Synthesis of Insecticidally Active Halofenozide-[(Acyloxy)alkoxy]carbonyl and (Acyloxy)alkyl Derivatives

Mark J. Mulvihill,* Steven H. Shaber, Brian S. MacDougall, Chris Ajello, Blanca Martinez-Teipel, Rhoda Joseph, Duyan V. Nguyen, Damian G. Weaver, KiHo Chung, Arkady Gusev, Joel M. Wierenga, William D. Mathis

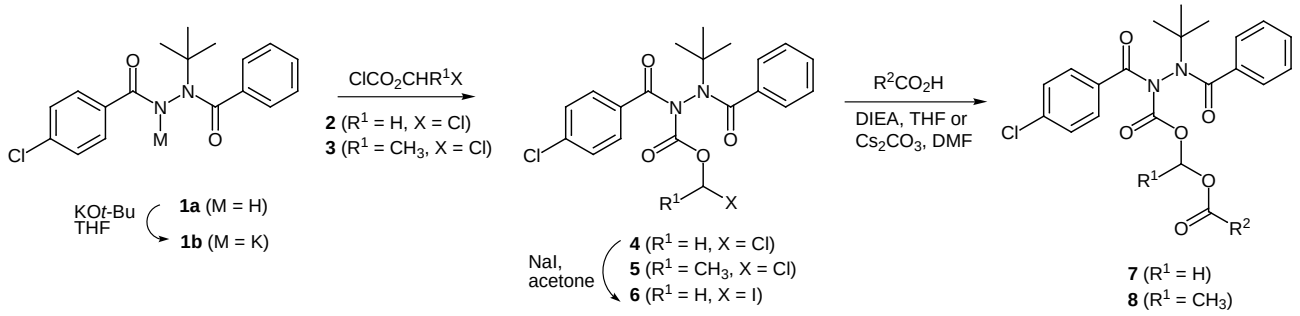
Rohm and Haas Company, 727 Norristown Road, Spring House, Pennsylvania, 19477, USA
Fax +1(215)6191617; E-mail: mark.mulvihill@osip.com

Received 9 June 2001; revised 28 September 2001

Abstract: The synthesis of a diverse series of novel insecticidally active carboxylic acid *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinocarbonyloxy methyl and ethyl esters as well as carboxylic acid *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazino methyl esters are reported.

Key words: carboxylic acids, drugs, esters, diacyl hydrazines, parallel synthesis

N-*tert*-Butyl diacyl hydrazines are an important class of environmentally safe and selective insecticidal compounds.[1] One such example, halofenozide (**1a**) (*N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazide) (Scheme 1), won the Presidential Green Chemistry Award for its environmental friendliness and is commercially used as an ecdysone agonist to selectively control *Coleoptera* and *Lepidoptera* in turf and ornamentals.[2,3] Halofenozide, due to its highly crystalline nature and low water solubility (12.3 ppm), tends to have a non-optimal use rate and formulation difficulties.[4] With this in mind, we set out to change the physical properties associated with halofenozide while attempting to retain or increase its biological efficacy through functionalization of the NH moiety with [(acyloxy)alkoxy]carbonyl and (acyloxy)alkyl moieties, commonly utilized in the pharmaceutical industry to enhance the properties of drugs.[5] In the case of halofenozide [(acyloxy)alkoxy]carbonyl derivatives, this paper will report the reaction of halofenozide with commercially available chloromethyl and 1-chloroethyl chloroformate and the further reaction with carboxylic acids (R^2CO_2H) via a parallel synthesis approach to afford various halofenozide-*N*-[(acyloxy)alkoxy]carbonyl derivatives (**7** and **8**, Scheme 1, Table 1). To our knowledge, this is the first attempt to apply the [(acyloxy)alkoxy]carbonyl moiety to diacyl hydrazines.[6] In the case of halofenozide-(acyloxy)alkyl derivatives, various methods exist which allow for the conversion of amines to (acyloxy)alkylamino derivatives.[7] Such methods include the reaction of nitrogen derivatives (tertiary amines, triazoles, amides, etc.) with commercially available halomethyl acetates.[8] However, the limited number of commercially available halomethyl acetates, as well as a synthesis of them which involves the reaction of a carboxylic acid with formaldehyde in the presence of a Lewis acid such as $ZnCl_2$ (procedure known to produce chloromethyl methyl ether [CME] and bis-CME), does not allow for an efficient or safe route to the production of a thorough library of *N*-(acyloxy)alkyl derivatives.[7] In attempts to by-pass such difficulties, this paper will report our novel approach to the synthesis of *N*-(acyloxy)alkyl derivatives via reaction of halofenozide **1a** with thiocarbonic acid *S*-ethyl ester *O*-iodomethyl ester **9** followed by treatment with sulfuryl chloride to afford chloromethyl intermediate **11**, which then can be further reacted with various carboxylic acids (R^3CO_2H) in the final step via a parallel synthesis approach to afford various halofenozide-*N*-(acyloxy)alkyl derivatives (**12**) (Scheme 2, Table 2) in an efficient high throughput fashion. To our knowledge, this is the first approach to substituted-*N*-(acyloxy)alkyl derivatives via a thiocarbonate approach.



Scheme 1 Synthesis of halofenozide-*N*-[(acyloxy)alkoxy]carbonyl derivatives **7** and **8**

Synthesis 2002, No. 1, 28 12 2001. Article Identifier:
1437-210X,E;2002,0,01,0053,0058,ftx,en;M02901SS.pdf.

ISSN 0039-7881

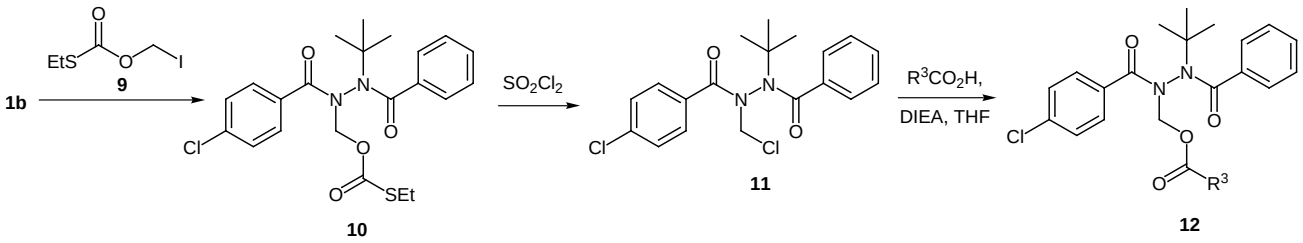
Table 1 Halofenozide-*N*-[(acyloxy)alkoxy]carbonyl Derivatives **7** and **8**

Compound #	R^1	R^2	Mass Found	% UV purity
7a	H	Me	446	100
7b	H	Ph	508	100
7c	H	*t*-Bu	488	100
7d	H	cyclopropyl	472	100
7e	H	diethoxyphosphorylmethyl	582	86
7f	H	2-methoxyethoxymethyl	520	92
7g	H	hept-1-ynyl	526	100
7h	H	tetrahydrofur-3-yl	502	100
7i	H	3,3,3-trifluoropropyl	528	100
7j	H	1-cyclopentenyl	498	100
7k	H	2-(3-fluorophenyl)ethenyl	552	100
7l	H	5-methylthien-2-yl	528	95
7m	H	5-nitro-2-furyl	543	100
7n	H	hexyl	516	100
7o	H	methylthiomethyl	492	100
7p	H	1-formylaminomethyl	489	86
7q	H	1-acetylaminovinyl	515	100
7r	H	3,5-dinitro-4-hydroxyphenyl	614	100
7s	H	4-formylphenyl	536	95
7t	H	2,6-dimethoxy-3-pyridyl	569	100
7u	H	2-(thien-2-yl)ethenyl	540	100
7v	H	acetoxymethyl	504	88
7w	H	5-(methoxycarbonyl)pyridin-2-yl	567	100
7x	H	1-acetylaminopentyl	559	95
7y	H	1-(*tert*-butoxycarbonylamino)ethyl	575	91
7z	H	1-formylamino-2-phenylethyl	579	95
8a	Me	Me	460	100
8b	Me	4-formylphenyl	550	100
8c	Me	1-(*tert*-butoxycarbonyl)piperidin-4-yl	629	96
8d	Me	*N*-methyl-2-pyrrolidinyl	525	100
8e	Me	2,6-dimethoxy-3-pyridyl	583	100
8f	Me	5-methylthien-2-yl	542	100
8g	Me	2-(2-fluorophenyl)ethenyl	566	100
8h	Me	vinyl	472	100
8i	Me	3-methylthien-2-yl	542	96
8j	Me	thien-3-yl	528	100

We began our efforts with the synthesis of halofenozide-*N*-[(acyloxy)alkoxy]carbonyl derivatives by treating halofenozide **1a** with potassium *tert*-butoxide followed by reaction with commercially available chloromethyl chloroformate **2** or 1-chloroethyl chloroformate **3** to afford chloromethyl analog **4** and chloroethyl analog **5**, respectively. Chloromethyl derivative **4** was reacted with NaI in acetone under typical Finkelstein reaction conditions[9] to afford iodo analog **6**, which then was reacted with various carboxylic acids (R^2CO_2H) in the presence of diisopropylethylamine (DIEA) in THF in a parallel synthesis fashion, to afford various halofenozide-*N*-[(acyloxy)-methoxy]-carbonyl derivatives (**7a**–**7z**) (Scheme 1, Table 1). In a

Table 2 Halofenozide-*N*-(acyloxy)alkyl Derivatives **12**

Compound #	R^3	Mass Found	% UV purity
12a	Me	402	100
12b	2-propyl	430	92
12c	Ph	464	100
12d	vinyl	414	86
12e	1-(*tert*-butoxycarbonylamino)ethyl	531	100
12f	1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl	557	100
12g	1-(*tert*-butoxycarbonyl)piperidin-4-yl	571	96
12h	3,6-dichloro-2-pyridyl	533	100
12i	*t*-Bu	444	84
12j	diethoxyphosphorylmethyl	538	93
12k	1-*tert*-butoxycarbonyl-4-hydroxypyrrolidin-2-yl	573	95
12l	1-(*tert*-butoxycarbonylamino)methyl	517	88
12m	1-(formylamino)methyl	445	100
12n	1-acyl-4-hydroxypyrrolidin-2-yl	515	100
12o	3-amino-4-methylphenyl	493	89
12p	3,5,6-trichloro-4-amino-2-pyridyl	582	96
12q	hydroxyethyl	432	100
12r	2-aminophenyl	479	100
12s	4-aminophenyl	479	100
12t	3,4-diaminophenyl	494	100
12u	3-amino-4-methoxyphenyl	509	100
12v	2-hydroxy-3-pyridyl	481	100
12w	H	388	100
12x	benzyloxymethyl	508	100
12y	3-amino-2-pyrazinyl	481	91



Scheme 2 Synthesis of halofenozide-*N*-(acyloxy)methyl derivatives **12**

further reaction of chloroethyl derivative **5**, we discovered that chloroethyl analog **5** did not undergo halogen interconversion under Finkelstein conditions. Direct reaction of chloroethyl analog **5** with carboxylic acids (R^2CO_2H) in the presence of DIEA in THF was very sluggish and many times afforded no reaction. However, reaction in the presence of cesium carbonate in DMF smoothly afforded various halofenozide-*N*-[(acyloxy)-1-ethoxy]carbonyl derivatives **8a**–**j** (Scheme 1, Table 1). Compounds **7a**, **7b**, **7c**, **8a** and **8b** were fully characterized as representative examples of this class of chemistry. The chemistry was then scaled down from 500 mg to 50 mg and a parallel synthesis approach (utilizing a 96 well reaction block [496 MBS, Advanced Chemtech] and a Genevac HT-12) was applied to the synthesis of compounds **7d**–**z** and **8b**–**j**, which were characterized by LC/UV/MS and are shown in Table 1.

Our efforts toward the synthesis of halofenozide-*N*-(acyloxy)alkyl derivatives began with the reaction of the potassium salt of halofenozide **1b** with thiocarbonic acid *S*-ethyl ester *O*-iodomethyl ester **9**[5e] to afford thiocarbonate **10**. Thiocarbonate **10** was treated with sulfuryl chloride, to afford chloromethyl derivative **11**,[10] which was reacted with various carboxylic acids (R^3CO_2H) in the presence of diisopropylethylamine (DIEA) in THF in a parallel synthesis fashion to afford various halofenozide-*N*-(acyloxy)methyl derivatives (**12**) (Scheme 2, Table 2). Halofenozide-*N*-(acyloxy)methyl derivatives **12a**, **12b** were prepared and fully characterized as representative examples of this class of chemistry. The chemistry was then scaled down from 500 mg to 50 mg and a parallel synthesis approach (utilizing a 96 well reaction block [496 MBS, Advanced Chemtech] and a Genevac HT-12) was applied to the synthesis of compounds **12b**–**y**, which were characterized by LC/UV/MS as shown in Table 2.

In conclusion, various halofenozide-*N*-[(acyloxy)-alkoxy]carbonyl derivatives (**7** and **8**) were synthesized. Also, various halofenozide-*N*-(acyloxy)alkyl derivatives (**12**) were synthesized via a novel route utilizing thiocarbonate **10**. In general, both the halofenozide-*N*-[(acyloxy)alkoxy]carbonyl (**7** and **8**) and (acyloxy)alkyl derivatives (**12**), ranged in biological activity from 1–12, in potency in feeding assays relative to the parent compound, halofenozide (**1a**). Generally, the [(acyloxy)alkoxy]carbonyl derivatives (**7** and **8**) displayed higher insecticidal activity than their (acyloxy)alkyl counterparts (**12**). The physical properties ranged from oils to solids and the water solubility ranged from 1 ppb to 100 ppm. Hydrolytic stability was measured as a function of pH (4.5, 6.5, and 8.5) to determine the chemical stability of this class of compounds. In most cases, the (acyloxy)alkyl derivatives were more hydrolytically stable than their [(acyloxy)alkoxy]carbonyl counterparts. The hydrolytic stability and biological results in accordance with the entire library of compounds synthesized will be reported at a later date.

Reagents and solvents were used as received from commercial vendors and no further attempts were made to purify or dry these items. TLC with UV detection was performed on 4×8 cm, SIL 6UV/254 silica gel plates with fluorescent indicator (Alltech Associates, Inc.). Column chromatography was performed on silica gel (Merck, 70–230 mesh). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker 300 MHz spectrometer. All ^1H NMR spectra are reported in ppm relative to TMS. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.00 ppm. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra (reported in cm^{-1}) were obtained on a Mattson Genesis II FT-IR spectrophotometer after dissolving the compound in chloroform and then applying the solution to a polyethylene film. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., 29 Samson Avenue, P.O. Box 927, Madison, New Jersey 07940.

LC/UV MS Procedures

For liquid chromatography (LC)/ultraviolet (UV) mass spectrometry (MS) analysis, the samples were dissolved in CH_3CN–H_2O (1:1) at concentrations of 100 μg/mL to 1000 μg/mL. The LC/UV MS analysis was performed using the HPLC 1100-VG Platform. The UV and MS instruments were connected in sequence, and the analysis was carried out in one injection where LC/UV afforded the purity (%) and MS confirmed the molecular weight. UV analysis was carried out using a scanning diode array detector (200–300 nm). MS analysis was carried out in positive scanning mode (100–1000 daltons). A short C18 HPLC column (3 mm ID, 5 cm length) was used with a flow rate of 1 mL/min. The eluent was split 1:25 after UV detection and 1 part was sent to the MS. The typical HPLC gradient was H_2O–CH_3CN (25:75) $\rightarrow CH_3CN$ (100%) over 5 min (0.1% formic acid added). Injection volume varied between 1 and 25 μL. In some cases, it was necessary to change certain parameters, e.g., ion mode (positive or negative), UV wavelength, or solvent buffer (no buffer, formic acid, HOAc, or ammonia acetate). The data is presented in Tables 1 and 2.

N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazine-carboxylic Acid Chloromethyl Ester (4)

To a suspension of *t*-BuOK (18.5 g, 165 mmol) in THF (1500 mL) was added halofenozide **1a** portionwise (40.0 g, 121 mmol) over 5 min. The mixture was heated to reflux for 30 min, allowed to cool to r.t. and stirred for an additional 30 min. Chloromethyl chloroformate (**2**) (13.5 mL, 71.5 mmol) was added dropwise to the yellow homogeneous mixture over 5 min. The mixture was stirred at r.t. for 1 h, after which time, the THF was removed in vacuo and the resulting slurry was taken up into Et_2O (800 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. Silica gel chromatography (hexanes–EtOAc, 5:1) afforded the title compound **4** (43.0 g, 85%) as a white solid; mp = 113–115 °C.

IR (cm^{-1}): 2983, 1769, 1711, 1675.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 5.64 (s, 2 H), 6.56 (d, 2 H, *J* = 9.0 Hz), 7.16 (d, 2 H, *J* = 9.0 Hz), 7.29–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 62.6, 70.2, 123.8, 127.4, 127.8, 128.1, 128.4, 131.1, 136.6, 137.6, 151.3, 168.5, 170.9

Anal. calcd for $C_{20}H_{20}Cl_2N_2O_4$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.71; H, 4.47; N, 6.50.

N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazine-carboxylic Acid 1-Chloroethyl Ester (5)

Compound **5** was prepared according to the procedure described for compound **4** above except for the substitution of 1-chloroethyl chloroformate **3** for chloromethyl chloroformate **2**; mp = 130–131 °C.

IR (cm^{-1}): 2981, 2942, 1768, 1712, 1680.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, 3 H, *J* = 6.0 Hz), 1.63 (s, 9 H), 6.27 (q, 1 H, *J* = 6.0 Hz), 6.55 (d, 2 H, *J* = 9.0 Hz), 7.16 (d, 2 H, *J* = 9.0 Hz), 7.29–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 27.4, 63.2, 83.6, 124.9, 128.3, 128.6, 128.8, 129.2, 132.5, 137.5, 138.3, 151.7, 169.4, 171.9.

Anal. calcd for $C_{21}H_{22}Cl_2N_2O_4$: C, 57.68; H, 5.07; N, 6.41. Found: C, 57.94; H, 4.98; N, 6.36.

N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazine-carboxylic Acid Iodomethyl Ester (6)

To a solution of *N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinecarboxylic acid chloromethyl ester **4** (32.0 g, 75.6 mmol) of acetone (200 mL) was added NaI (22.6 g, 151 mmol) and heated to 30 °C for 3 h. The acetone was removed in vacuo and the slurry was treated with Et_2O. The resulting precipitated white solids were filtered off and the filtrate was concentrated to afford the title compound **6** as a yellow solid (recrystallized from Et_2O–hexanes, 36 g, 93%); mp = 123–125 °C.

IR (cm^{-1}): 2980, 1765, 1710, 1675.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 9 H), 5.82 (m, 2 H), 6.55 (d, 2 H, *J* = 9.0 Hz), 7.17 (d, 2 H, *J* = 9.0 Hz), 7.26–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 30.4, 62.6, 124.0, 127.6, 128.0, 128.2, 128.5, 131.2, 136.7, 137.7, 151.2, 168.5, 171.0.

Anal. calcd for $C_{20}H_{20}ClIN_2O_4$: C, 46.67; H, 3.92; N, 5.44. Found: C, 46.76; H, 3.88; N, 5.31.

Acetic Acid N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazinocarbonyloxy-methyl Ester (7a)

To a solution of *N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinecarboxylic acid iodomethyl ester **6** (500 mg, 0.97 mmol) in THF (10 mL) was added glacial HOAc (0.11 mL, 1.85 mmol) and diisopropylethylamine (DIEA) (0.34 mL, 1.94 mmol). The mixture was stirred for 16 h, after which time, the resulting white precipitate was filtered off and the THF solution was concentrated in vacuo to an oil. Silica gel chromatography (hexanes–EtOAc, 4:1) afforded 395 mg (91%) of the title compound **7a** as an oily solid.

IR (cm^{-}): 1771, 1709, 1678.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 9 H), 2.07 (s, 3 H), 5.65 (m, 2 H), 6.55 (d, 2 H, *J* = 9.0 Hz), 7.14 (d, 2 H, *J* = 9.0 Hz), 7.29–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 27.3, 63.3, 81.2, 124.8, 128.2, 128.6, 128.7, 129.2, 132.5, 137.7, 138.2, 152.6, 168.7, 169.5, 171.9.

Anal. calcd for $C_{22}H_{23}ClN_2O_6$: C, 59.13; H, 5.19; N, 6.27. Found: C, 58.96; H, 5.22; N, 6.18.

Benzoic Acid N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazinocarbonyloxymethyl Ester (7b)

Compound **7b** (oily solid) was prepared according to the procedure described for compound **7a** above except for the substitution of benzoic acid for HOAc.

IR (cm^{-1}): 1765, 1745, 1709, 1679.

^1H NMR (300 MHz, $CDCl_3$): δ =1.61 (s, 9 H), 5.91 (m, 2 H), 6.51 (d, 2 H, *J* = 6.0 Hz), 6.98 (d, 2 H, *J* = 9.0 Hz), 7.17–7.31 (m, 5 H), 7.52 (m, 2 H), 7.65 (m, 1 H), 8.01 (d, 2 H, *J* = 9.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 63.3, 81.3, 124.7, 128.1, 128.2, 128.6, 128.7, 128.8, 129.1, 130.1, 132.4, 134.2, 137.7, 138.2, 152.9, 164.3, 169.6, 171.9.

Anal. calcd for $C_{27}H_{25}ClN_2O_6$: C, 63.72; H, 4.95; N, 5.50. Found: C, 63.61; H, 4.77; N, 5.39.

Trimethylacetic Acid N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chloro-benzoyl)hydrazino-carbonyloxymethyl Ester (7c)

Compound **7c** (oily solid) was prepared according to the procedure described for compound **7a** above except for the substitution of trimethlylacetic acid for HOAc.

IR (cm^{-1}): 1763, 1711, 1680.

^1H NMR (300 MHz, $CDCl_3$) δ = 1.20 (s, 9 H), 1.62 (s, 9 H), 5.69 (s, 2 H), 6.54 (m, 2 H), 7.13 (d, 2 H, *J* = 9.0 Hz), 7.29–7.31 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 27.3, 38.8, 63.3, 81.9, 124.7, 128.2, 128.6, 128.7, 129.2, 132.3, 137.7, 138.2, 152.6, 169.6, 171.8, 176.4.

Anal. calcd for $C_{25}H_{29}ClN_2O_6$: C, 61.41; H, 5.98; N, 5.73. Found: C, 61.21; H, 5.84; N, 5.70.

Acetic Acid 1-[N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chloro-benzoyl)-hydrazinocarbonyloxy]-ethyl Ester (8a)

Compound **8a** was prepared according to the procedures described for compound **7a** above except for the substitution of *N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazine-carboxylic acid 1-chloroethyl ester **5** for *N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazinecarboxylic acid iodomethyl ester **6**, the substitution of Cs_2CO_3 for DIEA, and the substitution of DMF for THF with a reaction temperature of 50 °C; mp = 129–131 °C.

IR (cm^{-1}): 1769, 1709, 1679.

^1H NMR (300 MHz, $CDCl_3$) δ = 1.34 (d, 3 H, *J* = 6.0 Hz), 1.54 (s, 9 H), 1.91 (s, 3 H), 6.45 (d, 2 H, *J* = 9.0 Hz), 6.63 (q, 1 H, *J* = 6.0 Hz), 7.05 (d, 2 H, *J* = 9.0 Hz), 7.20–7.31 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.5, 26.4, 62.1, 90.0, 123.7, 127.1, 127.6, 127.8, 128.2, 131.7, 136.7, 136.9, 150.6, 167.4, 168.7, 170.8.

Anal. calcd for $C_{23}H_{25}ClN_2O_6$: C, 59.94; H, 5.47; N, 6.08. Found: C, 59.85; H, 5.44; N, 5.97.

4-Formylbenzoic Acid 1-[N'-Benzoyl-N'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazino-carbonyloxy]ethyl Ester (8b)

Compound **8b** was prepared according to the procedure described for compound **8a** above except for the substitution of 4-formylbenzoic acid for HOAc; mp = 137–139 °C.

IR (cm^{-1}): 1763, 1743, 1707, 1678.

^1H NMR (300 MHz, $CDCl_3$) δ = 1.58 (m, 3 H), 1.62 (s, 9 H), 6.48 (m, 2 H), 7.05 (m, 4 H), 7.30 (m, 5 H), 8.00 (d, 2 H, *J* = 9.0 Hz), 8.07 (d, 2 H, *J* = 9.0 Hz), 10.11 (s, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 27.6, 63.6, 92.0, 125.1, 128.5, 129.0, 129.1, 129.6, 130.1, 130.8, 133.0, 133.6, 138.1, 138.4, 140.2, 152.0, 163.5, 170.0, 172.2, 191.7.

Anal. calcd for $C_{29}H_{27}ClN_2O_7$: C, 63.22; H, 4.94; N, 5.08. Found: C, 63.29; H, 4.85; N, 5.05.

Carboxylic Acid *N'*-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazino-carbonyloxy Methyl and Ethyl Esters 7a-z and 8a-j; Cyclopropanecarboxylic Acid *N'*-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinocarbonyloxymethyl Ester (7d); Typical Parallel Synthesis Procedure

Compound **7d**: cyclopropanecarboxylic acid (16 mg, 0.19 mmol) in THF (350 μL) was delivered to a 96 well reaction block (496 MBS, Advanced Chemtech) followed by DIEA (34 μL) in THF (300 μL). The block was stirred at r.t. for 30 min, at which time a solution of *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinecarboxylic acid iodomethyl ester **6** (50 mg, 0.097 mmol) in THF (350 μL) was delivered. Stirring was continued at r.t. for up to 48 h. The reaction was monitored by TLC (hexanes–EtOAc, 3:1). The reaction was filtered into the cleavage block, the solvent was removed in a Genevac HT-12, and the residue was dissolved in a minimal amount of CH_2Cl_2 and placed on a preconditioned (hexanes) 2 g silica solid phase extraction cartridge. The unreacted starting material was eluted with hexanes (5 mL) and the product with hexanes–EtOAc, 1:1 (5 mL). Alternatively, the compound was purified by preparative HPLC. The solvent was stripped and the product was dried in vacuo, yielding the title compound **7d** (40 mg, 87%) (Table 1). Compounds **8** were synthesized according to the method above except for the substitution of *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinecarboxylic acid 1-chloroethyl ester **5** for *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinecarboxylic acid iodomethyl ester **6**, the substitution of Cs_2CO_3 for DIEA and the substitution of DMF for THF with a reaction temperature of 50 °C (Table 1).

Thiocarbonic Acid *O*-[N'-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazino-methyl] Ester *S*-Ethyl Ester (10)

To a suspension of halofenozide (*N'*-benzoyl-*N'*-*tert*-butyl-*N*-[4-chlorobenzoyl]hydrazide) **1a** (0.31 g, 0.93 mmol) in THF (9.3 mL) was added *t*-BuOK (0.11 g, 0.93 mmol). The mixture was allowed to stir at r.t. for 2 h after which time thiocarbonic acid *S*-ethyl ester *O*-iodomethyl ester **9**[5e] (0.25 g, 0.93 mmol) was added. The mixture was allowed to stir at r.t. for 16 h. The THF was removed under reduced pressure and the resulting slurry was treated with Et_2O. The resulting white precipitated solids were filtered off and the filtrate was concentrated to an oil. Silica gel chromatography (hexanes–EtOAc, 7:3) afforded compound **10** as a white solid (300 mg, 61%); mp = 125–127 °C.

IR (cm^{-1}): 2944, 1695, 1671.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, 3 H, *J* = 7.2 Hz), 1.65 (s, 9 H), 2.86 (q, 2 H, *J* = 7.2 Hz), 5.15 (m, 2 H), 7.06 (d, 2 H, *J* = 9.0 Hz), 7.30–7.47 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 25.4, 27.8, 62.5, 78.8, 125.4, 128.1, 128.2, 129.0, 129.6, 131.7, 137.4, 137.5, 170.2, 171.0, 172.4.

Anal. calcd for $C_{22}H_{25}ClN_2O_4S$: C, 58.86; H, 5.61; N, 6.24. Found: C, 58.96; H, 5.45; N, 6.14.

Benzoic Acid *N*-*tert*-Butyl-*N'*-(4-chlorobenzoyl)-*N'*-chloromethylhydrazide (11)

To a suspension of thiocarbonic acid *O*-[*N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazinomethyl] ester *S*-ethyl ester **10** (5.00 g, 11.14 mmol) in 50 mL of CH_2Cl_2, cooled to –78 °C in a dry ice/acetone bath, was added sulfuryl chloride (1.20 mL, 14.48 mmol). The mixture was allowed to stir at r.t. for 1 h after which time, the solution was concentrated in vacuo to afford the desired product **11** as a white solid (recrystallized from hot hexanes, 3.7 g, 88% yield); mp = 116–118 °C.

IR (cm^{-1}): 2944, 1692, 1670.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 9 H), 4.89 (m, 2 H), 7.24–7.49 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.8, 62.6, 65.0, 125.6, 127.8, 128.3, 129.1, 129.9, 131.6, 137.2, 137.6, 170.9, 172.1.

Anal. calcd for $C_{19}H_{20}Cl_2N_2O_2$: C, 60.17; H, 5.32; N, 7.39. Found: C, 59.91; H, 5.07; N, 7.41.

Acetic Acid *N'*-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazinomethyl Ester (12a)

A solution of benzoic acid *N*-*tert*-butyl-*N'*-(4-chlorobenzoyl)-*N'*-chloromethylhydrazide **11** (0.50 g, 1.32 mmol) in THF (1 mL) was added to a solution of HOAc (0.17 mL, 2.90 mmol) and DIEA (0.52 mL, 2.90 mmol) dissolved in THF (2 mL). The mixture was allowed to stir at r.t. for 16 h. The THF was removed under reduced pressure and the resulting slurry was treated with Et_2O. The resulting white precipitated solids were filtered off and the filtrate concentrated in vacuo. Silica gel chromatography (hexanes–EtOAc, 85:15) afforded the desired product **12a** as an oil (360 mg, 76%).

IR (cm^{-1}): 2944, 1752, 1669.

^1H NMR (300 MHz, $CDCl_3$) δ = 1.65 (s, 9 H), 2.02 (s, 3 H), 5.07 (m, 2 H), 7.05 (d, 2 H, *J* = 6.6 Hz), 7.29–7.47 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.9, 27.8, 62.3, 77.3, 125.5, 128.0, 128.2, 129.0, 129.6, 132.0, 137.4, 137.6, 169.2, 171.1, 172.3.

Anal. calcd for $C_{21}H_{23}ClN_2O_4$: C, 62.61; H, 5.75; N, 6.95. Found: C, 62.52; H, 5.57; N, 6.86.

Carboxylic Acid *N'*-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazino Methyl Esters 12a-y; Isobutyric Acid *N'*-Benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)-hydrazinocarbonyloxymethyl Ester (12b); Typical Parallel Synthesis Procedure

Compound **12b** was prepared according to the parallel synthesis procedure described for compound **7d** above except for the substitution of isobutyric acid for cyclopropanecarboxylic acid and the substitution of benzoic acid *N*-*tert*-butyl-*N'*-(4-chlorobenzoyl)-*N'*-chloromethylhydrazide **11** for *N'*-benzoyl-*N'*-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazine carboxylic acid iodomethyl ester **6**. Compounds **12c**−**y** were prepared as described above for compound **12b** and were characterized by LC/UV MS and are shown in Table 2.

IR (cm^{-1}): 2974, 1742, 1690, 1671.

^1H NMR (300 MHz, $CDCl_3$) δ = 1.44 (m, 6 H), 1.66 (s, 9 H), 2.50 (m, 1 H), 5.03 (s, 2 H), 7.06 (d, 2 H, *J* = 9.0 Hz), 7.35–7.49 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 27.7, 33.9, 62.3, 78.1, 125.4, 127.9, 128.2, 128.9, 129.7, 132.0, 137.3, 137.5, 171.1, 172.4, 175.3.

Anal. calcd for $C_{23}H_{27}ClN_2O_4$: C, 64.11; H, 6.32; N, 6.50. Found: C, 64.37; H, 6.55; N, 6.26.

Acknowledgements

We thank Drs. Dennis Patterson and Harvey Scribner for many fruitful discussions and support of the project as well as Kristen M. Mulvihill for her help in preparation of the manuscript.

References

(1) Thomson, W. T. *Agricultural Chemicals, Book 1*, 14th ed.; Thomson Publications: Fresno, **1998**, Insecticides, 142–144.

(2) James, W. N. Jr.; Aller, H. E. U.S. Patent 5358966, **1994**; *Chem. Abstr.* **1994**, *122*, 3593.

(3) The Presidential Green Chemistry Award for Rohm and Haas diacyl hydrazines can be found on the following web pages: http://www.turfnet.com/news/rohm_haas.asp and http://www.epa.gov/greenchemistry/past.htm.

(4) Tomlin, C. D. S. *The Pesticide Manual*; British Crop Protection Council: Farnham, Surrey, GU9 7PH, UK, **1997**, 11th ed., 388–389.

(5) (a) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, CA, **1992**, 361–375. (b) Omar, F. A.; Farag, H. H.; Bodor, N. *Journal of Drug Targeting* **1994**, *2*, 309. (c) Gogate, U. S.; Repta, A. J.; Alexander, J. *Int. J. Pharm.* **1987**, *40*, 235. (d) Gogate, U. S.; Repta, A. J. *Int. J. Pharm.* **1987**, *40*, 249. (e) Folkmann, M.; Lund, F. J. *Synthesis* **1990**, 1159.

(6) (a) It should be noted that chloroalkyl chloroformates such as chloromethyl and 1-chloroethyl chloroformates, **2** and **3**, respectively, have been reported as carbonyl equivalents in the synthesis of carbamates: Barcelo, G.; Senet, J. P.; Sennyey, G. *Synthesis* **1986**, 627. (b) We recently reported the novel cyclization reaction in which treatment of the potassium salt of *N*'-benzoyl-*N*'-*tert*-butyl-*N*-(4-chlorobenzoyl)hydrazide **1b** with a carbonyl equivalent such as phosgene at –78 °C afforded 3-(4-chlorobenzoyl)-5-phenyl-3*H*-[1,3,4]oxadiazol-2-one: Mulvihill, M. J.; Nguyen, D. V.; MacDougall, B. S.; Weaver, D. G.; Mathis, W. D. *Synthesis* **2001**, 1965. (c) In light of these results, it was to our pleasant surprise that treatment of the potassium salt of halofenozide (**1b**) with known carbonyl equivalents such as chloroformates **2** and **3** did not afford cyclized oxadiazol-2-one products but afforded stable isolable compounds **4**, **5** and **6** which were further reacted to afford stable isolable esters **7** and **8**.

(7) (a) Roberts, W. J.; Sloan, K. B. *J. Pharm. Sci.* **2000**, *89*, 1415. (b) Madec-Lougerstay, R.; Florent, J. C.; Monneret, C. *J. Chem. Soc., Perkin Trans. 1* **1999**, *10*, 1369. (c) Redden, P. R.; Melanson, R. L.; Jo-Anne, E.; Dick, A. J. *Int. J. Pharm.* **1999**, *180*, 151. (d) Falch, E.; Perregaard, J.; Frolund, B.; Sokilde, B.; Buur, A.; Hansen, L. M.; Frydenvang, K.; Brehm, L.; Bolvig, T.; Larsson, O. M.; Sanchez, C.; White, H. S.; Schousboe, A.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1999**, *42*, 5402. (e) Davidsen, S. K.; Summers, J. B.; Albert, D. H.; Holms, J. H.; Heyman, R. H.; Magoc, T. J.; Conway, R. G.; Rhein, D. A.; Carter, G. W. *J. Med. Chem.* **1994**, *37*, 4423. (f) Alexander, J.; Renyer, M. L.; Rork, G. S. *J. Pharm. Sci.* **1994**, *83*, 893. (g) Waranis, R. P.; Sloan, K. B. *J. Pharm. Sci.* **1988**, *77*, 210. (h) Bundgaard, H.; Buur, A. *Int. J. Pharm.* **1987**, *37*, 185. (i) Buur, A.; Bundgaard, H.; Falch, E. *Int. J. Pharm.* **1985**, *24*, 43. (j) Bodor, N.; Woods, R.; Raper, C.; Kearney, P.; Kaminski, J. J. *J. Med. Chem.* **1980**, *23*, 474.

(8) (a) Ozawa, N.; Yazawa, N. WO 9308152 A1, **1993**; *Chem. Abstr.* **1993**, *119*, 138756. (b) Benneche, T.; Strande, P.; Wiggen, U. *Acta Chem. Scand.* **1989**, *43*, 74. (c) Grynkiewicz, G.; Tsien, R. Y. *Pol. J. Chem.* **1987**, *61*, 443. (d) Gruszecki, W.; Gdulewicz-Gruszecka, M.; Dunajska, B.; Kolodziejczyk, P.; Borowski, E. PL 78-206892, **1984**; *Chem. Abstr.* **1984**, *102*, 45492.

(9) (a) Finkelstein, H. *Ber.* **1910**, *43*, 1528. (b) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell Univ. Press: London, **1969**, 2nd ed., 435.

(10) Treatment of thiocarbonates with sulfuryl chloride typically affords the respective chloroformates (ref.[5e]). However, in this case, treatment of thiocarbonate **10** with sulfuryl chloride afforded chloromethyl derivative **11** with no trace of the respective chloroformate. Chloromethyl derivative **11** was not stable to silica gel column chromatography. However, chloromethyl derivative **11** could be recrystallized from hot hexanes to afford the pure product, which was stored at –20 °C.