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New methods for the selective alkylation of 3-thioxo-1,2,4-triazin-5-ones

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ABSTRACT

A method for regioselective alkylation of the 3-thiono-1,2,4-triazinone **10** at the sulfur atom is reported. Subsequent Claisen rearrangements, triggered either thermally or using a palladium catalyst, deliver *N*-alkylated products **13**, while acid-catalysed rearrangements of examples where a tertiary carbenium ion can be generated, result in the formation of *N*-thioalkyl derivatives.

The 1,2,4-triazine nucleus is well represented in the pharmaceutical sector, in particular as a core component of a diversity of modern drugs, in both its aromatic form **1** along with many, variously oxidised derivatives. Illustrative of this is the structure of 6-azauracil **2**, which exhibits growth inhibition in many organisms as well as anti-viral activity;[1] in addition, the 1,2,4-triazine nucleus forms a crucial part of many herbicides and insecticides (Fig. 1).[2]

The impact of such triazine derivatives (e.g., **3**) has also been significant in the anti-cancer area,[3,4] in kinase inhibition,[5–8] antiproliferation,[9] and anti-inflammation,[10] including COX-2 inhibitory properties comparable to the well established drug celecoxib[11] and non-dopaminergenic therapy for Parkinson's disease.[12,13] The parent triazine nucleus is also at the core of a series of platinum(II) complexes having antimicrobial and antiviral properties,[14] while some benzotriazines are active against age-related macular degeneration[15] and compounds based on a pyrimidotriazine unit are capable of lowering plasma glucose levels.[16]

The high nitrogen content of 1,2,4-triazines, along with the incorporation of other substituents, leads to compounds which should be able to readily form many hydrogen bonds, suggesting a considerable potential for drug development in this area. With this in mind, we embarked upon a project to discover new ways in which the amino-triazin-dione nucleus **4** (Fig. 2) could be homologated using efficient and versatile methodology. The perceived advantages of using this type of starting material were the ease of synthesis[17] and the incorporation of a pendant amino group as an additional hydrogen-bonding centre. On the other hand, distinguishing between the multiple nucleophilic centres was clearly going to present something of a challenge.

In general, most synthetic approaches to 1,2,4-triazines rely on imine/enamine formation between a carbonyl and amino group; in the present case, suitable precursors **4** are derived from an α-keto-acid **5** and thiocarbonylhydrazide **6** (Fig. 2). Additional simplicity is added by formation of the former keto-acid from *N*-benzoyl glycine **7** (hippuric acid) by sequential dehydrative cyclisation and condensation with benzaldehyde to give the readily isolated azlactone **8**. This is then hydrolysed to give the keto-acid salt **9**, which is condensed in situ with the hydrazide **6**. Again, work-up is simple and the overall yield acceptable, despite the number of individual steps involved (Scheme 1).

The present studies began with attempts to selectively alkylate the triazinone **10** using allylic halides, so that an additional functional group would be introduced. Initial attempts using acetonitrile as the solvent, potassium carbonate as the base and methallyl chloride as the alkylating agent gave mixtures (ca. 3:1) of the *S*- and *N*-alkyl derivatives **11** and **12** (Scheme 2).

The separable products **11** and **12** were readily distinguished by their NMR data: the *S*-alkylated products such as **11** showed *S*-methylene resonances in the range δ_H 3.75–4.10 and δ_C 29–36 ppm whereas in the corresponding *N*-alkylated products,

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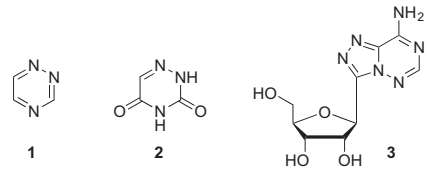


Figure 1. The 1,2,4-triazine nucleus and modifications.

including **12**, such resonances occurred in the ranges δ_H 5.0–6.2 and δ_C 60–69 ppm, respectively.

Fortunately, a brief solvent study established that substituting 1:1 aqueous ethanol for acetonitrile resulted in complete selectivity in favour of the *S*-alkylated product **11**. This had good levels of both chemical yields and regioselectivity for a range of primary allylic halides, as set out in Table 1.[18] No traces of *N*-alkylated products arising from attack at the pendant *N*-amino group were ever observed.

Having achieved this first objective, we then wondered if the corresponding *N*-alkylated derivatives [cf. **12**] could be obtained by carrying out a thio-Claisen rearrangement[19] of the initial allylated products **13**, without any interference from the pendant amino group, which potentially could attack the new allyl group by an S_N2' mechanism. Initially, we examined purely thermal activation, the simplest way in which such rearrangements can be triggered. It was soon established that relatively high temperatures were required to trigger such thio-Claisen rearrangements with prolonged heating in xylene at 120–140 °C delivering reasonable isolated yields of the *N*-allylated products **14a**–**g** (Table 2).[20] However, we were concerned that prolonged exposure to such high temperatures could preclude the use of more sensitive substrates in future studies.

Milder conditions are available by using a palladium-based catalyst to induce such rearrangements.[21] We were pleased to find that these were successful when the precursors **13** were heated at reflux in dry tetrahydrofuran for somewhat briefer periods (Table 2).[22] Isolated yields were generally higher or at least comparable with the purely thermal procedure, except in the two examples where the rearrangement involved migration of a 1,1-disubstituted alkene (entries f, g). Various attempts to improve such returns by using higher boiling ether solvents failed. At present, it is not clear why these two cases were inefficient. The one exception to the foregoing positive results was the complete failure of the prenyl-substituted derivative **13h** to undergo rearrangement using either the purely thermal or the palladium-catalysed method to give the isomeric species **15** (Scheme 3). Excessive steric requirements may be responsible for this.

Having succeeded in alkylating both the sulfur and the ring nitrogen centres, we then tried to derivatize the pendant amino group in the initial alkylation products **13** in anticipation of being able to effect acid-catalysed cyclisation of such modified amino groups onto the newly introduced alkene side chains.[23]

We were surprised to find that attempts to add typical amine protecting groups to this likely reactive amine group, which can be considered as a monoacylated hydrazine functional group, were unsuccessful. Substrates including the *S*-allyl and *S*-cinnamyl derivatives **13a**,**b** proved inert to 'standard' tosylation conditions

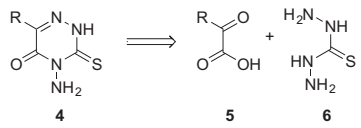
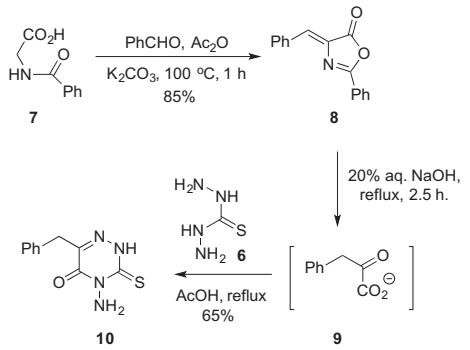
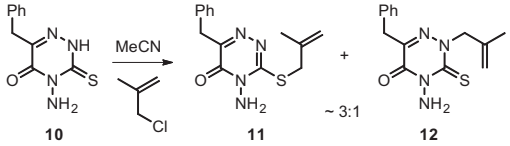


Figure 2. 1,2,4-Triazin-3-thiono-5-one synthesis.



Scheme 1. Synthesis of the starting material **10**.



Scheme 2. Initial alkylation attempt in MeCN.

(tosyl chloride, CH_2Cl_2, Et_3N or pyridine) and to similar reactions with chloroformates. However, we were successful in adding a benzyl group by exposing precursors **13f**,**g** to benzyl bromide in aqueous ethanol containing 1.5 equiv of potassium hydroxide (Scheme 4).

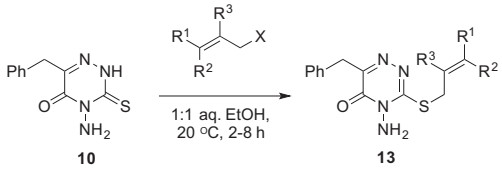
Despite the presence of what should be a readily protonated amino group in both the initial precursors **13f**,**g** and the *N*-benzylated derivatives **16a**,**b**, we examined the possibility of carrying out acid-catalysed cyclisations of such substrates on the grounds that these all also contain easily protonated side chains, which could result in the formation of a tertiary carbenium ion. We also included the homologous prenylated precursor **13h** in this group for the same reasons. We observed complete disappearance of all these precursors when exposed to an equivalent of trifluoromethanesulfonic (triflic) acid in toluene at reflux for 1 h.

In the case of precursor **16a**,[24] the product was separated by column chromatography in 80% yield. ^{1}H NMR data revealed the disappearance of the terminal alkene protons and clearly showed the continued presence of an NH group as a triplet but which was shifted from δ_H 5.37 to δ_H 5.83, together with a six-proton resonance at δ_H 1.46, due to freely rotating geminal methyl groups attached to an sp^3 carbon. Crucially, two new resonances at δ_H 3.02 (2H, d, J = 9.1 Hz) and δ_H 0.98 (1H, t, J = 9.1 Hz) pointed to the presence of a new CH_2SH thiol group and hence to the formation of the rearranged structure **20c**, the origin of which is suggested in Scheme 5.

As anticipated, an initial protonation would give rise to a tertiary carbenium ion **17**, trapping of which by a ring imine nitrogen would then lead to the iminium species **18**, stabilised by a number of resonance forms, which could then be neutralised by addition of adventitious water to give a hemiacetal species **19**. This would then collapse to give the observed products **20**. Throughout this pathway, it is likely that the benzylamine group is also protonated; this feature has been omitted for clarity.

This rearrangement is general for this structural type, at least in the case of the five substrates tested [**13f**,**g**,**h**; **16a**,**b**], as set out in Table 3. The yields quoted are for reactions which were followed by TLC until complete disappearance of the starting material. Lower temperatures, such as that of refluxing dichloromethane, were insufficient to trigger the rearrangement. In the context of

Table 1
Selective S-alkylation of 3-thioxo-1,2,4-triazin-5-one **10**

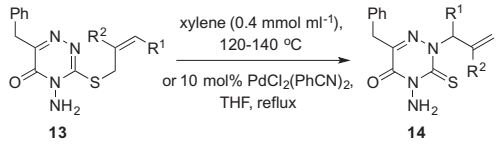


10 **13**

Entry	R^1	R^2	R^3	X	Time	Yield (**13**; %)
a	H	H	H	Br	2 h	85
b	Ph	H	H	Cl	8 h	75
c	Me	H	H	Cl	8 h	73
d	H	Pr	H	Br	4 h	64
e	Bu	H	H	Br	4 h	77
f	H	H	Me	Cl	2 h	80 (= **11**)
g	H	H	Ph	Br[a)]	4 h	85
h	Me	Me	H	Br	8 h	80

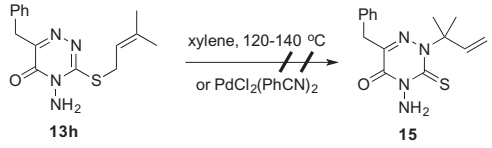
[a]Contained ca. 20% of the corresponding (unreactive) vinyl bromide, (*E*)-1-bromo-2-phenyl-1-propane, the presence of which was compensated for by using 1.3 equiv of the isomeric mixture.

Table 2
Thermal and Pd-catalysed thio-Claisen rearrangements



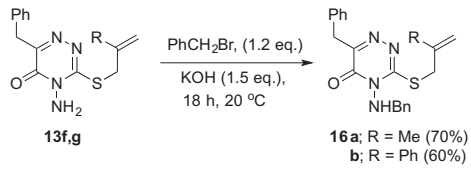
13 **14**

			Thermal		Pd-catalysed	
Entry	R^1	R^2	Time/temp.	Yield **14**	Time	Yield **14**
a	H	H	14 h; 140 °C	66%	12 h	78%
b	Ph	H	14 h; 130 °C	40%	12 h	50%
c	Me	H	5 h; 130 °C	33%	8 h	86%
d	Pr (**Z-13**)	H	14 h; 130 °C	50%	8 h	50%
e	Bu	H	14 h; 120 °C	25%	8 h	84%
f	H	Me	14 h; 130 °C	25%	14 h	15%
g	H	Ph	14 h; 120 °C	50%	14 h	15%



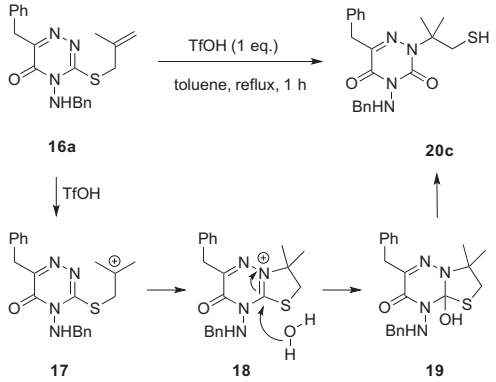
13h **15**

Scheme 3. Failure of a distally-substituted example.



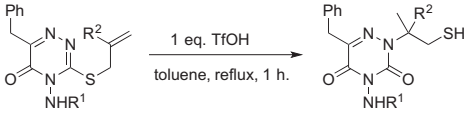
13f,g **16a**; R = Me (70%) **b**; R = Ph (60%)

Scheme 4. N-benzylation of the 4-amino group.

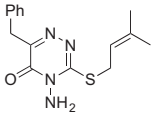
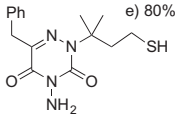


Scheme 5. The structure of the acid-catalysed rearrangement product **20c** and a proposed mechanism for its formation.

Table 3
Acid-catalysed rearrangements of **13f,g,h**; **16a,b**



13f,g,h; 16a,b. **20**

Precursor	R^1	R^2	Yield **20**
13f	H	Me	a) 70%
13g	H	Ph	b) 75%
16a	Bn	Me	c) 80%
16b	Bn	Ph	d) 67%
13h			e) 80%

the aims of the present project, this finding provides a solution to the problem of obtaining alkylated derivatives having a tertiary centre adjacent to the nitrogen atom and should be extendable to the elaboration of many similar derivatives. The incorporation of the thiol group is, of course, also very useful as this could be used in many ways to introduce additional substituents.

We have therefore established highly selective methods for the selective S- and N-alkylation of this type of 1,2,4-triazine derivatives and have also discovered a new type of acid-catalysed rearrangement, which provides an approach to highly substituted products which would not be available from direct alkylation reactions.

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18. A typical alkylation procedure of precursor **10** is as follows: The triazine **10** (0.50 g, 2.14 mmol, 1 equiv) was added to a solution of potassium carbonate (0.45 g, 3.21 mmol, 1.5 equiv) in water and ethanol (1:1; 30 mL) and the resulting solution stirred for 10 min. The alkylating agent (2.35 mmol, 1.1 equiv) was then added and the reaction stirred for 2-8 h at ambient temperature. The resulting precipitate was filtered off and washed with water then re-crystallised from ethanol. *3-(Allylthio)-4-amino-6-benzyl-1,2,4-triazin-5(4H)-one* **13a** was isolated as colourless crystals (0.49 g, 85%), mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.10 (5H, m, 5 × Ar—H), 5.90 (1H, ddt, J = 17.0, 10.0, 7.0 Hz, —CH=), 5.29 (1H, app. dd, J = 17.0, 1.3 Hz, =CH_2), 5.13 (1H, app. dd, J = 10.0, 1.1 Hz, =CH_2), 4.74 (s, 2H, NH_2), 4.02 (2H, s, CH_2Ph), 3.76 (2H, app. d, J = 7.0 Hz, SCH_2); ^{13}C NMR (125 MHz; $CDCl_3$): 159.9 (C=O), 155.6 (S—C=N), 152.1 (C—C=N), 135.9 (Ar—C), 131.7 (CH=), 129.3, 128.4, 126.8 (3 × Ar—CH), 119.3 (=CH_2), 37.2 (CH_2Ph), 33.8 (CH_2S); IR(neat) ν/cm^{-1} 3267, 3203, 3182, 3022, 2933, 1666, 1597, 1450, 1423, 1215, 925, 717; HRMS (APCI+) m/z calcd for $C_{13}H_{15}N_4OS$ [M+H]+ = 275.0967; found 275.0969.
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20. *General procedure for the thermal Claisen rearrangements:* In a flame dried flask, a 3-(ally1thio)1,2,4-triazin-5-ones **13** (0.5 g) were dissolved in xylene (5 mL) and the solution refluxed under N_2 for 5–14 h then allowed to cool to room temperature then the solvent evaporated in vacuo to afford the desired *N*-allyl derivative **14** after flash column chromatographic purification (petroleum ether/ethyl acetate 9:1). *4-Amino-6-benzyl-2-(2-allyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one* **14a** was obtained as a yellow oil, (0.33 g, 66%). ^{1}H NMR (400 MHz; $CDC1_3$) δ 7.28–7.17 (5H, m, 5 × Ar—H), 6.28 (2H, s, NH_2), 5.99–5.90 (1H, m, —CH=), 5.30–5.24 (2H, m, =CH_2), 5.00 (2H, app. d, J = 6.1 Hz, NCH_2), 3.93 (2H, s, CH_2Ph); ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.9 (C=S), 147.3 (C=O), 145.9 (C—C=N), 135.5 (Ar—C), 130.1 (CH=), 129.3, 128.7, 127.2 (3 × Ar—CH), 120.1 (=CH_2), 60.3 (N—CH_2—), 36.7 (CH_2—Ph); IR(neat) ν/cm^{-1}: 3335, 3306, 3088, 3065, 3028, 2937, 2922, 1682, 1446, 1423, 1273, 931, 730; HRMS (EI+) m/z calcd for $C_{13}H_{14}N_4OS$ = 274.0888; found 274.0878.
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22. *General procedure for the Pd(II)-catalyzed Claisen rearrangement:* To a solution of a 3-(allylthio)-1,2,4-triazin-5-one **13** (1 equiv) in dry tetrahydrofuran (5 mL per mmol), bis(benzonitrile)-palladium(II) chloride [$PdCl_2(PhCN)_2$)] (10 mol %) was added and the resulting solution stirred and heated to reflux under N_2 for the time indicated in Table 2. After evaporation of the solvent, the residue was directly subjected to column purification (petroleum ether/ethyl acetate 9:1; silica gel) to obtain the corresponding *N*-allyl-1,2,4-triazin-5-one **14**. Specifically, the *S*-allyl derivative **13a** (0.50 g, 1.8 mmol) and $PdCl_2(PhCN)_2$ (0.069 g, 0.18 mmol) were reacted for 12 h to give *4-amino-6-benzyl-2-(2-allyl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one* **14a** as a yellow oil (0.40 g, 78%), which exhibited spectroscopic and analytical data identical to those reported above.
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24. *General procedure for acid-catalysed rearrangements:* In flame dried flask, a 3-(ally1thio)-1,2,4-triazin-5-one **13f,h** or **16a,b,h** (1 equiv) was dissolved in dry toluene (5 mL per mmol) and the stirred solution cooled to 0 °C. Trifluoromethanesulfonic acid (1 equiv) was added via syringe and the flask placed in an oil bath, which was then heated to 110 °C for 1–4 h. The cooled solution was diluted with ethyl acetate then neutralised with saturated aqueous potassium carbonate (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined extracts dried over magnesium sulphate then filtered and evaporated. The crude residue was separated by flash chromatography (petroleum ether/ethyl acetate 8:2). *4-Amino-6-benzyl-2-(1-mercapto-2-methylpropan-2-yl)-1,2,4-triazine-3,5(2H,4H)-dione* **20a** was thus obtained as a yellow oil (0.35 g, 70%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.26–7.16 (5H, m, 5 × Ar-H), 5.24 (2H, s, NH_2), 3.89 (2H, s, CH_2Ph), 3.09 (2H, d, J = 9.0 Hz, CH_2SH), 1.53 (6H, s, 2 × CH_3), 1.18 (1H, t, J = 9.0 Hz, SH); ^{13}C NMR (125 MHz/$CDCl_3$): 152.5, 146.5 (2 × C=O), 141.2 (C=N), 136.2 (Ar—C), 129.3, 128.5, 126.9 (3 × Ar—CH), 67.6 ($C(CH_3)_2$), 36.7 ($PhCH_2$), 34.1 (SCH_2), 25.7 (2 × CH_3); IR (neat) ν/cm^{-1}: 3332, 3234, 3053, 3028, 2976, 2935, 1710, 1645, 1438, 1263, 1136; HRMS (EI+) m/z calcd for$C_{14}H_{17}N_4O_2S$ [M−H]$^+$ = 305.1072; found 305.1070.