J. Pestic. Sci., **34**(3), 161–172 (2009)
DOI: 10.1584/jpestics.G09-12

Original Article

N-Thiophenylethyl-2,2-dichloro-1-cyclopropanecarboxamides: modification of the amide part of carpropamid and examination of fungicidal activity

Shinzo KAGABU*, Maiko SHIMIZU,
Masaru MORI†, Yoshio KURAHASHI†† and
Isamu YAMAGUCHI††

Department of Chemistry, Faculty of Education, Gifu University, Gifu 501–1193, Japan
† Research Center, Kureha Corporation, 16 Ochiai, Nishiki-machi, Iwaki, Fukushima, 974–8686, Japan
†† Laboratory for Remediation Research Science Center, Riken, 1–7–22 Suehiro-cho, Tsurumi-ku, Yokohama 2300–45, Japan

(Received March 9, 2009; Accepted May 1, 2009)

The synthetic route for a halo-substituted thiophenylethyl variant of blasticide carpropamid is described. First, halo-substituted acetylthiophene was homologated to thiophenylacetic acid using $Pb(OAc)_4$ and BF_3OEt_2, followed by reduction to CH_2CH_2OH with $NaBH_4/I_2$ or BH_3Me_2S, and then to the azide *via* the tosylate. The azide was transformed to the amine using triphenylphosphine, which was then allowed to react with the corresponding acyl chloride to yield the final amide product. Fungicidal tests of 50 related products for gray mold and downy mildew on cucumber, and leaf rust and powdery mildew on wheat were conducted in 500 mg/l on pot. Many compounds showed efficacy to control these plant diseases. It should be noted that several blasticide-oriented compounds displayed high control effectiveness on downy mildew.

Keywords: carpropamid, entry to $ArCH_2CO_2H$, thiophenylethylamine, fungicidal activity, downy mildew.

Introduction

Carpropamid (**1**) has been widely used in Japan since 1998 for long-term control of rice blast disease.[1–2] In 2001, however, strains of *Pyricularia oryzae* that were not sensitive to this melanin biosynthesis inhibitor emerged in Saga Prefecture.[3] To control the insensitive rice blast fungus, we attempted structural modifications of carpropamid based on the molecular model devised through systemic genomic analyses. We found that amides constructed with a phenyl- or heteroarylethylene moiety, *i.e.*, $ArCH_2CH_2-$, in place of the α-phenethyl group, *i.e.*, ArCHMe-, of carpropamid displayed significant activity on both susceptible and resistant strains. We have also established that a few variants of diclocymet, another melanin inhibitor, have a similar blasticidal capability (Fig. 1).[4] In the subsequent paper, we described the synthesis of amides composed of alkyl, alicyclic, and substituted phenylethylamine groups of these modified products.[5]

This paper describes the preparation method of the heteroaromatic products, focusing on the transformation methodology to $ArCH_2CH_2NH_2$ from ArCOMe. Since the start of this project, we have been examining the fungicidal behavior of the modified amides listed in Table 1(1) and 1(2) on several pathogens other than *Pyricularia oryzae*. This article presents the control effect against the diseases caused by these fungi.

Materials and Methods

1. *Preparation of compounds*

All melting points (mp) are uncorrected. IR spectra were measured using a Perkin Elmer FTIR 1600 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded using a JEOL ECA-500 spectrometer at 500 and 125 Hz, respectively. Chemical shifts were recorded in δ (ppm) and coupling constant J in Hz unless otherwise stated. Mass spectra were recorded at 70 eV using a JEOL JMS-700 instrument. The preparation of compounds **2**–**12**, **16**–**29**, and the procedures for the final step for products **37**, **40**, **44**, **46**, and **51** were described previously.[4,5]

* To whom correspondence should be addressed.
E-mail: kagabus@gifu-u.ac.jp
Published online June 22, 2009

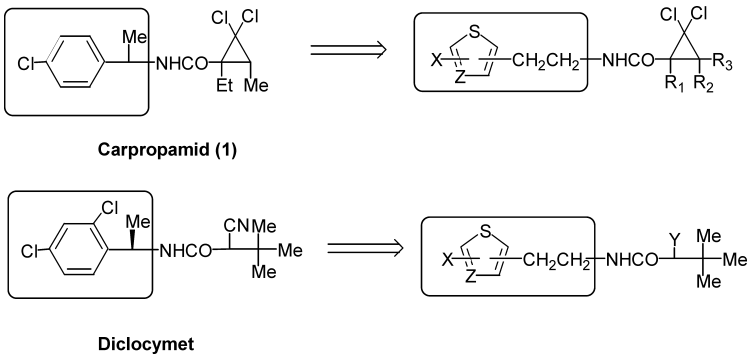


Fig. 1. Molecular design based on carpropamid and diclocymet.

Carpropamid (**1**), and compounds **13**–**15** were prepared according to the published procedures.[6–8] The other products bearing the $ArCH_2CH_2NHCO$ moiety, except for compounds **43** and **47**, were prepared according to Synthetic Scheme 1 (Fig. 2). The preparation procedure for compound **35** is a representative protocol for these compounds. Compounds **43** and **47** were prepared from commercially available starting material, based on Scheme 2. The precursory amines for compounds (**30**–**33**), bearing ArCH(Me)NHCO moiety, were prepared by reducing ArC(=NOH)Me using $NaBH_4/WO_3$. A representative description is given for 1-(3-chlorothiophen-5-yl)ethylamine. Compound **45** was isolated without separating the azide and amine intermediates as described.

The following amines and acyl chlorides used for the last step, 2-(thiophen-3-yl)ethylamine,[9] 2-(2-chlorothiophen-5-yl)ethylamine,[10] 2,2-dichloro-1-methylcyclopropanoyl chloride,[5] 2,2-dichloro-1-propylcyclopropanoyl chloride,[5] 2,2-dichloro-3,3-dimethylcyclopropanoyl chloride,[5] 2,2-dichloro-1,3,3-trimethylcyclopropanoyl chloride,[5] 2-chloro-3,3-dimethylbutanoyl chloride,[11] 2-bromo-3,3-dimethylbutanoyl chloride[12], and 2-cyano-3,3-dimethylbutanoyl chloride[13] were prepared according to the published procedures. (2-Bromothiophen-4-yl)acetic acid, (2-aminothiazol-4-yl)methanol and 3,3-dimethybutanoyl chloride are commercially available. The melting points and spectral data of the final products together with the missing ^{13}C NMR data for the previously published products are given in Tables 2–4. The synthetic scheme for the new products is summarized in Fig. 2 and 3.

(2-Chlorothiophen-4-yl)acetic acid

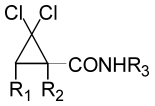
A cooled mixture of 4-acetyl-2-chlorothiophene[14] (6.12 g, 38 mmol), boron trifluoride etherate (22.0 g, 150 mmol) and methanol (10 ml) was added in one portion to a stirred suspension of lead (IV) tetraacetate (17.7 g, 40 mmol) in benzene (100 ml). The reaction mixture was continuously stirred at room temperature for 24 hr, diluted with cold water (280 ml), extracted with benzene (3×50 ml), washed sequentially with satd. aqueous $NaHCO_3$ solution and brine, and then dried over sodium sulphate. After evaporating the solvent, the residue (5.0 g; ca. 1 : 1 mixture of 4-acetyl-2-chlorothiophene and methyl 2-chlorothiophen-4-ylacetate) was, without separation, treated with a solution of NaOH (5.2 g) in 50 ml water and 5 ml methanol. After continuous stirring at room temperature for 24 hr, the reaction mixture was washed with isopropyl ether (IPE) and the fraction containing mainly 4-acetyl-2-chlorothiophene was discarded. The aqueous layer was acidified with 6N HCl solution and left to stand overnight. The precipitated crystals were collected by suction, and the filtrate was extracted with ethyl acetate, dried, evaporated, and the residue was combined with the above-obtained precipitates. The whole solid was washed with hexane. The yield was 1.60 g (24% based on 4-acetyl-2-chlorothiophene). A small portion was sublimated for analysis. Mp 56°C. IR (KBr) cm^{-1}: 2650, 1715, 1700. ^1H NMR $\delta(CDCl_3)$: 3.60 (2H, s), 6.89 (1H, d, J=1.8 Hz), 6.93 (1H, d, J=1.8 Hz), 10.6 (1H, bs). EI-MS m/z (%): 176 (M^+, 72), 131 (100).

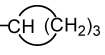
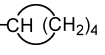
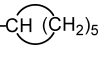
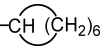
2-(2-Chlorothiophen-4-yl)ethanol

Method 1. A solution of (2-chlorothiophen-4-yl)acetic acid (1.13 g, 6.4 mmol) in 10 ml THF was added dropwise to a suspension of $NaBH_4$ (1.25 g, 3.3 mmol) in 20 ml THF. When the evolution of hydrogen ceased (about10 min), a solution of iodine (3.04 g, 12 mmol) in 20 ml THF was added slowly. The reaction mixture was stirred for a further 12 hr, and acidified with 10% HCl solution. The IPE extracts were dried over sodium sulphate. After evaporating the solvent, the product was separated by column chromatography on SiO_2 with hexane/IPE 10 : 1. The yield was 493 mg (48%).

Method 2. A toluene solution of boran-dimethyl sulfide complex (2M solution, 7.8 ml, 15.6 mmol) was added dropwise to a solution of (2-chlorothiophen-4-yl)acetic acid (1.55 g, 8.8 mmol) in 20 ml THF under an argon atmosphere. The mixture was stirred at the reflux temperature for 3 hr. It was cooled and methanol was added to destroy residual boran, and then the solvents were evaporated. IPE extracts from the residue were washed with satd. $NaHCO_3$ solution and dried. The work-up, as described in Method 1, afforded 1.0 g (70% yield) of liquid product. IR (KBr) cm^{-1}: 3370 (broad), 1420, 1050, 1010. ^1H NMR δ ($CDCl_3$): 2.00 (1H, bs), 2.79 (2H, t, J=6.3 Hz), 3.81 (2H, t, J=6.3 Hz), 6.81 (2H, s). EI-MS m/z (%): 162 (M^+, 34), 131 (100).

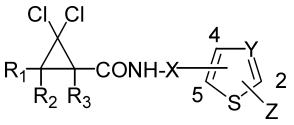
Table 1(1). Prepared carpropamid-modified compounds–1–



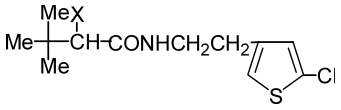
Compound No.	R_1	R_2	R_3
2	Me	Et	$CHMe_2$
3	Me	Et	$CHMeCH_2Me$
4	Me	Et	$CHMeCH_2CF_3$
5	Me	Et	
6	Me	Et	
7	Me	Et	
8	Me	Et	
9	Me	Et	
10	Me	Et	
11	Me	Et	(4-ClPh)
12	Me	Et	CH_2(4-ClPh)
1(Carpropamid)	Me	Et	CHMe(4-ClPh)
13	H	$CHMe_2$	CHMe(4-ClPh)

Compound No.	R_1	R_2	R_3
14	H		CHMe(4-ClPh)
15	H	Ph	CHMe-(4-ClPh)
16	Me	Et	CH_2CH_2Ph
17	Me	Et	CH_2CH_2(2-ClPh)
18	Me	Et	CH_2CH_2(3-ClPh)
19	Me	Et	CH_2CH_2(4-ClPh)
20	Me	Et	CH_2CH_2(4-BrPh)
21	Me	Et	CH_2CH_2(4-FPh)
22	Me	Et	CH_2CH_2(4-MePh)
23	Me	Et	CH_2CH_2(4-CF3Ph)
24	Me	Et	CH_2CH_2(2,4-diClPh)
25	Me	Et	CH_2CH_2(2,4-diFPh)
26	Me	Et	CH_2CH_2(3,4-diClPh)
27	Me	Et	$CHMeCH_2$(4-ClPh)
28	Me	Et	CH_2CHMe(4-ClPh)
29	Me	Et	$CH_2CH_2CH_2$(4-ClPh)

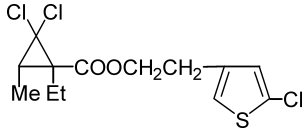
Table 1(2). Prepared carpropamid-modified compounds–2–



Compound No.	R_1/R_2	R_3	X	Y	Z
30	Me/H	Et	4-CHMe	CH	2-Cl
31	Me/H	Et	5-CHMe	CH	2-Cl
32	Me/H	Et	5-CHMe	CH	3-Cl
33	Me/H	Et	5-CHMe	CH	2,3-Cl,Cl
34	Me/H	Et	3-CH_2CH_2	CH	H
35	Me/H	Et	4-CH_2CH_2	CH	2-Cl
36	Me/H	Et	5-CH_2CH_2	CH	2-Cl
37	Me/H	Et	5-CH_2CH_2	CH	3-Cl
38	H/H	Me	4-CH_2CH_2	CH	2-Cl
39	H/H	$CH_2H_2CH_2CH_3$	4-CH_2CH_2	CH	2-Cl
40	H/H	$CHMe_2$	4-$CH_2H_2CH_2$	CH	2-Cl
41	Me/Me	H	4-CH_2CH_2	CH	2-Cl
42	Me/Me	Me	4-CH_2CH_2	CH	2-Cl
43	Me/H	Et	5-CH_2CH_2	CH	3-Br
44	Me/H	Et	5-CH_2CH_2	CH	2,3-Cl,Cl
45	Me/H	Et	4-CH_2CH_2	CH	2,5-Cl,Cl
46	Me/H	Et	4-CH_2CH_2	N	2-Cl
47	Me/H	Et	5-CH_2CH_2	N	2-Cl



Compound No.	X
48	H
49	Cl
50	Br
51	CN



52

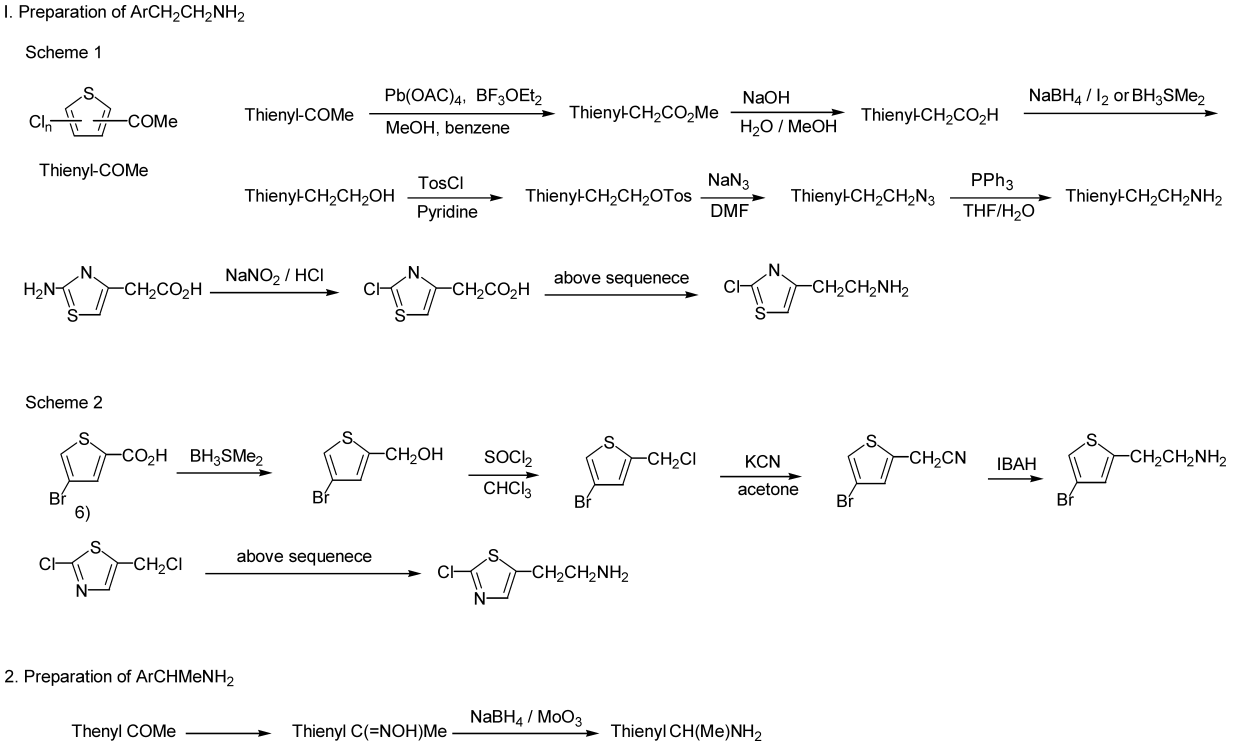


Fig. 2. Synthetic scheme for amines.

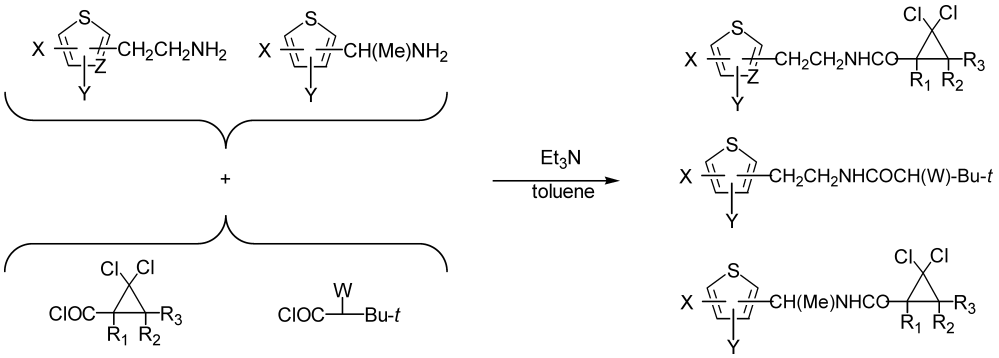


Fig. 3. Preparation of new products.

2-(2-Chlorothiophen-4-yl)ethyl p-toluenesulfonate

A solution of 2-(2-chlorothiophen-4-yl)ethanol (1.0 g, 6.2 mmol) and *p*-toluenesulfonyl chloride (2.04 g, 11 mmol) in 8 ml pyridine was left to stand overnight at 0°C. The mixture was poured into 20 ml ice-cold water and extracted with IPE (3×15 ml). The IPE solution was successively washed with 1% HCl solution and brine, and then dried over magnesium sulfate. After evaporating the solvent, the residue was subjected to column chromatography on SiO_2 with IPE as an eluent. Colorless crystals were obtained. Yield: 1.66 g (84%). Mp 48–49°C. IR (KBr) cm^{-1}: 1600, 1360. ^1H NMR δ ($CDCl_3$): 2.45 (3H, s), 2.87 (2H, t, J=6.2 Hz), 4.16 (2H, t, J=6.2 Hz), 6.61 (1H, d, J=1.6 Hz), 6.73 (1H, d, J=1.6 Hz), 7.31 (2H, d, J=8.0 Hz), 7.69 (2H, d, J=8.0 Hz). EI-MS *m/z* (%): 316 (M^+, 2), 144 (100).

4-(2-Azidoethyl)-2-chlorothiophene

A mixture of 2-(2-chlorothiophen-4-yl)ethyl *p*-toluenesulfonate (1.66 g, 5.2 mmol) and sodium azide (500 mg, 7.7 mmol) in 8 ml DMF was stirred at 80°C for 16 hr. The cooled mixture was poured into 60 ml brine and extracted with IPE. The IPE phase was washed with brine and dried over magnesium sulphate. The solvent was evaporated below 40°C, and the residue was subjected to column chromatography on SiO_2 with IPE/hexane 1 : 10. The product was obtained as a colorless liquid. Yield: 900 mg (92%). IR (KBr) cm^{-1}: 2100. ^1H NMR δ ($CDCl_3$): 2.81 (2H, t, J=6.8 Hz), 3.47 (2H, t, J=6.8 Hz), 6.79 (1H, d, J=1.7 Hz), 6.81 (1H, d, J=1.7 Hz). EI-MS *m/z* (%): 145 (M–42, 28), 99 (38), 85 (39), 57 (100).

2-(2-Chlorothiophen-4-yl)ethylamine

A mixture of 4-(2-azidoethyl)-2-chlorothiophene (900 mg,

Table 2. mp, IR and MS data of the final products[a)]

Compound No.	mp (°C)	CO absorption[b)]	EIMS *m/z* (%)[c)]
30	140–142	1637	341(M^+, 4), 339(4), 304 (21), 180 (22), 145 (100)
31	97–98	1645	341 (M^+, 2), 339 (2), 304 (27), 179 (7), 145 (100)
32	97–99	1645	341 (M^+, 2), 339 (2), 304 (32), 179 (7), 145 (100)
33	85–87	1652	376 (M^+, 2), 180 (91), 178 (dichlorothienylethyl, 47), 144 (100)
34	112–113	1634	307 (M^+, 13), 305 (19), 179 (25), 110 (thienylethyl, 100)
35	106–107	1635	339 (M^+, 14), 324 (24), 304 (15), 181 (100)
36	96–97	1635	341 (M^+, 5), 339 (5), 179 (11), 144 (chlorothienylethyl, 100)
38	56–58	1652	311 (M^+, 12), 180 (20), 144 (100)
39	138	1635	339 (M^+, 29), 310 (71), 179 (51), 144 (100)
41	75–77	1653	327 (M^+, 8), 290 (32), 232 (39), 144 (100)
42	105–106	1652	339 (M^+, 2), 304 (28), 144 (55), 59 (100)
43	111–112	1621	385 (M^+, 15), 190 (bromothienylethyl, 100), 179 (26)
45	128	1651	376 (M^+,26), 178 (dichlorothienylethyl, 100), 179 (86)
47	103–105	1653	341 (M^+, 51), 179 (98), 145 (chlorothiazolylethyl, 100)
48	141–144	1642	259 (M^+, 10), 181 (3), 179 (5), 144 (90), 110 (100)
49	47–49	1659	293 (M^+, 17), 288 (15), 188 (7), 144 (100)
50	87–88	1653	339 (M^+, 4), 258 (26), 144 (100)
51	liquid	1733	340 (M^+, 1), 179 (4), 144 (100)

[a)] The data for compounds **37**, **40**, **44** and 46 are in ref. 4). [b)] νmax (KBr) cm^{-1}. [c)] EI, 70 eV.

4.8 mmol), triphenyl phosphine (1.0 g, 3.8 mmol) in 0.5 ml water and 15 ml THF was stirred overnight at room temperature. The solvent was evaporated, and the residue was dispersed with IPE. The solid was filtered off, the filtrate was evaporated, the residue was dispersed with IPE, and the solid was filtered off. This operation was repeated twice. Crude amine containing mainly triphenyl phosphine oxide and triphenyl phosphine (~300 mg) was used in the next step without further purification. ^{1}H NMR assigned for the amine in the mixture; δ ($CDCl_3$): 1.90 (2H, bs), 2.65 (2H, t, J=6.7 Hz), 2.95 (2H, t, J=6.7 Hz), 6.80 (2H, s).

N-[2-(2-Chlorothiophen-4-yl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (**35**)

A solution of 2,2-dichloro-1-ethyl-3-methylcyclopropanoyl chloride (215 mg, 1 mmol) in toluene (5 ml) was added dropwise to an ice-cold solution of crude 2-(2-chlorothiophen-4-yl)ethylamine (~300 mg), and triethylamine (152 mg, 1.5 mmol) in toluene (15 ml). Stirring was continued at ambient temperature for 10 hr, and then at 80°C for 20 min. After cooling, the mixture was diluted with 15 ml toluene, and washed with water (30 ml), 1% HCl solution (20 ml), and brine, and dried over anhydrous magnesium sulfate. The toluene was evaporated and column chromatography of the residual liquid on SiO_2 with *n*-hexane/IPE 3 : 1 gave 278 mg (91% yield) of product.

(4-Chlorothiophen-2-yl)acetic acid was similarly prepared from 2-acetyl-4-chlorothiophene[14)]. Mp 45–48°C. IR (KBr) cm^{-1}: 2600–2500, 1715. ^{1}H NMR δ ($CDCl_3$): 3.80 (2H, s), 6.82 (1H, s), 7.01 (1H, s). EI-MS *m/z* (%): 176 (M^+, 50), 131 (100).

2-(4-Chlorothiophen-2-yl)ethanol

The reduction was followed by Method 2. Yield: 340 mg (58%), bp 145–148°C (30 mmHg). IR (KBr) cm^{-1}: 3330 (broad), 1540, 1040. ^{1}H NMR δ ($CDCl_3$): 2.00 (1H, bs), 2.99 (2H, t, J=6.3 Hz), 3.83 (2H, t, J=6.3 Hz), 6.74 (1H, s), 6.94 (1H, s). EI-MS *m/z* (%): 162 (M^+, 45), 131 (100).

2-(4-Chlorothiophen-2-yl)ethyl p-toluenesulfonate

Mp 42–46°C. IR (KBr) cm^{-1}: 1540, 1360. ^{1}H NMR δ ($CDCl_3$): 2.45 (3H, s), 3.09 (2H, t, J=6.6 Hz), 4.20 (2H, t, J=6.6 Hz), 6.61 (1H, d, J=0.8 Hz), 6.90 (1H, d, J=0.8 Hz), 7.32 (2H, d, J=8.0 Hz), 7.72 (2H, d, J=8.0 Hz). EI-MS *m/z* (%): 316 (M^+, 10), 144 (100).

2-(2-Azidoethyl)-4-chlorothiophene

IR (KBr) cm^{-1}: 2110. ^{1}H NMR δ ($CDCl_3$): 3.02 (2H, t, J=6.6 Hz), 3.53 (2H, t, J=6.6 Hz), 6.76 (1H, d, 1H, J=0.8 Hz), 6.96 (1H, d, J=0.8 Hz).

2-(4-Chlorothiophen-2-yl)ethylamine

^{1}H NMR assigned for the amine; δ ($CDCl_3$): 1.50 (2H, bs), 2.87 (2H, t, J=6.4 Hz), 2.96 (2H, t, J=6.4 Hz), 6.70 (1H, d, J=1.1 Hz), 6.91 (1H, d, J=1.1 Hz).

4-Bromothiophen-2-ylmethanol

This alcohol was obtained in 30 % yield from 4-bromo-2-thiophenecarboxylic acid using boran dimethyl sulfide complex according Method 2. Bp 130–150°C (20 mmHg),

Table 3 (1). ^{1}H-NMR data for compounds **30**–**47**[a)]

Compd	cyclopropyl				NCH_2CH_2- / $NCH(CH_3)$- [d)]	thienyl / thiazole ring	NH[e)]
	R_3	R_3	R_1[b)]	R_2[c)]			
30	0.98 (m)[f)]	1.52, 1.93 [g)]	1.21 (J=6.6)	2.23 (m)	1.57 (m), 5.18 (m)	6.90 (2H, bs)	5.89
31	0.97 (J=7.4)[f)]	1.57, 1.96[g)]	1.20 (J=6.9)	2.21(J=6.9)	1.58 (d, J=6.9) 5.34 (m)	6.77 (2H, bs)	6.07
32	0.98 (J=7.6)[f)]	1.55, 1.98[g)]	1.21 (J=6.7)	2.19(J=6.6)	1.60 (d, J=6.9) 5.40 (m)	6.89 (d, J=1.4), 6.99 (d, J=1.4)	6.10
33	0.98 (J=7.4)[f)]	1.57, 1.93[g)]	1.21 (J=6.3)	2.21(J=6.9)	1.58 (d, J=6.9) 5.31 (m)	6.80	5.90
34	0.90 (J=7.5)[f)]	1.51, 1.89[g)]	1.19 (J=6.3)	2.19 (J=6.6)	2.90, 3.61	6.98 (dd, J=4.5 /1.0), 7.03 (dd, J=2.8 /1.0), 7.29 (J=4.5/2.8)	6.02
35	0.92 (J=7.3)[f)]	1.52, 1.87[g)]	1.20 (J=6.6)	2.19 (J=6.6)	2.80, 3.57	6.80	5.90
36	0.92 (J=7.5)[f)]	1.51, 1.91[g)]	1.20 (J=6.6)	2.17(J=6.6)	2.97, 3.58	6.62 (d, J=4.1), 6.73 (d, J=4.1)	5.94
38	1.54 (3H, s)		1.37 (J=7.5)	2.17 (J=7.5)	2.78, 3.54	6.79 (2H, bs)	6.06
39	0.92 (3H, t, J=7.2), 1.46 (4H, m)		1.37 (J=7.4)	2.07 (J= =7.4)	2.80, 3.56	6.79 (2H, bs)	5.90
41	1.92 (1H, s)		1.32 (3H, s)	1.43 (3H, s)	2.77, 3.57	6.78 (2H, bs)	5.86
42	1.25 (3H, s)		1.30 (3H, s)	1.44 (3H, s)	3.48, 3.58	6.78 (2H, bs)	5.92
43	0.89 (J=7.3)[f)]	1.50, 1.88	1.17 (J=6.6)	2.16(J=6.6)	2.80, 3.54	6.80 (bs), 7.26 (bs)	6.00
45	0.91(J=7.6)[f)]	1.54, 1.89	1.19 (J=6.4)	2.19(J=6.4)	3.51, 3.58	6.70	5.80
47	0.92 (J=7.5)[f)]	1.50, 1.93[g)]	1.17 (J=6.3)	2.18 (J=6.3)	3.00, 3.55	7.27	6.34

[a)] Measured in $CDCl_3$; J in Hz. Data for compounds **37**, **40**, **44** and **46** are in ref. 4). [b)] R_1: doublet. [c)] R_2: quartet unless otherwise stated. [d)] Two multiplets unless otherwise stated. [e)] Broad singlet. [f)] $CH_3C\underline{H}_2$; *quasi* triplet unless otherwise stated. [g)] $CH_3C\underline{H}_2$: nonequivalent multiplets unless otherwise stated.

Table 3 (2). 1H-NMR data for compounds for **48**–**50** and **52**[a)]

Compound No.	cyclopropyl/*t*-butylCHX	$NCH_2C\underline{H}_2$-	thienyl	NH[b)]
48	0.99 (9H, s), 2.01 (2H, s)	2.74 (2H, t, J=7.0), 3.47 (2H, t, J=7.0)	6.74 (1H, d, J=1.6) 6.77 (1H, d, J=1.6)	5.45
49	1.06(9H, s), 4.08 (1H, s)	2.78 (2H, m), 3.51 (2H, m)	6.79 (2H, bs)	6.37
50	1.09(9H, s), 4.08 (1H, s)	2.76 (2H, t, J=6.6), 3.50 (2H, m)	6.79 (2H, bs)	6.08
52	0.88(3H, t, J=7.4), 1.21 (3H, d, J=6.6), 1.42 (1H, m), 2.20 (1H, m), 2.31 (1H, q, J=6.6)	2.94 (2H, m), 4.37 (2H, m)	6.83 (2H, bs)	–

[a)] Measured in $CDCl_3$; J in Hz. Data for compound **51** are in ref 4). [b)] Broad singlet.

(86–88°C (0.4 mmHg)[15]). IR (KBr) cm^{-1}: 3098, 1418, 1264, 986, 699. ^{1}H NMR δ ($CDCl_3$): 1.82 (1H, bs), 4.52 (2H, s), 7.08 (1H, d, J=1.0 Hz), 7.17 (1H, d, J=1.0 Hz). ^{13}C NMR δ ($CDCl_3$): 40.5, 113.5, 125.3, 130.3, 138.7.

4-Bromo-2-chloromethylthiophene

Thionyl chloride (6 ml) was added dropwise to a stirring solution of 5-bromo-3-thiophenylmethanol (3.86 g) in chloroform (20 ml). The mixture was refluxed for 6 hr. The cooled solution was poured carefully into ice-water. After neutralization with satd. $NaHCO_3$ solution, it was extracted with chloroform, and dried over magnesium sulphate. Crude product was distilled. Yield: 2.3 g (55%), bp 110–120°C (20 mmHg), (63–68°C (0.2 mmHg)[15]). ^{1}H NMR δ ($CDCl_3$): 4.50 (2H, s), 7.05 (1H), 7.15 (1H).

Table 4. ^{13}C-NMR data of the final products[a)]

Compound	
30	8.6, 10.9, 20.6, 22.0, 29.8, 43.4, 45.4, 66.6, 119.6, 125.5, 130.8, 143.0, 167.3
31	8.6, 10.9, 21.2, 22.0, 29.6, 43.2, 45.1, 66.4, 123.3, 125.7, 129.0, 145.0, 167.1
32	8.6, 10.9, 21.4, 22.0, 29.8, 43.2, 45.0, 66.4, 119.1, 124.5, 124.9, 146.8, 167.2
33	8.7, 11.0, 21.1, 22.1, 30.0, 43.3, 45.3, 66.5, 123.1, 123.6, 124.3, 143.2, 167.5
34	8.8, 11.0, 22.1, 29.8, 30.3, 40.6, 43.6, 66.7, 121.6, 126.2, 128.1, 139.1, 168.3
35	8.7, 11.0, 22.1, 29.9, 30.9, 40.2, 43.5, 66.6, 120.2, 127.0, 130.5, 138.7, 168.3
36	8.7, 11.0, 22.0, 29.8, 30.5, 41.2, 43.5, 66.5, 124.9, 126.1, 127.9, 140.1, 168.3
37	8.7, 10.9, 22.0, 29.8, 30.3, 41.1, 43.4, 66.4, 118.4, 124.8, 125.9, 141.9, 168.3
38	19.5, 30.4, 30.6, 36.3, 40.3, 62.3, 120.1, 127.0, 130.3, 138.6, 168.3
39	14.0, 20.2, 29.5, 30.8, 36.1, 40.2, 41.5, 62.0, 120.3, 127.0, 130.6, 138.7, 167.7
40	19.7, 30.7, 31.5, 35.1, 40.1, 46.2, 62.6, 120.3, 127.0, 130.6, 138.6, 166.3, 130.1, 130.6, 156.2, 158.4
41	18.4, 24.8, 30.9, 39.9, 41.8, 68.6, 120.4, 127.1, 130.6, 138.8, 165.4
42	17.6, 18.4, 22.0, 30.8, 31.9, 39.9, 40.6, 66.4, 120.4, 127.1, 130.6, 138.7, 169.3
43	8.8, 11.0, 22.1, 29.9, 30.6, 40.3, 43.5, 66.6, 112.7, 123.2, 130.8, 139.8, 168.4
44	8.7, 11.0, 21.1, 22.1, 30.0, 43.3, 45.3, 66.5, 123.1, 123.6, 124.3, 143.2, 167.5
45	8.7, 11.0, 22.2, 28.2, 29.9, 39.5, 43.5, 66.5, 123.1, 126.7, 126.9, 135.5, 168.4
46	8.8, 11.0, 21.9, 29.8, 31.1, 39.4, 43.5, 66.7, 116.8, 151.7, 153.4, 168.3
47	8.7, 11.1, 22.1, 27.7, 29.9, 41.1, 43.5, 66.5, 116.2, 139.2, 150.5, 168.8
48	27.9, 29.8, 30.9, 39.5, 50.7, 116.2, 120.1, 127.0, 139.0, 171.9
49	27.0, 30.6, 35.6, 39.9, 71.3, 120.3, 127.0, 130.5, 138.6, 168.0
50	27.6, 30.6, 35.0, 40.1, 64.2, 120.4, 127.0, 130.6, 138.5, 168.0
51	27.9, 30.5, 34.8, 40.2, 50.9, 117.8, 120.5, 126.9, 130.8, 138.2, 163.8
52	8.9, 11.1, 20.9, 30.1, 30.4, 42.9, 65.2, 66.6, 120.4, 127.3, 130.2, 137.5, 169.3

[a)] Measured in $CDCl_3$

(*4-Bromothiophen-2-yl)acetonitrile*

A mixture of 4-bromo-2-chloromethylthiophene (2.12 g, 10 mmol) and KCN (710 mg, 10.9 mmol) in acetone/water (25 ml/10 ml) was stirred under reflux for 20 hr. The acetone was distilled off and the residue was extracted with IPE (3×20 ml). The combined IPE layer was washed with water and dried. After evaporating the IPE, the residual mixture was separated by chromatography on SiO_2 with hexane/IPE 5 : 1. The nitrile was obtained as liquid. Yield: 1.32 g (65%). IR (KBr) cm^{-1}: 2250. ^{1}H NMR δ ($CDCl_3$): 3.67 (2H, s), 6.99 (1H, d, J=1.5 Hz), 7.26 (1H, d, J=1.5 Hz). EI-MS m/z (%): 202 (M^+, 21), 176 (100).

2-(4-Bromothiophen-2-yl)ethylamine

A toluene solution of 2M solution of boran-dimethyl sulfide complex (5.2 ml, 10.4 mmol) was added portionwise to a refluxing solution of (4-bromothiophen-2-yl)acetonitrile (2.02 g, 10 mmol) in 5 ml THF under an argon atmosphere. After 2 hr stirring at the reflux temperature of THF, 20 ml of 10% HCl solution was added dropwise and stirring was continued at this temperature for a further 30 min. The mixture was cooled to room temperature and treated with 5 ml of 6N HCl solution and, after washing with IPE, the IPE layer was discarded. The aqueous layer was cooled in an ice bath and alkalized with NaOH pellets. IPE extract from the alkaline solution was washed with brine and dried. Evaporation of IPE left 0.7 g amine, which was used in the next step without further purification. ^{1}H NMR δ ($CDCl_3$): 1.24 (2H, bs), 2.70 (2H, t, J=6.9 Hz), 2.93 (2H, t, J=6.9 Hz), 6.90 (2H, s).

2-(2,3-Dichlorothiophen-5-yl)ethanol

This compound was obtained by reduction of 2,3-dichlorothiophen-5-ylacetic acid according to the Method 2 for 2-(2-chlorothiophen-5-yl)ethanol. Liquid. IR (KBr) cm^{-1}: 3310 (broad), 1545, 1045, 875, 820. ^{1}H NMR δ ($CDCl_3$): 1.80 (1H, bs), 2.939 (2H, t, J=6.2 Hz), 3.82 (2H, t, J=6.2 Hz), 6.66 (1H, s). EI-MS m/z (%): 196 (M^+, 42), 165 (100).

2-(2,3-Dichlorothiophen-5-yl)ethyl p-toluenesulfonate

Mp 79°C. IR (KBr) cm^{-1}: 1355, 1175. ^{1}H NMR δ ($CDCl_3$): 2.45 (3H, s), 3.01 (2H, t, J=6.3 Hz), 4.18 (2H, t, J=6.3 Hz), 6.52 (1H, s), 7.31 (2H, d, J=8.0 Hz), 7.70 (2H, d, J=8.1 Hz). EI-MS m/z (%): 350 (M^+, 4), 178 (100).

5-(2-Azidoethyl)-2,3-dichlorothiophene. IR (KBr) cm^{-1}: 2100. ^{1}H NMR δ ($CDCl_3$): 2.94 (2H, t, 2H, J=6.6 Hz), 3.51

(2H, t, J=6.6 Hz), 6.67 (1H, s).

2-(2,3-Dichlorothiophen-5-yl)ethylamine. ^{1}H NMR assigned for the amine in the mixture, δ ($CDCl_3$): 1.80 (2H, bs), 2.81 (2H, t, J=6.6 Hz), 2.94 (2H, t, J=6.6 Hz), 6.62 (1H, s).

(2,5-Dichlorothiophen-3-yl)acetic acid

Boron trifluoride etherate (8.71 g, 61 mmol) was added slowly to a solution of 3-acetyl-2,5-chlorothiophene[14] (5.93 g, 30 mmol) in methanol (4.0 ml) at 10–20°C. The resultant solution was added in one portion to a magnetically stirred suspension of lead (IV) acetate (13.3 g, 30 mmol) in benzene (40 ml). The reaction mixture was stirred at room temperature for 18 hr, diluted with cold water (200 ml), extracted with toluene (200 ml), washed sequentially with satd. $NaHCO_3$ solution (50 ml), and brine (50 ml), and then dried. Evaporation of the solvents yielded crude methyl 2,5-dichloro-3-thienylacetate (5.7 g), which was treated with a solution of 5 g NaOH in 50 ml water and 5 ml methanol. After stirring at room temperature for 3 hr, the reaction mixture was washed with IPE. The IPE layer, including some 3-acetyl-2,5-dichloro-thiophene, was discarded. The aqueous layer was acidified with 4N HCl and left to stand in an ice bath. The precipitated solid was separated and recrystallization from ether afforded 1.53 g product (24% yield based on 3-acetyl-2,5-dichlorothiophene). Mp 104°C. IR (KBr) cm^{-1}:1704. ^{1}H NMR δ ($CDCl_3$): 3.66 (2H, s), 6.78 (1H, s), 10.8 (1H, bs). EI-MS *m*/*z* (%.): 209 (M^+, 25), 165 (100), 131 (19).

2-(2,5-Dichlorothiophen-3-yl)ethanol

A solution of 2,5-dichloro-3-thiophenylacetic acid (1.06 g, 5.0 mmol) in THF (10 ml) was slowly added at room temperature over 10 min to a suspension of $NaBH_4$ (500 mg, 13.5 mmol) in THF (10 ml). The mixture was stirred until evolution of gas ceased. Iodine (1.20 g, 4.7 mmol) was added slowly over 10 min. The contents were stirred overnight. Five milliliters of 3N HCl was added carefully and the mixture was extracted with IPE. The combined extracts were washed successively with 3N NaOH solution (3×10 ml) and brine, and dried over $MgSO_4$. Evaporation of the organic solvents gave crude alcohol, which was purified by column chromatography on SiO_2 with hexane/IPE 1 : 1. Colorless liquid. Yield: 520 mg (53%). IR (KBr) cm^{-1}: 3272, 1049. ^{1}H NMR δ ($CDCl_3$): 1.59 (1H, bs), 2.79 (2H, t, J=6.4 Hz), 3.81 (2H, t, J=6.4 Hz), 6.73 (1H, s). EI-MS *m*/*z* (%): 196 (M^+, 42), 165 (100), 131 (36).

2-(2,5-Dichlorothiophen-3-yl)ethyl p-toluenesulfonate

It was prepared conventionally from alcohol and *p*-toluenesulfonyl chloride in pyridine. Mp 76–77°C. ^{1}H NMR δ ($CDCl_3$): 2.44 (3H, s), 2.85 (2H, t, J=6.3 Hz), 4.16 (2H, t, J=6.3 Hz), 6.53 (1H, s), 7.31 (2H, d, J=8.6 Hz), 7.70 (2H, d, J=8.6 Hz). EI-MS *m*/*z* (%): 350 (M^+, 2), 180 (86), 178 (100), 165 (35).

*N-[2-(2,5-Dichlorothiophen-3-yl)ethyl]-2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxamide (**45**)*

A mixture of 2-(2,5-dichlorothiophen-3-yl)ethyl *p*-toluenesulfonate (620 mg, 1.8 mmol) and sodium azide (180 mg, 2.8 mmol) in DMF (3 ml) was stirred at 80°C for 3 hr. The cooled reaction mixture was diluted with 20 ml water and extracted with ethyl acetate (2×20 ml). The extracts were combined, washed with brine (2×20 ml), and dried over magnesium sulfate. Evaporation of the organic layer yielded crude azide (426 mg), which was dissolved in THF (5 ml) and treated with triphenyl phosphine (300 mg) and water (20 mg). The mixture was stirred overnight. The THF was evaporated and the residual liquid was dispersed with 6N HCl solution (20 ml) and IPE (10 ml). The separated acid layer, after being washed with IPE (10 ml), was cooled in an ice bath, carefully alkalized with solid NaOH, and then extracted with chloroform. After drying over magnesium sulfate, the chloroform was evaporated, and toluene (15 ml) was added to the residue to remove the remaining water by azeotropic distillation. The residue was dissolved with dry toluene (15 ml), mixed with triethylamine (243 mg), and then cooled in an ice bath. A solution of 2,2-dichloro-1-ethyl-3-methylcyclopropanoyl chloride (426 mg) in toluene (5 ml) was added dropwise. Stirring was continued at ambient temperature for 10 hr, and then at 80°C for 20 min. After cooling, the mixture was diluted with 10 ml toluene, washed with water (30 ml), 1% HCl solution (20 ml), and brine, and dried over anhydrous magnesium sulfate. The toluene was evaporated and column chromatography of the residual liquid on SiO_2 with n-hexane/IPE 1 : 1 yielded 172 mg product (Yield: 25% based on the tosylate).

(2-Chlorothiazol-4-yl)acetic acid

To an ice-cooled solution of (2-aminothiazol-4-yl)acetic acid (3.0 g, 19 mmol) in 15 ml conc. HCl was added dropwise a solution of sodium nitrite (2.1 g) in 3 ml water. After further one-hour stirring with ice cooling, powdered copper (120 mg, 1.9 mmol) was added, and the mixture was stirred overnight at ambient temperature, and then at 60°C for 1 hr. The mixture was cooled and poured into water, extracted with ethyl acetate, and dried over magnesium sulphate. The solvent was evaporated and the residue was dispersed with 20 ml of 5% NaOH solution and 20 ml IPE. The IPE extract was discarded, and the aqueous phase was acidified to pH 3–4 with conc. HCl, extracted with ethyl acetate and dried. Evaporation of ethyl acetate afforded crude product, which was washed with cold hexane. Yield: 710 mg (21%). Mp 93–96°C. IR (KBr) cm^{-1}: 2590, 1730. ^{1}H NMR δ ($CDCl_3$): 3.83 (2H, s), 7.14 (1H, s), 10.5 (1H, bs). EI-MS *m*/*z* (%): 177 (M^+, 8), 133 (100).

2-(2-Chlorothiazol-4-yl)ethanol

This compound was prepared from 2-(2-chlorothiazol-4-yl)acetic acid by Method 2 using boran-dimethyl sulfide complex for compound 2-(2-chlorothiophen-5-yl)ethanol. Yield: 33%. Liquid. IR (KBr) cm^{-1}: 3320, 1430, 1050. ^{1}H NMR δ ($CDCl_3$): 2.40 (1H, bs), 2.95 (2H, t, J=6.3 Hz), 3.94 (2H, t, J=6.3 Hz), 6.92 (1H, s). EI-MS *m*/*z* (%): 163 (M^+, 12), 134 (100).

2-(2-Chlorothiazol-4-yl)ethyl p-toluenesulfonate

Mp 65–66°C. IR (KBr) cm^{-1}: 1600, 1435, 1350. ^{1}H NMR δ ($CDCl_3$): 2.45 (3H, s, 3H), 3.03 (2H, t, J=6.2 Hz), 4.32 (2H, t, J=6.2 Hz), 6.91 (1H, s), 7.31 (2H, d, J=7.7 Hz), 7.69 (2H, d, J=7.7 Hz). EI-MS *m*/*z* (%): 319 (M^+, 25), 144 (100).

4-(2-Azidoethyl)-2-chlorothiazol

Liquid. IR (KBr) cm^{-1}: 2105, 1520, 1430, 1050. ^1H NMR δ ($CDCl_3$): 2.97 (2H, t, J=5.9 Hz), 3.64 (2H, t, J=5.9 Hz), 6.95 (1H, s). EI-MS *m/z* (%): 188 (M^+, 16), 132 (100).

2-(2-Chlorothiazol-4-yl)ethylamine

^1H NMR δ ($CDCl_3$):1.35 (2H, bs), 2.84 (2H, t, J=6.6 Hz), 3.05 (2H, t, J=6.6 Hz), 6.88 (1H, s). EI-MS *m/z* (%): 162 (M^+, 14), 133 (100).

(*2-Chlorothiazol-5-yl)acetonitrile*

A solution of 2-chloro-5-chloromethylthiazol (1.67 g, 10 mmol) in 10 ml DMF was added to a suspension of KCN (1.3 g, 20 mmol) in 10 ml DMF. The mixture was stirred at room temperature for 18 hr, and poured into 50 ml water. IPE extracts were washed with brine and dried over magnesium sulphate. The product was separated on SiO_2 column with IPE/hexane 1:1. Yield: 948 mg (60%). Liquid. IR (KBr) cm^{-1}: 2250, 1410. ^1H NMR δ ($CDCl_3$): 3.87 (2H, s), 7.48 (1H, s). EI-MS *m/z* (%): 157 (M^+, 7), 123 (100).

2-(2-Chlorothiazol-5-yl)ethylamine

A solution of (2-chlorothiazol-5-yl)acetonitrile (345 mg, 2.2 mmol) in 5 ml toluene was added dropwise to a solution of 1 M diisobutylaluminium hydride in toluene (10 ml, 10 mmol) under an argon atmosphere at −10°C. The mixture was stirred for 5 hr at −10°C and then allowed to warm to room temperature. After 10 hr at room temperature, the mixture was cooled to 0°C and the reaction was quenched by slow addition of 2N HCl solution (30 ml). After diluting with 20 ml hexane, the organic layer was discarded. The cooled aqueous layer was carefully made basic with 40% NaOH solution and mixed with 20 ml ether under stirring for 20 min. The ether phase was separated and the aqueous phase was extracted further with ether (2×15 ml). The combined extract was dried over KOH pellets. After evaporation of ether, the residual amine was used in the next step. Crude yield: 110 mg (31%). Liquid. IR (KBr) cm^{-1}: 3400, 1420, 1045. ^1H NMR δ ($CDCl_3$):1.4 (2H, bs), 2.90 (2H, t, J=6.4 Hz), 2.97 (2H, t, J=6.4 Hz), 7.25 (1H, s). EI-MS *m/z* (%): 163 (M^+, 46), 133 (100).

1-(3-Chlorothiophen-5-yl)ethylamine

A mixture of 2-acetyl-4-chlorothiophene[14] (3.0 g, 1.9 mmol), hydroxylamine×HCl (1.70 g, 2.4 mmol) in water (15 ml) was warmed at 60°C for 30 min. The mixture was then cooled to room temperature, and the crystals were filtered and washed with hexane. Yield: 1.70 g (51%), Mp 132–134°C. IR (KBr) cm^{-1}: 1420, 1340, 1010, 840. ^1H-NMR δ ($CDCl_3$): 2.27/2.34 (3H, s, *cis/trans* mixture), 7.05/7.09 (1H, s, *cis*/*trans* mixture), 7.26/7.34 (1H, s, *cis*/*trans* mixture), 8.6 (1H, bs). EI-MS *m/z* (%): 175 (M^+, 100), 158 (22), 143 (31), 118 (70). The obtained oxime (1.66 g, 9.43 mmol) was mixed with MoO_3 (1.87 g, 13.0 mmol) in 100 ml methanol. The mixture was cooled in an ice-water bath and treated with powdered $NaBH_4$ (3.70 g, 10 mmol) portionwise. The work-up according to the procedures written in the previous publication afforded 810 mg product in 50% yield. Bp 110–120°C (22 mmHg). ^1H NMR δ ($CDCl_3$): 1.45 (3H, d, J=6.3 Hz), 1.58 (2H, bs), 4.30 (1H, q, J=6.3 Hz), 6.78 (1H, d, J=1.1 Hz), 6.97 (1H, d, J=1.1 Hz). EI-MS *m/z* (%): 161 (M^+, 2), 145 (9), 47 (100).

The following amines were prepared similarly.

2-Chloro-5-acetylthiophene oxime[16]

^1H NMR δ ($CDCl_3$): 2.52 (3H, s), 6.95 (1H, d, J=1.1 Hz), 7.45 (1H, d, J=1.1 Hz).

1-(2-Chlorothiophen-5-yl)ethylamine

Bp 119–124°C/22 mmHg. ^1H NMR δ ($CDCl_3$): 1.44 (3H, d, J=6.7 Hz), 1.58 (2H, bs), 4.27 (1H, q, J=6.7 Hz), 6.66 (1H, d, J=3.9 Hz), 6.73 (1H, d, J=3.9 Hz). EI-MS *m/z* (%): 161 (M^+, 10), 145 (30), 47 (100).

2-Chloro-4-acetylthiophene oxime

^1H NMR δ ($CDCl_3$): 2.20 (3H, s), 7.22 (1H, s), 7.97 (1H, s). This compound was used in the next step without purification for further analysis.

1-(2-Chlorothiophen-4-yl)ethylamine

Bp 115–130°C (22 mmHg). ^1H NMR δ ($CDCl_3$): 1.36 (3H, d, J=6.3 Hz), 1.46 (2H, bs), 4.07 (1H, q, J=6.3 Hz), 6.87 (1H, d, J=1.7 Hz), 6.89 (1H, d, J=1.7 Hz). EI-MS *m/z* (%): 161 (M^+, 11), 145 (100).

2,3-Dichloro-5-acetylthiophene oxime

Mp 127–130°C. IR (KBr) cm^{-1}: 1419, 1371, 1325, 1015, 832. ^1H NMR δ ($CDCl_3$): 2.21/2.27 (3H, s, *cis*/*trans* mixture), 6.99/7.10 (1H, s, *cis*/*trans* mixture), 8.2 (1H, bs). EI-MS *m/z* (%): 209 (M^+, 92), 175 (100), 152 (63), 118 (86).

1-(2,3-Dichlorothiophen-5-yl)ethylamine

Bp 140–145°C (20 mmHg). ^1H NMR[1] δ ($CDCl_3$): 1.43 (3H, d, J=6.6 Hz), 1.58 (2H, bs), 4.26 (1H, q, J=6.6 Hz), 6.67 (1H, s). EI-MS *m/z* (%): 195 (M^+, 12), 179 (100), 145 (52).

1-(2-Chlorothiophen-4-yl)ethyl 2,2-dichloro-1-ethyl-3-methylcyclopropanecarboxlate (**52**)

A solution of 2,2-dichloro-1-ethyl-3-methylcyclopropanoyl chloride (215 mg, 1 mmol) in toluene (5 ml) was added dropwise to an ice-cold solution of 2-chloro-4-thiophenethanol (163 mg, 1.0 mmol) and triethylamine (120 mg, 1.2 mmol) in toluene (10 ml). After stirring overnight at room temperature, the reaction mixture was poured into ice-water and the separated organic layer was washed successively with 1% HCl solution, satd. $NaHCO_3$ solution, and brine, and dried. The solvent was evaporated and the residue was subjected to column chromatography on SiO_2 with hexane/IPE 10 : 1. The product was obtained as liquid. Yield: 193 mg (57%).

2. *Fungicidal assay by foliar spraying on pot*

The control efficacy of the newly synthesized compounds against downy mildew and gray mold on cucumber and leaf rust and powdery mildew on wheat was tested. Test compounds were dissolved in acetone at 10% (w/v), and a small amount of surfactants (Gramin®-S; Sankyo) was added to the solution. The acetone solution was diluted with ion-exchanged water to 500 μg/ml as a.i. and then sprayed onto seedlings of cucumbers (cultivar, SHARP 1) or wheat (cultivar, Norin No. 61) grown in plastic pots. The cucumber and wheat plants were inoculated by spraying each with a spore

suspension of *Pseudoperonospora cubensis* or *Puccinia recondite*, respectively. The plants were inoculated with *Botrytis cinerea* by placing paper disks (8 mm in diameter), which had been dipped into a spore suspension in potato dextrose broth, on the cucumber cotyledons. *Erysiphe graminis* for wheat powdery mildew was inoculated by dusting the spores onto wheat lesions. Seedlings inoculated with downy mildew and gray mold were incubated in a high-humidity chamber at 20°C until evaluation. Wheat seedlings inoculated with leaf rust were incubated in a chamber at 25°C for 24 hr, transferred to a greenhouse at 25–30°C, and cultured until evaluation. Wheat seedlings inoculated with powdery mildew were cultured in the same greenhouse. Disease infection assessments are carried out 4 days after inoculation with gray mold, 7 days after inoculation with downy mildew, and 10 days after inoculation with leaf rust and powdery mildew.

The damage was assessed by eye using an infection grade of 0–5 based on the lesion area (LA) of the disease/leaf, as follows:

Infection grade:	0	1	2	3	4	5
LA (%):	0	<20	$\geq 20-<40$	$\geq 40-<60$	$\geq 60-<80$	≥ 80

Table 5 gives the average values of two replications of the prepared compounds together with three commercial standard samples, maneb 75WP (75% wettable powder), fludioxonil 20SC (20% suspension concentrate) and fenpropidin 75EC (75% emulsion concentrate) as references.

Results and Discussion

The final products for the fungicidal tests can be obtained by following the established procedures of reacting acyl chlorides with the corresponding amines (Fig. 3).[4] We have focused our efforts on the construction of chlorine-substituted thiophenylethylamines. The preparation strategy was determined by considering the efficiency of introducing a precursory functional group to the thiophene ring and subsequent transformation to the ethylamines. From this approach, thiophenyl-CH_2CO_2H would be a practicable candidate, because several selective reduction methods of CH_2CO_2H to CH_2CH_2OH have already been exploited and a recent comprehensive overview by Badham[17] has provided a wealth of information on the homologation of ArCOMe into $ArCH_2CO_2H$.

A few chlorine-substituted acetylthiophenes are accessible by modified Friedel–Crafts acylation under controlled conditions instead of the conventional method using aluminum chloride to avoid rupture of the chlorine atom from the nucleus.[16] Another appropriate approach would be optionally selective chlorination on commercially available 2-acetyl and 3-acetylthiophenes.[14] After trying a few examples taken from the reviewed methodologies by considering that halogen atoms on the acylthiophenes are rather sensitive to basic reagents, radical sources, or strong acidic media, we found the method for transformation of ArCOMe to $ArCO_2Me$ using $BF_3(OEt)_3$ and lead (IV) acetate exploited by Myrboh, Ila and Junjappa[18] adaptable for our compound class (Fig 2).

For the next step from $ArCH_2CO_2H$ to $ArCH_2CH_2OH$, because we have noticed that nuclear dechlorination partially occurred in the treatment of 4-chloro-2-thiophenyl acetic acid with the commonly-used lithium aluminum hydride, we have adopted a milder reduction method using $NaBH_4/I_2$[19] or BH_3Me_2S.[20] Tosylation of the alcohol followed by substitution with an azide proceeded smoothly. The rather labile azides were mostly transformed *in situ* to the amines without separation. The corresponding 2-(2-chlorothiazole-3-yl)ethylamine was similarly obtained from (2-chlorothiazol-4-yl)acetic acid, which was prepared by applying Sandmeyer reaction to commercially available (2-aminothiazol-3-yl)acetic acid. Chlorothiazolylacetic acid was transformed to the final amine following the preparative sequence described above.

Scheme 2 in Fig. 2 provides another entry to the arylethylamine moiety. As described, (4-bromothiophen-2-yl)acetic acid was transformed first to the CH_2OH derivative, followed by chlorination to CH_2Cl. The chloride was substituted with a nitrile by treating with KCN in acetone. The last transformation proceeded well using a mild reducing reagent, isobutyl aluminum hydride, after the published protocol.[19] A similar method was used to prepare 2-(2-chlorothiazol-5yl)ethylamine.

On the other hand, for the preparation of $ArCH(Me)NH_2$-type compounds, we applied Ipaktschi's method to reduce oxime using $NaBH_4$ and MoO_3 (Fig. 2).[20] This procedure also worked well for the present heteroaromatic compounds, as for our previous acyclic analogs.[5]

The structures of amides derived from the above amines are supported by ^1H and ^{13}C NMR, MS, and IR spectral data (Tables 2–4).

Table 5 lists the infection grades of four diseases on the respective host plants sprayed with the tested compounds and the standard products, maneb for downy mildew and leaf rust, fludioxonil for gray mold, and fenpropidin for powdery mildew.

At a glance, we can see the different control abilities of these compounds for the tested fungi from that for *Pyricularia oryzae*.[4] This would be reasonable because the pathogens and infection mechanisms are different. In this respect, it is worthy of attention that the commercial blasticide carpropamid (**1**) and compounds designed for rice blast reduced the lesion due to downy mildew on cucumber. In particular, *N*-isopropylcyclopropanecarxoamid (**2**), *N*-alicyclic analogues (**7** and **9**), *N*-$PhCH_2CH_2$ derivative (**16**), *N*-3-Cl-$PhCH_2CH_2$- (**18**), its 2,4-difluoro- or 3,4-dichloro-phenethyl analogs (**25** and **26**), and 4-chlorophenylpropyl derivative (**29**) completely controlled this cucumber disease. Bromothiophene and chlorothiazole derivatives (**43** and **46**) also showed high efficiency. Amides (**28**, **30**, **35** and **38**) controlled the infection to over 80%. It is surprising that these compounds designed for rice blast disease showed a remarkable effect against downy mildew, even though the infection mode of action of this fungus is not involved in melanin biosynthesis in-

Table 5. Pot test results[a)]

Compound No.	Infection grade[b)]			
	gray mold[c)]	downy mildew[c)]	leaf rust[d)]	powdery mildew[d)]
1[e)]	5.0	0.5	5.0	5.0
2	3.5	0.0	5.0	5.0
3	2.0	5.0	5.0	5.0
4	5.0	5.0	5.0	5.0
5	5.0	5.0	5.0	5.0
6	5.0	5.0	5.0	5.0
7	3.5	0.0	5.0	5.0
8	5.0	5.0	5.0	5.0
9	5.0	0.0	5.0	5.0
10	3.0	5.0	5.0	5.0
11	5.0	5.0	5.0	5.0
12	5.0	2.0	5.0	5.0
13	5.0	5.0	1.0	5.0
14	5.0	5.0	5.0	5.0
15	5.0	5.0	5.0	5.0
16	5.0	0.0	1.5	0.5
17	5.0	5.0	5.0	5.0
18	5.0	0.0	3.0	2.5
19	5.0	3.5	5.0	5.0
20	5.0	5.0	5.0	5.0
21	5.0	5.0	3.0	2.0
22	5.0	5.0	5.0	2.5
23	5.0	5.0	5.0	0.5
24	5.0	5.0	5.0	5.0
25	1.0	0.0	5.0	2.5
26	5.0	0.0	3.5	5.0
27	5.0	5.0	5.0	5.0
28	5.0	1.0	5.0	5.0
29	5.0	0.0	5.0	5.0
30	5.0	1.0	5.0	5.0
31	5.0	5.0	1.5	5.0
34	5.0	5.0	3.0	5.0
35	5.0	0.5	5.0	5.0
36	5.0	5.0	1.5	5.0
37	5.0	5.0	3.0	5.0
38	5.0	0.5	0.5	5.0
39	0.5	5.0	5.0	5.0
41	5.0	1.5	1.5	5.0
42	5.0	5.0	0.5	1.0
43	3.0	0.0	5.0	5.0
44	5.0	5.0	5.0	5.0
45	5.0	5.0	5.0	5.0
46	5.0	0.0	0.5	5.0
48	5.0	5.0	5.0	1.5
49	5.0	5.0	5.0	5.0
50	5.0	5.0	2.0	5.0
51	5.0	5.0	1.5	5.0
52	2.5	1.0	5.0	5.0
Maneb[f)]	NT	0.0	0.0	NT
Fludioxonil[g)]	0.0	NT	NT	NT
Fenpropidin[h)]	NT	NT	NT	0.0

[a)] Dose: 500 mg/l; on pot; NT stands for not tested. [b)] Grade 1–5 (see text). [c)] On cucumber. [d)] On wheat. [e)] Carpropamid. [f)] 75% wettable powder. [g)] 20% suspension concentrate. [h)] 75% emulsion concentrate.

hibition. The present finding may provide a possible lead to identify new fungicides for downy mildew. As far as the tested compounds are concerned, we could not discern the structural features of the chain length, the substituents on the aromatic nucleus, and the position or sort of alkyl substituents on the cyclopropane ring that the active molecules commonly bear. Regarding the structural similarity in this context, we would mention two commercial fungicides against downy mildew, iprovalicarb and benthiavalicarb-isopropyl,[21] which actually share a related structural element with carpropamid.

Against leaf rust on wheat, 2-chloro-4-thiophenylethyl derivatives (**39**, **42** and **46**) were almost entirely effective and, in contrast with carpropamid with nil activity for this disease, the isopropyl variant on the cyclopropane ring (**13**) showed significant activity. It is noteworthy that efficacy against powdery mildew on wheat was observed in compounds such as **16** and **23**, where the 4-chloro-α-phenethyl moiety is replaced with phenethyl or 4-trifluoromethylphenethyl moieties. Homologation and replacement with a thiophene ring seem confer few antifungal properties against gray mold on cucumber except for the 1-propylcyclopropyl variant (**39**), which had a notable effect. None of diclocymet homologs (**48**–**51**) showed any remarkable activity against the tested fungi. Interestingly, 2-chlorothiophenylethyl ester (**52**) indicated some potency against downy mildew. The molecular design based on the ester structure may be another approach to new fungicides from this class.

In this paper, we described the preparative route to halo-substituted thiophenylethylamines and showed that some thiophenyl or thiazolyl variants of carpropamid displayed control efficacy against some diseases other than rice blast, especially downy mildew. We are now planning to change the structures of these lead compounds systematically to explore new fungicide targeting on downy mildew and other important diseases.

References

1) S. Kagabu and Y. Kurahashi: *J. Pestic. Sci.* **23**, 145–147 (1998).
2) Y. Kurahashi, S. Kurogochi, N. Matsumoto and S. Kagabu: *J. Pestic. Sci.* **24**, 204–216 (1999).
3) K. So, M. Fuji, H. Iwabuchi, M. Kanayama and J. Yamaguchi: *Jpn. J. Phytopathol.* **68**, 262 (2002) (in Japanese).
4) Y. Kurahashi, S. Kagabu, N. Yamada, Y. Mitsugi, M. Shimizu, M. Nakasako and I. Yamaguchi: *J. Pestic. Sci.* **31**, 85–94 (2006).
5) S. Kagabu, S. Oshima, Y. Kurahashi and I. Yamaguchi: *J. Pestic. Sci.* **32**, 45–48 (2007).
6) Y. Kurahashi, S. Kagabu, S. Sakawa, N. Matsumoto and T. Yamada: *Jpn. Kokai Tokkyo Koho JP* 62–201855 (1986) (in Japanese).
7) Y. Kurahashi, S. Kagabu, N. Matsumoto, T. Yamada, K. Wada and T. Kondo: *Jpn. Tokkyo Koho JP* 63–054349 (1988) (in Japanese).
8) T. Motoyama, S. Kagabu, M. Matsuoka and I. Yamaguchi: *J. Pestic. Sci.* **27**, 141–144 (2002).
9) R. V. Davies, B. Iddon, T. M. Paterson, M. W. Pickering, H. Suschtzky and M. W. Gittos: *J. Chem. Soc. Perkin Trans*. 1. 1976, 138–141.
10) G. Yu, H. J. Mason, K. Galdi, X. Wu, L. Cornelius, N. Zhao, M. Witkus, W. R. Ewing and J. E. Macor: *Synthesis* 2003, 403–407.
11) H. Quast and H. Leybach: *Chem. Ber.* **124**, 849–859 (1991).
12) I. Lengyel, V. Cesare, H. Karram, T. Taldone: *J. Heterocyclic Chem.* **38**, 997–1002 (2001).
13) E. Schaumann and H. Mrotzek: *Tetrahedron* **35**, 1965–1968 (1979).
14) P. Stanetty, E. Puschautz and G. Friedbacher: *Monats. Chem.* **120**, 53–63 (1989).
15) F. F. Frickel and W. W. Wiersdorff: *Ger.Offen.* DE 78–2831871 (1980).
16) H. D. Hartough and A. I. Kosak: *J. Am. Chem. Soc.* **69**, 3093–3096 (1947).
17) N. F. Badham: *Tetrahedron* **60**, 11–42 (2004).
18) B. Myrboh, H. Ila and H. Junjappa: *Synthesis*, 1981, 126–127.
19) J. V. B. Kanth and M. Periasamy: *J. Org. Chem.* **56**, 5964–5965 (1991).
20) J. Ipaktschi: *Chem. Ber.* **117**, 856–858 (1984).
21) C. D. S. Tomlin (ed): "The Pesticide Manual, 14th Ed.", BCPC, Hampshire (UK), 2006.