Tetrahedron Letters No. 10, pp 791 -,794, 1976. Pergamon Press. Printed in Great Britain.

INSECT CHEMISTRY IV[1]. TRIFLUOROMETHYL ANALOGS OF JUVENILE HORMONES

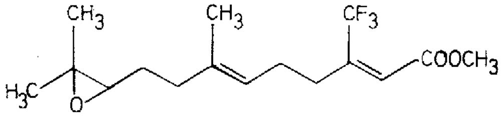
F. Camps, J. Coll, A. Messeguer, A. Roca
Instituto de Química Orgánica de Barcelona. Patronato "Juan de la Cierva".
(C.S.I.C.). Barcelona, 17. Spain.

(Received in UK 19 January 1976; accepted for publication 29 January 1976)

Fluorine atoms have been widely used in medicinal chemistry as substitute for hydrogen in bioactive molecules. In particular, the introduction of trifluoromethyl groups (TFM) in a given compound enhances greatly its liposolubility and alters its electronic and steric properties, modifying its bioactivity[2].

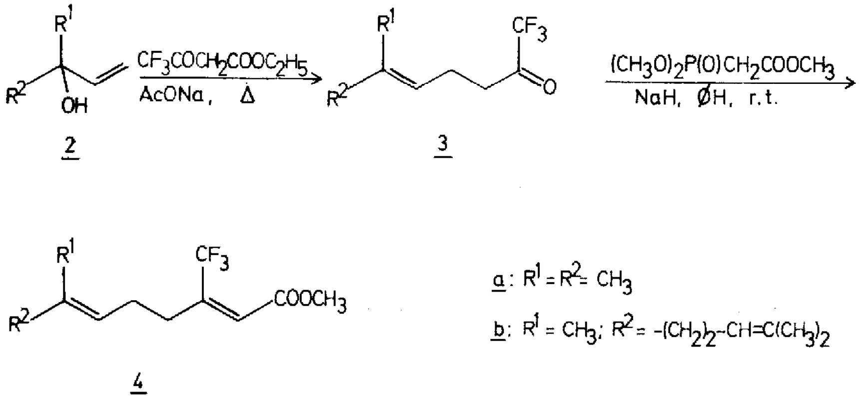
In a research program of this laboratory, devoted to the chemistry of bioanalogs of insect juvenile hormones, we decided to substitute fluorine for hydrogen in the molecules of the natural juvenile hormones JH-1, JH-2 and JH-3[3], considering that these new compounds could exhibit JH mimetic or inhibitory activities.

The present communication reports some preliminary results on the synthesis of the TFM-analog of JH-3, 1,



1

according to the sequence developed by Mori *et al*[4] for the preparation of juvenoids, shown in the following Scheme:

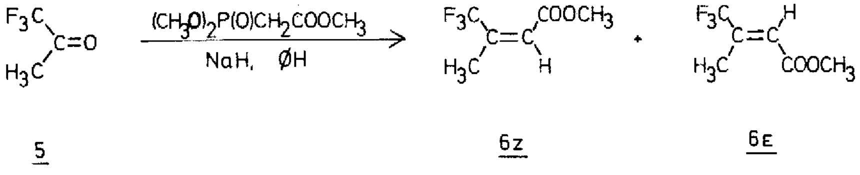


a: $R^1 = R^2 = CH_3$

b: $R^1 = CH_3$; $R^2 = -(CH_2)_2-CH{=}C(CH_3)_2$

In a model experiment, treatment of 2-methyl-3-buten-2-ol (2a) with a stoicheiometric amount of ethyl γ,γ,γ-trifluoroacetoacetate[5] 15 h at 150°, in the presence of sodium acetate as catalyst, afforded TFM-ketone 3a in 80% yield (b.p. 62-4°/66-9 Torr; tosylhydrazone, m.p. 100-2°). In a similar reaction with linalool (2b), using a 30% excess of TFM-ester, a 84% yield of a 40:60/Z:E isomeric mixture of the corresponding TFM-ketone 3b was obtained. These results show that the TFM-ester gives in Carroll reactions[6], under milder reaction conditions, yields comparable to those reported for ethyl acetoacetate.

The Wittig-Horner reaction of trifluoromethyl alkyl ketones was studied with 1,1,1-trifluoroacetone (5) as a model. Treatment of a benzene solution of this ketone with a 50% excess of the sodium salt of dimethyl (methoxycarbonyl)methylphosphonate - generated by the action of sodium hydride in benzene-, 1 h at 0° and 3 h at 20°, caused the complete reaction of the ketone. Column chromatography on silica gel of the crude reaction mixture afforded a 90% yield of a 22:78/Z:E isomeric mixture of methyl β-trifluoromethylcrotonates 6z and 6ε[7,8].



5 6z 6ε

When the reaction was carried out with the TFM-ketone 3a (NaH, benzene, 50% excess phosphonate, 1 h, r.t.), after column chromatography on silica gel, a 94% yield of a 38:62/Z:E isomeric mixture of the α,β-unsaturated esters 4a was obtained. Similarly, a 40:60/Z:E isomeric mixture of the TFM-ketone 3b afforded a 95% yield of a 31:69/Z:E isomeric mixture at C-2 of the four corresponding α,β-unsaturated esters 4b. These results indicate an enhanced reactivity of the TFM-ketones, as expected, in front of Wittig-Horner reagents, the reactions proceeding in near quantitative yields under very mild conditions.

Epoxidation of these α,β-unsaturated esters, precursors of JH-3 analog, with m-chloroperbenzoic acid 3h at 0° in methylene chloride, afforded the corresponding terminal epoxides. Results of biological activities of these compounds will be reported elsewhere.

	IR (CCl_4)		^{1}H NMR (CCl_4) (τ, values)		^{19}F NMR (ppm)$^+$
	$\nu_{C=O}$	$\nu_{C=C-C=O}$	$\underline{H}$-C=C-C=O	$C\underline{H_3}$-C=C-C=O	
3a	1765				1.20
3b(Z)	1762				0.98
3b(E)	1762				0.75
4a(Z)	1747	1670	4.05		-15.9
4a(E)	1735	1670	3.75		- 9.3 (d; J=1.5)
4b(Z,Z)	1747	1670	4.05		-15.9
4b(Z,E)	1748	1670	4.05		-15.9
4b(E,Z)	1737	1670	3.76		- 9.8
4b(E,E)	1739	1670	3.73		-10.0
6(Z)	1748	1675	3.98 (q; J=1.5)	8.02 (d, J=1.5)	-13.2
6(E)	1735	1680	3.72 (m; J=1.5)	7.77 (d, J=1.5)	- 8.4 (d; J=1.5)

$^+$ Trifluoroacetic acid was used as external reference. Negative values indicate lower fields.

Acknowledgment. Financial support from the Fondo Nacional para el Desarrollo de la Investigación Científica is gratefully acknowledged.

NOTES AND REFERENCES

1. Part III, F. Camps, J. Coll, A. Guerrero, Anales de Quim., in press.
2. R. Filler, Chem Tech., 4, 752 (1974).
3. K. Slama, M. Romanuk, F. Sorm, "Insect Hormones and Bioanalogues", Springer Verlag, New York, 1974.
4. K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, W. S. Bowers, Tetrahedron, 25, 1667 (1969).
5. J. Burdon, V. C. R. McLoughlin, Tetrahedron, 20, 2163 (1964).
6. M. F. Carroll, J. Chem. Soc., 704, 1966 (1940).
7. E. T. McBee, Y. S. Kim, H. P. Braendlin, J. Amer. Chem. Soc., 84, 3154 (1962).
8. D. L. Dull, I. Baxter, H. S. Mosher, J. Org. Chem., 32, 1622 (1967), obtained one single isomer from the reaction of ketone 5 with (carboethoxy)-methylenetriphenylphosphorane. In our hands, this reaction afforded a 5:95/6_Z:6_E isomeric ratio.