Novel Desulphurization of Thiourea Derivatives by Alkaline Autoxidation

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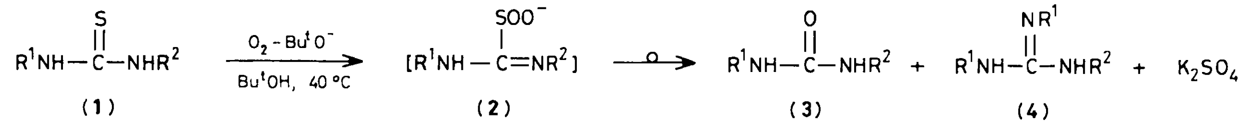
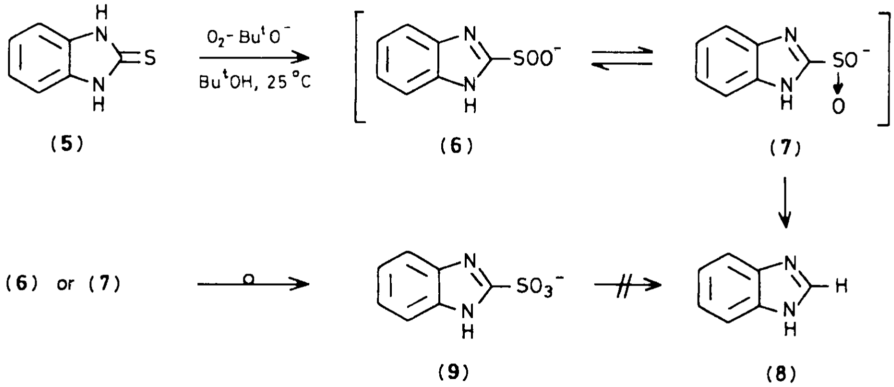
Autoxidation of 1,3-disubstituted thioureas in the presence of oxygen and tertiary butoxide in tertiary butanol afforded the corresponding ureas in good yields together with small amounts of the corresponding guanidines while the same treatment of benz- or naphth-imidazole-2-thiones gave the parent imidazoles and the 2-sulphonic acids.

Considerable interest has focused on the desulphurization of thioureas using alkali metal bromates,[1] sodium peroxide,[2] or alkaline hydrogen peroxides,[3] all in aqueous solvents. Intensive studies on the alkaline autoxidation of thiols[4,5] and disulphides[6] to the corresponding sulphinic and sulphonic acids have been reported. Only recently, however, have examples of oxidations of compounds containing a C=S bond appeared.

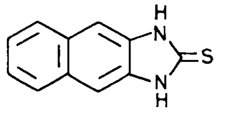
Oxidative desulphurization of cyclic thioureas such as thiouracil or ethionamide[7] is known to occur in *in vivo* metabolism to give the corresponding carbonyl compounds without any evidence that an activated oxygen species such as superoxide, distributed widely in living cells, is involved. In our previous paper,[8] we described the reaction of potassium superoxide with 1,3-disubstituted thioureas in tetrahydrofuran to give as the main products, 1,2,3-trisubstituted



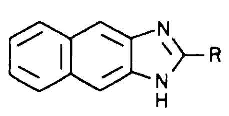
$$\underset{(1)}{R^1NH-\overset{\overset{S}{||}}{C}-NHR^2} \xrightarrow[Bu^tOH,\ 40\,^\circ C]{O_2-Bu^tO^-} \underset{(2)}{[R^1NH-\overset{\overset{SOO^-}{|}}{C}=NR^2]} \xrightarrow{o} \underset{(3)}{R^1NH-\overset{\overset{O}{||}}{C}-NHR^2} + \underset{(4)}{R^1NH-\overset{\overset{NR^1}{||}}{C}-NHR^2} + K_2SO_4$$



(5) (6) (7) (9) (8)



(10)



(11) R = H

(12) R = SO_3^-

Table 1. Desulphurization of (**1**), (**5**), and (**10**).

Run	Substrate	Solvent	Reaction time/h	Yield/%	
1	(**1**; R^1 = Ph, R^2 = Ph)	Bu^{t}OH	18	74[a]	4[b]
2	(**1**; R^1 = Ph, R^2 = Ph)	DMSO	48	18[a]	45[b]
3	(**1**; R^1 = Ph, R^2 = 4-ClC$_6$H$_4$)	Bu^{t}OH	20	73[a]	[c]
4	(**1**; R^1 = 4-ClC$_6$H$_4$, R^2 = 4-ClC$_6$H$_4$)	Bu^{t}OH	20	75[a]	3[b]
5	(**1**; R^1 = 4-ClC$_6$H$_4$, R^2 = 4-ClC$_6$H$_4$)	Bu^{t}OH–DMSO[d]	48	41[a]	37[b]
6	Ph$_2$NC(=S)NPh$_2$	Bu^{t}OH	50	0[e]	0[e]
7	$c\text{-}C_6H_{11}NHC(SO_n^-)=\overset{+}{N}H(c\text{-}C_6H_{11})$[f] n = 2,3	Bu^{t}OH	15	92—98[a]	
8	(**5**)	Bu^{t}OH[g]	5	(**8**) 74	(**9**) 22
9	(**5**)	HMPA	48	(**8**) 7	(**9**) 91
10	(**10**)	Bu^{t}OH	24	(**11**) 58	(**12**) 32

[a] Isolated yield of (**3**). [b] Isolated yield of (**4**) based on –NHR^1 and –NHR^2 groups. [c] Not determined. [d] Mixed solvent Bu^{t}OH : DMSO 1 : 1 (v/v). [e] Starting material was recovered quantitatively. Formation of a tetrahedral intermediate formed by direct nucleophilic attack of $O_2^{\cdot -}$ on the thiocarbonyl carbon atom as in carbonyl compounds (ref. 10) may be ruled out because tetraphenylthiourea, where the electrophilic thiocarbonyl carbon atom would be expected to be more readily attacked by $O_2^{\cdot -}$ than that in 1,3-diphenylthiourea, did not react with $O_2^{\cdot -}$. [f] c-C$_6$H$_{11}$ = cyclohexyl. [g] The yields of (**8**) and (**9**) were dependent upon the mixture of solvents used: Bu^{t}OH : HMPA (v/v) 10 : 1, (**8**) 66%, (**9**) 33%; 1 : 1, (**8**) 58%, (**9**) 37%.

guanidines and small amounts of 1,3-disubstituted ureas, the former probably *via* unstable peroxysulphur intermediates such as the peroxysulphenates. If an activated oxygen atom of a superoxide anion[9] and such a peroxysulphur intermediate are involved in alkaline autoxidation, the latter may be expected to be a useful intermediate in desulphurization owing to its lability under the strongly alkaline conditions.

We have now found that 1,3-disubstituted thioureas (**1**) react readily with oxygen in the presence of tertiary butoxide in tertiary butanol under mild conditions to afford the corresponding ureas (**3**) as the main products and small amounts of the guanidines (**4**) but that the same treatment of benz- and naphth-imidazole-2-thiones (**5**) and (**10**) gave the imidazoles (**8**) and (**11**) and the sulphonic acids (**9**) and (**12**), respectively. The results obtained are summarized in Table 1.

In a typical run, 1,3-diphenylthiourea (0.5 mmol) was dissolved in tertiary butanol (4 ml) containing potassium tertiary butoxide (2.0 mmol). Oxygen gas was slowly bubbled into the reaction mixture with stirring at *ca.* 40 °C for 18 h and after concentration cold water was added to precipitate a mixture of 1,3-diphenylurea and 1,2,3-triphenylguanidine which were separated by low pressure liquid column chromatography or preparative t.l.c. [silica gel, CHCl$_3$–MeOH 15 : 1 (v/v), 74% of the urea and 4.5% of the guanidine were formed]. Potassium sulphate (*ca.* 50%) or barium sulphate (*ca.* 50%) was precipitated by adding barium hydroxide to the aqueous layer obtained by addition of the water.

Use of more than 3 equiv. of base and protic solvent (tertiary butanol) gave higher yields of (**3**) and (**8**). Dimethyl sulphoxide (DMSO) or hexamethylphosphoramide (HMPA) as protic solvents gave more (**4**) or (**9**) in agreement with their effects on the reaction[11] of (**5**) with $O_2^{\cdot -}$. Thus, key steps would appear to involve the formation of peroxysulphenate intermediate (**2**) by coupling of the thioyl radical of (**1**) and $O_2^{\cdot -}$ which may occur in alkaline conditions[9] [equation (1)]

$$(\mathbf{1}) \rightleftharpoons \text{RNH-C(SH)=NR} \xrightarrow{O_2^{\cdot -}} \text{RNHC(S}\cdot\text{)=NR} \xrightarrow{O_2} \text{RNH-C(SOO)}^-\text{=NR} \xrightarrow{HO_2^-} \text{RNHC(OOH)=NR} \rightarrow (\mathbf{3}) \tag{1}$$

and then nucleophilic attack by HO_2^- on the formamidine carbon atom to form (**3**) and SO_2^- which is a good leaving group and is further oxidized to SO_4^{2-}.† In support of this, the stable 1,3-dicyclohexylthiourea-*S,S*-dioxide and -*S,S,S*-trioxide were both converted into the urea in quantitative yields (run 7, Table 1).

Though the possible peroxysulphur intermediate (**2**) has not been isolated or detected, it has been shown to be an unstable intermediate in the alkaline autoxidation of thiols[4] and in the oxidations of related disulphide compounds with $O_2^{\cdot -}$.[12] The formation of (**4**) may involve another, competitive route which is initiated by the reaction of (**1**) with (**2**).[8] It is interesting that for the first time the desulphurized product has been obtained under alkaline conditions probably through the lability[13] of (**6**) or (**7**), which in a competitive reaction also gives (**9**).

It is noteworthy that the product ratios of (**3**) and (**4**) or (**8**) and (**9**) are very dependent on the solvents used. The work described herein may be of synthetic use and sheds further light on the mechanism of autoxidation by $O_2^{\cdot -}$.

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† Sodium sulphite was oxidized to SO_4^{2-} quantitatively under the same conditions. The sulphonic acid (**9**) was not desulphurized to (**8**) and instead was recovered quantitatively.