Synthesis of the Insecticide Prothrin and Its Analogues from Biomass-Derived 5-(Chloromethyl)furfural

Fei Chang,† Saikat Dutta,† James J. Becnel,‡ Alden S. Estep,§ and Mark Mascal*†

†Department of Chemistry, University of California Davis, 1 Shields Avenue, Davis, California 95616, United States
‡Center for Medical, Agricultural, and Veterinary Entomology (CMAVE), Agricultural Research Service (ARS), United States Department of Agriculture (USDA), 1600 Southwest 23rd Drive, Gainesville, Florida 32608, United States
§Navy Entomology Center of Excellence, Box 43, Naval Air Station, Jacksonville, Florida 32212, United States

Supporting Information

ABSTRACT: Prothrin, a synthetic pyrethroid insecticide, was synthesized from the biomass-derived platform chemical 5-(chloromethyl)furfural in six steps and overall 65% yield. Two structural analogues of prothrin were also prepared following the same synthetic approach. Preliminary testing of these furan-based pyrethroids against the yellow fever mosquito Aedes aegypti indicates promising insecticidal activities.

KEYWORDS: biomass, furans, pyrethroids, synthesis, 5-(chloromethyl)furfural

INTRODUCTION

Previously, we have described the synthesis of the natural herbicide δ-aminolevulinic acid (2)† and the anti-ulcer drug ranitidine (Zantac) (3)‡ from the renewable platform chemical 5-(chloromethyl)furfural (CMF) (1), which can be derived in a single step from either sugars, cellulose, or raw biomass in isolated yields between 80 and 90%. In a continuing effort to expand the derivative markets of CMF (1), we now report a simple, six-step approach to the furan-based pyrethroid insecticide prothrin (4) alongside five-step routes to analogues 5 and 6.

The naturally occurring insecticide pyrethrum, isolated from flowers of Chrysanthemum sp., has been in commercial use for over 100 years.¹ Elucidation of the chemical structure of its active constituents [i.e., pyrethrins (7)] in 1924 ultimately led to the production of several synthetic pyrethroids.⁵ As a result of extensive structure–activity studies, the insecticidal and toxicological properties of these compounds typically surpass those of the natural products. Prothrin (4) is a member of the synthetic furan-based pyrethroids,⁶ which class also includes resmethrin (8), a high-volume commercial insecticide.⁷

Pyrethroids are generally well-suited for agricultural and household uses because of their biodegradability and low mammalian toxicity, and demand for these products has increased in the past decade with the declining use of organophosphates. However, all United States Environmental Protection Agency (U.S. EPA)-registered pesticides are regularly submitted to a process by which they are systematically reviewed to establish that they can still perform their intended function without unreasonable adverse effects on human health or the environment, and this process applies constant pressure on the development of new generations of products that are even more selective in their mode of action.

The synthesis of prothrin (4) was first reported in 1969 and is always completed by esterification of S-propargylfurfuryl alcohol (10) with chrysanthemic acid chloride.⁸ Because chrysanthemic acid is commercially available as a synthetic version of the natural product,⁸ the actual target of prothrin syntheses becomes compound 10, and most approaches to this molecule have centered around either the reaction of a metalated derivative of furfuryl alcohol (9) with a propargyl electrophile⁹ or a metalated acetylene with a S-methyl-substituted furfuryl alcohol derivative incorporating a leaving group (11) (Scheme 1).¹⁰,¹¹ Looking to the structures of both compound 10 and CMF (1), it becomes apparent that a concise route connecting them should be achievable, and we...
# Synthesis of the Insecticide Prothrin and Its Analogues from Biomass-Derived 5-((Chloromethyl)furfural)

Prothrin, a synthetic pyrethroid insecticide, was synthesized from the biomass-derived platform chemical 5-((chloromethyl)furfural) in six steps and overall 65% yield. Two structural analogues of prothrin were also prepared following the same synthetic approach. Preliminary testing of these furan-based pyrethroids against the yellow fever mosquito Aedes aegypti indicates promising insecticidal activities.
were naturally attracted to published methods that involved CMF (1) as a precursor to structure 11 but considered the use of organometallics a serious drawback to any industrial application of this synthetic approach. We proposed that the installation of the propargyl group could instead be achieved by copper(I)-mediated coupling of the chloromethyl functionality of CMF (1).12 The synthesis is shown in Scheme 2. Attempts to couple compound 1 and trimethylsilyl (TMS) acetylene in the presence of the aldehyde group were unsuccessful; thus, CMF (1) was protected as the dibutyl acetal (12).14 Coupling of the alkyne to compound 12 proceeded to give compound 13 in good yield, which was hydrolyzed to the furfural derivative (14). Reduction of compound 14 with sodium borohydride gave alcohol 15. Compound 15 is essentially a protected form of compound 10, but to complete the synthesis of prothrin (4), we esterified compound 15 with chrysanthemic acid chloride and, finally, desilylated with tetrabutylammonium fluoride. It was necessary to retain the TMS protecting group until the end of the synthesis, because any attempt to remove it at an earlier stage resulted in gradual isomerization of the triple bond to the allene.

The above-described route to prothrin (4) does not necessitate the synthesis of a 5-methylfurfuryl precursor to compound 10 but rather derives it directly from biomass. It also involves no organometallic reagents, requires no chromatographic separations until the final step, and proceeds in an overall 65% yield. The efficiency of this approach and the ready availability of CMF (1) presented an attractive opportunity to carry out analoging studies on the prothrin framework.

A highly apparent analogue to prothrin (4) is the cyanomethylfuran derivative (5), and this was targeted for synthesis along with the known resmethrin-like aryloxymethyl analogue (6).15 Thus, in the approach to analogues 5 and 6, the acetylene nucleophile is exchanged for cyanide and phenoxide, respectively. We had initially supposed that conversion of CMF (1) into acetal 12 would not be necessary in these cases, because compound 1 is known to be effectively substituted with nucleophiles, such as alcohols5a and azide anion. However, attempts to directly substitute the chloromethyl group in compound 1 with either phenol or cyanide were unsuccessful. From substituted acetals 16 and 17, the syntheses proceeded as for compound 4 but are one step shorter, because no deprotection is required at the end (Scheme 3). The overall yields of analogues 5 and 6 from CMF (1) were 51 and 70%, respectively.

**Scheme 1. Approaches to the Synthesis of 5-Propargylfurfuryl Alcohol (10)**

```
  M O
  | OPG
  | LG
  | goggles
  9
  | M = 10
  | O
  | OH

“LG, leaving group; PG, protecting group.
```

**Scheme 2.**

```
  1
  | O
  | H
  | Cl
  | Cl
  | 12
  | Obu

“Reagents: a, 1-butanol, concentrated HCl (catalyst), 98%; b, TMS-acetylene, CuI, K2CO3, CH3CN, 55 °C, 88%; c, 1 M aqueous HCl, 97%; d, NaBH4, MeOH, 0 °C, 98%; e, Chrysanthemic acid chloride, benzene, reflux, 95%; and f, Bu4NF, THF, −20 °C, 84%.
```

**Scheme 3.**

```
  12
  | Obu

“Reagents: a, for compound 16, NaCN, DMSO, 85 °C, 78%; for compound 17, phenol, K2CO3, DMSO, 50 °C, 87%; b, 1 M aqueous HCl; c, NaBH4, MeOH/CH2Cl2, 0 °C; and d, chrysanthemic acid chloride, benzene, reflux.
```

**MATERIALS AND METHODS**

2-(Chloromethyl)-5-(dibutoxy)methyl)furan (12).14 CMF (1) (2.00 g, 13.8 mmol) was dissolved in 1-butanol (40 mL), and concentrated HCl (0.1 mL) was added. The solvent was then removed using a rotary evaporator under high vacuum (0.1 mmHg) while cooling the evaporating flask in an ice-water bath. The product 12 was obtained as a yellow oil (3.721 g, 98%).1H NMR (300 MHz, CDCl3) δ: 6.32 (s, 1H), 6.29 (s, 1H), 5.47 (s, 1H), 4.53 (s, 2H), 3.51 (m, 4H), 1.52 (m, 4H), 1.35 (m, 4H), 0.88 (t, 7.3 Hz, 6H).13C NMR (75 MHz, CDCl3) δ: 153.1, 150.1, 110.4, 109.4, 96.5, 65.7, 37.7, 31.9, 19.3, 14.0. HRMS: (M − OBu)+, C10H14O2Cl calculated, 201.0682; found, 201.0678.

2-(Dibutoxymethyl)-5-[3-(trimethylsilyl)prop-2-yn-1-yl]furan (13). Copper(I) iodide (0.269 g, 1.41 mmol), potassium carbonate (0.328 g, 2.37 mmol), and (trimethylsilyl)acetylene (0.21 mL, 0.15 g, 1.5 mmol) were added to a solution of compound 12 (0.328 g, 1.19 mmol) in DMF (10 mL). The mixture was stirred for 30 min at room temperature, then concentrated HCl (0.1 mL) was added. The solvent was then removed using a rotary evaporator under high vacuum (0.1 mmHg), and the residue was purified by flash column chromatography (SiO2, hexanes/EtOAc 10:1), giving 13 (1.239 g, 87%).1H NMR (300 MHz, CDCl3) δ: 6.37 (s, 1H), 6.08 (s, 1H), 4.55 (s, 2H), 3.6 (m, 4H), 2.2 (t, 7.3 Hz, 6H).13C NMR (75 MHz, CDCl3) δ: 153.1, 150.1, 110.4, 109.4, 96.5, 65.7, 37.7, 31.9, 19.3, 14.0. HRMS: (M − OBu)+, C10H14O2Cl calculated, 201.0682; found, 201.0678.
mmol) in anhydrous acetonitrile (10 mL) under argon. The suspension was heated to 55 °C and stirred overnight. Saturated aqueous NaHCO₃ (50 mL) was added and the layers were separated. The aqueous layer was evaporated to give compound 13 as a yellow oil (0.353 g, 88%). H NMR (300 MHz, CDCl₃): δ: 6.31 (d, 3.1 Hz, 1H), 6.17 (d, 3.1 Hz, 1H), 5.45 (s, 1H), 3.61 (s, 2H), 3.56–3.44 (m, 4H), 1.59–1.52 (m, 4H), 1.40–1.32 (m, 4H), 0.90 (t, 7.5 Hz, 6H), 0.16 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ: 151.0, 150.1, 109.0, 106.7, 101.0, 96.5, 86.5, 65.4, 31.8, 20.1, 19.4, 13.9, 0.0. HRMS: (M + H)+, C₂₁H₃₁O₃Si calculated, 359.2037; found, 359.2032.

Mixture of (±)-cis- and (±)-trans-Prop-Thr (4). A mixture of (±)-cis- and (±)-trans-5-[3-(Trimethylsilyl)prop-2-yn-1-yl]fururan-2-yl)methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (0.143 g, 0.399 mmol) was dissolved in tetrahydrofuran (THF) (10 mL) and the solution was cooled to −20 °C in a dry-ice/ethylene glycol bath. A solution of tetrabutylammonium fluoride in THF (1.0 M, 0.44 mL, 0.44 mmol) was added dropwise with stirring. After 15 min at −20 °C, saturated ammonium chloride (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) to give compound 4a as a pale yellow oil (0.095 g, 84%). H NMR (300 MHz, CDCl₃): δ: 6.30 (t, 3.0 Hz, 1H, H₂ and H₃), 5.35 (d, 8.4 Hz, 0.4H, H₂), 5.04–4.90 (m, 2H, H₂ and H₃), 4.85 (d, 7.9 Hz, 0.6H, H₂), 3.56 (d, 2.4 Hz, 2H, H₂ and H₃), 2.13 (t, 2.4 Hz, 1H, H₂ and H₃), 2.05 (dd, 7.9 Hz, 5.4 Hz, 0.6H, H₂), 1.87 (t, 8.4 Hz, 0.4H, H₂), 1.72–1.65 (m, 6H, H₆, H₇, H₈, and H₉), 1.40 (d, 5.4 Hz, 0.6H, H₂), 1.24–1.09 (m, 6H, H₂, H₃, H₇, and H₈). ¹³C NMR (75 MHz, CDCl₃): δ: 171.9, 170.5, 150.5, 150.4, 149.2, 149.1, 136.4, 134.1, 121.1, 118.1, 111.4, 111.3, 107.3, 78.6, 70.3, 57.9, 57.5, 34.5, 32.9, 32.4, 30.9, 28.8, 28.7, 26.6, 25.9, 25.5, 22.1, 20.3, 18.5, 18.4, 18.2, 14.7. HRMS: (M + H)+, C₇H₇NO₂ calculated, 287.1642; found, 287.1639.

2-(Cyanomethyl)-5-(dibutoxymethyl)fururan (16). Sodium cyanide (0.174 g, 3.55 mmol) was added to a solution of compound 12 (0.811 g, 2.95 mmol) in dimethyl sulfoxide (DMSO) (6 mL) and the mixture was stirred at 90 °C under argon for 3 h. Saturated aqueous NaHCO₃ (50 mL) was added and the mixture was extracted with hexanes. The combined organic layers were washed with saturated aqueous NaHCO₃, dried over sodium sulfate, and decolorized with charcoal. The solvent was evaporated to give compound 16 as a light yellow oil (0.608 g, 78%). H NMR (300 MHz, CDCl₃): δ: 6.34 (s, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 3.60–3.42 (m, 4H), 1.65–1.47 (m, 4H), 1.45–1.27 (m, 4H), 0.90 (t, 7.5 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ: 152.8, 143.1, 115.6, 109.4, 99.2, 96.5, 63.9, 19.5, 17.8, 14.1. HRMS: (M + H)+, C₇H₆NO₂ calculated, 192.1019; found, 192.1019.

2-(Cyanomethyl)-5-(hydroxymethyl)fururan (20). Sodium borohydride (0.0650 g, 1.67 mmol) was added to a solution of compound 18 (0.155 g, 1.15 mmol) in methanol (10 mL) at 0 °C. The reaction was allowed to stir for 2 h at 0 °C. Saturated aqueous NH₄Cl (25 mL) was added and the mixture was extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound 20 as a brown oil (0.109 g, 95%). H NMR (300 MHz, CDCl₃): δ: 9.55 (s, 1H), 7.20 (d, 3.0 Hz, 1H), 6.56 (d, 3.0 Hz, 1H), 3.88 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ: 177.6, 153.2, 149.9, 122.7, 114.6, 111.7, 18.2. HRMS: (M + H)+, C₇H₆NO calculated, 136.0393; found, 136.0389.

2-(Cyanomethyl)-5-[(-cyanomethyl)furan-2-ylcarbonyl]-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (5). Compound 20 (0.152 g, 1.11 mmol) was dissolved in dry benzene (25 mL) under argon. A mixture of (±)-cis- and (±)-trans-3-[5-(Cyanomethyl)furan-2-yl)methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (0.143 g, 0.399 mmol) was dissolved in tetrahydrofuran (THF) (10 mL) and the solution was cooled to −20 °C in a dry-ice/ethylene glycol bath. A solution of tetrabutylammonium fluoride in THF (1.0 M, 0.44 mL, 0.44 mmol) was added dropwise with stirring. After 15 min at −20 °C, saturated ammonium chloride (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give compound 5 as a light yellow oil (0.244 g, 77%). H NMR (300 MHz, CDCl₃): δ: 6.28 (s, 1H, H₂ and H₃), 6.22 (s, 1H, H₂ and H₃), 5.28 (d, 8.3 Hz, 0.4H, H₂), 5.01–4.84 (m, 2H, H₂ and H₃), 4.80 (d, 7.0 Hz, H₂), 3.70 (s, 2H, H₂ and H₃), 1.99 (t, 7.0 Hz, 0.6H, H₂), 1.83 (t, 8.3 Hz, 0.4H, H₂), 1.68–1.56 (m, 6H, H₆, H₇, H₈, and H₉), 1.33 (d, 5.4 Hz, 0.6H, H₂), 1.20–1.00 (m, 6H, H₆, H₇, H₈, and H₉). ¹³C NMR (75 MHz, CDCl₃): δ: 172.0, 170.6, 150.9, 150.8, 149.0, 144.0, 135.7, 135.0, 121.1, 118.1, 115.6, 111.8, 111.7, 109.6, 57.8, 54.6, 33.2, 32.7, 31.0, 29.1, 28.6, 26.0, 25.6, 22.7, 20.5, 18.6, 18.5, 17.6. HRMS: (M + H)+, C₇H₇NO₂ calculated, 288.1600; found, 288.1612.

2-(Butoxymethyl)-5-(phenoxymethyl)fururan (17). Phenol (0.232 g, 2.47 mmol) and potassium carbonate (0.360 g, 2.61
mmol) were added to a solution of compound 12 (0.564 g, 2.05 mmol) in DMSO (5 mL), and the mixture was stirred at 50 °C under argon for 5 h. Saturated aqueous NaHCO3 (50 mL) was added and the mixture was extracted with hexanes. The organic layers were combined, washed with saturated aqueous NaHCO3 and dried over sodium sulfate. The solvent was evaporated, and the residue was taken up in dichloromethane (20 mL). The organic layers were combined, dried over sodium sulfate, and the solvent was evaporated. The residue was taken up in dichloromethane (25 mL), 7.25 (m, 2H), 7.02 (s, 1H, OH).13C NMR (75 MHz, CDCl3): δ: 157.0, 153.0, 137.5, 129.8, 120.7, 115.2, 108.9, 71.2, 62.6, 57.6. HRMS: (M + H)+, C12H13O3 calculated, 205.0859; found, 205.0860.

5-(Phenoxy)methyl]furural (19).15 A mixture of compound 17 (0.322 g, 0.970 mmol) and 1 M HCl (10 mL) was stirred for 2 h and then extracted with dichloromethane (20 mL). The organic layers were combined, washed with saturated aqueous NaHCO3, and dried over sodium sulfate. The solvent was evaporated. The residue was taken up in dichloromethane (25 mL), and the mixture was stirred at 50 °C for 5 h. Saturated aqueous NaHCO3 (50 mL) was added and the mixture was extracted with dichloromethane (20 mL). The organic layers were combined, dried over sodium sulfate, and the solvent was evaporated.

**RESULTS AND DISCUSSION**

Preliminary entomological testing of pyrethroids 5 and 6 was conducted against prothrin (4) and the commercial insecticide permethrin as standards using the "Orlando" strain of the pesticide-susceptible mosquito A. aegypti, as described above.

Mortality was recorded at 24 h post-application, and three replicates were performed. Averaged mortality counts are included in Table S1 of the Supporting Information, and the estimated LD50 values are listed in Table 1. The activities of analogues 5 and 6 are thus within about a log of that of prothrin (4), which itself is more active than the natural pyrethrins.17 Further testing will determine whether these derivatives show any useful selectivity in their action.

In conclusion, CMF (1), a biomass-derived platform chemical, is an attractive starting material for the high-yield synthesis of prothrin (4) and analogues 5 and 6. This scalable synthetic approach could be generalized toward the renewable-sourced production of a variety of furan-based pyrethroids, which will enable further structure–activity studies and potential commercial development of this important family of insecticides.

**ASSOCIATED CONTENT**

Supporting Information

Details of entomological data and 1H and 13C NMR data for all compounds prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

---

**Table 1. Estimated LD50 Values (ng/Mosquito) of Analogues 5 and 6 with Prothrin (4) and Permethrin Standards against A. aegypti "Orlando" Strain Mosquitoes**

<table>
<thead>
<tr>
<th>toxicant</th>
<th>LD50 (ng)</th>
</tr>
</thead>
<tbody>
<tr>
<td>permethrin</td>
<td>0.07</td>
</tr>
<tr>
<td>prothrin (4)</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Author Information

Corresponding Author

*E-mail: mjmascal@ucdavis.edu.

Notes

The authors declare no competing financial interest.

References

(8) Commercial chrysanthemic acid is a synthetic mixture of cis and trans isomers.