Pergamon

Tetrahedron Letters, Vol. 37, No. 27, pp. 4711-4712, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00947-1

A New Strategy for the Conversion of Aldehydes into Difluoromethyl Ketones.

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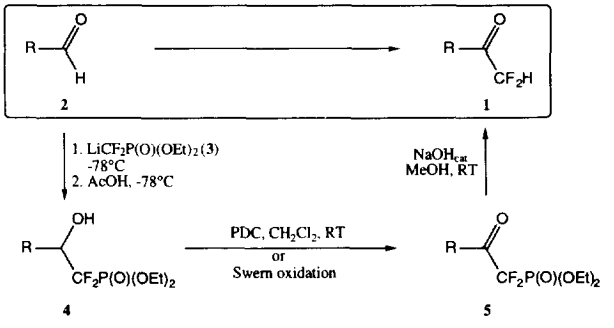
Abstract: A three-step sequence of reactions involving the lithium salt of diethyl difluoromethylphosphonate as a difluoromethyl carrier is shown to efficiently convert aliphatic and arylic aldehydes **2** into difluoromethyl ketones **1** *via* an unusual carbon-phosphorus bond scission. Copyright © 1996 Elsevier Science Ltd

The presence of fluorine atoms in biologically active molecules often induces profound changes in terms of selectivity and/or spectrum of activity.[1] Within the realm of fluorinated compounds, fluoromethyl ketones have been the focus of a renewed interest.[2] More specifically difluoromethyl ketones **1** have been traditionally prepared using different approaches relying on i) the use of difluoroacetic acid derivatives, ii) 1,1-difluoro-2-lithioalkenes obtained from trifluoroethanol, iii) oxidation of a vicinal *trans* difluoroalkenyl silane and iv) electrophilic fluorination of acetylenes.[3] All of these strategies but three are introducing a *two-carbon* unit to construct the HCF_2CO moiety. Matsuda's route describes the reaction of $BrZnCF_2COOEt$ with an aldehyde, followed by oxidation of the alcohol thereby formed, hydrolysis of the ester function and subsequent decarboxylation to produce the target difluoromethyl ketone with a low overall yield of 14%.[3i] A more efficient route described in a patent and reminiscent of Matsuda's method is making use of aryl difluoromethyl sulfones.[3g] Finally difluoromethyl iminium salts have been shown to be acylating reagents of electron-rich aromatic nuclei.[3c] The whole process thus results in these three cases in the formal introduction of a *one-carbon* unit bearing the two fluorine atoms.

We herein describe a new and efficient approach to difluoromethyl ketones **1** that also relies on the introduction of a single carbon unit in the parent skeleton. The strategy calls for the use of the lithium salt of diethyl difluoromethylenephosphonate **3** as the CF_2 carrier (Scheme). Thus 1,1-difluoro-2-oxo-phosphonates **5** were routinely produced (Table) by reacting THF solutions of **3** at -78°C with precooled (-78°C) THF solutions of aldehydes, quenching the resultant adduct at low temperature with glacial acetic acid and oxidizing the obtained alcohols **2** (PDC or Swern oxidation).[4] 1,1-Difluoro-2-oxo-phosphonates **5** were found to undergo a slow dephosphonylation reaction under the influence of alumina in CH_2Cl_2 to provide difluoromethylketone **1**.[5] A much more practical and more efficient transformation was achieved by using protic conditions and a stronger base. We found that reacting **5** (0.25M solution in methanol) with sodium hydroxide (0.2 equivalent; 1M solution in water)



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or sodium methanolate (0.2 equivalent; 1M solution in methanol) resulted in a rapid (30 minutes)[6] cleavage of the CF_2-P bond, release of a phosphate and concomitant production of the desired difluoromethyl ketones in fair to excellent yields (Table). To the best of our knowledge, such a carbon-phosphorus bond breaking has only one (intramolecular) precedent in the literature[7] and has never been observed before on difluorophosphonates.

The present procedure, by allowing the preparation of alkyl, aryl and heteroaryl difluoromethylketones, possesses a flexibility that makes it complementary to those already published.

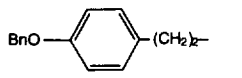
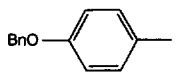
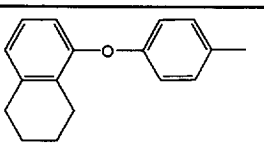
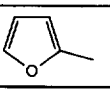
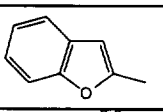
Entry	R	Yields 3 [a]	Yields 4 [a]	Yields 1
a	$H_3C-(CH_2)_4-$	68	56 [b]	100 [d]
b	$H_3C-(CH_2)_{10}-$	54	71 [c]	87 [a]
c		63	62 [b]	65 [a]
d		77	94 [b]	90 [a]
e		67	84 [b]	84 [a]
f		72	93 [c]	88 [d]
g		81	89 [c]	57 [a]

Table. Yields of compounds **3**, **4** and **5**.[8,9] a) Isolated yields. b) PDC oxidation. c) Swern oxidation d) ^{1}H-NMR yields.[10]

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4. Very recently a one-step preparation of α,α-difluoro-β-ketophosphonates from the cerium-mediated reaction between carboxylic esters and the lithium salt of diethyl 1,1-difluoromethyl phosphonate was published; see Lequeux, T. P.; Percy, J. M. *Chem. Commun.*, **1995**, 2111-2112.
5. For instance, stirring **4d** (0.2mmol) and Al_2O_3 (800% w/w) in CH_2Cl_2 (1mL) for 5 days resulted in the formation of **1d** in 65% isolated yield.
6. We have found that longer reaction times result in lower yields by involving aldol condensation reactions, thus indicating the intermediacy of a difluoroenolate.
7. Minami, T.; Kamitamari, M.; Utsunomiya, T.; Tanaka, T.; Ichikawa, j. *Bull. Chem. Soc. Jpn* **1993**, *66*, 1496-1500.
8. ^{19}F NMR spectroscopy chemical shifts ($CDCl_3$ solutions, C_6F_6=internal reference) for **1** are as follows: **1a**: 34.73 (d, $^2J_{F-H}$=54.00Hz); **1b**: 34.92 (d, $^2J_{F-H}$=53.55Hz); **1c**: 34.68 (d, $^2J_{F-H}$=53.55Hz); **1d**: 40.59 (d, $^2J_{F-H}$=53.9Hz); **1e**: 40.46 (d, $^2J_{F-H}$=53.45Hz); **1f**: 37.61 (d, $^2J_{F-H}$=53.47Hz); **1g**: 38.13 (d, $^2J_{F-H}$=53.39Hz).
9. All compounds displayed spectroscopic and analytical data in accordance with the structures depicted.
10. Products were too volatile to be isolated on a 1 mmol scale; thus yields were estimated from the ^{1}H NMR spectra of the crude product taking diethyl methyl phosphate as internal standard.

(*Received in France* 22 *April* 1996; *accepted* 14 *May* 1996)