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Kilogram-Scale Synthesis of $Ph_3P^+CF_2CO_2^-$

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ABSTRACT: $Ph_3P^+CF_2CO_2^-$ (PDFA), a reagent that was developed by us recently, has found widespread applications in the synthesis of fluorinated molecules. Its great synthetic potential stimulates us to develop an effective synthetic route on a kilogram scale, which is described in this work. The used reagents are all cheap and easily available. We also demonstrate that the aldehyde group is significantly more reactive than the double bond group toward PDFA even though both of these two groups are very reactive toward PDFA.

KEYWORDS: *fluorine, kilogram-scale synthesis, PDFA, aldehyde, alkenes*

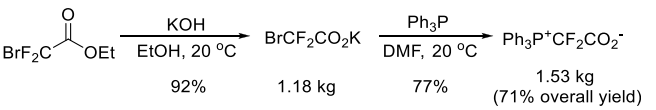
1. INTRODUCTION

The incorporation of a fluorine element into organic molecules may modify their physicochemical properties since the element possesses some "magic effects".[1] In pharmaceutical chemistry, many fluorinated groups have been identified as valuable units as they usually can improve biological properties of target molecules, including lipophilicity, metabolic stability, and bioavailability.[2] The high value of the fluorine element has encouraged significant efforts to develop fluorine-containing reagents for the efficient installation of fluorinated groups,[3] such as trifluoromethoxy (CF_3O)[4] and trifluoromethyl groups (CF_3).[5] Recently, we developed a phosphonium ylide and difluorocarbene reagent, $Ph_3P^+CF_2CO_2^-$ (PDFA).[6] PDFA was proposed as a key intermediate by the Herkes and Burton[7] in 1967, but their attempts to synthesize this intermediate failed, and it remained a hypothetical molecule until our successful preparation.[8] Our research efforts have shown that PDFA is highly effective for fluorine incorporation.[6]

PDFA can easily undergo decarboxylation to generate the phosphonium ylide $Ph_3P^+-CF_2^-$. In sharp contrast to common phosphonium ylides in which the P^+-C^- bond has a double bond character, ylide $Ph_3P^+-CF_2^-$ has a weak P^+-CF_2^- bond and, thus, the cleavage of the $P-CF_2$ bond would readily occur to release difluorocarbene.[8,9] In other words, PDFA is not only a phosphonium ylide reagent but also a difluorocarbene reagent. Compared with other difluorocarbene reagents, PDFA has some striking features. It can be prepared from cheap starting materials, no tedious workup process is required for its purification, and mild heating of PDFA can directly produce difluorocarbene without the need of any other additive. As a reactive intermediate, difluorocarbene has found widespread applications in organic synthesis.[10] The successful synthesis of PDFA allowed us to discover some interesting difluorocarbene chemistry.[6] We found that difluorocarbene generated in situ can be further transformed into carbonyl fluoride,[11] thiocarbonyl fluoride,[12] and cyanide anion,[13] and these processes have been developed as synthetic tools to achieve challenging reactions, such as ^{18}F-labeling trifluoromethylthiolation.[12a,b] We also found that difluorocarbene can be transfer by a catalytic Pd source[14] to combine two aryl groups together to provide $ArCF_2Ar'$.[14b] Our accomplishments have stimulated other groups to use PDFA as a reagent for a wide range of reactions,[15] such as ^{18}F-labeling.[15f]

The great synthetic utility of PDFA encouraged us to develop a kilogram-scale synthetic route. PDFA can be prepared through a quaternization of Ph_3P with $BrCF_2CO_2K$, which is obtained from $BrCF_2CO_2Et$ by hydrolysis. All of the reagents needed for the synthesis are cheap and widely available. Our previous synthetic route to PDFA is suitable for a scale of dozens of grams.[8] However, it is still unknown whether this procedure can be applied to a large scale. Herein, we describe the kilogram-scale synthetic route and then demonstrate the different reactivity of PDFA toward aldehydes and alkenes (Scheme 1).

Scheme 1. Kilogram-Scale Synthesis of PDFA



2. RESULTS AND DISCUSSION

2.1. Kilogram-Scale Synthesis of PDFA. In our previous synthetic route, methanol is used as the reaction solvent for the hydrolysis of $BrCF_2CO_2Et$.[8] Since the hydrolysis reactions would generate ethanol, the use of ethanol as the reaction solvent may be favorable for the recovery of the solvent in a large-scale reaction. We then screened other reaction conditions in ethanol. As shown in Table 1, the hydrolysis

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Table 1. Optimization of Hydrolysis Reaction Conditions[a]

$BrCF_2CO_2Et$ + KOH —(Temp., 3 h; EtOH)→ $BrCF_2CO_2K$

entry	temp.	yield (%)[b]	peak area ratio (byproduct/product)[c]
1	20	96	0:1
2	40	97	0.03:1
3	60	93	0.05:1
4	80	90	0.1:1

[a]Reaction conditions: $BrCF_2CO_2Et$ (20 mmol) and KOH (20 mmol) in EtOH (10 mL) for 3 h. [b]The yields were determined by liquid chromatography. [c]Peak area ratios of the unknown $-CF_2-$ species to $BrCF_2CO_2K$ were determined by ^{19}F NMR spectroscopy.

Scheme 2. Recovery and Reuse of Ethanol

$BrCF_2CO_2Et$ (0.2 mol) + KOH (0.2 mol) —(EtOH)→ $BrCF_2CO_2K$

	EtOH	Yield (%)
run 1	200 mL (148 mL recovered)	96
run 2	200 mL (reusing the recovered 148 mL)	96

Table 2. Kilogram-Scale Hydrolysis of $BrCF_2CO_2Et$[a]

$BrCF_2CO_2Et$ (6 mol) + KOH (6 mol) —(below 20 °C; EtOH (1.2 L))→ $BrCF_2CO_2K$ (1.18 kg (92% yield))

input		output	
reagent	loading	reagent or product	mass (g)
$BrCF_2CO_2Et$	1218 g, 6 mol	$BrCF_2CO_2Et$	95
KOH (95% purity)	353 g, 6 mol	EtOH	1159
EtOH	936 g, 1.2 L	$BrCF_2CO_2K$	1181 (92% yield)

[a]Reaction conditions: KOH (353 g, 6.0 mol) and $BrCF_2CO_2Et$ (1218g, 6.0 mol) in ethanol (1.2 L, 936 g) at a temperature below 20 °C.

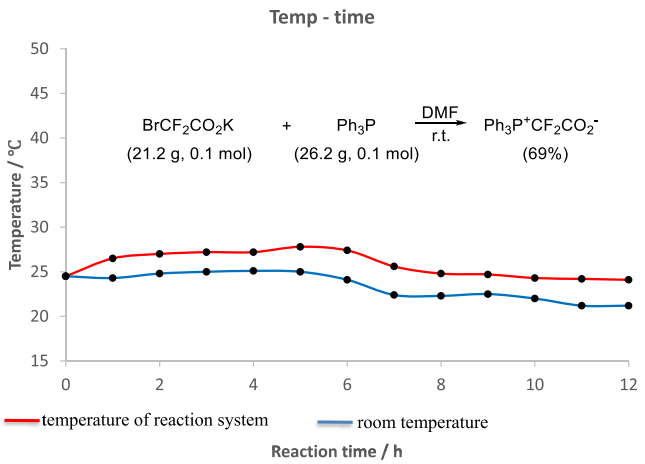

Figure 1. Temperature changes for the preparation of PDFA.

proceeded very well at different temperatures to give the desired $BrCF_2CO_2K$ in high yields. Especially, the reaction at 20 °C was very clean, and the desired product was the only fluorine signal detected by ^{19}F NMR spectroscopy. However, under heating conditions (entries 2−4), an unknown $-CF_2-$ byproduct was detected. Even though the unknown species

Scheme 3. Kilogram-Scale Synthesis of PDFA

$BrCF_2CO_2K$ (5.55 mol) + Ph_3P (5.55 mol) —(DMF, r.t.)→ $Ph_3P^+CF_2CO_2^-$ PDFA (1.53 kg, 77%)

was generated in low yields, it led to difficulties in the purification of $BrCF_2CO_2K$.

Subsequently, the viability of ethanol recovery was examined (Scheme 2). The 0.2 mol scale reaction in ethanol (200 mL) gave $BrCF_2CO_2K$ in a 96% yield. Ethanol (148 mL) was recovered by concentration of the reaction mixture under vacuum. The recovered ethanol was mixed with fresh ethanol to a volume of 200 mL. The resulting ethanol was then used as a solvent for another 0.2 mol scale hydrolysis of $BrCF_2CO_2Et$. $BrCF_2CO_2K$ was produced also in a 96% yield, reflecting the feasibility of ethanol recovery.

We then performed a kilogram-scale reaction (Table 2). The hydrolysis reaction is exothermic, and its enthalpy change (ΔH) has been determined using density functional theory (DFT) at the M062X/6-311++G** level with the SMD solution model in ethanol to be −137.71 kJ/mol (please see the Supporting Information for details). The enthalpy change indicates that the direct mixing of $BrCF_2CO_2Et$ and KOH together would elevate the temperature of the reaction system, which may result in the formation of the unknown $-CF_2-$ species mentioned above. Therefore, $BrCF_2CO_2Et$ has to be added slowly (about 2 h was needed to finish adding) to the mixture of KOH and EtOH and the reaction temperature needs to be kept under 20 °C by an ice bath. After the reaction was finished (about 1 day), 1.26 kg of a mixture of EtOH and the unreacted $BrCF_2CO_2Et$ were collected by a rotary evaporator via concentration of the reaction system. The calibration of the mixture with the use of CF_3CH_2OH as an internal standard revealed that 1.47 L of EtOH and 95 g of $BrCF_2CO_2Et$ were recovered. This solution could be reused for the hydrolysis reaction. After concentration, pure $BrCF_2CO_2K$ was obtained in a high yield (1.18 kg, 92% yield).

It has been reported that the sodium salt, $BrCF_2CO_2Na$, would undergo decomposition at a temperature above 100 °C.[16] We found that $BrCF_2CO_2K$ would decompose even at 40 °C in DMF to produce some unknown species detected by ^{19}F NMR spectroscopy (please see the Supporting Information for details). Therefore, the quaternization of Ph_3P with $BrCF_2CO_2K$ was carried out without being heated in order to avoid the decomposition of $BrCF_2CO_2K$. The reaction temperature was measured during the course of the reaction on a 0.1 mol scale in order to determine whether the reaction is an exothermic reaction. As shown in Figure 1, the reaction temperature was only slightly higher than room temperature, suggesting that this is a negligibly exothermic reaction. Therefore, a kilogram-scale reaction can also be performed at room temperature without a cooling bath.

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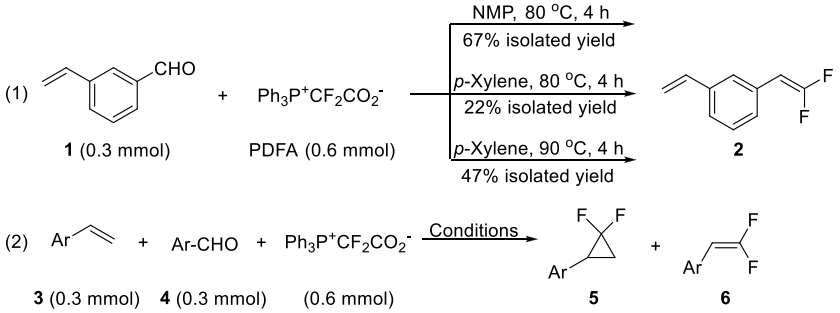
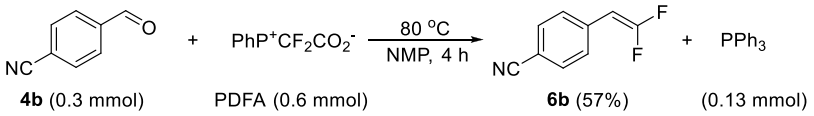
Scheme 4. Reactivity of PDFA toward Aldehyde and Double Bond Groups[a]



Conditions	Ar = 4-PhC_6H_4		Ar = 4-NC-C_6H_4	
	Yield of **5a** (%)	Yield of **6a** (%)	Yield of **5b** (%)	Yield of **6b** (%)
NMP, 80 °C, 4 h	ND	59	ND	54
p-Xylene, 90 °C, 4 h	ND	53	ND	23

[a]The shown yields are isolated yields.

Scheme 5. Recycle of Ph_3P



The reaction indeed proceeded smoothly at room temperature, and 1.53 kg of $Ph_3P^+CF_2CO_2^-$ (77% yield) was obtained as a white solid. In this quaternization process, 1:1 molar ratio of $BrCF_2CO_2K$:Ph_3P was used. Increasing the loading of Ph_3P may increase the yield, but excessive use is less cost-effective. Since this quaternization reaction is an operationally convenient step and a good yield was obtained (77%) on a kilogram scale, we did not further optimize the reaction conditions. The kilogram-scale two-step process gave PDFA in a 71% overall yield (Scheme 3). PDFA was purified by a convenient washing process. The reaction of $BrCF_2CO_2K$ with Ph_3P would generate a KBr byproduct. Water is used to remove this byproduct. After washing with water, a water-soluble solvent, acetone, which cannot dissolve PDFA, is used to remove water. Finally, ethyl ether is used as a washing agent to remove residual acetone from PDFA. This allows for easy drying of PDFA under vacuum, effectively eliminating the only remaining solvent, ethyl ether, which has a low boiling point.

2.2. Reactivity of PDFA. PDFA is a bench-stable reagent that does not require an inert atmosphere for storage. It can be safely stored in sealed glassware at room temperature. This stability has been confirmed through testing, as detailed in the Supporting Information. Almost no decomposition was observed after 5 days of storage. Even after 17 days, only a slight decomposition (<5%) was observed, further demonstrating its robustness.

We have previously shown that PDFA can act as a phosphonium ylide reagent[8] and a difluorocarbene reagent.[9] It is quite reactive toward both aldehyde and double bond groups. However, it is unknown which group, aldehyde or double bond, is more reactive. Reactions of compound **1**, containing both of these two groups, with PDFA were investigated (Scheme 4). As we have revealed before, a low-polarity reaction solvent, such as *p*-xylene, is favorable for the generation of difluorocarbene and the subsequent cyclopropanation of double bonds,[9] and a high-polarity solvent, such as NMP (*N*-methyl pyrrolidone), would favor the formation of phosphonium ylide and the following Wittig *gem*-difluoro-olefination.[8] However, for the reaction of **1** with PDFA, cyclopropanation of the double bond did not occur no matter which solvent was used. Instead, the Wittig process proceeded smoothly to give the desired product **2** (Scheme 3, eq 1). A good yield (67%) was obtained in NMP, and a higher reaction temperature (90 °C) was necessary to give a moderate yield (47%) with the use of *p*-xylene as a solvent. These results revealed that aldehydes may be more reactive than alkenes toward PDFA. If the double bond and the aldehyde groups sit at different substrates, the aldehyde groups still show significantly higher reactivity (Scheme 3, eq 2). Both of these two substrates, **3a**[9] and **4a**,[8] have been shown to be quite reactive toward PDFA to undergo cyclopropanation in *p*-xylene and Wittig reaction in NMP, respectively. However, cyclopropanation product **5a** was not detected in the competitive reaction of **3a** and **4a** with PDFA, irrespective of whether *p*-xylene was the reaction solvent (Scheme 3, eq 2). Instead, **6a** was observed as the major product. The competition reactions between the substrates containing a strong electron-withdrawing group, nitrile (∼CN), also gave alkene **6a** as the major product, further reflecting that PDFA is more reactive toward aldehydes than alkenes.

$Ph_3P^+CF_2CO_2^-$ can act as a ylide precursor and a difluorocarbene reagent. The generation of difuorocarbene would also release Ph_3P, which may be recycled for the preparation of $Ph_3P^+CF_2CO_2^-$. Even though an excess amount of $Ph_3P^+CF_2CO_2^-$ is required in the ylide reaction to account for the potential full decomposition into difluorocarbene and Ph_3P, Ph_3P produced during the reaction can still be recycled and reused. Indeed, for the *gem*-difluoro-olefination of aldehyde **4b**, Ph_3P was isolated from the reaction mixture, providing evidence for the recyclability of Ph_3P and the practical utility of $Ph_3P^+CF_2CO_2^-$ (Scheme 5).

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3. CONCLUSIONS

In summary, we have described the kilogram-scale synthesis of $Ph_3P^+CF_2CO_2^-$ (PDFA), a reagent that was developed by us and has found widespread applications for fluorine incorporation. All reagents needed for the synthesis are cheap and widely available. PDFA exhibits higher reactivity toward aldehydes than toward alkenes. The kilogram-scale synthesis further demonstrates the great synthetic potential of PDFA.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.3c00302.

The reaction procedures are described; materials and methods, experimental procedures, and ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, and MS data (PDF)

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Author Contributions

#H.-Y.S. and J.-L.H. contributed equally to this work.

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Notes

The authors declare no competing financial interest.

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