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Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine†‡

Cite this: *Chem. Commun.*, 2013, **49**, 7513

Received 6th June 2013,
Accepted 26th June 2013

DOI: 10.1039/c3cc44271c

www.rsc.org/chemcomm

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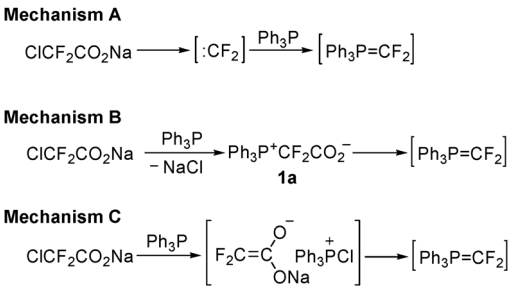
A key intermediate, difluoromethylene phosphobetaine, in the Wittig reaction of $ClCF_2CO_2Na$–Ph_3P with aldehydes was synthesized and characterized, which confirmed the reaction mechanism. The decarboxylation of this stable intermediate was a convenient approach for Wittig difluroolefination. Its reactivity could be adjusted by the modification of the substituent on the phosphorus.

gem-Difluoroolefins constitute a distinct class of fluorine-containing compounds.[1] They have attracted much interest in various fields such as medical and agricultural chemistry and materials science because the *gem*-difluorovinyl moiety greatly affects the biological functions and physical properties of organic molecules.[2] Consequently, considerable effort has been made to develop efficient methods for their preparation. Basically, there are three approaches to construct the *gem*-difluoroolefin framework.[3] β-Elimination is a general method but it requires tedious multi-step synthesis of the fluorinated precursors.[4] A second approach to construction of *gem*-difluoroalkenes utilizes organometallic reagents such as *gem*-difluorovinyl lithium or borane, which need careful handling due to their sensitivity to moisture.[3a,5] A third method employs Julia, Horner–Wadsworth–Emmons (HWE) or Wittig reaction for the difluoroolefination of aldehydes and ketones.[6] Of these approaches, the Wittig type reaction is one of the most straightforward methods to achieve difluoroalkenes.

As part of our continuing interest in fluorinated olefins,[7] we investigated the Wittig difluoroolefination of carbonyl compounds. In this reaction, the difluoromethylene unit was mostly derived from dibromodifluoromethane (CF_2Br_2)[8] or sodium chlorodifluoroacetate ($ClCF_2CO_2Na$).[9] Due to the high ozone-depleting potential of CF_2Br_2, its use is prohibited. For the Wittig reaction involving $ClCF_2CO_2Na$, there was a debate on the process of the reaction. Three mechanisms were proposed to explain the formation of difluoromethylene(triphenyl)phosphorane ($Ph_3P{=}CF_2$) (Scheme 1).[9a] $ClCF_2CO_2Na$ had already been known to be an efficient difluorocarbene ($:CF_2$) precursor.[10] Therefore, Fuqua tended to think that $Ph_3P{=}CF_2$ was generated through the capture of $:CF_2$ from $ClCF_2CO_2Na$ by triphenylphosphine (mechanism A).[9a] However, a later study showed that the thermal decomposition of $ClCF_2CO_2Na$ could be greatly accelerated by triphenylphosphine.[9d] And the trap of $:CF_2$ with tetramethylethylene or isopropyl alcohol was not observed in the Wittig reaction of $ClCF_2CO_2Na$.[9d] So Herkes and Burton proposed that (triphenylphosphonio)difluoroacetate ($Ph_3P^+CF_2CO_2^-$, PDFA, **1a**) was first generated and its subsequent decarboxylation led to the formation of $Ph_3P{=}CF_2$ (mechanism B). However, their attempts to prepare $Ph_3P^+CF_2CO_2^-$ failed.[9d]



Scheme 1 Mechanisms for the Wittig reaction of $ClCF_2CO_2Na$.

To gain more insight into the mechanism of this Wittig reaction, we explored the reaction of 4-phenylbenzaldehyde, triphenylphosphine and $ClCF_2CO_2Na$ under the same reaction conditions as described by Fuqua and Burton.[9a,c,d] However, not any $Ph_3P^+CF_2CO_2^-$ could be observed by ^{19}F NMR spectroscopy when the reaction was performed in various solvents (DG, DMF or NMP) at different temperatures (160 °C, 100 °C or 80 °C). The result is still the same without the presence of aldehydes. It is speculated that such a difluoromethylene phosphobetaine (**1a**) might easily undergo decarboxylation at

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† Dedicated to Professor Jean'ne M. Shreeve on the occasion of her 80th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization of data for all compounds. CCDC 929401 (**1a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44271c

§ These authors contributed equally to this work.

$$Ph_3P + BrCF_2CO_2K \xrightarrow[rt]{DMF} Ph_3P^+CF_2CO_2^-$$
1a

Scheme 2 Preparation of (triphenylphosphonio)difluoroacetate (PDFA, **1a**).

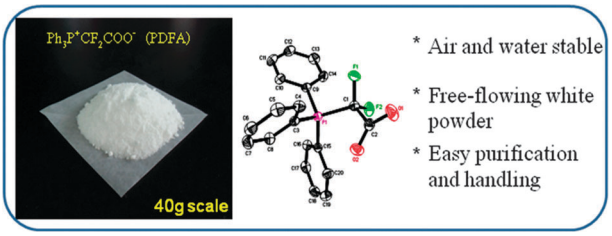


Fig. 1 Reaction intermediate: (triphenylphosphonio)-difluoroacetate (PDFA, **1a**).

the tested temperature. When the reaction was performed in DMF at 55 °C, a weak doublet at −94.10 ppm (J = 100.3 Hz) appeared in the ^{19}F NMR spectrum, which might be the signal of –CF_2– in PDFA. Nevertheless, the reaction was too weak to be worthy of further isolation.

Due to the easier breaking of C–Br bonds as compared with that of C–Cl bonds, $BrCF_2CO_2K$ was employed instead of $ClCF_2CO_2Na$ in the above reaction. It was found that the reaction of $BrCF_2CO_2K$ with PPh_3 proceeded very well in DMF at room temperature, giving PDFA in 67% yield (Scheme 2). Its structure was characterized by NMR spectroscopy, mass spectrometry, elemental analysis, and further confirmed by single crystal X-ray analysis (Fig. 1). Its low solubility in H_2O and DMF allows for simple work-up and easy scale-up. The phosphobetaine is stable in air and water. Thermal analysis (DSC-TGA) showed no decomposition below 105 °C (see the ESI‡), demonstrating relatively good thermal stability. However, as shown by ^{19}F NMR spectroscopy, slow decomposition commenced in the presence of polar solvent such as DMF or CH_3OH even at room temperature.

Given that the above (triphenylphosphonio)difluoroacetate (PDFA) was produced from $BrCF_2CO_2K$, it was therefore necessary to know if PDFA is the right intermediate in the Wittig reaction of $ClCF_2CO_2Na$ (mechanism B, Scheme 1). As described above, heating a solution (S_{Cl}) of $ClCF_2CO_2Na$ and Ph_3P in DMF at 55 °C gave a trace amount of product showing a doublet signal at −94.10 ppm in the ^{19}F NMR spectrum (Fig. 2A), which is exactly the same as that observed in the ^{19}F NMR spectrum of PDFA prepared from $BrCF_2CO_2K$. Furthermore, the external addition of the prepared PDFA to the solution (S_{Cl}) increased the signal intensity at −94.10 ppm (Fig. 2B). Subsequent addition of 4-phenylbenzaldehyde led to the signal disappearance at −94.10 ppm and the formation of the *gem*-difluoroolefination product after keeping the resulting solution at 55 °C for 1 h (Fig. 2C). This indicated that mechanism B involving phosphobetaine is the most probable process for the Wittig reaction of $ClCF_2CO_2Na$ (Scheme 1).

With the stable reaction intermediate PDFA in hand, we then investigated its application as a ylide precursor in Wittig difluoroolefination. The screening of reaction conditions showed that 2 : 1 of phosphobetaine to aldehyde at 80 °C for 4 h in NMP was the optimal reaction condition (see the ESI‡).

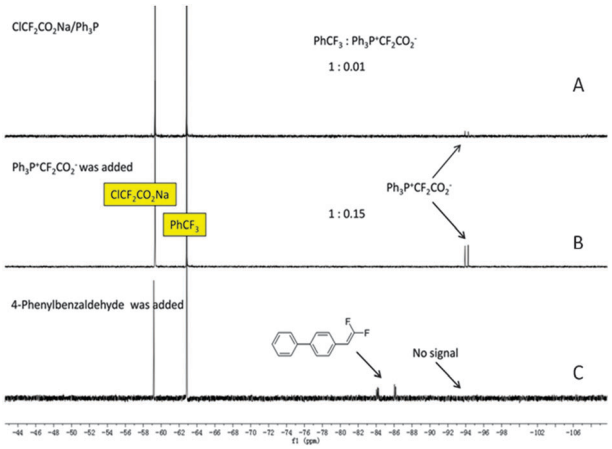
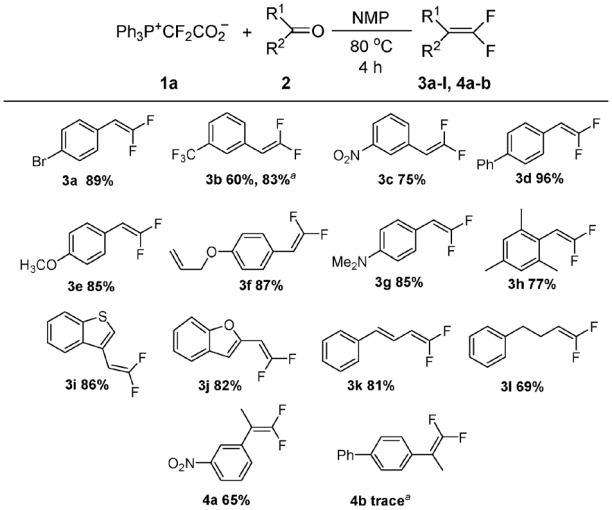
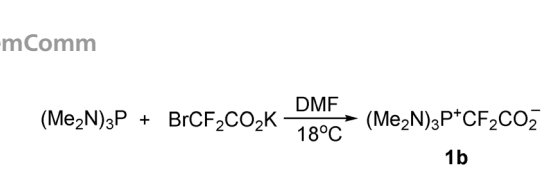


Fig. 2 ^{19}F NMR analysis of the reaction mixture.

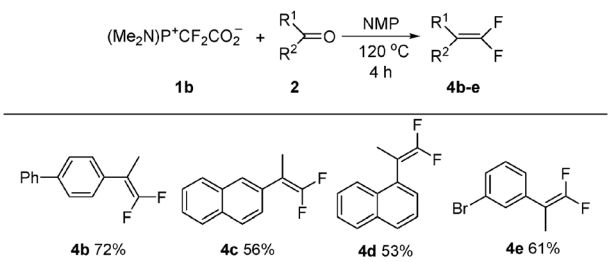


Scheme 3 *gem*-Difluoroolefination of aldehydes and ketones. Reaction conditions: **1a** (1.6 mmol) and **2** (0.8 mmol) in NMP at 80 °C for 4 h. Isolated yields obtained after column chromatography. [a] Determined by ^{19}F NMR through the quantitative addition of trifluoromethylbenzene (0.1 mmol) as the standard.

Then a series of carbonyl compounds were tested for their suitability for use in this difluoroolefination under the optimal reaction conditions (Scheme 3). It was found that the reaction with aryl aldehydes displayed a remarkable tolerance towards different electron-donating and -withdrawing groups on the aryl ring, giving the desired difluoroolefinated product in moderate to excellent yield (**3a–h**). The relatively lower yield for *m*-trifluoromethyl benzaldehyde is partially due to the high volatility of the product, because the yield determined by ^{19}F NMR analysis was 83% (**3b**). The double bond present in the substrate remained intact during the reaction, indicating that few or no difluorocarbene was formed under the reaction conditions (**3f**). The steric hindrance did not significantly affect the reaction (**3h**). The reaction proceeded equally well for the heteroaromatics (**3i**, **3j**) and α,β-unsaturated aldehyde (**3k**). In the case of enolizable aldehyde, relatively good yield was obtained (**3l**). Moderate yield could be obtained in the reaction of PDFA with activated ketone (**4a**). But as for nonactivated ketones,



Scheme 4 Preparation of [tris(dimethylamino)phosphonio]difluoroacetate (ADFA).



Scheme 5 *gem*-Difluoroolefination of ketones. Reaction conditions: **1b** (1.0 mmol) and **2** (0.5 mmol) in NMP at 120 °C for 4 h. Isolated yields obtained after column chromatography.

only a trace amount of product was detected by ^{19}F NMR analysis (**4b**).

It has been reported that the difluoromethylene tris(dimethylamino)phosphonium ylide formed *in situ* could react well with nonactivated ketones.[8b] This prompted us to synthesize [tris(dimethylamino)phosphonio]difluoroacetate [$(Me_2N)_3P^+CF_2CO_2^-$, ADFA, **1b**]. It was found that $(Me_2N)_3P^+CF_2CO_2^-$ can be similarly obtained using the same procedure as that used for obtaining PDFA (Scheme 4).

The phosphobetaine (ADFA) was then applied in the reaction with nonactivated ketone, 4′-phenylacetophenone. Under the same reaction conditions as those used for PDFA, the desired difluoroolefinated product (**4b**) was formed in 12% yield. However, much of the salt (**1b**) remained unreacted after being heated at 80 °C for 4 h. Further screening of the reaction temperature showed that a yield of 72% was achieved when the reaction was performed at 120 °C for 4 h (**4b**, Scheme 5). The reaction with other nonactivated ketones also proceeded smoothly under these reaction conditions (**4c–4e**). This indicated that the reactivity of the phosphobetaine could be modified through changing the substituents on the phosphorus.

It is obvious that this Wittig reaction was driven by the decarboxylation of the phosphobetaine, giving the corresponding difluoromethylene phosphonium ylide (R_3P^+–CF_2^-). Although the decarboxylation of a carboxylate often generates an anion, this strategy was seldom employed in Wittig reactions,[11] probably because of the usually high decarboxylation temperature. The relatively lower decarboxylation temperature of the phosphobetaine made this Wittig difluoroolefination feasible and practical. Compared with other difluoroolefination methods using $ClCF_2CO_2Na$[9] or CF_2Br_2,[8] which suffer from high hygroscopicity or commercial availability of the reagents or forcing reaction conditions, the present reaction starting from the isolated phosphobetaine appears more simple and convenient because no catalyst or additive is required.

In conclusion, the reaction intermediate, difluoromethylene phosphobetaine (PDFA), was successfully synthesized and characterized as the ylide precursor of the Wittig difluoroolefination, which provided direct evidence for the reaction mechanism. The generation of the ylide through decarboxylation was found to be an efficient and simplest pathway for Wittig reaction. The difluoromethylene phosphobetaine might reasonably be expected to become a convenient difluoroolefination reagent due to its stability, adjustable reactivity and ease of handling. Further research on the application of difluoromethylene phosphobetaine to other reactions is currently underway.

We thank the National Natural Science Foundation (21032006, 21172240), the 973 Program of China (2012CBA01200) and the Chinese Academy of Sciences.

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