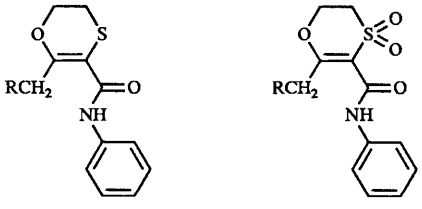
New synthesis of carboxin and oxycarboxin pesticides: application to the preparation of their new analogues substituted at the C-2 methyl group[1]

Romualdo Caputo, Carla Ferreri, Annalisa Guaragna, Giovanni Palumbo * and Silvana Pedatella
Dipartimento di Chimica Organica e Biologica, Università di Napoli Federico II, Via Mezzocannone 16, I-80134 Napoli, Italy

A new synthesis of carboxin **1a** and its 4,4-dioxide derivative, oxycarboxin **2a**, has been devised *via* *N*-bromosuccinimide-promoted oxidative rearrangement of acetoacetanilide 1,3-oxathiolane **3**. The replacement of *N*-bromosuccinimide with molecular bromine leads to the formation, from compound **3**, of a C-2 bromomethylcarboxin derivative **1b**. The latter is conveniently exploited to prepare a new class of carboxins and oxycarboxins (after oxidation of the sulfur) substituted at the C-2 methyl, by replacement of the bromine atom with various nucleophiles.

Introduction

Carboxin **1a** (2-methyl-5,6-dihydro-1,4-oxathiine-3-carboxanilide) (Vitavax®) and its 4,4-dioxide analogue, oxycarboxin **2a** (Plantavax®), are well established†,[2] as systemic fungicides and both are the active components of many effective commercially available pesticides used worldwide to control crop smuts and rust diseases.[3,4] As a consequence, a great deal of synthetic work has been done aimed at their preparation, as well as the synthesis of their variously substituted derivatives, with the purpose of investigating structure–activity relationships.[3,5,6] A convenient industrially relevant synthesis[3] of commercial carboxin **1a**, starting from methyl acetoacetate, is a six-step synthesis leading to the final product in ~80% yield.



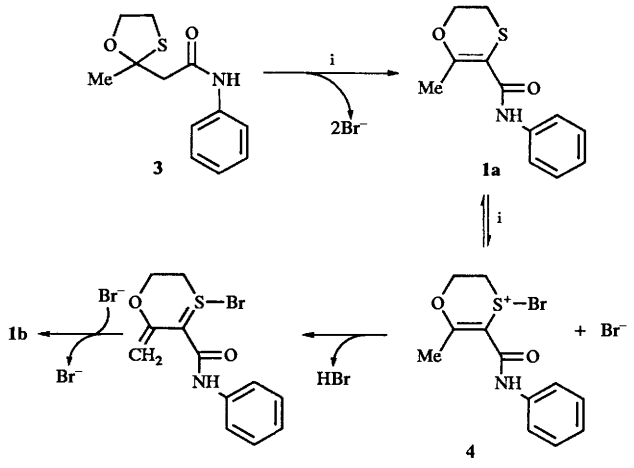
1 **2**

a; R = H
b; R = Br

Our interest towards carboxin and its derivatives was aroused by their 5,6-dihydro-1,4-oxathiine moiety that, according to our previous work,[7] could be readily obtained in only one step by Br^+-induced oxidative rearrangement of suitable 1,3-oxathiolane precursors.‡

Results and discussion

Preliminary experiments carried out utilizing acetoacetanilide 1,3-oxathiolane **3** and one molar equivalent of *N*-bromosuccinimide (NBS) as the bromonium-ion source in anhydrous chloroform led to quite encouraging results. Indeed, carboxin **1a** was obtained quickly and under mild conditions in very high yield (>90% overall yield). The replacement of NBS with simple molecular bromine still afforded carboxin **1a**, although in a sharply lower yield (~60%). Besides, carboxin was accompanied in this case by its C-2 methyl-brominated derivative **1b** (~20%) and unchanged 1,3-oxathiolane **3** (~20%).



Scheme 1 *Reagent:* i, Br_2

Nevertheless, compound **1b** attracted our attention since it could be suitable for the preparation of carboxin derivatives carrying substituents at the C-2 methyl group, by replacement of the bromine atom by various nucleophiles. To the best of our knowledge, carboxins carrying any substituents at the C-2 methyl group have been only occasionally reported,[9] presumably due to the lack of a suitable, ready synthetic methodology for their preparation. Therefore, we tried to devise proper conditions to increase the yield of compound **1b** in the reaction of the oxathiolane **3** with molecular bromine. On the basis of our previously reported results[10] its formation could be accounted for by a reaction path such as that depicted in Scheme 1. This means that when molecular bromine replaces NBS, a high concentration of bromide ions favours abstraction of a proton from the methyl group in intermediate **4** thus shifting the **1a** ⇌ **4** equilibrium to the right, towards **1b** (*via* **4**).

Therefore, we carried out the rearrangement of compound **3** by use of a two-fold bromine excess. As expected, under these conditions the ratio between **1a** and **1b** was reversed and the

† Vitavax® and Plantavax® are trademarks by Uniroyal Inc.
‡ This synthetic approach is also interesting in view of its extension to the preparation of several known drugs (tranquilizers, anticonvulsants, hypnotics, antivirals, *etc.*) having a 5,6-dihydro-1,4-oxathiine ring system.[8]

Table 1 Miscellaneous C-2 methyl-substituted derivatives of carboxin **1a** and carboxin dioxide **2a**

Compound	R	Mp/°C	Yield (%)
1c	MeS	82–83	92
1d	AcS	101–102	87
1e	NCS	113–114	98
1f	MeO	oil	80
1g	NH-L-Phe-OAll	oil	75
1h	NH-L-Val-OAll	oil	78
1i	NH-L-Ala-OMe	oil	79
1j	(β-D-Glu*p*)S	190–191	92
2j	(β-D-Glu*p*)S	195 (decomp.)	86

latter could be obtained in almost quantitative yield (>90% overall yield).

The subsequent reactions of compound **1b** with various nucleophiles were quite successful and the substituted carboxins thus obtained (Table 1) are now under investigation to test their fungicidal activity. Compound **1j** seems to be a very appealing one, due to its high water solubility (and the consequent better translocation in plants[11]) that should avoid the environmentally damaging use of organic solvents, like xylenes, *N*,*N*-dimethylformamide (DMF), or dimethyl sulfoxide, which are currently utilized as emulsifying agents to suspend carboxin in water.[12] Its 4,4-dioxide analogue **2j** (Table 1) was also prepared from the brominated oxycarboxin **2b** which in its turn is readily obtained by oxidation [*m*-chloroperbenzoic acid (MCPBA)] of compound **1b**. The product **2j** is in fact expected[13] to be effective in the control of rust diseases of cereals, ornamentals, and vegetables whereas its analogue **1j** should be active in seed treatments of cereals against bunts or smuts.

In our opinion the synthetic procedure described by this paper may disclose a quite new area for the study of structure–activity relationships in carboxin- and oxycarboxin-based pesticides characterized by high translocation in plant tissues.

Experimental

Mps were measured on a Kofler-type hot-stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 1760 spectrophotometer. ^{1}H NMR (270 MHz) spectra of $CDCl_3$ solutions (unless otherwise specified) were recorded on a Bruker WH 270 instrument; chemical shifts are in ppm (δ) downfield from internal $SiMe_4$; *J*-values are in Hz. GLC–MS analyses were performed on a Hewlett-Packard 5980 GS/5971 MS instrument. Fast-atom bombardment (FAB) MS spectra were recorded on a VG ZAB 2SE instrument. Silica gel (70–230 mesh) and TLC plates (60 F_{254}) were purchased from Merck. Polystyryl diphenylphosphine was purchased from Fluka.

α-(2-Methyl-1,3-oxathiolan-2-yl)acetanilide 3

To a magnetically stirred suspension of polystyryl diphenylphosphine–iodine complex (22.6 mmol—iodine units; prepared *in situ*) in anhydrous acetonitrile (150 cm^3) at room temp. under dry nitrogen was added a solution of acetoacetanilide (4.0 g, 22.6 mmol) in the same solvent (25 cm^3) *via* syringe in one portion. After 10 min, 1 mol dm^{-3} 2-mercaptoethanol in anhydrous acetonitrile (23 cm^3) was also added in one portion. Acetoacetanilide was fully consumed (TLC monitoring) within 4 h. Solid K_2CO_3 (excess) was then added, and the suspension was stirred for a couple of minutes and eventually filtered. The residual solid was washed with chloroform (3 × 100 cm^3) and the combined filtrate, after being shaken successively with 2.5 mol dm^{-3} aq. sodium thiosulfate (50 cm^3) and water until neutral (universal indicator), was evaporated under reduced pressure to leave a residue consisting of practically pure title compound **3** (5.2 g, 98%), mp 86–87 °C (from ethyl acetate–hexane) (Found: C, 60.8; H, 6.3%; M^+, 237. $C_{12}H_{15}NO_2S$ requires C, 60.73; H, 6.37%; *M*, 237); ν_{max}(KBr)/cm^{-1} 1650 (C=O); δ_H 1.73 (3 H, s, Me), 2.90 (2 H, s, CH_2CO), 3.10 (2 H, m, CH_2S), 4.25 (2 H, m, OCH_2), 7.00–7.60 (5 H, m, ArH) and 8.24 (1 H, br s, NH).

Carboxin 1a

To a magnetically stirred solution of the pure 1,3-oxathiolane **3** (1.0 g, 4.2 mmol) in anhydrous chloroform (80 cm^3) was added a solution of NBS (0.8 g, 4.5 mmol) in the same solvent (30 cm^3) in one portion. After 30 min at room temp. saturated aq. $NaHCO_3$ (15 cm^3) was added and the organic layer was separated and shaken with 2.5 mol dm^{-3} aq. sodium thiosulfate (10 cm^3), washed with water until neutral (universal indicator), dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue, chromatographed on silica gel (chloroform), afforded the pure carboxin **1a** (0.9 g, 92%), mp 94–95 °C (from EtOH), identical with a commercial (Instytut Przemyslu Organicznego) authentic sample; *m*/*z* 235 (M^+, 47%) and 143 (100, $M^+ - C_6H_5NH$); δ_H 2.26 (3 H, s, Me), 2.99 (2 H, m, CH_2S), 4.41 (2 H, m, OCH_2), 7.09 (1 H, t, *J* 7.4, 4′-H), 7.31 (2 H, dd, *J* 7.4 and 8.0, 3′- and 5′-H), 7.51 (2 H, d, *J* 8.0, 2′- and 6′-H) and 7.89 (1 H, br s, NH).

2-Bromomethyl-2-demethylcarboxin 1b

To a magnetically stirred solution of the 1,3-oxathiolane **3** (2.0 g, 8.4 mmol) in anhydrous chloroform (100 cm^3) was added a solution of dry bromine (0.9 cm^3, 16.8 mmol) in the same solvent (100 cm^3) dropwise. After 30 min at room temp. the mixture was treated with saturated aq. $NaHCO_3$ (30 cm^3) and the organic layer was separated, and shaken with 2.5 mol dm^{-3} aq. sodium thiosulfate (30 cm^3), washed with water until neutral (universal indicator), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded an oily residue, which by chromatography on silica gel (chloroform) yielded *bromo compound* **1b** (2.5 g, 95%), mp 105–106 °C (from EtOH) [Found: C, 45.95; H, 3.8%; M^+, 313 and (M^+ + 2), 315. $C_{12}H_{12}BrNO_2S$ requires C, 45.87; H, 3.85%; *M*, 314]; δ_H 3.07 (2 H, m, CH_2S), 4.43 (2 H, s, $BrCH_2$), 4.44 (2 H, m, OCH_2), 7.14 (1 H, t, *J* 8.0, 4′-H), 7.32 (2 H, t, *J* 8.0, 3′- and 5′-H), 7.55 (2 H, d, *J* 8.0, 2′- and 6′-H) and 7.94 (1 H, br s, NH).

Reaction of compound 1b with sodium methanethiolate. Typical procedure

To a magnetically stirred solution of bromo compound **1b** (0.4 g, 1.2 mmol) in anhydrous DMF (15 cm^3) at room temp. under dry argon (or nitrogen) was added a suspension of sodium methanethiolate (0.2 g, 3.0 mmol) in the same solvent (5 cm^3) in one portion. After 2 h at room temp. (TLC monitoring) the suspension was treated with saturated aq. $NaHCO_3$ and extracted with chloroform (100 cm^3). The organic layer was then washed with water until neutral (universal indicator), dried (Na_2SO_4), and evaporated under reduced pressure. The semicrystalline product, chromatographed on silica gel (chloroform), afforded the pure *methyl sulfide* **1c** (0.3 g, 92%), mp 82–83 °C (from hexane–benzene) [Found: C, 55.4; H, 5.4%; M^+, 281. $C_{13}H_{15}NO_2S_2$ requires C, 55.48; H, 5.37%; *M*, 281]; δ_H 2.17 (3 H, s, MeS), 2.99 (2 H, m, CH_2S), 3.67 (2 H, s, SCH_2C=), 4.34 (2 H, m, OCH_2), 7.10 (1 H, t, *J* 7.9, 4′-H), 7.31 (2 H, t, *J* 7.9, 3′- and 5′-H), 7.51 (2 H, d, *J* 7.9, 2′- and 6′-H) and 8.09 (1 H, br s, NH).

Under the same conditions the following carboxin derivatives were also prepared:

S-*Thioacetate* **1d**, from bromo compound **1b** and potassium *S*-thioacetate: (87%), mp 101–102 °C (from hexane–benzene) [Found: C, 54.4; H, 4.85%; M^+, 309. $C_{12}H_{15}NO_2S$ requires C, 54.34; H, 4.88%; M, 309]; δ_H 2.36 (3 H, s, Ac), 3.03 (2 H, m,

CH_2S), 4.11 (2 H, s, SCH_2C=), 4.40 (2 H, m, OCH_2), 7.12 (1 H, t, *J* 8.0, 4'-H), 7.33 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.56 (2 H, d, *J* 8.0, 2'- and 6'-H) and 8.30 (1 H, br s, NH).

Thiocyanate **1e**, from bromo compound **1b** and potassium thiocyanate: (98%), mp 113–114 °C (from hexane) [Found: C, 53.3; H, 4.2%; M^+, 292. $C_{13}H_{12}N_2O_2S_2$ requires C, 53.40; H, 4.13%; *M*, 292]; δ_H 3.09 (2 H, m, CH_2S), 4.14 (2 H, s, SCH_2C=), 4.54 (2 H, m, OCH_2), 7.14 (1 H, t, *J* 8.0, 4'-H), 7.34 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.48 (2 H, d, *J* 8.0, 2'- and 6'-H) and 7.95 (1 H, br s, NH).

Methoxy compound **1f**, from bromo compound **1b** and sodium methoxide: (80%) oil [Found: C, 58.7; H, 5.75%; M^+, 265. $C_{13}H_{15}NO_3S$ requires C, 58.84; H, 5.69%; *M*, 265]; δ_H 3.07 (2 H, m, CH_2S), 3.51 (3 H, s, MeO), 4.20 (2 H, s, OCH_2C=), 4.34 (2 H, m, OCH_2), 7.13 (1 H, t, *J* 8.0, 4'-H), 7.32 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.55 (2 H, d, *J* 8.0, 2'- and 6'-H) and 8.71 (1 H, br s, NH).

Compound **1g**, from bromo compound **1b** and L-phenylalanine allyl ester: (75%), oil [Found: C, 65.8; H, 5.9%; M^+, 438. $C_{24}H_{26}N_2O_4S$ requires C, 65.73; H, 5.97%; *M*, 438]; δ_H 2.30 (1 H, s, Phe NH), 2.98 (2 H, m, CH_2S), 3.05 (2 H, d, *J* 6.0, Phe CH_2), 3.55 (2 H, d, *J* 1.5, NCH_2C=C), 3.68 (1 H, t, *J* 6.0 Phe CHN), 4.28 (2 H, m, OCH_2), 4.58 (2 H, d, *J* 7.0, CO_2CH_2), 5.22 (2 H, m, C=CH_2), 5.80 (1 H, m, CH=C), 7.01–7.31 (8 H, m, 3'-, 4'-, 5'-H and Phe ArH), 7.42 (2 H, d, *J* 8.0, 2'- and 6'-H) and 7.91 (1 H, br s, NH).

Compound **1h**, from bromo compound **1b** and L-valine allyl ester: (78%), oil [Found: C, 61.5; H, 6.7%; M^+, 390. $C_{20}H_{26}N_2O_4S$ requires C, 61.51; H, 6.71%; *M*, 390]; δ_H 1.02 (6 H, d, *J* 7.0, CMe_2), 2.03 (1 H, m, C*H*Me_2). 2.60 (1 H, s, Val NH), 3.02 (2 H, m, CH_2S), 3.32 (1 H, d, *J* 6.0, Val CHN), 3.58 (2 H, m, NCH_2C=C), 4.31 (2 H, m, OCH_2), 4.65 (2 H, d, *J* 6.0, CO_2CH_2), 5.28 (2 H, m, C=CH_2), 5.92 (1 H, m, CH=C), 7.08 (1 H, t, *J* 8.0, 4'-H), 7.32 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.55 (2 H, d, *J* 8.0, 2'- and 6'-H) and 7.90 (1 H, br s, NH).

Compound **1i**, from bromo compound **1b** and L-alanine methyl ester: (79%), oil [Found: C, 57.0; H, 6.0%; M^+, 336. $C_{16}H_{20}N_2O_4S$ requires C, 57.12; H, 5.99%; *M*, 336]; δ_H 1.39 (3 H, d, *J* 8.0, Ala Me), 2.20 (1 H, s, Ala NH), 3.00 (2 H, m, CH_2S), 3.47 (1 H, q, *J* 8.0, Ala CHN), 3.57 (2 H, s, NCH_2C=C), 3.73 (3 H, s, CO_2Me), 4.34 (2 H, m, OCH_2), 7.05 (1 H, t, *J* 8.0, 4'-H), 7.31 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.55 (2 H, d, *J* 8.0, 2'- and 6'-H) and 9.97 (1 H, br s, NH).

Compound **1j**, from bromo compound **1b** and sodium 1-thio-β-D-glucosylate dihydrate: (92%), mp 190–191 °C (from MeCN); [Found: C, 50.3; H, 5.4%; M^+ (FAB), 429. $C_{18}H_{23}NO_7S_2$ requires C, 50.33; H, 5.39%; *M*, 429]; δ_H(MeOD) 3.12 (2 H, m, SCH_2), 3.22–3.40 (3 H, m, Glu 2-, 4-and 5-H), 3.34 (2 H, s, SCH_2C=), 3.58 (1 H, m, Glu 3-H), 3.75 (2 H, dd, *J* 14.0, Glu 6-H), 4.44 (2 H, m, OCH_2), 4.59 (1 H, d, *J* 9.7, Glu 1-H), 7.10 (1 H, t, *J* 8.0, 4'-H), 7.30 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.59 (2 H, d, *J* 8.0, 2'- and 6'-H) and 8.00 (1 H, br s, NH).

2-Bromomethyl-2-demethyl-4,4-dioxocarboxin 2b

To a magnetically stirred solution of 2-bromomethyl-2-demethylcarboxin **1b** (1.0 g, 3.1 mmol) in anhydrous dichloromethane (50 cm^3) at 0 °C was added a solution of *m*-chloroperbenzoic acid (1.1 g, 6.2 mmol) in the same solvent (100 cm^3) dropwise over a period of 40 min. After being stirred for 2 h at 0 °C (TLC monitoring) the solution was extracted with saturated aq. $NaHCO_3$ (100 cm^3) and the organic layer was then washed with water until neutral (universal indicator), dried (Na_2SO_4), and evaporated under reduced pressure. The semicrystalline product, chromatographed on silica gel (chloroform), afforded the pure *sulfone* **2b** (1.0 g, 97%), mp 134–135 °C (from hexane) [Found: C, 41.5; H, 3.4%; M^+, 345 and (M^+ + 2), 347. $C_{12}H_{12}BrNO_4S$ requires C, 41.63; H, 3.49%; *M*, 346]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1380 (O=S=O); δ_H 3.54 (2 H, m, CH_2SO_2), 4.39 (2 H, s, $BrCH_2$) 4.84 (2 H, m, OCH_2), 7.17 (1 H, t, *J* 7.9, 4'-H), 7.36 (2 H, t, *J* 7.9, 3'- and 5'-H), 7.57 (2 H, d, *J* 7.9, 2'- and 6'-H) and 8.76 (1 H, br s, NH).

2-Demethyl-4,4-dioxo-2-[(1-thio-β-D-glucopyranosyl)methyl]-carboxin 2j

To a magnetically stirred solution of bromo sulfone **2b** (0.5 g, 1.4 mmol) in anhydrous DMF (20 cm^3) at room temp. under dry argon was added a suspension of sodium 1-thio-β-D-glucosylate dihydrate (2.0 g, 1.4 mmol) in the same solvent (10 cm^3) in one portion. After being stirred for 2 h the solution was evaporated under reduced pressure to give an oily residue, which was chromatographed on silica gel chloroform–MeOH (4:1) to afford the pure crystalline *title product* **2j** (0.5 g, 86%), mp 195 °C (decomp.) (from MeCN) [Found: C, 46.9; H, 5.1%, M^+ (FAB), 461. $C_{18}H_{23}NO_9S_2$ requires C, 46.84; H, 5.02%; *M*, 461]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1375 (O=S=O); δ_H 3.16 (1 H, m, Glu 2-H), 3.30 (1 H, m, Glu 4-H), 3.32 (3 H, m, SCH_2C= and Glu 3-H), 3.72 (5 H, m, CH_2SO_2 and Glu 5-H and 6-H_2), 4.53 (1 H, d, *J* 9.0, Glu 1-H), 4.87 (2 H, m, OCH_2), 7.14 (1 H, t, *J* 8.0, 4'-H), 7.34 (2 H, t, *J* 8.0, 3'- and 5'-H), 7.60 (2 H, d, *J* 8.0, 2'-and 6'-H) and 8.05 (1 H, br s, NH).

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1 Considered as Part 11 in the series *Chemistry of Ethanediyl* S,S-*Acetals*. For Part 10 in the same series, see ref. 7(*b*).
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