Pergamon

Tetrahedron Letters, Vol. 37, No. 33, pp. 5881-5884, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01267-1

Reinvestigation of the Wadsworth-Emmons Reaction Involving Lithium Difluoromethylenephosphonate.

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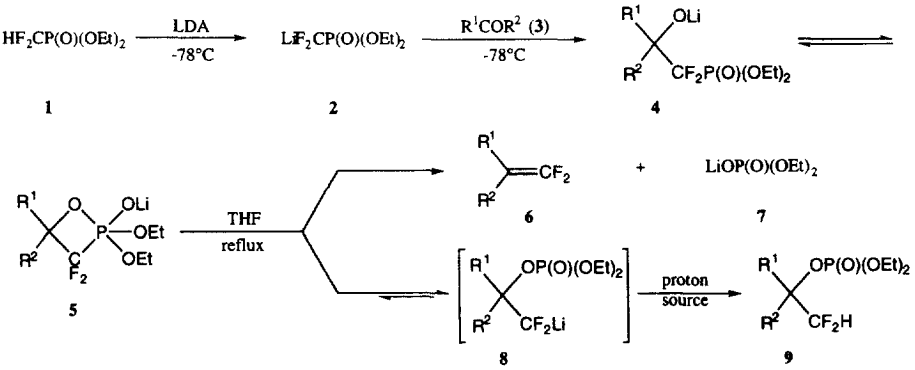
Abstract: Application of the published reaction conditions for the Wadsworth-Emmons transformation of ketones or aldehydes into 1,1-difluoroolefins with lithium difluoromethylenephosphonate failed to give the expected product, affording instead phosphates of the general structure **9** in a nearly exclusive fashion. As variations of the conditions did not bring any change to the unexpected course taken by the reaction, a new procedure was worked out, that allows *reproducible* preparation of the desired difluoroolefins.

For several decades the introduction by researchers of fluorine atoms into biologically active molecules has been a method of predilection to induce changes in their metabolic behavior.[1] Amongst the classes of fluorinated compounds prepared so far, difluoroolefins have been the focus of increasing attention due to their role as mechanism-based inhibitors, the fact that they can be bioisosteric to the corresponding aldehyde or ketone, as well as their importance as intermediates *en route* to other classes of fluorinated compounds.[2]

In connection with a program centered on the preparation of enzyme inhibitors we needed to prepare 1,1-difluoroalkenes as synthetic intermediates.[3] Published methods of formation of such compounds include the *in situ* thermal decomposition of sodium chlorodifluoroacetate in the presence of an aldehyde or a ketone or the use of difluoromethylene phosphorus ylides.[4-8] An interesting approach is represented by a three-step process involving an electrophilic fluorination of (fluorovinyl)stannanes.[9] A paper published by Kondo and coworkers describes the Wadsworth-Emmons reaction between the lithium salt of dialkyl difluoromethylene phosphonates and carbonyl compounds and a recent publication is making use of difluoromethyl phenyl sulfones to achieve a three-step synthesis of 1,1-difluoroalkenes *via* a SmI_2 reduction.[10,11] Finally, very recently was published a new method which avoids the addition of a terminal difluorocarbon and relies on the chemical transformation of a carboxylic acid into the difluoromethylene moiety.[12]

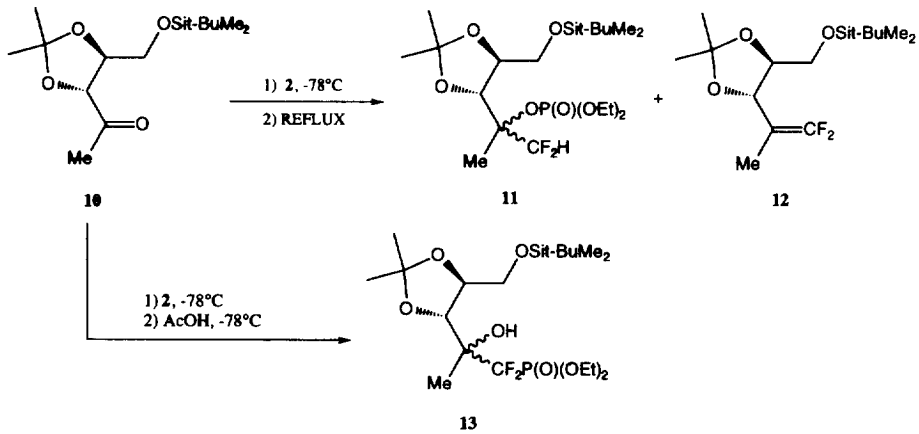
In terms of yields, rapidity and possibility of scale-up, the method of choice appears to be Kondo's (Scheme 1). The published procedure calls for the formation of the reactive lithium salt of diethyl difluorome-



SCHEME 1

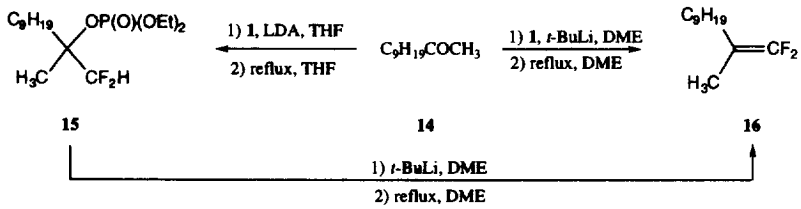
thylene phosphonate **2** from lithium diisopropylamide and phosphonate **1** at -78°C; the carbonyl compound is then added at the same temperature to form the adduct **4** and the resultant solution is warmed up and refluxed to allow the Wadsworth-Emmons reaction to proceed. A usual work-up delivers the desired difluoroolefin **6** in yields between 54 and 75 percent. In a few cases, minor amounts of phosphate **9** are obtained.[13]

When this procedure was applied to ketone **10** however the results were found to be erratic. Phosphates **11** were almost always obtained as the exclusive products (48-52% isolated yield), the desired 1,1-difluoroolefin **12** being formed only in trace quantity (less than 3%) (Scheme 2). Phosphonate **1** and ketone **10** were usually recovered in isolated yields ranging from 21 to 36 %.[14] In only one of the many times the reaction was carried out was the olefin formed in a more significant amount (25%). Exhaustive purification of the reagents, use of diethyl ether as solvent, addition of one equivalent of hexamethylphosphoramide, use of n-butyl lithium or lithium (or sodium) bis(trimethylsilyl)amide, or addition of LiCl did not bring any change to the course of the reaction. Quenching the initial adduct at -78°C with acetic acid permitted the isolation of phosphonates **13** (55% isolated yield), along with recovered phosphonate **1** and ketone **10**.[14]



SCHEME 2

The use of undecanone **14** (one of the ketones described in the original publication) as starting material brought little clue to the causes underlying the unexpected course taken by the reaction (Scheme 3). In this case even quenching the initial adduct at -78°C with acetic acid afforded only phosphate **15** (96% isolated yields). There have been some independent reports that this behavior was observed in other cases as well.[15]



SCHEME 3

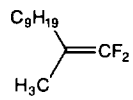
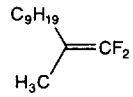
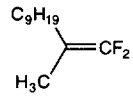
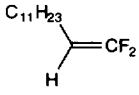
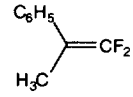
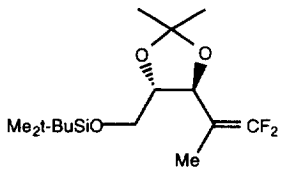
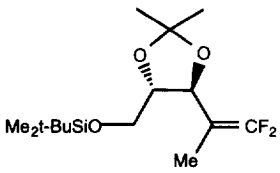
Because of all those repeated problems we undertook the search for a potential solution that would allow us to *reproducibly* obtain the 1,1-difluoroolefins, the account of which is reported hereafter.

As shown in Scheme 1, the only two species being formed in an irreversible way (under the reaction conditions) are difluoroolefin **6** and phosphate **9**. We reasoned that the highly reactive lithiated anion **8**, once formed, would *rapidly* pick up a proton from diisopropylamine, or even from tetrahydrofuran.

We therefore searched *strictly* aprotic conditions. The reversibility of the rearrangement reaction was demonstrated by deprotonation of the CF_2H moiety with a strong base (treatment of an ethereal solution of diastereoisomeric phosphates **11** with *tert*-butyllithium at -78°C), stirring for an additional 120 minutes at the same temperature and quenching the resultant mixture with acetic acid. Analysis of the crude material indicated a 89:4:7 mixture of phosphonates **13**/phosphates **11**/1,1-difluoroolefin **12**.[16] When the same ether

solution was refluxed before quenching, the ratio of compounds **13/11/12** was found to be 47:29:24. [17] To further increase the amount of difluoroolefin, solvents with a higher boiling point were then tested. Di*iso*propyl ether, glyme and the dimethyl ether of ethyleneglycol (DME) were all found to furnish adequate mediums, with the latest proving to be the solvent of choice. Thus, using DME as solvent allowed the isolation of 1,1-difluoroolefin **12** in 55% yield starting from a diastereomeric mixture of phosphates **11**, and in 59% yield starting from a diastereomeric mixture of phosphonates **13**.[18] The two-step process from the ketone therefore provides the difluoroolefin in a *reproducible* 30% overall yield.[19] Similarly a DME solution of phosphate **15** was treated with *tert*-butyllithium at -78°C and refluxed to afford the desired difluoroolefin **16** in 60 % isolated yield (Scheme 3).[20]

We next investigated whether it was possible to adapt this new procedure to develop a single-step preparation of the difluoroolefin from the ketone. Phosphonate **1** was dissolved in a 5:1 mixture of DME-pentane (m.p. of DME: -55°C), cooled down to -78°C and sequentially treated with *tert*-butyllithium (1.1 equivalent) and undecanone **14** (1 equivalent). Warming up the solution to room temperature, distilling off the pentane and refluxing the residual solution for 13 hours left a crude solution whose purification furnished a 69% yield of 1,1-difluoroolefin **16** (Scheme 3). The table shows a few representative examples. In some cases, the two-step process seems to give a better overall result than the single-step preparation.[18]

Difluoroolefin	Method[a]	Yield[b,c] (%)	Reflux Time (hrs)
	A	58	6.5
	A	69	13
	B[d]	60	6.5
	A	60	6.5
	A	27	6.5
	A	14	6.5
	B[e]	30	6.5

a: Method A: single-step preparation of difluoroolefin; Method B: two-step preparation of difluoroolefin. b: isolated yields. c: All new compounds had analytical data in agreement with the assigned structure. d: starting from phosphate **15**. e: starting from either phosphate **11** or phosphonate **13**.

Typical procedures are as follows: *Two-step preparation:* A 1.7M pentane solution of *tert*-butyllithium (5.5 mmol) is added dropwise to a cooled (-65°C) solution of phosphates **11** (2.38 g, 5 mmol) in 6 mL of DME under argon. The resultant solution is stirred for 15 minutes, warmed up to room temperature and refluxed for 6.5 hours. The crude mixture is poured into water (15 mL), extracted three times with CH_2Cl_2 (3x10mL), and dried over $MgSO_4$. Filtration and concentration of the combined organic phases left a crude material which was chromatographed on silica gel and eluted with a 7:3 mixture of heptane-CH_2Cl_2 to furnish the pure product **12** (903mg, 56%) as a colorless liquid.[21] *Single-step preparation:* A 1.7M pentane solution of *tert*-butyllithium (5.5 mmol) is added dropwise to a cooled (-78°C) solution of diethyl difluoromethylene-phosphonate **1** in a mixture of DME (7.5mL) and pentane (1.5 mL) under argon. After 15 minutes of stirring at the same temperature a solution of ketone **14** in DME (3mL) and pentane (0.5mL) is added drop by drop. The resultant solution is stirred at -78°C for an additional 30 minutes and warmed up to room temperature. The pentane is distilled off and the residual solution is refluxed for 13 hours. A work-up identical to the one described above and a short chromatography on silica gel (elution with n-heptane) liberates difluoroolefin **16** (69% yield).[21]

Conclusion. The most reasonable explanation for the lack of reproductibility of the Kondo procedure is the contamination of n-butyllithium by inhibiting or activating traces of metal ions.[22] The procedures described in this paper compare favorably with other published methods. For instance difluoroolefin **12** was also prepared in an overall 32% yield using the three-step synthesis published by Sabol and McCarthy.[11] The two-step work described hereabove provided the same compound in 30% isolated yield. An additional advantage is the avoidance of the expensive and radioactive reagent SmI_2.

References and footnotes.

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10. Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.*, **1982**, *23*, 2323-2327.
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13. Nitroaryl and pyridyl aldehydes or ketones failed to yield the desired difluoroolefins. Phosphates **9** were isolated instead in low yields (10-14%).
14. This probably reflects an acid-base reaction between lithiated species **2** and ketone **10**.

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16. This is indicative of a higher stability of species **4** at -78°C compared to anion **8**.
17. Whether the difluoroolefin is formed *via* a β-elimination process or through the formation of an oxaphosphetane is debatable; the result clearly shows that in the absence of *any* proton source, the formation of the olefin is indeed favored at higher temperature.
18. 22-26% of phosphates **11** were also isolated.
19. This reaction was carried out several times on multigram scales.
20. 28% of phosphate **15** was recovered.
21. Analytical data for all compounds are in accordance with the structures depicted in the paper.
22. Both situations are possible depending on which step of the process the contaminant would interact. Over the period of time during which this study was conducted several lots of n-BuLi from different companies were used without inducing any change in the course of the reaction.

(*Received in France* 4 *June* 1996; *accepted* 27 *June* 1996)