ORGANIC LETTERS

2005
Vol. 7, No. 4
721−724

New Methodology for the Deoxygenative Difluoromethylenation of Aldehydes and Ketones; Unexpected Formation of Tetrafluorocyclopropanes

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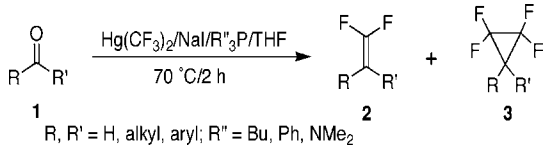
Received December 16, 2004

ABSTRACT



Generation of difluoromethylene phosphorus ylides in the presence of aldehydes and ketones results in Wittig-type reactions to give *gem*-difluoroalkenes. Subsequent in situ addition of difluorocarbene (carbenoid) can occur (increased with triphenylphosphine and decreased with tributylphosphine) to give tetrafluorocyclopropanes.

Selective introduction of fluorine into organic molecules is an active research goal. It is well-known that replacement of a hydrogen atom by fluorine can profoundly alter chemical as well as biological properties of molecules.[1] We have become interested in the synthesis and biological evaluation of *gem*-difluorocyclopropyl derivatives of nucleosides. One successful approach employs our recently communicated addition of difluorocarbene (carbenoid) to electron-rich double bonds.[2] However, this carbene addition reaction did not work well with some other sugar- and nucleoside-derived alkenes.

The LUMO and HOMO energies of carbon−carbon double bonds are not affected dramatically by vinylic fluorine substituents.[3] Therefore, we envisioned an alternative cycloaddition−extrusion approach, which we had used successfully with methylene-substituted furanosyl rings on intact nucleosides. In those cases, addition of diazomethane to the methylene-furanoses followed by photochemical extrusion of nitrogen from the intermediate spiropyrazolines resulted in ring contraction to give the desired spirocyclopropane derivatives.[4]

Methods reported for the preparation of alkenes with a *gem*-difluoromethylene terminus often employ gaseous or low-boiling reagents and rigorously anhydrous conditions and may not be applicable in some cases.[5] We have used the $(CF_3)_2Hg$/NaI reagent combination to generate difluorocarbene, which underwent addition to enamines under mild conditions.[2] We reasoned that decomposition of bis(trifluoromethyl)mercury[6] with sodium iodide in the presence of a phosphine and a carbonyl compound might generate a transient "difluoromethylene ylide" that could undergo

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(2) Nowak, I.; Cannon, J. F.; Robins, M. J. *Org. Lett.* **2004**, *6*, 4767−4770.

(3) Brundle, C. R.; Robin, M. B.; Kuebler, N. A.; Basch, H. H. *J. Am. Chem. Soc.* **1972**, *94*, 1451−1465.

(4) (a) Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007−4008. (b) Samano, V.; Robins, M. J. *Tetrahedron Lett.* **1994**, *35*, 3445−3448.

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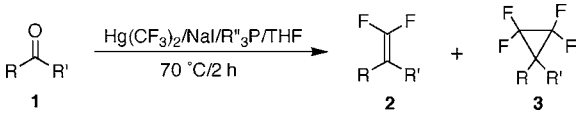
10.1021/ol047416s CCC: $30.25 © 2005 American Chemical Society
Published on Web 01/25/2005

Wittig-type reactions. We now report such conversions of selected aldehydes and ketones into alkenes with a *gem*-difluoromethylene terminus.

The difluoromethylene ylides were generated in situ by heating $(CF_3)_2Hg$ (*CAUTION!* See Supporting Information) and excess NaI with tributylphosphine, triphenylphosphine, or HMPT in THF. A 3-fold excess of the ylide was generated in the presence of an aldehyde or ketone (Scheme 1). The

Scheme 1. Aldehyde and Ketone Difluoromethylenation

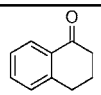
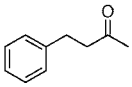
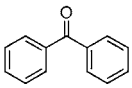
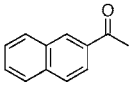
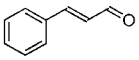
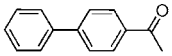
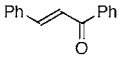
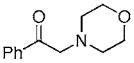
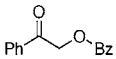


reaction mixture was filtered through silica gel and evaluated by ^{19}F NMR. The products **2** were purified and isolated by chromatography. In most cases, Bu_3P promoted formation of the difluoroalkenes **2** with less of the tetrafluorocyclopropanes **3** (and other byproducts). HMPT gave similar results but no yield advantages and produced HMPA as a byproduct. Triphenylphosphine gave the difluoroalkenes **2** but also promoted greater formation of the tetrafluorocyclopropane adducts **3**. As noted in Table 1 (entry 2), the ratio of alkene to adduct (**2a**/**3a**) was 2:5 after 2 h at 70 °C (1:6 at 90 °C) with Ph_3P. In contrast, Bu_3P gave a 61% yield of **2a** with only trace formation of **3a** (entry 1). Tetrafluorocyclopropanes were formed in lower relative quantities (**2**/**3** ratios of 7:1 to 1:1) during syntheses of compounds **2b**,**d**,**g**,**h** (entries 4, 8, 14, 16) under the standard conditions with Ph_3P. Aldehydes **1e**,**f** (entries 10, 12) and ketones **1c**,**i**,**j** (entries 6, 18, 20) underwent conversion to the respective difluoromethylene compounds **2** with minimal formation of **3**. NMR and HRMS data for **3** were consistent with the adduct structures, and an X-ray crystal structure of **3** (R = Me, R′ = 4-bromo-3-nitrophenyl) confirmed the assignment.

Effects of triphenylphosphine on the formation of the tetrafluorocyclopropanes are unclear and have not been reported previously. Aldehydes and ketones have been converted into their difluoromethylene analogues with metal chlorodifluoroacetate salts and triphenylphosphine in various solvents (including reactions at 80−160 °C with Ph_3P as a component).[5d] Tetrafluorocyclopropane formation has not been noted. Riesel et al.[7] reported that thermal decomposition of $(CF_3)_2Cd$ in the presence of benzaldehyde and R_3P (R = Bu, Et_2N, Ph) gave tetrafluoroethene (the product of carbene dimerization) instead of the expected *gem*-difluoroalkene. Formation of tetrafluorocyclopropane adducts was not mentioned.

It is noteworthy that the difluoromethylene compounds **2** and their cyclopropane adducts **3** are formed by independent

Table 1. Difluoromethylenation of Carbonyl Compounds **1**[a]

entry	1	R"	2 (%)	3 (%)
1	 **1a**	Bu	61	1
2		Ph	19[b]	49[b]
3	 **1b**	Bu	63	3
4		Ph	67	9
5	 **1c**	Bu	67	-
6		Ph	50	3
7	 **1d**	Bu	61	8
8		Ph	55	14
9	**1e**	Bu	[c]	[c]
10		Ph	67	-
11	 **1f**	Bu	[c]	[c]
12		Ph	41	2
13	 **1g**	Bu	52	7
14		Ph	37	41
15	 **1h**	Bu	43	-
16		Ph	20	16
17	 **1i**	Bu	52	-
18		Ph	-	-
19	 **1j**	Bu	[c]	[c]
20		Ph	56	-

[a] Reactions were performed by the general procedure (see Supporting Information). [b] **2a** (10%) and **3a** (58%) when heated at 90 °C. [c] Complex product mixture.

pathways. The alkenes **2** are generated by a Wittig-type process involving a carbonyl group and a difluoromethylene phosphorus ylide. The tetrafluorocyclopropanes **3** are formed subsequently by addition of difluorocarbene (carbenoid) to **2** (Scheme 2). However, this latter process also required the presence of a phosphine, and the highest adduct ratios were obtained with Ph_3P. No conversions of purified **2** into **3** were observed upon heating **2**/$(CF_3)_2Hg$/NaI/THF combinations in the absence of R_3P.

It is possible that association of difluorocarbene with a phosphine (especially Ph_3P) extends its lifetime and/or

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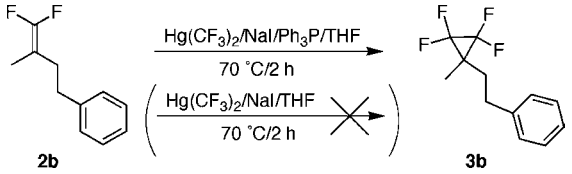
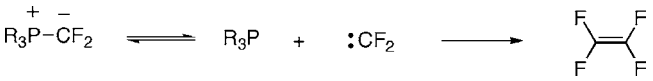
(7) Riesel, L.; Vogt, H, Kolleck, V. *Z. Anorg. Allg. Chem.* **1989**, *574*, 143−152.

Scheme 2. Difluoromethylene Compound Cyclopropanation



modifies its reactivity. Because of the low binding energies, difluoromethylene ylides are thought to equilibrate with their phosphine and difluorocarbene components (Scheme 3).[8]

Scheme 3. Postulated Dissociation of Difluoromethylene Ylides To Give Tetrafluoroethene



Difluorocyclopropanation of tetramethyethylene with a difluoromethylene ylide was postulated to involve ylide dissociation.[9] Reactions of difluorocarbene with solvent molecules (with no phosphines present) gave byproducts that were not detected (^{19}F NMR) in our reaction mixtures that contained phosphines. This suggests that changes in the association and/or reactivity of our difluorocarbene complexes might result in enhanced attraction/addition with the electron-poor difluoroolefins. The absence of reports on analogous difluorocyclopropanation reactions might suggest the formation of additional difluorocarbene−mercury and/or difluorocarbene−mercury−phosphine complexes in our systems. We lack evidence to support or disprove such possibilities.

Formation of adducts **3a**,**b**,**d**,**g** occurred within the first 2 h of heating in parallel with difluoromethylenation of **1a**,**b**,**d**,**g** to give **2a**,**b**,**d**,**g** [i.e., until the decomposition of $(CF_3)_2Hg$ was complete]. Longer reaction times did not improve yields of the tetrafluorocyclopropanes **3**. However, mixtures of **2** and **3** were converted completely into **3** upon successive cycles of purification and resubmission to the standard reaction conditions (until **2** was no longer present).

With dienes **2f** and **2h**, difluorocarbene addition to either the −HC═CH− or C═CF_2 π-bond was possible. However, only the latter addition was observed (as indicated by the presence of only two ^{19}F signals resulting from the planar symmetry of **3** and the similarity of the ^{19}F NMR data for all of our tetrafluorocyclopropanes **3**). The ^{19}F chemical shifts for **3** are in the range of δ 141−154 ppm, and the geminal couplings are in the range of $^2J_{F,F}$ = 170−180 Hz.

The scope of our present evaluation for efficient difluoromethylenation reactions includes less easily enolized aldehydes and ketones. Basicities of the difluoromethylene ylides are sufficient to promote condensation reactions with readily enolizable carbonyl compounds, in agreement with results noted by Wheaton and Burton.[10] Our standard conditions with **1a**,**b**,**d**,**g**,**i**,**j**, which have α-hydrogen atoms, gave the desired difluoroalkenes. However, insoluble resins resulted from analogous treatment of β-tetralone (**4**), as well as the aldehyde **5** and ketones **6** and **7** (Figure 1). Steric hindrance

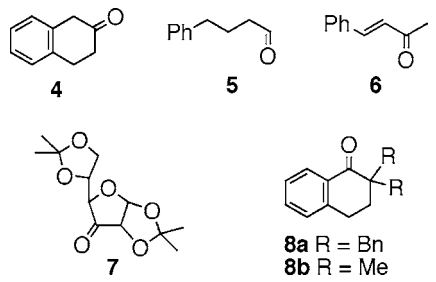


Figure 1. Substrates that did not undergo the standard difluoromethylenation reaction.

at the α-carbon(s) is another important factor. Tetralone (**1a**) underwent difluoromethylenation readily, whereas its 2,2-dibenzyl, **8a**, and 2,2-dimethyl, **8b**, derivatives were recovered unchanged under identical conditions.

Our new methodology provides convenient access to the difluoromethylene compounds **2** on a small scale. For example, we isolated 61% of purified **2a**, whereas 6-fluorotetralone had been converted into its 6-fluoro-1-(difluoromethylene) derivative with HMPT and sodium chlorodifluoroacetate in 3% isolated yield.[11] Our method gave **2c** in 67% yield, whereas it had been obtained previously (13%) by a decomposition of difluoroacetate.[12] We isolated diene **2f** in 41% yield on a 1.65 mmol scale, whereas Burton and co-workers had prepared **2f** (30%) by treatment of cinnamaldehyde (**1f**) (20 mmol scale) with the volatile CBr_2F_2 plus Zn/Ph_3P[13] or by the 72 h treatment of cinnamylidenetriphenylphosphorane (80 mmol scale) with $CHClF_2$ (15%).[10] Apart from its severe toxicity, the ready availability[6] and low cost of $(CF_3)_2Hg$ and its convenient applicability for small-scale reactions make it a useful new reagent for difluoromethylenations.

In conclusion, we have developed a convenient new method for conversion of carbonyl compounds into alkenes and dienes with a difluoromethylene terminus. These selectively fluorinated compounds are important starting materials for synthesis of other classes of *gem*-difluoro compounds.[5,14] Also, we have observed the previously unreported formation of tetrafluorocyclopropane adducts and describe conditions under which the difluoromethylene compounds can be

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converted into these interesting, strained[15] molecules. More detailed studies are required to delineate the phosphine and substrate structural effects on these difluoromethylene- and tetrafluorocyclopropane-forming processes. Applications of this chemistry for synthesis of novel nucleoside-derived products are under investigation.

Acknowledgment. We gratefully acknowledge NIH Grant GM029332, pharmaceutical company gift funds (M.J.R.), and Brigham Young University for support of this research. We thank Professor John F. Cannon for the X-ray crystal structure determination.

Supporting Information Available: Simplified synthesis of $(CF_3)_2Hg$; experimental procedures, spectral data, and ^1H and ^{13}C NMR spectra for compounds **2a**−**j** and **3a**,**b**,**d**,**g**; and ^1H and ^{13}C NMR spectra and X-ray crystal structure for 1,1,2,2-tetrafluoro-3-(4-bromo-3-nitrophenyl)-3-methylcyclopropane. This material is available free of charge via the Internet at http://pubs.acs.org.

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