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Reactions of Nitroxides with Sulfur-Containing Compounds, Part IV: Synthesis of Novel Nitroxide (Thio)ureas

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ABSTRACT: *The reactions of 4-isothiocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl* **2** *and 4-isocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl* **3** *with selected amines and lower alcohols give the corresponding novel thioureas* **4**, *ureas* **5**, *thiocarbamates* **6**, *and carbamates* **7**, *all bearing the nitroxyl moiety. The characteristic features of EI mass spectra of (thio)ureas* **4** *and* **5** *are described. Some of the synthesized thioureas* **4**, *ureas* **5**, *thiocarbamates* **6**, *and carbamates* **7** *are moderately or weakly active against pathogenic fungi.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:393–401, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20228

INTRODUCTION

Due to the significant biological importance of (thio)-urea derivatives, their synthesis is the subject of a number of recently published papers [2–9]. Proecological synthesis of N,N′ symmetric substituted ureas has recently been described [10].

To the best of our knowledge, no thiourea derivatives bearing nitroxyl groups are known. However, some urea nitroxides have already been reported [11–17]. Here, in relation to our previous studies on the nitroxides containing sulfur functional groups [1], we present the synthesis, mass spectral features, and some pesticidal properties of the novel (thio)ureas bearing the nitroxyl moiety [18].

RESULTS AND DISCUSSION

Thioureas (**4a–h**), ureas (**5a–h**), thiocarbamates (**6a, b**), and carbamates (**7a,b**) bearing nitroxyl moiety were synthesized according to Scheme 1.

The synthesis of 4-isothiocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl **2** from 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl **1** and thiophosgene has been described earlier [19–21]. The reaction of the isothiocyanate **2** with corresponding secondary amines leads to the thioureas **4a–g** (Table 1).

In order to obtain 4-isocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl **3**, the nitroxyl amine **1** was phosgenated with phosgene dimer (trichloromethyl chloroformate) [12,22,23]. The isolation and purification of **3** by crystallization resulted in a low yield of **3**. Attempts to purify **3** by column chromatography (silica gel) caused the decomposition of **3**. The crude nitroxyl isocyanate **3** was used without further purification in the synthesis of the ureas **5**. The crude **3** was converted to the ureas **5a–g** by the reaction with the corresponding secondary amines (Table 1).

When the starting amine radical **1** was applied as an amine, the bi-radicals **4h** and **5h** were obtained (Table 1). When 2,2,6,6-tetramethylpiperidine **8** was used as an amine, none of the expected (thio)ureas

Part III: [1].

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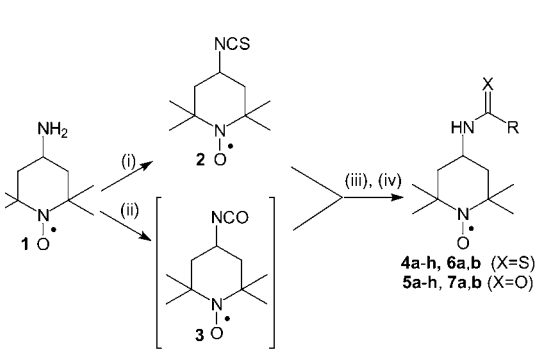


X=S 4a-h 6a-b	X=O 5a-h 7a-b	R
4a	5a	$N(CH_3)_2$
4b	5b	$N(C_2H_5)_2$
4c	5c	$N(n\text{-}C_3H_7)_2$
4d	5d	$N(iso\text{-}C_3H_7)_2$
4e	5e	$N(n\text{-}C_4H_9)_2$
4f	5f	
4g	5g	
4h	5h	
6a	7a	OCH_3
6b	7b	OC_2H_5

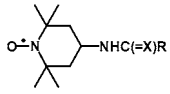
SCHEME 1 (i) $CSCl_2$[19]; (ii) $ClCOOCCl_3$, Bz_3N, benzene; (iii) (**4a–h, 5a–h**) HR, benzene; (iv) (**6a,b, 7a,b**) HR/NaR.

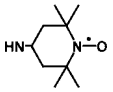
were obtained. This was probably due to the limited access to the nitrogen atom in **8** caused by steric hindrance.

The alternative preparation of **5g** and **5h** from 4-isocyano-2,2,6,6-tetramethylpiperidine-1-oxyl [24] was recently reported [17].

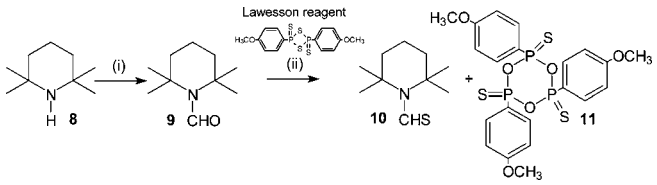
The reactions of isothiocyanate **2** and isocyanate **3** with methanol or ethanol led to the corresponding nitroxyl thiocarbamates **6a,b** and carbamates **7a,b** (Table 1).

In order to synthesize **4, 6** by an alternative route, we tried to use the Lawesson reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulphide) with the intention to convert the carbonyl group in **5, 7** directly to the thiocarbonyl group in **4, 6**. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO, a test nitroxyl radical), **5e** (as an example of a nitroxide urea), TEMPO-4-ONE, TEMPO-4-OL were heated in toluene with the Lawesson reagent. No expected thiourea **4e** was observed. A darkening of the reaction mixture and decomposition of the starting radicals was observed. Many unidentified, strongly colored and polar products were detected by means of TLC.

TABLE 1 Synthesized Thioureas (**4a–h**), Ureas (**5a–h**), Thiocarbamates (**6a,b**), and Carbamates (**7a,b**) 

		X = S, **4a–h, 6a–b**					*X = O,* **5a–h, 7a–b**			
R	*Cmpd*	*Puri cation Method*[a]	*Yield (%)*	*mp (°C)*	R_f *(BM9)*	*Cmpd*	*Puri cation Method*[a]	*Yield (%)*[b]	*mp (°C)*	R_f *(BM9)*
$N(CH_3)_2$	**4a**	K (B)	66.1	157—159	0.15	**5a**	K (B), C (BM9)	35.2	165—169	0.08
$N(C_2H_5)_2$	**4b**	K (B)	76.7	166.5—167.5	0.21	**5b**	K (B), C (BM9)	49.5	145—148	0.10
$N(n\text{-}C_3H_7)_2$	**4c**	K (B)	67.6	154—156	0.25	**5c**	K (B), C (BM9)	73.9	148—152	0.17
$N(i\text{-}C_3H_7)_2$	**4d**	K (B)	64.5	155—157	0.35	**5d**	K (B), C (BM9)	74.5	182—186	0.19
$N(n\text{-}C_4H_9)_2$	**4e**	K (B)	74.3	143—145	0.36	**5e**	K (B), C (BM9)	89.7	162—166	0.23
	**4f**	K (B)	82.4	172.5—173.5	0.20	**5f**	K (B), C (BM9)	83.5	glass	0.17
	**4g**	K (B)	42.0	173—174	0.23	**5g**	C (BM9), K (B), C (BM9)	90.9	157—161[c]	0.23
	**4h**	C (BM9) (twice)	48.4	Glass	0.16	**5h**	C (BM9)	88.7	118—120[d]	0.18
OCH_3	**6a**	C (BM9)	62.8	135—137.5	0.33	**7a**	C (BM9), K (CHx)	75.7	123—126	0.29
OC_2H_5	**6b**	C (BE9)	72.4	153—155	0.40[f]	**7b**	C (BE9), K (CHx)	63.8	118—120[e]	0.32[f]

[a]K (B), K (CHx): crystallization from benzene and cyclohexane, respectively, C: Column chromatography.
[b]The yields refer to the isolated ureas **5** and carbamates **7** and are calculated on the starting nitroxyl amine **1** used in the preceding step.
[c]Earlier this value was erroneously described as 85—87C [17].
[d]116—118C (EtOAc/pentane) [13], 145°C (benzene) [14], 198—199C (hexane) [15], and 203—204C (ethyl acetate) [16].
[e]mp 121—122C [16].
[f]Mobile phase: BE9.



SCHEME 2 (i) $CHCl_3$, 50% NaOH, TEBACl; (ii) boiling toluene, 3.5 h.

In order to confirm that the nitroxide group is unstable in the reaction conditions, the test compound **9**, the simplest 2,2,6,6-tetramethylpiperidine derivative bearing the formyl group instead the nitroxyl one, was designed and synthesized [25,26]. **9** was converted with a poor yield (probably due to steric hindrance) to **10** by the thionation with the Lawesson reagent (Scheme 2, Table 2). The formation of the side-product **11** was observed. The structure of **11** was attributed by means of its spectral data, especially by the A_2B nature of its $^{31}P\{^1H\}$ NMR spectrum (Table 4, footnotes d–f). Recently, a trimer, analogous and similar to **11**, has been identified by $^{31}P\{^1H\}$ NMR analysis [27,28].

The purities of all synthesized nitroxyl radicals (**1–7**) were checked by means of the iodometric titration according to [29]. The structures of synthesized compounds were confirmed by MS, IR and for **8–11** additionally by NMR (^1H, ^{13}C, ^{31}P) spectra (Tables 3 and 4).

The EI mass spectra of synthesized thioureas **4a–g** and ureas **5a–g** were analyzed. Example graphs for **4b** and **5g** are presented on Figs. 1 and 2, respectively.

TABLE 2 Synthesized Derivatives of 2,2,6,6-Tetramethylpiperidine **8**

Cmpd	*m (g)*	*Yield (%)*	*bp (°C/mmHg)*	*mp (°C)*	*R_f*
9	2.3	45.4	65/0.2	47.5–49[a]	0.20 (BA95)
					0.60 (BM9)
10	0.0518	28.0	–	89–92	0.05 (HA9)
					0.67 (BM9)
					0.53 (BA9)
					0.65 (CM9)
11	0.1692	–	–	155–163	0.23 (HA9)[c]
				(benzene)[b]	0.83 (BM9)
					0.66 (BA9)
					0.79 (CM9)

[a] 47.5—48.5C [25].
[b] 160°C [35], 158—159C [36], 155—156C (benzene) [37, 38].
[c] 0.14 (HA6) [36].

The distinct molecular ions are observed in the mass spectra of all described thiourea and urea nitroxides. However, the molecular peaks in mass spectra of thiourea nitroxides **4a–g** are greater than the molecular peaks of urea nitroxides **5a–g** (int. 25–42% and 10–23%, respectively) except for that of **4e**.

As expected, the signal of a carbamoyl fragment $(R^1)_2N{-}C{=}O$ is abundant (except **5a**). It is the base peak in the mass spectra of the urea nitroxides **5b,c,e,g**. On the contrary, the thiocarbamoyl fragments $(R^1)_2N{-}C{=}S$ are observed, but (except **4a**, int. 100%) their intensity (**4b–g**) is much less abundant.

The most characteristic feature of the mass spectra for both (thio)urea nitroxides **4a–g** and **5a–g** is the presence of the signal M-73 (**4a–g**) and M-86 (**5a–g**). In the case **4b–g** and **5a**, they are the base signals. The probable origin of the M-73 for **4a–g** is $M - (CH_3)_2C{=}N{-}OH$ [30] and of the M-86 for **5a–g** is $M - O{=}N{-}C(CH_3)_2{-}CH_2$.

Surprisingly, signal M-33 (M-SH), which is very characteristic for thiourea derivatives [31] is not observed in the spectra of thiourea nitroxides **4a–g**.

Due to the similarity of the structures of the synthesized (thio)ureas **4a–h, 5a–h**, and (thio)carbamates **6a,b, 7a,b** with the structure of the known pesticide isoproturon [4-*i*-$C_3H_7{-}C_6H_4{-}NHCON(CH_3)_2$] [32] and its thio analog [33], pesticidal activity of the synthesized **4–7** was tested using preliminary screening tests.

Several fungicidally active compounds against pathogenic fungi have been identified (Table 5).

In vitro test. A slight inhibition of the colony formation of the following fungi at the concentration 200 mg L^{-1} was observed:

- *Botrytis cinerea*: **6a** (weak activity), **4h** and **6b** (moderate activity);
- *Fusarium culmorum*: **4c, 4d, 6a**, and **6b** (weak activity);
- *Phytophthora cactorum*: **4h, 5e, 6a**, and **6b** (weak activity);
- *Rhizoctonia solani*: **4c, 4d**, and **6b** (weak activity).

In vivo test. The infection of wheat leaves induced by powdery mildew (*Blumeria graminis*) was reduced by up to 50% and 90% after single sprayings with **7b** and **6a** solution (1000 mg L^{-1}), respectively.

The additional experiments were conducted with several weed species to investigate herbicidal activity of synthesized compounds at the dose 1 kg/ha. None of the compounds showed significant activity against weeds when applied via leaves or via soil.

TABLE 3 Spectral Data of (Thio)ureas **4, 5** and (Thio)carbamates **6, 7**

Cmpd	*MS, EI, 70 eV, m/e int (%)*	*IR, ν(cm^{-1}), KBr*	*Cmpd*	*MS, EI, 70 eV, m/e int (%)*	*IR, ν (cm^{-1}), KBr*
4a	259 (28), 258 (33, M), 185 (74), 88 (100)	3363, 2982, 2929, 1542, 1344	**5a**	243 (8), 242 (23, M), 156 (100), 141 (49), 72 (39)	3391, 2988, 2972, 2940, 1641, 1529
4b	287 (19), 286 (42, M), 213 (100)	3374, 2971, 2932, 1534, 1358, 1331, 1261	**5b**	271 (7), 270 (10, M), 184 (52), 100 (100)	3408, 2974, 2932, 1633, 1528
4c	315 (20), 314 (25, M), 241 (100)	3365, 2966, 1531, 1347	**5c**	299 (7), 298 (13, M), 212 (70), 145 (53), 128 (100), 72 (89), 43 (67)	3324, 2968, 2934, 2873, 1617, 1538
4d	315 (18), 314 (34, M), 241 (100)	3442, 2965, 1537, 1328	**5d**	299 (4), 298 (12, M), 212 (34), 145 (34), 128 (85), 86 (100), 44 (42), 43 (43)	3418, 2969, 2930, 1635, 1529
4e	343 (16.5), 342 (31, M), 269 (100)	3310, 2957, 1533, 1362	**5e**	327 (9), 326 (16, M), 240 (80), 197 (34), 173 (59), 156 (100), 86 (99), 57 (89)	3329, 2962, 2932, 1616, 1544
4f	301 (21), 300 (36, M), 227 (100), 147 (58), 130 (50), 124 (34)	3347, 2970, 2955, 2926, 2861, 1533, 1336	**5f**	285 (8), 284 (15, M), 198 (100), 183 (39), 154 (43), 140 (43), 131 (60), 124 (62), 114 (91), 88 (70), 70 (53)	3429, 2973, 2931, 2856, 1627, 1536
4g	299 (17), 298 (35, M), 225 (100), 169 (27), 145 (41), 128 (53)	3304, 3000, 2977, 2939, 2858, 1539, 1347	**5g**	283 (9), 282 (10, M), 196 (74), 129 (54), 112 (100)	3424, 2975, 2934, 2851, 1617, 1537
4h	385 (4), 384 (3, M), 140 (38), 124 (100), 58 (70), 55 (45), 42 (32), 41 (50)	3470, 3322, 2972, 2935, 1541	**5h**	369 (3), 368 (M, 5), 199 (23), 140 (32), 124 (100), 84 (56.5), 70 (40)	3380, 2976, 2938, 1645, 1580
6a	246 (17), 245 (12, M), 172 (38), 154 (86), 140 (70.5), 124 (100), 109 (60), 41 (74)	3224, 3033, 2994, 2943, 1533, 1208	**7a**	229 (15, M), 154 (23), 143 (44), 128 (100), 124 (56), 109 (33)	3334, 2976, 2940, 1695, 1544, 1317, 1241, 1035
6b	260 (15), 259 (10.5, M), 154 (82), 140 (67), 124 (100), 109 (53), 41 (66)	3223, 2977, 2937, 1536, 1206	**7b**	243 (27, M), 157 (59), 142 (71), 128 (100), 124 (57)	3297, 2992, 2941, 1718, 1536, 1307, 1237, 1137, 1041

EXPERIMENTAL

General

4-Isothiocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **2** and 2,2,6,6-tetramethylpiperidine **8** were synthesized as described previously [19,34]. All reagents were commercially available and used as received without further purification.

All experiments were performed in a multinecked round-bottomed flask equipped with a magnetic stirrer, a thermometer, a dropping funnel, and a reflux condenser protected against humidity. The formation of products was monitored by means of TLC. Molar ratios of reactants, parameters of the particular procedures, melting points, and chromatographic data are shown in Tables 1 and 2. Spectral data are shown in Tables 3 and 4.

TLC control and column chromatography were done on silica gel Merck Alurolle 5562, Alufolien 5554 and Merck 1.09385.1000 (0.040–0.063 mm, 230–400 mesh), respectively.

The following abbreviations for mobile phases were used throughout the text:

- BM9 = benzene : methanol 9 : 1;
- BE9 = benzene : ethanol 9 : 1;
- BA9, BA95 = benzene : ethyl acetate 9 : 1, 95 : 5, respectively;
- HA6, HA9 = hexane : ethyl acetate 6 : 1, 9 : 1, respectively;
- CM9 = carbon tetrachloride : methanol 9 : 1.

MS (EI, 70 eV, m/e, int. (%)) data were recorded using AMD 604 apparatus, except **9**: Finnigan MAT 8200 and **10**: GC Varian 3300 with Finnigan MAT ITD 800. IR (ν/cm^{-1}) data were recorded using FT/IR Jasco 420 apparatus. ^{1}H NMR (δ/ppm, J (Hz), $CDCl_3$, TMS),^{13}C NMR (δ/ppm, $CDCl_3$, TMS), and

TABLE 4 Spectral Data of **9**, **10**, and **11**

Cmpd	*MS (EI, 70 eV, m/e, int (%))*	*IR (v, cm^{-1}, KBr)*	*^{1}H NMR*	*^{13}C NMR*	*^{31}P NMR*
9	169 (23, M), 154 (83), 109 (100), 86 (77), 69 (82), 58 (43), 41 (76)[a]	2945, 1660, 1313	(100 MHz, $CDCl_3$): 1.44 (s, 6H, 2 × CH3), 1.49 (s, 6H, 2 × CH3), 1.60 (s, 6H, 3 × CH_2), 8.54 (s, 1H, CHO)[b]	(25 MHz, $CDCl_3$): 16.35 (CH_2), 28.01 (CH_3), 32.47 (CH_3), 40.12 (CH_2), 41.29 (CH_2), 55.32 (C), 55.75 (C), 164.52 (CHO)	—
10	185 (58, M), 184 (93), 152 (52), 69 (100)	2950, 2933, 1427, 1380, 1343	(200 MHz, $CDCl_3$): 1.45 (s, 6H), 1.75 (m, 6H), 1.85 (s, 6H), 9.72 (s, 1H, CHS)	(50 MHz, $CDCl_3$): 15.40 (CH_2), 26.43 (CH_3), 32.15 (CH_3), 38.42 (CH_2), 41.20 (CH_2), 61.54 (C), 62.93 (C), 189.53 (CHS)	—
11	558 (12. M), 542 (16.5), 526 (12), 510 (11), 202 (100), 139 (73)[c]	1594, 1504, 1301, 1265, 1121, 927, 748, 611[d]	(500 MHz, $CDCl_3$): 3.87 (s, 6H, 2 × OCH_3), 3.89 (s, 3H, OCH_3), 7.01 (4H, m /pseudo-doublet, $J \approx 5$ Hz), 7.05 (2H, m/pseudo-quartet, $J \approx 4$ Hz), 8.09 (4H, m/pseudo-quartet, $J \approx 8$ Hz), 8.25 (2H, m/pseudo-quartet, $J \approx 9$ Hz)[e]	(125 MHz, $CDCl_3$): 55.60 (s, 2 × OCH_3), 55.61 (s, 1 × OCH_3), 114.08 (d), 114.14 (s), 114.23 (d), 121.76 (m), 121.95 (m), 123.05 (m), 123.28 (d), 134.08 (t), 134.53 (d), 164.17 (m), 164.31 (d)	(202.65 MHz, $CDCl_3$) (A_2B): 69.3 (2P, pseudo-doublet, $J \approx 50$ Hz), 71.4 (1P, dd, $J \approx 50$ Hz)[f]

[a] 169 (10, M), 154 (52), 109 (67), 86 (97), 69 (100), 58 (58), 46 (28) [25].
[b] 1.43 (12H, br s), 1.61 (6H, s), 8.53 (1H, s) [25].
[c] 558(M) [35].
[d] 807 (P═S), 930 (OPO) [35]. 610 (s), 680 (m), 695 (m), 750 (s), 805—840(grp 4, ms), 930 (s, P—O), 1500, 1600 (s, aromatic bands) [36]. 670, 680 (P═S), 930—950(POP), 1500, 1590, 3080 (benzene nucleus) [37, 39].
[e] 3.8, (s, 3H), 6.8—9.2(m, 2H), 7.8—8.3(m, 2H) [35]. 3.85 (s, 6H), 3.87 (s, 3H), 6.95—7.08(m, 6H), 8.03—8.30(m, 6H) [36]. 2.63 (s, 9H, CH3O), 5.87—8.07(m, 12H, C_6H_4) [37, 39].
[f] 72 [36, 39], 71 [37, 38].

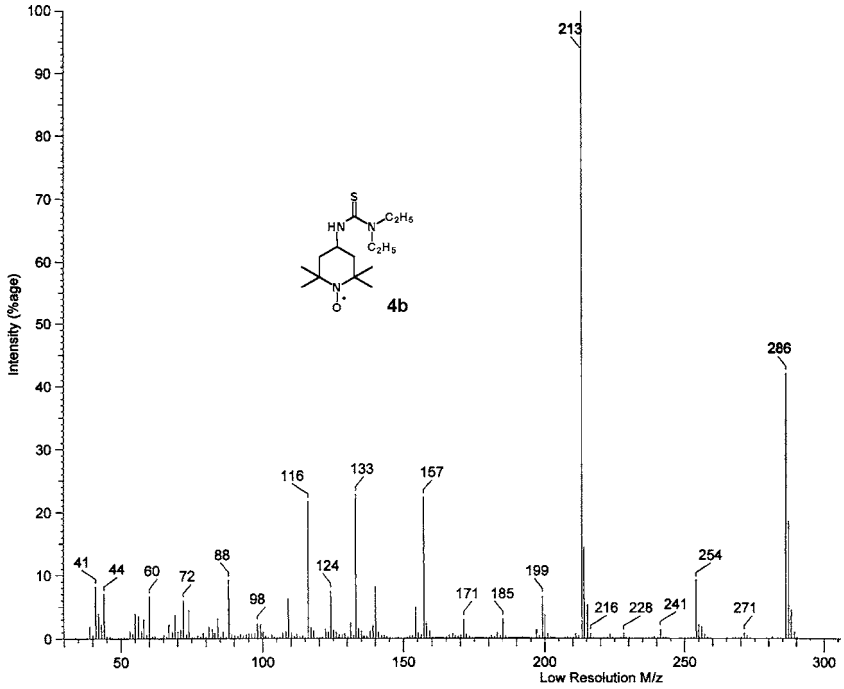


FIGURE 1 The mass spectrum of the thiourea nitroxide **4b**.

^{31}P NMR (δ/ppm, J (Hz), $CDCl_3$, H_3PO_4) (for non-radical compounds **9–11**) data were recorded using Bruker WP 100 SY (100 MHz) (**9**), Varian UNITY-plus 200 (200 MHz) (**10**), and Varian UNITYplus 500 (500 MHz) (**11**) apparatus.

Thioureas **4a–g***: General Procedure*

4-Isothiocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **2** (0.3195 g, 1.5 mmol) and anhydrous benzene (8–10 mL) were placed in the reaction flask. The appropriate amine (1.7 mmol) was added with

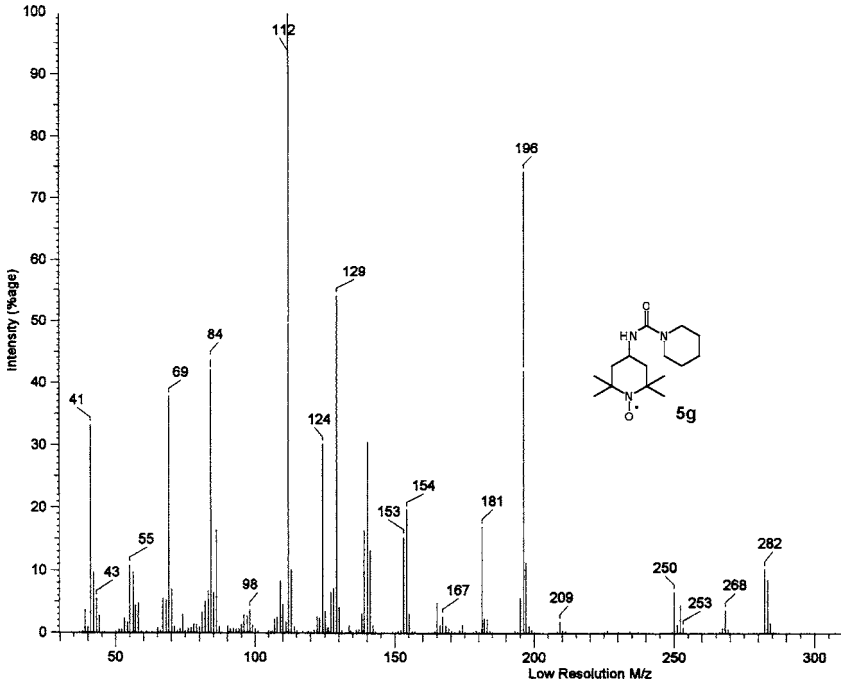


FIGURE 2 The mass spectrum of the urea nitroxide **5g**.

TABLE 5 The Effect of Compounds on Mycelial Growth of Phytopathogenic Fungi

	% Growth reduction[a]				
Compound No.	*Botrytis cinerea*[b]	*Fusarium culmorum*[b]	*Phytophthora cactorum*[b]	*Rhizoctonia solani*[b]	*Blumeria graminis*[c]
4c	0	1	0	1	0
4d	0	1	0	1	0
4h	2	0	1	0	0
6a	1	1	1	0	2
6b	2	1	1	1	0
5e	0	0	1	0	0
7b	0	0	0	0	1

[a]Scale:
0 = 0—20% growth reduction —no effect.
1 = 20.1—50% growth reduction —week activity.
2 = 50.1—90% growth reduction —moderate activity.
3 = 90.1—100% growth reduction —good activity.
[b]*in vitro.*
[c]*in vivo.*

a syringe at 15°C. In the case of **4a**, the gaseous dimethylamine is introduced either through an inlet tube, or as excess, chilled liquid directly into the flask. The temperature of the suspension rises up to about 20°C, then lowered to about 18°C. Pink, crystalline precipitate is formed (**4a–d, f**), and the suspension is partially concentrated. If no precipitate is observed (**4e, g**), the reaction mixture is allowed to stand at about 0°C (in a refrigerator) overnight and/or partially concentrated. The pink, fine, crystalline precipitate is collected, washed with chilled benzene or hexane and repeatedly crystallized from a small amount of benzene. The crystals are air dried. The preparation details and spectroscopic data of the synthesized nitroxide thioureas **4a–g** are presented in Tables 1 and 3, respectively.

N,N′-Bis(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl) thiourea **4h**

4-Isothiocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **2** (0.1385 g, 0.65 mmol) and anhydrous benzene (3 mL) were placed in the reaction flask. The solution of 4-amine-2,2,6,6-tetramethylpiperidin-1-oxyl **1** (0.1167 g, 0.68 mmol) in anhydrous benzene (0.5 mL) was added with a syringe at 22°C. The stirring was continued at ambient temperature for 24 h. The formation of the product was monitored by means of TLC (BM9). Benzene was evaporated under reduced pressure. The residue (0.3146 g) was subjected to column chromatography (mobile phase: BM9). to give the red, glassy *N,N′*-bis(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl) thiourea **4h** (0.1216 g, 48.4%); R_f 0.16 (BM9).

4-Isocyanate-2,2,6,6-tetramethylpiperidine-1-oxyl **3**

Tribenzylamine (1.745 g, 6.1 mmol), benzene (28 ml) were placed in the reaction flask. Stirred solution was cooled to 5°C with ice-water bath. The solution of trichloromethyl chloroformate ("diphosgene") (0.415 g, 253 μL, 2.1 mmol) in benzene (3.5 mL) was added dropwise. The solution of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl **1** (0.513 g, 3 mmol) in benzene (7 mL) was added in the same way at 5–7°C. The dropping funnel was washed with additional amount of benzene (2 mL). The reaction mixture becomes cloudy, brown and the precipitate is formed. Ice-water bath was removed and reactants were stirred at ambient temperature for additional 2 h. Tribenzylamine hydrochloride was filtered off. Benzene was evaporated under reduced pressure to give the crude, red 4-isocyanate-2,2,6,6-tetramethylpiperidine-1-oxyl **3**. It is acceptable as a starting material for the next step (the reaction with either amines or alkoxylates). The crude **3** may be purified by means of crystallization from hexane (10–15 mL of hexane /0.1–0.15 g of crude **3**) (18–34%), mp 100–102°C (102°C [23]), MS (70 eV, *m/e*, int /%): 197 (39, M), 140 (43), 124 (66), 110 (100), 96 (78), 68 (66), 56 (25), 55 (23), 41 (47), IR (ν, cm^{-1}, KBr): 2981, 2942, 2260.

Ureas **5a–h***: General Procedure*

Crude 4-isocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **3** (obtained from 3 mmol of 4-amine-2,2,6,6-tetramethylpiperidin-1-oxyl **1**) and anhydrous benzene (16 mL) were placed in the reaction flask. The appropriate amine was added dropwise at 15–20°C. The solution was stirred at ambient temperature for

1 h (control with TLC, BM9) and evaporated under reduced pressure. The residue was carefully crystallized (chilling and concentration) from benzene (2–3 mL) and then purified by means of column chromatography (BM9) to give pink crystals of ureas **5**. The preparation details and spectroscopic data of the synthesized nitroxide ureas **5a–h** are presented in Tables 1 and 3, respectively.

Thiocarbamates **6** *and carbamates* **7***: General Procedure*

The solution of sodium alkoxide (1 mmol/1 mL) was prepared by dissolving of elemental natrium (0.23 g, 0.01 g atom) in the appropriate anhydrous alcohol and diluting the resulting solution with the same alcohol up to the 10 mL volume. The starting 4-isothiocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **2** (0.3195 g, 1.5 mmol), or crude 4-isocyanate-2,2,6,6-tetramethylpiperidin-1-oxyl **3** (obtained from 3 mmol of 4-amine-2,2,6,6-tetramethylpiperidin-1-oxyl) is placed in the reaction flask and dissolved in the anhydrous alcohol (methanol, ethanol, 4–8 mL). The mixture is slightly warmed if necessary to dissolve the starting **2** or **3**. The alcohol solution of the appropriate sodium alkoxide (1.2 mmol/1 mmol of the starting **2** or **3**) was added with a pipette at 20°C. The temperature of the solution raised up to 24°C. The solution was stirred for 10 min at ambient temperature. The solvent was evaporated under reduced pressure. Diethyl ether (20–30 mL) was added to the residue. The mixture was stirred for about 30 min, and additional amount of diethyl ether (15 mL) was added. White precipitate was thoroughly triturated with diethyl ether, filtered off, and washed with the same solvent (5–10 mL). The filtrate was dried over anhydrous magnesium sulfate overnight. Drying agent was filtered off, ether was evaporated under reduced pressure. The crude thiocarbamates **6** or carbamates **7** were subjected to column chromatography (mobile phase benzene: appropriate alcohol 9:1, i.e. BM9 or BE9, respectively). The preparation details and spectroscopic data of the synthesized nitroxide thiocarbamates **6a–b** and carbamates **7a–b** are presented in Tables 1 and 3, respectively.

1-Formyl-2,2,6,6-tetramethylpiperidine **9**

Triethylbenzylammonium chloride (0.5 g, 2.2mmol), chloroform (about 25 mL), and 2,2,6,6-tetramethylpiperidine **8** (4.23 g, 0.03 mol) were placed in the reaction flask. Into the vigorously stirred reaction mixture, 50% aqueous sodium hydroxide solution (16 mL) was added dropwise. The temperature of the reaction mixture raised up to 60°C. Cooling with cold water bath was applied if needed. The reaction mixture was vigorously stirred at 50°C for 5.5 h, then allowed to cool to ambient temperature, diluted with water and methylene chloride. Organic layer was separated, washed with water and dried over magnesium sulfate. Drying agent was filtered off, and solvent was evaporated under reduced pressure. The residue (5.4 g) was subjected to distillation under reduced pressure to give **9** (2.3 g, 45.4%); bp 65°C/0.2 mmHg, mp 47.5–49°C (47.5–48.5°C [25]); R_f 0.2 (BA95); 0.6 (BM9).

1-Thioformyl-2,2,6,6-tetramethylpiperidine **10**

1-Formyl-2,2,6,6-tetramethylpiperidine **9** (0.169, 1 mmmol), Lawesson's reagent (0.55 g, 1.36 mol), and toluene (about 3–4 mL) were placed in the reaction flask. The reaction mixture was stirred at reflux for 3.5 h, then at ambient temperature overnight. The progress of the reaction was monitored by means of TLC (silica gel, BM9). Reaction mixture was filtered through Cellite and washed with benzene. Benzene was evaporated and the residue (0.5021 g) was subjected to twice repeated column chromatography (mobile phase BA95) to give

- **11**-colorless side-product of the Lawesson's reagent transformation as the first fraction: 0.1692 g, 155–163°C.
- the yellow zone of the expected product **10** as the second fraction: 0.0518 g, 28.0%, 89–92°C.

In vitro Fungicidal Bioassay

Fungitoxicity of compounds against phytopathogenic fungi*: Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum*, *Phytophthora cactorum* was assessed in vitro using agar growth medium poison technique.

PDA media in 100 mm Petri plates containing synthesized compounds (at concentration 200 g L^{-1}) were infected with agar disks with thin mycelium of fungi cultures. Linear growth of each colony was determined after 3–5 days. The effect of each compound on mycelial growth was assessed by calculating the percentage of growth reduction.

In vivo Fungicidal Bioassay

Wheat plants (*Triticum aestivum*, L.) were grown to growth stage 11 (Zadoks scale) under normal glasshouse propagation conditions (temperature, 20–25°C; lighting, 14 h photoperiod of daylight supplemented by lamps 400 W). They were inoculated

with powdery mildew (*Blumeria graminis*) 2 h after spraying using dry inoculums from diseased plants. Plants sprayed with solutions (1000 mg L^{-1}) were transferred to the growth chamber (temperature, day/night 20/16°C; lighting, 14 h photoperiod; relative humidity, 80(±5)%). Visual assessment of infestation was scored 6 days after spraying.

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