A One-Pot Synthesis of 2*H*-1,2,4-Thiadiazin-3(4*H*)-one 1,1-Dioxides and 5,6-Dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-Dioxides

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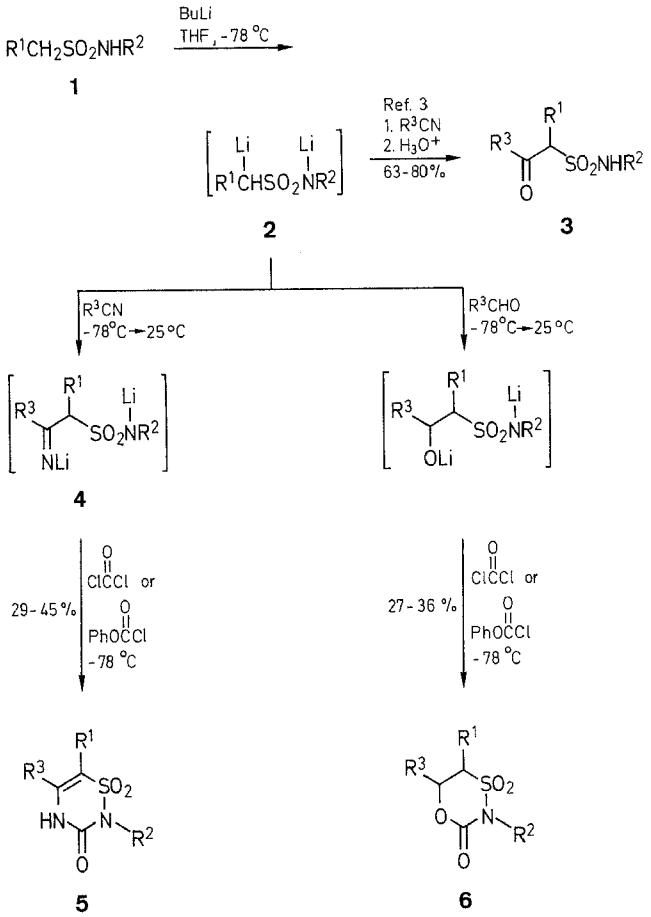
Dianions of alkanesulfonamides add to nitriles, and the resultant imine dianions are cyclized with a carbonyl equivalent to afford the known 2*H*-1,2,4-thiadiazin-3-(4*H*)-one 1,1-dioxide ring system. The use of aldehydes as electrophiles provides the novel 5,6-dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-dioxide ring system.

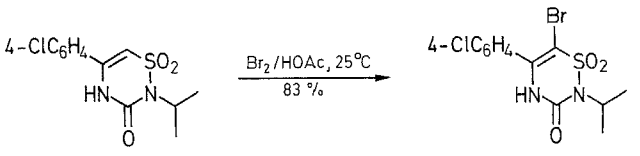
As part of an ongoing effort to identify biologically active sulfonamides, we sought entry into the relatively unexplored 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide ring system. Considerable attention has been focused on the closely related 5,6-dihydro analogs of this heterocycle and on the pharmacologically interesting 2*H*-1,2,4-benzothiadiazine 1,1-dioxides.[1] However, the only reported synthesis of 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxides, to our knowledge, involved six steps and was restricted to compounds possessing a phenyl substituent at the 4-position.[2] We have improved upon this synthesis considerably through the use of α,*N*-alkanesulfonamide dianions as described below.

Treatment of various alkanesulfonamides **1** with two equivalents of strong base generates the corresponding α,*N*-dianions **2**, which react with electrophiles chemoselectively on the carbon atom.[3] When nitriles are employed as electrophiles, aqueous acid work-up affords the β-ketosulfonamides **3** in good yield. Addition of the α,*N*-alkanesulfonamide dianion **2** to the cyano group presumably gives a new imine dianion **4** which is easily hydrolyzed to the ketone.

We have discovered that the newly-formed dianions **4** can be treated with a carbonyl equivalent, such as phosgene or phenyl chloroformate, to afford the desired 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxides **5**. The imine double bond is completely isomerized to the C5-C6 position, either during the ring closure step or upon work-up. Although the yields are moderate, the ring system is assembled in a convenient, one-pot procedure from readily available starting materials. The products are typically crystallized from the crude reaction mixtures in pure form by addition of a solvent such as ether. All examples in the Table were prepared using phosgene to effect closure of the heterocyclic ring. Phenyl chloroformate also serves as an effective carbonyl equivalent and is more easily handled; however, the yields of products are no higher and, in some cases, are even slightly lower.

Although the alkylation of dianions **2** with nitriles proceeds efficiently to afford the corresponding β-ketosulfonamides **3**, the added element of cyclization provides the heterocycles **5** in diminished yields. Undoubtedly, intermolecular cross-condensation processes compete with the desired ring closure as other components are evident in the crude reaction mixtures. However, the dianion methodology represents an improvement in overall yield of the heterocycles, and offers the convenience of a one-flask operation and simple product recovery. Furthermore, the present methodology allows for the preparation of a wider variety of substituted 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxides, which was our primary objective. Most nitriles will react with the α,*N*-alkanesulfonamide dianions. One notable exception is acetonitrile, which fails to give an appreciable amount of the desired heterocycle in which R^3 would be methyl.





A variety of alkanesulfonamides of formula **1** may be employed in the synthesis of these heterocycles, including those derived from methane-, ethane- and α-toluenesulfonyl chloride. Sulfonamides in which R^2 is *tert*-butyl are particularly useful as the products readily lose isobutylene upon being heated in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the analogs of formula **5** with both nitrogen atoms unsubstituted (R^2 = H). In fact, these heterocycles typically melt with vigorous gas evolution, which suggests that the *tert*-butyl substituent is thermally labile.

Aldehydes can be used in lieu of nitriles as electrophiles to afford the apparently novel 5,6-dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-dioxides **6**.[4] However, acceptable yields of heterocycles have so far been obtained only with aromatic aldehydes (see Table). Enolizable aldehydes give complex mixtures from which the desired products are difficult to isolate. Again, the reasons for such modest yields relative to the simple alkylation of dianion **2** with aldehydes to give β-hydroxyalkanesulfonamides are not clear. Detailed examination of the crude reaction mixtures in order to identify side products was not carried out.

The 2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide ring system offers a number of potentially reactive sites for further functionalization. Styryl sulfonamides normally undergo bromin-

Table. 2*H*-1,2,4-Thiadiazin-3(4*H*)-one 1,1-Dioxides **5** and 5,6-Dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-Dioxides **6** Prepared

Product	R^1	R^2	R^3	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	IR (KBr) ν(cm^{-1})	MS *m/z*	^{1}H-NMR δ, *J*(Hz)
5a	H	*t*-Bu	Ph	38	235–238 (dec)	$C_{13}H_{16}N_2O_3S$ (280.3)	3240, 1670, 1640	281 (M + 1)[d]	$CDCl_3$: 1.76 (s, 9H); 6.1 (d, 1H, *J* = 2); 7.4–7.6 (m, 5H); 9.1 (br s, 1H)
5b	H	*t*-Bu	*i*-Pr	40	123–125 (dec)	$C_{10}H_{18}N_2O_3S$ (246.3)	3240, 1680, 1660	247 (M + 1)[d]	$CDCl_3$: 1.23 (d, 6H, *J* = 7); 1.79 (s, 9H); 2.5 (m, 1H); 5.72 (d, 1H, *J* = 2); 9.36 (br s, 1H)
5c	H	*i*-Pr	4-ClC_6H_4	31	271–273 (dec)	$C_{12}H_{13}ClN_2O_3S$ (300.8)	3240, 1675, 1630	300 (M^+)[e]	DMSO-d_6: 1.46 (d, 6H, *J* = 7); 4.6 (m, 1H); 6.96 (s, 1H); 7.61 (AB quartet, 4H, *J* = 8); 11.05 (br s, 1H)
5d	H	*i*-Pr	*t*-Bu	45	241–243.5	$C_{10}H_{18}N_2O_3S$ (246.3)	3240, 1685, 1635	246 (M^+)[e]	DMSO-d_6: 1.15 (s, 9H); 1.42 (d, 6H, *J* = 7); 4.54 (m, 1H); 6.28 (s, 1H); 10.25 (br s, 1H)
5e	CH_3	CH_2Ph	Ph	29[f]	172.5–174	$C_{17}H_{16}N_2O_3S$ (328.4)	3310, 1720, 1710, 1655	329 (M + 1)[d]	$CDCl_3$: 2.13 (s, 3H); 4.91 (s, 2H); 7.25–7.60 (m, 10H); 8.6 (br s, 1H)
5f	Ph	*t*-Bu	Ph	40	149–150 (dec)	$C_{19}H_{20}N_2O_3S$ (356.5)	3240, 1680, 1650	356 (M^+)[e]	$CDCl_3$: 1.72 (s, 9H); 7.25–7.28 (m, 10H); 8.4 (br s, 1H)
6a	H	*t*-Bu	Ph	36	110–112 (dec)	$C_{13}H_{17}NO_4S$ (283.4)	1720, 1255	284 (M + 1)[d]	$CDCl_3$: 1.77 (s, 9H); 3.68–3.73 (m, 2H); 5.76 (dd, 1H, *J* = 6, 10); 7.4–7.54 (m, 5H)
6b	H	*c*-C_6H_{11}	2-ClC_6H_4	27[g]	111–112	$C_{15}H_{18}ClNO_4S$ (343.8)	1715, 1260	344 (M + 1)[d]	$CDCl_3$: 1.12–1.48 (m, 3H); 1.67 (br d, 1H); 1.87 (br d, 3H); 1.87 (br d, 1H); 2.18–2.42 (m, 2H); 3.51 (dd, 1H, *J* = 12, 14); 3.91 (dd, 1H, *J* = 2, 14); 4.20 (tt, 1H, *J* = 4, 12); 6.15 (dd, 1H, *J* = 2, 12); 7.28–7.35 (m, 3H); 7.65 (dd, 1H, *J* = 2, 10)

[a] Yield (unoptimized) of isolated product which proved homogeneous by TLC and ^{1}H-NMR analysis.
[b] Compounds **5a–f** are recrystallized from MeOH and compounds **6a, b** from petroleum ether (35–60 °C)/ether.
[c] Satisfactory microanalyses obtained: C ±0.31, H ±0.34, N ±0.37.
[d] Thermospray ionization.
[e] Electron impact.
[f] After purification by flash chromatography (SiO_2, 1:1 EtOAc/hexane).
[g] After purification by flash chromatography (SiO_2, 40% EtOAc/hexane).

ation at moderate rates and the reaction is reportedly catalyzed by both oxygen and sunlight.[5] In contrast, addition of bromine to a suspension of certain heterocycles of formula **5** in glacial acetic acid results in rapid bromination at the 6-position, presumably via an addition-hydrogen bromide elimination. For example, 5-(*p*-chlorophenyl)-2-isopropyl-2*H*-1,2,4-thiadiazin-3-(4*H*)-one 1,1-dioxide (**5c**) reacts rapidly and cleanly with one equivalent of bromine at room temperature to give 6-bromo-5-(*p*-chlorophenyl)-2-isopropyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide (**7**), which is isolated in 83% yield by simple filtration from the reaction solution. Further modifications of these richly-functionalized ring systems will be the subject of future work.

Reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. In general, reagent quality solvents and reagents were used without purification. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 783 grating IR spectrophotometer. ^{1}H-NMR spectra were recorded at either 200 MHz on a Varian XL-200 or at 300 MHz on a General Electric QE-300 instrument. Mass spectra were obtained on a Finnigan Model 4500 or 4600 mass spectrometer. TLC plates and silica gel (230–400 mesh) were obtained from EM Reagents.

2-*tert*-Butyl-5-phenyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-Dioxide (5a); Typical Procedure:
A solution of *N*-*tert*-butylmethanesulfonamide (**1**; R^1 = H, R^2 = *t*-Bu; 3 g, 20 mmol) in THF (65 mL) is cooled to −78 °C and treated with 1.6 M BuLi in hexane (26 mL, 42 mmol). The solution is stirred at −30 °C for about 30 min, recooled to −78 °C, and treated with benzonitrile (2.2 mL, 22 mmol). The mixture is then stirred at room temperature for 2 h, recooled to −78 °C and treated with liquid phosgene (3.0 mL, 42 mmol), added in a slow, dropwise manner. This mixture is stirred at room temperature for 12 h, cooled to 0 °C and treated with water (~ 10 mL). Removal of the volatiles *in vacuo* gives an oil, which is extracted with EtOAc (4 × 20 mL). The organic layer is dried ($MgSO_4$) and the solvent evaporated to give an orange semisolid. Addition of ether results in crystallization of the pure product, which is isolated by filtration; yield: 2.1 g (38%); mp 235–238 °C (dec) (methanol) (Table).

5-Phenyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-Dioxide (5; $R^1 = R^2 = H$, R^3 = Ph):
A suspension of 2-*tert*-butyl-5-phenyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide (**5a**; 0.50 g, 1.8 mmol) and TsOH · H_2O (1–2 mg) in toluene (8 mL) is heated to reflux temperature. After approximately 15 min, the solution clears, and then a precipitate gradually forms. The suspension is heated for an additional 45 min, cooled to room temperature, and the product is collected by filtration and dried; yield: 0.37 g (92%); mp 238–240 °C (EtOAc/hexane).

$C_9H_8N_2O_3S$	calc.	C 48.21	H 3.60	N 12.49
(224.2)	found	48.27	3.69	12.47

IR (KBr): ν = 3320, 3090, 1710, 1630, 1310, 1145 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.73 (d, 1 H, J = 2 Hz); 7.4–7.6 (m, 3 H); 7.6–7.7 (m, 2 H); 11.0 (br s, 1 H).

6-(*o*-Chlorophenyl)-3-cyclohexyl-5,6-dihydro-1,4,3-oxathiazin-2(3*H*)-one 4,4-dioxide (6a); Typical Procedure:
A solution of *N*-cyclohexylmethanesulfonamide (**1**; R^1 = H, R^2 = *c*-C_6H_{11}; 3.0 g, 17 mmol) in THF (84 mL) is cooled to −78 °C and treated with 1.6 M BuLi in hexane (22 mL, 35 mmol). The solution is stirred at −30 °C for about 30 min, recooled to −78 °C, and treated with *o*-chlorobenzaldehyde (2.1 mL, 19 mmol). The mixture is then stirred at room temperature for 4 h, recooled to −78 °C and treated with liquid phosgene (2.5 mL, 35 mmol). This mixture is stirred at room temperature for 12 h, cooled to 0 °C and treated with 5% aq. HCl (10 mL). Removal of the volatiles *in vacuo* gives an oil which is diluted with water (50 mL) and extracted with ether (3 × 20 mL) and CH_2Cl_2 (20 mL). The combined organic layer is dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil, which is purified by flash chromatography. Elution with 40% EtOAc/hexane affords the desired product; yield: 1.6 g (27%); mp 111–112 °C [petroleum ether (35–60 °C)/ether] (Table).

6-Bromo-5-(*p*-chlorophenyl)-2-isopropyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-Dioxide (7):
To a suspension of 5-(*p*-chlorophenyl)-2-isopropyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide (**5c**; 0.70 g, 2.3 mmol) in glacial AcOH (21 mL) is added bromine (0.12 mL, 2.3 mmol) in a dropwise manner. As each drop of bromine enters the solution, the red color dissipates immediately. The mixture is stirred at room temperature for 2 h, and the desired product isolated by filtration and washing with water; yield: 0.72 g (83%); mp 208–210 °C (benzene).

$C_{12}H_{12}BrClN_2O_3S$	calc.	C 37.96	H 3.18	N 7.38
(379.6)	found	37.86	3.14	7.50

IR (KBr): ν = 3220, 3120, 1690, 1620 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.46 (d, 6 H, J = 7 Hz); 4.66 (m, 1 H); 7.57 (br s, 4 H); 11.32 (br s, 1 H).

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