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BENZISOSELENAZOL-3(2H)-ONES AND BIS(2-CARBAMOYL)PHENYL DISELENIDES AS NEW CATALYSTS FOR HYDROGEN PEROXIDE OXIDATION OF ORGANIC COMPOUNDS

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Abstract: Bis (2-carbamoyl)phenyl diselenides and benzisoselenazol-3(2H)-ones, particularly ebselen , have been found as new catalysts for hydrogen peroxide oxidation of sulfides into sulfoxides, N,N-dimethylhydrazones into nitriles, and azines into carbonyl compounds.

Oxidation of organic compounds with hydrogen peroxide is a current problem of synthetic organic chemistry because an oxidant is cheap, ecologically neutral and useful for large-scale synthesis.[1,2] Nevertheless, activity of hydrogen peroxide towards some organic substrates is too low and numerous oxygen-transfer catalysts making oxidation more effective have been used. Among them, selenium compounds such as selenium dioxide, bisaryl diselenides and areneseleninic acids have been reported as efficient hydrogen peroxide activators.[3-7]

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In our previous works it was revealed that 2,4-dinitro- and 2,4-nitrobenzenese leninic acid (NBSA), and bis(2-nitrophenyl) diselenide acted as oxygen-transfer catalysts most probably via benzeneperoxyseleninic acids formed in situ.[8] These catalysts were used in our laboratory for styrene epoxidation,[9] the Baeyer-Villiger oxidation of aromatic and α,β-unsaturated aldehydes and ketones,[10,11] conversion of oximes into carboxylic acid esters[12] and for transformation of N,N-dimethylhydrazones into nitriles.[13] Although the elaborated methods have synthetical value, some of the reactions required a long time and some of products were obtained in moderate yields.

In the present work, we directed our attention to benzisoselenazol-3(2H)-ones **1**, selenoxide **2**, and bis(2-carbamoyl)phenyl diselenides **3** as potential oxygen-transfer catalysts because it was known that ebselen **1a** interacts with the oxygen species in the living cells in the manner similar to that of enzyme glutathione peroxidase.[14]

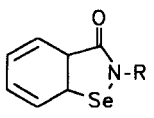
Although it has recently been reported[15] that ebselen was ineffective as catalyst for hydrogen peroxide oxidation of thiols into disulfides, we tested compounds **1-3** as hydrogen peroxide activators in other reactions. There were oxidation of sulfides **4** into sulfoxides **5** (1), of aromatic N,N-dimethylhydrazones **6** into nitriles **7** (2), and of azines **8** into parent carbonyl compounds **9** (3). In all cases, substantial catalytical effects were observed particularly for the reactions carried out for relatively short times when the substrate was not completely consumed (Table 1). When sulfides **4b-d** were oxidized in the presence of catalysts **1, 2** or **3** sulfoxides **5b-d** were formed as sole products and only rarely they were accompanied by minute amounts of sulfones. When selenium dioxide or NBSA were used as catalysts, results strongly depended on the structure of substrate. For example, selenium dioxide, being a good catalyst for oxidation of sulfides **4c** and **4d**, was ineffective for oxidation of **4b**. When benzisoselenazolones **1** or diselenides **3** were used as catalysts, these differencies were less strongly expressed. Most of benzisoselenazolones **1**

Table 1. Oxidation of Compounds **4,6,8** with Hydrogen Peroxide in the Presence of Organoselenium Catalysts.

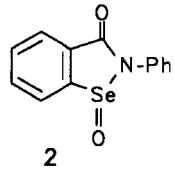
Cata-lyst	Product, (reaction time), yield [%]						
	Sulfoxide (sulfone)			Nitrile			Ketone
	5b (3h)	**5c** (3h)	**5d** (3h)	**7a** (1.5h)	**7b** (10min)	**7c** (15min)	**9b** (20h)
1a	73 (0.0)	99 (1.0)	99 (0.3)	82	66	67	64
1b	80 (0.8)	98 (1.3)	97 (2.3)	33	47	63	6
1c	67 (2.8)	100	100	29	51	62	6
2	41 (0.0)	98 (1.8)	100	70	70	7	48
3a	78 (0.0)	97 (2.2)	99 (0.1)	74	79	81	100
3b	84 (0.0)	99 (1.0)	99 (0.0)	22	57	82	16
3c	71 (5.7)	99 (1.0)	98 (0.2)	33	43	71	19
SeO_2	16 (0.0)	95 (0.0)	93 (0.0)	41	51	51	16
NBSA	52 (0.0)	85 (0.0)	100(0.0)	55	89	64	14
none	3.0 (0.0)	6.0 (0.0)	1.0 (0.0)	0.0	0.0	0.0	0.0

and diselenides **3** exhibited appreciable catalytical activity for oxidation of N,N-dimethyl hydrazones **6** into nitriles **7**. Ebselen **1a** and diselenide **3a** were also active as catalysts for the oxidative regeneration of ketone **9b** from ketazine **8b**, although the reaction was slower and required more severe conditions than reactions (1, 2). Optimal molar ratio of catalyst to the substrate for all reactions tested was 1:20. Contrary to catalytical effects observed in the reactions (1-3), none of compounds **1-3** was active as a catalyst for hydrogen peroxide epoxidation of vinylarenes, such as styrene or stilbene under the same reaction conditions as reported in Ref.[9]

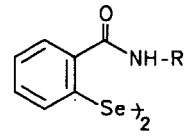
Based on the results presented in Table 1, ebselen **1a** was selected as most versatile catalyst because it was highly active, ease to prepare by four-steps procedure from anthranilic acid[16,17] and it was not toxic.[18]



1



2



3

1,3	R
a	Ph
b	Me
c	t-Bu

$$R^1\text{-}S\text{-}R^2 \xrightarrow[MeOH]{H_2O_2,\,cat.} R^1\text{-}S(=O)\text{-}R^2 \qquad (1)$$

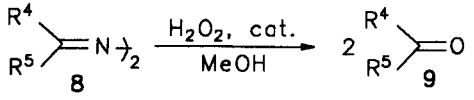
4 5

4,5	R^1	R^2
a	Ph	Ph
b	Me	2-$NO_2C_6H_4$
c	Me	Ph
d	Me	4-$CH_3C_6H_4$

$$R^3\text{-}CH{=}N\text{-}NMe_2 \xrightarrow[MeOH]{H_2O_2,\,cat.} R^3\text{-}CN \qquad (2)$$

6 7

6,7	R^3
a	4-$NO_2C_6H_4$
b	4-BrC_6H_4
c	1-naphtyl



8 9

8,9	R^4	R^5	8,9	R^4	R^5
a	H	Ph	f	Me	3-pyridyl
b	Me	Ph	g	Et	Ph
c	Me	4-$MeOC_6H_4$	h	Pr	Ph
d	Me	4-BrC_6H_4	i	Ph	Ph
e	Me	4-$NO_2C_6H_4$			

Table 2. Synthesis of sulfoxides **5**, nitriles **7**, aldehyde and ketones **9** by oxidation of sulfides **4**, N,N-dimethylhydrazones **6** and azines **7** with hydrogen peroxide in the presence of ebselen.

Product	Reaction Conditions		Yield (%)	M.p.[a], Ref.	
	Time (h)	Temp (°C)			
5a	3	20	92	70-72	(70-22)[20]
5b	48	20	95	101-102	(101-101)[21]
5c	3	20	98	29-30	(29.5-30.0)[26]
5d	3	20	95	52-54	(50-54)[22]
7a	14	20	98	148	(193)[13]
7b	3	20	92	114	(114)[13]
7c	17	20	97	37-39	(37-38)[23]
9a	72	20	62	oil[b]	—
9b	48	20	100	20	(20.5)[24]
	2	65	100		
9c	3	65	91	38	(38-39)[24]
9d	24	65	96	53	(50-51)[24]
9e	72	65	90	81	(80-82)[24]
9f	72	65	93	11-12	(13-14)[25]
9g	1.5	65	100	18.6-19.5	(18.6)[24]
9h	1.5	65	100	oil	(11-13)[24]
9i	72	65	98	47	(48.1)[24]

[a] Products were identified and their purity was confirmed by GC/MS and ^{1}H NMR

[b] Mixture of benzaldehyde and its dimethyl acetal (62%), accompanied by methyl benzoate (30%).

Oxidation of sulfides into sulfoxides, of N,N-dimethylhydrazones into oximes and regeneration of carbonyl compounds from azines with hydrogen peroxide in the presence of ebselen **1a** have a synthetic value. For this purpose, the reactions were continued until all substrate was exhausted during the period reported in Table 2.

In comparison with synthesis of nitriles reported earlier,[13] using ebselen as catalyst effected in shortening reaction time and increasing the product yields. Oxidative regeneration of parent carbonyl compounds from azines by their oxidation with MCPBA has been recently reported[19] but it had not preparative value. The reaction presented here is useful for this purpose and it can be used when the bisimine function is used as a blocking group and should be removed. The results presented in Table 2 show that ketones **9b-i** are simply regenerated in excellent yields contrary to benzaldehyde **9a** which was accompanied by substantial amounts of its diethyl acetal and methyl benzoate.

Experimental:

Melting points: Digital Melting Point Apparatus Electrothermal IA 9100. ^{1}H NMR: Bruker 300 MHz Spectrometer. Products of oxidation were analysed using Hewlett-Packard 5890 apparatus with capillary column HP-1.25 m, 0.2 mm, 100^{o}C, 3^o/min, 250^{o}C or 120^{o}C, 6^o/min, 300^{o}C, or 150^{o}C, 8^o/min and identified by comparison with the original samples as well as by comparison of their MS spectra (Hewlett-Packard 5971A) with data reported in the library NBS 49K and 75K.

Sulfide **4b** was synthesized according to known procedure[27], other sulfides were purchased from Aldrich Chem.Co. N,N-Dimethylhydrazones **6** were prepared from the corresponding aldehydes freshly distilled or recrystallized before use.[13] Azines **8** were obtained from benzaldehyde (**8a**) or corresponding ketones (**8b-i**) according to procedure reported in ref.[19]

Oxidation of Sulfides 4 into Sulfoxides 5.

To a magnetically stirred solution of sulfide **4** (2.0 mmol) in methanol (30 ml) and catalyst **1-3** (0.1 mmol), aqueous hydrogen peroxide (30% ; 0.23 ml, 2.23 mmol) was added and the reaction was continued at room temperature for 3h.

After this period satd. aqueous sodium chloride (80 ml) was added, and unreacted substrate, and products were extracted with dichloromethane (3x30 ml). The organic solution was dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated in vacuo to a small volume (ca.5 ml) and analysed by means of gas chromatography. The reaction was carried out in the same way for preparative purposes using ebselen (**1a**) (0.27g, 0.1 mmol) as a catalyst (for sulfide **4b** reaction time was prolonged to 48 h). After extraction of product with chloroform, extract was evaporated to dryness in vacuo and the residue was recrystallized from ethanol (**5a,d**) or chromatographed on silica gel using chloroform-ethyl acetate 3:1 as an eluent (**5b,c**).

Oxidation of N,N-Dimethylhydrazones 6 into Nitriles 7.

Aqueous hydrogen peroxide (30% ; 1.0 ml, 9.6 mmol) was added to a stirred solution of dimethylhydrazone **6** (2.5 mmol) and the catalyst **1-3** (0.125 mmol) in methanol (30 ml), and the mixture was maintained at room temperature for the time given in Table 1. After this period, the reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3x15 ml). The extracts were combined, washed with satd. aqueous sodium hydrogen carbonate (3x15 ml), dried over anhydrous sodium sulfate and filtered. The solvent was evaporated off in vacuo and the residue was analysed by means of gas chromatography. The reaction was carried out in the same way for preparative purpose using ebselen (**1a**) (0.34g, 0.125 mmol) as a catalyst. Reaction times are given in Table 2. The residues after solvent evaporation were essentially pure nitriles 7 (Table 2), if need they could be recrystallized from hexane.

Oxidation of Azines 8 into Carbonyl Compounds 9.

To a magnetically stirred suspension of ketazine **8b** (0.12g, 0.5 mmol) and catalyst **1-3** (0.025 mmol), aqueous hydrogen peroxide (30% ; 0.17 ml, 1.65 mmol) was added and the reaction was continued at room temperature for 20 h. After

this period, aqueous solution (7 ml) containing sodium chloride (0.35g) and sodium hydrogen carbonate (0.07g) was added and the mixture was extracted with dichloromethane (2x1 ml). The organic solution was dried over anhydrous sodium sulfate and analysed by means of gas chromatography.

For preparative purpose, aqueous hydrogen peroxide (30% ; 1.7 ml, 16.5 mmol) and ebselen (**1a**) (0.68g, 0.25 mmol) were added in one portion to the stirred solution or suspension of azine **8** (5.0 mmol) in methanol (15 ml) and reaction was continued at 65^{o}C for a period given in Table 2. When the reaction time was longer than 24 h, additional portions of oxidant (1 ml of aq. H_2O_2 in 5 ml of MeOH) were added each day. After the reaction was finished, the mixture was poured into aqueous solution of sodium chloride (5%, 70 ml) and product was extracted with dichloromethane (3x10 ml). Combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to a small volume (ca. 5 ml) The concentrate was filtered through short column packed with silica gel (20 g) and ketone was eluted using dichloromethane (**9b-e, 9g-i**) or ethyl acetate (**9f**).

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