A New Method for the Synthesis of Heterocyclic *S*-Alkyl Thiolactams

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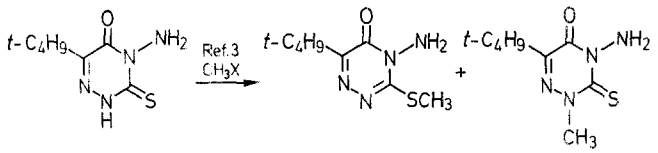
The reaction of *S*-substituted heterocyclic thiolactams with thiols is described. In some cases, rearrangement or tricyclic products were produced instead of the compounds expected from simple alkylthiol displacement.

4-Amino-6-*tert*-butyl-3-methylthio-1,2,4-triazin-5(4*H*)-one **(2)** is a commercially important substance because it is a herbicide[2] widely used for the control of broadleaf weeds in soybeans. It can be prepared by the alkylation of heterocyclic thiolactam **1** with alkyl halides,[3] but as usual with the alkylation of ambident anions, the reaction is not regiospecific.[4,5] With methyl bromide about 6% of the non-herbicidal *N*-isomer **3** is produced.



1 2 3

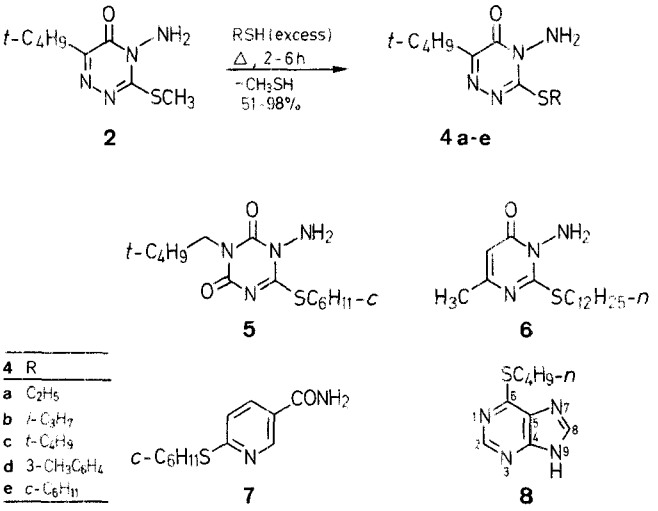
Other potentially useful herbicides might be synthesized from **1** and various alkyl halides, but the percentage of *N*-alkylation rises sharply with alkyl groups larger than methyl. For example, ethyl bromide gives about 17% *N*-isomer, and secondary halides give *N*-isomer and elimination products almost exclusively. It was thus of considerable interest to develop a new non-alkylation route to compounds of type **2**.

It seemed plausible to us that *S*-alkyl compounds such as **2** would react with thiols, presumably by a Michael-type addition-elimination sequence,[6] to produce what would formally be new *S*-alkylated derivatives of **1**. This view was supported by the known reaction of amines with other 1,2,4-triazin-5-ones to give alkylthiol displacement products.[7]

Indeed, when triazine **2** was refluxed in ethanethiol in the presence of a catalytic amount of acid or base a reversible exchange of thiols took place. By distilling out the lower boiling thiol the reaction could be driven to completion and the *S*-ethyl derivative **4a** produced in essentially quantitative yield.

The only previous report[8] of thiol exchange reactions of this type deals only with pyrimidine derivatives, and in this case, the reaction was unsuccessful with secondary or tertiary thiols. We have found that the reaction has considerable generality and has been extended to other ring systems represented by structures **5–8**. Additionally, secondary, tertiary, and aromatic thiols have been utilized in our work which makes a large number of new compounds readily available that would be far more difficult to prepare by other methods.

Not all thiols reacted in such a straight forward manner (Scheme **A**). Compound **2** and 1,2-ethanedithiol gave **1** and unidentified by-products, which may have formed from thiirane, since they had the same GLC retention times as the reaction products of thiirane and 1,2-ethanedithiol. Interestingly, a similar reaction of **2** with 2-mercaptoethanol gave **10** instead of **1** or the desired hydroxyethyl compound. In as much as **2** does not react appreciably with ethylene glycol under similar conditions, it seems likely that oxygen becomes attached to the triazine 3-position by an intramolecular process involving a spiro oxathiolane intermediate (Scheme **B**) followed by ring opening and an intramolecular displacement of **1** with the concomitant formation of thiirane.



2 4a-e 5 6 7 8

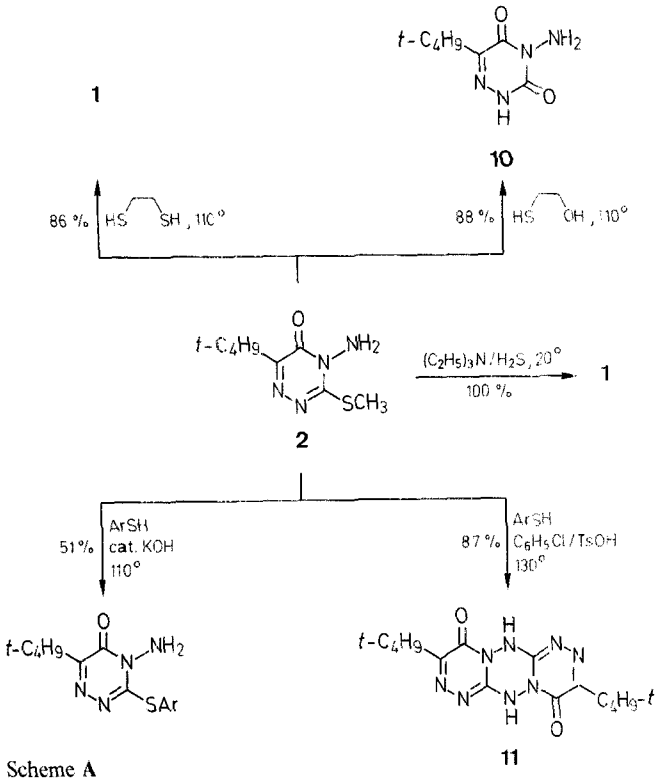
4	R
a	C_2H_5
b	*i*-C_3H_7
c	*t*-C_4H_9
d	3-$CH_3C_6H_4$
e	*c*-C_6H_{11}

In an attempt to improve the yields of the *S*-aryl compounds, **2** was refluxed in toluene with *m*-thiocresol and *p*-toluenesulfonic acid. Instead of the desired product, a very high melting

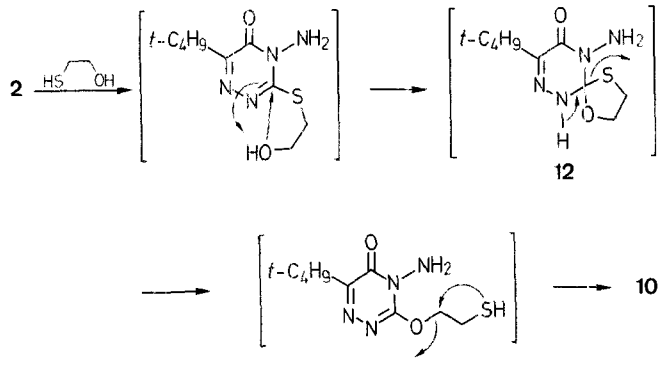
Table. Reaction Products of Heterocyclic *S*-Alkylisothioureas with Mercaptans

Product	Yield[a] (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c] or Lit. m.p. (°C)	^{1}H-NMR[d] δ, J(Hz)	MS (50 ev)[e] *m/e* (%)
4a	98	95–96 (heptane)	$C_9H_{16}N_4OS$ (228.3)	($CDCl_3$): 1.35 (m, 12H); 3.15 (q, 2H, J = 7); 5.0 (s, 2H)	228 (M^+) 29 (100)
4b	86	113–114 (heptane)	$C_{10}H_{18}N_4OS$ (242.3)	($CDCl_3$): 1.43 (s, 9H); 1.45 (d, 6H, J = 7); 4.1 (m, 1H, J = 7); 4.9 (s, 2H)	242 (M^+) 41 (100)
4c	76	139–140 ($EtOH/H_2O$, 1:1)	$C_{11}H_{20}N_4OS$ (256.4)	($CDCl_3$): 1.4 (s, 9H); 1.65 (s, 9H); 3.8 (s, 2H); 4.8 (s, 2H)	200 (M^+ – 56) 57 (100)
4d	51	154–155 ($EtOH/H_2O$, 1:1)	$C_{14}H_{18}N_4OS$ (290.4)	($CDCl_3$): 1.4 (s, 9H); 2.4 (s, 3H); 4.9 (s, 2H); 7.3 (m, 4H)	290 (M^+) 41 (100)
4e	96	139–140 ($EtOH/H_2O$, 1:1)	$C_{13}H_{22}N_4OS$ (282.4)	($CDCl_3$): 1.5 (m, 19H); 4.0 (m, 1H); 4.9 (s, 2H)	282 (M^+) 201 (100)
5	94	224–225 ($EtOH/H_2O$, 1:1)	$C_{14}H_{24}N_4O_2S$ (312.4)	($CDCl_3$): 0.97 (s, 9H); 1.6 (m, 11H); 3.81 (s, 2H); 4.49 (s, 2H)	312 (M^+) 56 (100)
6	91	86–87 (heptane)	$C_{17}H_{31}N_3OS$ (325.5)	($CDCl_3$): 1.3 (m, 23H); 2.2 (s, 3H); 3.1 (t, 2H, J = 7); 4.8 (s, 2H); 6.1 (s, 1H)	325 (M^+) 157 (100)
7	93	190–191 (toluene)	$C_{12}H_{16}N_2OS$ (236.3)	(DMSO-d_6): 1.5 (m, 10H); 3.15 (s, 1H); 3.3 (s, 1H); 3.85 (m, 1H); 7.2 (d, 1H, J = 8); 8.0 (dd, 1H, J = 2, 8); 8.9 (d, 1H, J = 2)	236 (M^+) 154 (100)
8	92	147–148 (toluene)	150[10]	($CDCl_3$/DMSO-d_6): 1.0 (t, 3H, J = 7); 1.65 (m, 4H); 3.4 (t, 2H, J = 7); 8.15 (s, 1H); 8.7 (s, 1H)	208 (M^+) 166 (100)
11	87	>410 (DMSO/i-PrOH, 1:1)	$C_{14}H_{20}N_8O_2$ (332.4)	(DMSO-d_6): 1.18 (s)	332 (M^+, 100)

[a] Yields not optimized.
[b] Uncorrected, measured on a Thomas Hoover 4267-H10 apparatus.
[c] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.2, S +0.2.
[d] Obtained on a Varian EM 390 Spectrometer; internal standard: TMS.
[e] Recorded on a Finnigan Model 450 GC/MS.



Scheme A



Scheme B

crystalline yellow solid was obtained, the analytical data for which support structure **11**. This ring system was previously made by Dornow and Pietsch,[9] who produced it from an analog of **2** and sodium methoxide. Since the tricyclic compound does not form under these conditions in the absence of aromatic thiol, it appears that the *S*-aryl derivate is an intermediate. In fact, when **4d** was heated in toluene compound **11** formed much more readily than it did from compound **2**. Under the more vigorous condition of refluxing chlorobenzene instead of toluene, the aromatic thiol is no longer needed, although its presence increases the yield of **11** and decreases the reaction time.

4-Amino-6-*tert*-butyl-3-alkylthio-1,2,4-triazin-5(4*H*)-ones 4a–e, 1-Amino-3-neopentyl-6-cyclohexylthio-1,3,5-triazine-2,4(1*H*,3*H*)-dione (5), 3-Amino-2-dodecylthio-6-methyl-4(3*H*)pyrimidinone (6), 6-Cyclohexylthionicotinamide (7), and 6-Butylthiopurine (8); General Procedure:
To a solution of the methylthio compound (10 mmol) (ethylthio in the case of compound 5[11]) in 6 equiv of low-boiling (< 100 °C) or 2 equiv of high-boiling (> 100 °C) thiol is added KOH (20 mg, 0.4 mmol) and the mixture is heated at reflux or 120 °C, whichever is lower, until the starting material is consumed as indicated by TLC, normally about 2–6 h. The excess thiol is then evaporated and the residue recrystallized from the solvent indicated on the Table.

Reaction of 2 with 2-Mercaptoethanol and 1,2-Ethanedithiol:
To a solution of **2** (10.7 g, 50 mmol) and 2-mercaptoethanol or 1,2-ethanedithiol (10 mL) is added KOH (30 mg, 0.6 mmol) and the mixture heated at 100 °C for 16 h. The solution is cooled and triturated with a cold mixture of heptane and toluene (3:7, 60 mL). Filtration and washing the solid with toluene (20 mL) then 2-propanol (10 mL) affords *4-amino-6-tert-butyl-1,2,4-triazine-3,5(2H,4H)-dione* **(10)**; yield 8.1 g (88%); m.p. 166–167.5 (Lit.[12] m.p. 166 °C) or *4-amino-6-tert-butyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine* **(1)**; yield 8.6 g (86%); m.p. 211–213 °C (Lit.[12] m.p. 214 °C).

3,9-Di-*tert*-butyl bis([1,2,4]triazino[4,3-*b*:4′,3′-*e*][1,2,4,5]tetrazine-4,10(6*H*,12*H*)-dione (11):
A solution of triazine **2** (32.1 g, 150 mmol), TsOH (2.8 g, 15 mmol), and *m*-thiocresol (9.3 g, 75 mmol) in PhCl (200 mL) is refluxed for 56 h. The product is filtered from the hot solution, washed with EtOH (200 mL) and air-dried to give **11** as yellow crystals: yield: 21.6 g (87%) (Table).

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