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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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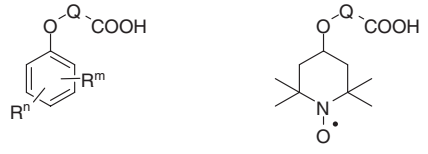
Introduction

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 = CH_2 or substituted CH_2; R^n, R^m = various substituents

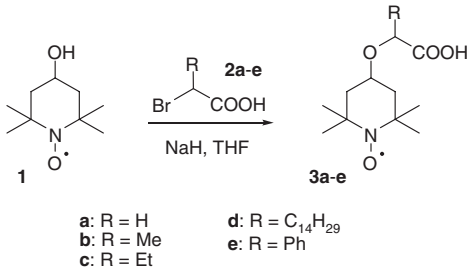
To synthesize the compounds generally abbreviated above as **N-O**, alkylation of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) with a bromoalkanoic acid in the presence of a base is required. Alkylation of the hydroxyl group in **1** is usually performed under basic conditions. Examples are 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-bromoalkanecarboxylic 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 ^{1}H 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 alkanoic acid derivatives bearing a nitroxyl moiety **3a–e**.

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

No.	*Botrytis cinerea*	*Fusarium culmorum*	*Phytophthora cactorum*	*Rhizoctonia solani*
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, CH_3OH 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-bromoalkanecarboxylic 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 (ν, 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, $M^{\cdot}$), 229 (100, $[M\text{-}H]^-$), 171 (5); HR ESI MS. Calcd for $C_{11}H_{19}NO_4$ ($[M\text{-}H]^-$): 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 (ν, cm^{-1}, film): 3395, 2976, 2950 (C-H, stretch), 1732 (C=O, stretch), 1460 (CH_3, bend), 1365 (CH_2, CH_3, 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, $M^{\cdot}$), 243 (100, $[M\text{-}H]^-$), 171 (3); HR ESI MS. Calcd for $C_{12}H_{21}NO_4$ $[M\text{-}H]^-$: 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 (ν, cm^{-1}, KBr): 2974, 2930 (C-H, stretch), 1726 (C=O, stretch), 1460 (CH_3, bend), 1389 (CH_2, CH_3, 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, $M^{\cdot}$), 257 (100, $[M\text{-}H]^-$); HR ESI MS. Calcd for $C_{13}H_{23}NO_4$ $[M\text{-}H]^-$: 257.1627, found: m/z 257.1622.

2-[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy]hexadecanoic acid (3d) Yield 3%; IR (ν, cm^{-1}, KBr): 2925, 2854 (C-H, stretch), 1717 (C=O, stretch), 1462 (CH_3, bend), 1378 (CH_2, CH_3, 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, $M^{\cdot}$), 313 (5), 221 (10); HR ESI MS. Calcd for $C_{25}H_{48}NO_4$ ($M^{\cdot}$): 426.3583, found: m/z 426.3569.

[(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-yl)oxy](phenyl)acetic acid (3e) Yield 53%; IR (ν, cm^{-1}, KBr): 3430, 2976, 2960 (C-H, stretch), 1736 (C=O, stretch), 1460 (CH_3, bend), 1389 (CH_2, CH_3, 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, $M^{\cdot}$), 305 (100, $[M\text{-}H]^-$), 261 (10), 239 (8), 171 (35); HR ESI MS. Calcd for $C_{17}H_{23}NO_4$ $[M\text{-}H]^-$: m/z 305.1627, found: m/z 305.1640.

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References

[1] Krawczyk, M.; Legocki, J. Badania estrów alkilowych kwasu 2,4-dichlorofenoksyoctowego (2,4-D) i kwasu 4-chloro-2-metylofenoksyoctowego (MCPA). *Przem. Chem*. **2007**, *86*, 506–509.

[2] Bovey, R. W.; Young, A. L. The Science of 2,4,5-T and Associated Phenoxy Herbicides; John Wiley & Sons: Hoboken, NJ, 1980.

[3] Schulz, C. O.; Segal, S. A.; Reichardt, W. D. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. *Chemosphere* **1990**, *20*, 1001–1004.

[4] Zakrzewski, J. Reactions of nitroxides XIII: synthesis of the Morita-Baylis-Hillman adducts bearing a nitroxyl moiety using 4-acryloyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl as a starting compound, and DABCO and quinuclidine as catalysts. *Beilstein J. Org. Chem.* **2012**, *8*, 1515–1522.

[5] Wunderlich, W.; Clauss, M.; Roth, M.; Fuso, F.; Ciba Specialty Chemicals Corp. *Use of 2,2,6,6 tetraalkylpiperidine-N-oxyl radicals having long alkyl chains as polymerization regulators*. US Patent 6864313, **2005**.

[6] Luston, J.; Smieskova, E.; Vass, F. 4-(2,3-Epoxypropoxy)-2,2,6,6-tetrametylpiperidin-1-oxyl a sposob jeho priprawy. Czech. Patent 254699, **1987**; *Chem. Abstr.* **1987**, *111*, 115143.

[7] Chang, C.; Zhu, J.; Zhang, Z.; Zhou, N.; Cheng, Z.; Zhu, X. Synthesizing and characterization of comb-shaped carbazole containing copolymer via combination of ring opening polymerization and nitroxide-mediated polymerization. *Polymer* **2010**, *51*, 1947–1953.

[8] Song, C.; Hu, K.-N.; Joo, C.-G.; Swager, T. M.; Griffin, R. G. TOTAPOL: a biradical polarizing agent for dynamic nuclear polarization experiments in aqueous media. *J. Am. Chem. Soc.* **2006**, *128*, 11385–11390.

[9] Zakrzewski, J. Synthesis of 2-hydroxybenzophenone derivatives bearing 2,2,6,6-tetramethylpiperidine moiety. Thesis, Technical University of Poznan, **1997**.

[10] Wagner, H.; Brinks, M. K.; Studer, A.; Hirtz, M.; Chi, L.; Schaefer, A. Chemical surface modification of self-assembled monolayers by radical nitroxide exchange reactions. *Chem. Eur. J.* **2011**, *17*, 9107–9112.

[11] Matsumoto, K.; Iwata, T.; Suenaga, M.; Okudomi, M.; Nogawa, M.; Nakano, M.; Sugahara, A.; Bannai, Y.; Baba, K. Mild oxidation of alcohols using soluble polymer-supported TEMPO in combination with oxone: effect of a basic matrix of TEMPO derivatives. *Heterocycles* **2010**, *81*, 2539–2553.

[12] Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. Selective oxidation of alcohols by oxoaminium salts. *J. Org. Chem.* **1985**, *50*, 1332–1334.

[13] Debuigne, A.; Caille, J.-R.; Jerome, R. Synthesis of end-functional poly(vinyl acetate) by cobalt-mediated, radical polymerization. *Macromolecules* **2005**, *38*, 5452–5458.

[14] Endo, T.; Takuma, K.; Takata, T.; Hirose, C. Synthesis and polymerization of 4-(glycidyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl. *Macromolecules* **1993**, *26*, 3227–3229.

[15] Zeika, O.; Li, Y.; Jockusch, S.; Parkin, G.; Sattler, A.; Sattler, W.; Turro, N. J. Synthesis of polynitroxides based on nucleophilic aromatic substitution. *Org. Lett.* **2010**, *12*, 3696–3699.

[16] Einhorn, J.; Einhorn, C.; Ratajczak, F.; Durif, A.; Averbuch, M.-T.; Pierre, J.-L. Synthesis and resolution of a chiral analogue of 2,2,6,6-tetramethylpiperidine and of its corresponding nitroxide. *Tetrahedron Lett*. **1998**, *39*, 2565–2568.

[17] Barrett, A. G. M.; Hanson, G. R.; White, A. J. P.; Williams, D. J.; Micallef, A. S. Synthesis of nitroxide-functionalized phthalocyanines. *Tetrahedron* **2007**, *63*, 5244–5250.

[18] Gubskaya, V. P.; Berezhnaya, L. Sh.; Gubaidullin, A. T.; Faingold, I. I.; Kotelnikova, R. A.; Konovalova, N. P.; Morozov, V. I.; Litvinov, I. A.; Nuretdinov, I. A. Synthesis, structure and biological activity of nitroxide malonate methanofullerenes. *Org. Biomol. Chem.* **2007**, *5*, 976–981.

[19] Yi, S.; Mileo, E.; Kaifer, A. E. EPR and NMR investigation on the interactions of nitroxide probes with resorcin[4]arene molecular capsules. *Org. Lett.* **2009**, *11*, 5690–5693.

[20] Fairfull-Smith, K. E.; Debele, E. A.; Allen, J. P.; Pfrunder, M. C.; McMurtrie, J. C. Direct iodination of isoindolines and isoindoline nitroxides as precursors to functionalized nitroxides. *Eur. J. Org. Chem.* **2013**, 4829–4835.

[21] Brière, R.; Lemaire, H.; Rassat, A. Nitroxides XV: Synthèse et étude de radicaux libres stables pipéridiniques et pyrrolidinique. *Bull. Soc. Chim. Fr.* **1965**, 3273–3283.

[22] Sosnovsky, G.; Konieczny, M. Preparation of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl. A reinvestigation of methods using hydrogen peroxide in the presence of catalysts. *Z. Naturforsch. B* **1976**, *31B*, 1376–1378.

[23] Zakrzewski, J. A reaction of nitroxides with ethyl mercaptane: a mild method for the conversion of nitroxides into their corresponding amines. *Monat. Chem.* **1990**, *121*, 803–808.

[24] Zakrzewski, J.; Krawczyk, M. Reactions of nitroxides with sulphur-containing compounds, part IV: synthesis of novel nitroxide (thio)ureas. *Heteroatom Chem*. **2006**, *17*, 393–401.