Nonmetal-Catalyzed Iodination of Arenes with Iodide and Hydrogen Peroxide

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Received 29 March 2004

Abstract: Oxidative iodination of arenes was carried out with one equivalent of KI and two equivalents of 30% hydrogen peroxide in MeOH in the presence of strong acid. Reactions of various substituted anisoles, phenols and anilines, as well as mesitylene and uracil, were selective and effective with very good yields of isolated halogenated aromatic molecules.

Key words: iodination, haloperoxidation, hydrogen peroxide, oxidative halogenation, aromatics

Halogenated organic molecules are important compounds in pharmaceutical and agricultural chemistry,[1] and they are important synthetic intermediates in chemical synthesis, especially for C-C coupling reactions.[2] The use of molecular halogens for direct halogenation has drawbacks in the difficult and dangerous handling of chlorine and bromine, while iodine is less reactive. Nature has solved this problem by evolving haloperoxidases, enzymes that oxidize halide salts into reactive hypohalous derivatives.[3] Its counterpart in chemistry, named oxidative halogenation, has been utilized for iodination with a plethora of catalysts and oxidants in combination with molecular iodine or less frequently with a metal iodide.[1,4]

Hydrogen peroxide has enormous potential as a green oxidant from which the only waste product is water.[5] There is some hazard connected with the use of concentrated solutions and this risk could be avoided by applying 30% aqueous H_2O_2. However, for oxidative halogenation of arenes this requires the use of a metal catalyst for activation.[4b,6] In the nonmetal-catalyzed haloperoxidation with H_2O_2 and hydrohalic acid the only waste product is water (Equation 1) which presents a clear case of green chemical reaction. Until now, this reaction with aromatic molecules was reported only with HBr and HCl with an excess of oxidant or acid.[7] The use of HI is limited by its instability while utilization of its salt has no such difficulties. In this case of haloperoxidation, hydroxide is formed during reaction (Equation 2). If acid is added to the reaction system, it could serve for activation of H_2O_2, generation of HI in situ and at the same time neutralization of hydroxide formed (Equation 3).

As the nonmetal-catalyzed oxidative iodination of aromatic molecules with H_2O_2 has not been reported yet, it seemed to be the most promising task. Our aim was to utilize only 30% H_2O_2 for iodination of arenes with KI without addition of any metal catalyst.

$$ArH + H_2O_2 + HX \longrightarrow ArX + 2\ H_2O$$

Equation 1

$$ArH + H_2O_2 + MX \longrightarrow ArX + MOH + H_2O$$

Equation 2

$$ArH + H_2O_2 + MX + HA \longrightarrow ArX + MA + 2H_2O$$

Equation 3

We chose anisole as a model arene and the first experiment was the simplest one; we used only anisole, 30% H_2O_2 and KI in MeOH (10 mL). Immediately after addition of oxidant, bubbles started to evolve abundantly, indicating the decomposition of H_2O_2 instead of oxidation of iodide. Therefore we added H_2SO_4 acid in order to neutralize the hydroxide formed during oxidation of iodide and at the same time to activate H_2O_2. This proved to be an excellent choice since addition of one equivalent of concentrated H_2SO_4 completely inhibited the decomposition of H_2O_2 and promoted the iodination process, resulting in the regioselective formation of 4-iodoanisole after 17 hours at 60 °C. The important role of the acidity in iodination with H_2O_2–KI is clearly shown on Figure 1, where it could be seen that quantitative conversion was achieved by the addition of no less than 1.5 molar equivalents of H_2SO_4 and 4-iodoanisole was isolated in 93% yield. A weaker acid like HOAc did not inhibit decomposition of H_2O_2 and reaction proceeded in an identical manner as in the absence of acid.

Due to the pronounced effect of fluorinated alcohols on the activity of H_2O_2,[8] we tried to apply hexafluoroisopropanol and trifluoroethanol as solvents for the above mentioned reaction. Unfortunately, the solubility of molecular iodine formed during the process is very low in these solvents and it precipitated during reaction. Iodination was consequently very slow. Reaction in MeCN was found to be also slower and conversion was incomplete after 24 hours of reflux. On the other hand, water could be a suitable solvent and quantitative iodination of anisole was also achieved in the mixture of H_2O–MeOH (4:1).

SYNTHESIS 2004, No. 11, pp 1869–1873
Advanced online publication: 01.07.2004
DOI: 10.1055/s-2004-829136; Art ID: Z06904SS

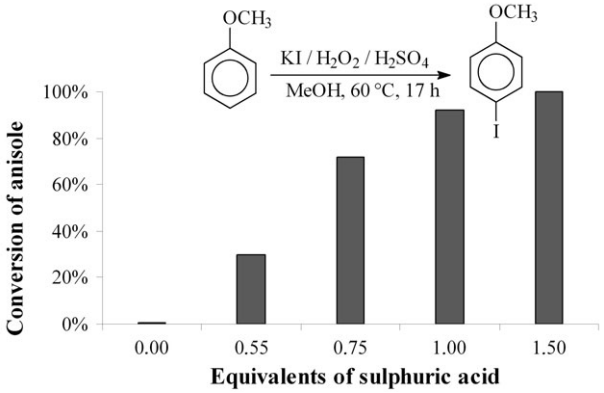

Figure 1 The effect of the amount of acid on the iodination of anisole with 1 equiv KI, 2 equiv 30% H_2O_2 and H_2SO_4 in MeOH.

Next, we have examined the reaction scope of H_2O_2–KI–H_2SO_4 system for various aromatic molecules. As could be seen from Table 1 (entries 1–4), representative methoxy substituted aromatic derivatives were quantitatively and regioselectively transformed to the corresponding iodides without formation of diiodinated products, while iodination of deactivated anisoles like 4-bromoanisole failed under the mentioned reaction conditions.

Target aromatic molecules bearing hydroxy substituents could also be iodinated by this method. Here, 4-*tert*-butylphenol was converted regioselectively to the 2-iodo derivative, but further iodination to 2,6-diiodo-4-*tert*-butylphenol was also observed (Table 1, entry 5). Complete formation of 2,6-diiodo-4-*tert*-butylphenol was achieved by using four equivalents of 30% H_2O_2, two equivalents of KI and 1.5 equivalents of H_2SO_4 (entry 6). 2-Naphthol was also selectively converted to the corre-

Table 1 Oxidative Iodination of Arenes with the 30% H_2O_2–KI–H_2SO_4–MeOH System[a]

Entry	Substrate	MX	Condition	Product	Conversion (%)[b]	Yield (%)[c]
1	Anisole	KI[d]	r.t., 3 h	4-Iodo-anisole	100	93
2	1,3-Dimethoxybenzene	KI[d]	r.t., 3 h	4-Iodo-1,3-dimethoxybenzene	100	97
3	1-Methoxynaphthalene	KI[d]	60 °C, 3 h	4-Iodo-1-methoxynaphthalene	100	94
4	2-Methoxynaphthalene	KI[d]	60 °C, 3 h	1-Iodo-2-methoxynaphthalene	100	90
5	4-*tert*-Butylphenol	KI	40 °C, 2 h	4-*tert*-Butyl-2-iodo-phenol	80	60, 19
6		2 KI[e]	40 °C, 2 h	4-*tert*-Butyl-2,6-diiodophenol	100	88
7	2-Hydroxynaphthalene	KI	0 °C, 1 h	1-Iodo-2-hydroxynaphthalene	100	93
8	4-Nitrophenol	KI	60 °C, 2 h	2-Iodo-4-nitrophenol	60	42, 18
9		2 KI[e]	60 °C, 2 h	2,6-Diiodo-4-nitrophenol	100	90
10	4-*tert*-Butylaniline	KI	r.t., 6 h	4-*tert*-Butyl-2-iodo-aniline	85	70, 7
11	Aniline	KI	r.t., 4 h	4-Iodoaniline	100	96
12		KI[f]	r.t., 4 h		100	94
13	4-Nitroaniline	KI	60 °C, 5 h	2-Iodo-4-nitroaniline	100	98
14	4-Trifluoromethylaniline	KI	60 °C, 3 h	2-Iodo-4-trifluoromethylaniline	100	90
15	*m*-Phenylenediamine	KI	0 °C, 5 h	2,4-Diamino-1-iodobenzene	100	80
16		2KI[e]	r.t., 1 h	2,4-Diamino-1,5-diiodobenzene	100	91
17		3KI[g]	50 °C, 1 h	2,4-Diamino-1,3,5-triiodobenzene	100	95
18	1,3,5-Trimethylbenzene	KI	60 °C, 24 h	2-Iodo-1,3,5-trimethylbenzene	100	88
19	Uracil	KI	40 °C, 24 h	Iodouracil	100	90

[a] Substrate–KI–H_2O_2–H_2SO_4 = 1:1:2:1.
[b] Determined by ^{1}H NMR spectrospcopy of crude product.
[c] Yield of isolated products after flash chromatography; second number the yield of diiodinated product isolated by column chromatography.
[d] Substrate–MX–H_2O_2–H_2SO_4 = 1:1:2:1.5.
[e] Substrate–MX–H_2O_2–H_2SO_4 = 1:2:4:1.5.
[f] Solvent system used was H_2O–MeOH (4:1).
[g] Substrate–MX–H_2O_2–H_2SO_4 = 1:3:6:2.

sponding 1-iodo derivatives, while 4-nitrophenol showed the same reactivity pattern as its *tert*-butyl analogues (entries 8, 9).

Very attractive results of application of this eco-friendly, inexpensive and easy to use method of iodination were also obtained when aromatic amines were tested as the target molecules. An amino group present on the aromatic ring was found to be compatible with this method and anilines were iodinated in quantitative yields without the need to protect the amino functionality (entries 10–17). Interestingly, *m*-phenylenediamine was converted selectively to the mono-, di- and tri-iodinated products in very good yields (entries 15–17). With aniline, reaction was conducted in water with 20% of MeOH to increase the solubility of iodine formed during the reaction. Work-up in this case requires only addition of a 0.5 M solution of sodium thiosulfate and filtration of the precipitated aniline derivatives, representing an additional attribute of this clean chemical transformation (entry 12). Mesitylene and uracil were also selectively and effectively iodinated using KI as the iodine atom source (entries 18 and 19).

Chemicals and solvents were obtained from commercial sources and were used as received. Silica gel 60 (60–200 μm mesh) was used for column chromatography. ^{1}H and ^{13}C NMR spectra were measured on a Varian Unity-300 spectrometer with TMS and $CDCl_3$ as internal standards, respectively. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Mass spectra were acquired on an AutoSpec hybrid spectrometer.

Oxidative Iodination of Arenes; General Procedure

Concd H_2SO_4 acid (3 mmol) was dissolved in MeOH (10 mL); substrate (2 mmol) and KI (2 mmol) were added into the solution. Finally, 30% H_2O_2 (4 mmol) was added and stirred. After the reaction was finished, the reaction mixture was poured into CH_2Cl_2 (30 mL), organic phase was washed with 0.1 M $NaHSO_3$ (20 mL), water (20 mL), dried (Na_2SO_4) and solvent was evaporated. Crude reaction product was analysed by ^{1}H NMR spectroscopy and purified by flash chromatography or by column chromatography if diiodo product was formed. Structure of products was determined by ^{1}H and ^{13}C NMR, MS and confirmed by HRMS.

4-Iodoanisole

Yellow crystals; mp 46–48 °C (Lit.[9] mp 51–53 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 6.67 (d, *J* = 9.0 Hz, 2 H), 7.55 (d, *J* = 9.0 Hz, 2 H).

MS: *m*/*z* (%) = 234 (100), 219 (31), 191 (12), 92 (18).

4-Iodo-1,3-dimethoxybenzene

White crystals; mp 36.5–37.5 °C (Lit.[10] mp 40–41 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.84 (s, 3 H), 6.31 (dd. *J* = 8.6, 2.7 Hz, 1 H), 6.42 (d, *J* = 2.7 Hz, 1 H), 7.61 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 55.5, 56.2, 74.1, 99.2, 106.9, 139.1, 158.8, 161.3.

MS: *m*/*z* (%) = 264 (100), 221 (11), 122 (22), 107 (26).

HRMS: *m*/*z* calcd for $C_8H_9IO_2$: 263.9647; found: 63.9655.

4-Iodo-1-methoxynaphthalene

Yellow crystals; mp 52–53 °C (Lit.[11] mp 55–55.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 6.51 (d, *J* = 8.2 Hz, 1 H), 7.47 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1 H), 7.55 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1 H), 7.90 (ddd, *J* = 8.3, 1.3, 0.7 Hz, 1 H), 7.98 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 55.6, 88.1, 105.5, 122.4, 125.9, 126.5, 128.1, 131.7, 134.6, 136.8, 156.2.

MS: *m*/*z* (%) = 284 (100), 269 (42), 241 (43), 157 (21), 114 (77), 14 (22).

HRMS: *m*/*z* calcd for $C_{11}H_9IO$: 263.9698; found: 263.9705.

1-Iodo-2-methoxynaphthalene

White crystals; mp 82–84 °C (Lit.[12] mp 88 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 7.16 (d, *J* = 8.9 Hz, 1 H), 7.36 (ddd, *J* = 8.2, 6.9, 0.8 Hz, 1 H), 7.52 (ddd, *J* = 8.5, 6.9, 0.7 Hz, 1 H), 7.71 (dd, *J* = 8.2, 0.7 Hz, 1 H), 7.78 (d, *J* = 8.9 Hz, 1 H), 8.13 (dd, *J* = 8.5, 0.8 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 57.2, 87.7, 112.9, 124.3, 128.1, 128.2, 129.8, 130.3, 131.1, 135.6, 156.6.

MS: *m*/*z* (%) = 284 (100), 241 (32), 142 (40), 114 (36).

HRMS: *m*/*z* calcd for $C_{11}H_9IO$: 283.9698; found: 283.9690.

4-*tert*-Butyl-2-iodophenol

Red oil.[13]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 6.91 (d, *J* = 8.6 Hz, 1 H), 7.25 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.63 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.4, 34.0, 85.5, 114.5, 127.3, 135.0, 145.5, 152.5.

MS: *m*/*z* (%) = 276 (28), 261 (100), 233 (10), 134 (30).

HRMS: *m*/*z* calcd for $C_{10}H_{13}IO$: 276.0011; found: 276.0022.

4-*tert*-Butyl-2,6-diiodophenol

Red oil.[14]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 7.64 (s, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.2, 33.9, 82.1, 136.3, 147.3, 151.2.

MS: *m*/*z* (%) = 402 (36), 387 (100), 260 (20).

HRMS: *m*/*z* calcd for $C_{10}H_{12}I_2O$: 401.8978; found: 401.8991.

1-Iodo-2-naphthol

Grey crystals; mp 87–88 °C (Lit.[11] mp 92–93.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 1 H), 7.35 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1 H), 7.51 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1 H), 7.69 (d, *J* = 8.7 Hz. 1 H), 7.70 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.90 (dd, *J* = 8.5, 1.1 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 86.2, 116.4, 124.1, 128.1, 128.3, 129.6, 130.2, 130.6, 134.7, 153.7.

MS: *m*/*z* (%) = 270 (100), 144 (28), 127 (10), 115 (73).

HRMS: *m*/*z* calcd for $C_{10}H_7IO$: 269.9542; found: 269.9550.

2,6-Diiodo-4-nitrophenol

Orange crystals; mp 150–151 °C (Lit.[15] mp 155.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 80.8, 134.8, 140.7, 159.0.

MS: *m*/*z* (%) = 391 (100), 361 (23), 218 (38), 127 (20), 91 (27), 62 (33).

HRMS: *m*/*z* calcd for $C_6H_3I_2NO$: 390.8202; found: 390.8209.

4-*tert*-Butyl-2-iodoaniline
Red oil.[16]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 6.68 (d, *J* = 8.3 Hz, 1 H), 7.16 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.61 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.4, 33.8, 84.5, 114.4, 126.5, 135.6, 143.2, 144.2.

MS: *m*/*z* (%) = 275 (37), 260 (100), 133 (29).

HRMS: *m*/*z* calcd for $C_{10}H_{14}IN$: 275.0171; found: 275.0177.

4-*tert*-Butyl-2,6-diiodoaniline
Red oil.[16]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 7.61 (s, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 31.3, 33.7, 81.7, 136.5, 143.7, 144.6.

MS: *m*/*z* (%) = 401 (62), 386 (100), 259 (20), 132 (25), 117 (16).

HRMS: *m*/*z* calcd for $C_{10}H_{13}I_2N$: 400.9138; found: 400.9147.

4-Iodoaniline
Brown crystals; mp 55–56.5 °C (Lit.[11] mp 62.5–63 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.45 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 79.3, 117.2, 137.8, 146.0.

MS: *m*/*z* (%) = 219 (25), 127 (10), 92 (64), 65 (100).

HRMS: *m*/*z* calcd for C_6H_6IN: 218.9545; found: 218.9551.

2-Iodo-4-trifluoromethylaniline
Orange crystals; (Lit.[17] mp 50–50.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.72 (dd, *J* = 8.4, 0.7 Hz, 1 H), 7.36 (ddd, *J* = 8.4, 1.4, 0.7 Hz, 1 H), 7.86 (d, *J* = 1.4 Hz, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 82.1, 113.5, 121.4 (q, *J* = 33 Hz), 123.5 (q, *J* = 271 Hz), 126.5 (q, *J* = 3 Hz), 136.2 (q, *J* = 4 Hz), 149.5.

MS: *m*/*z* (%) = 287 (100), 160 (37), 140 (15), 113 (10).

HRMS: *m*/*z* calcd for $C_7H_5F_3IN$: 286.9419; found: 286.9427.

Anal. Calcd for $C_7H_5F_3IN$: C, 29.29; H, 1.79; N, 4.88. Found: C, 29.48; H, 1.79; N, 4.76.

2-Iodo-4-nitroaniline
Yellow crystals; mp 98–100 °C (Lit.[18] 107 °C).

^{1}H NMR (300 MHz, DMSO): δ = 6.71 (d, *J* = 9.0 Hz, 1 H), 8.05 (dd, *J* = 9.0, 2.4 Hz, 1 H), 8.55 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (300 MHz, DMSO): δ = 60.4, 112.2, 124.0, 125.7, 135.4, 153.4.

MS: *m*/*z* (%) = 264 (72), 234 (44), 218 (18), 127 (15), 107 (16), 91 (100), 63 (55).

HRMS: *m*/*z* calcd for $C_6H_5IN_2O_2$: 263.9396; found: 263.9493.

2,4-Diamino-1-iodobenzene[19]
Grey crystals; mp 81 °C (decomp).

^{1}H NMR (300 MHz, DMSO): δ = 5.70 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.04 (d, *J* = 2.5 Hz, 1 H), 7.10 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (300 MHz, DMSO): δ = 67.1, 99.9, 106.8, 138.1, 148.3, 149.6.

MS: *m*/*z* (%): 234 (100), 107 (51), 80 (44).

HRMS: *m*/*z* calcd for $C_6H_7IN_2$: 233.9654; found: 233.9661.

2,4-Diamino-1,5-diiodobenzene[19]
Grey crystals; mp 88 °C (decomp).

^{1}H NMR (300 MHz, DMSO): δ = 6.23 (s, 1 H), 7.53 (s, 1 H).

^{13}C NMR (300 MHz, DMSO): δ = 69.0, 99.2, 145.2, 149.0.

MS: *m*/*z* (%) = 360 (100), 254 (17), 233 (17), 106 (19).

HRMS: *m*/*z* calcd for $C_6H_6I_2N_2$: 359.8621; found: 359.8611.

Anal. Calcd for $C_6H_6I_2N_2$: C, 20.02; H, 1.68; N, 7.78. Found: C, 20.2; H, 1.67; N, 7.61.

2,4-Diamino-1,3,5-triiodobenzene
Grey crystals; mp 127 °C (decomp).

^{1}H NMR (300 MHz, DMSO): δ = 7.72 (s, 1 H).

^{13}C NMR (300 MHz, DMSO): δ = 66.7, 69.6, 145.2, 147.5.

MS: *m*/*z* (%) = 486 (100), 359 (18), 261 (16).

HRMS: *m*/*z* calcd for $C_6H_5I_3N_2$: 485.7587; found: 485.7599.

Anal. Calcd *m*/*z* for $C_6H_5I_3N_2$: C, 14.83; H, 1,04, N, 5.77; found: C, 15.02; H, 0.98; N, 5.56.

2-Iodo-1,3,5-trimethylbenzene
White crystals; mp 29.5–30.5 °C (Lit.[20] 31 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 2.42 (s, 6 H), 6.87 (s, 2 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 20.6, 29.5, 105.9, 127.9, 137.3, 141.7.

MS: *m*/*z* (%) = 246 (33), 160 (84), 128 (64), 64 (100).

HRMS: *m*/*z* calcd for $C_9H_{11}I$: 245.9906; found: 245.9912.

5-Iodouracil
White crystals; mp 225 °C (decomp) (Lit.[21] 198 °C).

^{1}H NMR (300 MHz, DMSO): δ = 7.87 (s).

^{13}C NMR (300 MHz, DMSO): δ = 66.8, 150.0, 153.1, 161.9.

MS: *m*/*z* (%) = 238 (100), 195 (52), 168 (28), 152 (15), 127 (11).

HRMS: *m*/*z* calcd for $C_4H_3N_2O_2I$: 237.9239; found: 239.9232.

Acknowledgment

The financial support from the Ministry of Science and Technology of the Republic of Slovenia is acknowledged. We are grateful to Dr. Dusan Zigon and Dr. Bogdan Kralj for HRMS measurements and to Mrs. T. Stipanovic and Prof. Dr. B. Stanovnik for elemental analysis.

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