Activation of Superoxide; Efficient Desulphurization of Thioamides to the Corresponding Amides using a Peroxyphosphorus Intermediate generated from Phenylphosphonic Dichloride and Superoxide

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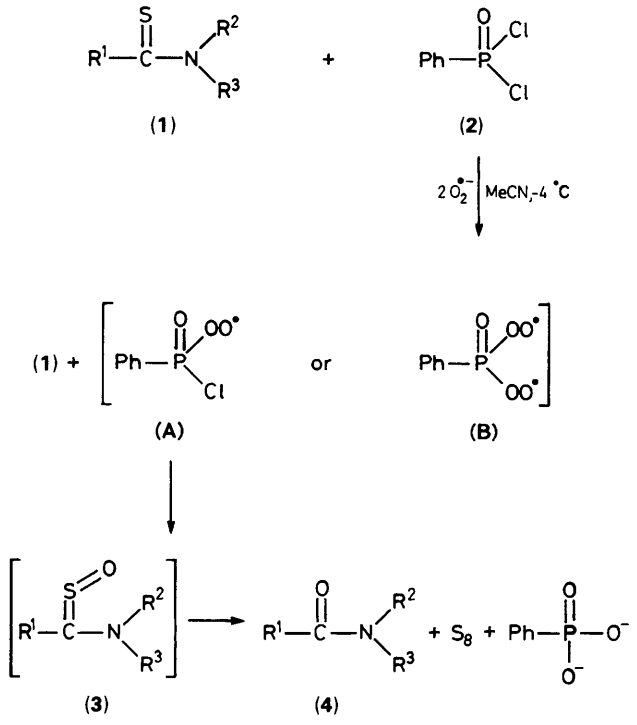
Treatment of thioamides with a peroxyphosphorus intermediate generated from phenylphosphonic dichloride and superoxide ($O_2^{\cdot -}$) at −4 °C in acetonitrile gave the corresponding amides in excellent yields.

Considerable interest has recently been focused on the desulphurization of the biologically important thiocarbonyl compounds.[1] Oxidative desulphurization of thioamides such as thiobarbital, ethionamide, or thiouracil is known to occur in *in vivo* metabolism to form the corresponding amides,[2,3] though there is no direct evidence for the involvement of any activated oxygen species such as superoxide which is distributed widely in living cells. Arylthioureas have been reported to be desulphurized by reaction with superoxide in the KO_2–Me_2SO system[4,5] and in the alkaline autoxidation system.[6] Recently it was demonstrated that superoxide itself is not exceptionally reactive in chemical and in biological systems.[7] Though superoxide itself is not so reactive in chemical reactions in aprotic organic solvents, it is likely that it would be activated by forming more active peroxy species which are generated by the reaction of $O_2^{\cdot -}$ with other suitable substrates. Although the peroxyphosphorus intermediate $R_2P(O)OO^-$ has been postulated as a possible intermediate in certain biological transformations, it has neither been isolated nor its presence confirmed.[8] We have now found that phenylphosphonic dichloride reacted with superoxide ($O_2^{\cdot -}$) at −4 °C in acetonitrile to form a peroxyphosphorus intermediate which shows strong oxidizing ability and converts various aryl and alkyl thioamides into the correspnding amides in excellent yields.

In a typical experiment, phenylphosphonic dichloride (2 mmol) was slowly added to a heterogeneous mixture of KO_2 (4.0 mmol) and MeCN (4 ml). 4-(*p*-Nitrothiobenzoyl)morpholine (0.5 mmol) in MeCN (3 ml) was added to the mixture at



Scheme 1

Table 1. Conversion of (1) into (4) with (A) or (B) at −4 °C in MeCN.

Substrate			Ratio[a]	Reaction	Yield[b]
R^1	R^2	R^3	KO_2:(2):(1)	time/h	/%
4-$NO_2C_6H_4$	$-(CH_2)_2O(CH_2)_2-$[c]		8:4:1	3	95
4-ClC_6H_4	$-(CH_2)_2O(CH_2)_2-$		8:4:1	3	94
4-BrC_6H_4	$-(CH_2)_2O(CH_2)_2-$		8:4:1	3	94
Ph	$-(CH_2)_2O(CH_2)_2-$		8:4:1	2.5	93
Ph	$-(CH_2)_2O(CH_2)_2-$		4:2:1[d]	6	94
Ph	$-(CH_2)_2O(CH_2)_2-$		8:0:1[e]	24	—[e]
4-$MeOC_6H_4$	$-(CH_2)_2O(CH_2)_2-$		8:4:1	2.5	95
Me	H	4-$NO_2C_6H_4$	8:4:1	3.5	93
Me	H	Ph	8:4:1	3	90
Ph	H	Me	8:4:1	2.5	90
Ph	H	CH_2Ph	8:4:1	3	92
Me	H	c-C_6H_{11}[f]	8:4:1	1.5	97
Me	$-(CH_2)_2O(CH_2)_2-$		8:4:1	1.5	93

[a] A molar ratio of 8:4:1 was used to shorten the reaction time. [b] Isolated yield. [c] Morpholine moiety. [d] KO_2:(2):(1), reaction time, yield; 4:4:1, 5 h, 95%; 8:8:1, 1 h, 92%. [e] In the absence of $PhP(O)Cl_2$, amide product was not detected, but starting material was recovered (95%). [f] Cyclohexyl.

−4 °C under nitrogen. The mixture was stirred for 3 h, poured into cold water, and then extracted with dichloromethane (30 ml × 5). The dichloromethane layer was dried ($MgSO_4$), filtered, and then concentrated under reduced pressure to give almost pure 4-(*p*-nitrobenzoyl)morpholine (*ca.* 100%), which was purified by preparative TLC (silica gel, Merck GF_{254}, 200 × 200 × 1 mm; CH_2Cl_2–MeOH, 25:1, v/v) to give the pure product (95%, m.p. 100—104 °C, lit.[9] 101—106 °C).† Products from other reactions of similar substrates were purified by preparative TLC or column chromatography (silica gel, Merck, Kieselgel 60, 70—230 mesh, 1 × 20 cm; CH_2Cl_2–MeOH, 25:1, v/v) and identified by comparison (IR, m.p.) with authentic samples. The results obtained are summarized in Table 1.

Phenylphosphonic dichloride reacts with $O_2^{\cdot-}$ probably to form a monoperoxyl phosphorus intermediate (**A**) which may undergo further reaction with $O_2^{\cdot-}$ to form the diradical (**B**).‡

Desulphurization of the thioamide is probably initiated *via* formation of the unstable sulphine (**3**) by oxidation with (**A**) or (**B**); the sulphine may be converted to the product (**4**) and elemental sulphur by intramolecular desulphurization, as occurs in the conversion of thiones to ketones *via* a sulphine intermediate.[10] Use of > 2 equiv. of (**2**) and 4 equiv. of $O_2^{\cdot-}$ with respect to (**1**) gave higher yields of (**4**). Our new method has the advantage that it results in almost quantitative yields and is also useful for tertiary thioamide substrates which are not oxidized by superoxide itself.[4] Thus it may provide an efficient synthetic method in view of the chemical yields and also may shed further light on the mechanism of oxidation by $O_2^{\cdot-}$. The structure of (**A**) or (**B**) and the scope of the reaction are under investigation.

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† Elemental sulphur (S_8) was formed in >80% yield. When either KO_2 or $PhP(O)Cl_2$ was omitted from the reaction mixture, no desulphurization of the thioamide was observed.

‡ Attempted spin trapping of the radical (**A**) was not successful, although $Ph_2P(O)OO\cdot$ [from $Ph_2P(O)Cl$ and KO_2] has been successfully trapped by the same method.[11] The desulphurization of thioamides can be accomplished with $Ph_2P(O)Cl$ (or $POCl_3$) in place of $PhP(O)Cl_2$, but the reactions are slow and less clean.

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