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Selective oxidation of aromatic aldehydes to arenecarboxylic acids using ebselen-*tert*-butyl hydroperoxide catalytic system

Halina Wójtowicz, Monika Brząszcz, Krystian Kloc and Jacek Młochowski*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, Wyb. Wyspiańskiego 27, 50-370 Wrocław, Poland

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Abstract—It has been found that aromatic aldehydes with electron-withdrawing as well as electron-donating substituents are oxidized to arenecarboxylic acids using *tert*-butyl hydroperoxide in the presence of ebselen (2-phenylbenzisoselenazol-3(2*H*)-one) as a catalyst. The reaction is highly chemoselective and formation of phenols, being the products of competitive Baeyer–Villiger rearrangement, is marginal. It has been assumed that this rearrangement is inhibited by steric hindrance of the electron-deficient oxygen atom in the transient tetrahedral intermediate.

1. Introduction

Oxidation of aldehydes to carboxylic acids is one of the most common reactions in organic chemistry. Although many oxidizing agents have been used for this purpose the problem of the efficient conversion of aromatic aldehydes to arenecarboxylic acids remains still open.[1] The most common oxidants such as chromic acid, potassium permanganate in acid, basic and neutral solution, bromine, nitric acid, silver oxide and others are not attractive because they do not fulfill the requirements of modern practical organic synthesis and environmental restrictions. On the other hand, oxidation with environmentally friendly reagents such as dioxygen gives poor results. Using peroxyacids or hydrogen peroxide in the presence of various catalysts leads to phenols since competitive Baeyer–Villiger rearrangement takes place.[1,2]

It is known that hydrogen peroxide, in the presence of 2,4-dinitrobenzeneseleninic acid, or selenium dioxide, oxidizes aromatic aldehydes with electron-donating substituents to phenol formates which are easily hydrolyzed to phenols.[3,4] When of the same oxidant and benzeneseleninic acid as catalyst were used for oxidation of aromatic aldehydes, unsubstituted or substituted with electron-withdrawing groups, arenecarboxylic acids were obtained mostly in fair yields.[5]

Most recently a convenient method for oxidation of aromatic, heteroaromatic and aliphatic aldehydes to carboxylic acid with 30% hydrogen peroxide–SeO_2 (5% mol) in THF has been elaborated in our laboratory. Nevertheless, when the starting aldehydes have had electron-donating substituents in *ortho* or *para* positions substantial amounts of phenols were formed or even the phenol was a sole product.[6] It raises a question about the role of oxidant and catalyst in this reaction. Is the electronic environment of the carbonyl carbon atom the only decisive factor for alternative pathways leading to acid or phenol formation?

2. Results and discussion

In this work we provide the evidence that oxidation of aromatic aldehydes **1**, having electron-withdrawing (**1a**,**b**) as well as electron-donating substituents (**1c**–**h**), with *tert*-butyl hydroperoxide (TBHP), leads almost exclusively to arenecarboxylic acids **2** when 2-phenyl-benzisoselenazol-3(2*H*)-one (ebselen) **4** is used as an oxygen-transfer catalyst. None or only minute amounts of phenols **3** were produced. TBHP is the cheap reagent, which to our knowledge has not been previously used for the oxidative conversion of aldehydes to acids except in the oxidation of methylacrolein.[7,8] On the other hand, different selenium compounds have been used as stoichiometric oxidants and catalysts for oxidation of organic substrates.[9–11] Our particular interest was focused on ebselen because this compound, as well as related diselenides and other cyclic selenenamides, are known as glutathione mimics reacting with bioactive oxygen species.[12] Ebselen has been used as catalyst in a few cases only: for hydroperoxide oxidation of thiols into disulfides,[13,14] oxidation of sulfides into sulfoxides and for oxidative conversion of the azomethine group.[15] It is known to be a nontoxic compound[12] and can be easily obtained

Keywords: aldehydes; *tert*-butyl hydroperoxide; carboxylic acids; ebselen; oxidation.

* Corresponding author. Tel.: +48-71-3202419; fax: +48-71-3284064; e-mail: mlochowski@kchf.ch.pwr.wroc.pl

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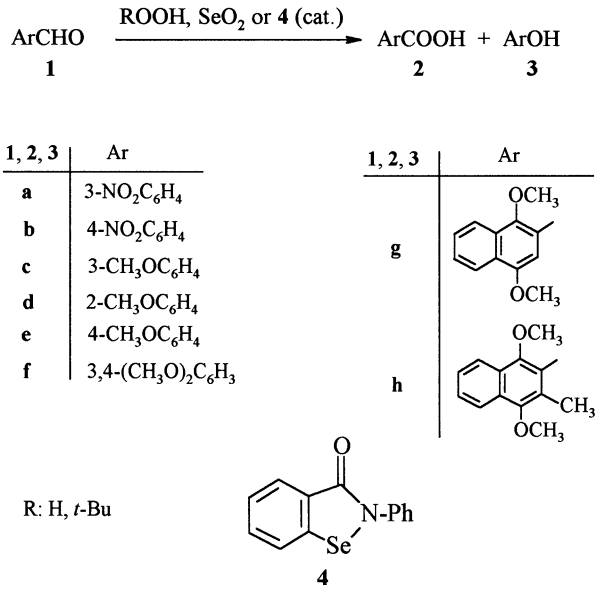


Scheme 1.

according to known procedure in a four-step reaction sequence starting from anthranilic acid[16] or in a one-pot synthesis from benzanilide.[17]

The results of our studies are presented in Scheme 1 and Table 1. When the oxidant was 30% H_2O_2–SeO_2 and an electron-withdrawing substituent was present in the *meta* or *para* position or when an electon-donating substituent was situated in the *meta* position the corresponding acids **2a–c** were produced and no phenol formation was observed. Substantial amounts of phenols (**3d**,**e**) were formed when the aldehyde was substituted with an electron-donating methoxy group in the *ortho* or *para* position. Further substitution of electron-donating groups provided the phenol **3f–h** as the main product. The results were quite different when TBHP–ebselen was used as an oxidant. The reaction proceeded more slowly but most of the aldehydes were oxidized exclusively to acids **2a–f** or acids **2g**,**h** were accompanied only by minute amounts of the corresponding phenols **3g**,**h**. Moreover, when the reaction was done on a larger scale (50 mmol) with aldehydes **1d–f** the results were fully satisfactory, thus demonstrating that the reaction is of practical value.

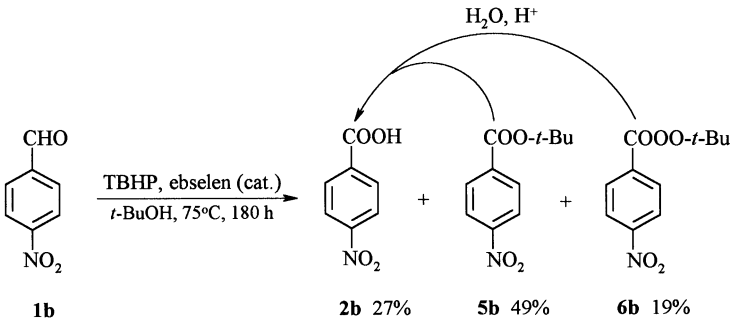
The reactions carried out on the selected aldehydes **1d–h** using TBHP and selenium(IV) oxide instead of ebselen were less effective (Table 1). In addition, when aldehydes **1f–h** were oxidized with 80% TBHP–ebselen in THF rather than *t*-BuOH the progress of the reaction was very slow. Conversion of the substrates after 94 h was only 5–54%. Another oxidant, 30% H_2O_2–ebselen was also ineffective. These results lead to the assumption that TBHP–ebselen is the optimal reagent combination for selective oxidation of electron-rich aromatic aldehydes to carboxylic acids.

More detailed studies of the oxidation of aldehydes **1** have shown that the reaction resulted in a mixture of acids **2** accompanied with substantial amounts of their *tert*-butyl esters **5** and *tert*-butylperoxycarboxylic esters **6** which

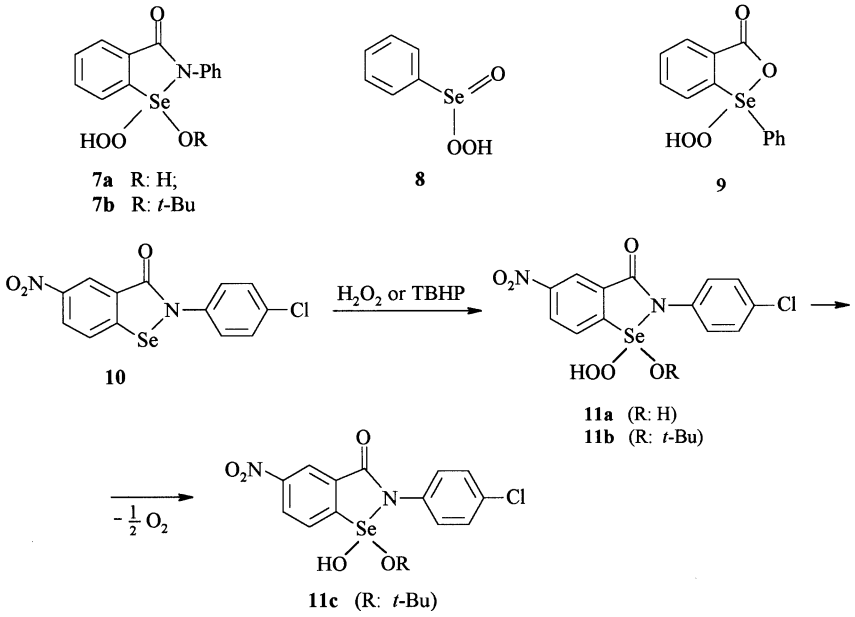
Table 1. Oxidation of aromatic aldehydes **1**

1	Oxidant: H_2O_2–SeO_2 THF, reflux[a]			Oxidant: TBHP–ebselen *t*-BuOH, 75°C				Oxidant: TBHP–SeO_2 *t*-BuOH, 75°C			
	Reaction time, (h)	Yields[b] (%)		Reaction time, (h)	Conversion (%)	Yields[c] (%)		Reaction time, (h)	Conversion (%)	Yields[c] (%)	
		2	**3**			**2**	**3**			**2**	**3**
a	5	99	–	48	100	94	–				
b	3	87	–	180	100	90	–				
c	24	96	–	24	100	95	–				
d	24	44	49	72	100	96 (92)[d]	–	200	35	31	10
e	24	46	41	48	100	97 (94)[d]	–	24	100	95	–
f	24	21	76	120	100	99 (96)[d]	–	200	100	75	5
g	96	22	55	120	42	67	4	200	37	46	–
h	48	–	81	120	90	58	10	200	22	68	5

[a] Data for oxidation **1b–h** taken from Ref. 6.
[b] Conversion of substrate **1** was 100%.
[c] Isolated yields of acids **2** and yields of phenols **3** determined by GC, both referred to the converted substrate **1**.
[d] Data in parentheses are given for the reaction carried out at 50 mmol scale.



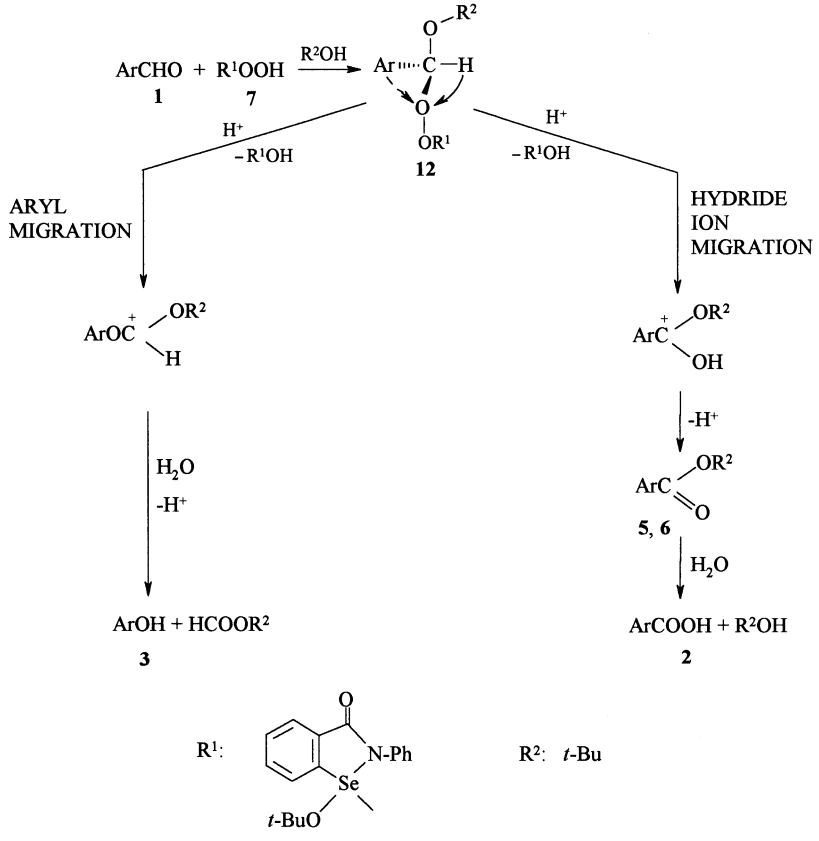
Scheme 2.



Scheme 3.

easily hydrolyzed when the reaction mixture was worked up. The esters **5** and **6** also decomposed to acids **2** under the conditions of GC analysis. For example, 4-nitrobenzaldehyde **1b** produced a mixture of 4-nitrobenzene-carboxylic acid **2b**, *tert*-butyl 4-nitrobenzoate **5b** and peroxy-*tert*-butyl 4-nitrobenzoate **6b** which easily hydrolyzed to **2b**. (Scheme 2).

The role of ebselen as an oxygen transfer agent remained ambiguous. By analogy to benzene-peroxyseleninic acid **8**[18] and postulated hydroperoxyselenurane **9**[19] it seemed to be possible that hydroperoxyselenurane **7** was an active intermediate. When ebselen was treated with hydrogen peroxide an unstable crystalline compound, most probably **7a**, was produced but could not be identified because upon isolation



Scheme 4.

it immediately fragmented to ebselen selenoxide, water and molecular oxygen. More stable hydroperoxyselenurane **11a** was obtained when ebselen analog **10** was treated with hydrogen peroxide. Another hydroperoxyselenurane **11b** was also obtained but it quickly lost oxygen, producing **11c** (Scheme 3). Nevertheless, identification of **11a** and **11c** is strong support for the hypothesis that in TBHP–ebselen system active oxidant is the hydroperoxyselenurane **7b**.

The results presented above explain the role of TBHP and ebselen in the chemoselective oxidation of aromatic aldehydes into arenecarboxylic acids. In light of the widely accepted mechanism for reaction of carbonyl compounds with peroxyacids[20–22] the first step is addition of hydroxyperoxide **7** to the carbonyl compound **1** resulted in the formation of tetrahedral intermediate **12** (Scheme 4). The subsequent step of the Baeyer–Villiger rearrangement, which is rate-determining, should be migration of the aryl group to the electrophilic oxygen atom of the peroxide bridge and simultaneously, cleavage of the O–O-bond along with release of hydroxyselenurane R^1OH. The phenol **3** should be the final product. Nevertheless, two bulky groups R^1 and R^2 in the vicinity of the electrophilic oxygen atom in the peroxy bridge hinder aryl migration and competitive hydride ion migration predominates. This pathway leads to esters **5**,**6** and finally to the acid **2**.

3. Conclusions

We have described a highly selective and practical method for conversion of both electron-deficient and electron-rich aromatic aldehydes to arenecarboxylic acids using *tert*-butyl hydroperoxide in the presence of ebselen. It has also been shown that ebselen can act as an oxygen-transfer agent via hydroperoxyselenurane as an active intermediate. The postulated mechanism is similar to the mechanism of action of peroxyseleninic acids and quite different from the enzymic.

4. Experimental

4.1. General

The reaction products, presented in Table 1, were analyzed using Hewlett–Packard 5990/II apparatus with capillary column HP-1 (25 m, 0.22 mm). The products were identified by comparison of their MS spectra (Hewlett–Packard 5971A) with data reported in the library NBS 49K and 75K, of their melting points (Digital Melting Point Apparatus Electrothermal IA 91100), by analysis of their ^{1}H NMR data ($CDCl_3$ or DMSO, TMS, Bruker DRX 300 spectrometer) and by analysis of IR spectra (Perkin–Elmer 2000 FT spectrometer).

Hydrogen peroxide (30%), *tert*-butyl hydroperoxide (80% in di-*tert*-butylperoxide/water 3:2), *tert*-butanol, selenium(IV) oxide and aldehydes **1a**–**e** were purchased from Aldrich and Fluka. Aldehydes **1f**–**h**, synthesized according to the procedure reported in Ref. 23, were delivered by Professor Dr Ludwik Syper. 2-Phenylbenzisoselenazol-2(2*H*)-one (ebselen) was obtained in the way reported in Ref. 16.

4.2. General procedure for oxidation of aldehydes 1 with TBHP–ebselen or TBHP–SeO_2

A solution of aldehyde **1** (5 mmol) *tert*-butyl hydroperoxide (1.26 ml, 10 mmol) and ebselen (0.068 g, 0.25 mmol), or selenium(IV) oxide (0.028 g, 0.25 mmol) in *tert*-butanol (7.5 ml), was stirred at 75°C for the periods given in Table 1. The solid (if any) was filtered off and the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane (10 ml) 5% HCl (20 ml) was added and the mixture was stirred at room temperature for 2 h. The organic and aqueous layers were separated, and from the aqueous layer acid **2** was extracted with dichloromethane (3×10 ml). The organic solutions were collected, dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. The residue was found to consist of pure acid (**2a**–**f**),[24] except in the case of acids (**2g**,**h**), which were accompanied with unreacted substrate (**1g**,**h**). For the latter compounds, solution was treated with 2.5% aqueous solution of sodium hydrogencarbonate (20 ml), and the water layer was acidified with 5% HCl (20 ml). The precipitated acid (**2g**,**h**) was filtered off, dried and recrystallized from toluene–hexane (**2g**) or dichloromethane–hexane (**2h**). Additional amounts of these acids were isolated from the filtrate by extraction with dichloromethane.

The above method was also used for the oxidation of aldehydes in ten-fold larger scale. The solution of aldehyde (**1d**–**f**) (50 mmol) and ebselen 0.68 g, 2.5 mmol) in *tert*-butanol (75 ml), was treated with *tert*-butyl hydroperoxide in the same manner as described above. After the reaction finished, a pinch of Pd/carbon was added to decompose peroxides, and the mixture was allowed to stand overnight. The solvent was evaporated in vacuo and the acids were then isolated in the way described earlier using proportionally enlarged amounts of HCl and dichloromethane.

4.2.1. 1,4-Dimethoxy-2-naphthoic acid (2g). White prisms, mp 168–169°C from toluene–hexane (found: C, 67.53, H, 4.95; $C_{13}H_{12}O_3$ requires: C, 67.23, H, 5.21%). ν_{max} (KBr) 3020, 2962, 2840 (CH), 2616 (broad, OH), 1693 (CO). δ_H ($CDCl_3$), 3.98 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.31 (s, 1H, ArH), 7.59 (dd, 2H, J=6.4 and 3.2 Hz, ArH), 8.03 (dd, 1H, J=6.4 and 3.2 Hz, ArH), 8.24 (dd, 1H, J=6.4 and 3.2 Hz, ArH), 10.60 (bs, 1H, OH).

4.2.2. 1,4-Dimethoxy-3-methyl-2-naphthoic acid (2h). Pale yellow prisms, mp 83–85°C from dichloromethane–hexane (found: C, 68.35, H, 5.52; $C_{14}H_{14}O_3$ requires: C, 68.28; H, 5.73%). ν_{max} (KBr) 3005, 2936, 2842 (CH), 2785–1935 (OH), 1685 (CO). δ_H ($CDCl_3$), 2.60 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.47 (t, 1H, J=8.3 Hz, ArH), 7.58 (t, 1H, J=8.3 Hz, ArH), 8.03 (d, 1H, J=8.3 Hz, ArH), 8.12 (d, 1H, J=8.3 Hz, ArH), 10.65 (s, 1H, OH).

4.3. Conversion of 4-nitrobenzaldehyde (1b) into esters 5b, 6b and acid 2b

A solution of the aldehyde **1b** (0.776 g, 5 mmol) and ebselen (0.068 g, 0.25 mmol) in *tert*-butanol (15 ml) was treated

with *tert*-butyl hydroperoxide in the same manner as described in Section 4.2, and the reaction was continued for 180 h. After this period, the solvent was evaporated in vacuo and the products were isolated on silica gel column. The esters **5b** and **6b** were eluted with chloroform–hexane (2:1) and then acid **2b** was eluted with acetone. In another experiment, the reaction mixture was hydrolyzed with 70% sulfuric acid (35 ml) at 100°C for 1 h. The formed solid, filtered off and dried in air was pure acid **2b** (yield 89%).

4.3.1. *tert*-Butyl 4-nitrobenzoate (5b). White prisms, yield 49%, mp 114–116°C, Ref. 25 115–116°C.

4.3.2. Peroxy-*tert*-butyl 4-nitrobenzoate (6b). White prisms, yield 19%, mp 71–74°C, Ref. 26 68–70°C.

4.4. Oxidation of 2-(4-chlorophenyl)-5-nitrobenziso-selenazol-3(2*H*)-one (10) with hydrogen peroxide

A solution of compound **10** (0.88 g, 2.5 mmol) in THF (100 ml) was added dropwise, over 1 h with vigorous stirring, to 30% aqueous hydrogen peroxide (20 ml) which was cooled on an ice/salt bath. The reaction was continued for an additional 1.5 h while temperature grew up to 0°C, and then the reaction mixture was concentrated in vacuo to half of the initial volume. The solution was cooled to −20°C and crystallized **11a** was filtered off and dried in vacuo over phosphorus pentoxide.

4.4.1. 1-Hydroxy-1-hydroperoxy-2(4-chlorophenyl)-5-nitrobenzisoselenazolon-3(2*H*)-one (11a). Pale yellow powder, yield 0.735 g (73%), mp 207–209°C (decomposition with gas evolving), (found: C, 38.65, H, 2.32, Cl, 9.00, N, 6.70%; $C_{13}H_9ClN_2O_6Se$ requires: C, 38.68, H, 2.25, Cl, 8.78, N, 6.94%). ν_{max} (KBr) 3252–2720 (OH, CH), 2358 (OOH), 1634 (CO), 1523, 1350 (NO_2), 827 (SeO) cm^{-1}; δ_H (DMSO-d_6), 3.37 (bs, 2H, OH), 7.53 (d, 2H, *J*=8.8 Hz, ArH), 7.58 (d, 2H, *J*=8.8 Hz, ArH), 8.52 (d, 2H, *J*=8.3 Hz, ArH), 8.68 (dd, 1H, *J*=8.3 and 2.1 Hz, ArH).

4.5. Oxidation of 2-(4-chlorophenyl)-5-nitrobenziso-selenazol-3(2*H*)-one (10) with *tert*-butyl hydroperoxide

A solution of **10** (0.353 g, 1.0 mmol) in THF (25 ml) was added dropwise over 30 min with vigorous stirring, to *tert*-butyl hydroperoxide (10 ml) which was cooled on an ice/salt bath. The reaction was continued for an additional 1.5 h while the temperature warmed to 0°C. The solvent was evaporated in vacuo without heating. The residue was dissolved in ethyl ether (10 ml) and the solution was left to stand for a night at −20°C. The crystalline **11b** was filtered off and dried for a short time (1 h) in vacuo over phosphorus pentoxide. A cream-colored powder was obtained 0.335 g (73%) mp 119–120°C (decomposition with gas evolving). The compound **11b** was unstable, losing molecular oxygen to give **11c** even during a short period of storage (24 h), as when KBr discs were prepared, or when it was dissolving in NMR solvents.

4.5.1. 1-Hydroxy-1-*tert*-butoxy-2(4-chlorophenyl)-5-nitrobenzisoselenazolon-3(2*H*)-one (11c). Pale yellow powder, yield 0.735 g (73%), mp 194–200°C (decomposition) (found: C, 46.27, H, 4.02, Cl, 8.10, N, 6.43. $C_{17}H_{17}ClN_2O_5Se$ requires: C, 46.01, H, 3.86, Cl, 7.99, N, 6.31%). ν_{max} (KBr) 3243–2868 (OH, CH), 1621 (CO), 1550, 1342 (NO_2), 858, 837 (SeO) cm^{-1}; δ_H (DMSO-d_6), 1.09 (s, 9H, CH_3), 7.53 (d, 2H, *J*=9.0 Hz, ArH), 7.58 (d, 2H, *J*=9.0 Hz, ArH), 8.52 (d, 2H, *J*=8.1 Hz, ArH), 8.70 (dd, 1H, *J*=8.1 and 2.1 Hz, ArH), 10.73 (bs, 1H, OH).

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