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Ozonolysis of Olefins VIII [1]. Synthesis of Phenoxyacetaldehydes by Ozonolysis of Allylphenylethers

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Summary. A new route for the preparation of a series of phenoxyacetaldehydes (**2a–j**) which are useful intermediates or products, is described. It starts from the easily available allylphenylethers **1a–j** which are ozonized at −40 °C and further treated with dimethylsulfide to give solutions of the corresponding phenoxyacetaldehydes **2a–j**; these are purified by column chromatography. Reaction of **2a–j** with 1-methyl-1-phenylhydrazine leads to the corresponding hydrazones **3a–c**, **3e–g**, **3i**, and **3j**. The aldehydes can also be transformed into the stable dimethylcetals **4a**, **4e**, **4h**, and **4i** by reaction with trimethyl orthoformate.

Keywords. Olefin; Ozonolysis; Synthesis

Ozonolyse von Olefinen, 8. Mitt. [1]. Synthese von Phenoxyacetaldehyden durch Ozonolyse von Allylphenylethern

Zusammenfassung. Ein neuer Weg, die als Synthone nützlichen Phenoxyacetaldehyde **2a–j** darzustellen, wird beschrieben. Dazu werden die leicht zugänglichen Allylphenylether **1a–j** bei −40 °C ozonisiert und anschließend mit Dimethylsulfid reduziert, um Lösungen von **2a–j** zu erhalten. Reaktion von **2a–j** mit 1-Methyl-1-phenylhydrazin führt zu den entsprechenden N-Methyl-N-phenylhydrazonen **3a–c**, **3e–g**, **3i** und **3j**. Die Aldehyde können auch durch Reaktion mit Trimethylorthoformiat in die stabileren Dimethylacetale **4a**, **4e**, **4h** und **4i** übergeführt werden.

Introduction

Phenoxyacetaldehydes are useful intermediates in the synthesis of different heterocycles like aminochromanes [2] and compounds with biological activity, for example plant-growth regulating substances like 2-chloro-phenoxypropionitriles [3] and 4-phenoxy-crotonic acids [4]. Phenoxyacetaldehyde-guanylhydrazones were tested successfully as antibacterial compounds [5]. The unsubstituted phenoxyacetaldehyde **2a** is also used as a starting material for the preparation of cortisone and testosterone derivatives [6, 7].

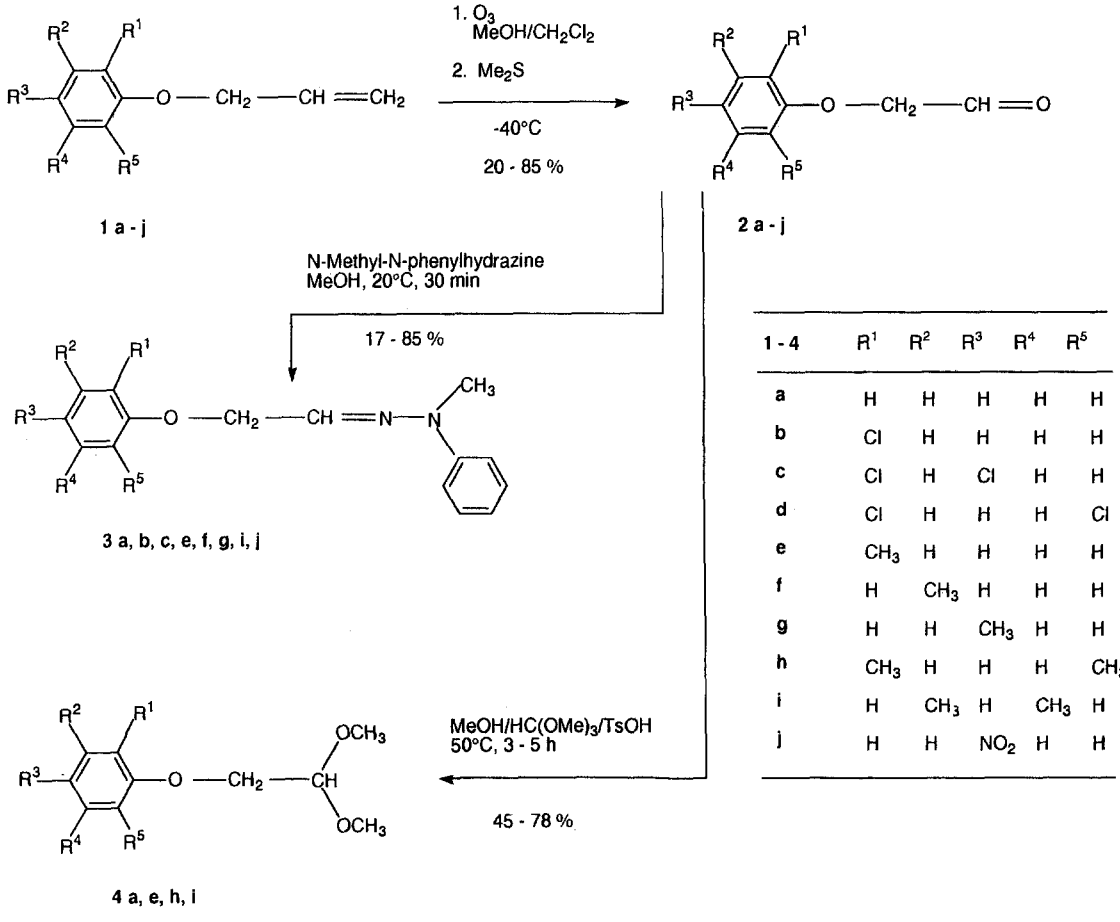
Several methods have been developed for the preparation of these highly reactive and useful intermediates. **2a** can be obtained by reaction of sodium-phenolate and 2-bromoacetaldehyde-diethylacetal under pressure [8–10]. Hydrolysis of the acetal

gives phenoxyacetaldehyde-hydrate which can be dehydrated by distillation under reduced pressure [4, 11–13]. Oxidation of glycol-monophenylether with a mixture of potassium dichromate and sulfuric acid [14] or *p*-benzoquinone [15], the oxidation of glycerol-α-phenylether with leadtetraacetate in benzene [16–18] or some gas-phase oxidations of different starting materials with the help of various catalysts [19–21] also lead to phenoxyacetaldehydes. **2a** is also set free from its sodiumbisulfite derivative by treatment with sulfuric acid [22]. These procedures have the disadvantage of requiring either not easily available starting materials and catalysts or complicated work-up of the reaction mixtures.

Results and Discussion

In this paper we want to report a new and convenient route for the preparation of a series of phenoxyacetaldehydes **2a–j** by ozonization of the easily available allylphenylethers **1a–j** at −40 °C in a mixture of methanol and dichloromethane followed by reduction with dimethylsulfide.

The aldehydes **2a–j** were purified by column chromatography on silica-60 using different mixtures of ethyl-acetate/petrolether as eluent. After recrystallization from



1 - 4	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	Cl	H	H	H	H
c	Cl	H	Cl	H	H
d	Cl	H	H	H	Cl
e	CH_3	H	H	H	H
f	H	CH_3	H	H	H
g	H	H	CH_3	H	H
h	CH_3	H	H	H	CH_3
i	H	CH_3	H	CH_3	H
j	H	H	NO_2	H	H

Scheme 1

methanol, the *p*-nitro derivative **2j** could be isolated as the semi-methylacetal. **2a–j** can also be transformed into the more stable acetals **4** by reaction with trimethyl orthoformate in methanol under catalysis with *p*-tolyl-sulfonic acid. Derivatization with 1-methyl-1-phenylhydrazine leads to the corresponding hydrazones **3a–j**.

The phenoxyacetaldehydes **2a–j** were characterized by gas chromatography with mass selective detection as well by IR and NMR spectroscopy. An interesting aspect was observed concerning the ^{1}H NMR spectra where the aldehydic and α-protons appear as singlets. This is in accordance with the literature where the smallest coupling constants for substituted acetaldehydes were found for phenoxyacetaldehyde and methoxyacetaldehyde [23].

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer at 200 and 60 MHz, respectively. *TMS* was used as an internal standard. IR spectra were recorded on a Perkin-Elmer 421 spectrometer. GC/MS was performed with a Hewlett-Packard MSD instrument equipped with a fused silica column, 60 m × 0.32 mm, 0.25 µm DB-5 (J&W Scientific Inc.). Ozone was generated using a Fischer instrument model 503.

Table 1. Phenoxyacetaldehydes (**2a–j**)

	Yield (%)	^{1}H NMR ($CDCl_3$/*TMS*) δ (ppm)
2a [4]	45	4.51 (s, 2H, CH_2), 6.69–7.38 (m, 5H, aromatic H), 9.76 (s, 1H, CHO)
2b [4]	85	4.64 (s, 2H, CH_2), 6.80–7.47 (m, 4H, aromatic H), 9.93 (s, 1H, CHO)
2c [4]	80	4.62 (s, 2H, CH_2), 6.71–7.44 (m, 3H, aromatic H), 9.90 (s, 1H, CHO)
2d	75	4.58 (s, 2H, CH_2), 6.97–7.42 (m, 3H, aromatic H), 10.02 (s, 1H, CHO)
2e [4]	50	2.33 (s, 3H, *o*-CH_3), 4.59 (s, 2H, CH_2), 6.65–7.30 (m, 4H, aromatic H), 9.90 (s, 1H, CHO)
2f [4]	35	2.32 (s, 3H, *m*-CH_3), 4.57 (s, 2H, CH_2), 6.65–6.89 (m, 4H, aromatic H), 9.87 (s, 1H, CHO)
2g [4]	70	2.60 (s, 3H, *p*-CH_3), 4.55 (s, 2H, CH_2), 6.68–6.89 (m, 2H, aromatic H), 6.97–7.21 (m, 2H, aromatic H), 9.84 (s, 1H, CHO)
2h	80	2.30 (s, 6H, 2 × *o*-CH_3) 4.40 (s, 2H,CH_2), 6.86–7.23 (m, 3H, aromatic H), 9.98 (s, 1H, CHO)
2i	80	2.29 (s, 6H, 2 × *m*-CH_3), 4.54 (s, 2H, CH_2), 6.44–6.71 (m, 3H, aromatic H), 9.87 (s, 1H, CHO)
2j	20	4.72 (s, 2H, CH_2), 7.00 (d, 2H, aromatic H), 8.20 (d, H, aromatic H), 9.87 (s, 1H, CHO)

Phenoxyacetaldehydes (**2a–j**, *General Procedure*)

A solution of allylphenylethers (**1a–j**, 40 mmol), either purchased or self-prepared [24], in a mixture of dichloromethane (100 ml) and methanol (100 ml) was ozonized with a mixture of 4–5% O_3/O_2 at −40 °C until formation of iodine was observed in a solution of potassium iodide in distilled water (5 g in 100 ml) which was connected to the reaction vessel. Dimethylsulfide (60 mmol) was carefully added, N_2 was passed through the reaction mixture for 10 min, and then the solution was allowed to warm up to room temperature. The solvents were removed under reduced pressure and dichloromethane (80 ml) was added. After the solution was washed twice with cold water to remove dimethylsulfoxide, the separated organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Finally, the aldehydes **2a–j** were purified by column chromatography on silica-60 using different ethyl-acetate/petrolether-mixtures. Prior to separation, the optimum conditions were tested by TLC. For experimental and spectroscopic data see Table 1.

4-Nitrophenoxyacetaldehyde-semimethylacetal

After ozonization and reduction with dimethylsulfide according to the general procedure, the solvents were removed under reduced pressure. The resulting solid was treated with cold methanol (10 ml) to remove dimethyl sulfoxide, filtered, and recrystallized from methanol to give colorless crystalls; m.p.:

Table 2. N-Methyl-N-phenylhydrazones (**3a–c, e–g, i, j**)

	Yield (%)	M.p. (°C)	^{1}H NMR ^{13}C NMR ($CDCl_3$/*TMS*; δ (ppm))
3a	19	95	3.31 (s, 3H, CH_3), 4.84 (d, 2H, CH_2), 6.95 (t, 1H, CH), 6.90–7.08, 7.26–7.40 (m, 10H, aromatic H) 35.2 (CH_3), 70.5 (CH_2), 160.8 (C = N), arom: 117.0, 117.5, 123.0, 131.0, 131.2, 131.5, 149.7
3b	70	65	3.32 (s, 3H, CH_3), 4.94 (d, 2H, CH_2), 6.96 (t, 1H, CH), 7.09–7.48 (m, 9H, aromatic H)
3c	59	70	3.32 (s, 3H, CH_3), 4.89 (d, 2H, CH_2), 6.89 (t,1H, CH), 7.03–7.40 (m, 8H, aromatic H)
3e	47	48	2.29 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 4.85 (d, 2H, CH_2), 6.95 (t, 1H, CH), 6.85–7.04, 7.11–7.39 (m, 9H, aromatic H))
3f	70	55	2.35 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 4.80 (d, 2H, CH_2), 6.93 (t, 1H, CH), 6.75–6.87, 7.12–7.40 (m, 8H, aromatic H), 7.54 (s, 1H, aromatic H) 21.9 (*m*-CH_3), 33.4 (CH_3), 68.8 (CH_2), 158.8 (C = N), arom: 110.0, 115.6, 116.0, 121.0, 122.0, 129.0, 129.2, 134.0, 139.8, 147.9
3g	81	70	2.33 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 4.81 (d, 2H, CH_2), 6.95 (t, 1H, CH), 6.82–7.45 (m, 9H, aromatic H)
3i	17	73	2.31 (s, 6HH, CH_3), 3.30 (s, 3H, CH_3), 4.78 (d, 2H, CH_2), 6.92 (t, 1h, CH), 6.65 (s, 1H, aromatic H), 6.86–7.01, 7.22–7.40 (m, 7H, aromatic H) 21.6 (2 × *m*-CH_3), 33.2 (CH_3), 68.5 (CH_2), 158.7 (C = N), 112.7, 115.5, 120.9, 122.8, 128.9, 139.3, 147.7
3j	85	82	3.32 (s, 3H, CH_3), 4.91 (d, 2H, CH_2), 6.87 (t, 1H, CH), 6.93–7.12, 7.20–7.41 (m, 9H, aromatic H)

92–94 °C; yield: 3.41 g (40%); $C_9H_{11}NO_5$ (213.2); calcd: C 50.71, H 5.20, N 6.57; found: C 50.97, H 5.21, N 6.58. GC/MS shows only the molecular mass and fragmentations of 4-nitrophenoxyacetaldehyde (**2j**) due to the instability of its semiacetal. IR (KBr): $\nu = 3420, 1600, 1515, 1347, 1265\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 2.84$ (d, 1H, OH), 3.55 (s, 3H, OCH_3), 4.12 (d, 2H, CH_2), 4.93 (m, 1H, CH), 7.00 (d, 2H, aromatic H), 8.24 (d, 2H, aromatic H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 55.5$ (OCH_3), 70.8 (CH_2), 95.8 (CH), 114.7, 126.0, 163.3 (aromatic C) ppm.

Phenoxyacetaldehyde-N-methyl-N-phenylhydrazones (**3a, b, c, e, f, g, i, j**; *General procedure*)

Phenoxyacetaldehydes (7 mmol) were dissolved in methanol (15 ml), and N-methyl-N-phenylhydrazine (8 mmol) was added at once and stirred for 30 min at room temperature. The reaction mixture was kept at r.t. for 3 h and at least for 12 h in a refrigerator. The filtered crystals were washed with cold methanol (8 ml), filtered again, and recrystallized from absolute ethanol. For experimental and spectroscopic data see Table 2.

Phenoxyacetaldehyde-dimethylacetals (**4a, e, h, i**; *General procedure* [25])

To a solution of phenoxyacetaldehydes (24.4 mmol) in methanol (25 ml), trimethylorthoformate (98 mmol) and *p*-tolylsulfonic acid (4.9 mmol) were added. This reaction mixture was stirred at 50 °C for 3–5 hours (TLC-control). After removing the solvent under reduced pressure, the oily residue was treated with chloroform (30 ml) and distilled water (30 ml). The separated organic layer was dried over anhydrous sodium sulfate, the solvent removed under reduced pressure, and the product purified by distillation under reduced pressure. For experimental and spectroscopic data see Table 3.

Table 3. Phenoxyacetaldehyde-dimethylacetals (**4a, e, h, i**)

	Yield (%)	B.p. (°C)	^1H NMR ^{13}C NMR ($CDCl_3$/*TMS*; δ (ppm))
4a	45	128 °C/20 mbar	3.46 (s, 6H, OCH_3), 4.02 (d, 2H, CH_2), 4.74 (t, 1H, CH), 6.88–7.01, 7.22–7.36 (m, 5H, aromatic H) 56.1 (OCH_3), 69.5 (CH_2), 104.2 (CH), arom: 2 × 116.6, 123.1, 2 × 131.5, 160.5
4e	75	124 °C/19 mbar	2.27 (s, 3H, CH_3), 3.49 (s, 6H, OCH_3), 4.04 (d, 2H, CH_2), 4.75 (t, 1H, CH), 6.79–7.23 (m, 4H, aromatic H) 15.9 (CH_3), 53.9 (OCH_3), 69.9 (CH_2), 102.3 (CH), arom: 111.0, 2 × 121.0, 127.0, 130.8, 157.0
4h	78	120 °C/19 mbar	2.31 (s, 6H, CH_3), 3.48 (s, 6H, OCH_3), 3.83 (d, 2H, CH_2), 4.76 (t, 1H, CH), 6.87–7.04 (m, 3H, aromatic H) 18.2 (CH_3), 56 (OCH_3), 73.5 (CH_2), 104.7 (CH), arom: 2 × 125.9, 2 × 130.8, 132.7, 157.6
4i	56	136 °C/22 mbar	2.28 (s, 6H, CH_3), 3.45 (s, 6H, OCH_3), 3.99 (d, 2H, CH_2), 4.71 (t, 1H, CH), 6.50–6.69 (m, 3H, aromatic H) 21.3 (CH_3), 53.9 (OCH_3), 67.3 (CH_2), 102.1 (CH), arom: 2 × 112.3, 122.8, 2 × 139.1, 158.4

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