Synthesis of *N*-Benzoyl-*N*-alkyl-2-aminothiazole *Heliothis virescens* Proinsecticides

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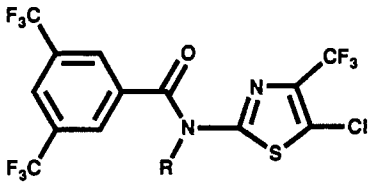
N-Benzoyl-2-amino-5-chloro-4-(trifluoromethyl)thiazole amides 1 were prepared as potential *Heliothis virescens* [tobacco budworm (TBW)] insecticides. The insecticidal compound **1a** (R = H) also exhibited phytotoxic and rat toxicity effects, diminishing its utility as a crop insecticide. To improve selectivity, a series of *N*-benzoyl-*N*-alkyl-2-aminothiazoles were synthesized by varying the *N*-alkyl substituent via nucleophilic substitution or preintegration into the thiazole. Introduction of an *N*-alkyl substituent such as *N*-methyl at the amide nitrogen greatly improved selectivity by eliminating phytotoxicity and reducing acute rat toxicity. In the amide *N*-methyl case, the effect of deuterium incorporation in the *N*-methyl group on TBW mortality was investigated. The NCH_3 derivative **1b** exhibited a diet incorporation LC_{50} of 109 ppm (±20 ppm) against TBW, whereas the NCD_3 derivative **1j** was inactive against TBW, suggesting a deuterium isotope effect in abstraction of the hydrogen atoms by cytochrome P_{450} enzymes.

In the course of chemical screening efforts for novel classes of insecticides, we identified a class of *N*-(2-thiazolyl)benzamides 1 with *Heliothis virescens* [tobacco budworm (TBW)] insecticidal activity in a diet incorporation assay. **1a** also exhibited undesired plant and rat toxicity



1a R=H
1b R=CH_3

1

effects, reducing its value as a crop insecticide. In attempts to improve this selectivity pattern, we investigated the effects of N-substitution of *N*-(2-thiazolyl)benzamides 1 and mechanistic aspects of N-demethylation of **1b**.

In the insecticide arena several metabolic conversions are described for NCH_3 and amide groups. For example, an N-demethylation sequence has been elucidated for chlordimeform metabolism in insects (Brooks, 1984). The first step involves MFO oxidation of the *N*-methyl group to an *N*-hydroxymethyl group, which is further oxidized to an *N*-formyl group and then hydrolyzed to an amine. For carbofuran (Furadan) and most *N*-methyl-containing insecticides, MFO demethylation leads to a nontoxic metabolite (Chio and Metcalf, 1979). In the present thiazolylamide case, however, this "detoxification" pathway produces the toxin **1a**. Two other likely metabolic processes are amide hydrolysis and a hybrid case where the *N*-methyl group in carbofuran is oxidized to a hydroxymethyl group followed by accelerated hydrolysis of the amide (Cheng and Casida, 1973; Metcalf et al., 1968). Hypothetically, **1b** may be acting as a "proinsecticide" (Drabek and Neumann, 1985) in which the NCH_3 group can be viewed as a metabolically removable protecting group for the relatively acidic amide NH that appears to impart the general toxicity associated with the *N*-thiazolylamide derivatives.

Synthesis. To prepare the thiazoles needed for this study, several synthetic routes were investigated. The most widely applicable synthesis involved three steps A–C shown in Scheme I beginning with the Hantzch thiazole synthesis (Kaye et al., 1981). Direct N-alkylation of thiazole amide **1a** was not generally feasible due to competing O-alkylation or thiazole N-alkylation (Kaye and Parris, 1952), so *N*-alkylthiazolylamides were prepared via acylation of *N*-alkylthiazoles **2**. Chlorination of the aminothiazoles **3** with *N*-chlorosuccinimide in acetonitrile gave high yields of the corresponding 5-chlorothiazoles **2**. General methods for these steps are detailed under Experimental Procedures, and specific examples prepared are presented in Table I. In two cases an alternate synthesis involving acylation of the sodium salt of the thiazole amide was used to avoid side-product formation giving **1d** and **1f** in 51% and 28% yields, respectively.

Scheme I

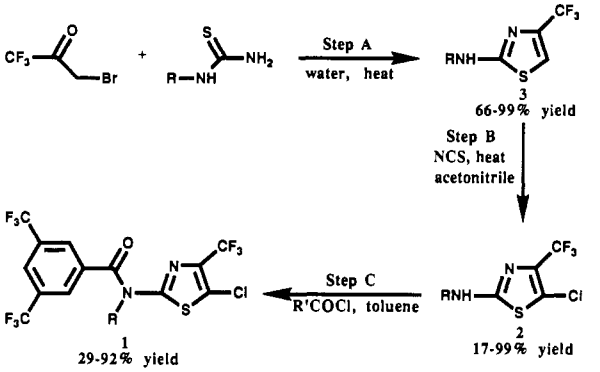


Table I. Synthesis of Thiazolylamides

no.	R	total % yield
1a	H	73
1b	methyl	70
1c	ethyl	26
1d	allyl	34
1e	isopropyl	62
1f	acetyl	17
1g	$CH_3OCH_2CH_2$	38
1h	benzyl	44
1i	phenyl	8

NCH_2–R derivatives were prepared to facilitate hydrogen abstraction, lower the activation barrier to removal of

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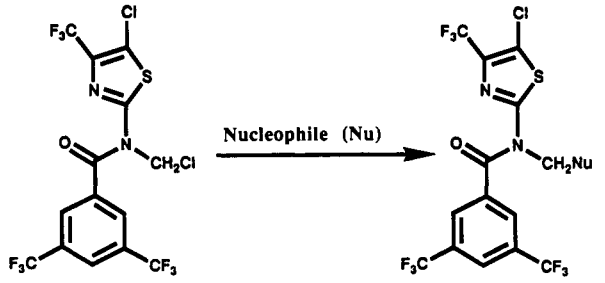
Scheme II. Method A



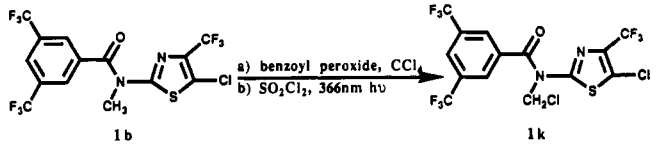
1k

Table II. Nucleophilic Reactions of 1k

nucleophile	no.	% yield	solvent
HSC_6H_5	1l	75	chloroform
KCN	1m	54	acetonitrile
KSCN	1n	86	acetone
KOAc	1o	38	acetonitrile
$3,5\text{-}(CF_3)_2C_6H_3CO_2^-$	1p[a]	12	acetonitrile
KI	1q	70	acetone

[a] Side product in the preparation of 1o.

the N-substituent, and enhance insecticidal activity. Initially, 1b was reacted with benzoyl peroxide in carbon tetrachloride (process a below) (Walter et al., 1966). The thiazole product observed was the desired *N*-chloromethyl derivative 1k, although the yield was limited to 24%. To improve the yield the reagent sulfuryl chloride was used, irradiating with 366-nm light to give a 98% yield of 1k (process b).



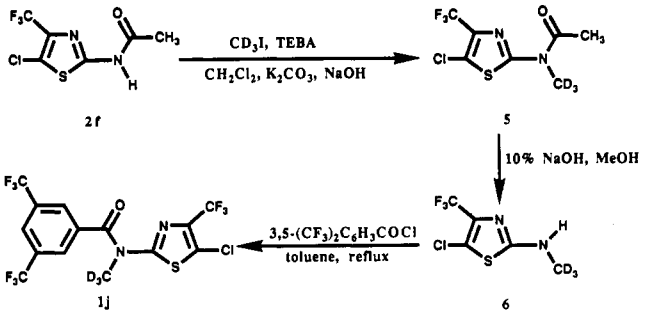
1b 1k

Although no examples of *N*-methyl chlorination reactions of this type were found in the literature, methyl sulfides have previously been chlorinated with this reagent (Truce et al., 1952). With a supply of 1k in hand, attention turned to nucleophilic reactions of the *N*-chloromethyl group.

In general, nucleophilic substitution outlined in Scheme II (Method A under Experimental Procedures) was complicated by amide hydrolysis, and its success was found to depend on the nucleophile and the solvent employed. Four nucleophiles in Table II added cleanly in an S_N2 fashion to 1k without competing amide hydrolysis (i.e., triethylammonium salt of thiophenol, potassium cyanide, potassium iodide, and potassium thiocyanate). When potassium acetate was used, benzoyl ester 1p formed as a side product. For the potassium salts 18-crown-6 (Liotta and Grisdale, 1975) was found to be an effective catalyst in either acetone or acetonitrile. Three other nucleophiles examined, sodium methylthiolate, methanol, and *tert*-butyl alcohol, caused amide hydrolysis. Due to competing amide methanolysis, methanol could not be used as a solvent for nucleophilic reactions.

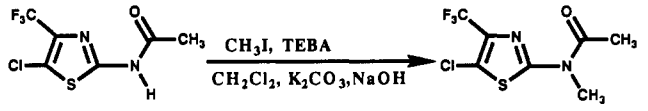
The preparation of 1j is outlined in Scheme III. Although the first step involving direct N-alkylation of thiazole amides is not usually feasible due to competing O-alkylation and thiazole ring N-alkylation, a method was found to exclusively N-alkylate *N*-acetylthiazolylamides such as 2f. When the acetyl group has no electron-withdrawing substituents, the amide nitrogen becomes the nucleophilic center. This process may be used to introduce N-substituents after which the acetamide pro-

Scheme III



2f 5 1j 6

tecting group may be removed. As shown, acetamide 2f was N-alkylated with methyl iodide under phase-transfer conditions to afford 4. None of the corresponding O-alkylated amidate was produced.



2f 4 94% yield

^1H NMR of 4 showed two equal intensity methyl peaks for the N-methyl and the acetamide methyl while ^{13}C NMR and APT showed five quaternary carbons and two methyl carbons.

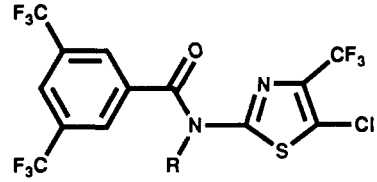
The above sequence was then repeated by using CD_3I to obtain the CD_3 analogue 5. ^1H NMR of the CD_3 analogue 5 showed one acetamide methyl peak while ^{13}C NMR and APT showed six quaternary carbons and one methyl carbon. The NCD_3 carbon appeared as a heptet centered at 34.6 ppm, directly confirming the presence of the CD_3 group. The acetamide was readily hydrolyzed with sodium hydroxide in methanol to give 6. Acylation of 6 with 3,5-bis(trifluoromethyl)benzoyl chloride yielded the desired CD_3 analogue 1j.

Biological Data. N-Substituted *N*-thiazolylbenzamides prepared in this study were tested in TBW diet incorporation insect assays and the results are summarized in Table III. Although several of the NCH_2–R derivatives were insecticidal to TBW, most were phytotoxic as well. The only two exceptions to this pattern were the *N*-benzyl derivative 1h and the *N*-methyl derivative 1b. These compounds exhibited selective activity vs TBW with no herbicidal effects.

Although no positive insecticidal controls for synergistic or antagonistic activity of piperonyl butoxide (PB) on TBW could be identified [chlordimeform was not active against TBW in our assays, and the carbamate thiodicarb (Larvin) exhibited no effect on addition of PB], several tests with 1a and 1b in the presence and absence of PB were carried out. No significant differences in insect mortality were noted with these compounds either in the presence or in the absence of PB.

Metabolic N-Demethylation Studies. In relation to the above work, it was of interest to study N-demethylation processes of 1b in TBW. Although little is known about insect cytochrome P_{450} enzymes (Brattsten and Gunderson, 1981) relative to mammalian and other systems, parallels can be drawn in biochemical mechanisms (Guengerich and Macdonald, 1984; Shea et al., 1983). As mentioned above, basic studies were conducted on N-demethylation of insecticides. In particular, stable insecticide metabolites were identified by ^{14}C-labeling studies (Crecelius and Knowles, 1976). Although many of these metabolites likely are produced by cytochrome P_{450}

Table III. TBW Insecticidal Activity of *N*-Alkyl-*N*-thiazolylbenzamides



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	R	TBW LC_{50}[a]	concn, ppm	% mort
1a	H	bc	10	100
			1	6
1b	CH_3	109 (89–129) (4.8)[d]		
1c	ethyl		100	0
1d	allyl		100	37
1e	isopropyl		100	0
1f	acetyl	3.1 (1.9–5.6) (2.8)[b]		
1g	$CH_3OCH_2CH_2$		100	12
1h	benzyl	6.1 (4.1–9.6) (2.0)		
1i	phenyl		100	0
1j	CD_3		100	0
1k	$ClCH_2$	b	100	0
1l	$PhSCH_2$		100	0
1m	$NCCH_2$	b	100	94
			50	37
			10	12
1n	$NCSCH_2$	b	50	100
			10	19
			1	0
1o	$AcOCH_2$	b	10	100
			1	5
1p	$3,5\text{-}(CF_3)_2C_6H_3CO_2CH_2$		100	0
1q	ICH_2	3.1 (1.7–5.6) (2.3)[b]		
methomyl		2.5 (2.2–2.9) (5.7)		

[a] Diet LC_{50} ppm, 95% fiducial limits, and slope or concn and % corrected mort. [b] Phytotoxic to one or more plant species. [c] Rat acute oral LD_{50} 69 mg/kg. [d] Rat acute oral LD_{50} 501 mg/kg.

enzymes, almost no mechanistic information is available for insecticides. Parallel studies in plants are similarly basic (Cabanne et al., 1987).

In contrast, metabolic N-demethylation of drugs containing *N*-methyl groups has been studied in detail in mammalian systems via intramolecular isotope effects (Testa and Jenner, 1976). These isotope effects allowed differentiation between deprotonation and hydrogen atom abstraction steps during demethylation reactions catalyzed by various heme proteins. Several postulated mechanisms were investigated by comparing NCD_3 and NCH_3 demethylations (Miwa et al., 1983).

For a deprotonation mechanism, the isotope effect is expected to be small ($k_H/k_D < 3.6$). For hydrogen atom abstraction mechanisms, large isotope effects are expected. In practice, rat liver cytochrome P_{450} exhibits $k_H/k_D < 3.1$, demonstrating a preference for deprotonation. For horseradish peroxidase $k_H/k_D > 8.72$, indicating that hydrogen atom abstraction occurs.

Deuterium-labeled thiazole **1j** was compared with **1b** to see if these isotope effects on a molecular level would result in a reduction in insect mortality in the deuterated case. Assuming the hydrogen abstraction or deprotonation steps are rate-limiting in the demethylation process and assuming N-demethylation is rapid in comparison with insect toxicity (from the liberated thiazolylamide or other metabolites) an isotope effect of ≈3–10 was expected.

This hypothesis was tested by comparing **1b** and **1j** in side by side assays against TBW. **1j** showed no significant mortality to TBW up to 500 ppm (using 16 insects per replicate). On the other hand, **1b** showed an LC_{50} value of 109 ppm (±20 ppm) in repeated tests. Thus, we can estimate the deuterium isotope effect (TBW-D_3/TBW-H_3) in TBW mortality to be 5 or greater. This isotope effect is due to the sum of different *N*-methyl oxidative processes present in TBW (assuming a negligible deuterium isotope transport effect). The possibility that other N-demethylation pathway intermediates are also intrinsically insecticidal cannot be excluded.

Conclusion. Judging from the biological data obtained on the *N*-alkylthiazolylamides **1**, the *N*-methyl and *N*-benzyl groups appear to be the best substituents for the amide nitrogen in conferring selective insecticidal activity. *N*-Alkylthiazoles with unsubstituted *N*-alkyl groups consistently exhibit reduced herbicidal effects. The remarkable difference in TBW insecticidal activity between **1b** and **1j** indicates that **1b** is acting as a proinsecticide. Deuterium incorporation studies may be a valuable mechanistic tool for investigation of other whole organism processes in plants, mammals, and insects.

EXPERIMENTAL PROCEDURES

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Thin-layer chromatography was performed on 5 × 10 cm (0.25 mm) (Merck) silica gel glass plates (5719-2), visualizing components with 254- or 366-nm UV light. Flash chromatography was performed with Aldrich columns.

Proton NMR spectra were recorded at 300 MHz on a Varian VXR or VXL-300 spectrometer. ^{19}F NMR, ^{13}C NMR, and APT spectra were recorded on the same instruments. To increase ^{13}C NMR and APT peak heights in thiazole spectra for nonprotonated carbons, D1 was set to 3 s.

Step A: Formation of Thiazolamines via the Hantzch Thiazole Synthesis (3a–i). General Procedure. To a round-bottomed flask with reflux condenser were added 1 equiv of N-substituted thiourea (10–25 g) and 50–100 mL of water. The mixture was heated to dissolve the thiourea. After complete dissolution of the thiourea, 1 equiv of 1,1,1-trifluoro-3-bromo-2-propanone was added, and the mixture was refluxed 1–18 h. The mixture was cooled, and 100 mL of dichloromethane was added followed by 1 equiv of sodium hydroxide pellets dissolved in 20 mL of water. After vigorous stirring, the product was isolated by extraction with 50 mL of dichloromethane three times, drying over magnesium sulfate, treating with 50/50 carbon/Celite (v/v), and stripping off the solvent. The crude product was recrystallized from ethyl acetate/hexanes until pure by NMR analysis (Table IV).

Step B: Chlorination of Thiazolamines with *N*-Chlorosuccinimide (2a–i). General Procedure. To a round-bottomed flask with reflux condenser were added 1 equiv of aminothiazole **3** (20 g), 50 mL of acetonitrile, and 1.1 equiv of *N*-chlorosuccinimide. The mixture was heated to reflux for 1–18 h, cooled, and stripped. The residue was partitioned between 200 mL of toluene and 200 mL of warm water. The layers were separated, and the water layer was extracted two times with 50 mL of toluene. (This extraction removes the byproduct succinimide.) The combined toluene layers were extracted with 50 mL of water, dried over magnesium sulfate, filtered, and stripped. The crude product was recrystallized from ether/hexanes. If the product was impure by NMR, it was decolorized with 50/50 carbon/Celite (v/v) and passed through a 50-mL pad of silica gel eluting with 15% ethyl acetate/hexanes (Table V).

Step C: Preparation of 1a–c, 1e, 1g–j. General Procedure. To a round-bottomed flask with reflux condenser were added 1 equiv (2 g) of aminothiazole **2**, toluene, and 1.1 equiv of acid chloride. The mixture was heated to reflux, and reaction progress was monitored by TLC over 1–18 h. On completion, the reaction was cooled and the crude product was decolorized by treating it with 50/50 carbon/Celite (v/v), pouring the mixture through a 50-mL pad of silica gel, and eluting off the product with 10% ethyl acetate/hexanes. The crude thiazolylamides were then recrystallized from ethyl acetate/hexanes until pure samples were obtained by TLC and NMR analyses.

***N*-[5-Chloro-4-(trifluoromethyl)-2-thiazolyl]-*N*-2-propenyl-3,5-bis(trifluoromethyl)benzamide (1f).** To a flask with

Table IV. ^1H, ^{13}C, and ^{19}F NMR $CDCl_3$ (ppm), Melting Points, and Analyses of 3b–i

								analyses					
								calcd			found		
	R	H-5	C-2	C-4	C-5	CF_3	mp, °C	C	H	N	C	H	N
3b	methyl	6.90	173.2	140.6q	107.2	−65.9	98–102	32.97	2.77	15.38	31.84	2.83	14.90
3c	ethyl	6.86	172.2	140.5q	107.0	−65.7	67–68	36.73	3.60	14.28	36.75	3.57	14.26
3d	allyl	6.88	172.1	140.3q	107.5	−65.6	76–77	40.38	3.39	13.45	40.48	3.39	13.44
3e	isopropyl	6.88	170.2	140.7q	107.7	−65.5	60–62	39.99	4.32	13.33	40.10	4.37	13.41
3f	acetyl	7.40	168.5	139.3q	115.3	−64.7	180–182	34.29	2.40	13.33	34.31	2.43	13.30
3g	$CH_3OCH_2CH_2$	6.84	171.4	140.5q	107.9	−65.6	oil	37.16	4.01	12.38	36.87	3.93	12.25
3h	benzyl	6.88	172.0	140.5q	107.9	−65.4	90–95	51.16	3.51	10.85	51.33	3.52	10.79
3i	phenyl	7.00	168.5	140.6q	108.9	−65.1	80–86	49.18	2.89	11.47	49.26	2.93	11.47

Table V. ^{13}C and ^{19}F NMR in $CDCl_3$ (ppm), Melting Points, and Analyses of 2a–i

							analyses					
							calcd			found		
	R	C-2	C-4	C-5	CF_3	mp, °C	C	H	N	C	H	N
2a	H	178.8	135.3q	113.0	−62.8	111–113	23.71	1.00	13.83	23.75	1.00	13.83
2b	methyl	168.8	135.2q	113.1	−62.9	109–112	27.72	1.86	12.93	27.82	1.88	12.93
2c	ethyl	178.8	135.3q	113.0	−62.8	61–63	31.25	2.62	12.15	31.33	2.63	12.07
2d	allyl	167.2	135.4q	113.7	−62.8	58–60	34.65	2.49	11.54	34.69	2.49	11.50
2e	isopropyl	165.7	135.4q	113.5	−62.7	65–67	34.36	3.30	11.45	34.42	3.32	11.40
2f	acetyl	169.4	133.7q	122.1	−62.4	195–196	29.46	1.65	11.45	29.51	1.69	11.45
2g	$CH_3OCH_2CH_2$	166.6	135.3q	113.6	−63.0	oil	32.25	3.09	10.75	32.31	3.11	10.72
2h	benzyl	167.7	134.9q	113.9	−62.6	81–85	45.14	2.75	9.57	45.18	2.74	9.45
2i	phenyl	164.4	134.8q	120.3	−62.5	80–85	43.10	2.17	10.05	43.11	2.21	10.03

reflux condenser was added (0.33 g, 8.2 mmol) (1.2 equiv) 60% sodium hydride oil emulsion. After the sodium hydride was washed with dry petroleum ether, 25 mL of dry ether was added followed by (1.80 g, 7.36 mmol) **2f**. The mixture was stirred for 3 h with occasional heating to reflux.

To the white mixture was added (2.26 g, 8.2 mmol) (1.2 equiv) 3,5-bis(trifluoromethyl)benzoyl chloride. The mixture was stirred overnight with occasional heating to reflux to wash material off of the flask walls. Reaction progress was monitored by TLC on silica gel plates with 15% ethyl acetate/hexanes.

The product mixture was poured through a 100-mL pad of silica gel eluting with 300 mL of 5% ethyl acetate/hexanes followed by 300 mL of 10% ethyl acetate/hexanes and stripped. The product was purified by flash chromatography on 200 mL of silica gel eluting with 500 mL of 10% ethyl acetate/hexanes followed by 500 mL of 20% ethyl acetate/hexanes (collecting 20-mL fractions). Fractions 23–30 contained 0.98 g of **1f**, a clear viscous oil. Fractions 3–12 contained 0.31 g of **1a**.

***N*-Acetyl-*N*-[5-chloro-4-(trifluoromethyl)-2-thiazolyl]-3,5-bis(trifluoromethyl)benzamide (1d).** To a flask with reflux condenser was added (0.54 g, 13.6 mmol) (1.1 equiv) 60% sodium hydride oil emulsion. After the sodium hydride was washed with dry petroleum ether, 50 mL of dry tetrahydrofuran (distilled from a purple solution of benzophenone ketil) was added followed by (3.00 g, 12.0 mmol) **2d**. While stirring for 3 h, the mixture turned dark brown. To the mixture was added (3.76 g, 13.6 mmol) (1.1 equiv) 3,5-bis(trifluoromethyl)benzoyl chloride. A slight exotherm was observed, and the mixture was stirred overnight (18 h). The crude product was poured through a 100-mL pad of silica gel eluting with 300 mL of hexanes. After the solvent was removed, 4.51 g of a viscous orange oil was obtained. The product was purified by flash chromatography on 150 mL of silica gel eluting with 2.5% ethyl acetate/hexanes (collecting 20-mL fractions). Fractions 6–15 contained 2.97 g of the product which slowly crystallized on standing. The product was recrystallized from 3 mL of hexanes to give 2.43 g of large clear plates of **1d**.

***N*-[5-Chloro-4-(trifluoromethyl)-2-thiazolyl]-*N*-(chloromethyl)-3,5-bis(trifluoromethyl)benzamide (1k).** To a flask with addition funnel, thermometer, and reflux condenser were added (8.35 g, 18.3 mmol) **1b** and 100 mL of carbon tetrachloride. The reaction was heated to reflux, and a General Electric H100-BL4 366-nm mercury lamp was situated 1 cm from the reaction flask with surrounding foil shielding. Sulfuryl chloride (12.0 mL, 148 mmol) (8.1 equiv) was added dropwise from the addition funnel while the reaction temperature was maintained at 77 °C with the lamp on. Reaction progress was monitored periodically by taking NMRs of aliquots of the reaction mixture.

After refluxing for 2 days, the reaction mixture was cooled and stripped on a water aspirator rotary evaporator followed by further stripping on a vacuum pump to remove the last traces of reagent. Due to static charges, the product crystals are difficult to manipulate. To obtain a weighable powder, petroleum ether was added and slowly stripped off to induce the formation of larger crystals: 8.90 g of **1k** was obtained.

Method A: Nucleophilic Additions of 1k, Preparation of 1l–q. General Procedure. To a round-bottomed flask under nitrogen were added (1.00 g, 2.04 mmol) **1k**, 75 mL of solvent (shown in Table II), and 2.24 mmol of the nucleophile [and 18-crown-6 (0.54 g, 2.04 mmol) for the potassium salts]. The mixture was stirred at room temperature, and reaction progress was monitored by TLC (silica gel 15% ethyl acetate/hexanes). On completion of the reaction, the solvent was stripped and the residue was passed through a 50-mL pad of silica gel eluting with 200 mL of 10% ethyl acetate/hexanes. After the solvent was removed, the product was recrystallized if it was a solid (Table VI).

***N*-[5-Chloro-4-(trifluoromethyl)-2-thiazolyl]-*N*-methylacetamide (4).** To a 250-mL round-bottomed flask were added **2f** (1.00 g, 4.09 mmol), potassium carbonate (2.00 g, 14.5 mmol), 10 mL of water, 15 mL of dichloromethane, triethylbenzylammonium chloride (1.00 g, 4.39 mmol), iodomethane (5.00 mL, 80.3 mmol), and 5 mL of 10% sodium hydroxide. The mixture was stirred vigorously overnight. The dichloromethane layer was stripped, and the residue was dissolved in 20 mL of ether. The ether solution was extracted with 20 mL of 10% aqueous hydrochloric acid. The resulting ether layer was stripped, and the residue was dissolved in 4 mL of chloroform. After addition of 10 mL of petroleum ether, the solution became cloudy, resulting in crystal formation: yield, 1.00 g of yellowish crystals of **4**; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3 H), 2.36 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ −62.8 (s, 3 F); ^{13}C NMR ($CDCl_3$) δ 171.5 (s, CO), 156.7 (s, C2), 134.5 (q, C4), 124.0 (s, C5), 121.4 (q, CF_3), 35.3 (s, NCH_3), 23.4 (s, CH_3).

***N*-[5-Chloro-4-(trifluoromethyl)-2-thiazolyl]-*N*-[*methyl-d*$_3$]acetamide (5).** To a 250-mL round-bottomed flask were added **2f** (2.00 g, 8.18 mmol), potassium carbonate (2.00 g, 14.5 mmol), iodomethane-d_3 (10.0 g, 69.0 mmol) (99 atom % D), triethylbenzylammonium chloride (1.00 g, 4.39 mmol), 20 mL of water, 20 mL of dichloromethane, and 5 mL of 10% sodium hydroxide. The mixture was stirred vigorously overnight. The

Table VI. ^{13}C NMR $CDCl_3$ (ppm), Melting Points, and Analyses of 1a-q

	R	$^{13}C(C{=}O)$	mp, °C	analyses					
				calcd			found		
				C	H	N	C	H	N
1a	H	163.2	154–158	35.27	0.91	6.33	35.57	0.89	6.06
1b	methyl	167.6	76–78	36.82	1.32	6.13	36.75	1.33	6.09
1c	ethyl	167.8	83–84	38.27	1.71	5.95	38.45	1.76	5.92
1d	allyl	168.2	67–69	39.81	1.67	5.80	39.95	1.61	5.89
1e	isopropyl	168.3	98–99	39.64	2.08	5.78	39.73	2.04	5.72
1f	acetyl	168.2	oil	37.17	1.25	5.78	37.00	1.25	5.80
1g	$CH_3OCH_2CH_2$	169.0	78–79	38.37	2.01	5.59	38.55	2.03	5.59
1h	benzyl	168.5	105–109	45.08	1.89	5.26	45.16	2.14	5.11
1i	phenyl	166.4	118–119	43.99	1.55	5.40	43.77	1.54	5.33
1j	CD_3	167.6	88–90						
1k	$ClCH_2$	167.6	68–69	34.23	1.03	5.70	34.42	1.00	5.74
1l	$PhSCH_2$	167.6	89–91	42.52	1.78	4.96	42.73	1.77	4.95
1m	$NCCH_2$	166.7	128–130	37.40	1.05	8.72	36.82	1.05	8.20
1n	$NCSCH_2$	167.1	oil	35.06	0.98	8.18	35.40	1.13	8.18
1o	$AcOCH_2$	168.6	oil	37.33	1.57	5.44	37.14	1.60	5.83
1p	$3,5\text{-}(CF_3)_2C_6H_3CO_2CH_2$	168.1	42–46	38.75	1.13	3.93	38.89	1.18	3.82
1q	ICH_2	167.5	54–55	28.86	0.87	4.81	29.60	0.96	4.81

aqueous layer was washed with 20 mL of dichloromethane two times. The combined dichloromethane layer was extracted with 25 mL of 10% aqueous hydrochloric acid two times. On stripping off the dichloromethane, 2.06 g of white crystals of **5** was obtained: ^1H NMR ($CDCl_3$) δ 2.34 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ −62.8 (s, 3 F); ^{13}C NMR ($CDCl_3$) δ 171.5 (s, CO), 156.7 (s, C2), 134.5 (q, C4), 123.9 (s, C5), 121.4 (q, CF_3), 34.6 (h, CD_3), 23.3 (s, CH_3).

5-Chloro-*N*-[*methyl-d*$_3$]-4-(trifluoromethyl)-2-thiazolamine (6). To a round-bottomed flask with reflux condenser were added **5** (1.50 g, 5.73 mmol), 25 mL of methanol, and 10% aqueous sodium hydroxide (5 mL, 12.5 mmol). The flask was heated to reflux for 5 min and then cooled; 200 mL of water was added, and the white crystals formed were filtered off, dissolved in 20 mL of chloroform, and extracted with 10 mL of water. The chloroform layer was stripped to give 0.99 g of white crystals of **6**: ^1H NMR ($CDCl_3$) δ 7.74 (br s, 1 H); ^{19}F NMR ($CDCl_3$) δ −62.9 (s, 3 F); ^{13}C NMR ($CDCl_3$) δ 168.9 (s, C2), 135.4 (q, C4), 120.3 (q, CF_3), 113.0 (s, C5), 31.3 (h, CD_3).

Tobacco Budworm Diet Incorporation Assay Procedure. Test compounds were incorporated into an agar-based synthetic insect diet described by Marrone (1985). Acetone dilutions of test compounds and standards were added to 50-mL polypropylene centrifuge tubes each containing 200 mg of the cellulose component of the insect diet. After the acetone was evaporated under a fume hood, the compounds and cellulose were suspended in 6 mL of deionized water. To each tube was added 24 mL of liquid insect diet from which the cellulose and 20% of the water had been withheld. The liquid diet was kept in 500-mL squeeze bottles, and the temperature was maintained at 45 °C in a water bath. Compounds and cellulose were thoroughly incorporated into the diet with a hand-held BioVortexer. Diet was poured into 1-mL wells of 96-well insect diet trays (Jarold Manufacturing, St. Louis, MO) and allowed to cool and gel.

A single neonate *H. virescens* larva was placed into each well by using a small camel's hair brush. A thin sheet of Mylar (Clear Lam Packaging Inc., Elk Grove Village, IL) was tacked over each tray with an electric tacking iron (Seal Products, Inc., Naugatuck, CT), and an aeration hole was carefully punched over each well with an insect pin. Trays were held at room temperature for 6 days at which time mortality was assessed.

For each concentration of compound or standard 16–20 larvae were tested. In some cases LC_{50} values with 95% fiducial limits and slopes were determined via SAS probit analysis (Statistical Analysis System, SAS Institute, Cary, NC). In all other cases Abbott's formula (Abbott, 1925) was used to calculate percent corrected mortality for each treatment concentration.

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