

processes are proposed for other oxime ethers: Ito and Matsuura (1975); Sato et al. (1972)]; the imine would rapidly hydrolyze or polymerize. Thermally, oxime ethers are very stable relative to their imine counterparts, showing little tendency even to isomerize (Curtin et al., 1966). Photochemically, PBald is probably formed directly rather than via PBalc since the alcohol is present in <1% amount and is not photooxidized to PBald.

The present studies show pyrethroid-like activity with relatively non-lipophilic propyretroids that undergo metabolic conversion to neuroactive products; i.e., 2-H, 2-Me, and 2-CHO appear to be propyretroids acting only after conversion to 1. Their toxicity to insects decreases in the sequence 1 > 2-H > 2-Me or 2-CHO and on the cockroach cercal sensory nerve in the order 1 > 2-Me or 2-CHO. The use of DEF with 2-CHO and Pip with 2-Me has little or no effect on their 24-h LD₅₀ values but clearly increases the time for KD₅₀, presumably via inhibition of activation (Sun and Johnson, 1960). Although 1 is active at 5×10^{-8} M in the nerve assay, 2-Me and 2-CHO are inactive at 10^{-6} M and their activity at 10^{-5} M is attenuated or blocked by Pip and DEF, respectively. There is thus in vivo and in vitro evidence that the cercal nerve and/or other insect tissues hydrolyze 2-CHO and oxidize 2-Me to 2-H, which in turn is oxidized to 1, the active pyrethroid. The principles of derivatization used in the present study may be applicable in other pyrethroid series to obtain propyretroids of modified and possibly improved physical or toxicological properties.

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Registry No. (E)-1, 67038-97-5; (Z)-1, 67038-98-6; 2-H, 86374-22-3; 2-Me, 86374-23-4; 2-CHO, 86374-24-5.

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Direct Synthesis of Dipteran Sex Pheromones by the Wittig Reaction in a Heterogeneous Medium

Yves Le Bigot, Michel Delmas,* and Antoine Gaset

The Wittig reaction carried out in a solid-liquid medium under mild experimental conditions led to the single-step synthesis of various Dipteran sex pheromones from nonanal and tetradecanal. This method of synthesis was characterized by its excellent yield.

The synthesis of pheromones specific to some insect species has proved to be liable to improve the efficiency of pest control in agriculture (Morgan et al., 1974; Jacobson, 1975; Rossi, 1977; Campion et al., 1978). The use of the attractant power of these derivatives, coupled with that of an insecticide (Boyd et al., 1974; Carlson and Beroza, 1973; Carlson et al., 1971; Kinzer and Mc Daniel, 1978),

affords a more efficient action on a particular insect species; there is no harmful ecological interaction with the environment, contrary to what is often observed when high rates of insecticides are sprayed.

The most active *Musca domestica* pheromones are (Z)-9-tricosene (Carlson et al., 1971, 1974; Richter et al., 1976) and (Z)-9-heneicosene (Richter, 1974). Their mixture in the 7:3 ratio is known to be particularly efficient (Bestmann et al., 1974). In *Musca autumnalis*, (Z)-14-nonacosene has been used as a mating stimulant (Uebel et al., 1975).

The potential interest of the housefly pheromones (Julia, 1976; Kuepper and Streck, 1976) led to the investigation of various methods of synthesis. Kuepper and Streck

Faculté des Sciences et Techniques—B.P. W, Sfax, Tunisia (Y.L.B.), and Laboratoire de Chimie Organique et d'Agrochimie, Ecole Nationale Supérieure de Chimie, Institut National Polytechnique, 118 route de Narbonne, 31077 Toulouse Cédex, France.

Table I^a

$$\text{CH}_3(\text{CH}_2)_7\text{CHO} + \text{Ph}_3\text{P}^+(\text{CH}_2)_{13}\text{CH}_3, \text{Br}^- \xrightarrow[\text{solvent (20 mL)}]{\text{base}}$$

$$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{12}\text{CH}_3 + \text{Ph}_3\text{PO}$$

base	X solvent					
	THF (60 °C)		1,4-dioxane (60 °C)		1,4-dioxane (90 °C)	
	X, %	Y, %	X, %	Y, %	X, %	Y, %
NaOH	5	95	7	93	20	80
KOH	5	95	6	94	20	80
K ₃ PO ₄	0	5	4	7	50	5
Na ₂ CO ₃	0	0	0	0	5	0
KHCO ₃	0	0	2	0	5	0
K ₂ CO ₃	0	0	5	0	73	0

^a Reaction time = 6 h. Y is the aldolization product $\text{CH}_3(\text{CH}_2)_7\text{CHOHCH}(\text{CHO})[(\text{CH}_2)_6\text{CH}_3]$. The difference with respect to 100% corresponds to the unreacted aldehyde.

(1975, 1976) used condensation reactions catalyzed by transition metals and obtained 10% overall yields for the isomer mixture. Yoshida (1976) and Huelsmann (1977) reacted a Grignard reagent with a halide. Kovalev et al. (1977), as well as Shani (1979), could achieve the synthesis in several steps. Krasavtsev (1979, 1980) used an electrochemical process whereas Bestmann et al. (1974) called upon the Wittig reaction to obtain the active isomer with a maximum overall yield of 32%. The proportions of isomers could be improved to 95% Z in a "directed Wittig reaction" (Uebel et al., 1975).

A solid-liquid transfer process can be applied to the Wittig reaction. This original method used successfully for some aliphatic aldehydes (Delmas et al., 1980, 1982; Le Bigot et al., 1982) was therefore liable to lead to the direct synthesis of Dipteran sex pheromones in excellent yield.

EXPERIMENTAL SECTION

Chemicals. Pelargonaldehyde, 1-bromododecane, 1-bromotridecane, 1-bromotetradecane, 1-bromopentadecane, and 1-bromohexadecane were Fluka Chemicals. Tetradecylaldehyde was an Aldrich chemical. All these derivatives were used without any further purification.

Phosphonium Salts. Alkyltriphenylphosphonium bromides were prepared in toluene (250 mL) from 1-bromoalkanes (0.25 mol) and triphenylphosphine (0.2 mol). The mixture was stirred and refluxed for 8 h and then cooled to room temperature. The solvent was evaporated under vacuum and the residue could be used directly

without any further purification.

Wittig Reaction. The phosphonium salt (0.12 mol), potassium carbonate (15 g), 1,4-dioxane (100 mL), water (2 mL), and the aliphatic aldehyde (0.1 mol) were successively introduced into a three-necked reaction vessel equipped with a mechanical stirrer, a thermometer, and a reflux condenser.

The reaction mixture was stirred and heated to 90 °C (Table I and II). After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was treated with ether and the mixture filtered to remove the triphenylphosphine oxide. Ether was then evaporated under reduced pressure.

The reaction product was then suspended in hexane (300 mL) and filtered rapidly on 100 g of silica gel, Merck 40. After the solvent had been evaporated, the pure alkene was characterized by GLC.

The two geometrical isomers were separated according to the technique described by Gupta and Dev (1963), using a column of alumina impregnated with silver nitrate (50 g of Al₂O₃/g of alkene) and a hexane-ether mixture as the eluent. The stereochemical purity of the Z isomer was corroborated by the absence of the absorption band at 967 cm⁻¹ (Carlson et al., 1971; Gribble and Sanstead, 1973; Sonnet, 1974).

Gas Chromatography. The reaction was followed by using a vapor-phase chromatograph, Varian 2700, equipped with a flame ionization detector and an OV-101 column (3% methyl silicone on Chromosorb W-HP, 80-100 mesh, 1.65 m long). The carrier gas was nitrogen. The following temperatures were selected: injector, 350 °C; detector, 250 °C; oven, 100-300 °C, 20 °C/min.

IR and ¹H NMR Spectra. The IR spectra were recorded on a Perkin-Elmer 177 spectrophotometer, and the NMR spectra on a Varian T 60 apparatus at 60 MHz in CDCl₃ with Me₄Si as the internal standard.

The spectra of the closely structurally related derivatives investigated exhibited the following characteristics: ¹H NMR (CDCl₃) δ 0.9 (t, 2 CH₃), 1.3 (m, n-CH₂), 2 (m, CH₂), 5.3 (m, CH=CH, J = 5 Hz) (the high value of the coupling constant of the two vinylic protons is characteristic of the occurrence of the pure cis alkene); IR (film) 3010, 720 cm⁻¹ [the absence of the absorption band at 967 cm⁻¹ corroborated that the cis alkene obtained was stereoisomerically pure (Carlson et al., 1971)].

RESULTS AND DISCUSSION

The synthesis of (Z)-9-tricosene from nonanal and tetradecyltriphenylphosphonium bromide was followed to maximize production of product and minimize or eliminate the aldol product that usually occurs when the Wittig reaction is carried out in heterogeneous media (Weber and Gokel, 1977; Keller, 1979).

Table II

$$\text{R}_1\text{CHO} + \text{Ph}_3\text{P}^+\text{CH}_2\text{R}_2, \text{Br}^- \xrightarrow{1,4\text{-dioxane}} \text{R}_1\text{CH}=\text{CHR}_2 + \text{Ph}_3\text{PO}$$

R ₁	R ₂	major product	insect species (reference)	reaction time, h	yield in alkenes, % ^a	Z isomer, % ^b
CH ₃ (CH ₂) ₇	CH ₃ (CH ₂) ₁₂	(Z)-9-tricosene	<i>M. domestica</i> (Rossi, 1977)	6	73	82
CH ₃ (CH ₂) ₇	CH ₃ (CH ₂) ₁₀	(Z)-9-heneicosene	<i>M. domestica</i> (Bestmann, 1974)	5.5	72	83
CH ₃ (CH ₂) ₇	CH ₃ (CH ₂) ₁₄	(Z)-9-pentacosene	<i>M. domestica</i> (Krasavtsev, 1979)	6.5	70	85
CH ₃ (CH ₂) ₁₂	CH ₃ (CH ₂) ₁₁	(Z)-13-heptacosene	<i>M. autumnalis</i> (Sonnet, 1974)	6	75	83
CH ₃ (CH ₂) ₁₂	CH ₃ (CH ₂) ₁₃	(Z)-14-nonacosene	<i>M. autumnalis</i> (Sonnet, 1974)	6.5	71	80

^a Yields estimated by GLC using a nonpolar column (Varian OV-101) and corrected after the separation of the products.

^b Percentage determined after the separation of the isomers over a column of alumina impregnated with 20% silver nitrate.

Since it had been previously shown, in the case of aliphatic or aromatic aldehyde (Delmas et al., 1980, 1982); Le Bigot et al., 1982), that the reaction could not proceed in anhydrous media, a reaction medium hydration rate of two water molecules per nonanal molecule was selected.

The data obtained in THF at 60 °C and in 1,4-dioxane at 60 and 90 °C, in the presence of various bases, are listed in Table I.

When the olefin formed is not stabilized by resonance as in this reaction, the rate-limiting step is decomposition of the betaine. For aldehydes, this step is exothermic. The temperature effect found here may be due to increased mass transfer at higher temperatures.

The use of strong bases, such as NaOH and KOH, led to the preferential formation of the aldolization product, irrespective of the reaction conditions. These results suggested that the most suitable base should lead to the formation of the ylide without reacting with the hydrogen atom α to the carbonyl function. Phosphates and carbonates seem to comply satisfactorily with this double requirement. Potassium phosphate, which is not usually used in this type of condensation, allowed (*Z*)-9-tricosene to be obtained in a yield close to 50%. Although sodium carbonate is known to be a poor catalyst of aldolization reactions (Yahagi, 1978), it did not prove to be efficient for the synthesis of this olefin. The highest yields in (*Z*)-9-tricosene were obtained in the presence of potassium carbonate. The difference observed in the behavior of these two carbonates can be accounted for by the lower value of the lattice energy of the crystalline network of K_2CO_3 which thus promotes the involvement of the basic entities (Artaud et al., 1980).

Phosphonium salts bearing a long alkyl chain could be used directly after the evaporation of the solvent. Weak bases do not promote any elimination reaction from the halogenated derivative used in slight excess and do not interact with the other reactants, such as the residual amounts of triphenylphosphine.

This method of synthesis in heterogeneous media is also characterized by its good selectivity. The data listed in Table II clearly show that the *Z* isomer is markedly prevailing. The activity of an 85:15 *Z-E* mixture is known to be nearly equivalent to that of the pure *Z* isomer on *M. domestica* (Carlson and Beroza, 1973). As a result, the procedure reported here could be applied directly to the industrial synthesis of these pheromones. However, the *Z* isomer could be obtained pure. The isomer mixture was chromatographed over alumina impregnated with 20% silver nitrate (Gupta and Dev, 1963). As the *Z* isomer than forms a π complex with silver ions, it is strongly retained by the column (Tumlinson et al., 1975).

After the *E* isomer had been eluted, a more polar eluent could be used to obtain the pure *Z* isomer. The purity of the product was shown by the absence of the IR absorption band at 967 cm^{-1} which corresponds to the out-of-plane deformation vibrations characteristic of the *E* isomer and was corroborated by the value of the coupling constant between the two vinylic protons: $J_{AB} = 5$ Hz.

The very mild experimental conditions selected (hydrated medium, reaction temperature, weak base preventing the aldolic condensation) led to (*Z*)-9-tricosene in high yield together with a good selectivity. This process could be applied successfully to the preparation of other Diptera pheromones: (*Z*)-9-heneicosene and (*Z*)-9-pentacosene (*M. domestica*) and (*Z*)-13-heptacosene and (*Z*)-14-nonacosene (*M. autumnalis*). The phosphonium salt

was not previously purified; the reaction yield and stereoselectivity were quite satisfactory (Table II). The operation of the Wittig reaction in solid-liquid heterogeneous media therefore appears as a process that can readily be transported on a larger scale and is thus liable to make easier the synthesis of *Z*-unsaturated pheromones.

Registry No. $CH_3(CH_2)_7CHO$, 124-19-6; $CH_3(CH_2)_{12}CHO$, 124-25-4; $Ph_3P^+CH_2(CH_2)_{12}CH_3Br^-$, 25791-20-2; $Ph_3P^+CH_2(CH_2)_{10}CH_3Br^-$, 15510-55-1; $Ph_3P^+CH_2(CH_2)_{14}CH_3Br^-$, 14866-43-4; $Ph_3P^+CH_2(CH_2)_{11}CH_3Br^-$, 13266-02-9; $Ph_3P^+CH_2(CH_2)_{13}CH_3Br^-$, 1944-80-5; (*Z*)-9-tricosene, 27519-02-4; (*Z*)-9-heneicosene, 39836-21-0; (*Z*)-9-pentacosene, 51865-00-0; (*Z*)-13-heptacosene, 54863-75-1; (*Z*)-14-nonacosene, 54863-80-8.

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