Organic LETTERS

Letter

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Difluoromethylene Phosphabetaine as an Equivalent of Difluoromethyl Carbanion

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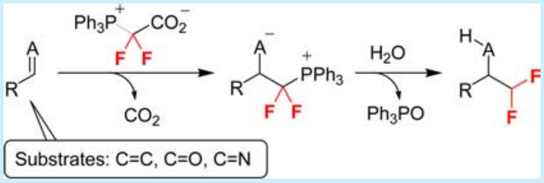
Supporting Information

ABSTRACT: A method for nucleophilic difluoromethylation of reactive Michael acceptors, aldehydes, and azomethines is described. The reaction is performed using the readily available and air-stable reagent difluoromethylene phosphabetaine. The process involves interaction of an electrophilic substrate with in situ generated difluorinated phosphonium ylide followed by hydrolysis of the carbon−phosphorus bond under mild conditions.

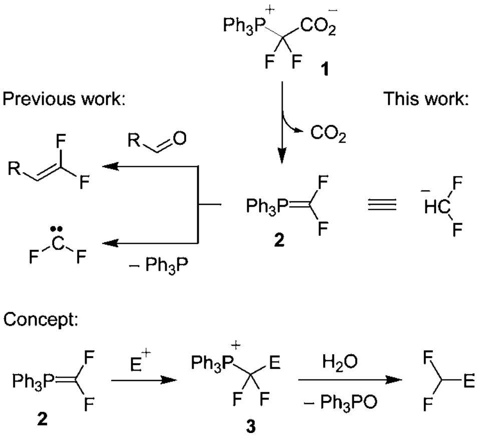


Organofluorine compounds play important roles in medicinal chemistry and related fields, as evidenced by the great number of fluorine-containing drugs and agrochemicals.[1] While the trifluoromethyl group has for a long time been the most frequently used and studied fragment,[1,2] today partially fluorinated groups attract significant attention. For example, the difluoromethyl substituent (CHF_2) exhibits unique pharmacoforic properties that make it capable of serving as a lipophilic hydrogen bond donor, thus being bioisosteric to the hydroxyl group.[3]

Nucleophilic fluoroalkylation has emerged as a reliable methodology for the direct introduction of fluorinated groups into organic molecules.[2a−c,4] Although it is well developed for trifluoromethylation,[2a−c] difluoromethylation is more challenging to perform.[4−7] To this end, several reagents for the introduction of CHF_2-carbanion were described, but limited substrate scope, high reagent cost, and availability issues constitute major limitations of existing methods.[8] In this work, we describe a robust difluoromethylation protocol involving inexpensive, shelf-stable, and easy-to-handle reagent.

Recently, Xiao reported preparation of difluoromethylene phosphabetaine (**1**) from triphenylphosphine and potassium bromodifluoroacetate[9] (Scheme 1). While a stable crystalline compound at room temperature, upon mild heating, betaine **1** undergoes decarboxylation to generate transient phosphonium ylide **2**.[10,11] The latter species has not been identified,[11] but it can react with aldehydes affording olefination product[9,10a,11,12] or it can expel phosphine to generate difluorocarbene.[10b,c] Herein we demonstrate that ylide **2** can serve as an equivalent of difluoromethyl carbanion.[13] Our concept is based on using ylide **2** as a nucleophile followed by hydrolytic cleavage of the C−P bond in intermediate phosphonium salt **3**, thereby affording a product of nucleophilic difluoromethylation (Scheme 1, bottom equation).

Scheme 1. Use of Difluorinated Phosphonium Ylide



Given our interest in performing fluoroalkylation of electron-defficient alkenes,[14] we selected arylidene derivatives of Meldrum's acid (**4**) owing to high electrophilicity of the double bond.[14b,15] Thus, the interaction of compound **4a** with betaine **1** was performed in dimethylformamide at 60 °C (Scheme 2). The formation of phosphonium intermediate **5a** can be proved by ^{19}F NMR spectroscopy. Zwitterionic species **5a** was isolated in individual state and fully characterized, and its structure was confirmed by single-crystal X-ray analysis (Figure 1). A solution of generated phosphonium salt **5a** was treated with water (ca. 10 equiv) followed by heating to effect

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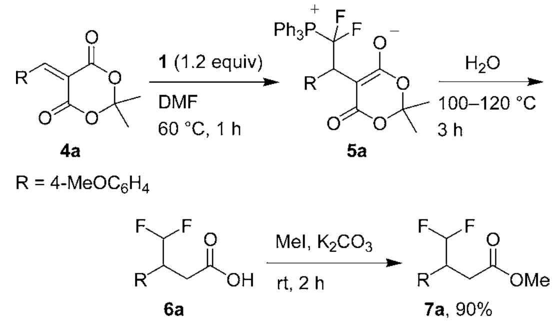
Scheme 2. Difluoromethylation of Substrate 4a



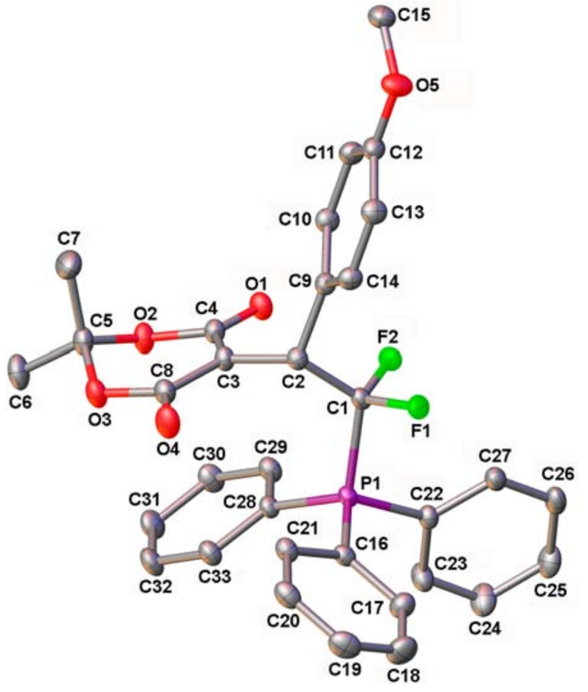
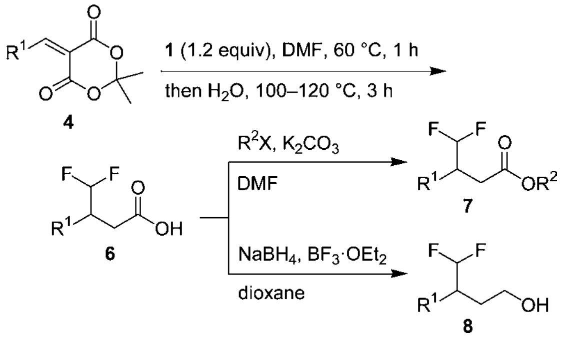
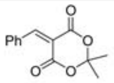
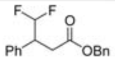
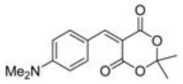
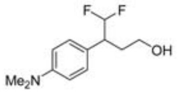
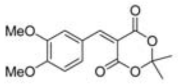
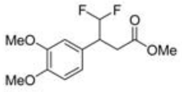
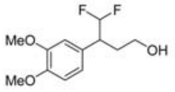
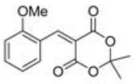
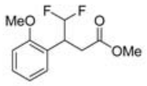
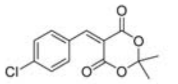
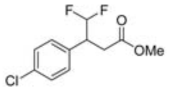
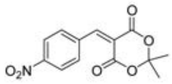
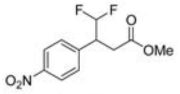
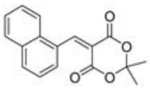
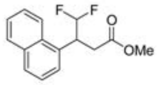
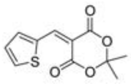
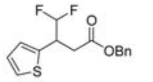
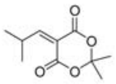
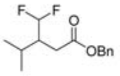
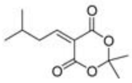
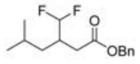


Figure 1. X-ray structure of zwitterion **5a**. Hydrogen atoms are omitted for clarity.

Table 1. Reactions of Aryl- and Alkylidene Meldrum's Acids 4



no.	substrate		product		yield, %[a]
1		**4b**		**7b**	75
2		**4c**		**8c**	78
3		**4d**		**7d**	88
4		**4d**		**8d**	84
5		**4e**		**7e**	54
6[b]		**4f**		**7f**	93
7[b]		**4g**		**7g**	76
8		**4h**		**7h**	78
9[c]		**4i**		**7i**	75
10[d]		**4j**		**7j**	75
11		**4k**		**7k**	71

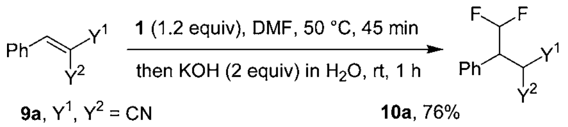
[a] Isolated yield based on substrate **4**. [b] Aqueous KOH at 60 °C was used for the protodephosphorylation step. [c] MeCN was used as solvent in the reaction with **1**. [d] 2 equiv of **1** was used.

hydrolysis of the C−P bond along with transformation of Meldrum's acid moiety into carboxylic acid. In fact, protodephosphorylation proceeded at room temperature (vide infra), but heating was required for decarboxylation. It proved to be difficult to purify carboxylic acid **6a** by chromatography owing to significant tailing on silica gel, and crude acid was converted to methyl ester **7a**, which was isolated in 90% yield based on starting **4a**.

A series of arylidene susbtrates **4** reacted with betaine **1** with subsequent protodephosphorylation (Table 1). The intermediate acids **6** were either esterified (using MeI or BnBr) to afford esters **7** or reduced with a sodium borohydride/boron trifluoride combination to afford alcohols **8**. Reactions worked well with substrates derived from aromatic aldehydes bearing electron-donating or electron-withdrawing susbtituents. Only for compound **4e** having an *o*-methoxy group was product **7e** formed in reduced yield of 54% (entry 5). Rewardingly, alkylidenes **4j,k** obtained from enolizable aliphatic aldehydes gave good yields of products **7j,k** (entries 10 and 11). Apparently, the successful addition to enolizable substrates is associated with relatively low basicity of phosphonium ylide **2**. However, the reaction of a substrate derived from Meldrum's acid and phenyl methoxycarbonyl ketone afforded no difluoromethylation product.

The reactivity of other Michael acceptors was briefly evaluated (Scheme 3). Benzylidene derivatives of malononitrile and cyanoacetic ester **9a,b** gave difluoromethylated products **10a,b** in reasonable yields. At the same time, benzylidene malonate **9c** was unreactive because of its low electrophilicity.[16] It should be pointed out that for substrates **9a,b**, proto-

Scheme 3. Difluoromethylation of Substrates 9

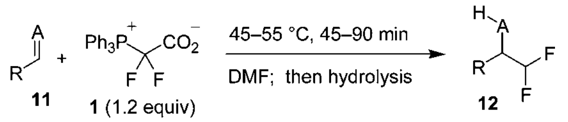


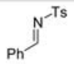
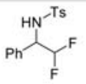
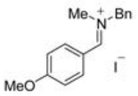
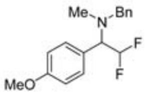
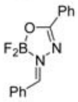
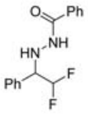
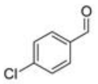
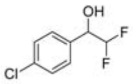
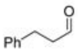
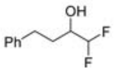
9a, Y^1, Y^2 = CN — **10a**, 76%
9b, Y^1 = CO_2Me, Y^2 = CN — **10b**, 66% (dr 1.5:1)
9c, Y^1, Y^2 = CO_2Me — **10c**, no reaction

dephosphorylation of intermediate phosphonium salts was performed at room temperature using 2 equiv of aqueous alkali.

It was interesting to investigate difluoromethylation of aldehydes and azomethines since resulting difluorinated alcohols and amines are useful building blocks. *N*-Tosylimine, iminium ion, and difluoroboryl complex derived from *N*-benzoylhydrazone[17] gave corresponding products **12a−c** in good yields (Table 2, entries 1−3). The progress of the reaction can be visually monitored either by dissolution of poorly soluble reagent **1** or by gas evolution, which allows precise selection of reaction time and temperature (45−55 °C depending on substrate). When *p*-chlorobenzaldehyde was treated with betaine **1** at 50 °C, only a product of Wittig reaction,[9] the corresponding difluoroalkene, was observed in the reaction mixture (^{19}F NMR control). However, when the reaction was performed in the presence of a stoichiometric amount of Me_3SiCl, the desired product **12d** was isolated after the hydrolysis step in excellent yield (entry 4). Of special note is that in the latter case difluoroalkene was not detected. The reaction can also be applied to unbranched aliphatic aldehydes, as exemplified by difluoromethylation of dihydrocinnamaldehyde, with the best yield achieved using dichloroethane as solvent (entry 5). Concerning the effect of chlorosilane, we believe that the interaction of phosphonium ylide **2** with aldehydes generates betaine **13** which is rapidly trapped by silylating reagent affording salt **14** (Scheme 4).[18] Acetophenone was unreactive toward betaine **1** under standard conditions.

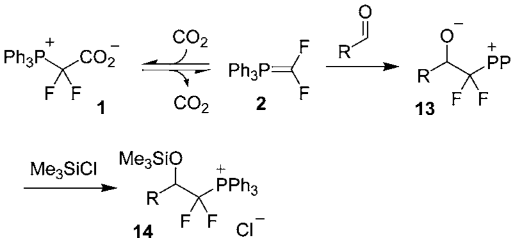
Table 2. Difluoromethylation of C═O and C═N Bonds



no.	substrate		T, °C	product		yield, %[a]
1[b,c]		**11a**	55		**12a**	84
2[d]		**11b**[e]	45		**12b**	71
3[d]		**11c**	50		**12c**	93
4[c,f]		**11d**	50		**12d**	95
5[b,c,g]		**11e**	55		**12e**	90

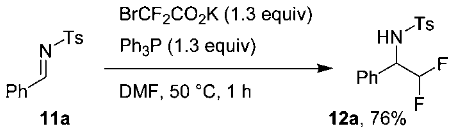
[a]Isolated yield. [b]Betaine **1** (1.3 equiv) and Me_3SiCl (1.5 equiv) was added. [c]Aqueous KF was used for hydrolysis step. [d]Aqueous KOH was used for hydrolysis step. [e]Generated in situ from imine and MeI. [f]Me_3SiCl (1.3 equiv) was added. [g]Dichloroethane was used as solvent.

Scheme 4. Mechanism of Reaction of Betaine 1 with Aldehydes



Although betaine **1** is easily prepared,[9] difluoromethylation can be performed simply starting from its precursors (Scheme 5). Indeed, heating of imine **11a** with potassium bromodifluoroacetate and triphenylphosphine with subsequent dephosphorylative treatment gave product **12a** in good yield.

Scheme 5. Difluoromethylation of Imine 11a



In summary, a practical method for nucleophilic difluoromethylation of various π-electrophiles using a shelf-stable and readily available phosphorus reagent is described. The key features of the reaction involve (a) its applicability to enolizable substrates due to moderate basicity of nucleophilic species and (b) a facile protodephosphorylation step, which proceeds even at room temperature.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds, and X-ray data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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