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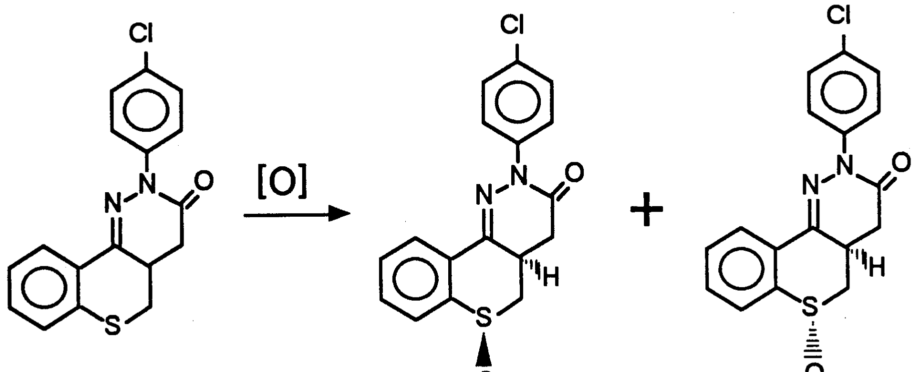
STEREOSELECTIVE OXIDATION OF 2-(4-CHLOROPHENYL)-4a,5-DIHYDRO-2*H*-(1)BENZOTHIOPYRANO[4,3-*c*]PYRIDAZIN-3(4*H*)-ONE TO SULFOXIDE

Tohru NAKAO,* Minoru OBATA, Minoru KAWAKAMI, Nobuhiro MARUBAYASHI, Kenji MORITA and Tetsuya TAHARA
Research Laboratories, Yoshitomi Pharmaceutical Industries, Ltd.,955 Koiwai, Yoshitomi-cho, Chikujo-gun, Fukuoka 871, Japan

Stereoselective oxidation of 2-(4-chlorophenyl)-4a,5-dihydro-2*H*-(1)benzothiopyrano[4,3-*c*]pyridazin-3(4*H*)-one (1) to sulfoxides with a variety of oxidants was examined under mild conditions. The oxidation with $Pb(OAc)_4$ and $NaBrO_2$ stereoselectively gave the *trans*-sulfoxide (2) in good yield. The peroxy reagents and $NaIO_4$ afforded mostly the *cis*-isomer (3).

KEYWORDS stereoselective oxidation; sulfide; sulfoxide; sodium bromite; lead tetraacetate; antianxiety

Previously, we reported that 2-(4-chlorophenyl)-4a,5-dihydro-2*H*-(1)benzothiopyrano-[4,3-*c*]-pyridazin-3(4*H*)-one (1) is oxidized with H_2O_2 to afford *trans* -2-(4-chlorophenyl)-4a,5-dihydro-2H-(1)benzothiopyrano[4,3-*c*]pyridazin-3(4*H*)-one 6-oxide (2) and its *cis*-isomer (3) in a ratio of 1:4.[1,2] Pharmacological activities, i.e. an anxiolytic activity and the affinity to the benzodiazepine receptors, reside almost entirely in the *trans*-isomer (2). Therefore, it was required to establish an industrially acceptable manufacturing method which produces predominantly compound 2. In this paper, we describe a newly developed stereoselective synthesis of the *trans*-sulfoxide (2). The reaction conditions were chosen to prevent any oxidation of the sulfone stage.



1 2 3

The general oxidative procedure is as follows: To a solution of 1 (0.015 mol) in an appropriate solvent was added the oxidant (0.0165 mol) below 10° C, then the mixture was stirred at room temperature until the spot of starting material disappeared on the TLC. The reaction mixture was poured into water, and the resulting precipitate was extracted with $CHCl_3$. The organic layer was separated, washed with aq. $NaHSO_3$, aq. saturated $NaHCO_3$, water, and then dried over anhyd. $MgSO_4$. After the solvent was evaporated, the *cis/trans* ratio of residual crude sulfoxides was determined by HPLC.[3]

Table I. The Reaction Conditions and *cis/trans* Ratios of the Sulfoxide

Reagents	Solvents	Time (h)	Yield (%)	Ratio *trans* (2)	Ratio *cis* (3)
$Pb(OAc)_4$	AcOH	3	90	93	7
$NaBrO_2 \cdot 3H_2O$	Ace-H_2O[b]	3	88	88	12
MCPBA	$CHCl_3$	4	88	24	76
	Diox-H_2O[b]	1	75	20	80
	AcOH	5	90	13	87
$NaIO_4$	AcOH	5	90	13	87
	Diox-H_2O[b]	24[c]	59	22	78
t-BuOOH	$CHCl_3$	24[c]	43	23	77
H_2O_2	AcOH	2.5	88	20	80

a) Yield of crude product. b) Ace : acetone, Diox : dioxane.
c) The reaction was stopped after 24 h due to its slow reaction.

As shown in Table I, oxidation with $Pb(OAc)_4$ and $NaBrO_2$ preferentially proceeded to afford **2** in good yield. On the other hand, *m*-chloroperbenzoic acid (MCPBA), $NaIO_4$, and *tert*-butyl hydroperoxide (*t*-BuOOH) gave predominantly **3** in a *cis/trans* ratio similar to that in the case of H_2O_2.[1] The yield of $NaIO_4$ oxidation in AcOH was higher than in dioxane-H_2O. With *t*-BuOOH oxidation in $CHCl_3$, the reaction proceeded very slowly.

There are many reports on the synthesis of sulfoxides by the oxidation of the corresponding sulfides.[4] The electrophilic oxidation of most organic sulfides is known to take place predominantly on the less hindered side of the sulfide.[5] Thus the axial oxygen of **3** must be more accessible than the equatorial oxygen of **2**, as is the case of 3-substituted thietane 1-sulfoxides.[5c] Our results on the oxidation with $Pb(OAc)_4$ and $NaBrO_2$ are opposite to these principles. The mechanism of this unusual stereoselective reaction is now under investigation.

While the oxidation with $Pb(OAc)_4$ shows good stereoselectivity in producing **2**, use of heavy metal is not desirable from the standpoint of environmental pollution. Thus we recommend $NaBrO_2$ as the oxidizing agents for the industrial production of **2**.

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2) In the present paper, *cis is* defined as the 4a hydrogen and sulfinyl oxygen oriented in the same direction as the plane of the (1)benzothiopyran ring and *trans* in the opposite.
3) Column: SHIM PACK CLC-SIL (Shimadzu corporation), 6.0 x 150 mm.
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