [Merck silica gel 0.40–0.63 mm, eluant pet.ether (60–80°)/ethyl acetate/chloroform (4:1:1)] to give N-*phenyl*-p-*toluenesulfonamide* **(8)**: yield: 0.23 g (62%); m.p. 98–101°C. (Lit.[12] m.p. 103–104°C). Product identity is confirmed by ^{1}H-NMR and IR.

Reaction of (1) and Acetyl chloride:

Reaction conditions are identical to those for the reaction of **1c** and *p*-toluenesulfonyl chloride above. A 40% yield (estimated by ^{1}H-NMR of crude products) of *acetanilide* **(9)** is obtained after 3 h.

Reaction of (1c) and N,N-Dimethylsulfamoyl Chloride:

Conditions are identical to the analogous reaction with *p*-toluenesulfonyl chloride above. TLC and ^{1}H-NMR indicated that *N*-substitution did not occur, even after 40 h at room temperature or after 21 h in refluxing chloroform.

Reaction of 4-Chlorophenyl sulfamate with Diketene:

To a stirred solution of 4-chlorophenyl sulfamate (415 mg, 2 mmol; prepared according to Ref. 7b) and triethylamine (202 mg, 2 mmol) in dry ether (4 ml) at ca. −5°C is added dropwise over 20 min. diketene (0.2 ml, 2.5 mmol) in dry ether (4 ml). The reaction mixture is stirred for a further 3 h, after which time distilled water (30 ml), sodium bicarbonate (0.8 g) and ether (10 ml) are added. The mixture is shaken and the aqueous layer separated and cooled to ca. 0°C before acidification with conc. hydrochloric acid. Extraction of the acid solution with ethyl acetate followed by drying and concentration (50°C/15 torr) affords 4-chlorophenyl N-acetoacetylsulfamate **(10)** as an oil which crystallizes on cooling; yield: 0.38 g (65%); m.p. 97–98°C (benzene).

IR (Nujol mulls): ν = 3185 (N–H), 1738, 1709 cm^{-1} (C=O)

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.05 (s, enol CH_3); 2.35 (s, keto CH_3); 3.58 (s, keto CH_2); 5.34 (s, enol =C–H); 6.99–7.52 (A_2B_2 system, C_6H_4); 10.15 (s, NH); 12.77 (s, OH).

^{13}C-NMR ($CDCl_3$/TMS): δ = 22.13, 31.08, 48.65, 89.19, 123.44, 130.26, 133.78, 148.16, 163.44, 168.86, 181.47, 203.58 ppm.

$C_{10}H_{10}ClNO_5S$	calc.	C 41.17	H 3.46	N 4.80
(291.70)	found	41.41	3.55	4.65

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