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Facile Synthesis of 2-Substituted Aminobenzoxazole. One Pot Cyclodesulfurization of N-(2-Hydroxyphenyl)-N'-phenylthioureas with Superoxide Radical Anion

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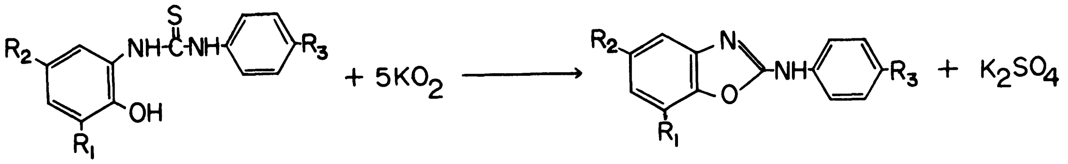
Treatment of N-(2-hydroxyphenyl)-N'-phenylthioureas with the superoxide radical anion ($O_2^{-\cdot}$) at 20 °C in CH_3CN, THF, or DMSO resulted in the formation of 2-substituted aminobenzoxazoles in excellent yields.

Considerable interest has recently been focused on the desulfurization of thiourea-[1)] and thioamide-[2)] derivatives using superoxide since oxidative desulfurization of cyclic thioureas[3)] of thiouracil, ethionamide and thiobarbital are known to occur *in vivo* metabolism to form the corresponding carbonyl compounds. Extensive references are now rapidly accumulating on the application of superoxide for the organic syntheses as an effective oxidizing agent for the involvement of electron transfer in the oxidation of organic sulfur compounds. Our previous works on the oxidative desulfurization of heterocyclic thioureas,[4)] 1,3-disubstituted thioureas[1)] and other thione compounds suggest that if peroxysulfur intermediates of dioxide or trioxide (5) are formed, they may be useful intermediates in organic syntheses owing to their lability under mild conditions.

We have now found that N-(2-hydroxyphenyl)-N'-phenylthioureas reacted smoothly with potassium superoxide at 20 °C in acetonitrile, tetrahydrofuran as well as in dimethyl sulfoxide to afford 2-substituted aminobenzoxazoles in excellent yields together with potassium sulfate.



In a typical experiment, a solution of N-(2-hydroxy-5-methylphenyl)-N'-phenylthiourea (258 mg, 1 mmol; CH_3CN, 2 ml) was added to a heterogeneous solution of potassium superoxide (370 mg, 5 mmol; CH_3CN, 1 ml) at 20 °C under dry argon atmosphere. After being stirred well for ca 2 h at 20 °C, the reaction mixture was poured into cold water, and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give highly pure 2-anilino-5-methylbenzoxazole (92%; mp. 204-207 °C in Run 1), which was purified by preparative thin layer chromatography. Potassium sulfate (81%) was obtained from the water layer. The products obtained were identified by comparing their IR and ^1H NMR, mp, and mass spectra with those of authentic samples. The results are summarized in Table 1.

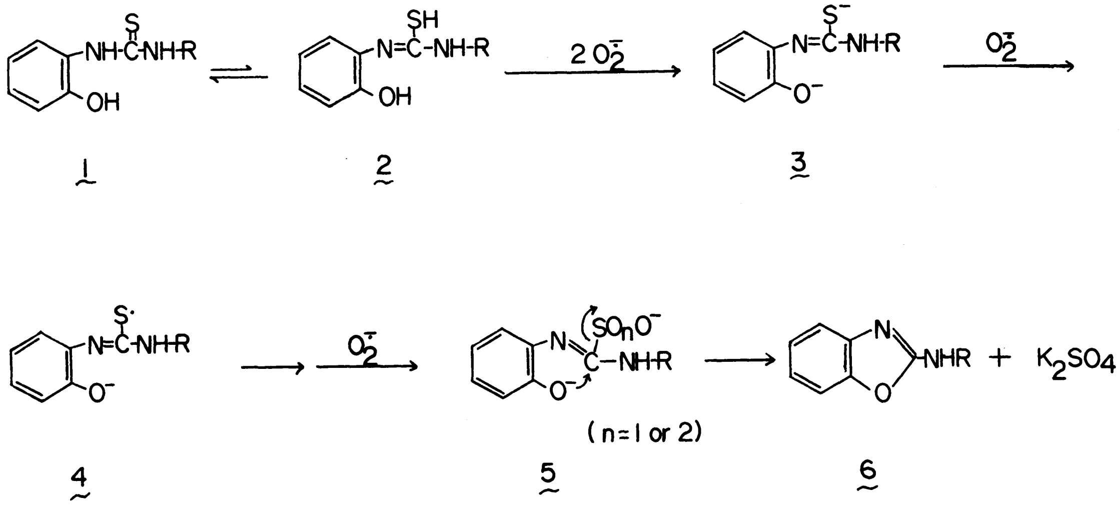
Table 1. Cyclization of N-(2-hydroxyphenyl)-N'-phenylthiourea derivatives to the 2-substituted aminobenzoxazoles by $O_2^{-}\cdot$

Run	R_1	R_2	R_3	Solvent	Reactn. temp/°C	Reactn. time/h	Yield/%[a)]
1	H	CH_3	H	CH_3CN	20	2.0	92
2	H	CH_3	H	THF	20	2.0	89
3	H	CH_3	H	DMSO	20	1.5	81
4	H	CH_3	H	CH_3CN	-35	8.0	88
5	H	H	H	CH_3CN	20	1.0	86
6	H	Cl	H	CH_3CN	20	2.5	96
7	CH_3	CH_3	H	CH_3CN	20	3.0	80
8	H	H	NO_2	CH_3CN	20	1.5	98
9	H	CH_3	NO_2	CH_3CN	20	3.0	91
10	H	Cl	NO_2	CH_3CN	20	2.0	94
11	H	CH_3	CH_3	CH_3CN	20	6.0	88
12	H	Cl	CH_3	CH_3CN	20	3.5	85

a) Isolated yields.

The cyclodesulfurization of N-(2-hydroxyphenyl)-N'-phenylthiourea appears to involve the formation of a key intermediate of peroxysulfur-dioxide or trioxide (5) like the case of desulfurization of thiourea derivatives.[1)] It seems to be initiated via the formation of an intermediate of phenolate anion and thiyl radical (4) in basic superoxide anion[5)] by one electron transfer from the thiolate anion (3) for $O_2^{-}\cdot$ followed by proton transfer to the resultant HOO•.[5)] Hydrogen abstraction of diphenols by $O_2^{-}\cdot$ to form semiquinones has been reported for a number of catecols.[5-7)] A behavior of $O_2^{-}\cdot$ as an oxidizing agent to accept one electron has been reported. The thiyl radical 4 may couple with

$O_2^{-}\cdot$ to form a peroxysulfenate followed by further oxidation to produce a peroxysulfur intermediate (5). An intramolecular nucleophilic attack by the phenolic hydroxyl anion on the formamidine carbon may form the 2-substituted aminobenzoxazole where sulfur dioxide or trioxide is a good leaving group and liberated SO_2^{-2} or SO_3^{-2} may be further oxidized to SO_4^{-2}.[8)]



In this cyclization, the combination of a neighboring group effect of a hydroxylate anion and the leaving group of SO_nO^{-} seems to play an important role. Benzoxazole derivatives are useful intermediates for the synthesis of antibiotics[9)] and fluorescent whitening agents.[10)] There have been quite a few studies on the cyclodesulfurization of N-(2-hydroxyphenyl)-N'-phenylthioureas using dicyclohexylcarbodiimdie in boiling benzene,[11)] and cyclization of N-(2-hydroxyphenyl)-N',N"-diarylguanidine using phosphoric acid at 140 °C, or in boiling acetic anhydride.[12)] These reactions require high reaction temperature and result in lower yields. N-(2-Hydroxyphenyl)-N'-phenylthioureas are known to react with nickel peroxide or methyl iodide in the presence of triethylamine to give benzoxazole derivatives; in the reaction using nickel peroxide, a radical mechanism is proposed by the isolation of elemental sulfur as one of the main products.[13)] Our reaction did not produce elemental sulfur. Potassium sulfate was mainly isolated instead of elemental sulfur. Our method seems to be involved of ionic nucleophilic substitution and to be promising for the synthesis of 2-substituted aminobenzoxazoles because it requires short reaction time and wide range of lower reaction temperatures (-35~20 °C) for higher yields than those from the known methods.

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