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SYNTHESIS OF FLUOROMETHOXYTHRIN AND ITS INSECTICIDAL ACTIVITY

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SUMMARY

Fluoromethoxythrin is a kind of pyrethroid. It was synthesized by an eight-step synthesis. The biological activity tests indicated that it has higher insecticidal activity against mosquitoes (larvae), houseflies and German cockroaches than the corresponding methoxythrin.

INTRODUCTION

Methoxythrin(1) is a kind of pyrethroid and was synthesized first by M.Matsuo[1]. Because of its low toxicity for humans and readily synthesized structure, research and studies of its applications are still in progress[2]. However its activity is not as high as other pyrethroids. For screening insecticides with higher biological activity and studying the influence of fluorine on the activity, we attempted to introduce a fluorine atom on the aromatic ring by substitution of a hydrogen atom. The key step is the synthesis of the fluoroalcohol (3). We used p-xylene(4) as the starting material (scheme 1). The alcohol(3) was determined by ^{1}H NMR to be a mixture of two isomers(62.5:37.5). The alcohols(3) are esterified separately with (±)-cis and (±)-trans-chrysanthemic acids[3] to give the corresponding esters. The compounds(2,3,8, 9,10,11) have not been reported previously. For comparison purposes, we also synthesized (±)-cis and (±)-trans-methoxythrin (1a,1b).

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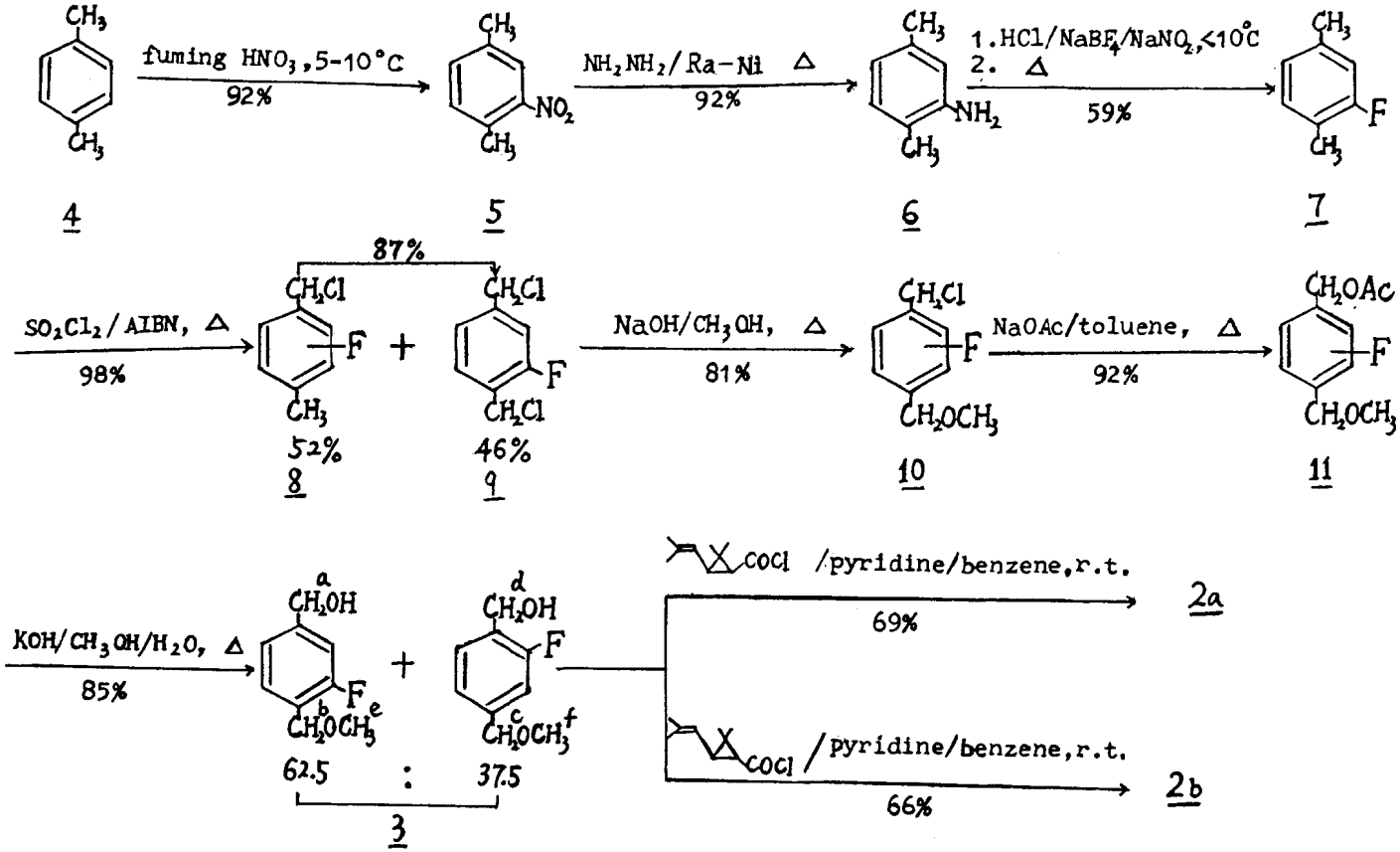
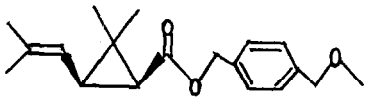
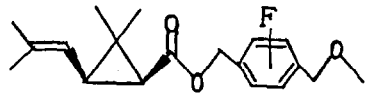

fuming HNO3, 5-10°C
92%
NH2NH2/Ra-Ni Δ
92%
1. HCl/NaBF4/NaNO2, <10°C
2. Δ
59%
4
5
6
7
87%
SO2Cl2/AIBN, Δ
98%
52%
46%
8
9
NaOH/CH3OH, Δ
81%
NaOAc/toluene, Δ
92%
10
11
KOH/CH3OH/H2O, Δ
85%
62.5 : 37.5
3
COCl /pyridine/benzene, r.t.
69%
2a
COCl /pyridine/benzene, r.t.
66%
2b

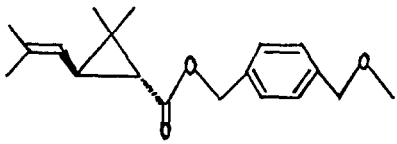
Scheme 1.



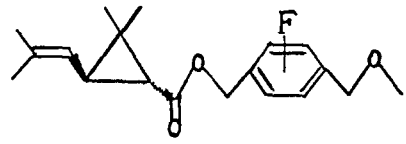
1a



2a



1b



2b

The four compounds(1a,1b,2a,2b) were tested for biological activity by the dipping method and the insecticidal film method [4]. The insects tested were mosquitoes(larvae), houseflies and German cockroaches. As expected, the tests indicated that the insecticidal activity is higher than the corresponding methoxythrin. (2b) shows the highest activity of all four compounds, its average activity being about twice as high as that of(1b).

EXPERIMENTAL

Boiling points and melting points were uncorrected. The latter were measured on a Yanaco Mp-500 instrument. Infrared spectra were recorded on a PE 580B spectrometer. ^{19}F and ^{1}H NMR spectra were obtained at 60 MHz or 200 MHz on a XL-200 spectrometer using TFA as external reference and TMS as internal reference.

Preparation [5] of 1,4-dimethyl-2-nitrobenzene(5)

Fuming nitric acid (375g,5.95mol) was added dropwise to p-xylene(4)(150g,1.415mol). The rate of addition was regulated to maintain a temperature of 5-10°C in the vigorously stirred reaction mixture which was cooled externally by an ice-salt-

bath. After the addition the reaction mixture was stirred at 15°C for 1 h and poured onto 500g of ice. The organic phases were washed with 10% sodium hydroxide solution(150 ml) and then with water(2x250ml). The mixture was dried and distilled in vacuum to give(5):yield: 196.0g(92%); bp 66-68°C/0.25mmHg; IR (film): 1570(s),1530,1540 ,1460,1350,890,830,815 cm^{-1}; ^1H NMR (CCl_4):δ2.42 (s,3H),2.52(s,3H), 7.2-7.7(m,3H).

Preparation [6] of 2,5-dimethylaniline(6)

An ethanolic solution of Raney-Ni(10ml) was added in portions to a stirred solution of (5)(95.5g,0.63mol),85% hydrazine hydrate(78.8g,1.57 5mol) and ethanol(100ml) at 30°C. After gas evolution ceased, the reaction mixture was stirred at 90°C for 1 h and cooled to room temperature. The precipitate was filtered off, the filtrate was evaporated and redistilled in vacuum to give (6): yield: 70g(92%), bp 72-74°C/1.5mmHg; IR (film):3460,3370,1635, 1590,1520,1470,1305,870, 805 cm^{-1};^1H NMR (CCl_4):δ 2.07(s,3H), 2.25(s,3H),3.32(s,2H),6.2-7.3(m,3H).

Preparation[7] of 2-fluoroxylene (7)

A solution of sodium nitrite(27g,0.391mol) in water(45ml) was added dropwise to a vigorously stirred pasty mixture of (6) (46.8g,0.39mol) hydrochloric acid (12M,52ml) and sodium fluoborate(60g,0.546mol) in water (150ml). The rate of addition was regulated to maintain a temperature of 5-10°C by an ice-salt-bath. When the addition was complete,the mixture was stirred at 25°C for 1 h and filtered. The solid was washed with ice-water (100ml), then with methanol (40ml) and ether (40ml). After drying in vacuum , the diazonium salt was obtained as a red solid(67.9g). The thermal decomposition of the diazonium salt was carried out carefully. After cooling, the mixture was extracted with ether(2x50 ml). The combined organic phases were washed with 10% sodium hydroxide solution (50ml), then with a saturated sodium chloride solution (50ml) and dried. The ether was removed by evaporation and the residual oil was distilled to give (7): yield: 28g (59%), bp 137-138°C; IR(film): 2920, 1640,1580,1260 ,1120,865, 810,760 cm^{-1}; ^1H NMR(CCl_4):δ6.6-7.1

(m,3H),2.31(s,3H),2.23(s, 3H). Anal: calcd for C_8H_9F :C 77.42, H 7.26,F 15.32; found: C 77.40,H 7.25,F 15.29.

Preparation of 2-fluoro-1,4-dichloromethylbenzene (9)

Sulfuryl chloride (172g,1.27mol) was added dropwise over 30 min, to stirred (7) (79g,0.637mol). The mixture was stirred at 100°C for 8-10 h and 0.5g azobisisobutyronitrile was added over one hour. The mixture was distilled in vacuum to give 2-(3)-fluoro -4-methylbenzylchloride (8)(52.6g,yield:52%, 90-100°C/9mmHg) and (9)(110-116 C/9mmHg). Yield:56.5g(46%) mp 26°C(recrystallized from ethanol); IR(KCl):1630,1585,1510,1430,1260,1110,885, 840,785,740,705 cm^{-1};^1H NMR (CCl_4):δ4.53(s,2H),4.62(s,2H),7.05-7.43(m,3H); Anal: calcd for $C_8H_7FCl_2$: C 49.74 ,H 3.63,F 9.84, Cl 36.79; found: C 49.50, H 3.70,F 9.87, Cl 36.72.

(8) can be readily turned into(9) by similar methods to give a yield of 87%. The reaction time was 3 hours instead of 8 hours.

Preparation of 3-(2)-fluoro-4-methoxybenzyl chloride(10)

Sodium hydroxide(6.2g,0.155mol) was added to methanol(50ml) and refluxed until a solution was formed. After cooling, (9) (30g,0.155 mol) was added and stirred at 45°C for 2 h. The mixture was refluxed for 2 h and allowed to cool to room temperature. The precipitate was filtered off, the filtrate was evaporated and the residue was washed with hydrochloric acid (1M,20ml) and then with a saturated sodium chloride solution (50ml). After drying, the product was distilled in vacuum to give (10) (92-95°C/0.6mmHg). Yield: 23.6g (81%);IR(film):1630, 1585,1510,1430,1260,1100,875,830,740 cm^{-1}; ^1H NMR (CCl_4):δ3.33 (s,3H),4.33-4.53(4s,4H),6.83-7.5(m,3H); Anal: calcd for $C_9H_{10}FClO$:C 57.29,H 5.31,F 10.08, Cl 18.83; found: C 57.30, H 5.35,F 10.02,Cl 18.79.

Preparation of 3-(2)-fluoro-4-methoxybenzyl acetate(11)

Sodium acetate(5.7g,0.07mol) and tetrabutylammonium bromide (0.5g) were added to (10)(13g,0.069mol) in toluene(20ml) and

refluxed for 3-4 h. After cooling, the precipitate was filtered off, the filtrate was evaporated and the residual oil was distilled in vacuum to give (11) (112-115°C/0.5mmHg);yield: 13.5g (92%); IR(film): 1745,1630,1590,1510,1430,1380,1230,1100,1030, 875,830,750 cm^{-1};^1H NMR(CCl_4): 7.1(m,3H),5.03,4.97,4.40,4.34 (4s,4H),3.3(s,3H),2.0(s,3H). Anal:calcd for $C_{11}H_{13}FO_3$:C 62.26, H 6.13; found: C 62.26,H 6.11.

Preparation of 3-(2)-fluoro-4-methoxybenzyl alcohol (3)

A solution of potassium hydroxide (12g,0.21mol) in water (20ml) was added to stirred (11)(30g,0.142mol) in methanol (50ml) and refluxed for 5 h. After evaporating the methanol, the residue was washed with hydrochloric acid (1M,20ml), then with a saturated sodium chloride solution (2x100ml), and then dried. The residual oil was fractionated in vacuum to give (3) (114-115°C/0.3mmHg); yield: 20.5g(85%); IR(film): 3400(s,b), 1630,1590,1510,1430,1390,1260,1100,875,835,750 cm^{-1}; 200MHz ^1H NMR($CDCl_3$):δ 7.319-6.980(m, H_{arom}),4.664(s,0.375x2H,-$CH_2{}^d$-), 4.588(s,0.625x2H, -$CH_2{}^a$-),4.481 (s,0.625x2H,-$CH_2{}^b$-),4.411(s, 0.375x2H,-$CH_2{}^c$-),3.377(s,0.625x3H,-$OCH_3{}^e$),3.365(s,0.375x3H, -$OCH_3{}^f$),3.211(s,b,1H,-OH);^{19}F NMR(CCl_4) :δ 44(s),43(s);Anal : calcd for $C_9H_{11}FO_2$: C 63.53,H 6.47,F 11.18 , found: C 63.60, H 6.52,F 11.20.

Preparation of 3-(2)-fluoro-4-methoxybenzyl-(±)-trans-2,2-dimethyl-3-isobutenylcyclopropane-1-carboxylate (2b)

(±)-Trans-chrysanthemic acid (2.0g,11.9mmol) was added to thionyl chloride(3.0g,25.2mmol). The mixture was stirred at 25°C for 4 h and excess thionyl chloride was evaporated by means of a water pump (10mmHg). The acyl halide in benzene (10ml) was added dropwise to a stirred solution of (3) (2.0g,11.8mmol) and pyridine (1.5g,19.0mmol) in benzene (30ml). When the addition was complete,the mixture was stirred at 25°C for 5 h. The mixture was washed with hydrochloric acid (1M,50ml),then with a saturated sodium bicarbonate solution(50ml) and then with a saturated sodium chloride solution (100ml). The water phase was

extracted with benzene(30ml) and the organic phases were dried. The residue obtained after evaporation of the solvent (water pump) was purified by column chromatography on silica gel. The eluate cyclohexane-ethyl acetate (4:1 v/v) was evaporated in vacuum,yielding the pure ester (2b). Yield:2.6g (69%);IR(film): 1730,1640,1590,1430,1390,1200,1160, 1120,860,830,760 cm^{-1}; ^1H NMR(CCl_4):δ 7.46-6.77(m,3H),5.03,4.97,4.37,4.30(4s,4H),4.83 (d,1H),3.27(s,3H),1.97(m,1H),1.63(s,6H),1.42(d,1H),1.17 (s,3H), 1.07 (s,3H); Anal:calcd for $C_{19}H_{25}FO_3$: C 71.25,H 7.81,F 5.93; found :C 71.30,H 7.78,F 5.89.

Similar procedures were used to obtain (2a): 66% yield; IR (film):1730,1630,1580,1430,1380,1160,1120,870,830,750cm^{-1}; ^1H NMR(CCl_4):δ7.50-6.80(m,3H),5.28(d,1H),5.02,4.93,4.40,4.33 (4s,4H),3.3(s,3H),2.03(m,1H),1.70,1.63(2s,6H),1.47(d,1H),1.17 (s, 6H);Anal: calcd for $C_{19}H_{25}FO_3$: C 71.25.H 7.81,F 5.93 found: C 71.26 ,H 7.75,F 5.80.

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