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AN EXPEDIENT ACCESS TO TRIFLUOROMETHYL KETONES FROM CARBOXYLIC ACIDS

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Abstract: *Trifluoromethyl ketones are prepared in good yield from carboxylic acid chlorides by reaction with pyridine and trifluoroacetic anhydride.*

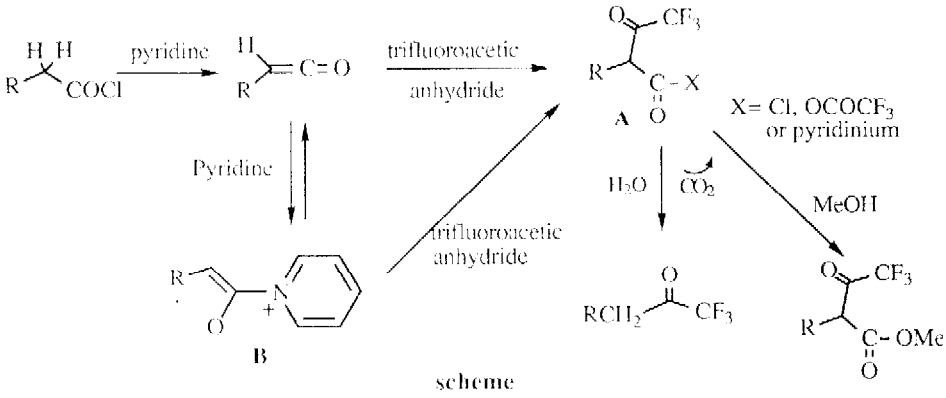
Since the discovery of the therapeutic effects displayed by 5-fluorouracil derivatives[1] and fluorosteroids[2] in the 1950's, the demand for new methods for the obtention of fluoro compounds with potential biological activities has not ceased. In this context, fluorocarbonyl derivatives have emerged as valuable intermediates and targets[3]. Various trifluoromethyl ketones, for example, have been found to possess a marked inhibitory effect on hydrolytic enzymes such as acetyl cholinesterase[4] or juvenile hormone esterase[5].

Trifluoromethyl ketones are usually obtained by elaborating simple fluorine containing molecules. To this end, several methods have been developed; the addition of a Grignard reagent to trifluoroacetic acid (the Dishart Levine method)[6] or one of its derivatives[7] and the decarboxylative hydrolysis of a Claisen type condensation adduct of an ester with ethyl trifluoroacetate[8] are among the oldest and perhaps most popular procedures. Recently, in a synthesis of fluoro derivatives of vitamin D3, the preparation of an intermediate trifluoromethyl ketone was achieved by trifluoroacylation of a lithiated sulphone derivative with ethyl trifluoroacetate followed by desulphonylation[9].

All these methods show important limitations as far as compatibility with the fonctionality of the starting material is concerned. In particular compounds with more than one carbonyl function or those containing different acidic hydrogens are ill-suited substrates. Mention must be made, however, of the procedure described by Coleman and *al* for the preparation[10] of perfluoroalkyl ketones via coupling of an alkyl halide with a perfluoro acyl chloride mediated by disodium tetracarbonyl ferrate, in which unprotected ketones or ester functions can be present.

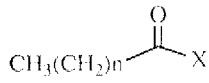
We report here a new, practical, and high yielding method which complements existing procedures, and which appears to be tolerant of various functional groups.This process involves the capture by trifluoroacetic anhydride (TFA) of a ketene produced from an acid chloride as depicted in Scheme 1. The use of ketenes as nucleophiles is well precedented[11], although this aspect of ketene chemistry has been rather neglected in spite of its tremendous synthetic potential.

Thus, upon treatment with pyridine, the primary acid chlorides yield a ketene which can be captured with TFA to give after hydrolysis and decarboxylation the corresponding trifluoromethyl ketones. Because TFA itself lacks α-hydrogens, it cannot lead to a fluoroketene in the presence of pyridine; however, it is however sufficiently electrophilic to prevent the ketene derived from the acid chloride from dimerising. The adduct **A** between the ketene and the anhydride (which can be an acid chloride, a mixed anhydride or even an N-acylpyridinium salt as indicated in the scheme below) was not isolated but hydrolysed to the corresponding keto acid which underwent decarboxylation spontaneously. If the reaction mixture is quenched with methanol instead of water, a Claisen condensation type keto ester is obtained. Our results are compiled in the Table. Examples **4**, **5**, and **7** illustrate some of the most interesting possibilities of this approach since the classical Claisen variation in these cases would almost certainly be difficult to apply.



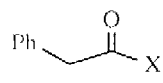
scheme

Yields are good to excellent (see Table); the lowest yields were obtained with acyl chlorides bearing particularly acidic hydrogens such as phenyl acetyl chloride (entry 5) for which the general procedure is unpractical. Moreover, NMR analysis of the crude reaction mixtures often indicated quantitative yields, significant losses occured through hydration on the silica gel during chromatography. Trifluoro ketones are known to give the corresponding hydrates readily[12]. In one variant the acid chloride was conveniently replaced with the sodium salt of the acid (entry 3). The mixed anhydride formed with trifluoroacetic anhydride is then the precursor to the ketene. So far, the reaction has failed with secondary acid chlorides presumably because of steric hindrance.

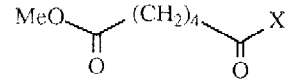


n=14
1a: X= Cl
1b: X=CF_3
1c: X= O Na^+

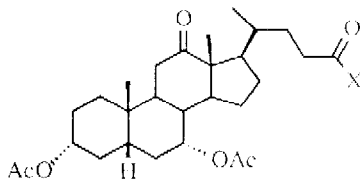
n=16
2a: X= Cl
2b: X=CF_3



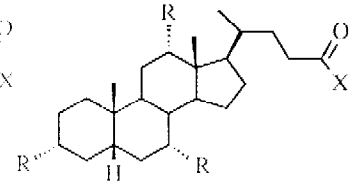
3a: X= Cl
3b: X=CF_3



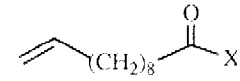
4a: X= Cl
4b: X=CF_3



5a: X= Cl
5b: X=CF_3



6a: X= Cl , R=H **7a**: X= Cl , R=OAc
6b: X=CF_3 , R=H **7b**: X=CF_3 , R=OAc



8a: X= Cl
8b: X=CF_3

Table: Reaction of acid chlorides with trifluoroacetic anhydride and pyridine

Entry	Starting material	Product	Time (hrs)	Temp, °C	% Yield, isolated[a]
1[b]	**1a**	**1b**	2.0	20	66
2	**1a**	**1b**	0.8	20	81[c]
3	**1c**	**1b**	2.0	20	60
4	**2a**	**2b**	1.5	20	73
5	**3a**	**3b**	8.5	-60[d]	40[e]
6	**4a**	**4b**	2.0	0	54
7	**5a**	**5b**	2.0	20	67
8	**6a**	**6b**	5.0	20	60
9	**7a**	**7b**	1.5	20	67
10	**8a**	**8b**	0.5	20	76[c]

a) The product was purified by chromatography on silica gel and gave satisfactory NMR (^1H,^{13}C), IR and elemental microanalysis.

b) Typical procedure: To a solution of **1a** (0.90g) in dry CH_2Cl_2 (25 ml) were successively added trifluoroacetic anhydride (2.7 ml, 6 eq.) and pyridine (2.1 ml, 8 eq.). The solution was stirred under argon, and, after completion the reaction mixture was cooled to 0°C and water (10 ml) was slowly added. Workup with 100 ml water, extraction of the aqueous phase with 3X30 ml CH_2Cl_2, and evaporation of the organic phase after drying(Na_2SO_4), gave 1.15 g of crude **1b**.

c) Diethyl ether was used instead of methylene chloride; analysis of the crude reaction mixture by NMR indicates an essentially quantitative yield.

d) When run at 0°C only tarry materials were recovered. Satisfactory results were obtained when the temperature was lowered and the quantity of pyridine decreased (8 eq. of anhydride for 4 of pyridine).

e) The NMR spectrum of the crude reaction mixture indicates a 60% conversion of the starting phenyl acetyl chloride.

Pyridine appears to be the best base for this transformation. Triethylamine and other tertiary amines with ß hydrogens, react irreversibly with the highly electrophilic TFA[13], and are therefore totally unsuitable. It is quite possible that pyridine accentuates the electrophilicity of the anhydride through formation of N-trifluoroacetylpyridinium trifluoroacetate and, at the same time, enhances the nucleophilicity of the ketene by giving an intermediate "enolate" such as **B**.

In summary, the present procedure provides a simple and practical access to trifluoromethyl ketones which are useful precursors for a variety of fluorine containing compounds. Further work is in progress in order to extend the reaction to secondary acids as well as to other perfluoro anhydrides, which, like TFA are highly electrophilic yet unable to produce a ketene in the presence of pyridine.

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