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FULL PAPER

Synthesis of retinoid analogues of juvenile hormones

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As part of a collaborative research project aimed at designing new chemicals active on mosquito larvae, we sought accessible raw materials and an efficient synthesis method for preparing large amounts of active substances. For this we selected retinoic acid, which has functionality close to that of juvenile hormones. From this molecule we developed ester and trifluoromethyl ketone synthesis that was fast and led to good yields.

KEYWORDS

juvenile hormones, larvicides, Mitsunobu reaction, retinoic acid, Ruppert reagent

1 | INTRODUCTION

Mosquitoes play an important role in the transmission of several diseases that cause health problems in many countries, such as malaria, dengue, yellow fever, chikungunya and now Zika.[1] The spread of the Zika virus through *Aedes aegypti* mosquito bites and the serious consequences for pregnant women (miscarriages) and their children (microcephaly) led us to seek effective means to combat mosquitoes transmitting the virus. It is particularly important to resolve this issue because this species is also responsible for the spread of other diseases such as dengue and chikungunya, and the area where this mosquito occurs is growing considerably because of global warming. This has led to a search for new compounds that are safe, effective and affordable, to ensure protection against these vectors. The various strategies adopted use active products that can be grouped into three families[2]:

- Larvicides, killing juvenile mosquitoes or preventing the maturation of larvae. These include agonists of juvenile hormone, such as methoprene and pyriproxyfen, and inhibitors of chitin synthesis for the insect cuticle, such as benzoylphenylureas (e.g. diflubenzuron).
- Adulticides, targeting adults, the most important of which are pyrethroids, such as deltamethrin and permethrin.
- Repellents, disrupting adult mosquitoes' ability to detect human odour. This is the mode of action of DEET (*N*,*N*-diethyl-3-methylbenzamide) and icaridin.

In its notice of 29 November 2011, ANSES (French National Agency for Environmental Safety, Food and Health)

indicates that vector control must be wise and sustainable.[3] The Agency stresses that for *Aedes* and *Culex*, the control must be preventive and, hence, the use of larvicide is a prerequisite. For these reasons, an attempt was made to find new larvicidal compounds.

The work reported here was a part of a collaborative research project aiming to design new chemicals active on mosquito larvae by means of a step-by-step approach based on structure–activity relationship modelling, the synthesis of new chemicals, and laboratory tests on susceptible (Bora-Bora) and resistant (Vauclin, Martinique) strains of *Aedes aegypti*.[4]

In the first part of our study we proposed to develop syntheses of potential juvenoids, having a structure based on that of juvenile hormone-III (Figure 1). These essentially include agonists of juvenile hormone, such as methoprene (Figure 2).[5] These agonists are involved in endocrine regulation in the insect, causing abnormal development and death of the larvae.

2 | RESULTS

From methoprene as a raw material, our early work focused on the substitution of the isopropyl ester group by the keto trifluoromethyl group, CF_3CO, effective in insect chemistry.[6] The low yields and, above all, difficulties in procuring the raw material led us to develop syntheses more in line with the problems posed by the actual use of these products. In fact, ANSES reiterates its opinion on the search for insecticides potentially usable for vector control: 'the treatment of breeding sites must be reasoned and sustainable. The treatment of breeding sites must be continuous, including inter-epidemic period, in order to keep the vector population with the lowest levels'.[3] Such requirements exclude, in a first approach, difficult-to-access materials, e.g. raw materials that are not readily available.

All these reasons led us to adopt a feedstock that was available and with functionality close enough to that of our target as a practical model for the development of syntheses: all-*trans*-retinoic acid[7,8] (Figure 3).

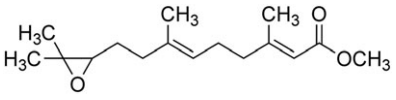


FIGURE 1 Juvenile hormone-III

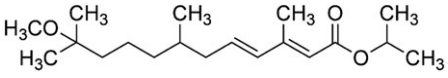


FIGURE 2 Methoprene

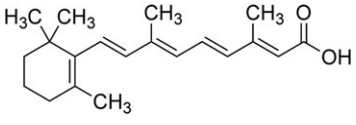


FIGURE 3 Retinoic acid

2.1 | Synthesis of Retinoic Acid Isopropyl and Hexafluoroisopropyl Esters

By analogy with our first tests, we developed a synthesis of retinoic acid isopropyl ester as a first step (Figure 4). For this we used the esterification reaction of Mitsunobu[9,10] or, more accurately, a modification of the Mitsunobu method proposed by Iranpoor *et al.*[11] The Mitsunobu method is summarized in Scheme 1 and its modification by Iranpoor *et al.*[11] in Scheme 2. In both cases the method used an oxidation–reduction reaction, in which triphenylphosphine was oxidized to triphenylphosphine oxide and diazo derivatives were reduced to their hydrogenated derivatives.

Experimentally, in the Iranpoor method, an equimolecular mixture of retinoic acid and isopropyl alcohol, in the presence of azopyridine and triphenylphosphine, was refluxed in solution in acetonitrile. After 3 h of this treatment, the ester was obtained and was purified by passing through a silica column. This purification continued until the infrared (IR), ^{1}H NMR and mass spectra were fully consistent with the formula of the ester.

The same method applied to hexafluoroisopropanol yielded the corresponding retinoic acid hexafluoroisopropyl ester (Figure 5), which was purified in the same way as for the isopropyl ester, with verification of the structure and purity.

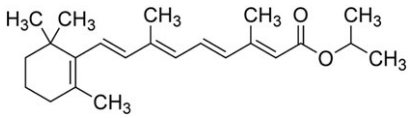
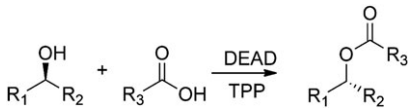
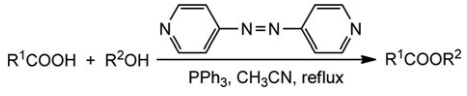


FIGURE 4 Retinoic acid isopropyl ester



SCHEME 1 Mitsunobu reaction



SCHEME 2 Iranpoor method

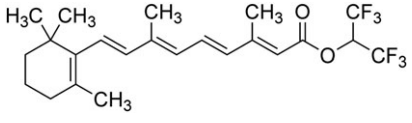


FIGURE 5 Retinoic acid hexafluoroisopropyl ester

2.2 | Synthesis of Trifluoromethyl Ketone (1-Trifluoromethyl-(2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenone)

Trifluoromethyl ketone (Figure 6) was synthetized both from isopropyl ester (by analogy with the previous syntheses from methoprene) and directly from retinoic acid.

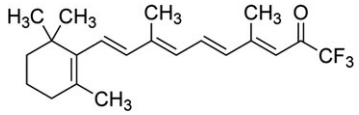


FIGURE 6 Trifluoromethyl ketone

2.2.1 | From isopropyl ester of retinoic acid (or methoprene)

The method used the Ruppert reagent $(CH_3)_3SiCF_3$.[12] In principle, esters react poorly with this reagent, but they readily react at room temperature in the presence of caesium fluoride as a catalyst, giving a silyl ether intermediate which leads to trifluoromethyl ketone after hydrolysis.[13] This synthesis has the double disadvantage of requiring the prior synthesis of the ester and of working in strictly anhydrous medium, with caesium fluoride to be used right out of an oven at 200 °C. These restrictions led us to develop a method using retinoic acid directly.

2.2.2 | Direct synthesis from retinoic acid

The comparison of these two ways of preparation showed that it was possible to develop an effective process from the acid itself without going through the ester stage. This process involved two steps: preparation of the acid chloride and then preparation of the ketone from this chloride.

(a) Chlorination

Scheme 3 shows the successive reactions that led to retinoic acid chloride. The mechanism implemented the formation of an intermediate complex with thionyl chloride (line2). This complex was then destroyed with liberation of sulfur dioxide and formation of the desired product.

(b) Trifluoromethylation

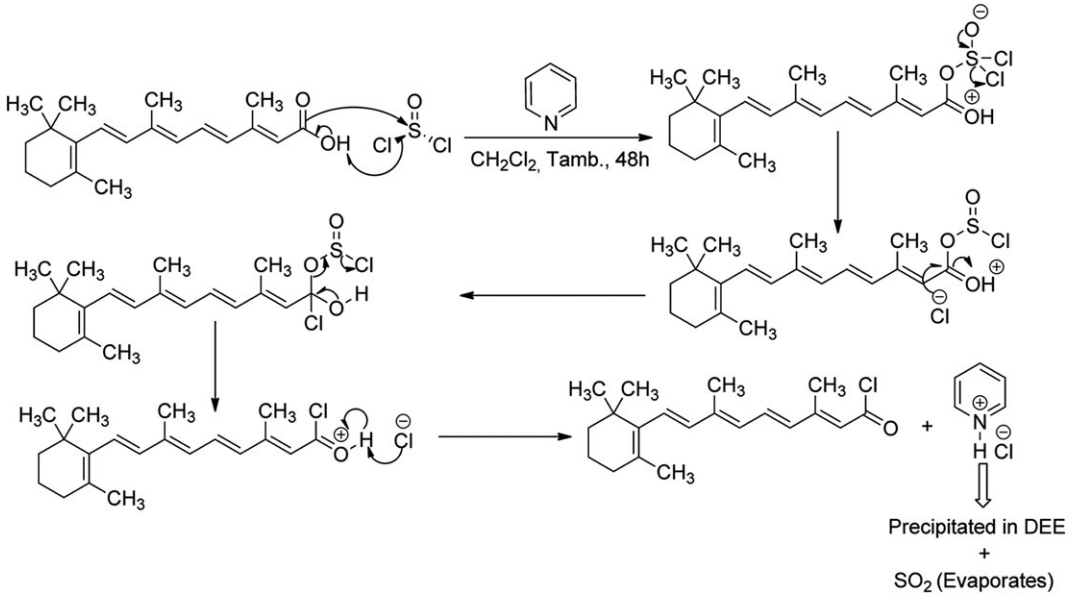
The second step was carried out from the retinoic acid chloride. Two methods were compared, both implementing an $AgCF_3$ or $CuCF_3$ organometallic compound prepared in the same way from Ruppert reagent. Both had the same requirements for their experimental conditions: anhydrous solvents and avoiding the presence of water during the reaction.

Method I. This method implemented trifluoromethylsilver prepared from silver fluoride; this organometallic then reacted directly with the acid chloride[14]:

$$AgF + (CH_3)_3SiCF_3 \rightarrow AgCF_3 + (CH_3)_3SiF$$
$$AgCF_3 + RCOCl \rightarrow RCOCF_3 + AgCl$$

This process has some drawbacks: it is necessary to work at low temperatures, the reaction occurs at −30 ° C and the yield does not exceed 35%.

Always with the aim of finding an experimental method that was easy to implement and gave better yields, and in order to apply it to raw materials which can be difficult to access, we used copper instead of silver.[15]



SCHEME 3 Mechanism of chlorination of retinoic acid

Method II. An additional step was necessary here: the exchange of the two metals to achieve trifluoromethylcopper, which was then condensed with the acid chloride:

$$AgF + (CH_3)_3SiCF_3 \rightarrow AgCF_3 + (CH_3)_3SiF$$
$$AgCF_3 + Cu \rightarrow CuCF_3 + Ag$$
$$RCOCl + CuCF_3 \rightarrow RCOCF_3 + CuCl$$

In spite of a longer reaction time (4 days), the reaction has advantages: it takes place at room temperature and yields are around 60%. These benefits led us to give preference to this method for all future syntheses of potential juvenile hormone agonists.

Other methods of synthesis of $CuCF_3$ have been described: our choice has been fixed on a transformation of the derivative of silver which we already had for prior work. In the event of an optimization of the process, or that of an industrial synthesis, two routes of access to this reagent seem interesting to us:

1. The direct generation of $CuCF_3$ from fluoroform,[16–18] the advantages of which are certain (fluoroform is cheap and easily accessible, direct access to Cu CF_3 at ambient temperature and atmospheric pressure). However, fluoroform is a gas with a strong greenhouse effect, which limits its use.
2. Preparation from trifluoromethyl sulfoxide, which is readily available or commercially available and which does not have the environmental disadvantages of fluoroform.[19]

3 | DISCUSSION

In this study we were able to combine two important synthetic methods, the Mitsunobu reaction and the use of the Ruppert reagent, in the preparation of esters and trifluoromethyl ketone derivatives of retinoic acid. Thus it could be shown that:

- Mitsunobu's method, modified by Iranpoor *et al.*, gives easy access to esters, even fluorinated ones;
- Ruppert's reagent, in the presence of caesium fluoride as a catalyst, allows trifluoromethyl retinoic ketone to be prepared, not only from the retinoic acid isopropyl ester but also via direct access from the acid itself;
- in the latter method, the use of copper instead of silver significantly improved the reaction, which could take place at room temperature with virtually double the yield;
- a variation of aqueous medium activity made us suspect a parasite hydration reaction of the fluorinated ketone, by analogy with the same reaction with chloral; this led us to synthesize the gem diol.

This was easily obtained by hydration in water at room temperature in the presence of sodium carbonate. It was isolated, purified and characterized in the same way as other derivatives of retinoic acid as described above.

4 | EXPERIMENTAL

4.1 | General remarks

All-*trans*-retinoic acid ($C_{20}H_{28}O_2$, 98% purity), triphenylphosphine ($C_{18}H_{15}P$, 99% purity), 1,1,1,3,3,3 hexafluoro-2-propanol ($C_3H_2OF_6$, 99.8% purity), thionyl chloride ($SOCl_2$, 99% purity), anhydrous pyridine (C_5H_5N, 99.8% purity), 4,4′-azopyridine ($C_{10}H_8N_4$, 98% purity), silver fluoride (AgF, 99.9% purity), trimethyl(trifluoromethyl) silane ($C_4H_9SiF_3$, 99% purity), copper powder (Cu spheroidal 14–25 µm, 99% purity), propionitrile (C_3H_5N, 99% purity), anhydrous 2-propanol (C_3H_8O, 99.5% purity), anhydrous dichloromethane (CH_2Cl_2, 99.8% purity), anhydrous diethyl ether ($C_4H_{10}O$, 99.8% purity), and anhydrous acetonitrile (CH_3CN, 99.8% purity) were all from Sigma Aldrich and were used without further purification. All purification operations were carried out at ambient temperature.

NMR spectra of the three new compounds were recorded with a Bruker AVANCE 300 MHz (^1H, 300.1 MHz; ^{19}F, 282.4 MHz; ^{13}C 75.4 MHz) spectrometer in $CDCl_3$ solutions. The chemical shifts δ are given in parts per million (reference peak =7.26 ppm) and the coupling constants (J) in Hz.

HRMS were measured with a Waters GCT 1 Premier using direct introduction DCI-CH_4 ionization technique equipped with TOF detector. IR spectra were recorded with a Nexus ThermoNicolet system equipped with ATR diamond and DTGS detector.

4.2 | Isopropyl (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate

To a flask containing a stirred mixture of all-*trans*-retinoic acid (0.100 g, 0.33 mmol) and 4,4′-azopyridine (0.072 g, 0.4 mmol) in dry acetonitrile (3 ml) was added a solution of triphenylphosphine (0.104 g, 0.4 mmol) and anhydrous 2-propanol (26 mg, 0.4 mmol) in CH_3CN. The reaction mixture was refluxed for 12 h. After completion of the reaction, the pyridine hydrazine produced was filtered and the solution was concentrated on a rotary evaporator to give viscous oil. After purification using a short column of silica gel and cyclohexane as eluent, the product was obtained as light yellow oil. Isolated yields and spectral data for this compound are given below.

IR (cm^{-1}): 3100–3030 w, 2956.88 s, 2924.36 s and 2853.29 m, 1728.91 m (C═O), 1584.23 w (C═C), 1462.93–1435.80 m, 1378.60 w, 1261.14 m, 1120.35–1073.41–1027.11 m (C─C─O/COO), 743.12–721.83–695.91 w. ^1H NMR ($CDCl_3$, δ_H, ppm): 0.96 (s, 6H, CH_3─C─CH_3), 1.18 (d, 6H, CH_3─CH─CH_3), 1.40 (m, 2H,

CH_2—C—), 1.56 (m, 2H, CH_2—CH_2—CH_2), 1.64 (s, 3H, CH_3—C), 1.93 (s, 3H, CH_3—C), 1.95 (m, 2H, CH_2—CH_2—C), 2.28 (s, 3H, CH_3—C), 4.98 (m, 1H, CH_3—CH—CH_3), 5.67 (s, 1H, C—CH—C), 6.05 (d, 1H, CH—CH—C), 6.09 (s, 1H, CH—CH—C), 6.18 (s, 1H, C—CH—CH), 6.23 (s, 1H, CH—CH—C), 6.91 (t, 1H, CH—CH—CH). ^{13}C NMR ($CDCl_3$, δ_C, ppm): 11.87, 12.79, 18.20, 20.98, 27.93, 28.68, 32.08, 33.23, 38.58, 65.75, 118.14, 127.57, 128.51, 128.94, 129.70, 134.23, 136.25, 136.67, 138.37, 151.31, 165.70. HRMS: *m/z* (%): 342.26 (100) M^+, 343.26 (75.5) [M − H], 344.26 (21) $[M - 2H]^+$, 371.30 (7.5) $[M - C_2H_5]^+$.

4.3 | 1,1,1,3,3,3-Hexafluoropropan-2-yl-(2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate

To a flask containing a stirred mixture of retinoic acid (0.100 g, 0.33 mmol) and 4,4′-azopyridine (0.072 g, 0.4 mmol) in dry acetonitrile (3 ml) was added a solution of triphenylphosphine (0.104 g, 0.3 mmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (73 mg, 0.4 mmol) in CH_3CN. The reaction mixture was refluxed for 12 h. After completion of the reaction, the pyridine hydrazine produced was filtered and the solution was concentrated on a rotary evaporator to give a viscous oil. After purification using a short column of silica gel and cyclohexane as eluent, the product was obtained as very bright yellow oil. Isolated yields and spectral data for this compound are given below.

IR (cm^{-1}): 3100–3030 w, 2960.19–2928.39–2864.65 m, 1738.32 m, 1577.48 m, 1434.72 w, 1385.42–1358.65 m, 1288.16–1267.61 m, 1233.66–1199.38 m, 1110.15 s, 1027.55 w, 950.58 m, 906.60 w,743.48–695.96 w. ^{1}H NMR ($CDCl_3$, δ_H, ppm): 0.96 (s, 6H, CH_3—C—CH_3), 1.35 (s, 1H, CF_3—CH—CF_3), 1.40 (m, 2H, CH_2—CH_2—C—), 1.56 (m, 2H, CH_2—CH_2—CH_2), 1.65 (s, 3H, CH_3—C), 1.95 (s, 3H, CH_3—C), 1.98 (m, 2H, CH_2—CH_2—C), 2.33 (s, 3H, CH_3—C), 5.74 (m, 1H, C—CH—C), 6.06 (d, 1H, CH—CH—C), 6.12 (s, 1H, CH—CH—C), 6.22 (m, 1H, C—CH—CH), 6.27 (m, 1H, CH—CH—C), 7.07 (t, 1H, CH—CH—CH). ^{13}C NMR ($CDCl_3$, δ_C, ppm): 12.98, 14.44, 19.19, 21.74, 28.94, 29.71, 33.14, 34.26, 39.60, 65.72, 113.83, 129.15, 129.83, 130.50, 133.50, 133.90, 137.03, 137.61, 141.60, 158.78, 162.93. ^{19}F NMR ($CDCl_3$, δ_F, ppm): −73.30. HRMS: *m/z* (%): 451.2062 (100) $[M - H]^+$ 450.1995 (92) $[M]^+$, 452.2107 (21) $[M - 2H]^+$, 479.2386 (15) $[M - C_2H_5]^+$.

4.4 | (3*E*,5*E*,7*E*,9*E*)-1,1,1-Trifluoro-4,8-dimethyl-10-(2,6,6-trimethylcyclohex-1-en-1-yl)deca-3,5,7,9-tetraen-2-one

To a flask containing a stirred mixture of retinoic acid (0.100 g, 0.33 mmol) and anhydrous pyridine (10 µl, 0.13 mmol) in dry CH_2Cl_2 (20 ml), thionyl chloride (30 µl, 0.41 mmol) was added dropwise. The reaction mixture was stirred for 48 h at room temperature. After completion of the reaction, the solution obtained was filtered and was concentrated on a rotary evaporator to give purple oil corresponding to acyl chloride of retinoic acid. This product was solubilized in dry diethyl ether to completely eliminate pyridine hydrochloride, dried over $MgSO_4$, filtered and solubilized in propionitrile.

To a stirred mixture of AgF (0.038 g, 0.3 mmol) in 5 ml of propionitrile, trimethyl(trifluoromethyl)silane (0.053 g, 0.37 mmol) was added at room temperature. The mixture was stirred for 30 min and copper powder (0.038 g, 0.6 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. The corresponding acyl chloride to retinoic acid was added and the reaction mixture was stirred for 48 h at room temperature. The solution obtained was filtered and concentrated on a rotary evaporator. Then, the solution was solubilized in 10 ml of dry diethyl ether, filtered and concentrated on a rotary evaporator to give dark yellow oil corresponding to our final product.

IR (cm^{-1}): 3600–3200 w, 2959.84–2923.85–2854.31 s, 1758.28 s, 1670.33 m, 1584.48 m, 1435.68 m, 1379.15 m, 1258.10 m, 1171.79–1095.06–1033.45–984.11–911.78–855.11–734.85 m. ^{1}H NMR ($CDCl_3$, δ_H, ppm): 0.96 (s, 6H, CH_3—C—CH_3), 1.40 (m, 2H, CH_2—CH_2—C—), 1.56 (m, 2H, CH_2—CH_2—CH_2), 1.65 (s, 3H, CH_3—C), 1.95 (s, 3H, CH_3—C), 1.98 (m, 2H, CH_2—CH_2—C), 2.33 (s, 3H, CH_3—C), 5.76 (s, 1H, C—CH—C), 6.06 (d, 1H, CH—CH—C), 6.12 (s, 1H, CH—CH—C), 6.22 (m, 1H, C—CH—CH), 6.27 (m, 1H, CH—CH—C), 7.07 (t, 1H, CH—CH—CH).

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