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An Efficient and Convenient Synthesis of Chain Lengthened Homologs of the Fungicide Metalaxyl

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AN EFFICIENT AND CONVENIENT SYNTHESIS OF CHAIN LENGTHENED HOMOLOGS OF THE FUNGICIDE METALAXYL

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Abstract: An efficient and convenient synthesis of chain lengthened homologs of the important fungicide Metalaxyl is described. The starting material utilized is 2,6-dimethylaniline and the sequence is accomplished utilizing Grignard reactions and ruthenium based oxidations to obtain the proper analogs.

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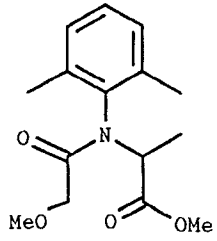
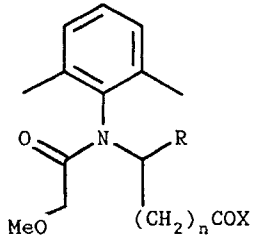
Compounds that are formally related to the commercial fungicide Metalaxyl (**1**) have received considerable attention[1] in recent years due to their systemic and broad spectrum activity in the area of crop protection. There has been some suggestions in the literature[2] that both the amide group and the side chain could be involved in binding to an active site of the target organism . In order to understand more about such structure activity relationships, we have begun a synthetic program to prepare analogs of the Metalaxyl type which have the amide unit and a carbonyl group separated by additional methylene units (**2**). Such analogs when bioassayed should reveal information regarding the nature of active site binding requirements.



1



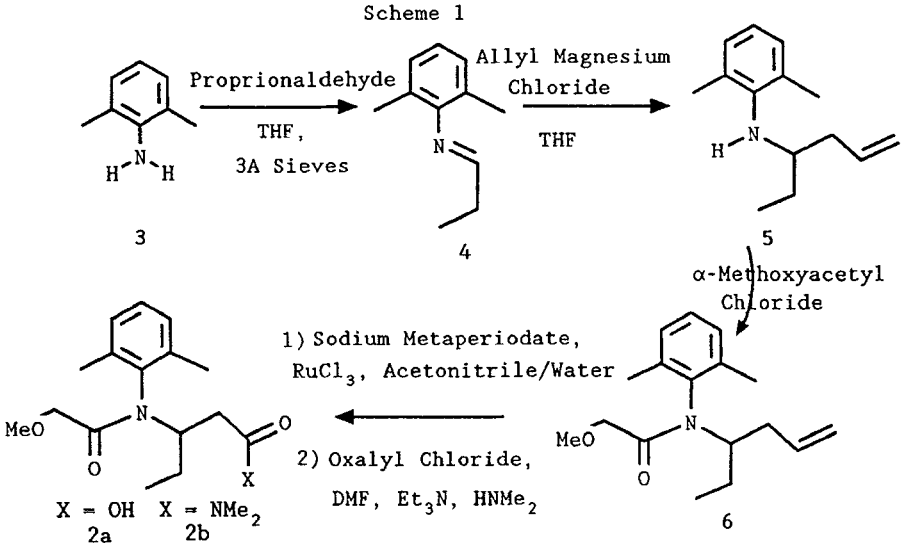
2

R= alkyl

X= amino or alkoxy

We now report a general and convenient synthesis of Metalaxyl analogs which contain one additional methylene unit (Scheme 1).

Scheme 1



The sequence involves forming an imine (**4**) derived from the reaction of 2,6-dimethylaniline and proprionaldehyde. The imine (**4**) which is relatively pure and somewhat moisture sensitive is utilized in the next step without substantial purification. Subsequent reaction with allyl magnesium chloride produces a highly functionalized secondary amine (**5**) in good yield. This amine is then reacted with α-methoxyacetyl chloride under standard acylation conditions to give an amide (**6**). At this point the alkene group is selectively oxidized utilizing ruthenium tetraoxide under Sharpless[3] conditions. This reaction is a key step and provides a clean and convenient method for

introduction of the acetic acid unit which is necessary for preparing the chain lengthened Metalaxyl analog. The allyl group has, therefore, served as a masked acetic acid equivalent. The synthesis of a Metalaxyl dimethylamide (**2b**) analog can be completed by reacting the amido acid (**2a**) with oxalyl chloride/DMF followed by dimethylamine addition. The overall yield for the five step process is approximately 35% and the reactions can be run on a reasonably large scale to provide intermediates and the desired final product in pure form.

We believe this procedure has general utility for the synthesis of chain extended analogs of Metalaxyl and further work on such analogs will be reported in due course.

Experimental Section

Proton NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR as thin films or nujol mulls. Boiling points and melting points are uncorrected. GC analyses were performed on a Gow Mac Model 69-350 chromatograph with a 6'x1/4" column containing 20% Carbowax 20M on Chromosorb P (80/100 mesh).

Preparation of N-(Hex-1-en-4-yl)-2,6-dimethylaniline (5)

A round-bottomed flask was equipped with a condenser, addition funnel, magnetic stirring bar and a nitrogen atmosphere. Into the flask was placed 2,6-dimethylaniline (20.0 g, 0.165 moles), 75 mL of dry THF, and 30 g of 3A molecular sieves. Proprionaldehyde (55.0 g, 0.947 moles) was added through the addition funnel in a dropwise fashion and the resulting mixture was stirred for 7 hrs. The reaction mixture was filtered and the solvent was removed *in vacuo*. This material (**4**) was sufficently pure to use in the subsequent step. Another round-bottomed flask was equipped with a condenser, rubber septum inlet, addition funnel, magnetic stirring bar and a nitrogen atmosphere. Into the flask was placed 50 mL of anhydrous THF and 90 mL of allyl magnesium chloride (a 2 M solution in THF), which was transferred by syringe. A 20.0 g (0.132 moles) portion of the imine (**4**) was placed in the addition funnel and was added dropwise to the reaction mixture with cooling. After 7 hrs, the reaction mixture was quenched with 100 mL of water with cooling and the resulting mixture was extracted with chloroform (3 x 100 mL). The combined chloroform extracts were dried over anhydrous magnesium sulfate,

filtered and concentrated *in vacuo* to produce 18.7 g (70 % yield) of a clear liquid (**5**) which was greater than 95 % pure by GC and had the following properties: bp 72°C (0.4 mm of Hg); ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J= 8.0 Hz, 3 H), 1.50 (m, 2 H), 2.25 (m, 8 H),3.00 (broad s, 1 H), 3.28 (pent, J= 5.6 Hz, 1 H), 5.11 (m, 2 H), 5.88 (m, 1 H), 6.83 (t, J= 8.0 Hz, 1 H) and 7.05 (d, J= 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 10.7, 19.5, 27.7, 39.2, 57.5, 117.8, 121.5, 129.1, 129.4, 129.5, 135.9 and 145.5; IR (thin film) 3381 and 991 cm^{-1}; mass spectrum, m/z 203 (M^+).

Preparation of N-(2,6-Dimethylphenyl)-N-(hex-1-en-4-yl)methoxyacetamide (6)

A round-bottomed flask was equipped with a condenser, addition funnel, magnetic stirring bar and a nitrogen atmosphere. Into the flask was placed 10.25 g (0.050 moles) of amine (**5**), 6.23 g (0.062 moles) of triethylamine and 100 mL of dry carbontetrachloride. A solution of 6.66 g (0.061 moles) of α-methoxyacetyl chloride in 50 mL of dry carbontetrachloride was added to the flask in a dropwise manner with cooling. The mixture was stirred overnight at room temperature and the triethylamine hydrochloride was removed by filtration. The filtrate was concentrated *in vacuo* and

distilled to yield 13.26 g (95% yield) of a liquid which was found to be greater than 95% pure by GC and had the following properties: bp 81 ^{o}C (0.1 mm of Hg); ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J= 8.0 Hz, 3 H), 1.50 (m, 2H), 2.10 (s, 6 H), 2.27 (m, 2 H), 3.20 (s, 3 H), 3.31 (s, 2 H), 3.78 (m, 1 H), 4.82 (m, 2 H), 5.61 (m, 1 H) and 7.00 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 19.1, 26.8, 38.02, 59.4, 60.6, 71.5, 117.1, 128.9, 129.6, 136.4, 137.5, 137.6, 138.1, 169.9; IR (thin film) 1672 cm^{-1}; mass spectrum, m/z 275 (M^{+}).

Preparation of N-(2,6-Dimethylphenyl)-N-(methoxyacetyl)-3-aminopentanoic Acid (2a)

A round-bottomed flask was equipped with a magnetic stirring bar and charged with 38 mL of acetonitrile, 38 mL of carbontetrachloride, 57 mL of water, 5.05 g (0.018 moles) of amide (**6**) and 16.0 g (0.075 moles) of sodium metaperiodate. To the resulting mixture was added 0.09 g ($4.34x10^{-4}$ moles) of ruthenium trichloride hydrate and this mixture was then stirred for 2 hrs. After separating the phases, the aqueous phase was extracted with methylene chloride (3x30 mL) and the combined organic phases were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield 5.08 g (94% yield) of a viscous oil (this material was

sufficiently pure for most purposes). The oil was then dissolved in chloroform (30 mL) and extracted with 5% aqueous sodium hydroxide (3x10 mL). The basic extracts were acidified in the cold with concentrated hydrochloric acid and then extracted with chloroform (3x30 mL). Drying and concentrating the chloroform extracts yielded 3.31 g (61%) of a light brown solid which had the following properties: mp 109-111°C; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J=7.2 Hz, 3 H), 1.42 (m, 2 H), 2.16 (s, 3H), 2.20 (s, 3 H), 2.71 (d of d, J=16.0 Hz, J=8.0 Hz, 1 H), 2.96 (d of d, J=16.0 Hz, J=3.0 Hz, 1 H), 3.26 (s, 3 H), 3.42 (s, 2 H), 4.10 (m, 1 H), 7.10 (m, 3 H) and 10.00 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 10.7, 18.9, 19.3, 26.7, 41.3, 58.2, 59.6, 71.2, 129.5, 129.8, 129.9, 136.9, 137.3, 137.7, 171.0 and 176.1; IR (nujol) 2800 (broad absorption), 1725 and 1618 cm^{-1}; mass spectrum m/z 293 (M^+).

Preparation of N,N-Dimethyl-N′-(2,6-dimethylphenyl)-N′-methoxyacetyl-3-aminopentamide (2b)

A round-bottomed flask was equipped with a condenser, magnetic stirring bar, rubber septum and a nitrogen atmosphere. Into the flask was placed 17 mL of methylene chloride and 0.748 g (0.010 moles) of DMF. The mixture was stirred with cooling and 0.356 ml

(0.00409 moles) of oxalyl chloride was added dropwise via syringe. A white precipitate formed while the mixture stirred for 15 mins. The carboxylic acid (**2a**) (1.0 g, 0.0034 moles) was added and the resulting pale yellow solution was stirred for another 15 mins at which point dimethylamine (0.384 g, 0.00341 moles) and triethylamine (0.692 g, 0.00685 moles) were added. The resulting mixture was stirred for another 15 mins and then was quenched with 25 mL of a cold brine solution. The organic phase was washed with aqueous sodium bicarbonate solution (3x20 mL), dried and filtered through a thin pad of silica gel. Concentration of the organic phase *in vacuo* produced 0.93 g (85% yield) of a viscous oil which had the following properties: bp 152^{0}C (0.05 mm of Hg); ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J=8.0 Hz, 3 H), 1.75 (m, 2 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 2.82 (s, 3 H), 2.90 (m, 2 H), 2.96 (s, 3 H), 3.28 (s, 3 H), 3.38 (s, 2 H), 4.02 (m, 1 H) and 7.06 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.1, 18.9, 19.1, 26.5, 35.7, 37.3, 37.5, 59.3, 59.7, 71.3, 128.8, 129.6, 129.8, 136.5, 137.1, 139.2, 169.9 and 171.4; IR (thin film) 1668 cm^{-1}; mass spectrum, m/z 320 (M^+).

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