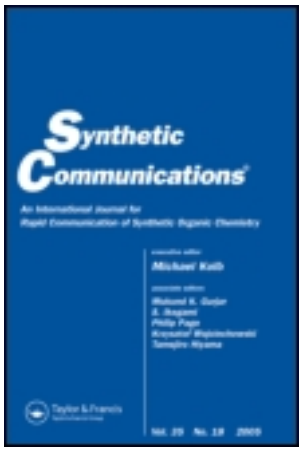

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ONE-POT OXIDATION OF AZOMETHINE COMPOUNDS INTO ARENECARBOXYLIC ACIDS

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ABSTRACT

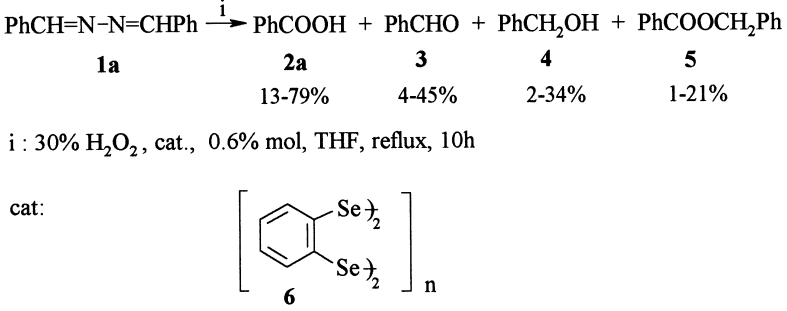
Aromatic azomethine compounds, such as aldazines **1**, aldoximes **7** and tosylhydrazones **8** oxidized with 30% hydrogen peroxide in the presence of poly(bis-1,2-phenylene) diselenide (**6**) as catalyst produce arenecarboxylic acids **2** mostly in high to excellent yields. The presented one-pot procedure has a synthetic value.

*Corresponding author.

The carboxylic acids are group of compounds important for industrial and preparative organic chemistry.[1,2] One of the simplest method applied for their synthesis is oxidation of the carbonyl compounds,[2,3] also with hydrogen peroxide in the presence of selenium compounds, such as selenium(IV) oxide,[4] benzeneseleninic acid[5] and poly(bis-9,10-anthracenyl) diselenide (PADS).[6]

The main goal of the work presented here was to extend the methodology of arenecarboxylic acids synthesis through hydrogen peroxide oxidation of aromatic aldehyde derivatives having azomethine moiety C=N instead of carbonyl group. This approach seems to be attractive because azomethine compounds are easily available crystalline species and some of them (e.g. azines, oximes and hydrazones) can also be obtained by the particular ways other than direct synthesis from aldehydes and ketones.[7] Moreover, they also play an important role in the protecting and deprotecting procedures of carbonyl compounds.[8] According to the tendency of contemporary organic chemistry the oxidant should be easily available, cheap and environmentally friendly. The hydrogen peroxide fulfill these requirements, although in most of the reactions is used in the presence of suitable catalyst.[9]

Continuing our studies on hydrogen peroxide oxidation catalyzed by selenium compounds,[4,6,9,10] we have found that oxidation of benzaldazine (**1a**) in THF[11] leads to the mixture of benzoic acid (**2a**), benzaldehyde (**3**), benzyl alcohol (**4**) and benzyl benzoate (**5**) (Scheme 1).



Scheme 1.

A variety of diaryl diselenides and other selenium compounds such as selenium(IV) oxide, 2-phenylbenzisoselenazol-3(2H)-one (ebselen), and benzene-1,2-diseleninic acid were examined as catalyst in this model reaction.[12]

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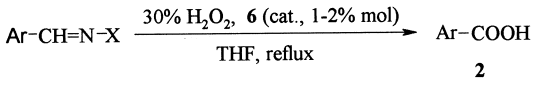
The highest total yield (95%) of the oxidation products **2a**, **3** and **5** was found when poly(bis-1,2-phenylene)diselenide (**6**) was used as catalyst. The major product was desired acid **2a** (79%), accompanied by the aldehyde **3** (16%) and trace amounts of the alcohol **4** and ester **5**. Thus, diselenide **6** was selected as a catalyst for preparative hydrogen peroxide oxidation of various aromatic aldazines (**1**), aldoximes (**7**) and tosylhydrazones (**8**) (Scheme 2). The reaction was carried out in THF under reflux for the period from 6 hours to 10 days depending on the substrate used (Table 1).



X : –N=CH–Ar (**1**); – OH (**7**); – NHTs (**8**)

1,2,7,8	R	1,2,7,8	R	1,2,7,8	R
a	Ph	**i**	4-$MeOCOC_6H_4$	**q**	2-$MeOC_6H_4$
b	2-naphthyl	**j**	4-$NO_2C_6H_4$	**r**	4-$MeOC_6H_4$
c	4-MeC_6H_4	**k**	3-$NO_2C_6H_4$	**s**	3,4,5-$(MeO)_3C_6H_2$
d	4-$iPrC_6H_4$	**l**	2-$NO_2C_6H_4$	**t**	1-naphtyl
e	4-$tBuC_6H_4$	**m**	2-ClC_6H_4	**u**	3-$MeOC_6H_4$
f	4-FC_6H_4	**n**	2,4-$Cl_2C_6H_3$	**v**	3-$PhOC_6H_4$
g	4-ClC_6H_4	**o**	2,6-$Cl_2C_6H_3$		
h	4-BrC_6H_4	**p**	2-Cl-6-FC_6H_3		

Scheme 2.

Oxidation of the aromatic azomethine compounds having no substituents **1a**,**b**, **7a**,**b**, **8a**,**b** and these ones bearing alkyl group **1c–e**, **7c–e**, **8c–e** and electron withdrawing substituents **1f–i**, **1k–n**, **1p**, **7f–p**, **8f–p** gave corresponding carboxylic acid despite of the type of azomethine group. When the substituent was present in ortho-position **1l–n**, **7l–n**, **8l–n** or two substituents were in both of ortho-positions **1p**, **7o**,**p**, **8o**,**p** the reaction proceded more slowly. In all these cases, arenecarboxylic acids (**2a–p**) were isolated in yields above 90%.

When the electron-donating methoxy groups were present in the ortho or para positions of aromatic ring, the yields of acid **2q–s** were substantially lower (15–68%). The acids were accompanied with tarry mixtures of the phenols and the products of their subsequent transformations.

Exceptionally, oxidation of azine **1t**, oxime **7t** and tosylhydrazone **8t** lead to 1-naphthoic acid (**2t**) and (1-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid (**9**)[15] resulted from oxidative transformations of the generated

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Table 1. Oxidation of Aldazines **1**, Aldoximes **7**, and Tosylohydrazones **8** into Carboxylic Acids **2**

Product **2**	Yield of Acid **2** [%] (Reaction Time [h]) from **1**	from **7**	from **8**	Mp., (Ref.[14])	
a	99 (18)	99 (10)	98 (9)	120–122	(121–123)
b	99 (72)	99 (36)	97 (20)	185–186	(185–187)
c	99 (60)	100 (42)	96 (18)	179–180	(180–182)
d	96 (72)	100 (70)	95 (15)	117–118	(117–120)
e	97 (75)	92 (40)	93 (16)	164–166	(165–167)
f	94 (48)	100 (24)	98 (12)	184–186	(184–187)
g	91 (38)	92 (24)	92 (15)	240	(239–241)
h	99 (20)	98 (28)	90 (10)	254–256	(252–254)
i	95 (24)	96 (24)	98 (8)	220–221	(221–223)
j	–[a]	94 (38)	94 (12)	238–239	(239–245)
k	100 (40)	96 (42)	98 (10)	140–141	(140–142)
l	93 (86)	100 (63)	96 (8)	142–145	(146–148)
m	98 (140)	90 (63)	98 (85)	140–141	(138–140)
n	100 (240)	98 (145)	100 (48)	156–159	(157–160)
o	–[b]	92 (240)	94 (144)	142–143	(143–145)
p	100 (160)	100 (72)	99 (52)	157–158	(159–161)
q	18 (50)	15 (41)	41 (6)	99–100	(99–100)
r	25 (50)	23 (65)	40 (16)	181–183	(182–185)
s	33 (40)	16 (50)	68 (20)	168–170	(168–171)
t	24[c] (115)	30[c] (115)	16[c] (24)	159–161	(160–162)
u	92 (41)	96 (42)	99 (14)	104–105	(106–108)
v	91 (66)	94 (28)	90 (24)	147–148	(149–150)

[a]The substrate **1j** was completely insoluble in THF-H_2O_2; [b]after 10 days only a little reaction progress was observed; [c]accompanied with (1-oxo-1,3-dihydroisobenzofuran-1-yl)-acetic acid (**9**[15] 24–70% yield).

in situ 1-naphtol.[16] 3-Methoxy, and 3-phenoxybenzaldazines **1u–v**, related oximes **7u**,**v** and tosylhydrazones **8u**,**v** were oxidized exclusively to acids **2u**,**v** (90–99%).

EXPERIMENTAL

All isolated acids **2** presented in Table were identified after their recrystallization from ethanol-water (**2a**,**k**,**l**,**q**,**v**), methanol-water (**2c–e**, **2n–p**, **2u**), chloroform (**2b**,**f**,**j**,**r**), THF-water (**2g–i**), by their melting points (Digital

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Melting Point Apparatus Electrothermal IA 91100) and by comparison of their ^{1}H NMR data ($CDCl_3$ or DMSO-d_6, TMS, Bruker DRX 300 Spectrometer) with these reported in ref.[19] Commercially available starting materials Aldrich and Fluka of purity above 95% were used without additional purification. Aldazines **1a–v** and aldoximes **8a–v** were obtained from corresponding aldehydes **3a–v** by their treating with hydrazine or hydroxylamine respectively, according to the procedures reported in ref.[20] Tosylhydrazones **8a–v** were prepared with modified procedure reported in ref.[21,22]

Poly(*bis*-1,2-phenylene) Diselenide (6)[23]

The solution of lithium diselenide prepared according to ref.[6] from lithium (0.75 g, 0.10 mol) and selenium (8.0 g, 0.10 mol) in HMPT (30 ml) was added to a stirred solution of 1,2-diiodobenzene[26] (16 g, 0.048 mol) in THF (40 ml). Tetrahydrofuran was distilled off and the reaction was continued at 100°C for 6 h, and then at 130°C for 24 h. After cooling, methanol (200 ml) was added to the reaction mixture and it was stirred at room temperature for 24 h. The product **6** was filtered off and washed subsequently with methanol and dried in air. Yellow-brown powder. Yield 10.21 g (90%), softening at 73–150°C, IR (KBr) cm^{-1} 3039, 2956, 2849 (CH), 1558, 1473, 1463, 1432 (C-C aromatic) 742 (CH aromatic out of plane) 689, 642 (CSe). Sparingly soluble in the solvents used for NMR spectroscopy. Found: C, 30.25; H, 2.01. $(C_6H_4Se_2)_n$, $(234.03)_n$ requires C, 30.79; H, 1.72.

Oxidation of Aldazines (1). General Procedure

The solution or suspension of aldazine **1a–i**, **1k–v** (10 mmol) in tetrahydrofuran (20 ml), 30% hydrogen peroxide (6 ml, 60 mmol) and diselenide **6** (0.024 g, 0.10 mmol), was magnetically stirred and slowly heated to gently reflux (*ca.* 1 h). The reaction progress was monitored by TLC using dichloromethane as an eluent, and it was continued until the spot of parent aldehyde **3** vanished. When the reaction was prolonged above 12 h, the additional portions of hydrogen peroxide (2.5 ml) and THF (in the amount made the reaction homogenous) were added after each 12 h period. The acids **(2g–i)** crystallized directly after the cooling of the reaction mixture in 60–80% yield and were filtered off. The filtrates **(2g–i)** or the reaction mixtures containing acids **2a–f**, **2k–n**, **2p–v** were treated with a pinch of Pt/C and then the solution of $NaHCO_3$ (5g) and

NaCl (15 g) in water (200 ml) was added stepwise until evolution of carbon dioxide ceased. The solution was washed with chloroform (3×25 ml) and the layers were separated. The aqueous layer was acidified with concentrated hydrochloric acid (pH 1–2) and it was extracted with diethyl ether (3×150 ml) (**2i**) or with chloroform (100 ml and 4×25 ml) (**2a–h**, **2k–n**, **2p–v**). The extract was dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* and the residue was a pure acid **2a–k**, **2q–s**, **2u**, **2v**. The acids **2i–n**, **2p**, **2t** were purified on the column with silicagel (70–230 mesh) using hexane-ethyl acetate-acetic acid as an eluent. The additional amounts of the acids soluble in chloroform (**2b–e**) were obtained from chloroform layer by alkaline extraction as described above.

Oxidation of Aldoximes (7). General Procedure

The solution of aldoxime **7a–v**, (20 mmol) in tetrahydrofuran (30 ml), 30% hydrogen peroxide (10 ml, 0.1 mol) and diselenide **6** (0.047 g, 0.20 mmol), was magnetically stirred and slowly heated to gently reflux (*ca*. 1 h) and the reaction was carried out in the same manner as described for the azines **1**. After the reaction finished, the acids (**2g–i**) crystallized directly after the cooling of the reaction mixture and were filtered off. The filtrates (**2g–i**) or the reaction mixtures containing acids **2a–f**, **2j–v** were worked up as described for the azines **1**. The acid was purified chromatographically.

Oxidation of Tosylhydrazones (8). General Procedure

To the magnetically stirred solution of tosylhydrazone **8a–x** (20 mmol) in tetrahydrofuran (70 ml), containing suspended diselenide **6** (0.094 g, 0.40 mmol), 30% hydrogen peroxide (20 ml, 0.2 mol) was added dropwise. The mixture was slowly heated to gently reflux (*ca*. 1 h) and the reaction was carried out in the same manner as described for the azines **1**. When the reaction was prolonged above 24 h (for **8m–p**), the additional portions of hydrogen peroxide (20 ml) were added each day. After the reaction finished, a pinch of Pt/C was added, the reaction mixture was left stirred at room temperature overnight and then it was treated with solution of $NaHCO_3$ (5 g) and NaCl (15 g) in water (200 ml). The acids **2a–f**, **2j–v** were isolated in the same manner as described for oxidation of aldazines **1**. The acids **2g–i** crystallized from the solutions concentrated *in vacuo* to a half of the volume and cooled to -10°C.

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11. When other solvent such as acetic acid, methanol, dioxane and tert-butanol was used, the reaction was slower and oxidation was less selective.
12. The diselenides tested as catalyst, such as 2- and 4-pyridyl, 6-methyl-2-pyridyl, 2-quinolyl, 5-pyrimidinyl, 2- and 4-nitrophenyl and poly(*bis*-9, 10-anthracenyl) diselenide (PADS) were synthesized according to the ref.[6,13] Synthesis of diselenide RSeSeR (R: 3-nitro-2-pyridyl, 2-nitrio-4(trifluoromethyl)phenyl, 2-(trifluoromethyl) phenyl (*bis*-1,4-phenylene) and benzene-1,2-diseleninic acid will be published in due course.

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Selenium dioxide and diphenyl diselenide were purchased from Aldrich. Poly (bis-1,2-phenylene) diselenide (**6**) was synthesized in the way reported.

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15. The compound **9** was isolated in the 24% yield[16] from mixture **2t** and **9** by using column chromatography. Colorless prisms, mp = 149.5–150.5°C (toluene), lit.[17] mp = 150–151°C. IR (KBr): 3500–2200 cm^{-1} (COOH), 1759 and 1709 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 8.30 (s, 1H, COOH), 7.93 (d, 1H, J = 7.5 Hz, ArH), 7.72 (t, 1H, J = 7.5 Hz, ArH), 7.58 (t, 1H, J = 7.5 Hz, ArH), 7.54 (d, 1H, J = 7.5 Hz, ArH), 5.80 (t, 1H, J = 6.5 Hz, CH), 2.99 (d, 2H, J = 6.5 Hz, CH_2). ^{13}C NMR data are identical as these reported in ref.[18]
16. The compd. **9** was also obtained in 26% yield by the oxidation of 1-naphtol.
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23. Toxicity of poly(bis-1,2-phenylene) diselenide (**6**) is unknown. According to know rules its toxicity should be low.[24,25] Nevertheless avoid skin contact by use of gloves. All manipulations should be done in a hood.
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26. 1,2-Diiodobenzene was easily prepared (85% yield) in molar scale by conversion of 2-iodoaniline to diazonium salt by treatment with acidic sodium nitrite in acetic acid solution and subsequent reaction with aqueous sodium iodide. From the solution 1,2-diiodobenzene was extracted with dichloromethane and purified by destillation *in vacuo* at 152°/15 mm.

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