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Reactions of nitroxides XIV. Analogs of phenoxy carboxylic herbicides based on the piperidine scaffold; unexpected fungicidal activity of the 2-[(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]butanoic acid

Abstract: Alkanoic acid derivatives bearing a nitroxyl moiety **3a–e** were synthesized from 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) and the corresponding 2-bromoalkane carboxylic acids **2a–e**. The herbicidal and antifungal activity of **3a–e** was tested. No herbicidal activity of the tested compounds was found. The 2-[(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]butanoic acid **3c** revealed a strong antifungal activity against the pathogenic fungus *Phytophthora cactorum*.

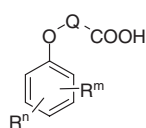
Keywords: bromoalkanoic acids; fungicides; herbicides; nitroxides; piperidine ring; sodium hydride.

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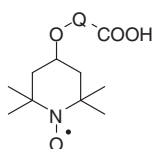
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Introduction

Aryloxy herbicides such as 2,4-D, MCPA, MCPB are widely known commercial products against many weeds [1–3]. Herein (as a continuation of the investigations of the research concerning nitroxides [4]), we present the synthesis and both herbicidal and fungicidal screening of the nitroxyl derivatives of alkanoic acids with the nitroxyl moiety instead of the aryl group found in the typical aryloxy herbicides. These compounds are schematically presented below as structures **Ar** and **N-O**.



Ar



N-O

Q = CH₂ or substituted CH₂; Rⁿ, R^m = various substituents

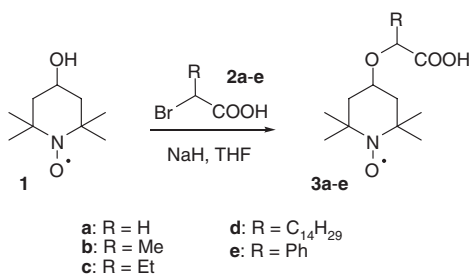
To synthesize the compounds generally abbreviated above as **N-O**, alkylation of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) with a bromoalkanoic acid in the presence of a base is required. Alkylation of the hydroxyl group in **1** is usually performed under basic conditions. Examples are phase transfer catalysis (PTC) method (50% aqueous sodium hydroxide as a base) with tetrabutylammonium bromide [5, 6], hydrogen sulfate [7, 8] or triethylbenzylammonium chloride [9] as PTC catalysts and the reactions conducted in the presence of sodium hydride [10–14], sodium amide, cesium fluoride or potassium carbonate [15].

Results and discussion

Alkanoic acid derivatives bearing the nitroxyl moiety **3a–e** were obtained by the alkoxylation of 2-bromoalkancarboxylic acids **2a–e** with an alkoxide anion of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl **1** generated in the presence of sodium hydride (Scheme 1). Briefly, 2-bromocarboxylic acid **2** was added to the excess of sodium hydride in THF, and then a nitroxyl alcohol **1** was added. The mixture was heated under reflux for 24 h.

The nitroxyl radicals **3a–e** were identified using spectroscopic methods (EI MS, ESI MS, HRMS and IR). The ¹H NMR spectra are not informative in these cases because signals of protons are paramagnetically broadened and unresolved owing to the presence of nitroxide radicals [16–20].

The herbicidal and antifungal activity of **3a–c**, **3e** was assayed. Compound **3d** was not tested, due to its negligible yield. The compounds **3a,b,e** show medium activity against four species of pathogenic fungi *Botrytis cinerea*, *Fusarium culmorum*, *Phytophthora cactorum* and *Rhizoctonia solani*. The butanoic acid derivative **3c** shows strong antifungal activity against pathogenic fungus *P. cactorum* (Table 1).



Scheme 1 Synthesis of alkanolic acid derivatives bearing a nitroxyl moiety **3a–e**.

Table 1 Antifungal activity of **3a–e** at a concentration of 200 ppm.

No.	<i>Botrytis cinerea</i>	<i>Fusarium culmorum</i>	<i>Phytophthora cactorum</i>	<i>Rhizoctonia solani</i>
3a	32	44	9	0
3b	32	46	16	20
3c	36	34	100	0
3e	24	40	29	26

Experimental

General

4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) was synthesized by oxidation of 2,2,6,6-tetramethyl-4-piperidinol with 30% hydrogen peroxide (76% yield, mp 71–73°C), as previously described [21–23]. THF was distilled over sodium under argon in the presence of benzophenone. The experiments were performed in a two-necked round-bottom flask of 25 mL capacity, equipped with a magnetic stir bar, reflux condenser protected against humidity, under an argon atmosphere. TLC was carried out on silica gel Merck Alurolle 5562 or Alufolien 5554. Column chromatography was performed using Merck silica gel, 230–400 mesh. TLC visualization was performed using UV 254 nm light and/or iodine vapor. EI MS data were recorded on an AMD 604 and Agilent Technologies 5975 B mass spectrometers. EI mass spectra were obtained at 70 eV. ESI mass spectra (negative ionisation, CH₃OH as solvent) were recorded on a Micromass LCT apparatus. IR spectra were recorded on an FT/IR Jasco 420 spectrophotometer. Conditions of the fungicidal bioassay *in vitro* are identical to those described previously [24].

General procedure for **3a–e**

Anhydrous THF (5 mL) and 2-bromoalkanoic acid **2a–e** (1 mmol) were placed in a flask and the resultant solution was treated with a 60% slurry of sodium hydride in mineral oil (0.9 g). After the evolution of hydrogen ceased, compound **1** (0.17 g, 1 mmol) was added. The mixture was stirred while it foamed again, then heated under gentle reflux under argon for 24 h. After cooling, water (20 mL) was carefully added and the resultant dark orange solution was transferred to a separation funnel. The aqueous mixture was washed with diethyl ether (2 × 25 mL), with dichloromethane (2 × 20 mL) and then

acidified with 1 N hydrochloric acid to pH 2. The acidified aqueous layer was extracted with dichloromethane (3 × 20 mL). The extract was dried with anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to silica gel chromatography eluting with benzene/methanol (9:1) to give product **3a–e** as red oils.

[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]acetic acid (3a**)** Yield 51%; IR (v, cm⁻¹, film): 2977, 2938 (C–H, stretch), 1737 (C=O, stretch), 1177, 1123 (C–O, stretch); EI MS: m/z 277 (4), 231 (7), 230 (7, M⁺), 216 (100), 200 (40), 160 (6), 143 (18), 140 (87), 129 (11), 124 (51), 109 (19), 108 (28), 107 (34), 102 (33), 98 (39), 85 (61), 84 (21), 83 (20), 82 (22), 81 (25), 74 (28), 71 (91), 69 (27), 67 (28), 58 (43), 57 (29), 56 (44), 55 (59), 45 (23), 43 (57), 42 (57), 41 (97); ESI MS: m/z 230 (15, M⁻), 229 (100, [M–H]), 171 (5); HR ESI MS. Calcd for C₁₁H₁₉NO₄ ([M–H]): m/z 229.1314, found: m/z 229.1325.

2-[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]propanoic acid (3b**)** Yield 46%; IR (v, cm⁻¹, film): 3395, 2976, 2950 (C–H, stretch), 1732 (C=O, stretch), 1460 (CH₃, bend), 1365 (CH₂, CH₃, bend), 1178, 1120, 1065 (C–O, stretch); EI MS: m/z 244 (4, M⁺), 230 (2), 172 (2), 157 (4), 154 (4), 149 (7), 143 (6), 140 (6), 139 (6), 124 (13), 109 (16), 98 (11), 85 (37), 71 (100), 69 (18), 57 (27), 56 (20), 55 (29), 45 (29), 43 (68), 42 (41), 41 (93); ESI MS: m/z 311 (3), 244 (20, M⁻), 243 (100, [M–H]), 171 (3); HR ESI MS. Calcd for C₁₂H₂₁NO₄ [M–H]: m/z 243.1471, found: m/z 243.1474.

2-[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]butanoic acid (3c**)** Yield 42%; IR (v, cm⁻¹, KBr): 2974, 2930 (C–H, stretch), 1726 (C=O, stretch), 1460 (CH₃, bend), 1389 (CH₂, CH₃, bend), 1178, 1130, 1080 (C–O, stretch); EI MS: m/z 258 (30, M⁺), 244 (32), 228 (4), 213 (2), 202 (4), 171 (14), 157 (21), 155 (15), 154 (17), 140 (26), 139 (24), 124 (60), 116 (7), 109 (48), 98 (24), 85 (100), 71 (26), 69 (34), 57 (13), 56 (19), 55 (27), 43 (15), 41 (43); ESI MS: 258 (5, M⁻), 257 (100, [M–H]); HR ESI MS. Calcd for C₁₃H₂₃NO₄ [M–H]: 257.1627, found: m/z 257.1622.

2-[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]hexadecanoic acid (3d**)** Yield 3%; IR (v, cm⁻¹, KBr): 2925, 2854 (C–H, stretch), 1717 (C=O, stretch), 1462 (CH₃, bend), 1378 (CH₂, CH₃, bend), 1109 (C–O, stretch); EI MS: m/z 426 (7, M⁺), 412 (100), 396 (57), 156 (16), 155 (11), 154 (9), 140 (43), 124 (43), 109 (11), 100 (14), 98 (17), 87 (10), 85 (21), 83 (19), 74 (20), 71 (22), 69 (21), 67 (9), 58 (19), 57 (20), 56 (16), 55 (30), 43 (43), 41 (25); ESI MS: 426 (100, M⁻), 313 (5), 221 (10); HR ESI MS. Calcd for C₂₅H₄₈NO₄ (M⁻): 426.3583, found: m/z 426.3569.

[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy](phenyl)acetic acid (3e**)** Yield 53%; IR (v, cm⁻¹, KBr): 3430, 2976, 2960 (C–H, stretch), 1736 (C=O, stretch), 1460 (CH₃, bend), 1389 (CH₂, CH₃, bend), 1177, 1099 (C–O, stretch); EI MS: m/z 306 (33, M⁺), 292 (55), 276 (10), 261 (10), 155 (23), 154 (24), 140 (28), 139 (18), 136 (80), 135 (100), 124 (52), 118 (18), 109 (31), 107 (42), 105 (10), 100 (13), 98 (16), 85 (17), 83 (12), 82 (13), 81 (14), 79 (44), 77 (27), 74 (11), 69 (23), 67 (12), 57 (17), 56 (19), 55 (25), 41 (34); ESI MS: 306 (30, M⁻), 305 (100, [M–H]), 261 (10), 239 (8), 171 (35); HR ESI MS. Calcd for C₁₇H₂₃NO₄ [M–H]: m/z 305.1627, found: m/z 305.1640.

Acknowledgment: This work was supported by the Polish Ministry of Science and Higher Education, 4180/E-142/S/2013.

Received November 4, 2013; accepted February 6, 2014

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