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A STEREOSELECTIVE SYNTHESIS OF METHYL TRANS- 3 - (2, 2 - DICHLOROETHENYL) - 2, 2 - DIMETHYLCYCLOPROPANECARBOXYLATE

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Abstract: A convenient method is described for the stereoselective synthesis of methyl trans - 3 - (2, 2 -dichloroethenyl) - 2, 2 - dimethylcyclopropanecarboxylate (5) via methyl 3, 3 - dimethyl - 4, 6, 6, 6 -tetrachlorohexanoate (4) as a key intermediate, which was obtained by addition of carbon tetrachloride to methyl 3,3-dimethyl-4-pentenoate (3). Treatment of (4) with sodium methoxide in a single-vessel via methyl 4,6,6-trichloro-3,3-dimethyl-5-hexenoate (6) gave trans-rich (5) in excellent yield.

Since the discovery of permethrin (**1**) and cypermethrin (**2**) by Elliott[1,2], esters of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxlic acids have become one of the most important classes of agricultural insecticides. For production of the acid part of this synthetic pyrethroid, two of the many possible methods have so far been utilized commercially. one is the addition of a diazoacetate to 2-methyl-5,5,5-trichloro-2-pentene[3], and the other is the dehydrochlorogenation of the 4,6,6,6-tetrachloro-3,3-dimethylhexanoate[4]. Under standard or

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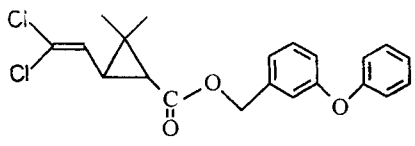
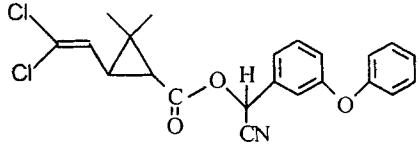
control conditions these methods usually produce an approximate 1:1 mixture of cis- and trans- isomers or a cis-rich product. Recently, however, much attention has been focused on the synthetic of trans- isomer, because the esters derived from the trans- acid, such as 3-phenoxybenzyl trans - 3 - (2, 2 - dichloroethenyl) - 2, 2 - dimethylcyclopropanecarboxylate and (s)-a-cyano - 3 - phenoxybenzyl (1R) - trans - 3 - (2, 2 - dichloroethenyl) - 2, 2 - dimethylcyclopropanecarboxylate, have been shown to exhibit highly potent insecticidal activity with much less toxic to mammals than the cis-esters[5~7].



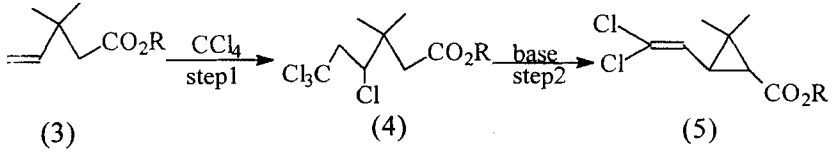
Permethrin (1)



Cypermethrin (2)

The method developed herein is based on the addition of carbon tetrachloride to methyl 3,3-dimethyl-4-pentenoate (**3**) (step 1), and the subsequent dehydrohalogenation and cyclization of the resulting halide with a base (step 2) to afford the desired cyclopropanecarboxylate (**5**), as shown in the following scheme 1 .

scheme 1



(3) (4) (5)

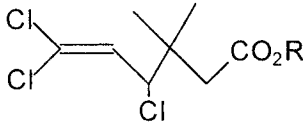
Addition of Carbon tetrachloride to (3) (step 1).

The addition was first investigated either in the presence of a radical initiator or under irradiation[7]. Many radical initiators, such as benzoyl peroxide (BPO) and transition metal-amine complexes[8, 9] , were found to be good alternatives in carbon tetrachloride case. The addition yield varied depending on amounts and varieties of radical initiators.

A modification for the addition requires adding BPO in several portions to a solution of (**3**) in carbon tetrachloride, while the mixture is heated at 80°C for 8 hours to produce (**4**) in 95% yield.

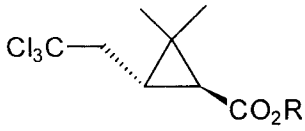
Preparation of Methyl 3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (5) (step 2).

The conversion of (**4**) to (**5**) requires two equivalents of the base. Theoretically, this double dehydrohalogenation would be expected to proceed consecutively, because one is a 1,2- and the other is a 1,3-elimination. The 1,2-dehydrohalogenation will afford either methyl 4,6,6-trichloro-3,3-dimethyl-5-hexenoate (**6**) or methyl 6,6,6-trichloro-3,3-dimethyl-4-hexenoate (**7**) while 1,3 - dehydrohalogenation, methyl 2, 2 -dimethyl - 3 - (2, 2, 2 - trichloroethyl) cyclopropanecarboxylate (**8**), as an intermediate.

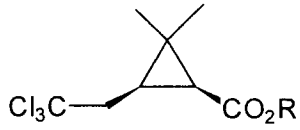


(6)

(7)



trans-(8)



cis-(8)

K. Kondo and his co-workers reported compounds (**7**) and cis-(**8**) were desirable intermediates for stereoselective preparation of cis-(**5**), while compounds (**6**) was selectively transformed into trans-(**5**). Treating ethyl 4,6,6,6-tetrachloro-3,3-dimethylhexanoate (4, R=Et) with an alkali ethoxide in ethanol, a trans-rich end-product (trans/cis=74/26) was obtained in 96% yield[10].

In fact, when the reaction mixture was analysized by gas chromatography (g.c.) at an intermediate stage, all possible intermediates (**6**, **7**, **8**) were observed. The ratio of these intermediates formed changed with the reaction conditions; it is reported in the literatures that treatment of compound (**4**) with sodium t-pentyloxide in benzene gave trans-(**8**), and with sodium t-butyloxide by using hexane in the presence of a highly dipolar aprotic solvent afforded cis-(**8**), selectively[11, 12]. In this paper suitable conditions were sought for the preparation of (**6**) from (**4**) and then its conversion to (**5**). Fortunately, selective dehydrohalogenation was achieved. For example, the compound (**6**) was prepared by treating (**4**) with sodium methoxid in methanol/N,N-dimethylacetamide (DMA) in 92% yield. Then cyclization of (**6**) was carried out by using sodium methoxide in methanol to afford trans-(**5**) as the main product (trans/cis=80/20) in 95% yield.

As an example of a single-vessel conversion of (**4**) to (**5**) via (**6**), we found that the 4.6.6.6-tetrachloro-3,3-dimethylhexanoate (**4**) was treated with sodium methoxide in methanol/DEA at about 10-20°C to produce the desired ester (**5**) in 95% yield, and the trans: cis ratio could be raised to 88: 12.

Experimental

General All the boiling points are uncorrected. IR spectra were obtained as films on a Shimadzu 435 spectrophotometer. ^{1}HNMR spectra were recorded on a Brucker AC-P200 spectrometer (δ values are in ppm from TMS in $CDCl_3$). GC spectra and MS spectra were measured on a HPG1800A GCD system.

Methyl 4,6,6,6-Tetrachloro-3,3-dimethylhexanoate (4). A mixture of 20.0g (140.8mmol) of **3**, 42ml of carbon tetrachloride and 0.5g of BPO (70%) was heated at 80°C under nitrogen atmosphere. After two hours an additional 0.5g of BPO (70%) was added and the mixture was refluxed for three more hours at 80°C, then an additional 0.5g of BPO (70%) was added and the reaction was stirred at 80°C for an additional three hours. After having been

cooled to room temperature,the reaction mixture was washed with aqueous $NaHCO_3$ and water. the mixture was dried ($MgSO_4$) and distilled to give 39.6g (95%) of **4**, bp101-103°C/0.1mmHg. IR(ν_{max}/cm^{-1}): 1733, 1195, 1147, 1010, 967, 801, 679. ^{1}HNMR ($CDCL_3$) δ = 4.40 (dd, 1H), 3.64 (s, 3H), 3.00-3.30 (m, 2H), 2.61 (d, 1H), 2.29 (d, 1H), 1.19 (s, 3H), 1.09 (s, 3H). MS m/z: 294 (M^+), 73 (base).

Methyl 4,6,6-Trchloro-3,3-dimethyl-5-hexenoate (6). A solution of 5.92g (20mmol) of **4** in 10ml of methanol was added dropwise to 1.30g (24mmol) of sodium methoxide in 16ml of methanol and 16ml of DMA at 5-10°C. The mixture was stirred for two hours, then poured into aqueous ammonium chloride, and extracted with petroleum ether(60-90°C). The petroleum ether extracts were combined, dried over magnesium sulfate, and concentrated to give, after distillation, 4.77g (91.9%) of 6, bp88-90°C/0.15mmHg, purity 95.0%. IR(ν_{max}/cm^{-1}): 1734, 1610, 1213, 1044, 873. ^{1}HNMR ($CDCL_3$): δ = 6.01 (d, 1H), 4.90 (d, 1H), 3.67 (s, 3H), 2.50 (d, 1H), 2.33 (d,1H), 1.16 (s, 6H). MS m/z 258 (M^+), 73 (base).

Methyl 3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (5) from (6). A solution of 4.41g (17mmol) of **6** in dry methanol (10ml) was added dropwise to 1.19g (22mmol) of sodium methoxide in 12ml of methanol at 15~20°C . The mixture was stirred overnight. The mixture was worked up and distillation of the crude product gave 3.60g (95.0%) of **5**, bp 78-80°C/0.2mmHg, trans/cis =80/20 (gc). IR(ν_{max}/cm^{-1}): 1752, 1220, 1185. ^{1}HNMR ($CDCL_3$) δ = 6.24 (d, cis-H), 5.58 (d, trans-H) (total 1H, trans/cis = 80/20), 3.62 (s, 3H), 2.40-1.50 (m, 2H), 1.50-1.16 (m,6H). MS cis- m/z 222 (M^+), 163 (base), trans- m/z 222 (M^+), 91 (base).

Methyl 3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (5) from (4). A solution of 5.92g (20mmol) of **4** in 10ml of methanol was added dropwise to 1.40g (26mmol) of sodium methoxide in 12ml of methanol and 12ml of DMA at 5-10°C. After two hours an additional 1.30 (24mmol) of sodium methoxide in 8ml methanol was added and the reaction

was stirred at 15~20°C overnight. The mixture was worked up and distillation of the crude product gave 4.24g (95.1%) of **5**, bp 78-80°C/0.2mmHg. The trans/cis ratio was 88/12 based on the gc analysis.

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