Methylene Group Modifications of the *N*-(Isothiazol-5-yl)phenylacetamides. Synthesis and Insecticidal Activity

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It has been shown that oxidation at the α-carbon of *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide (**1**) is conveniently brought about using dimethylformamide dimethylacetal to give *N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(dimethylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (**2**), which has served as a common starting point for a variety of functional group transformations. These transformations were found to proceed in moderate to good yields to give derivatives of **1** that retained much of the efficacy associated with the parent amide and have allowed for an expansion of the SAR to be developed. Examples of enamines, enols, enol (thio)-ethers, oximes, and hydrazones were prepared. In particular, the enamines derived from low molecular weight amines and amino acids were most active as broad-spectrum insecticides and were found to be even more active than **1** on root-knot nematode.

Keywords: *Isothiazolylatropamide; isothiazolylglyoxylamide; isothiazolylphenylacetamide; enol-ether; oxime; synthesis; insect control*

INTRODUCTION

The mitochondrial electron transport (MET) inhibitor **1** (Figure 1) was recently disclosed as a broad-spectrum insecticide and acaricide having potential agricultural use (Hackler et al., 1995). In a previous paper we described the syntheses of various *N*-alkylated derivatives of **1**, their efficacies on insects, and their improved safety toward nontarget organisms (Samaritoni et al., 1997). As part of a continued effort to define the structure−activity relationship, various derivatives of **1** that featured substitution at the α-methylene position of the acetamide moiety (variations of X) were targeted. It was of particular interest to us to examine derivatives that represented oxidations at the α position such as enamines, enols, enol (thio)ethers, oximes, and hydrazones. Functionalities such as these have received little or no attention in related MET inhibitors such as the *N*-benzylpyrazolecarboxamides (Okada et al., 1991) and thus may provide an opportunity to enhance efficacy or selectivity.

MATERIALS AND METHODS

Chemistry. Melting points are uncorrected. All reagents purchased were used without further purification. Solvents were dried using 3 Å molecular sieves. Chromatography was performed using 230−400 mesh ASTM silica gel 60 from EM Science, Darmstadt, Germany. Proton NMR spectra were obtained on a Varian Gemini 300 spectrometer using deuteriochloroform as solvent unless otherwise indicated and are reported in parts per million (*δ*) downfield from tetramethylsilane as internal reference. Infrared spectra were obtained on a Bio-Rad FTS-40 spectrophotometer using potassium bromide pellets or as neat oils and are reported as wavenumbers (cm^{-1}). Mass spectra were obtained on a Hewlett-Packard

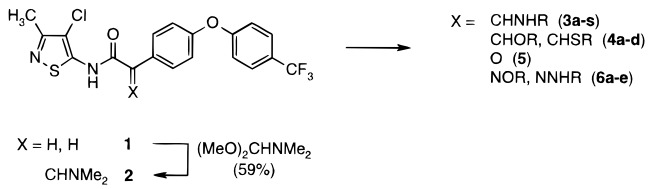

Figure 1.

Model 5989A mass spectrometer using the electron impact (EI), chemical ionization (CI), fast atom bombardment (FAB), chemical desorption (CD), or electrospray (ES) techniques and are reported as *m*/*z*. Microanalyses were performed by Midwest Microlab of Indianapolis.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-*β*-(dimethylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (2).** A solution of 300 mg (0.703 mmol) of the amide **1** (Hackler et al., 1995) and 170 mg (1.41 mmol) of dimethylformamide dimethylacetal in 5 mL of toluene was heated under reflux for 7 h, cooled, and concentrated to dryness. The residue was then triturated under ethyl ether to afford 200 mg (59%) of **2** as a tan solid, mp 194−200 °C: ^{1}H NMR *δ* 2.34 (s, 3H), 2.78 (br s, 6H), 7.06 (d, 2H, J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.61 (d, 2H, J = 8.8 Hz), 7.73 (s, 1H); IR (KBr) 1667, 3283 cm^{-1}; MS (EI) *m*/*z* 483 ([M + 2]$^+$, 31), 481 (M$^+$, 83), 334 (45), 43 (100).

Anal. Calcd for $C_{22}H_{19}ClF_3N_3O_2S$: C, 54.83; H, 3.97; N, 8.72. Found: C, 55.09; H, 4.08; N, 8.63.

General Procedure for the Preparation of 3a−l, 3n, and 3q−s. A solution of **2** in 10−30% aqueous tetrahydrofuran (0.05−0.15 M) was stirred with the amine hydrochloride (tosic acid salt in the case of **3l**) and was then poured onto ice water or concentrated to remove most of the tetrahydrofuran. The resulting aqueous mixture was treated with saturated sodium bicarbonate and extracted with ethyl acetate, and the extract was dried over magnesium sulfate and concentrated to give crude **3**, which was purified by recrystallization or chromatography. In cases where chromatographic separation of *E* and *Z* isomers was achieved, the *Z* isomer was eluted first from the column. Attempted recrystallizations invariably resulted in equlibrations of *E* and *Z* isomers. Table 1 contains infrared,

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10.1021/jf990095s CCC: $18.00
Published on Web 07/28/1999

mass spectroscopic, and analytical information. Table 2 contains specific procedural and experimental details and NMR data (given for the predominant isomer).

***N*-[(*E,Z*)-β-[(4-Chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]styryl]glycine (3m).** To a solution of 1.30 g (2.16 mmol) of the benzyl ester **3l** in 15 mL of methanol was added 0.300 g (2.17 mmol) of potassium carbonate followed by 3 mL of water. After 6 h, the mixture was poured onto ice water, which was then adjusted to pH 3 with dilute hydrochloric acid. The contents were extracted two times with ethyl acetate, and the combined extracts were washed with brine and dried ($MgSO_4$). Concentration gave 1.0 g of a solid, which was triturated under heptane/ethyl acetate to afford 0.68 g, mp 177−83 °C. This material was recrystallized from heptane and ethyl acetate (2:1) giving 0.27 g of **3m** (see Tables 1 and 2).

***N*-[(*E,Z*)-β-[(4-Chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]styryl]glycine, Sodium Salt (3o).** To a mixture of 0.185 g (0.361 mmol) of the acid **3m** in 5 mL of methanol was added 0.18 mL (0.36 mmol) of 2.0 N sodium hydroxide. After 3 h, the precipitate was collected and dried in vacuo at 120 °C for 3 h to afford 0.10 g (50%) of the sodium salt of **3m** as its monohydrate and as a 1:1 mixture of *Z* and *E* isomers in DMSO-d_6 (the methylene group is not observed but is believed to be under the broad water signal of the proton NMR spectrum, see Tables 1 and 2).

***N*-[(*E,Z*)-β-[(4-Chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]styryl]-β-alanine (3p).** A mixture of 0.770 g (1.39 mmol) of the ester **3n** and 0.390 g (2.82 mmol) of potassium carbonate in 15 mL of methanol, 5 mL of tetrahydrofuran, and 5 mL of water was stirred at room temperature for 24 h. The solution was concentrated, and the resulting mixture was partitioned between ethyl acetate and water. The pH of the aqueous phase was adjusted to 4 with 0.5 N hydrochloric acid, and the organic layer was then washed with brine and was dried ($MgSO_4$). Concentration gave a solid, which was triturated under heptane/ethyl acetate to afford 410 mg of crude acid, which was recrystallized from ethyl acetate to give 250 mg (34%) of **3p** (see Tables 1 and 2).

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-β-hydroxy-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (4a).** A solution of 0.40 g (0.83 mmol) of **2** and 0.080 g (0.83 mmol) of methanesulfonic acid in 25 mL of absolute methanol was heated at reflux for 3.5 h and allowed to cool. The methanol was removed in vacuo, and the resulting oil was partitioned between ethyl ether and aqueous sodium bicarbonate. The organic layer was washed with brine and was dried ($MgSO_4$). Concentration gave a residue that was chromatographed eluting with dichloromethane initially and progressing to 1:1 dichloromethane/ethyl acetate to afford 123 mg (33%) of **4a** as a white solid, mp 182−83.5 °C: ^{1}H NMR δ 2.38 (s, 3H), 7.12 (d, 2H, J = 8.3 Hz), 7.17 (d, 2H, J = 8.8 Hz), 7.32 (d, 1H, J = 12.5 Hz), 7.37 (d, 2H, J = 8.8 Hz), 7.63 (d, 2H, J = 8.6 Hz), 8.05 (s, 1H), 12.52 (d, 1H, J = 12.5 Hz); MS (CI) *m/z* 457 ([M + H + 2]$^+$, 14), 455 ([M + H]$^+$, 37), 306 (22), 149 (100).

Anal. Calcd for $C_{20}H_{14}ClF_3N_2O_3S$: C, 52.81; H, 3.10; N, 6.16. Found: C, 52.91; H, 3.16; N, 6.09.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-β-methoxy-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (4b).** To a suspension of 40.7 mg (1.02 mmol) of 60% sodium hydride−mineral oil dispersion in 0.5 mL of dry tetrahydrofuran cooled in ice water was added dropwise a solution of 0.460 g (1.02 mmol) of **4a** in 5 mL of THF. After 20 min, 0.60 mL (9.6 mmol) of methyl iodide was added. The contents were stirred for 40 h and were added to 60 mL of ice water that had been treated with 1.02 mL of 1.0 N hydrochloric acid. The mixture was extracted once with ethyl ether, and the extract was washed once with brine and dried ($MgSO_4$). Concentration gave 0.4 g, which was chromatographed using 4:1 heptane/ethyl acetate as the eluant to afford 0.24 g (50%) of **4b** as a solid, mp 153.5−6.5 °C: ^{1}H NMR δ 2.34 (s, 3H), 4.15 (s, 3H), 6.94 (s, 1H), 7.03−7.09 (m, 4H), 7.37 (d, 2H, J = 8.6 Hz), 7.58 (d, 2H, J = 8.6 Hz), 10.3 (br s, 1H); MS (CI) *m/z* 471 ([M + 2 + H]$^+$, 39), 469 ([M + H]$^+$, 100), 321 (54).

Anal. Calcd for $C_{21}H_{16}ClF_3N_2O_3S$: C, 53.79; H, 3.44; N, 5.98; S, 6.84. Found: C, 54.04; H, 3.77; N, 5.91; S, 6.63.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-β-isopropoxy-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (4c).** To a suspension of 0.045 g (1.1 mmol) of 60% sodium hydride−mineral oil dispersion in 2 mL of dry tetrahydrofuran was added dropwise a solution of 0.51 g (1.1 mmol) of **4a** in 10 mL of THF. After 0.5 h, 0.6 mL (6 mmol) of isopropyl iodide was then added. The contents were heated at 35 °C for 20 h and then at 45 °C for 9 h. Upon cooling the mixture was added to ice water that had been treated with 1.1 mL of 1.0 N hydrochloric acid. It was then extracted with ethyl acetate, and the extract was washed once with brine and dried ($MgSO_4$). Concentration gave 0.59 g of a brown oil, which was chromatographed eluting with 9:1 heptane/ethyl acetate and progressing to 4:1 to afford 220 mg (40%) of **4c** as a solid, mp 111.5−114 °C: ^{1}H NMR δ 1.28 (d, 6H, J = 6.4 Hz), 2.33 (s, 3H), 4.44 (m, 1H, J = 6.4 Hz), 7.02−7.10 (m, 5H), 7.39 (d, 2H, J = 9.3 Hz), 7.58 (d, 2H, J = 7.8 Hz), 10.52 (br s, 1H); IR (KBr) 1580, 1656, 2979, 3316 cm^{-1}; MS (EI) *m/z* 498 ([M + 2]$^+$, 6), 496 (M$^+$, 13), 279 (100).

Anal. Calcd for $C_{23}H_{20}ClF_3N_2O_3S$: C, 55.59; H, 4.06; N, 5.64; S, 6.45. Found: C, 57.44; H, 3.94; N, 5.67; S, 6.02.

β-(Butylthio)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide (4d). A mixture of 0.454 g (1.00 mmol) of **4a**, 90.2 mg (1.00 mmol) of *n*-butanethiol, and 0.190 g (1.00 mmol) of *p*-toluenesulfonic acid monohydrate in 10 mL of benzene was heated at 50 °C for 3 h and then at 60 °C for 8 h. Upon cooling the contents were diluted with ethyl acetate, washed three times with saturated sodium bicarbonate and once with brine, and dried ($MgSO_4$) and decolorized with carbon black. Concentration gave 500 mg, which was chromatographed eluting with dichloromethane and progressing to 97:3 dichloromethane/ethyl acetate to afford 180 mg (34%) of **4d** as a solid, mp 119.5−122.5 °C: ^{1}H NMR δ 0.90 (t, 3H, J = 7.4 Hz), 1.40 (m, 2H, J = 7.5 Hz), 1.66 (m, 2H, J = 7.5 Hz), 2.34 (s, 3H), 2.85 (t, 2H, J = 7.4 Hz), 7.10 (d, 2H, J = 8.5 Hz), 7.18 (d, 2H, J = 8.7 Hz), 7.37 (d, 2H, J = 8.6 Hz), 7.61 (d, 2H, J = 8.4 Hz), 7.94 (br s, 1H), 8.10 (s, 1H); IR (KBr) 1557, 1662, 3384 cm^{-1}; MS (CI) *m/z* 529 ([M + H + 2]$^+$, 29), 527 ([M + H]$^+$ 60), 379 (43), 57 (100).

Anal. Calcd for $C_{24}H_{22}ClF_3N_2O_2S_2$: C, 54.69; H, 4.21; N, 5.32; S, 12.16. Found: C, 54.45; H, 4.35; N, 5.22; S, 11.98.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]glyoxylamide (5).** To a mixture of 6.00 g (12.4 mmol) of **2** and 5.30 g (24.8 mmol) of sodium periodate in 45 mL of tetrahydrofuran cooled in ice water was added dropwise 23 mL of water. The mixture was allowed to warm to room temperature and stirred for 24 h. It was then filtered, and the filtrate was concentrated to remove most of the THF and then diluted with ethyl acetate and brine. The organic layer was washed with brine, dried ($MgSO_4$), and decolorized (carbon black). Concentration gave 6.1 g of a golden solid, which was flashed chromatographed eluting with dichloromethane to afford 4.36 g (80%) of **5** as a yellow solid, mp 130−2 °C: ^{1}H NMR δ 2.44 (s, 3H), 7.07 (d, 2H, J = 9.1 Hz), 7.16 (d, 2H, J = 8.3 Hz), 7.66 (d, 2H, J = 8.9 Hz), 8.53 (d, 2H, J = 9.1 Hz), 9.83 (br s, 1H); IR (KBr) 1675, 3357 cm^{-1}; MS (EI) *m/z* 442 ([M + 2]$^+$, 3), 440 (M$^+$, 7), 265 (100).

Anal. Calcd for $C_{19}H_{12}ClF_3N_2O_3S$: C, 51.76; H, 2.74; N, 6.36. Found: C, 51.58; H, 2.72; N, 6.19.

General Procedure for the Preparation of 6a−d. A solution of **5** in ethanol (0.10 M) and the amine hydrochloride was heated at 60 °C and then concentrated in vacuo to give **6**. Table 1 contains infrared, mass spectroscopic, and analytical information. Table 2 contains specific procedural and experimental details and NMR data.

***N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]glyoxylamide 2-Hydrazone (6e) and *N*-(4-Chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]glyoxylamide 2,2′-Azine (8).** A solution of 0.250 g (0.567 mmol) of **5**, 0.100 g (1.35 mmol) of acetic hydrazide, and 3.28 mL (1.35 mmol) of a 0.41 M ethanolic solution of dry hydrogen chloride gas in 10 mL of

Table 1. Microanalytical, Infrared, and Mass Spectral Data of 3 and 6

compd	X	% C (theory)	% H (theory)	% N (theory)	% S (theory)	IR (ν)	MS (m/z)
3a	(*E*,*Z*)-CHNHMe	54.17 (53.90)	3.70 (3.66)	8.82 (8.98)		(KBr) 1652, 3391, 3439	(EI) 469 ([M + 2]$^+$, 8), 467 (M$^+$, 20), 320 (23), 130 (32), 45 (100)
3b	(*Z*)-CHNHEt	54.88 (54.83)	4.01 (3.97)	8.61 (8.72)	6.56 (6.65)	(KBr) 1653, 3283, 3388	(CI) 484 ([M + H + 2]$^+$, 33), 482 ([M + H]$^+$, 86), 462 (38), 334 (100), 175 (62)
3c	(*E*)-CHNHEt	55.01 (54.83)	4.07 (3.97)	8.74 (8.72)	6.59 (6.65)	(KBr) 1582, 1666, 3300, 3389	(CI) 484 ([M + H + 2]$^+$, 3), 482 ([M + H]$^+$, 8), 462 (4), 334 (24), 308 (60), 288 (72), 175 (100)
3d	(*Z*)-CHNH$_2$	52.69 (52.96)	3.32 (3.33)	8.97 (9.26)		(KBr) 1657, 3292, 3408	(CI) 456 ([M + H + 2]$^+$, 16), 454 ([M + H]$^+$, 40), 306 (37), 192 (100), 149 (89)
3e	(*E*)-CHNH$_2$	52.95 (52.96)	3.26 (3.33)	9.18 (9.26)		(KBr) 1565, 3219, 3313, 3387	(CI) 456 ([M + H + 2]$^+$, 39), 454 ([M + H]$^+$, 100), 306 (88)
3f	(*Z*)-CHNH*n*-PrEt	55.96 (55.70)	4.06 (4.27)	8.37 (8.47)		(KBr) 1655, 3296, 3390	(CD) 498 ([M + H + 2]$^+$, 41), 496 ([M + H]$^+$, 99), 476 (40), 348 (100), 175 (41)
3g	(*E*)-CHNH*n*-PrEt	55.32 (55.70)	4.38 (4.27)	8.27 (8.47)	6.64 (6.47)	(KBr) 1588, 1663, 3301, 3390	(CD) 498 ([M + H + 2]$^+$, 36), 496 ([M + H]$^+$, 79), 476 (42), 348 (100), 175 (44)
3h	(*Z*)-CHNH*c*-C$_3$H$_5$	56.02 (55.92)	3.72 (3.88)	8.56 (8.51)	6.40 (6.49)	(KBr) 1655, 3389	(EI) 495 ([M + 2]$^+$, 2), 493 (M$^+$, 6), 426 (11), 319 (100), 251 (26)
3i	(*E*,*Z*)-CHNH*t*-Bu	56.39 (56.52)	4.75 (4.54)	8.07 (8.24)	6.13 (6.29)	(KBr) 1587, 1650, 3390	(EI) 511 ([M + 2]$^+$, 11), 509 (M$^+$, 23), 362 (100), 306 (53), 278 (67)
3j	(*E*,*Z*)-CHNHCH$_2$CO$_2$Me	52.71 (52.51)	3.41 (3.64)	8.05 (7.99)		(KBr) 1594, 1660, 1751, 3388	(EI) 527 ([M + 2]$^+$, 4), 525 (M$^+$, 11), 378 (100)
3k	(*Z*)-CHNHCH$_2$CH$_2$CF=CF$_2$	51.49 (51.29)	3.55 (3.23)	7.21 (7.48)	5.25 (5.71)	(KBr) 1587, 1655, 3383	(CI) 564 ([M + H + 2]$^+$, 36), 562 ([M + H]$^+$, 73), 414 (100), 175 (65), 149 (64)
3l	(*E*,*Z*)-CHNHCH$_2$CO$_2$CH$_2$Ph	57.62 (57.85)	3.86 (3.85)	7.07 (6.98)		(neat) 1595, 1658, 1747, 3388	(EI) 603 ([M + 2]$^+$, 1), 601 (M$^+$, 3), 454 (14), 91 (100)
3m	(*E*,*Z*)-CHNHCH$_2$CO$_2$H	51.62 (51.62)	3.37 (3.35)	8.16 (8.21)		(KBr) 1584, 1654, 1746, 2587−3044, 3384	(EI) 513 ([M + 2]$^+$, 4), 511 (M$^+$, 9), 467 (10), 364 (100), 320 (93), 251 (49), 146 (60), 130 (91)
3n	(*E*,*Z*)-CHNHCH$_2$CH$_2$CO$_2$Et	54.23 (54.20)	4.37 (4.18)	7.71 (7.58)	5.35 (5.79)	(KBr) 1594, 1657, 1731, 3275, 3393	(EI) 555 ([M + 2]$^+$, 1), 553 (M$^+$, 2), 406 (61), 265 (100)
3o	(*E*,*Z*)-CHNHCH$_2$CO$_2$Na	47.59 (47.87)	3.33 (3.29)	7.60 (7.61)			(EI) 551 (M$^+$, 22), 278 (23), 251 (54), 148 (100)
3p	(*E*,*Z*)-CHNHCH$_2$CH$_2$CO$_2$H	52.53 (52.51)	3.64 (3.51)	7.99 (7.99)	6.10 (5.92)		(EI) 526 ([M + H]$^+$, 7), 378 (100), 306 (85)
3q	(*E*,*Z*)-CHNHPh	59.19 (58.93)	3.61 (3.61)	8.05 (7.93)	6.30 (6.05)	(KBr) 1556, 1653, 3050, 3386	(EI) 531 ([M + 2]$^+$, 6), 529 (M$^+$, 18), 382 (100), 265 (34)
3r	CHNHOMe	52.13 (52.12)	3.66 (3.54)	8.60 (8.68)		(neat) 1565, 1684, 3265	(EI) 485 ([M + 2]$^+$, 4), 483 (M$^+$, 10), 309 (100)
3s	(*E*,*Z*)-CHNHOH	51.04 (51.12)	2.96 (3.22)	9.01 (8.94)	6.72 (6.82)		(EI) 471 ([M + 2]$^+$, 5), 469 (M$^+$, 14), 277 (100)
6a	NOMe	51.31 (51.12)	3.33 (3.22)	9.00 (8.94)		(neat) 1563, 1678	(CI) 472 ([M + H + 2]$^+$, 16), 470 ([M + H]$^+$, 37), 264 (81), 175 (100)
6b	NOCH$_2$CH=CH$_2$	53.23 (53.28)	3.50 (3.46)	8.46 (8.47)		(neat) 1563, 1679	(CI) 498 ([M + H + 2]$^+$, 9), 496 ([M + H]$^+$, 18), 364 (41), 264 (42), 181 (80), 91 (100)
6c	NNHCONH$_2$	48.04 (48.24)	3.16 (3.04)	14.02 (14.07)	6.34 (6.44)	(KBr) 1560, 1588, 1682, 1722, 3511	(ES) 500 ([M + H + 2]$^+$, 32), 498 ([M + H]$^+$, 100), 481 (28), 454 (15), 437 (17)
6d	NNHTs	51.30 (51.27)	3.60 (3.31)	9.00 (9.20)	10.43 (10.53)	(KBr) 1680, 3250	(EI) 424 ([M − TsNHN]$^+$, 2), 265 (38), 139 (89), 91 (100)

Table 2. Experimental and Proton NMR Data of 3 and 6

compd	amine·HCl (equiv)	°C/h	purifn/ratio *(Z:E)*	% yield	mp (°C)	^{1}H NMR δ ($CDCl_3$)
3a	CH_3NH_2 (44)	50/20	recryst (hept/EtOAc) 89:11	53	150−153	2.36 (s, 3H), 3.10 (d, 3H, J = 5.3 Hz), 6.85 (d, 1H, J = 13.3 Hz), 7.08−7.14 (m, 4H), 7.35 (d, 2H, J = 8.9 Hz), 7.64 (d, 2H, J = 8.9 Hz), 7.96 (s, 1H), 8.73 (br m, 1H)
3b	$CH_3CH_2NH_2$ (6)	50/26	SiO_2 (3/2 hept/EtOAc) 100:0	54	118−123	1.30 (t, 3H, J = 7.9 Hz), 2.37 (s, 3H), 3.34 (m, 2H), 6.88 (d, 1H, J = 12.4 Hz), 7.08−7.14 (m, 4H), 7.35 (d, 2H, J = 9.6 Hz), 7.62 (d, 2H, J = 9.1 Hz), 7.97 (s, 1H), 8.84 (br m, 1H)
3c	$CH_3CH_2NH_2$ (6)	50/26	SiO_2 (3/2 hept/EtOAc) 11:89	16	133−137	1.20 (t, 3H, J = 6.9 Hz), 2.35 (s, 3H), 3.30 (m, 2H), 4.61 (br m, 1H), 7.14 (d, 2H, J = 7.8 Hz), 7.22 (d, 2H, J = 7.8 Hz), 7.36 (d, 2H, J = 7.8 Hz), 7.64 (d, 2H, J = 8.8 Hz), 7.82 (d, 1H, J = 13.2 Hz)
3d	NH_3 (9)	23/20	SiO_2 (CH_2Cl_2/EtOAc)	31	160−165	2.37 (s, 3H), 6.75 (br s, 2H), 6.96 (t, 1H, J = 10.8 Hz), 7.08−7.14 (m, 4H), 7.35 (d, 2H, J = 8.7 Hz), 7.61 (d, 2H, J = 8.9 Hz), 7.99 (s, 1H)
3e	NH_3 (9)	23/20	SiO_2 (CH_2Cl_2/EtOAc) 0:100	33	183−187	2.36 (s, 3H), 4.60 (br d, 1H, J = 11.1 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 7.8 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.7 Hz), 7.74 (s, 1H), 7.88 (t, 1H, J = 11.3 Hz)
3f	n-$PrNH_2$ (5)	45/20, 55/7	SiO_2 (hept/EtOAc) recryst (hept/EtOAc) 90:10	37	117−123	1.00 (t, 3H, J = 7.6 Hz), 1.66 (m, 2H, J = 7.4 Hz), 2.37 (s, 3H), 3.33 (m, 2H, J = 6.7 Hz), 6.86 (d, 1H, J = 12.2 Hz), 7.06−7.11 (m, 4H), 7.33 (d, 2H, J = 9.2 Hz), 7.60 (d, 2H, J = 7.4 Hz), 7.75 (s, 1H), 8.87 (br m, 1H)
3g	n-$PrNH_2$ (5)	45/20, 55/7	SiO_2 (hept/EtOAc) 10:90	11	117−125	0.92 (t, 3H, J = 7.2 Hz), 1.56 (m, 2H), 2.35 (s, 3H), 4.64 (br m, 1H), 7.13 (d, 2H, J = 7.8 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.4 Hz), 7.65 (br s, 1H), 7.80 (d, 1H, J = 13.8 Hz)
3h	c-$C_3H_5NH_2$ (7)	55/20	SiO_2 (hept/EtOAc) 100:0	26	129−133	0.68−0.75 (m, 4H), 2.33 (s, 3H), 2.77 (br m, 1H), 6.96 (d, 1H, J = 12.7 Hz), 7.04−7.12 (m, 4H), 7.32 (d, 2H, J = 8.5 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.94 (s, 1H), 8.87 (br d, 1H, J = 13.3 Hz)
3i	*t*-$BuNH_2$ (4)	50/20	SiO_2 (hept/EtOAc) 80:20	40	165.5−166.5	1.37 (s, 9H), 2.37 (s, 3H), 7.00 (d, 1H, J = 14.1 Hz), 7.10−7.15 (m, 4H), 7.35 (d, 2H, J = 8.6 Hz), 7.62 (d, 2H, J = 9.2 Hz), 7.96 (s, 1H), 9.10 (br d, 1H, J = 12.9 Hz)
3j	$NH_2CH_2CO_2Me$ (4)	50/5	recryst (hept/Et_2O) 60:40	34	120−123	2.34 (s, 3H), 3.76 (s, 3H), 3.99 (d, 2H, J = 6.3 Hz), 6.74 (d, 1H, J = 12.8 Hz), 7.04−7.39 (m, 6H), 7.58 (d, 2H, J = 9.0 Hz), 7.97 (s, 1H), 8.91 (br m, 1H)
3k	CF_2=$CFCH_2CH_2NH_2$ (1)	50/8	SiO_2 (CH_2Cl_2/EtOAc) 100:0	34	129−131.5	2.37 (s, 3H), 2.61 (m, 2H), 3.49 (m, 2H), 6.81 (d, 1H, J = 12.8 Hz), 7.09−7.16 (m, 4H), 7.33 (d, 2H, J = 8.6 Hz), 7.63 (d, 2H, J = 8.6 Hz), 7.98 (s, 1H), 8.86 (br m, 1H)
3l	$NH_2CH_2CO_2CH_2Ph$ (1)	55/8	75:25 *Z:E*	93	oil	2.37 (s, 3H), 4.05 (d, 2H, J = 6.2 Hz), 5.22 (s, 2H), 6.78 (d, 1H, J = 12.9 Hz), 7.06−7.11 (m, 4H), 7.31−7.39 (m, 7H), 7.61 (d, 2H, J = 8.3 Hz), 8.00 (s, 1H), 8.91 (br m, 1H)
3m	*a*		recryst (hept/EtOAc) 7:3	24	195−196 (dec)	2.37 (s, 3H), 4.01 (d, 2H, J = 5.7 Hz), 6.83 (d, 1H, J = 12.7 Hz), 7.08−7.14 (m, 4H), 7.38 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.91 (s, 1H), 8.97 (br m, 1H)
3n	$NH_2CH_2CH_2CO_2Et$ (1)	50/10	85:15 *Z:E*	94	131−134.5	1.25 (t, 3H, J = 7.5 Hz), 2.32 (s, 3H), 2.59 (t, 2H, J = 6.4 Hz), 3.56 (q, 2H, J = 6.1 Hz), 4.15 (q, 2H, J = 7.2 Hz), 6.87 (d, 1H, J = 12.9 Hz), 7.04−7.11 (m, 4H), 7.30 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 7.94 (s, 1H), 8.88 (br m, 1H)
3o	*a*		1:1 *Z:E*	50		(DMSO-d_6, *Z*-isomer) δ 2.28 (s, 3H), 7.12−7.24 (m, 5H), 7.40 (d, 2H, J = 8.1 Hz), 7.44 (d, 2H, J = 9.8 Hz), 7.71−7.78 (m, 3H), 8.93 (br s, 1H)
3p	*a*		recryst (EtOAc) 100:0	34	189−192.5	2.37 (s, 3H), 2.63 (t, 2H, J = 6.2 Hz), 3.57 (q, 2H, J = 6.2 Hz), 6.92 (d, 1H, J = 13.0 Hz), 7.08−7.13 (m, 4H), 7.34 (d, 2H, J = 8.8 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.97 (s, 1H), 8.95 (br m, 1H)
3q	$PhNH_2$ (1)	23/20	SiO_2 (CH_2Cl_2/EtOAc) 85:15	62	163−170	2.39 (s, 3H), 7.04−7.46 (m, 12H), 7.63 (d, 2H, J = 8.9 Hz), 8.09 (s, 1H), 10.78 (br d, 1H, J = 12.4 Hz)

Table 2 (Cont'd)

compd	amine·HCl (equiv)	°C/h	purifn/ratio (*Z*:*E*)	% yield	mp (°C)	^{1}H NMR δ ($CDCl_3$)
3r	NH_2OCH_3 (6)	23/20	SiO_2 (hept/EtOAc) oximino form 1:1 *syn*:*anti*	69	oil	2.38 (s, 3H), 4.00 and 4.09 (2s, 3H), 4.65 and 5.32 (2d, 1H, J = 6.8 Hz), 7.02−7.09 and 7.65 (m, 5H), 7.35 and 7.37 (2d, 2H, J = 9.1 and 9.1 Hz), 7.56 (m, 2H), 9.28 and 10.12 (2br s, 1H)
3s	NH_2OH (7)	23/0.5	recryst ($CHCl_3$) 6:1	45	174 (dec)	2.32 (s, 3H), 5.69 (d, 1H, J = 6.3 Hz), 7.14 (m, 4H), 7.51 (d, 2H, J = 9.0 Hz), 7.73 (d, 2H, 9.0 Hz), 11.49 (s, 1H), 11.93 (s, 1H)
6a	NH_2OCH_3 (5)	60/4		86	glass	2.48 (s, 3H), 4.22 (s, 3H), 7.08−7.12 (m, 4H), 7.64 (d, 2H, J = 8.9 Hz), 7.70 (d, 2H, J = 8.9 Hz), 9.74 (br s, 1H)
6b	CH_2=$CHCH_2ONH_2$ (4)	60/3		90	glass	2.42 (s, 3H), 4.82 and 4.86 (2d, 2H, J = 6.0 Hz and J = 6.2 Hz), 5.35 and 5.42 (2dd, 2H, J = 10.4, 1.2, 17.3, and 1.4 Hz), 6.06 (2m, 1H), 7.01−7.12 (m, 4H), 7.58 (d, 2H, J = 9.2 Hz), 7.65 (d, 2H, J = 9.0 Hz), 9.62 and 9.92 (2br s, 1H)
6c	$NH_2CONHNH_2$ (4)	60/4	recryst (MeCN)	55	233.5−236.5 (dec)	2.35 (s, 3H), 6.67 and 6.90 and 7.54 (3br s, 2H), 7.12−7.26 (m, 4H), 7.40 (d, 2H, J = 7.4 Hz), 7.70−7.76 (m, 2H), 9.60 and 10.21 (2br s, 1H), 11.07 and 12.59 (2br s, 1H)
6d	$TsNHNH_2$ (3)	60/5	SiO_2 (CH_2Cl_2/EtOAc)	89	172−173 (dec)	2.46 (s, 3H), 2.47 (s, 3H), 7.16 (2d, 4H), 7.34 (d, 2H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.3 Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.90 (d, 2H, J = 8.2 Hz), 8.39 (br s, 1H), 9.64 (br s, 1H)

[a] See Materials and Methods.

ethanol was heated at 65 °C for 3 h and was allowed to cool. The ethanol was removed in vacuo, and the residue was partitioned between ethyl acetate and brine. The organic layer was then washed once with brine and dried ($MgSO_4$). Concentration gave 0.28 g of a yellow solid, which was recrystallized from ethyl acetate to afford 0.070 g (27%) of **8**, mp 233−40 °C: ^{1}H NMR δ 2.46 (s, 6H), 7.18 (d, 8H, J = 8.7 Hz), 7.66−7.72 (m, 8H), 9.86 (br s, 2H); IR (KBr) 1561, 1597, 3357 cm^{-1}; MS (FAB) *m*/*z* 879 ([M + H + 4]$^+$, 2), 878 ([M + H + 2]$^+$, 6), 876 ([M + H]$^+$, 9), 701 (65), 264 (100).

Anal. Calcd for $C_{38}H_{24}Cl_2F_6N_6O_4S_2$: C, 52.00; H, 2.76; N, 9.58; S, 7.31. Found: C, 52.15; H, 2.37; N, 9.61; S, 7.27.

The mother liquor was concentrated to a residue, which was chromatographed to afford 140 mg (54%) of **6e** as a mixture of *syn* and *anti* isomers, mp 161−74 °C: ^{1}H NMR δ 2.40 (s, 3H), 6.36 (br s, 2H), 7.10 (d, 2H, J = 8.5 Hz), 7.15 (d, 2H, J = 8.5 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 9.70 (br s, 1H); IR (KBr) 1567, 1666, 3421 cm^{-1}; MS (EI) *m*/*z* 456 ([M + 2]$^+$, 10), 454 (M$^+$, 24), 279 (100).

Anal. Calcd for $C_{19}H_{14}ClF_3N_4O_2S$: C, 50.17; H, 3.10; N, 12.32; S, 7.05. Found: C, 50.11; H, 3.40; N, 12.10; S, 7.32.

4-(4-Chloro-3-methyl-5-isothiazolyl)-6-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]-*as*-triazine-3,5(2*H*,4*H*)-dione (7). The semicarbazone **6c** (0.090 g, 0.18 mmol) was heated at 235−245 °C for 5 min and allowed to cool. The material was taken up in ethyl ether, and the solution was dried ($MgSO_4$) and concentrated to an oil, which was chromatographed eluting with 9:1 heptane/ethyl acetate and progressing to 7:3 heptane/ethyl acetate to afford 0.40 g (46%) of **7** as a solid, mp 179−84 °C: ^{1}H NMR δ 2.52 (s, 3H), 7.05−7.12 (m, 4H), 7.60 (d, 2H, J = 8.6 Hz), 8.01 (d, 2H, J = 8.4 Hz), 9.51 (br s, 1H); IR (KBr) 1687, 1740, 3263 cm^{-1}; MS (EI) *m*/*z* 482 ([M + 2]$^+$, 22), 480 ([M]$^+$, 55), 278 (98), 133 (100).

Anal. Calcd for $C_{20}H_{12}ClF_3N_4O_3S$: C, 49.94; H, 2.52; N, 11.65. Found: C, 50.05; H, 2.62; N, 11.32.

Biology. *Beet Armyworm (BAW, Spodoptera exigua) and Tobacco Budworm (TBW, Heliothis virescens).* Compounds were dissolved in a mixture of acetone and water to give a 50 ppm solution. One-fourth of a milliliter of the solutions/suspensions was pipetted onto insect diet (Southland Products, Stoneville, MS) in 1 oz plastic cups. Each cup was infested with ∼10−15 eggs and held under controlled conditions for 4−6 days (25 °C and 50% relative humidity). Activity was estimated by the number and size of live larvae in the treated cups relative to that in the untreated controls.

Cotton Aphid (CA, Aphis gossypii) and Two-Spotted Spider Mite (TSSM, Tetranychus urticae). One day before treatment, cotyledon-stage summer crookneck squash (*Cucurbita pepo*) plants were infested with leaf sections bearing immature and adult aphids and mites. Compounds were dissolved in a mixture of acetone and water to give a 50 ppm solution. The resulting solutions/suspensions were sprayed on the upper and lower surfaces of the infested cotyledons using an airbrush; ∼1 mL was sprayed over each surface. The plants were held for 3−4 days at 27 °C and 75% relative humidity and a 14 h photoperiod. Percent control was estimated visually by comparison with untreated plants.

Aster Leafhopper (ALH, Macrosteles fascifrons) and Corn Planthopper (CPH, Peregrinus maidis). Compounds were dissolved in acetone and water to yield a 50 ppm solution. One milliliter of each solution was pipetted onto a cotton dental wick in a 1 oz plastic cup. In some assays, agar was used as the substrate. Each cup was infested with 7−10 nymphs or adults and held for 1 day under controlled conditions (25 °C and 50% relative humidity). Mortality was determined by counting the number of live and dead insects.

Southern Root-Knot Nematode (RKN, Meloidogyne incognita). Compounds were dissolved in acetone and water and were serially diluted to achieve the desired range of concentrations. One milliliter of the final solution was pipetted into 1 oz plastic cups containing foxtail millet (*Setaria italica*) seeds covered with 20 g of washed quartz sand; three cups were treated at each concentration. The solvent was allowed to evaporate in a fume hood for 24 h. Each cup was infested with ∼6000 nematode eggs and J2 larvae delivered in 3 mL of water. The assay was held for 11 days at 27 °C and 50% relative humidity. Activity was assessed using a three-point scale: no galling = 100% control; partial galling = 50% control; complete galling = 0% control.

RESULTS AND DISCUSSION

Chemistry. Our initial foray into α-carbon oxidation began with the observation that **1** was conveniently converted to the enamineamide **2** in good yield (Figure 1). A readily accessible and well-behaved solid, **2** was eventually to serve as a versatile intermediate leading to various elaborations at the α-carbon via Michael addition followed by elimination of dimethylamine. For example, treatment of **2** with methylamine hydrochlo-

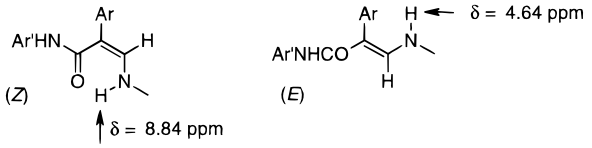

Figure 2.

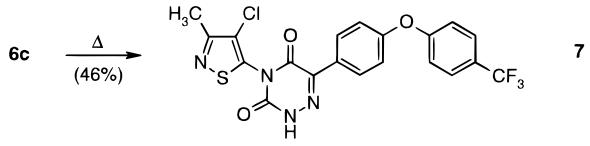

Figure 3.

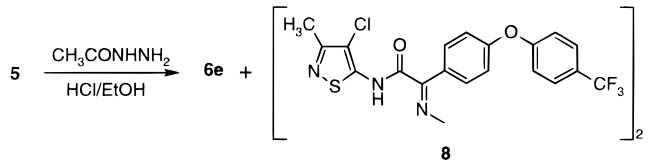

Figure 4.

ride in aqueous tetrahydrofuran afforded the amine exchange product **3a** in a 53% recrystallized yield (Table 1). When the exchange was carried out with ethylamine hydrochloride, purification was performed by silica gel chromatography resulting in the isolation of both *Z* and *E* isomers, **3b** and **3c**. The less polar isomer (first to be eluted) was assigned the *Z* configuration on the basis of proton NMR evidence. The *Z* isomer enamine NH proton is strongly deshielded relative to that of the *E* isomer (Figure 2), which can be accounted for by intramolecular hydrogen bonding in the *Z* isomer (Abraham and Loftus, 1978). Additionally, the magnitude of the ^3J coupling constants of the olefinic protons in **3b** and **3c** (13.3 and 12.4 Hz) indicate that these protons have adopted a *trans* relationship to their corresponding amino protons (Dahmani et al., 1998; Takagi et al., 1986). It was also found that upon recrystallization of the *E* isomer, significant conversion to the *Z* isomer occurred, the latter of which remained in solution. Separation of *Z* and *E* isomers by chromatography was also accomplished with other enamineamides (**3d**−**g**, Table 1), but, in general, the higher homologues were obtained as mixtures whether purification was attempted by chromatography or recrystallization (**3h**−**q**). Compound **3r** exists in the oximino form in deuteriochloroform as a mixture of *syn* and *anti* isomers. The acids **3m** and **3p** were prepared from the esters **3l** and **3n**, respectively, by mild hydrolysis using potassium carbonate in aqueous methanol followed by acidification.

In addition to undergoing amine exchange reactions, **2** was also hydrolyzed under acidic conditions to **4a** (Figure 1, see also Materials and Methods). This enolamide was alkylated in moderate yields to give the enolethers **4b** and **4c** using sodium hydride/alkyl iodide. Under acidic conditions, **4a** underwent exchange at the β-carbon with *n*-butanethiol to give **4d**. In each case a single isomer was obtained as evidenced by proton NMR spectroscopy but was not identified.

It is interesting to note that our first attempt to prepare the amino acid **3m** from glycine and **2** resulted in the formation of the ketoamide **5** in low yield. This transformation of aminomethylene to a keto group was also observed in low yield when **2** was treated with ethylamine hydrochloride in aqueous THF. A reverse aldol-type process would regenerate **1** rather than lead to **5**, but enamino carbonyl compounds are known to be converted to α-keto carbonyl compounds via oxidative cleavage of the carbon−carbon double bond using singlet oxygen (Wasserman and Han, 1984; Wasserman and Ives, 1985). This would require the presence of an initiator such as light or a peroxide as may exist in low concentration in unpurified THF.

The ketoamide **5** was seen as a valuble intermediate to oximes and hydrazones; consequently, a more efficient synthesis was required that would be amenable to its preparation in gram quantities. Ideally this would involve use of the readily accessible enamineamide **2**. Enamine oxidations to carbonyl compounds are well-documented in the literature (Gatta et al., 1989; Wasserman et al., 1985; Rao et al., 1990; Harris et al., 1997), and the method of Vetelino and Coe (1994), which employs sodium periodate as the oxidant, appeared quite promising as a solution to our problem. Treatment of **2** with 2 equiv of periodate in aqueous tetrahydrofuran for 24 h at room temperature afforded a 80% yield of **5**. The reaction proceeds cleanly, purification is quickly and conveniently carried out by flash chromatography, and it is reproducible on a gram scale. The α-ketoamide was then converted to the oximes **6a,b**, the semicarbazone **6c**, and the tosylhydrazone **6d** (Figure 1), all in ethanol, using the amine hydrochlorides at elevated temperatures (Tables 1 and 2). Separate signals for *syn* and *anti* isomers of **6** were not observable by proton NMR at room temperature.

Although cyclization of **6c** was not observed under the conditions of semicarbazone formation, it was possible to effect ring closure by heating **6c** at its melting point (Figure 3). Although NMR analysis of the reaction product had suggested that condensation had taken place, it could not say from which direction it had occurred, that is, with elimination of either ammonia or water. Mass spectral data corroborated the triazinedione structure **7** by indicating that cyclocondensation had occurred with the loss of ammonia.

Treatment of **5** with acetic hydrazide in dry ethanol containing 1 equiv of hydrogen chloride gas resulted in the isolation of the unsubstituted hydrazone **6e** in low yield. The major product in this reaction was the dimer **8**, which most likely arose from condensation of **6e** with the starting ketone **5** (Figure 4). The desired acetyl hydrazone is assumed to have been formed but was not stable under the reaction conditions in which solvolysis would be facilitated at acetyl carbonyl by an excellent hydrazone leaving group.

Biological Activity. The broad-spectrum activity associated with the parent amide **1** was retained on conversion to enamineamides **3** derived from ammonia and smaller primary amines (**3a,b**, **3d,e**, **3h**, see Table 3). Those derived from *n*-propylamine (**3f,g**), *tert*-butylamine (**3i**), aniline (**3q**), oxyamines (**3r,s**), and the fluorinated amine (**3k**) were not as broad-spectrum at 50 ppm. The glycine and β-alanine derivatives **3j**, **3m**, and **3n** were particularly active, especially **3j**, which is considered to be the most active enamineamide prepared. Compound **2**, derived from dimethylamine, was inactive on all pests except cotton aphid (CA) and represents the only enamineamide derived from a secondary amine. Although the enol **4a** was found to be one of the more active broad-spectrum compounds,

Table 3. Percent Mortality at 50 ppm and LC_{50} Values against RKN[a]

compd	BAW	TBW	TSSM	CA	ALH	RKN LC_{50} (ppm)
1	100	100	100	100	80	6.9
2	0	0	0	100	0	25
3a	100	100	100	100	0	3.3
3b	100	100	100	100	0	3.2
3c	nt	nt	nt	nt	nt	0.84
3d	0	100	90	80	100[b]	0.39
3e	0	0	100	90	100[b]	0.66
3f	100	0	0	60	80[b]	0.78
3g	0	0	0	0	40[b]	0.19
3h	100	100	90	100	80	12.5
3i	60	0	50	60	0	3.1
3j	100	100	90	100	100	<0.39
3k	100	60	0	0	0	25
3l	100	60	0	0	0	1.56
3m	90	100	90	80	nt	<0.39
3n	100	80	100	90	nt	<0.39
3o	100	60	70	80	nt	6.25
3p	0	0	100	100	0[b]	0.39
3q	0	0	100	100	0[b]	2.7
3r	0	100	0	0	0	8.8
3s	100	60	0	0	0	nt
4a	100	60	100	100	0[b]	1.56
4b	0	0	40	70	0	1.56
4c	0	80	0	60	0	12.5
4d	0	0	0	0	0	0.39
5	100	40	0	0	0	12.4
6a	100	0	0	0	0	4.7
6b	0	0	0	0	0	500
6c	0	0	0	0	0	2.3
6d	100	0	40	50	0	<0.78
6e	0	60	0	0	0	1.02
7	nt	nt	nt	nt	nt	44.7
8	0	0	0	0	0	23.5

[a] Abbreviations: BAW, beet armyworm, *Spodoptera exigua*; TBW, tobacco budworm, *Heliothis virescens*; TSSM, two-spotted spider mite, *Tetranychus urticae*; CA, cotton aphid, *Aphis gossypii*; ALH, aster leafhopper, *Macrosteles fascifrons*; RKN, Southern root-knot nematode, *Meloidogyne incognita*. nt = not tested. [b] Corn plant hopper (*Peregrinus maidis*) utilized as test subject.

O-alkylation (**4b,c**) or exchange with butanethiol (**4d**) resulted in a significant loss of activity. Oxidation to the ketoamide **5** also reduced broad-spectrum activity, and no advantage was seen by conversion to its oximes **6a,b** or hydrazine derivatives **6c**−**e** and **8**.

Of particular interest was the enhanced activity relative to **1** on root-knot nematode (RKN) of several of these derivatives. Table 3 lists LC_{50} values measured in a sand medium. Nearly all of the enamineamides **3** were found to control RKN better than the parent amide **1**. In particular, the amino acids and esters **3j** and **3m,n** all gave >50% control at the lowest rate tested of 0.39 ppm. Of **5**−**8** the tosylhydrazone **6d** afforded the best control of nematode.

Conclusions. It has been shown that oxidation at the α-carbon of **1** is conveniently brought about using dimethylformamide dimethylacetal to give the dimethylaminomethylene derivative **2**, which has served as a common starting point for a variety of functional group transformations. These transformations were found to proceed in moderate to good yields to give derivatives of **1** that retained much of the efficacy associated with the parent amide and have allowed for an expansion of the structure−activity relationship to be developed. In particular, the enamineamides derived from low molecular weight amines and amino acids were most active as broad-spectrum insecticides and were found to be even more active than **1** on root-knot nematode.

ABBREVIATIONS USED

1, *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]acetamide; **3a**, (*E*,*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(methylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3b**, (*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(ethylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3c**, (*E*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(ethylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)-oxy]atropamide; **3d**, (*Z*)-*β*-amino-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3e**, (*E*)-*β*-amino-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3f**, (*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(propylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3g**, (*E*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(propylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3h**, (*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(cyclopropylamino)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3i**, (*E*,*Z*)-*β*-(*tert*-butylamino)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*p*-[(α,α,α-trifluoro-*p*-tolyl)-oxy]atropamide; **3j**, *N*-[(*E*,*Z*)-*β*-[(4-chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-styryl]glycine, methyl ester; **3k**, (*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-[(3,4,4-trifluoro-3-butenyl)amino]-*p*-[(α,-α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3l**, *N*-[(*E*,*Z*)-*β*-[(4-chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]styryl]glycine, benzyl ester; **3n**, *N*-[(*E*,*Z*)-*β*-[(4-chloro-3-methyl-5-isothiazolyl)carbamoyl]-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]styryl]-*β*-alanine, ethyl ester, **3q**, (*E*,*Z*)-*β*-anilino-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3r**, (*E*,*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(methoxyamino)-*p*-[(α,-α,α-trifluoro-*p*-tolyl)oxy]atropamide; **3s**, (*E*,*Z*)-*N*-(4-chloro-3-methyl-5-isothiazolyl)-*β*-(hydroxyamino)-*p*-[(α,-α,α-trifluoro-*p*-tolyl)oxy]atropamide; **6a**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]glyoxylamide 2-(*O*-methyloxime); **6b**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]-phenyl]glyoxylamide 2-(*O*-allyloxime); **6c**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)-oxy]phenyl]glyoxylamide 2-semicarbazone; **6d**, *N*-(4-chloro-3-methyl-5-isothiazolyl)-2-[*p*-[(α,α,α-trifluoro-*p*-tolyl)oxy]phenyl]glyoxylamide 2-[(*p*-tolylsulfonyl)hydrazone].

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Received for review February 1, 1999. Revised manuscript received June 10, 1999. Accepted June 14, 1999.

JF990095S