A SHORT AND CONVENIENT SYNTHESIS OF (2*E*,4*E*)-*N*-ISOBUTYL-7-(3,4-METHYLENEDIOXYPHENYL)HEPTA-2,4-DIENAMIDE

Goverdhan L. KAD, Ajay K. ARORA, Sukhwinder SINGH and Jasvinder SINGH*

Department of Chemistry,
Panjab University, Chandigarh 160014, India

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(2*E*,4*E*)-*N*-Isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,4-dienamide (*I*) possessing insecticidal activity against flies and mosquitoes has been synthesized in fine yield from 3-(3,4-methylenedioxyphenyl)prop-1-ene (*II*) using hydroboration–oxidation with acetoxyborohydride and a modified Wittig reaction as the key steps.

Pepper (the genus *Piper*) has attracted considerable interest in recent years because of its reputation for providing a number of physiologically active compounds with properties ranging from anaesthetics to insecticides, most of the compounds isolated being amides of unsaturated arylalkanoic acids[1,2].

Parmar and coworkers[3] recently isolated (2*E*,4*E*)-*N*-isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,4-dienamide (*I*) from extracts of stem and leaves of *Piper falconeri* C. DC. Structure *I* was assigned to this compound on the basis of spectral studies. It was found to possess a significant insecticidal activity against *Musca domestica* (house fly) and *Aëdes aegypti* (mosquito). We report here a simple and unambiguous synthesis of *I* (Scheme 1).

Treatment of 3-(3,4-methylenedioxyphenyl)prop-1-ene (*II*) with acetoxyborohydride[4] (prepared in situ from sodium borohydride and mercuric acetate in tetrahydrofuran) followed by oxidation with alkaline hydrogen peroxide gave 3-(3,4-methylenedioxyphenyl)propan-1-ol (*III*) in an 80% yield. Compound *III* was subjected to oxidation[5] with pyridinium chlorochromate to yield the corresponding aldehyde *IV*. A modified Wittig[6] reaction of this aldehyde with dimethyl ethyl 4-phosphonocrotonate afforded ethyl (2*E*,4*E*)-7-(3,4-methylenedioxyphenyl)hepta-2,4-dienoate (*V*) which, upon alkaline hydrolysis, resulted in the corresponding acid *VI*. Treatment of this acid with thionyl chloride produced the acid chloride which, on

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* The author to whom correspondence should be addressed.

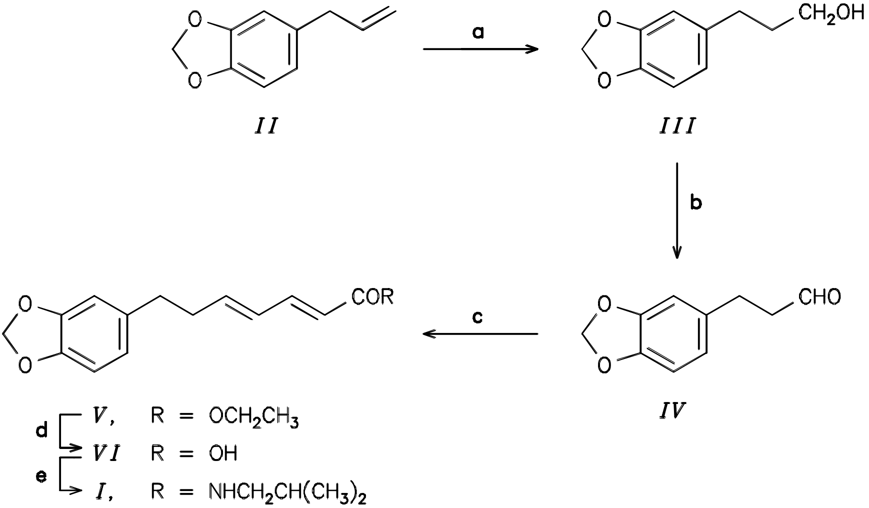
subsequent reaction with isobutylamine, afforded (2*E*,4*E*)-*N*-isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,4-dienamide (*I*) in fine yield (19% calculated on compound *II*).

EXPERIMENTAL

^1H NMR spectra were recorded in $CDCl_3$ on a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal standard; chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. IR spectra of thin films were recorded on a Perkin–Elmer IR 337 spectrophotometer (wavenumbers in cm^{-1}). Unless otherwise stated all organic extracts were dried over anhydrous sodium sulfate. Silica gel (ASC, Bombay) impregnated with calcium sulfate was used for TLC.

3-(3,4-Methylenedioxyphenyl)propan-1-ol (*III*)

Mercuric acetate (3.93 g, 12.3 mmol) was added slowly under cooling (ice bath) in a nitrogen atmosphere to a suspension of sodium borohydride (0.94 g, 24.7 mmol) in tetrahydrofuran (40 ml).



a, (i) $NaBH_4$, $(CH_3COO)_2Hg$, THF; (ii) H_2O_2

b, pyridinium chlorochromate, CH_2Cl_2

c, $(CH_3O)_2P(O)CH_2CH{=}CHCOOCH_2CH_3$, NaH, THF

d, NaOH, CH_3OH, H_2O

e, (i) $SOCl_2$; (ii) $(CH_3)_2CHCH_2NH_2$, ether

SCHEME 1

The mixture was stirred for 1 h at 0 °C and 15 min at room temperature, then 3-(3,4-methylenedioxyphenyl)prop-1-ene (*II*; 2.0 g, 12.3 mmol) was added dropwise. After stirring for 16 h at room temperature the reaction mixture was cooled to 0 °C and then 3 M aqueous sodium hydroxide (100 ml) was slowly added. Hydrogen peroxide (10 ml, 30% aqueous solution) was introduced dropwise with continuous stirring. The temperature was then raised slowly and the reaction mixture was heated for 1 h at 70 °C during which the mercury coagulated. The contents were brought to room temperature, decanted to separate the mercury, and saturated with sodium chloride. The aqueous layer was extracted with ether (3 × 20 ml). The combined organic extracts were washed with water (2 × 20 ml) and brine (10 ml), dried, and concentrated under reduced pressure. The residue was purified by column chromatography over neutral alumina to yield compound *III*, 1.76 g (80%). ^{1}H NMR spectrum: 1.7 m, 2 H ($\mathbf{CH_2}CH_2OH$); 2.6 t, 2 H, *J* = 6 ($ArCH_2$); 3.0 bs, 1 H (OH, exchangeable with D_2O); 3.6 t, 2 H, *J* = 6 (CH_2OH); 5.9 s, 2 H (OCH_2O); 6.8–7.0 m, 3 H (aromatic protons). IR spectrum: 3 370, 2 900, 1 510, 1 470, 1 250, 980, 930. For $C_{10}H_{12}O_3$ (180.2) calculated: 66.7% C, 6.7% H; found: 66.5% C, 6.8% H.

3-(3,4-Methylenedioxyphenyl)propan-1-al (*IV*)

To stirred suspension of pyridinium chlorochromate (2.8 g, 13.0 mmol) in anhydrous dichloromethane (30 ml) a pinch of anhydrous sodium acetate was added, followed by a solution of the hydroxy derivative *III* (1.76 g, 9.7 mmol) in dichloromethane (15 ml) and stirring was continued for 2 h. Ether (40 ml) was added and the mixture was allowed to settle and then passed through a short pad of silica gel. Removal of solvent under reduced pressure afforded aldehyde *IV*; 1.42 g (82%). ^{1}H NMR spectrum: 2.3 m, 2 H ($\mathbf{CH_2}CHO$); 2.6 t, 2 H, *J* = 6 ($ArCH_2$); 5.9 s, 2 H (OCH_2O); 6.8–7.0 m, 3 H (aromatic protons); 9.85 bs, 1 H (CHO). IR spectrum: 2 900, 2 720, 1 740, 1 510, 1 470, 1 250, 980, 930. For $C_{10}H_{10}O_3$ (178.2) calculated: 67.4% C; 5.7% H; found: 67.2% C, 5.8% H.

Ethyl (2*E*,4*E*)-7-(3,4-Methylenedioxyphenyl)hepta-2,4-dienoate (*V*)

A solution of dimethyl ethyl 4-phosphonocrotonate (1.94 g, 7.8 mmol) in tetrahydrofuran (10 ml) was added dropwise at room temperature to a stirred suspension of sodium hydride (0.38 g, 15.8 mmol) in tetrahydrofuran (10 ml). The reaction mixture was stirred till a clear solution was obtained. Thereafter aldehyde *IV* (1.40 g, 7.86 mmol) in tetrahydrofuran (20 ml) was added dropwise to the above solution and stirred for 3 h. The resulting mixture was decomposed with water (5 ml), extracted with ether (3 × 25 ml) and dried. Evaporation of the solvents gave the crude material, which on purification by column chromatography using light petroleum–ether (9 : 1) as eluent, furnished 1.53 g (71%) of compound *V* as a viscous liquid. ^{1}H NMR spectrum: 0.96 t, 3 H, *J* = 6 ($OCH_2\mathbf{CH_3}$); 2.6 m, 4 H ($ArCH_2CH_2$); 3.9 m, 2 H ($O\mathbf{CH_2}CH_3$); 5.7 m, 3 H (OCH_2O and OOC–**CH**=CH); 7.2 m, 1 H (OOC–CH=**CH**). IR spectrum: 2 910, 2 840, 1 740, 1 610, 1 520, 1 470, 1 265, 1 050, 860. For $C_{16}H_{18}O_4$ (274.3) calculated: 70.1% C, 6.6% H; found: 70.2% C, 6.8% H.

(2*E*,4*E*)-7-(3,4-Methylenedioxyphenyl)hepta-2,4-dienoic Acid (*VI*)

A mixture of ester *V* (1.1 g, 4.0 mmol), sodium hydroxide (0.27 g, 6.75 mmol), water (1 ml) and methanol (4 ml) was refluxed for 5 h. Methanol was removed under reduced pressure and the residue was diluted with water. The unreacted starting material was removed by extracting with ether and the aqueous phase was neutralized with hydrochloric acid (15%), extracted with ether (3 × 25 ml) and dried. Evaporation of solvent under reduced pressure afforded after recrystallization 0.64 g (65%) of pure acid *VI*. ^{1}H NMR spectrum: 2.5–2.7 m, 4 H ($ArCH_2CH_2$); 5.7–5.8 m, 3 H (OCH_2O and OOC–**CH**=CH); 6.0 m, 2 H (OOC–CH=CH–**CH**=**CH**); 6.7 m, 3 H (aromatic protons); 7.2 m, 1 H

(OOC–CH=**CH**); 8.6 bs, 1 H (COOH, D_2O exchangeable). IR spectrum: 3 400, 2 960, 2 800, 1 720, 1 620, 1 510, 1 470, 1 250, 850. For $C_{14}H_{14}O_4$ (246.3) calculated: 68.3% C, 5.7% H; found: 68.1% C, 5.6% H.

(2*E*,4*E*)-*N*-Isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,4-dienamide (*I*)

A mixture of acid *VI* (0.28 g, 1.14 mmol) and thionyl chloride (0.30 g, 2.39 mmol) was heated gently until evolution of gases stopped. Then the reaction mixture was cooled to 0 °C , diluted with ether (10 ml) and a solution of isobutylamine (0.37 ml, 3.72 mmol) in ether (10 ml) was added dropwise during 25 min. After stirring for 1 h the reaction mixture was diluted with ether (20 ml) and treated with 5% aqueous NaOH (20 ml), 10% aqueous HCl (20 ml) and then with water (20 ml). The separated ether layer was dried and evaporated. The residue after column chromatography using hexane–ether (1 : 1) yielded 0.212 g (62%) of pure amide *I*. ^{1}H NMR spectrum: 0.9 d, 6 H, *J* = 6 (CH(**CH**$_3$)$_2$); 1.8 m, 1 H (**CH**(CH_3)$_2$); 2.5–2.7 m, 4 H ($ArCH_2CH_2$); 3.1 t, 2 H, *J* = 7 (NH**CH**$_2$); 5.5–5.9 m, 3 H (OCH_2O and CH=**CH**CONH); 6.1 m, 2 H (**CH**=**CH**–CH=CH–CONH); 6.7 m, 3 H (aromatic protons); 7.2 m, 1 H (**CH**=CHCONH). IR spectrum: 3 300, 2 880, 1 650, 1 620, 1 510, 995. For $C_{18}H_{23}NO_3$ (301.4) calculated: 71.7% C, 7.7% H, 4.7% N; found: 71.5% C, 7.6% H, 4.7% N.

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