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N,*N*-Dialkyl-*N*′-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. IV. 3-Dialkylamino-1,1,8-trioxo-1*H*-1λ^6-pyrano[3,4-*e*][1,4,3]oxathiazines

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N,*N*-dialkyl-*N*′-chlorosulfonylchloroformamidines **1** reacted regioselectively with 4-hydroxy-2-pyrone derivatives **2** to give 3-dialkylamino-1,1,8-trioxo-1*H*-1λ^6-pyrano[3,4-*e*][1,4,3]oxathiazines **3**. Dichloride **1b** reacted regioselectively with 1,3-dimethylbarbituric acid **10** to give 3-diethylamino-5,7-dimethyl-1,1,6,8-tetraoxo-1*H*-1λ^6-pyrimido[5,4-*e*]-[1,4,3]oxathiazine **11**. The compounds **3** and **11** are derivatives of new ring systems.

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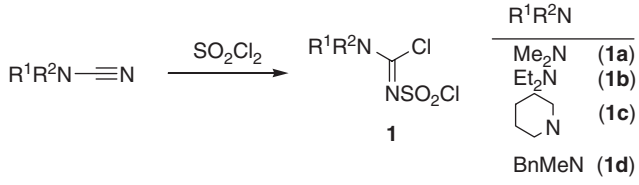
Introduction

As part of our ongoing interest in the synthesis of novel, low molecular weight heterocyclic compounds, we have been exploiting the use of *N*,*N*-dialkylated *N*′-chlorosulfonylchloroformamidines **1**, which embody readily available[1,2] but rarely used[3–5] 1,3-dielectrophiles. In Part I[6] of this series we reported the regioselective reaction between **1** and either hydrazines or hydroxamic acids (1,2-dinucleophilic species) which gave the uncommon 5-membered heterocyclic products, [1,2,3,5]thiatriazole dioxides or [1,3,2,4]oxathiadiazole dioxides, respectively. In Parts II[7] and III[8] of this series, we described reactions of dichlorides **1** with five classes of 2-amino-1-azaheterocycle (1,3-dinucleophilic species), where these species were based on the readily available thiazole, thiadiazole, oxadiazole, pyridine, and pyridazine systems. These reactions provided syntheses of a variety of novel, fused [1,2,4,6]thiatriazine dioxides.

We now report some results of reactions of **1** with a 1,3-dinucleophilic (:O–C–C:) system based on 4-hydroxy-2-pyrones, as a representative class of cyclic 1,3-dicarbonyl compounds.

Results and Discussion

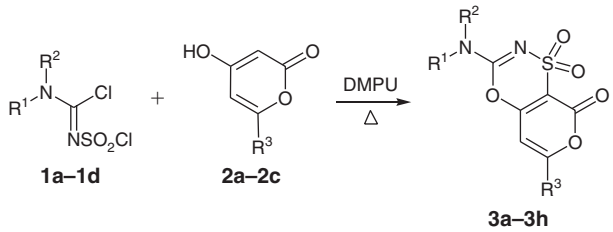
The dichlorides **1a**–**1d** were readily prepared according to procedures in the literature[1,2,6] from sulfuryl chloride and the corresponding dialkyl cyanamide (Scheme 1).



Scheme 1.

The reaction of dichlorides **1** with 4-hydroxy-2-pyrones **2** by heating in 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (dimethylpropylene urea, DMPU) provided 3-dialkylamino-1,1,8-trioxo-1*H*-1λ^6-pyrano[3,4-*e*][1,4,3]oxathiazines **3**, a stable, hitherto unknown heterocyclic system (Scheme 2, Table 1).

The ease of work-up partly compensated for the modest yields. Usually, the desired product was selectively precipitated at the interface between the organic and aqueous phases after addition of ethyl acetate and water. The mother liquor generally consisted of a complex mixture of by-products, and in some



Scheme 2.

Table 1.

R^1R^2N	R^3	Product	Yield [%]
Me_2N (**1a**)	Me (**2a**)	**3a**	20
Et_2N (**1b**)	Me (**2a**)	**3b**	10
N (**1c**)	Me (**2a**)	**3c**	8
BnNMe (**1d**)	Me (**2a**)	**3d**	30
Me_2N (**1a**)	$PhCH_2CH_2$ (**2b**)	**3e**	8
Et_2N (**1b**)	$PhCH_2CH_2$ (**2b**)	**3f**	15
N (**1c**)	$PhCH_2CH_2$ (**2b**)	**3g**	10
Et_2N (**1b**)	Ph (**2c**)	**3h**	9

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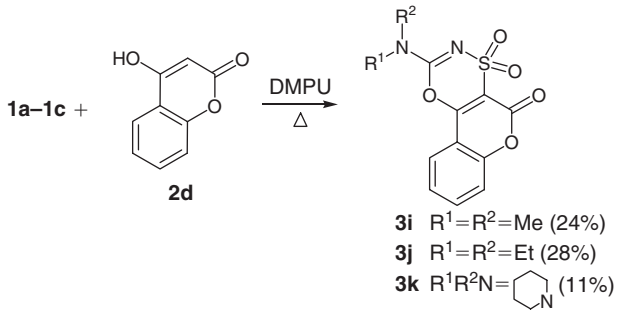
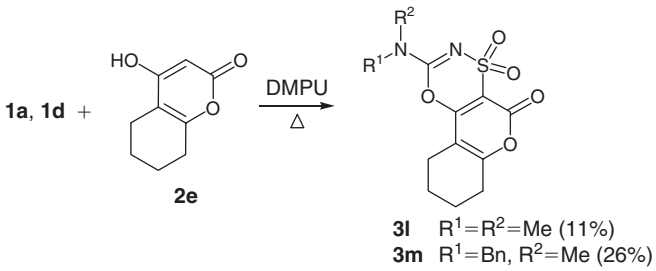
cases more desired product could be obtained by chromatography. However, this was not normally undertaken since the principal focus of the investigation was upon the discovery and rapid acquisition of novel compounds for biological screening.

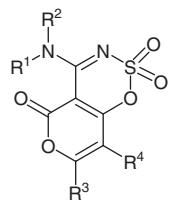
The reaction was successfully carried out in cases where a second, carbocyclic ring was fused to the pyrone moiety.



Scheme 3.



Scheme 4.



4

Fig. 1.

4-Hydroxycoumarin **2d** and 4-hydroxy-5,6,7,8-tetrahydrocoumarin **2e**[9] reacted with dichlorides **1a**–**1d** in DMPU to afford coumarino[3,4-*e*][1,4,3]oxathiazine dioxides **3i**–**3m** (Schemes 3 and 4).

To confirm that the structure of the products was **3**, rather than the possible isomeric structure **4** (Fig. 1), X-ray crystallographic studies were carried out on **3j** and **3l** (Fig. 2, Table 2).

The examples of the new heterocyclic system **3** described above were all stable, colourless, crystalline solids which showed no significant signs of decomposition after being stored for many months at room temperature and they were unaffected by recrystallization from methanol. The solubility of the compounds **3** in chloroform ranged from poor to moderate, but solubility in either diethyl ether or ethyl acetate was generally poor.

In the course of establishing preferred reaction conditions for preparing the pyrano- and coumarino[3,4-*e*][1,4,3]oxathiazine dioxides **3**, we initially evaluated more conventional solvents and bases. However, in no case were the conditions as effective as when DMPU was used as the solvent. Attempted preparation of the coumarino adduct **3i** in refluxing acetonitrile gave the desired product, but in lower yield and purity. Another attempt at this reaction using potassium carbonate in acetonitrile at room temperature afforded only the open-chain chloro compound **5** (Scheme 5) which is unable to undergo ring closure to oxathiazine **3i**.

We confirmed the structure of **5** by X-ray crystallography of the corresponding methyl ester **6a** (Fig. 3, Table 3), prepared by simply heating the chloride **5** in methanol and allowing the solution to cool.

Due to the simplicity of the esterification process and unexpected stability of the product, we also prepared the ethyl and isopropyl esters **6b** and **6c** (Scheme 5).

The possible isomeric product **7** (Fig. 4) was not isolated from the original reaction mixture (which gave **5**) under our workup conditions.

Another attempted preparation of **3i** was carried out using Hünig's base and dichloromethane as solvent and in this case a very low yield of the chloride **5** was directly precipitated from the reaction mixture. Chromatography of the residue from evaporation of the mother liquor provided a mixture of chloride **5** and methyl ester **6a** (methanol was a minor component of the mobile phase). Further elution afforded a solid, whose spectroscopic

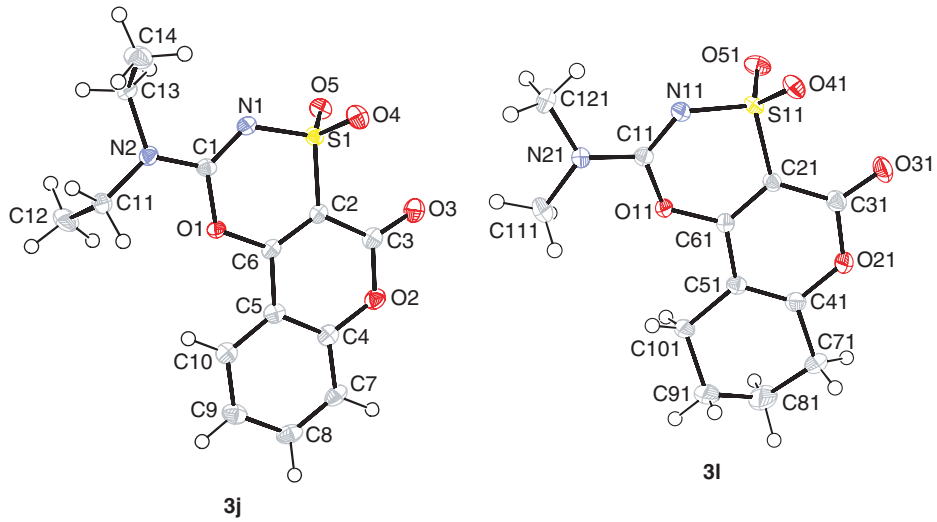


Fig. 2. *ORTEP* diagrams of **3j** and **3l**.

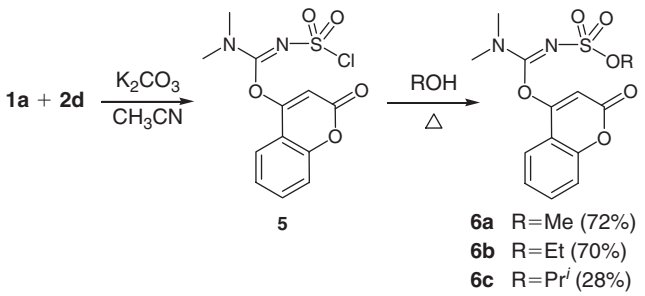
data, in particular the presence of two olefinic resonances and signals corresponding to eight aromatic hydrogens in the ^{1}H NMR spectrum, were consistent with the dicoumarino structure **8** (Fig. 5). None of the desired product **3i** was observed.

An attempted preparation of **3f** was also carried out using Hünig's base and dichloromethane as solvent and a very low yield of the desired product **3f** was obtained after chromatography. Further elution provided a solid, whose spectroscopic data, in particular the presence of four olefinic resonances and signals corresponding to two phenethyl groups in the ^{1}H NMR spectrum, indicated the dipyrono structure **9** (Fig. 5).

The above results suggest that the presence of added base promotes reaction of the hydroxyl group of **2** with one or both of the electrophilic sites of dichlorides **1** to produce compounds such as sulfamoyl chloride **5** (which is unable to undergo ring closure to **3**) or dipyrono derivatives such as **8** or **9**. Formation of the desired oxathiazine dioxides **3** requires initial reaction of the carbon α to the carbonyl group of **2** with the sulfonyl chloride moiety of **1** followed by reaction of the hydroxyl group with the amidinyl chloride centre. This latter pathway appears to be favoured in the absence of added base.

In ^{1}H NMR spectra of many of the compounds described above, a differentiation between, or significant broadening of, the resonances attributable to the methyl or methylene groups flanking the nitrogen atom of the dialkylamino substituent on the oxathiazine ring was observed. These effects may be a consequence of relatively slow (on the NMR time scale) rotation of this substituent and have been noted previously.[6] Variable temperature ^{1}H NMR studies on **6a** supported this conclusion. The ^{1}H NMR spectrum of **6a** showed sharpening of the initially two broad $(CH_3)_2N$ signals (at 20°C) to a single resonance at higher temperatures (>45°C) and resolution into two distinct and sharp singlets upon cooling to 5°C. In the ^{1}H and ^{13}C NMR spectra of **3d**, there were two separate resonances (of approximately equal integration) attributable to each of the vinylic, benzylic, pyrone-methyl, and *N*-methyl moieties. When the spectra were recorded at 140°C, all of these resonances coalesced to single signals. Upon cooling to 20°C, the resonances reverted to twin signals (along with additional, minor resonances indicating some thermal decomposition). Similar behaviour was observed in the NMR spectra of **3m**, which also possesses an *N*-methyl benzylamino moiety. These observations indicate that the *N*-methyl benzylamino compounds may exist as two conformers which interconvert slowly (on the NMR timescale).

With a successful preparation of the pyrano[3,4-*e*][1,4,3]-oxathiazine ring system **3** in hand, it became apparent that this methodology might be extended to include reactions with other 1,3-dicarbonyl systems. We briefly investigated one other example of this type of synthon. Treatment of 1,3-dimethylbarbituric acid **10** with the dichloro compound **1b** in DMPU provided a cyclic product, which by analogy with compounds **3**, was assigned the structure tetraoxopyrimido [5,4-*e*][1,4,3]oxathiazine **11** (Scheme 6), thus affording another new ring system.



Scheme 5.

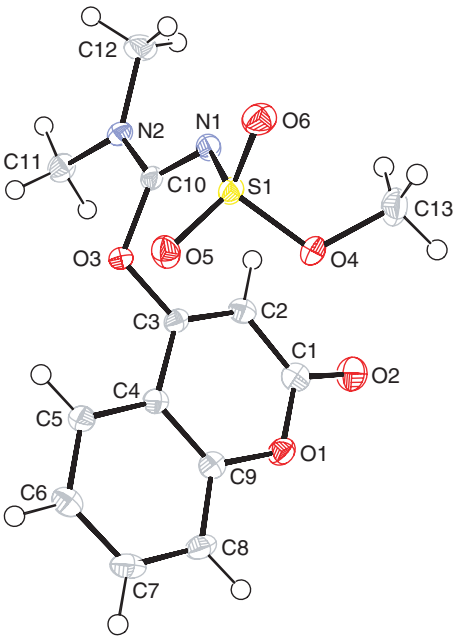


Fig. 3. *ORTEP* diagram of **6a**.

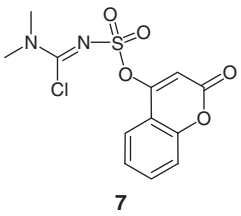


Fig. 4.

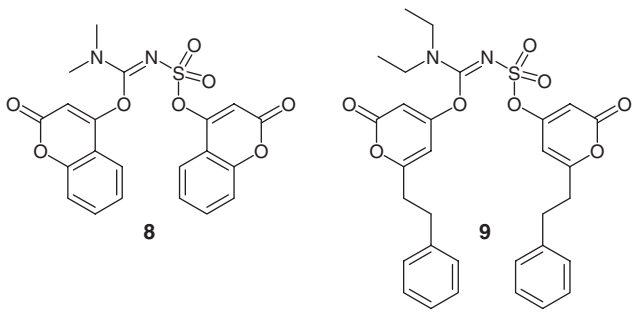
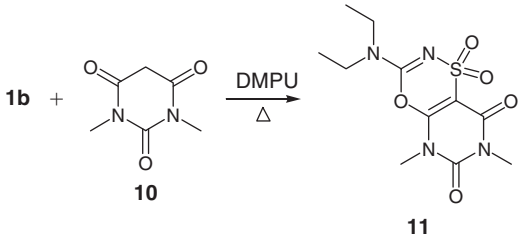


Fig. 5.



Scheme 6.

Conclusions

The dichloro compounds **1a**–**1d** have been shown to react regioselectively with some 4-hydroxy-2-pyrone derivatives **2** to form the novel pyrano[3,4-*e*][1,4,3]oxathiazine ring system **3**. It should be possible to extend this methodology to not only include reaction with 2-unsubstituted barbituric acids to afford tetraoxopyrimido[5,4-*e*][1,4,3]oxathiazines, but to also traverse other 1,3-dicarbonyl domains to produce related [1,4,3] oxathiazines.

Experimental

Materials

General experimental conditions have been described previously.[7] Atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) mass spectra were recorded on a Fisons Instruments VG Platform quadrupole using the positive ion mode with cone voltage 30 eV for both APCI and ESI, using either 1:1 acetonitrile/water or methanol as solvent. Samples were usually introduced dissolved in methanol/dichloromethane. Only the major fragments are given with their relative abundances shown in parentheses.

4-Hydroxy-6-phenethyl-2-pyrone **2b**,[10] 4-hydroxy-6-phenyl-2-pyrone **2c**,[11] 4-hydroxy-5,6,7,8-tetrahydrocoumarin **2e**,[9] and benzylmethylcyanamide[12] were prepared according to literature procedures. Other materials were obtained from commercial sources.

Synthesis Method

A stirred mixture of the 4-hydroxy-2-pyrone (or coumarin) **2** (4.8 mmol) and the dichloro compound **1** (7.2 mmol) in DMPU (3 mL) was heated at 80°C for 40 h. The mixture was cooled and ethyl acetate (10 mL) was stirred in, followed by water (20 mL). The resulting mixture was stirred vigorously for 1 h. The aqueous layer was carefully removed (without removing any precipitate) and more water (10 mL) was added. The mixture was stirred vigorously for a further 1 h and filtered. The solid was washed with ethyl acetate and purified by radial chromatography and/or recrystallization to afford the *title compounds*.

The following compounds were prepared by the above procedure.

*3-Dimethylamino-6-methyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3a***

Precipitated in 20% yield. An analytical sample was purified by radial chromatography, eluting with 3% methanol in dichloromethane, mp 278–279°C (Found: C 41.6, H 3.8, N 10.7. $C_9H_{10}N_2O_5S$ requires C 41.9, H 3.9, N 10.9%). δ_H ([D$_6$]DMSO) 6.57 (1H, s, C=CH), 3.10 (3H, s, NCH_3), 3.01 (3H, s, NCH_3), 2.30 (3H, s, CH_3). δ_C ([D$_6$]DMSO) 168.7, 162.5, 155.9, 149.0, 103.2, 98.4, 37.8, 36.6, 20.4. *m/z* (EI$^+$) 258 (80%, M$^{+\bullet}$), 194 (25), 70 (100).

*3-Diethylamino-6-methyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3b***

Purified by radial chromatography, eluting with 5–10% ethyl acetate in dichloromethane, followed by recrystallization from ethyl acetate, 10% yield, mp 276–277°C (dec.) (Found: C 46.2, H 4.9, N 9.8. $C_{11}H_{14}N_2O_5S$ requires C 46.2, H 4.9, N 9.8%). δ_H ($CDCl_3$ + [D$_6$]DMSO) 5.96 (1H, s, C=CH), 3.31 (2H, q, *J* 7, CH_2N), 3.30 (2H, q, *J* 7, CH_2N), 2.16 (3H, s, CH_3), 1.06 (6H, t, *J* 7, 2 × CH_3N). δ_C ($CDCl_3$ + ~10% [D$_6$]DMSO) 167.8, 161.1, 154.9, 147.3, 103.5, 97.0, 43.5, 42.2, 20.2, 13.4, 11.7. *m/z* (EI$^+$) 286 (2%, M$^{+\bullet}$), 254 (8), 245 (31), 217 (100).

*6-Methyl-3-piperidin-1-yl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3c***

Recrystallized from methanol, 8% yield, mp 264–266°C (dec.) (Found: C 48.1, H 4.8, N 9.4. $C_{12}H_{14}N_2O_5S$ requires C 48.3, H 4.7, N 9.4%). δ_H ([D$_6$]DMSO) 6.51 (1H, s, C=CH), 3.5–3.7 (4H, m, CH_2NCH_2), 2.30 (3H, s, CH_3), 1.62 (6H, br s, $CH_2CH_2CH_2$). δ_C ([D$_6$]DMSO) 167.1, 162.1, 155.4, 147.1, 102.9, 98.1, 45.5, 45.0, 25.0, 24.5, 23.2, 20.0. *m/z* (EI$^+$) 298 (57%, M$^{+\bullet}$), 245 (33), 234 (35), 217 (100).

*3-(*N*-Benzyl)methylamino-6-methyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3d***

Precipitated in 30% yield. An analytical sample was recrystallized from methanol, mp 245–246°C (Found: C 53.7, H 4.1, N 8.4. $C_{15}H_{14}N_2O_5S$ requires C 53.9, H 4.2, N 8.4%). δ_H (200 MHz, $CDCl_3$ + ~10% [D$_6$]DMSO) 7.16–6.98 (4H, m, ArH), 6.98–6.88 (1H, m, ArH), 5.91 (1H, s, C=CH), 4.39 (2H, s, CH_2N), 2.81 and 2.78 (2 singlets) (3H, NCH_3), 2.05 (3H, s, CH_3). When the spectrum was recorded at 200 MHz using 100% $CDCl_3$, the singlets at δ 5.91, 4.39, and 2.05 each split into two singlets (integrating approximately equally) at slightly higher chemical shifts than the above. δ_H (500 MHz, [D$_6$]DMSO, 20°C) 7.41–7.29 (5H, m, ArH), 6.65 and 6.61 (1H, 2 singlets, C=CH), 4.71 and 4.65 (2H, 2 singlets, CH_2N), 3.07 and 3.00 (3H, 2 singlets, NCH_3), 2.32 and 2.30 (3H, 2 singlets, CH_3). δ_H (500 MHz, [D$_6$]DMSO, 140°C) 7.41–7.31 (5H, m, ArH), 6.46 (1H, s, C=CH), 4.71 (2H, s, CH_2N), 3.08 (3H, s, NCH_3), 2.32 (3H, s, CH_3). δ_C (125.75 MHz, [D$_6$]DMSO, 20°C) 168.4, 168.3, 162.2, 162.1, 155.42, 155.41, 149.0, 148.3, 135.6, 135.1, 128.8, 128.7, 128.0, 127.9, 127.8, 127.7, 102.9, 102.8, 98.1, 98.0, 52.5, 52.1, 35.8, 34.3, 20.01, 19.97. δ_C (125.75 MHz, [D$_6$]DMSO, 140°C) 167.5, 161.2, 154.2, 148.4, 134.6, 127.9, 127.1, 127.0, 103.2, 97.0, 52.1, 34.4, 19.1. *m/z* (EI$^+$) 334 (2%, M$^{+\bullet}$), 245 (30), 217 (100).

*3-Dimethylamino-6-phenethyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3e***

Purified by radial chromatography, eluting with 0–2% methanol in dichloromethane, followed by recrystallization from methanol, 8% yield, mp 229–230°C (dec.) (Found: C 55.2, H 4.5, N 8.0; M$^{+\bullet}$ 348.0771. $C_{16}H_{16}N_2O_5S$ requires C 55.2, H 4.6, N 8.0%; M$^{+\bullet}$ 348.0774). δ_H 7.37–7.12 (5H, m, Ph), 5.91 (1H, s, C=CH), 3.13 (6H, s, NMe_2), 3.08–2.96 (2H, m, CH_2), 2.92–2.80 (2H, m, CH_2). δ_C 170.3, 161.2, 155.3, 148.5, 138.9, 128.8, 128.3, 126.8, 104.2, 97.3, 38.1, 36.6, 36.2, 32.5. *m/z* (EI$^+$) 348 (22%, M$^{+\bullet}$), 214 (6), 91 (100).

*3-Diethylamino-6-phenethyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3f***

Purified by radial chromatography, eluting with dichloromethane, followed by recrystallization from methanol, 15% yield, mp 204–205°C (Found: C 57.4, H 5.3, N 7.5. $C_{18}H_{20}N_2O_5S$ requires C 57.4, H 5.4, N 7.4%). δ_H 7.37–7.12 (5H, m, Ph), 5.90 (1H, s, C=CH), 3.50 (2H, q, *J* 7, NCH_2), 3.44 (2H, q, *J* 7, NCH_2), 3.08–2.96 (2H, m, CH_2), 2.92–2.80 (2H, m, CH_2), 1.25 (3H, t, *J* 7, CH_3), 1.23 (3H, t, *J* 7, CH_3). δ_C 170.2, 161.4, 155.4, 147.7, 138.9, 128.7, 128.2, 126.7, 104.2, 97.4, 43.9, 42.6, 36.1, 32.4, 13.8, 12.1. *m/z* (EI$^+$) 376 (73%, M$^{+\bullet}$), 297 (12), 214 (17), 99 (68), 91 (100).

*6-Phenethyl-3-piperidin-1-yl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3g***

Purified by radial chromatography, eluting with dichloromethane, followed by recrystallization from methanol, 10% yield, mp 239–240°C (Found: C 58.5, H 5.1, N 7.2. $C_{19}H_{20}N_2O_5S$ requires C 58.8, H 5.2, N 7.2%). δ_H 7.34–7.14 (5H, m, Ph), 5.91 (1H, s, C=CH), 3.68–3.54 (4H, m, CH_2NCH_2), 3.01 (2H, t, *J* 7.5, CH_2), 2.85 (2H, t, *J* 7.5, CH_2), 1.67 (6H, br s, $CH_2CH_2CH_2$). δ_C 170.2, 161.4, 155.3, 147.0, 138.9, 128.7, 128.2, 126.7, 104.1, 97.4, 46.4, 45.5, 36.1, 32.4, 25.5, 24.8, 23.6. *m/z* (EI^+) 388 (56%, $M^{+\bullet}$), 91 (100).

*3-Diethylamino-6-phenyl-1,1,8-trioxo-1*H-*1*λ^6-*pyrano[3,4-*e*][1,4,3]oxathiazine* ***3h***

Purified by radial chromatography, eluting with 1% methanol in dichloromethane, followed by recrystallization from methanol, 9% yield, mp 240–242°C (dec.) (Found: C 55.0, H 4.5, N 8.1. $C_{16}H_{16}N_2O_5S$ requires C 55.2, H 4.6, N 8.0%). δ_H 7.89–7.82 (2H, m, ArH), 7.62–7.45 (3H, m, ArH), 6.61 (1H, s, C=CH), 3.53 (4H, q, *J* 7, NCH_2), 1.30 (3H, t, *J* 7, CH_3), 1.27 (3H, t, *J* 7, CH_3). δ_C 165.0, 161.6, 154.7, 147.8, 133.0, 129.6, 129.4, 126.5, 104.7, 93.9, 44.1, 42.6, 14.0, 12.3. *m/z* (EI^+) 348 (4%, $M^{+\bullet}$), 320 (7), 307 (16), 279 (15), 265 (13), 250 (15), 202 (51), 174 (61), 142 (58), 133 (50), 105 (100).

*2-Dimethylamino-4,4-dioxo-4*H-*4*λ^6-*coumarino-[3,4-*e*][1,4,3]oxathiazine* ***3i***

Recrystallized twice from DMF/methanol (5:2) and washed with diethyl ether, 24% yield, mp 260–261°C (dec.) (Found: C 48.6, H 3.4, N 9.5; $M^{+\bullet}$ 294.0308. $C_{12}H_{10}N_2O_5S$ requires C 49.0, H 3.4, N 9.5%; $M^{+\bullet}$ 294.0305). δ_H ([D_6]DMSO) 8.00 (1H, dd, *J* 8,1.5, ArH), 7.92–7.82 (1H, m, ArH), 7.60–7.48 (2H, m, ArH), 3.30 (3H, s, NCH_3), 3.10 (3H, s, NCH_3). δ_C ([D_6]DMSO) 157.7, 154.0, 153.0, 148.4, 135.6, 125.5, 124.5, 117.1, 111.6, 105.9, 37.6, 36.6. *m/z* (EI+) 294 (30%, $M^{+\bullet}$), 230 (35), 224 (30), 120 (100).

*2-Diethylamino-4,4-dioxo-4*H-*4*λ^6-*coumarino-[3,4-*e*][1,4,3]oxathiazine* ***3j***

Precipitated in 28% yield. An analytical sample was purified by radial chromatography, eluting with 1% methanol in dichloromethane, followed by recrystallization from methanol, mp 240–241°C (Found: C 52.1, H 4.2, N 8.8; $M^{+\bullet}$ 322.0633. $C_{14}H_{14}N_2O_5S$ requires C 52.2, H 4.4, N 8.7%; $M^{+\bullet}$ 322.0618). δ_H 7.82–7.69 (2H, m, ArH), 7.50–7.39 (2H, m, ArH), 3.67 (2H, q, *J* 7, NCH_2), 3.59 (2H, q, *J* 7, NCH_2), 1.41 (3H, t, *J* 7, CH_3), 1.31 (3H, t, *J* 7, CH_3). δ_C 157.2, 153.9, 153.4, 147.6, 135.5, 125.6, 123.3, 117.7, 111.4, 106.9, 44.3, 43.1, 13.8, 12.2. *m/z* (EI^+) 322 (6%, $M^{+\bullet}$), 224 (17), 162 (34), 120 (100).

*4,4-Dioxo-2-piperidin-1-yl-4*H-*4*λ^6-*coumarino-[3,4-*e*][1,4,3]oxathiazine* ***3k***

Purified by radial chromatography, eluting with 0.5% methanol in dichloromethane, followed by recrystallization from methanol, 11% yield, mp 255–256°C (Found: C 53.4, H 4.1, N 8.3; $M^{+\bullet}$ 334.0617. $C_{15}H_{14}N_2O_5S$ requires C 53.9, H 4.2, N 8.4%; $M^{+\bullet}$ 334.0618). δ_H ([D_6]DMSO) 8.03 (1H, dd, *J* 8,1.5, ArH), 7.92–7.82 (1H, m, ArH), 7.59–7.47 (2H, m, ArH), 3.82 (2H, br s, NCH_2), 3.61 (2H, br s, NCH_2), 1.66 (6H, br s, $CH_2CH_2CH_2$). δ_C ([D_6]DMSO) 157.8, 153.9, 152.9, 147.0, 135.5, 125.4, 124.6, 117.1, 111.6, 106.0, 45.8, 45.4, 25.1, 24.5, 23.1. *m/z* (EI^+) 334 (14%, $M^{+\bullet}$), 270 (12), 242 (22), 120 (36), 110 (100).

*2-Dimethylamino-4,4-dioxo-4*H-*4*λ^6-*5,6,7,8-tetrahydrocoumarino[3,4-*e*][1,4,3]oxathiazine* ***3l***

Purified by radial chromatography, eluting with 1% methanol in dichloromethane, followed by recrystallization from methanol, 11% yield, mp 285–286°C (dec.) (Found: C 48.3, H 4.6, N 9.4. $C_{12}H_{14}N_2O_5S$ requires C 48.3, H 4.7, N 9.4%). δ_H 3.17 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 2.58 (2H, t, *J* 5.5, C=CCH_2), 2.46 (2H, t, *J* 5.5, C=CCH_2), 1.83 (4H, m, CH_2CH_2). δ_C 165.7, 160.9, 155.2, 148.9, 106.7, 103.6, 37.9, 36.6, 27.9, 20.9, 20.7, 20.2. *m/z* (EI^+) 298 (87%, $M^{+\bullet}$), 234 (12), 164 (25), 136 (60), 71 (100).

*2-(*N*-Benzyl)methylamino-4,4-dioxo-4*H-*4*λ^6-*5,6,7,8-tetrahydrocoumarino[3,4-*e*][1,4,3]oxathiazine* ***3m***

Precipitated in 26% yield. An analytical sample was purified by radial chromatography, eluting with 0–3% methanol in dichloromethane, followed by recrystallization from methanol, mp 245–246°C (Found: C 57.5, H 4.8, N 7.6. $C_{18}H_{18}N_2O_5S$ requires C 57.7, H 4.9, N 7.5%). δ_H 7.43–7.31 (4H, m, ArH), 7.20 (1H, d, *J* 6.5, ArH), 4.68 (2H, s, NCH_2Ph), 3.10 and 3.05 (3H, 2 singlets, NCH_3), 2.63–2.52 (2H, m, C=CCH), 2.45 (1H, m, C=CCH), 2.27 (1H, m, C=CCH), 1.91−1.68 (4H, m, CH_2CH_2). δ_C (125.75 MHz, [D_6]DMSO) 166.0, 165.8, 161.6, 161.5, 155.4, 149.6, 148.8, 136.0, 135.6, 129.3, 129.1, 128.34, 128.25, 128.1, 127.8, 107.1, 106.8, 103.6, 103.5, 53.0, 52.6, 36.4, 34.9, 27.7, 21.1, 21.0, 20.82, 20.75, 20.13, 20.10. *m/z* (EI^+) 374 (4%, $M^{+\bullet}$), 279 (5), 149 (46), 120 (30), 91 (100).

*[Dimethylamino-(2-oxo-2*H-*chromen-4-yloxy)-methylene]sulfamoyl Chloride* ***5***

A mixture of 4-hydroxycoumarin (0.98 g, 6 mmol), dichloro compound **1a** (1.85 g, 9 mmol), and potassium carbonate (2.48 g, 18 mmol) in dry acetonitrile (15 mL) was stirred at room temperature for 44 h. Ethyl acetate (40 mL) was stirred in, followed by water (80 mL). The resulting mixture was stirred vigorously for 20 min and the resultant precipitate was collected by suction filtration and air-dried to provide the *title compound* **5** (0.62 g, 31%) as an off-white solid. δ_H 7.93–7.90 (1H, m, ArH), 7.73–7.63 (1H, m, ArH), 7.45–7.35 (2H, m, ArH), 5.78 (1H, s, C=CH), 3.38 (3H, s, NCH_3), 3.18 (3H, s, NCH_3). *m/z* (EI^+) 330 (1%, $M^{+\bullet}$), 305 (1), 295 (9), 231 (52), 171 (35), 169 (100). Attempts to record the ^{1}H NMR spectrum in [D_6]DMSO resulted in significant decomposition of the sample. The compound was fully characterized as its methyl ester, using the following method. The chloride **5** (100 mg, 0.30 mmol) was dissolved in methanol (8 mL) with heating. The resultant solution was allowed to cool and stand at room temperature overnight. Filtration of the mixture afforded *[dimethylamino-(2-oxo-2*H-*chromen-4-yloxy)-methylene]sulfamic acid methyl ester* **6a** (70 mg, 72%) as colourless crystals, mp 167–168°C (Found: C 48.0, H 4.3, N 8.5. $C_{13}H_{14}N_2O_6S$ requires C 47.9, H 4.3, N 8.6%). δ_H 7.92–7.85 (1H, m, ArH), 7.70–7.60 (1H, m, ArH), 7.42–7.32 (2H, m, ArH), 5.77 (1H, s, C=CH), 3.87 (3H, s, OCH_3), 3.25 (3H, br s, NCH_3), 3.09 (3H, br s, NCH_3). δ_C 161.2, 161.0, 153.6, 152.5, 133.5, 124.7, 123.1, 117.0, 113.5, 95.0, 57.1, 39.2, 37.4. *m/z* (ESI^+) 349 (14%, $[M + Na]^{+\bullet}$), 344 (10, $[M + NH_4]^{+\bullet}$), 327 (47, $[M + H]^{+\bullet}$), 165 (100).

The following compounds were prepared by the above procedure.

*[Dimethylamino-(2-oxo-2*H-*chromen-4-yloxy)-methylene] sulfamic acid ethyl ester* **6b** (70%) as colourless crystals, mp 149.5–150°C (Found: C 49.5, H 4.7, N 8.2. $C_{14}H_{16}N_2O_6S$

Table 2. Crystal data and structure refinement for 3j and 3l

Parameter	**3j**	**3l**
CCDC deposition number	622913	622912
Empirical formula	$C_{14}H_{14}N_2O_5S$	$C_{12}H_{14}N_2O_5S$
Formula weight	322.33	298.31
Temperature [K]	123(2)	123(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	*P*21/*c*	*P*2/*c*
Unit cell dimensions		
a [Å]	10.0656(2)	15.3371(2)
b [Å]	10.4563(2)	8.7463(1)
c [Å]	13.8854(3)	19.2704(3)
β [°]	98.1809(9)	99.2470(4)
Volume [Å^3]	1446.55(5)	2551.39(6)
Z	4	8
Density (calc.) [Mg m^{-3}]	1.480	1.553
Absorption coeff. [mm^{-1}]	0.250	0.276
Crystal size [mm^3]	0.25 × 0.14 × 0.10	0.25 × 0.25 × 0.19
Theta range [°]	3.83 to 28.22	3.56 to 28.19
Reflections collected	22711	35252
Independent reflections	3514	6197
R(int)	0.0827	0.0359
No. reflections included in refinement	3514	6197
Final *R* indices [$I > 2\sigma(I)$]		
*R*1	0.0561	0.0374
*wR*2	0.1360	0.0926
R indices (all data)		
*R*1	0.0987	0.0498
*wR*2	0.1574	0.0987
Goodness-of-fit on F^2	1.009	1.027

Table 3. Crystal data and structure refinement for 6a

Parameter	**6a**
CCDC deposition number	622911
Empirical formula	$C_{13}H_{14}N_2O_6S$
Formula weight	326.32
Temperature [K]	123(2)
Wavelength [Å]	0.71073
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions	
a [Å]	10.9073(2)
b [Å]	15.2525(2)
c [Å]	8.7159(1)
β [°]	105.0416(6)
Volume [Å^3]	1400.33(4)
Z	4
Density (calculated) [Mg m^{-3}]	1.548
Absorption coefficient [mm^{-1}]	0.264
Crystal size [mm^3]	0.38 × 0.23 × 0.13
Theta range [°]	3.78 to 27.87
Reflections collected	19815
Independent reflections	3320
R(int)	0.0491
No. reflections included in refinement	3320
Final *R* indices [$I > 2\sigma(I)$]	
*R*1	0.0404
*wR*2	0.0898
R indices (all data)	
*R*1	0.0625
*wR*2	0.0993
Goodness-of-fit on F^2	1.029

requires C 49.4, H 4.7, N 8.2%). δ_H 7.92–7.85 (1H, m, ArH), 7.69–7.59 (1H, m, ArH), 7.42–7.32 (2H, m, ArH), 5.76 (1H, s, C=CH), 4.25 (2H, q, *J* 7, OCH_2), 3.24 (3H, br s, NCH_3), 3.08 (3H, br s, NCH_3), 1.33 (3H, t, *J* 7, CH_3). δ_C 161.2, 161.0, 153.6, 152.3, 133.5, 124.7, 123.1, 116.9, 113.5, 95.0, 67.4, 39.2, 37.3, 14.6. *m/z* (ESI$^+$) 363 (20%, $[M + Na]^{+\bullet}$), 341 (82, $[M + H]^{+\bullet}$), 163 (100).

*[Dimethylamino-(2-oxo-2*H*-chromen-4-yloxy)-methylene] sulfamic acid isopropyl ester* **6c** (28%) as colourless crystals, mp 130–131°C. (Found: C 50.9, H 5.1, N 7.9. $C_{15}H_{18}N_2O_6S$ requires C 50.8, H 5.1, N 7.9%). δ_H 7.92–7.86 (1H, m, ArH), 7.69–7.59 (1H, m, ArH), 7.42–7.32 (2H, m, ArH), 5.77 (1H, s, C=CH), 4.84 (1H, septet, *J* 6, Me_2CHO), 3.21 (3H, br s, NCH_3), 3.09 (3H, br s, NCH_3), 1.35 (6H, d, *J* 6, Me_2CH). δ_C 161.3, 161.1, 153.7, 152.2, 133.5, 124.7, 123.2, 117.0, 113.6, 95.1, 77.6, 38.8, 37.4, 22.7. *m/z* (ESI$^+$) 377 (10%, $[M + Na]^{+\bullet}$), 372 (22, $[M + NH_4]^{+\bullet}$), 355 (15, $[M + H]^{+\bullet}$), 233 (100).

*Attempted Preparation of **3i** using Hünig's Base/ Dichloromethane*

*[Dimethylamino-(2-oxo-2*H*-chromen-4-yloxy)methylene]sulfamoyl Chloride **5**, [Dimethylamino-(2-oxo-2*H*-chromen-4-yloxy)methylene]sulfamic Acid Methyl Ester **6a**, and (Z)-2-oxo-2*H*-chromen-4-yl(dimethylamino)(2-oxo-2*H*-chromen-4-yloxy)methylenesulfamate **8***

N,*N*-Diisopropylethylamine (3.88 g, 5.23 mL, 30 mmol) was added to a stirred suspension of 4-hydroxycoumarin **2d** (1.59 g, 9.8 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere. The resultant solution was cooled in ice and a solution of the dichloro compound **1a** (3.02 g, 14.7 mmol) in dichloromethane (8 mL) was added dropwise via syringe. The resultant mixture was allowed to warm to room temperature and was then stirred at that temperature for 24 h. Ethyl acetate (50 mL) was stirred in, followed by water (75 mL). The resulting mixture was stirred vigorously for 1 h and the resultant precipitate was collected by suction filtration and air-dried to provide the *title compound* **5** (0.27 g, 8%) as an off-white solid. The organic phase of the mother liquor was dried and evaporated. The residue was purified by radial chromatography. Elution with 0–1% methanol in dichloromethane gave a mixture of *chloride* **5** and corresponding *methyl ester* **6a** (0.15 g). Further elution gave a beige solid (0.18 g) which was tentatively identified as the *title compound* **8**. δ_H 7.88–7.80 (1H, m, ArH), 7.72–7.54 (3H, m, ArH), 7.46–7.18 (4H, m, ArH), 6.58 (1H, s, C=CH), 5.80 (1H, s, C=CH), 3.32 (3H, s, NCH_3), 3.16 (3H, s, NCH_3). *m/z* (ESI$^+$) 479 (100%, $[M + Na]^{+\bullet}$), 457 (20, $[M + H]^{+\bullet}$).

*Preparation of 3-Diethylamino-6-phenethyl-1,1,8-trioxo-1*H*-1λ^6-pyrano[3,4-e][1,4,3]oxathiazine **3f** and (Z)-2-oxo-6-phenethyl-2*H*-pyran-4-yl(diethylamino)(2-oxo-6-phenethyl-2*H*-pyran-4-yloxy)methylenesulfamate **9** using Hünig's Base/Dichloromethane*

A mixture of 4-hydroxy-6-phenethyl-2-pyrone **2b**[10] (0.65 g, 3 mmol), dichloro compound **1b** (1.05 g, 4.5 mmol), and *N*,*N*-diisopropylethylamine (1.16 g, 1.57 mL, 9 mmol) in dry dichloromethane (15 mL) was stirred at room temperature for 2.5 h. The mixture was diluted with more dichloromethane and washed with aqueous sodium carbonate solution. The aqueous layer was extracted with dichloromethane and the organic phases

were combined, washed with brine, dried, and evaporated. The residue was purified by radial chromatography. Elution with 0–1% methanol in dichloromethane gave a fraction (0.26 g) containing compound **3f** and another component. Trituration of this pale yellow solid with ethyl acetate and then decanting the supernatant afforded **3f** (72 mg, 6%) as a white solid. The supernatant was evaporated and the residue was further purified by radial chromatography. Elution with 40–50% ethyl acetate in dichloromethane gave a pale yellow, viscous gum (0.12 g) which was tentatively identified as the *title compound* **9**. δ_H 7.35–7.13 (10H, m, ArH), 6.11 (1H, d, *J* 2, C=CH), 5.97 (1H, d, *J* 2, C=CH), 5.86 (1H, d, *J* 2, C=CH), 5.49 (1H, d, *J* 2, C=CH), 3.51 (2H, q, *J* 7, CH_2N), 3.26 (2H, q, *J* 7, CH_2N), 3.06–2.91 (4H, m, 2 × CH_2), 2.88–2.74 (4H, m, 2 × CH_2), 1.26 (6H, t, *J* 7, 2 × CH_3). *m/z* ($APCI^+$) 593 ($[M + H]^{+\bullet}$).

*3-Diethylamino-5,7-dimethyl-1,1,6,8-tetraoxo-1*H*-1*λ^6*-pyrimido[5,4-e][1,4,3]oxathiazine* ***11***

A stirred mixture of 1,3-dimethylbarbituric acid **10** (1.11 g, 7.11 mmol) and the dichloro compound **1b** (2.48 g, 10.64 mmol) in DMPU (4 mL) was heated at 80°C for 23 h. The mixture was cooled and ethyl acetate (15 mL) was stirred in, followed by water (30 mL). The resulting mixture was stirred vigorously overnight. The aqueous layer was carefully removed (without removing any precipitate) and more water (10 mL) was added. The mixture was stirred vigorously for a further 1 h and suction filtered. The collected solid was washed with ethyl acetate to give the *title compound* (0.43 g, 19%). An analytical sample was recrystallized (using a little decolourizing charcoal) from methanol/dichloromethane, mp 240–241°C (dec.) (Found: C 41.9, H 5.0, N 17.9; $M^{+\bullet}$ 316.0834. $C_{11}H_{16}N_4O_5S$ requires C 41.8, H 5.1, N 17.7%; $M^{+\bullet}$ 316.0836). δ_H 3.51 (4H, q, *J* 7, 2 × NCH_2), 3.49 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 1.32 (3H, t, *J* 7, CH_3), 1.26 (3H, t, *J* 7, CH_3). δ_C ($CDCl_3$ + ~10% $[D_6]$DMSO) 155.5, 153.2, 148.4, 144.9, 94.7, 43.8, 42.4, 29.2, 27.8, 13.2, 11.6. *m/z* (EI^+) 316 (7%, $M^{+\bullet}$), 98 (64), 83 (57), 55 (100).

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