Ring expansion reactions of 4-amino-1,1-dioxo-[1,2,3,5]-thiatriazoles

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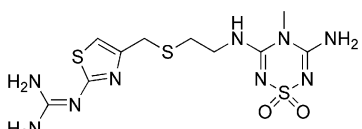
An unusual ring-expansion reaction of 4-amino-1,1-dioxo-[1,2,3,5]-thiatriazoles **4** has been identified that produces the relatively rare 5-amino-1,1-dioxo-[1,2,4,6]-thiatriazines **6** and **9**. Initial alkylation of the thiatriazole **4** with α-halo-esters at *N*-3 produces α-substituted esters which, under basic reaction conditions, undergo opening of the thiatriazole ring and re-closure to a thiatriazine ring. Similar alkylations of **4** with diethyl chloromalonate and ethyl dichloroacetate lead to the loss of SO_2 and the production of triazine **10a** and triazole **14**, apparently by an initial alkylation at *N*-5. The reaction of **4** with phenacyl bromides or a phenacyl dibromide forms fully unsaturated 5-amino-1,1-dioxo-[1,2,4,6]-thiatriazines **13**.

Introduction

Amino-substituted 1,2,4,6-thiatriazine-1,1-dioxides remain a relatively unexplored class of heterocyclic compounds. During the 1970s and 1980s, there was interest in their synthesis because of the potentially valuable biological activity of some members of this class. The 3,5-diamino derivatives in particular, were investigated for their histamine H_2 antagonism and antiulcer activity, as typified by Hoechst's HUK 978 (**1**).[1] The related 5-amino-2*H*-1,2,4,6-thiatriazin-3-ones received attention for their herbicidal activity. The dimethylamino derivative **2** can be used to control mildew and rust, and exhibits herbicidal action.[2] The key step in the syntheses of these compounds involves ring closure by intramolecular attack of a sulfamide onto a cyanamide[3] or carbamate.[2]



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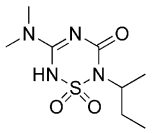
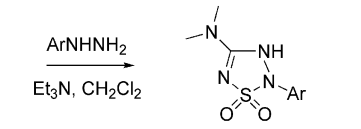


2

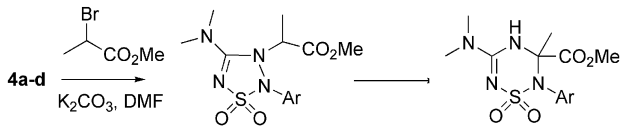
As part of a programme aimed at the discovery of novel, low molecular weight, heterocyclic compounds with potential biological activity, we have been investigating the use of *N*,*N*-dialkyl-(*N*′-chlorosulfonyl)chloroformamidines, such as **3** (Scheme 1), as versatile intermediates for the preparation of a diverse range of sulfur-containing heterocycles.[4,5] This has included a study of the synthesis and properties of 4-dialkylamino-1,2,3,5-thiatriazole 1,1-dioxides, such as **4**,[4] readily prepared by reaction between dichloride **3** and hydrazines. In the course of these investigations, we treated the thiatriazole **4b** with methyl 2-bromopropanoate in the presence of K_2CO_3, expecting to form the simple *N*-alkylated product **5b** (Scheme 2). Surprisingly, the major product from this reaction was not **5b**, but a ring-expanded compound. X-Ray analysis confirmed that the product was a derivative of the relatively rare 5-amino-1,2,4,6-thiatriazine 1,1-dioxide system, **6b**.[6] Herein we describe the results of an investigation of the scope of this reaction, and show that variation of the electrophile can result in additional reactions involving unsaturation or the loss of SO_2.



3

4a Ar = Ph
4b Ar = 3,5-di-Cl-Ph
4c Ar = 2,6-di-Cl-Ph
4d Ar = 4-CF_3-Ph

Scheme 1



a Ar = Ph, **b** Ar = 3,5-di-Cl-Ph, **c** Ar = 2,6-di-Cl-Ph, **d** Ar = 4-CF_3-Ph

Scheme 2

Results and discussion

Having established the identity of the unexpected ring-expanded product to be **6b**, the effect of changing the substitution on the phenyl substituent of **4** was investigated. The reactions of three more thiatriazoles **4a**, **4c** and **4d** with methyl 2-bromopropanoate were studied and the results are shown in Table 1. It was found that in these cases, if the reaction was performed at room temperature (20 °C), significant quantities of simple *N*-alkylated products **5a**, **5c** and **5d** were isolated, with **5a** being the exclusive product formed from **4a**. No *N*-alkylated products were isolated if these reactions were warmed to 50 °C; the major products in all three cases being the ring-expanded compounds **6a**, **6c** and **6d**.

This ring-expansion appears to be related to a reaction identified by Bartholomew and Kay in 1977 (Scheme 3).[7] Examination of

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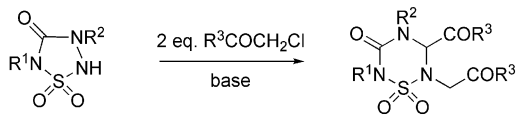
Table 1 Preparation of 5-dimethylamino-1,1-dioxo-1,2,4,6-thiatriazines

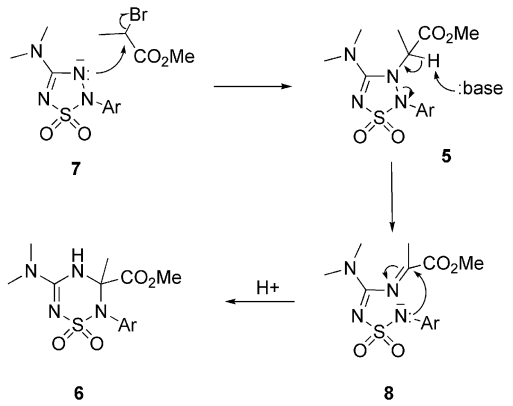
Product	Ar	Temperature/°C	Yield[a] (%)
6a	Ph	50 [b]	37
6b	3,5-Di-Cl–Ph	20	20
6c	2,6-Di-Cl–Ph	50 [c]	31
6d	4-CF_3–Ph	50 [c]	37

[a] Isolated yields after purification by crystallization or trituration. [b] No ring expansion at room temperature. [c] Mixture of *N*-alkylated and ring-expanded products at room temperature.



Scheme 3

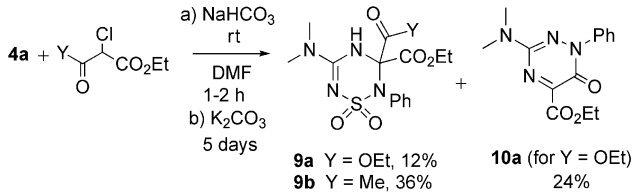
the mechanism suggested by these workers for their reaction, and the apparent promotion of the current reaction by electron withdrawing groups present on the aromatic ring of **4**, lead us to propose the mechanism shown in Scheme 4. According to this mechanism, the reaction begins by the removal of the proton on the ring nitrogen in **4**. This proton is known to be quite acidic, as demonstrated by the solubility of **4a** in aqueous $NaHCO_3$. Displacement of the bromide from methyl 2-bromopropanoate by anion **7** gives the *N*-alkylated product **5**, which ring-opens in the presence of base to give the sulfonamide anion **8**. Ring closure at the imine-type carbon, followed by protonation gives the ring expanded product **6**. Support for this proposed mechanism was found when the *N*-alkylated product **5a**, which had been isolated from the room temperature treatment of **4a** with methyl 2-bromopropanoate, was exposed to the same conditions that were used to prepare **6a** from **4a**. The result was the isolation of **6a** as the sole product in 82% yield.



Scheme 4

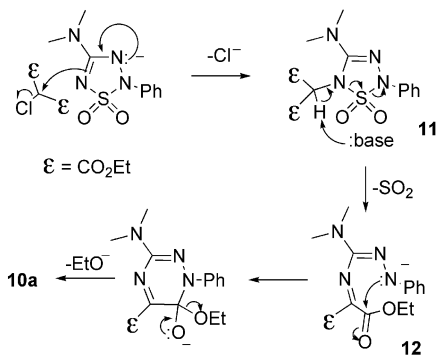
Electron withdrawing chlorine or trifluoromethyl substituents in **4b–d** presumably facilitate the ring-opening of **5** to form the intermediate **8**, leading to the moderate to exclusive production of the ring expanded products **6b–d** at room temperature, something that was not observed with **4a**. Interestingly, when the more strongly electron withdrawing 4-nitro substituent was present in the starting material **4** (Ar = 4-NO_2–Ph), the result was a complex mixture. It is likely that the nitro group increases the lifetime of the acyclic intermediate **8** (Ar = 4-NO_2–Ph) such that multiple reaction pathways then become accessible.

To further investigate the scope of this unusual ring-expansion reaction, **4a** was treated with a number of other electrophiles. Several of these, such as 3-chloropentan-2,4-dione, produced complex mixtures, but two in particular, diethyl chloromalonate and ethyl 2-chloroacetoacetate, produced identifiable products when mild reaction conditions were used (Scheme 5).



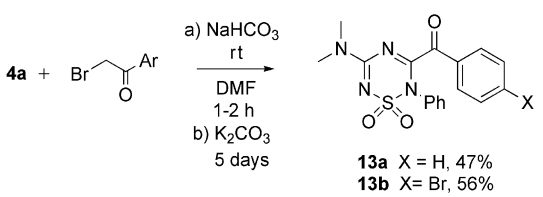
Scheme 5

Compounds **9a** and **9b** appear to result from ring expansion reactions analogous to those that produce **6a–d**, but in the case of the chloromalonate reaction, a second product was obtained. Analytical data for this compound were consistent with it being the triazine **10a**, and its strong yellow colour was reminiscent of related ring systems.[8,9] The formation of **10a** involves the expulsion of SO_2, and a suggested mechanism for this process is shown in Scheme 6. A distinguishing feature of this mechanism is the initial alkylation of *N*-5 rather than *N*-3 to give **11**. The action of base on this intermediate would lead to ring-opening and expulsion of SO_2, to give the highly delocalised anion **12**. Ring closure by attack on an ester functionality would lead to the observed triazinone **10a**.



Scheme 6

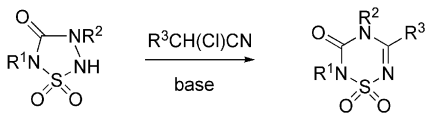
The thiatriazole **4a** was then treated with a third class of electrophile, the phenacyl bromides, which led to ring expanded products in moderate yields (Scheme 7). The analytical data for the products of these reactions were consistent with their assignment as **13a** and **13b**. It appears that the added conjugation possible



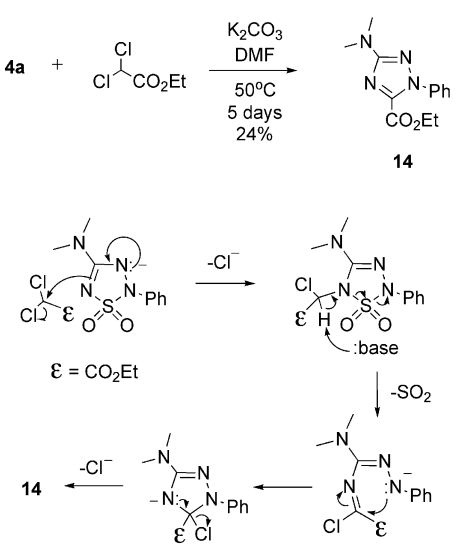
Scheme 7

with the attached phenacyl groups has promoted aerial oxidation of the intermediate ring-expansion products to give the highly conjugated compounds **13a** and **13b**. The structural assignment of **13b** was confirmed by X-ray analysis.[10]

Bartholomew and Kay also identified a related ring-expansion reaction in which the electrophile possessed two leaving groups so that, after alkylation and ring-expansion, elimination occurred, leading to an unsaturated product (Scheme 8).[7] It was of interest to learn if a similar process would occur in the current system, thus **4a** was treated with ethyl dichloroacetate and K_2CO_3 under the conditions described earlier. This reaction gave a major product that, surprisingly, did not contain sulfur and was shown to be the triazole **14** (Scheme 9). A mechanism that accounts for the formation of **14** is shown in Scheme 9, and is related to that proposed for the formation of **10a**, involving initial alkylation of *N*-5 and ring closure at the imine-type carbon rather than the carbonyl carbon of the ester moiety.

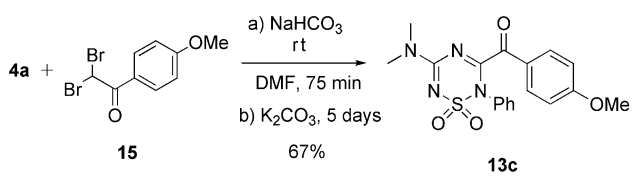


Scheme 8



Scheme 9

In contrast to the result obtained with ethyl dichloroacetate, when a dihalide lacking an ester functionality, the phenacyl dibromide **15**, was allowed to react with **4a**, the anticipated unsaturated ring-expansion product **13c** was produced in good yield (Scheme 10).



Scheme 10

Experiments were also performed with **4a** and other electrophiles, including 2-chloroamides and 2-chlorosulfonamides, and bromomethyl phenylsulfone, but none of these reactions produced significant quantities of *N*-alkylated or ring-expanded products. The electrophiles used in these reactions do not appear to be sufficiently activated to participate in reactions with anion **7** under the conditions employed, and were generally recovered from the reaction mixtures unchanged.

Experimental

General experimental methods

The general methods used in this study were the same as those previously reported.[4] ^{1}H NMR spectra were recorded at 298 K unless otherwise stated. Electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were recorded on a Fisons Instruments VG Platform quadrupole mass spectrometer using positive (+) and negative (−) ion modes with a cone voltage of 50 eV, and acetonitrile as the solvent, unless otherwise stated. The preparation of **4c** has been described previously.[4]

Preparation of triazoles

(1,1-Dioxo-2-phenyl-2,3-dihydro-1*H*-1λ^6-[1,2,3,5]thiatriazol-4-yl)dimethylamine (4a). Phenylhydrazine (9.0 g, 83 mmol) in CH_2Cl_2 (8 cm^3) was added over 20 min to the dichloride **3**[11,12] (17.0 g, 83 mmol) in CH_2Cl_2 (85 cm^3) at 5 °C. After 25 min, triethylamine (24 cm^3, 174 mmol) was added over 80 min at 5 °C. After 4 days at rt the reaction mixture was poured into ice-cold HCl (2 M, 100 cm^3) and enough diethyl ether was added to float the organic phase. The whole was filtered and the residue was washed with water, HCl (0.1 M) and water. The solid was added to aqueous Na_2CO_3 (1 M, 150 cm^3) and stirred until the majority had dissolved. The resulting brown solution was washed with CH_2Cl_2 (2 × 30 cm^3) and the aqueous phase was cooled in ice and acidified with conc. HCl. The mixture was filtered and the residue washed thoroughly with water and dried to give the title compound as a white solid (5.50 g, 28%). Mp 106–107 °C (dec.); found: C, 45.1; H, 5.15; N, 23.4; S, 13.6. Calc. for $C_9H_{12}N_4O_2S$: C, 45.0; H, 5.0; N, 23.3; S, 13.3%); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 3.04 (6H, s, 2 × CH_3), 7.16–7.22 (3H, m, ArH), 7.36 (2H, m, ArH), 10.53 (1H, br s, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 37.6 (br s), 120.2, 125.9, 129.3, 142.6, 160.2; *m*/*z* (ESI+) 263.1 (M + Na)$^+$, 279.0 (M + K)$^+$.

[2-(3,5-Dichlorophenyl)-1,1-dioxo-2,3-dihydro-1*H*-1λ^6-[1,2,3,5]-thiatriazol-4-yl]dimethylamine (4b). The dichloride **3** (0.5 g, 3 mmol) was added to a stirred suspension of 3,5-dichlorophenylhydrazine hydrochloride (0.42 g, 2 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C followed by triethylamine (0.6 g, 6 mmol) added dropwise. After 48 h at rt the solution was stirred into aqueous citric acid (50 cm^3, 10%) , the organic phase was separated and the solvent removed under reduced pressure. The residue was stirred with a mixture of diethyl ether (50 cm^3) and aqueous NaOH (20 cm^3, 5%), the aqueous phase was removed, extracted with a fresh portion of diethyl ether and acidified by addition of an excess of conc. HCl. After 3 h the precipitate was collected by filtration to give the product as a cream powder (0.28 g, 45%). A sample

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was recrystallized from ethyl acetate to give a white powder. Mp 118–120 °C (dec.); found: C, 35.1; H, 3.3; N, 18.1; S, 10.4. Calc. for $C_9H_{10}Cl_2N_4O_2S$: C, 35.0; H, 3.3; N, 18.1; S, 10.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 3.05 (6H, s, 2 × CH_3–N), 7.25 (2H, d, J 2.0 Hz, ArH), 7.41 (1H, t, J 2.0 Hz, ArH), 10.66 (1H, br s, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 37.7, 118.3, 125.2, 134.8, 145.0, 159.8; m/z (ESI−, MeOH) 307.1 $(M-H)^-$.

(1,1-Dioxo-2-(4-trifluoromethylphenyl)-2,3-dihydro-1*H*-1λ⁶-[1,2,3,5]thiatriazol-4-yl)dimethylamine (4d). 4-Trifluoromethylphenylhydrazine (0.88 g, 5 mmol) was stirred into a solution of the dichloride **3** (1.02 g, 6 mmol) in DMF (2.5 cm^3). After 30 min *N*,*N*-diisopropylethylamine (1.55 g, 12 mmol) was added dropwise over 5 min, the mixture was stirred overnight and poured into a mixture of HCl (20 cm^3, 2 M) and diethyl ether–cyclohexane (1 : 1, 10 cm^3). After 1 h the mixture was filtered and the solid washed with water and then diethyl ether–cyclohexane (1 : 1) to give the product (0.53 g, 35%) as a colourless powder. Mp 121–124 °C; found: C, 39.05; H, 3.7; N, 18.2; S, 10.4. Calc. for $C_{10}H_{11}F_3N_4O_2S$: C, 39.0; H, 3.6; N, 18.2; S, 10.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.17 (6H, s, 2 × CH_3–N), 7.33 (2H, d, J 8.4 Hz, ArH), 7.37 (1H, br s, NH), 7.59 (2H, d, J 8.4 Hz, ArH); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ_C 37.2 (br s), 119.1, 124.2 (q, $^1J_{CF}$ = 272 Hz), 125.2 (q, $^2J_{CF}$ = 33 Hz), 126.1 (d, $^3J_{CF}$ = 3 Hz), 145.4, 159.3; ^{19}F NMR (376.5 MHz, DMSO-d_6–$CFCl_3$) δ_F −61.0; m/z (ESI−) 307.1 $(M-H)^-$, 615.0 $(2M-H)^-$, 923.0 $(3M-H)^-$.

Reactions of triazoles

Representative procedures for the reactions of the 4-amino-[1,2,3,5]-thiatriazole dioxides with organohalides.

Method A. To a solution of the 4-amino-[1,2,3,5]-thiatriazole dioxide (**4**) in DMF (0.3 M solution) was added K_2CO_3 (2 eq.) and the halide (2 eq.) and the resulting mixture stirred for 5 days at either rt or 50 °C. Water (5 × vol. of DMF) and diethyl ether (2.5 × vol. of DMF) were added with stirring and the mixture left to stand for several hours. Where the product crystallized at the interface between the aqueous and organic layers, the whole was filtered, the crystals were washed with diethyl ether and dried. In all other cases the layers were separated, the aqueous layer was extracted with $CHCl_3$ (3×), the combined organic layers washed with water and dried ($MgSO_4$), filtered and concentrated to yield the crude product as an oil.

Method B. To a solution of the 4-amino-[1,2,3,5]-thiatriazole dioxide (**4**) in DMF (0.3 M solution) was added $NaHCO_3$ (1.2 eq.) and the mixture was left to stir for 5–10 min. The halide (1.2 eq.) was added and the resulting mixture was stirred at rt for 1–2 h. K_2CO_3 (1.2 eq.) was then added and the mixture stirred for a further 5 days. The workup was the same as in method A.

Methyl 2-(4-dimethylamino-1,1-dioxo-2-phenyl-1,2-dihydro-1λ⁶-[1,2,3,5]thiatriazol-3-yl)propanoate (5a). The title compound was prepared from the *N*-phenylthiatriazole dioxide **4a** and methyl 2-bromopropanoate at rt according to method A with the extractive workup and the reaction time reduced to 70 min. Yield 111 mg (41%). A sample was recrystallized from chloroform–diethyl ether (10 : 1) then precipitated from DMSO with water to afford a white solid. Mp 126–128 °C; found: C, 47.85; H, 5.7; N, 17.0, S, 9.6. Calc. for $C_{13}H_{18}N_4O_4S$: C, 47.8; H, 5.6; N, 17.2, S, 9.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.44 (3H, br s, CH_3–CH), 3.20 (6H, s, 2 × CH_3–N), 3.59 (3H, br s, CH_3–O), 4.31 (1H, q, J 6.95 Hz, CH–CH_3), 7.20–7.36 (5H, m, ArH); ^{1}H NMR (500 MHz, 368 K, DMSO-d_6) δ_H 1.30 (3H, d, J 6.9 Hz, CH_3–CH), 3.17 (6H, s, 2 × CH_3–N), 3.48 (3H, s, CH_3–O), 4.64 (1H, q, J 6.9 Hz, CH–CH_3), 7.17 (2H, d, J 7.3 Hz, ArH),7.23 (1H, t, J 6.9 Hz, ArH), 7.37 (2H, t, d, J 8.3 Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 13.3, 39.1 (br s), 51.2, 60.4, 121.3, 125,8, 128.1, 142.1, 164.6, 168.2; m/z (ESI+, MeOH–CH_3CN–H_2O, 2 : 1 : 1, ramped cone voltage) 327.0 $(M+H)^+$, 653.0 $(2M+H)^+$.

Methyl 5-dimethylamino-3-methyl-1,1-dioxo-2-phenyl-1,2,3,4-tetrahydro-1λ⁶-[1,2,4,6]thiatriazine-3-carboxylate (6a). The title compound was prepared from the *N*-phenylthiatriazole dioxide (**4a**) and methyl 2-bromopropanoate at 50 °C according to method A—the product crystallized during work up. Yield (100 mg, 37%) mp 197–199 °C; found: C, 47.9; H, 5.6; N, 17.2, S, 9.8. Calc. for $C_{13}H_{18}N_4O_4S$: C, 47.8; H, 5.6; N, 17.2, S, 9.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (3H, s, CH_3), 3.06 (6H, s, 2 × CH_3–N), 3.81 (3H, s, CH_3–O), 5.82 (1H, br s, NH), 7.35 (5H, s, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.6, 37.1, 53.46, 53.50, 128.5, 128.9, 130.8, 137.2, 153.9, 171.5. m/z (ESI−) 325.3 $(M-H)^-$, 651.1 $(2M-H)^-$, 977.2 $(3M-H)^-$.

Methyl 2-(3,5-dichlorophenyl)-5-dimethylamino-3-methyl-1,1-dioxo-1,2,3,4-tetrahydro-1λ⁶-[1,2,4,6]thiatriazine-3-carboxylate (6b). The title compound was prepared from the *N*-(3,5-dichlorophenyl)thiatriazole dioxide (**4b**) and methyl 2-bromopropanoate at rt according to method A—the product crystallized during work up (51 mg, 20%). A sample was recrystallized by slow evaporation from ethanol–water (6 : 1) to give thick, colourless needles. Mp 213–215 °C (dec.); found: C, 39.5; H, 4.3; N, 14.2, S, 7.9. Calc. for $C_{13}H_{16}Cl_2N_4O_4S$: C, 39.5; H, 4.1; N, 14.2, S, 8.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.50 (3H, s, CH_3), 3.12 (6H, s, 2 × CH_3–N), 3.85 (3H, s, CH_3–O), 5.56 (1H, br s, NH), 7.31 (2H, s, ArH), 7.38 (1H, s, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.9, 37.1, 53.9, 74.7, 129.2, 129.6, 135.0, 139.0, 153.7, 171.3; m/z (APCI−, MeOH–CH_3CN–H_2O, 2 : 1 : 1) 393.1 $(M-H)^-$.

Methyl 2-(2,6-dichlorophenyl)-5-dimethylamino-3-methyl-1,1-dioxo-1,2,3,4-tetrahydro-1λ⁶-[1,2,4,6]thiatriazine-3-carboxylate (6c). The title compound was prepared from the *N*-(2,6-dichlorophenyl)thiatriazole dioxide (**4c**) and methyl 2-bromopropanoate at 50 °C according to method A with the extractive work up. The product was recrystallized from chloroform to yield a white powder (79 mg, 31%). Mp 227–230 °C (dec.); found: C, 39.6; H, 4.2; N, 14.5, S, 8.1. Calc. for $C_{13}H_{16}Cl_2N_4O_4S$: C, 39.5; H, 4.1; N, 14.2, S, 8.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.69 (3H, s, CH_3), 3.08 (6H, s, 2 × CH_3–N), 3.75 (3H, s, CH_3–O), 5.62 (1H, br s, NH), 7.19 (1H, t, J 8.05 Hz, ArH), 7.36 (1H, d, J 8.05 Hz, ArH), 7.40 (1H, d, J 8.05 Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 22.7, 37.3, 53.3, 73.9, 129.7, 129.8, 131.1, 133.7, 137.5, 140.2, 154.1, 170.7; m/z (ESI−, MeOH) 395.1 $(M-H)^-$, 788.9 $(2M-H)^-$.

Methyl 5-dimethylamino-3-methyl-1,1-dioxo-2-(4-trifluoromethylphenyl)-1,2,3,4-tetrahydro-1λ⁶-[1,2,4,6]thiatriazine-3-carboxylate (6d). The title compound was prepared from the *N*-(4-trifluoromethylphenyl)thiatriazole dioxide (**4d**) and methyl 2-bromopropanoate at 50 °C according to method A with the extractive work up. Trituration of the product with diethyl ether gave a beige powder (46 mg, 37%). A sample was recrystallized

from chloroform to give colourless crystals. Mp 182–184 °C; found: C, 42.5; H, 4.4; N, 14.1, S, 7.9. Calc. for $C_{14}H_{17}F_3N_4O_4S$: C, 42.6; H, 4.3; N, 14.2, S, 8.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40 (3H, s, CH_3), 3.04 (6H, s, 2 × CH_3–N), 3.80 (3H, s, CH_3–O), 6.11 (1H, br s, NH), 7.49 (2H, d, *J* 8.05 Hz, ArH), 7.61 (2H, d, *J* 8.05 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 24.8, 37.1, 53.7, 74.8, 123.6 (q, $^1J_{CF} = 272$ Hz), 126.1 (q, $^3J_{CF} = 4$ Hz), 130.6 (d, $^2J_{CF} = 33$ Hz), 131.3, 140.6, 153.9, 171.2; ^{19}F NMR (376.5 MHz, $CDCl_3$–$CFCl_3$) δ_F −63.2; *m*/*z* (ESI−, MeOH) 393.1 (M − H)$^-$, 787.0 (2M − H)$^-$.

Treatment of *N*-phenylthiatriazole dioxide (4a) with diethyl chloromalonate. The *N*-phenylthiatriazole dioxide (**4a**) was treated with diethyl chloromalonate according to method B with the extractive work up. The crude product was crystallized from chloroform to yield the triazine (**10a**) as a yellow solid. The concentrated mother liquors were purified by radial chromatography using a hexane–ethyl acetate solvent gradient to yield more of the triazine (combined yield 100 mg, 24%) and the thiatriazine (**9a**) as a brown oil (71 mg, 12%).

Ethyl 3-dimethylamino-6-oxo-1-phenyl-1,6-dihydro-[1,2,4]triazine-5-carboxylate (10a). A sample of the above mentioned yellow solid was recrystallized from CH_2Cl_2–hexane to give the title compound as yellow crystals. Mp 207–209 °C; found: C, 58.4; H, 5.6; N, 19.5. Calc. for $C_{14}H_{16}N_4O_3$: C, 58.3; H, 5.6; N, 19.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.00 (3H, t, *J* 6.8 Hz, C*H*$_3$–CH_2), 3.15 (6H, br s, 2 × CH_3–N), 4.15 (2H, q, *J* 6.9 Hz, C*H*$_2$–CH_3), 7.54 (4H, m, ArH), 7.57–7.63 (1H, m, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.5, 36.9, 63.0, 123.7, 123.9, 129.6, 129.7, 131.6, 132.7, 142.8, 160.6, 162.6, 162.7; *m*/*z* (ESI+) 289.0 (M + H)$^+$, 311.1 (M + Na)$^+$, 599.0 (2M + Na)$^+$.

Diethyl 5-dimethylamino-1,1-dioxo-2-phenyl-1,4-dihydro-2*H*-1λ^6-[1,2,4,6]thiatriazine-3,3-dicarboxylate (9a). A sample of the above mentioned brown oil was crystallized from ethyl acetate–hexane to give the title compound as a pale purple solid. Mp 130–132 °C; found: C, 48.4; H, 5.7; N, 14.1, S, 7.9. Calc. for $C_{16}H_{22}N_4O_6S$: C, 48.2; H, 5.6; N, 14.1, S, 8.05%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.07 (6H, t, *J* 7.0 Hz, 2 × CH_3), 3.16 (6H, s, 2 × CH_3–N), 4.14 (4H, q, *J* 7.0 Hz, 2 × CH_2–O), 6.50 (1H, br s, NH), 7.27–7.33 (5H, m, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 13.4, 36.8, 64.2, 79.9, 128.16, 128.18, 128.9, 140.1, 152.9, 165.1; *m*/*z* (ESI+, MeOH) 399.1 (M + H)$^+$, 421.0 (M + Na)$^+$, 819.1 (2M + Na)$^+$.

Ethyl 3-acetyl-5-dimethylamino-1,1-dioxo-2-phenyl-1,2,3,4-tetrahydro-1λ^6-[1,2,4,6]thiatriazine-3-carboxylate (9b). The title compound was prepared from the *N*-phenylthiatriazole dioxide (**4a**) and ethyl 3-chloroacetoacetate according to method B and the extractive work up. The crude product was purified by radial chromatography using a hexane–ethyl acetate solvent gradient to give the ring-expanded compound in a partially crystalline state (165 mg, 36%). A sample was recrystallized from ethyl acetate–hexane to give a white solid. Mp 143–145 °C; found: C, 49.0; H, 5.6; N, 15.25, S, 8.7. Calc. for $C_{15}H_{20}N_4O_5S$: C, 48.9; H, 5.5; N, 15.2, S, 8.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (3H, t, *J* 7.3 Hz, CH_3), 2.33 (3H, s, CH_3CO), 3.26 (3H, s, CH_3–N), 3.28 (3H, s, CH_3–N), 4.19 (1H, q, *J* 7.0 Hz, 0.5 × CH_2–O), 4.26 (1H, q, *J* 7.3 Hz, 0.5 × CH_2–O), 6.51 (1H, br s, NH), 7.31–7.54 (5H, m, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.9, 22.0, 38.2, 39.6, 63.0, 70.8, 127.2, 128.0, 128.4, 129.0, 129.5, 138.5, 156.6, 167.0, 168.5; *m*/*z* (ESI+) 369.1 (M + H)$^+$, 391.0 (M + Na)$^+$, 759.1 (2M + Na)$^+$.

(5-Dimethylamino-1,1-dioxo-2-phenyl-1,2-dihydro-1λ^6-[1,2,4,6]-thiatriazin-3-yl)phenylmethanone (13a). The title compound was prepared from the *N*-phenylthiatriazole dioxide (**4a**) and phenacyl bromide according to method B—the product crystallized as a cream coloured solid during work up. Yield (67 mg, 47%). Mp 211–213 °C; found: C, 57.4; H, 4.6; N, 15.7; S, 8.9. Calc. for $C_{17}H_{16}N_4O_3S$: C, 57.3; H, 4.5; N, 15.7; S, 9.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.24 (3H, s, CH_3–N), 3.25 (3H, s, CH_3–N), 7.25–7.37 (5H, m, ArH), 7.45 (2H, t, *J* 7.6 Hz, ArH), 7.62 (1H, t, *J* 7.7 Hz, ArH); 7.83 (2H, d, *J* 8.0 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 37.5, 37.7, 129.0, 129.39, 129.44, 129.6, 130.2, 132.3, 133.0, 135.2, 157.5, 159.4, 185.3; *m*/*z* (ESI+, MeOH) 357.1 (M + H)$^+$, 379.0 (M + Na)$^+$, 713.0 (2M + H)$^+$, 735.1 (2M + Na)$^+$.

(4-Bromophenyl)-(5-dimethylamino-1,1-dioxo-2-phenyl-1,2-dihydro-1λ^6-[1,2,4,6]thiatriazin-3-yl)methanone (13b). The title compound was prepared as an orange foam from the *N*-phenylthiatriazole dioxide (**4a**) and 4-bromophenacyl bromide according to method B using the extractive work up. Yield (102 mg, 56%). A sample was further purified by radial chromatography using a hexane–ethyl acetate solvent gradient then recrystallized from CH_2Cl_2–ethyl acetate to yield the title compound as a white solid. Mp 154–156 °C; found: C, 47.2; H, 3.5; N, 12.9; S, 7.1. Calc. for $C_{17}H_{15}BrN_4O_3S$: C, 46.9; H, 3.5; N, 12.9; S, 7.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.23 (3H, s, CH_3–N), 3.24 (3H, s, CH_3–N), 7.27–7.36 (5H, m, ArH), 7.60 (2H, d, *J* 8.8 Hz, ArH), 7.70 (2H, d, *J* 8.8 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 37.5, 37.7, 129.2, 129.6, 130.3, 130.9, 131.0, 131.8, 132.2, 132.4, 157.3, 158.8, 184.3; *m*/*z* (APCI+, MeOH–CH_3CN–H_2O, 2 : 1 : 1, ramped cone voltage) 436.9 (M + H (^{81}Br))$^+$, 434.9 (M + H (^{79}Br))$^+$, 373.0 (M + H − SO_2(^{81}Br))$^+$, 371.0 (M + H − SO_2(^{79}Br))$^+$, 355.0 (M − Br)$^+$.

(5-Dimethylamino-1,1-dioxo-2-phenyl-1,2-dihydro-1λ^6-[1,2,4,6]-thiatriazin-3-yl)(4-methoxyphenyl)methanone (13c). The title compound was prepared from the *N*-phenylthiatriazole dioxide (**4a**) and 4-methoxyphenacyl dibromide (**15**)[13] according to method B—the product crystallized as a pastel-orange coloured solid during work up. Yield (130 mg, 81%). A sample was further purified with radial chromatography using a hexane–ethyl acetate solvent gradient then recrystallized from CH_2Cl_2–ethyl acetate to yield the title compound as a white solid. Mp 180–182 °C; found: C, 55.9; H, 4.9; N, 14.3; S, 8.1. Calc. for $C_{18}H_{18}N_4O_4S$: C, 55.95; H, 4.7; N, 14.5; S, 8.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.23 (3H, s, CH_3–N), 3.24 (3H, s, CH_3–N), 3.88 (3H, s, CH_3–O), 6.91 (2H, d, *J* 8.8 Hz, ArH), 7.28–7.34 (3H, m, ArH), 7.37 (2H, d, *J* 8.8, ArH), 7.81 (2H, d, *J* 8.8 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 37.5, 37.6, 55.7, 114.3, 126.0, 129.4, 130.1, 132.3, 132.4, 157.6, 159.8, 165.2, 183.8; *m*/*z* (ESI+, MeOH) 387.1, (M + H)$^+$, 409.1 (M + Na)$^+$, 394.9 (2M + Na)$^+$.

Ethyl 5-dimethylamino-2-phenyl-2*H*-[1,2,4]triazole-3-carboxylate (14). The title compound was prepared from the *N*-phenylthiatriazole dioxide (**4a**) and ethyl dichloroacetate at 50 °C

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according to method A. The product partially crystallized during work up and the remainder was recovered using the extractive procedure. Yield (68 mg, 24%). A sample was further purified by radial chromatography using a hexane–ethyl acetate solvent gradient then recrystallized from CH_2Cl_2–hexane to yield the title compound as a white solid. Mp 111–113 °C; found: C, 60.0; H, 6.4; N, 21.6. Calc. for $C_{13}H_{16}N_4O_2$: C, 60.0; H, 6.2; N, 21.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, t, *J* 7.2 Hz, CH_3), 3.08 (6H, s, 2 × CH_3–N), 4.32 (2H, q, *J* 7.2 Hz, CH_2), 7.41–7.49 (5H, m, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 13.9, 38.5, 62.3, 125.8, 128.8, 129.1, 138.3, 143.4, 157.6, 165.8; *m/z* (ESI+, MeOH) *m/z* 261.2 $(M + H)^+$, 283.1 $(M + Na)^+$.

Conclusions

Described herein is an unusual ring-expansion reaction resulting from the treatment of 1,1-dioxo-1,2,3,5-thiatriazoles with α-halo esters. The reaction allows the production of a range of relatively rare 5-dialkylamino-1,1-dioxo-1,2,4,6-thiatriazines,[14] in three simple steps from commercially available starting materials. The by-products generally partition into the aqueous phase on work-up, thus readily providing the ring-expanded products in high purity. When the 1,1-dioxo-1,2,3,5-thiatriazole **4a** is treated with phenacyl bromides or a phenacyl dibromide, fully unsaturated 1,1-dioxo-1,2,4,6-thiatriazines are produced in good yield and high purity.

The reactions that produce the 1,1-dioxo-1,2,4,6-thiatriazines involve initial alkylation at *N*-3 of the starting thiatriazole, but apparently initial alkylation at *N*-5 can also occur, leading to loss of SO_2 and formation of triazoles or triazines.

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