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Fluorinated Retinoids via Crossed Aldol Condensation of 1,1,1-Trifluoroacetone[1]

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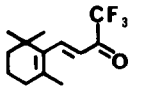
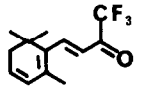
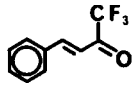
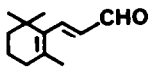
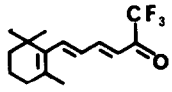
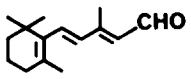
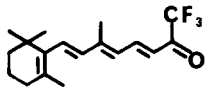
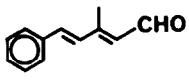
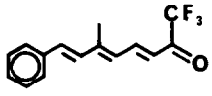
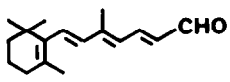
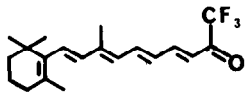
Piperidine-acetic acid catalyzed crossed aldol condensation of 1,1,1-trifluoroacetone with aryl or α,ß-unsaturated aldehydes was found to be a useful method for the preparation of unsaturated trifluoromethyl ketones. Chain extension of these ketones led to several new fluorinated retinoids including the hitherto elusive all-trans isomers of 19,19,19- and 20,20,20-trifluororetinal.

In recent years the fluorine atom has been increasingly utilized as a label for probing structural information and mechanistic details of bioorganic molecules and their associated processes.[2] In addition to the more common usage in NMR spectroscopy, recently it has also been employed in X-ray photoelectron spectroscopy (XPS) studies.[3]

The introduction of a trifluoromethyl group into a biomolecule has the obvious advantage of enhanced detectability. Among several possible reagents 1,1,1-trifluoroacetone is the most obvious candidate for introduction of such a label, especially when one considers that acetone is a commonly employed C_3-chain extension reagent in terpenoid synthesis.[4] However, its propensity to self-condense[5] makes the compound rather resistant toward crossed aldol condensation. The reluctance of the resultant aldol (ketol) to dehydrate under mild conditions[6] is also a complicating factor. Hence, there is a virtual absence in the literature of examples of successful preparation of α,ß-unsaturated trifluoromethyl ketones using trifluoroacetone.

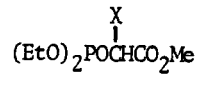
Secondary amines in the presence of a weak acid such as acetic acid is known to catalyze aldol condensation. Mechanistically, the intermediacy of enamines has been suggested.[7] We have now carried out the piperidine-acetic acid catalyzed aldol condensation of 1,1,1-trifluoroacetone with a series of aldehydes (Table I). In all cases under conditions when trifluoroacetone was maintained at low concentrations (see the specific example below) a moderate to high yields of products were obtained for aryl and α,ß-unsaturated aldehydes. Not too surprisingly, the new double bond was formed exclusively in the trans form. The unsaturated trifluoromethyl ketones prepared in this manner are shown in Table I. However, preliminary results showed that saturated aldehydes only led to low yields of crossed-aldol products. Competing enamine formation probably contributed to undesirable side reactions.

Table I. Trifluoromethyl Ketones by Amine Catalyzed Aldol Condensation of Aldehydes with Trifluoroacetone

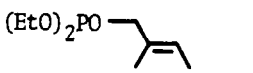
Entry	Aldehyde, A	Product, B	Reaction Conditions	Yield	δ, ^{19}F-nmr[a]
1	Cyclocitral		ϕH, R.T. (1:1)[b] 4 eq., 4h	40%	-78.15
2	Safranal		THF, R.T. (1:1)	28	-78.19
3	Benzaldehyde		ϕH, R.T. (1:1) 4 eq., 4h,	55	-78.17
4			THF, 0° (1.5:1) 2 eq., 30m	85	-78.12
5			THF, 0° (1:1) 2 eq., 30m	80	-78.02
6			Ether 0° (1:1) 2 eq., 1h	67	-78.02
7			THF, 0° (2:1) 2 eq., 30m	70	-77.81

a. Recorded on an IBM-NR-80 spectrometer with $CFCl_3$ as internal standard. Solvent: $CDCl_3$.
b. Ratio of piperidine to acetic acid.

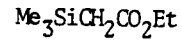
Preparation of trifluoro-C_{18}-ketone, 5B. The procedure is representative of the aldol condensations described in this paper. To a stirred solution of 1.0g (4.6 mmol) of the C_{15}-aldehyde, 5A, 0.4g each of acetic acid and piperidine in 40ml of THF (kept at room temperature under nitrogen) was added 2ml of trifluoroacetone over a 2 min period. The beginning of the reaction was indicated by darkening of the solution. TLC analyses after 2h indicated complete disappearance of the ketone but with substantial amounts of aldehyde remained. Two 2ml portions of trifluoroacetone were subsequently added in a similar manner. The reaction was then quenched with a saturated solution of NH_4Cl. After conventional work-up, and separation by flash chromatography on silica gel (solvent 30% CH_2Cl_2 in hexane) a yellow viscous oil was isolated, 1.03g (80% yield). Spectroscopic data[8] are consistent with the expected all-trans ketone.



8 a: X = H
b: X = F



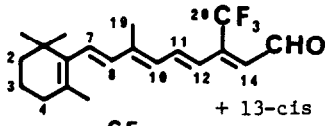
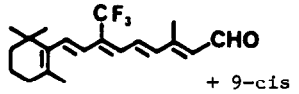
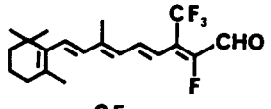
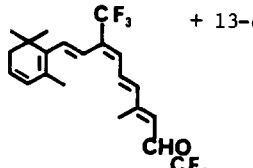
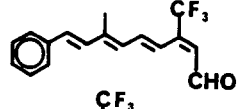
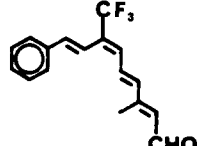
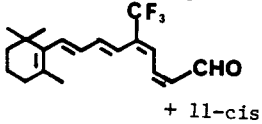
9



10

These newly formed ketones allowed us to prepare several retinoids with trifluoromethyl labels. Established methodologies in vitamin A synthesis were followed for chain extensions. Specifically the above reagents were used for two or five carbon homologation,[4,9,10]

Table II. New Fluorinated Retinoids

Entry	Compound[a]	Synthetic Route	Spectral data Vinyl ^{1}H-nmr[b]	^{19}F[c]
11	 + 13-cis	5B + C_2(8a)	6.40, 6.15, 6.17, 7.30, 6.20, 6.32.[d] $J_{7,8}$=16.1, $J_{11,12}$=15.5	-58.11
12	 + 9-cis	1B + C_2(8a) + C_5(9)	6.55, 5.99, 6.56, 7.19, 6.52, 6.01. $J_{7,8}$=16.5, $J_{11,12}$=15.0	-59.3
13	 + 13-cis	5B + F-C_2(8b)	6.42, 6.76, 6.22, 7.47, 6.38, --. $J_{7,8}$=16.0, $J_{11,12}$=16	-54.8 -120.5
14		2B + C_2(8a) + C_5(9)	6.53, 6.40, 6.65, 7.07, 6.61, 6.04. $J_{7,8}$=16.8, $J_{11,12}$=15.2	-64.5
15		6B + C_2(8a)	6.91, 6.77, 6.37, 7.2, 6.97, 6.31. $J_{7,8}$=16.0, $J_{11,12}$=15.5	-65.3
16		3B + C_2(8a) + C_5(9)	e, e, 6.74, 7.17, 6.65, 6.06 $J_{7,8}$=e, $J_{11,12}$=15	-64.3
17	 + 11-cis	4B + C_4-phosphonate	6.46, 6.21, 6.72, 6.44, 7.19, 7.13, 6.10.[f] $J_{7,8}$=15.6, $J_{9,10}$=15.9, $J_{13,14}$=10.3	

a. Purified by preparative hplc or flash chromatography. b. NM-300 spectrometer. Solvent: $CDCl_3$. TMS internal standard, δ in ppm, J in Hz. c. NR-80 spectrometer. $CFCl_3$ internal standard, δ in ppm. d. Listed in the following order: H_7, H_8, H_{10}, H_{11}, H_{12}, H_{14}. e. Signals unresolved. f. Listed in the following order: H_7, H_8, H_9, H_{10}, H_{12}, H_{13}, H_{14}.

followed by routine function group manipulations. Conditions for these processes are already in the literature.[10,11] The stabilized Wittig reagents (8 & 9) have been used exclusively in this work under conditions more susceptible for non-stereoselective formation of the new double bond.[10-12] The procedure provided a method to the elusive all-trans isomers of 19,19,19- and 20,20,20-trifluororetinal (11, 12).[11,13] In one preliminary experiment we found that the more reactive Peterson reagent 10[14] resulted in formation of addition products with 5B. Subsequent elimination under mild conditions was not successful. In agreement with the cis directing property of the CF_3-group[10] the all-trans isomer was found to be very unstable. For example during storage at -20°C all-trans-20,20,20-trifluororetinal was found to isomerize slowly to the 13-cis isomer. In Table II are listed the newly synthesized fluorinated retinoids along with their key spectral data. Currently, we are exploring possible use of several of these compounds in ^{19}F-NMR studies of the corresponding bacteriorhodopsin analogues.[15]

References and Footnotes

1. New Geometric Isomers of Vitamin A No. 13. For previous paper in the series: See Ref. 13. Part of the results were presented at the PAC Conference December 17-21, 1984, Honolulu.
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   (b) J. T. Gerig, in "Biochemical Magnetic Resonance" (L. J. Berliner and J. Ruebins ed.) Plenum Press, New York, 1978, pp. 139-203.
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4. See e.g., H. Mayer and O. Isler in "Carotenoids" (Ed. O. Isler) Chap. 6, Birkhauser-Verlag, Basel (1971).
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8. ^{1}H-nmr data ($CDCl_3$) for 5B: 1.03, 1.72, 2.11 (methyls) 6.60, 6.22, 6.26, 8.02, 6.43 ppm (H_{7-8} and H_{10-12}); $J_{7,8}$ = 16.5, $J_{10,11}$ = 11.1, $J_{11,12}$ = 14.8 Hz. For compound 7B: 1.02, 1.72, 2.06 (methyls), 6.42, 6.17, 6.40, 7.20, 6.41, 7.67, 6.19 (H_{7-8}, H_{10-14}); $J_{7,8}$ = 16.1, $J_{10,11}$ = 11.9; $J_{11,12}$ = 14.3, $J_{12,13}$ = 11.3, $J_{13,14}$ = 15.2.
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