Pestycydy/Pesticides, **2010**, (*1-4*), 21-31.
ISSN 0208-8703

Synthesis and fungicidal activity of substituted isoxazolecarboxamides

Mirosław GUCMA, W. Marek GOŁĘBIEWSKI and Alicja MICHALCZYK

Institute of Industrial Organic Chemistry
Annopol 6, 03-236 Warsaw, Poland
e-mail: golebiewski@ipo.waw.pl

Abstract: Several new 3-substituted isoxazolecarboxamides have been prepared from aromatic and aliphatic aldehydes. A key step was a 1,3-dipolar cycloaddition of nitrile oxides to ethyl acrylate or methacrylate esters. Some of the amides showed high fungicidal activities against *Alternaria alternate, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum*, and *Phytophthora cactorum* strains.

Key words: cycloaddition, fungicides, isoxazole derivatives, regioselectivity

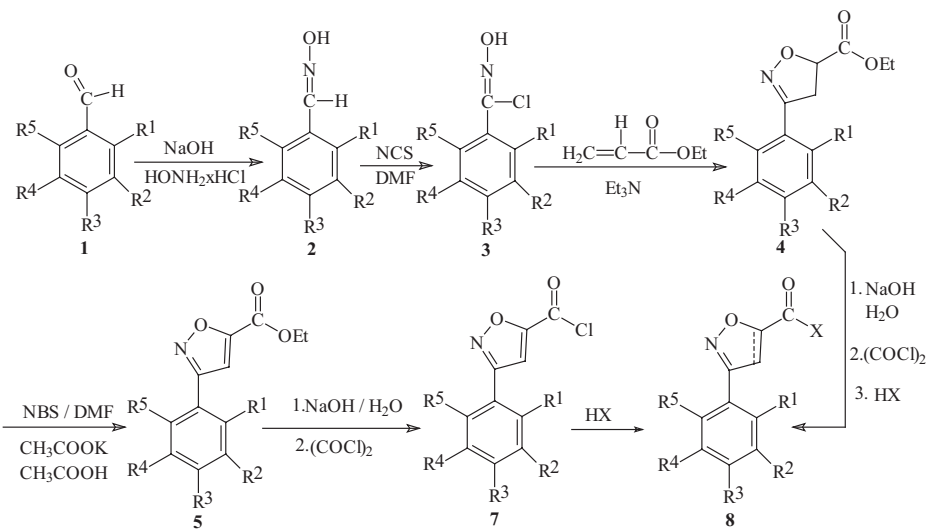
INTRODUCTION

Herbicidal and fungicidal activity of carboxamides is known for a long time [1]. Herbicidal potency can be explained by the inhibition of fatty acid biosynthesis, the inhibition of phytoenone desaturase involved in the biosynthesis of the carotenoids [2]), the inhibition of photosynthetic electron transport at the photosystem II receptor-site, the inhibition of cell division or cell wall biosynthesis. Fungicidal activity of some amides results from disrupting the succinate dehydrogenase complex in the respiratory electron transport chain [3] or sterol biosynthesis as well as inhibition of rybosomic RNA synthesis.

Simple derivatives of isoxazole show also biological activity [4] and this fact induced us to synthesize several 3-aryl- and 3-alkylisoxazolecarboxamides showing fungicidal activity [5-7]. In continuation of those studies we have prepared a number of new 3-arylisoxazolecarboxamides and examined their activity against *Alternaria alternate, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum,* and *Phytophthora cactorum*.

RESULTS AND DISCUSSION

The isoxazolecarboxamides shown in Tables 1 and 2 were prepared from the corresponding aldehydes by oximation, chlorination with NCS in DMF, 1,3-dipolar cycloaddition reaction of α,β-unsaturated esters and nitrile oxides generated *in situ* in the presence of triethylamine (Huisgen method) [8]. Reported reactions of ethyl acrylate and methacrylate esters were highly regioselective and gave 3-substituted-4,5-dihydroisoxazole-5-carboxylates.



Scheme 1. Synthesis of the isoxazole carboxylic acid amides.

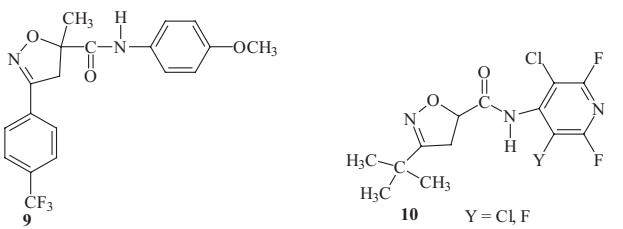


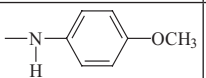
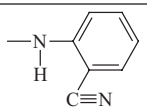
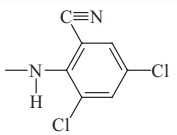
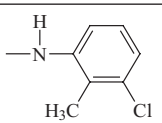
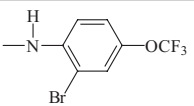
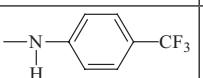
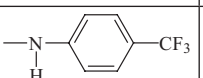
Figure 1. The other types of prepared amides (**9-10**).

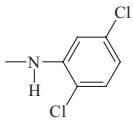
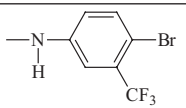
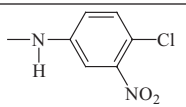
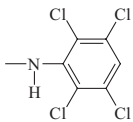
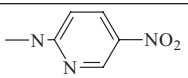
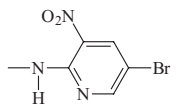
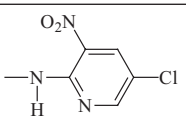
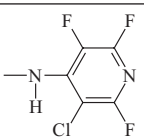
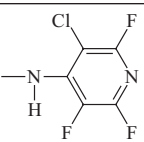
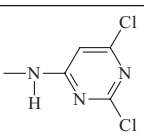
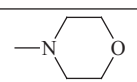
Some 4,5-dihydroisoxazolinecarboxylates were dehydrogenated to afford the corresponding isoxazoles by NBS bromination and potassium acetate induced dehydrobromination [9]. To prepare the title amides esters were saponified, converted to the acid chlorides by reaction of the acids with oxalyl chloride,

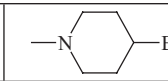
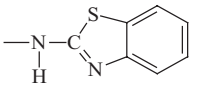
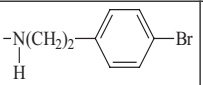
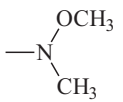
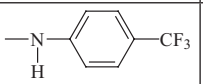
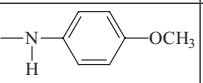
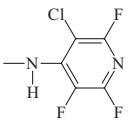
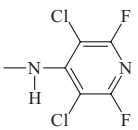
followed by acylation of different amines. Three methods of amide synthesis were applied. In method A the acylation reaction was carried out in the presence of triethylamine. Weakly nucleophilic aromatic amines required activation by formation of lithium amides with *n*-butyllithium in diethyl ether (method B) or with *t*-butyllithium (method C) to achieve satisfactory yields of the final products.

Three types of amides were prepared. To the first major group of amides belonged the 3-aryl-2-isoxazoline (isoxazole)-5-carboxamide **8**. The second type of compounds **9** included the 3-aryl-2-isoxazoline-5-methyl-5-carboxamides prepared from methyl methacrylate. The third group contained the 3-*tert*-butyl-2-isoxazoline-5-carboxamides **10** (Scheme 1, Figure **1**). Amine moiety was substituted anilines, aminopyridines, aminopyrimidine, morpholine, piperidine, benzothiazole or aliphatic amines **8v**, **8w**. The amides were characterized by spectral methods - IR, ^{1}H NMR (Table 2) and MS and elemental analyses.

Table 1. Synthesized amides (**8a-10b**)

Compd No.	X	Mol. formula	R^1	R^2	R^3	R^4	R^5	Yield [%]	Meth
[b]**8a**		$C_{18}H_{13}F_3N_2O_3$	H	H	CF_3	H	H	56	A_2
[a]**8b**		$C_{17}H_{13}N_3O_2$	H	H	H	H	H	44	A_2
[a]**8c**		$C_{19}H_{19}N_3O_2$	H	H	Et	H	H	8	A_1
8d		$C_{17}H_{11}Cl_3O_2N_2$	Cl	H	Cl	H	H	84	A_2
8e		$C_{18}H_9BrF_6O_3N_2$	H	H	CF_3	H	H	26	B
[a]**8f**		$C_{19}H_{16}O_2N_3ClF_3$	H	Cl	$N(Me)_2$	Cl	H	41	A_2
[a]**8g**		$C_{19}H_{16}ClF_3N_2O_4$	OMe	H	OMe	Cl	H	57	A_2

8h		$C_{17}H_9ClF_3N_2O_2$	H	H	CF_3	H	H	25	A_2
[a]8i		$C_{17}H_9BrCl_3F_3N_2O_2$	Cl	H	H	Cl	Cl	61	A_2
8j		$C_{17}H_8ClF_3N_3O_4$	H	H	CF_3	H	H	32	C
[a]8k		$C_{18}H_{13}Cl_5N_2O_4$	OMe	H	OMe	Cl	H	28	A_2
8l		$C_{15}H_7Cl_3N_4O_4$	Cl	Cl	H	H	Cl	45	A_2
8m		$C_{16}H_{10}BrF_3N_4O_4$	H	H	CF_3	H	H	28	B
8n		$C_{16}H_{10}ClF_3N_4O_4$	H	H	CF_3	H	H	42	C
[a]8o		$C_{15}H_6ClF_6N_3O_2$	F	H	F	F	H	85	C
[c]8p		$C_{16}H_6ClF_6N_3O_2$	H	H	CF_3	H	H	45	C
8r		$C_{15}H_7Cl_2F_3N_4O_2$	H	H	CF_3	H	H	43	A_2
8s		$C_{15}H_{13}F_3N_2O_3$	H	H	CF_3	H	H	41	A_1

[a]**8t**		$C_{15}H_{14}BrCl_3N_2O_2$	Cl	Cl	H	H	Cl	38	A_1
8u		$C_{18}H_{10}F_3N_3O_2S$	H	H	CF_3	H	H	31	A_1
[a]**8v**		$C_{18}H_{14}BrCl_3N_2O_2$	Cl	Cl	H	H	Cl	30	A_1
8w		$C_{13}H_{11}F_3N_2O_3$	H	H	CF_3	H	H	59	A_1
8x		$C_{21}H_{13}F_3N_2O_2$	H	H	H	C_4H_4		46	A_2
9		$C_{19}H_{17}F_3N_2O_3$	H	H	CF_3	H	H	56	A_2
[a]**10a**		$C_{13}H_{13}ClF_3N_3O_2$	---	---	---	---	---	49	C
[ac]**10b**		$C_{13}H_{13}Cl_2F_2N_3O_2$	---	---	---	---	---	71	C

[a] 4,5-dihydroisoxazole
[b] [6]
[c] [7]

Table 2. ^{1}H NMR Spectra of amides (**8a-10b**)

Compd.	^{1}H NMR (δ ppm)
8a	^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.77 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 7.60 (dm, *J* = 8.4 Hz, 2H, H-2'', H-6''), 7.38 (s, 1H, H-4), 6.94 (dm, *J* = 8.4 Hz, 2H, H-3'', H-5''), 3.84 (s, 3H, -O**$\underline{CH_3}$**)
8b	^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.12 (b, 1H, -NH-), 8.31 (ddd, *J* = 8.4; 2.2; 1.1 Hz, 1H, H-6''), 7.74–7.40 (m, 7H, H-2', H-6', H-2'', H-5'', H-3', H-4', H-5''), 7.22 (dt, *J* = 7.9; 1.2 Hz, 1H, H-4''), 5.32 (dd, *J* = 9.8; 7.1 Hz, 1H, H-5), 3.81 (d, *J* = 7.1 Hz, 1H, H -4a), 3.80 (d, *J* = 9.8 Hz, 1H, H-4b)

8c	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.65 (bs, 1H, -NH-), 7.65 (dd, *J* = 8.6; 2.2 Hz, 2H, H-2', H-6'), 7.60 (s, 1H, H-3"), 7.59 (s, 1H, H-5"), 7.24 (d, *J* = 8.6 Hz, 2H, H-5', H-3'), 5.36 (dd, *J* = 10.6; 6.6 Hz, 1H, H-5), 3.84 (d, *J* = 10.6 Hz, 1H, H-4a), 3.83 (d, *J* = 6.6 Hz, 1H, H-4b), 2.68 (q, *J* = 7.6 Hz, 2H, **C**$\mathbf{H_2}$$CH_3$), 1.28 (t, *J* = 7.6 Hz, 3H, **C**$\mathbf{H_3}$$CH_2$)
8d	^{1}H NMR ($CDCl_3$, 200MHz) δ 8.18 (s, 1H, NH), 7.84 (d, *J* = 8.1 Hz, 1H, H-4"), 7.73 (d, *J* = 8.3 Hz, 1H, H-6'), 7.57 (d, *J* = 2.2 Hz, 1H, H-3'), 7.50 (s, 1H, H-4), 7.40 (dd, *J* = 8.3; 2.2 Hz, 1H, H-5'), 7.32 (dd, *J* = 8.1; 1.7 Hz, 1H, H-6"), 7.22 (t, *J* = 8.1 Hz, 1H, z H-5"), 2.44 (s, 3H, CH_3Ph)
8e	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.86 (s, 1H, NH), 8.54 (d, *J* = 9.1 Hz, 1H, H-6"), 8.00 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.79 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 7.54 (dd, *J* = 2.0; 0.7 Hz, 1H, H-3"), 7.42 (s, 1H, H-4), 7.29 (dd, *J* = 9.1; 2.0 Hz, H-5")
8f	^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.4 (s, 1H, NH-), 7.92–7.56 (m, arom.), 5.35 (m, 1H, H-5), 3.75 (m, *J* = 7.6 Hz, 2H, H-4), 3.33 (s, 6H, $(CH_3)_2$N))
8g	^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.42 (s, 1H, NH), 7.82 (d, *J* = 8.4 Hz, 2H, H-5", H-3"), 7.69 (d, *J* = 8.4 Hz, 2H, H-6", H-2"), 7.54 (s, 1H, H-6'), 6.51 (s, 1H, H-3'), 4.90 (m, H-5), 3.94 (s, 3H, OCH_3), 3.92 (m, 2H, H-4), 3.90 (s, 3H, OCH_3)
8h	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.85 (s, 1H, NH), 8.57 (d, *J* = 2.2 Hz, 1H, H-6"), 8.00 (d, *J* = 7.8 Hz, 2H, H-5', H-3'), 7.79 (d, *J* = 8.0 Hz, 2H, H-2', H -6'), 7.42 (s, 1H, H-4), 7.40 (d, *J* = 8.3 Hz, 1H, H-3 „), 7.15 (dd, *J* = 8.3; 2.5 Hz, 1H, H-4")
8i	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.70 (bs, 1H, -NH-), 7.97 (s, 1H, H-2"), 7.69 (s, 1H, H-4'), 7.68 (s, 1H, H-5'), 7.51 (d, *J* = 8.7 Hz, 1H, H-5"), 7.34 (d, *J* = 8.7 Hz, 1H, H-6"), 5.35 (dd, *J* = 10.9; 5.3 Hz, 1H, H-5), 3.74 (d, *J* = 10.9 Hz, 1H, H-4a), 3.69 (d, *J* = 5.3 Hz, 1H, H-4b)
8j	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.48 (s, 1H, NH), 8.40 (d, *J* = 2.6 Hz, 1H, H-2"), 7.99 (d, *J* = 8.1 Hz, 2H, H-5', H-3'), 7.83 (dd, *J* = 8.7; 2.6 Hz, 1H, H-6"), 7.79 (d, *J* = 8.1 Hz, 2H, H-6', H-2'), 7.59 (d, *J* = 8.7 Hz, 1H, H-5"), 7.44 (s, 1H, H-4)
8k	^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H, NH), 7.75 (s, 1H, H-6'), 7.58 (s, 1H, H-4"), 6.50 (s, 1H, H-3'), 5.26 (dd, *J* = 9.5; 7.2 Hz, 1H, H-5), 3.96 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.86 (d, *J* = 7.2 Hz, 1H, H-4), 3.85 (d, *J* = 9.5 Hz, 1H, H-4)
8l	^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.31 (s, 1H, NH), 9.25 (d, *J* = 2.1 Hz, 1H, H-6"), 8.61 (dd, *J* = 8.8; 2.1 Hz, 1H, H-4"), 8.53 (d, *J* = 8.8 Hz, 1H, H-3"), 7.59 (d, *J* = 8.7 Hz, 1H, H-4'), 7.43 (d, *J* = 8.7 Hz, 1H, H-5'), 7.23 (s, 1H, H-4)
8m	^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.02 (s, 1H, NH), 8.86 (d, *J* = 2.2 Hz, 1H, H-4"), 8.73 (d, *J* = 2.2 Hz, 1H, H-6"), 8.01 (d, *J* = 8.3 Hz, 2H, H-5', H-3'), 7.79 (d, *J* = 8.3 Hz, 2H, H-6', H-2'), 7.48 (s, 1H, H-4)
8n	^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.02 (s, 1H, NH), 8.77 (d, *J* = 2.4 Hz, 1H, H-4"), 8.59 (d, *J* = 2.4 Hz, 1H, H-6"), 8.01 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 7.79 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.49 (s, 1H, H-4)
8o	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.59 (s, 1H, NH), 7.78–7.66 (dt, *J* = 10.5; 6,6 Hz, 1H, H-3'), 7,12-6,98 (td, *J* = 10.0; 6,4 Hz, 1H, H-6'), 5.39 (dd, *J* = 8.9; 8.5 Hz, 1H, H-5), 3.87 (d, *J* = 8.5 Hz, 1H, H-4), 3.86 (d, *J* = 8.9 Hz, 1H, H-4)

8p	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.32 (s, 1H, NH), 8.00 (d, *J* = 8.1 Hz, 2H, H-3', H-5'), 7.80 (d, *J* = 8.1 Hz, 2H, H-2', H-6'), 7.50 (s, 1H, H-4)
8r	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.73 (s, 1H, NH), 7.97 (d, *J* = 8.2 Hz, 2H, H-5', H-3'), 7.77 (d, *J* = 8.2 Hz, 2H, H-6', H-2'), 7.40 (s, 1H, H-4), 6.22 (s, 1H, H-5")
8s	^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, *J* = 8.4 Hz, 2H, H-5', H-3'), 7.76 (d, *J* = 8.4 Hz, 2H, H-6', H-2'), 7.17 (s, 1H, H-4), 3.82 (m, 4H, H-2", H-6"), 3.71 (m, 4H, H-3", H-5")
8t	^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49 (d, *J* = 8.6 Hz, 1H, H-4'), 7.34 (d, *J* = 8.6 Hz, 1H, H-5'), 5.49 (dd, *J* = 11.5; 8.6 Hz, 1H, H-5), 4.57 (m, 1H, H-6"), 4.42 (m, 1H, H-2"aq), 4.19 (dd, *J* = 17.5; 8.6 Hz, 1H, H-4a), 4.10 (m, 2H, H-6"ax, H-2"ax), 3.82 (m, 1H, H-4", HCBr), 3.20 (dd, *J* = 17.5; 11.2 Hz, 1H, H-4b), 2.25-1.95 (m, 4H, H-5", H-3")
8u	^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.96 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.84 (td, *J* = 7.8 Hz, 1H, H-1"), 7.78 (d, *J* = 7.8 Hz, 1H, H-4"), 7.76 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 7.51 (m, 1H, H-3"), 7.49 (s, 1H, H-4), 7.39 (t, *J* = 7.8 Hz, 1H, H-2")
8v	^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, *J* = 8.8 Hz, 1H, H-4'), 7.44 (t, 1H, -NH), 7.43 (d, *J* = 8.2 Hz, 2H, H-3", H-5"), 7.33 (d, *J* = 8.8 Hz, 1H, H-5'), 7.09 (d, *J* = 8.2 Hz, 2H, H-2", H-6"), 5.19 (dd, *J* = 11; 5.8 Hz, 1H, H-5), 3.73-3.44 (m, 4H, H-4, NH**CH_2**CH_2), 2.84 (m, 2H, NH-CH_2**CH_2**)
8w	^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.98 (d, *J* = 8.2 Hz, 2H, H-6', H-2'), 7.75 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.23 (s, 1H, H-4), 3.75 (s, 3H, OCH_3), 3.25 (s, 3H, NCH_3)
8x	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.50 (bs, 1H, NH), 8.04-7.94 (m, 2H, H-naphth.), 7.85 (d, *J* = 8.6 Hz, 2H, H-3", H-5"), 7.80-7.73 (md, 1H, H-naftal.), 7.68 (d, *J* = 8.6 Hz, 2H, H-2", H-6"), 7.66-7.55 (m, 4H, H-naphth.), 7.42 (s, 1H, H-4)
9	^{1}H NMR ($CDCl_3$, 200MHz) δ 8.51 (s, 1H - NH), 7.77 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.67 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.49 (dm, *J* = 9.0 Hz, 2H, H-2", H-6"), 6.87 (dm, *J* = 9.0 Hz, 2H, H-3", H-5"), 3.97 (d, *J* = 17.5 Hz, 1H, H-4), 3.79 (s, 3H, CH_3OPh), 3.32 (d, *J* = 17.5 Hz, 1H, H-4), 1.84 (s, 3H, CH_3)
10a	^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.64 (s, 1H, NH), 5.18 (dd, *J* = 9.2; 6.6 Hz, 1H, H-5), 3.43 (d, *J* = 6.6 Hz, 1H, H-4), 3.42 (d, *J* = 9.2 Hz, 1H, H-4), 1.24 (s, 9H, $C(CH_3)_3$)
10b	^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H, NH), 5.17 (dd, *J* = 8.8; 6.7 Hz, 1H, H-5), 3.43 (d, *J* = 8.8 Hz, 1H, H-4), 3.42 (d, *J* = 6.7 Hz, 1H, H-4), 1.24 (s, 9H, z ($\underline{\mathbf{CH_3}}$)$_3$C)

The products synthesized were tested for herbicidal, insecticidal, acaricidal and fungicidal activity. The most promising biological potency was found against fungal isolates (Table 3).

High activity was found for isoxazolineamides substituted at both aromatic rings with electron-withdrawing groups (EWG) **8o, 8p**. The other active compounds **10a,b** were derivative of pivalic aldehyde and 4-aminopyridine

substituted with halogen atoms. Moderate fungicidal activity was observed for morpholine-derived amide **8s** and compound **8k** with substituents of mixed electronic character. An increase of biological activity due to the presence of EWG was interpreted as retardation of oxidative metabolism involving the aromatic ring [10, 11]. High electronic density in the ring system would facilitate oxidative processes such as hydroxylation.

Table 3. Fungicidal activity of compounds (**8a-10b**) at 200 μ / ml

Comp. No.	Fungicidal activity				
	Alternaria alternata	*Boritis cinerea*	*Fusarium culmorum*	*Phytophtora cactorum*	*Rhizoctonia solani*
[b]**8a**	2	1	1	0	2
[a]**8b**	---	0	0	0	0
[a]**8c**	---	1	0	1	---
8d	0	0	1	0	1
8e	---	0	0	0	0
[a]**8f**	---	0	0	0	0
[a]**8g**	0	0	0	0	0
8h	0	0	0	0	0
[a]**8i**	---	0	0	2	1
8j	---	0	0	0	1
[a]**8k**	---	2	0	2	---
8l	---	---	2	1	1
8m	---	0	0	0	0
8n	---	0	0	0	1
[a]**8o**	---	3	2	2	2
[b]**8p**	---	3	2	3	3
8r	0	0	0	0	0
8s	---	1	0	2	2
[a]**8t**	---	---	1	0	---
8u	---	0	0	0	---
[a]**8v**	---	0	1	2	0
8w	---	1	1	1	2
8x	0	0	0	0	0
9	0	1	0	0	0
[a]**10a**	---	2	2	2	1
[ac]**10b**	---	3	1	3	3

At 0-3 scale: 0 = 0-20% growth inhibition, 1 = 21-50% growth inhibition, 2 = 51-80% growth inhibition, 3 = 81-100% growth inhibition.

In conclusion, the biological activity of the amides reported herein depends on a combination of electronic and steric effects. High biological potency can be correlated with low electron density of the ring systems.

EXPERIMENTAL

Elemental analyses were performed at Microanalysis Laboratory of Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw. Melting points were determined in capillary tubes and are uncorrected. Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^{1}H NMR spectra on Varian 500 UNITY plus-500 and Varian 200 UNITY plus 200 spectrometers in deuterated chloroform using TMS as internal standard, ESI mass spectra on Micromass LCT. Flash-chromatography was carried out using silica gel S 230-400 mesh (Merck).

General procedure for the cycloaddition reactions

A solution of chlorooxime (13 mmol) in anhydrous toluene or Et_2O (15 mL) was added dropwise over 30 min to a stirred mixture of anhydrous toluene, anhydrous NEt_3 (6 mL), $MgSO_4$ (2 g) and ethyl acrylate [methyl methacrylate] (8 mL, 80.0 mmol). The reaction mixture was stirred overnight at room temperature, diluted with toluene (50 mL), washed with water (5 x 100 mL) and evaporated *in vacuo*.

General procedure for amide synthesis with tertiary amines (Method A_1)

A solution of an aniline derivative (1.2 mmol) in anhydrous metyl chloride (10 ml) was added with stirring to an acid chloride followed by dry triethyl amine (4 ml, 30.0 mmol). The solution was stirred for 1 h at 0 °C. Water (10 ml) was added, the organic layer was washed with 3% hydrochloric acid solution and water, and was dried over magnesium sulfate. A crude amide obtained after evaporation of the solvent was purified by crystallization.

General procedure for amide synthesis with tertiary amines (Method A_2)

A solution of an aniline derivative (1.2 mmol) in anhydrous toluene (10 ml) was added with stirring to an acid chloride followed by dry triethyl amine (4 ml, 30.0 mmol). The solution was stirred under reflux for 1 h and overnight at room temperature. Water (10 ml) was added, the organic layer was washed with 3% hydrochloric acid solution and water, and was dried over magnesium sulfate. A crude amide obtained after evaporation of the solvent was purified by crystallization.

General procedure for amide synthesis with n-butyl lithium (Method B)

2.5 M solution of *n*-BuLi in hexanes (0.2 ml, 0.5 mmol) was added dropwise at -78 °C to a stirred solution of 4-aminopyridine derivative (0.4 mmol) in dry diethyl ether. Stirring was continued for 1 h and a solution of acid chloride (0.3 mmol) in dry diethyl ether (or HMPA) was added dropwise. The mixture was stirred for 5 h at 0 °C and overnight at room temperature. The reaction was quenched with ammonium chloride solution, product was extracted with methylene chloride and purified by flash chromatography.

General procedure for amide synthesis with n-butyl lithium (Method C)

1.7 M solution of *tert*-BuLi in hexanes (0.2 ml, 0.5 mmol) was added dropwise at 0 °C to a stirred solution of 4-aminopyridine derivative (0.4 mmol) in dry diethyl ether. Stirring was continued for 1 h and a solution of acid chloride (0.3 mmol) in dry diethyl ether (or HMPA) was added dropwise. The mixture was stirred for 5 h at 0 °C and overnight at room temperature. The reaction was quenched with ammonium chloride solution, product was extracted with methylene chloride and purified by flash chromatography.

Fungicidal testing

The compounds were screened for fungicidal activity *in vitro* test carried out for *Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl.(Fr.), *Rhizoctonia solani* Kuhn, *Botrytis cinerea* Pers. Ex Fr, which involved determination of mycelial growth retardation in potato-glucose agar (PGA). Stock solutions of test chemicals in acetone were added to agar medium to give a concentration of 200 μg x ml^{-1} and dispersed into Petri dishes. Four discs containing test fungus were placed at intervals on the surface of the solidified agar and the dishes were then inoculated for 4-8 days depending on the growth rate of the control samples, after which fungal growth was compared with that in untreated control samples. The fungicidal activity was expressed as the percentage of plant infection compared to that on the control. The results of the screening are given in Table 3.

Acknowledgement

This work was supported in part by the Polish Ministry of Science and Higher Education Research (Grant 429E-142/S/2009)

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