Novel Desulphurization of 1,3-Disubstituted Thioureas by Superoxide Anion ($O_2^{\cdot -}$): One-step Synthesis of 1,2,3-Trisubstituted Guanidines from 1,3-Disubstituted Thioureas

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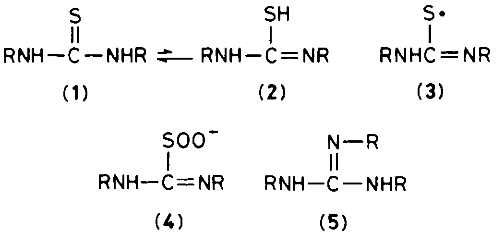
Treatment of 1,3-diarylthioureas with superoxide anion ($O_2^{\cdot -}$) at 20 °C in tetrahydrofuran or acetonitrile resulted in the formation of 1,2,3-triarylguanidines in excellent yields.

Although biological reactions of superoxide anion ($O_2^{\cdot -}$) have been intensively studied over the past two decades since superoxide dismutase was discovered in 1969 to be a respiratory intermediate in aerobic organisms,[1] only a few reports have appeared on the reactivity of $O_2^{\cdot -}$ with simple organic compounds.[2] Recently, numerous groups have shown interest[2,3] in the physical and chemical properties of superoxide anion and stimulated its use in the development of organic synthesis. Oxidative desulphurization of thioamides[4] such as thiobarbital, ethionamide, or thiouracil has been known to be metabolized *in vivo* to give the corresponding carbonyl compounds without any evidence that an activated oxygen species like superoxide, which is distributed widely in living cells, is involved. Our previous work on the oxidation of diaryldisulphide[5] and arylsulphonyl halides[6] to the corresponding sulphonates suggests that if peroxysulphur compounds or sulphonates are formed, they may be useful intermediates in organic syntheses owing to their lability under alkaline conditions.

During the study of model metabolic reactions for desulphurization, we found that 1,3-diarylthioureas (**1**) (R = aryl) reacted readily with potassium superoxide in acetonitrile or tetrahydrofuran (THF) under mild conditions to form 1,2,3-triarylguanidines (**5**) in excellent yields together with trace amounts of the corresponding 1,3-diarylurea.

In a typical run, a mixture of 1,3-diphenylthiourea and dry powdered potassium superoxide (4 equiv.) in THF was stirred well for 8 h at 20 °C, then poured into cold water, and finally extracted with chloroform. The chloroform layer, dried over anhydrous magnesium sulphate, was concentrated to give 1,2,3-triphenylguanidine, which was purified by low pressure liquid column chromatography or preparative thin layer chromatography (94%). Potassium sulphate (*ca.* 80%) was obtained from the water layer. The products obtained were identified by comparing their i.r., ^1H n.m.r., u.v., and mass spectra with those of authentic samples. The results are summarized in Table 1.



$$\underset{(1)}{\mathrm{RNH{-}\overset{\overset{\Large S}{\|}}{C}{-}NHR}} \rightleftharpoons \underset{(2)}{\mathrm{RNH{-}\overset{\overset{\Large SH}{|}}{C}{=}NR}} \qquad \underset{(3)}{\mathrm{RNH\overset{\overset{\Large S\cdot}{|}}{C}{=}NR}}$$

$$\underset{(4)}{\mathrm{RNH{-}\overset{\overset{\Large SOO^-}{|}}{C}{=}NR}} \qquad \underset{(5)}{\mathrm{RNH{-}\overset{\overset{\Large N{-}R}{\|}}{C}{-}NHR}}$$

Using more than three equiv. of $O_2^{\cdot -}$ with (**1**) gave higher yields of (**5**)† (Table 1). The thiolate anion of (**2**) in basic $O_2^{\cdot -}$[1] may be converted into the thiyl radical (**3**) by one electron transfer from $O_2^{\cdot -}$. The radical (**3**) then couples with $O_2^{\cdot -}$ to form (**4**). Although the possible peroxysulphenate intermediate has not been isolated or detected, it has been demonstrated to be a key intermediate in the alkaline oxidation of thiols[7] and in the oxidation of disulphides[5] and arylsulphonyl chloride[6] with $O_2^{\cdot -}$. The formation of peroxysulphenate or its functional equivalent (peroxysulphinate or peroxysulphonate) is indicated by the oxidation of dimethyl sulphoxide to the sulphone (80%) when the former is used as a trapping agent for the activated oxygen of (**4**). There have been few syntheses of 1,2,3-triarylguanidines: the reaction of aryl isocyanide dichloride with amines[8] or diarylcarbodi-imides with amines.[9] These reactions require two or more reaction steps. Our method,

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† The amount of KO_2 effects the yield of (**5**). KO_2/substrate, reaction time, yield: 1/1, 15 h, 35%; 2/1, 15 h, 42%; 1/1, 48 h, 36%; 2/1, 48 h, 44%; 3/1, 48 h, 65%.

Table 1. (**1**) + $KO_2 \xrightarrow{20\,°C}$ (**5**) + K_2SO_4[a] + $R^1NH\text{-}C(:O)\text{-}NHR^2$[b]

R^1	R^2	Solvent	Ratio of KO_2 : substrate	Reaction time/h	Yield of (**5**)	
					%[c]	(%)[d]
Ph	Ph	THF	4	8	94	(63)
Ph	Ph	THF	3	10	65	(43)
Ph	Ph	THF	2	48	44	(29)
2-Me-C_6H_4	2-Me-C_6H_4	THF	4	35	90	(60)
Ph	4-Me-C_6H_4	THF	4	48	85[e]	(57)
4-Cl-C_6H_4	4-Cl-C_6H_4	THF	4	6	75	(50)
Ph	4-Cl-C_6H_4	THF	4	48	81[f]	(54)
Ph	Ph	Me_2SO : THF 0.05	4	8	81[g]	(54)
Ph	Ph	MeCN	4	8	83[h,i]	(55)

[a] K_2SO_4 was isolated in yields of 55—80% in THF or MeCN. [b] Trace amount. [c] Isolated yield based on –NHR groups. [d] Isolated yield based on moles of (**5**) per mole of (**1**). [e] Mixture of 4 different guanidines which were not separated: h.p.l.c. (column: μ Bondapak C-18, 3000 lb in^{-2}, solvent H_2O–MeOH 1 : 1) shows 4 main peaks from guanidines (see footnote f). [f] Total yield: 81%, 4 different guanidines were separated and identified; 1,2,3-triphenylguanidine (7%), 1,2-diphenyl-3-(*p*-chlorophenyl)guanidine (24%), 1-phenyl-2,3-bis(*p*-chlorophenyl)guanidine (27%), 1,2,3-tris(*p*-chlorophenyl)guanidine (23%). [g] Me_2SO was oxidized to dimethylsulphone (80%). [h] Main products: triphenylguanidine (83%) and acetamide (54%). [i] The peroxy intermediate (**4**) probably attacks acetonitrile *via* a known process to produce acetamide (J. Gibian and T. Ungermann, *J. Am. Chem. Soc.*, 1979, **101**, 1291).

however, is a simple one-step reaction and work-up after the reaction is complete is easier.

Diarylthioureas are known to react with PbO_2[9b] or PbO[10] to give diarylcarbodi-imides, amines, or disubstituted guanidines. In our reactions, the formation of diarylcarbodi-imide or disubstituted guanidine was not detected. When 1,3-diphenylthiourea was allowed to react with $O_2^{\cdot -}$ in the presence of *p*-toluidine (equimolar amount) in THF, 1,2,3-triphenylguanidine (94%) was obtained together with the quantitative recovery of *p*-toluidine.

Although the mechanism of triarylguanidine formation is not clear, it is likely that the reaction is initiated by the formation of the intermediate (**4**).

We thank Professor Shigeru Oae for helpful discussions. This investigation was supported by the Asan Foundation.

Received, 22nd February 1983; Com. 247

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