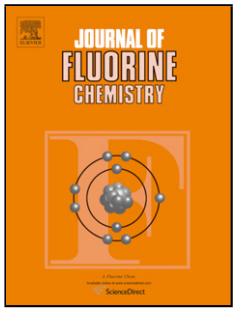

Title: Base-Free *O*-Difluoromethylation of 1,3-Diones with Difluorocarbene

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Base-Free *O*-Difluoromethylation of 1,3-Diones with Difluorocarbene

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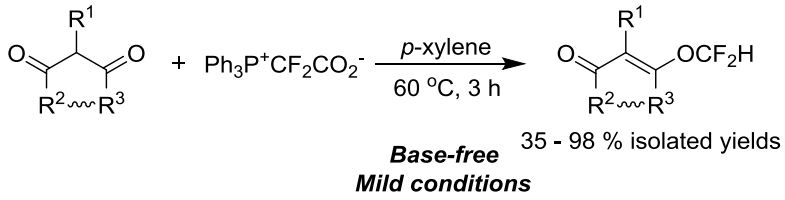
Abstract Graphic



The base-free *O*-difluoromethylation of 1,3-diones with difluorocarbene generated from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) is described to give difluoromethyl enol ethers.

Highlights

1. Under mild conditions, *O*-difluoromethylation of 1,3-diones with difluorocarbene occurred smoothly.
2. No base or additive was required for this transformation.
3. The conversion gave difluoromethyl enol ethers as products, which may act as valuable intermediates for further transformations

Abstract: The base-free *O*-difluoromethylation of 1,3-diones with difluorocarbene generated from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) is described. The convenient reactions proceeded smoothly to give difluoromethyl enol ethers in moderate to good yields.

Keywords: *O*-Difluoromethylation, Difluorocarbene, Base-free, 1,3-diones.

1. Introduction

Since OCF_2H moiety in difluoromethyl ethers has served as a valuable pharmacophore in medicinal chemistry and drug discovery [1-6], significant efforts have been directed towards the development of efficient methods for the construction of this functionality [3, 7-11]. *O*-Difluoromethylation of *O*-nucleophiles with difluorocarbene has proved to be one of the most attractive strategies due to its straightforward procedures [12-20]. Difluorocarbene is a moderately electrophilic species and therefore its reaction with *O*-nucleophiles would readily occur [7, 8]. Intensive studies have been focused on the *O*-difluoromethylation of alcohols[12, 17, 19] and phenols[12-18] with difluorocarbene to afford difluoromethyl alkyl- and aryl-ethers, respectively. The researches on *O*-difluoromethylation of 1,3-diones have been largely ignored, even though these conversions would furnish difluoromethyl enol ethers [20], which may act as valuable intermediates for further transformations.

Recently, Shibata et al. [21, 22], Weng et al. [23] and our group [24] have independently disclosed the *O*-difluoromethylation of 1,3-diones. Shibata and coworkers reported that *S*-(bromodifluoromethyl)diarylsulfoniumsalts [$ArS^+(CF_2Br)Ar'\ X^-$] can act as a difluorocarbene reagent to realize *O*-difluroomethylation [21, 22]. In contrast to Shibata's studies, we found that

S-(difluoromethyl)diarylsulfonium salt [$ArS^+(CF_2H)Ar'$ X^-] is not only a difluorocarbene reagent, but also a difluoromethylation reagent which can directly transfer the CF_2H group to *O*-nucleophiles [24]. The group of Weng discovered that ethyl chlorodifluoroacetate ($ClCF_2CO_2Et$) is also very effective for the *O*-difluoromethylation of 1,3-diones [23]. Although these methods are quite efficient, they suffer from the use of basic reaction conditions. In some cases, low reaction temperature [21, 22] or strong basic conditions [23] are even required. Difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA), a difluorocarbene reagent which was developed by us recently [18, 25-28] and was applied by other groups [29-33], was previously found to be able to realize X-difluoromethylation via the insertion of difluorocarbene into X-H bond (X = N, O and S) without the presence of base [18]. Interestingly, the base-free *O*-difluoromethylation of 1,3-diones with PDFA can also proceed smoothly simply by heating. The preliminary results are described herein.

2. Results and discussion

Since we have shown that low-polarity solvent such as *p*-xylene would favour for the generation of difluorocarbene from PDFA [26], *p*-xylene was firstly used as the reaction solvent for the *O*-difluoromethylation of substrate **1a** with PDFA. To our surprise, our initial attempts were successful to give the desired product **2a** in a good yield (Table 1, entry 1). A comparable yield was obtained by using toluene instead of *p*-xylene (Table 1, entry 2). More-polar solvent led to the decrease in the yield (Table 1, entries 3-6), and the yield was dramatically decreased in DMF (entry 6 vs. entry 1). The reaction temperature can also affect the yield of the product (Table 1, entries 7-9). Lowering the temperature decreased the yield slightly (Table 1, entry 7 vs. entry 1), but the yield was not increased with the elevation of the temperature (Table 1, entries 8-9 vs. entry 1). 2 equiv of PDFA seems to be a suitable loading, as evidenced by the results that lowering the loading decreased the yield (Table 1, entry 10 vs. entry 1) and increasing the loading did not obviously led to the rise in the yield (Table 1, entries 11-12 vs. entry 1). The yield was not increased by prolonging reaction time, meaning that the starting materials were fully converted in 3 h (Table 1, entry 13 vs. entry 1).

With the optimized reaction conditions in hand (Table 1, entry 1), we then explored the substrate scope for this base-free *O*-difluoromethylation of 1,3-diones with PDFA (Scheme 1). A variety of 1,3-cyclohexanediones (**2a-2h**) and 1,3-cyclopentanediones (**2i-2m**) were converted smoothly into the corresponding products in moderate to high yields. The transformation is not quite sensitive to steric effects, as evidenced by the good yields obtained for the conversions of substrates containing 2-position substituents (**2b, 2d, 2j-2m**). Surprisingly, in contrast to the high yield for the difluoromethylation of 2-phenyl 1,3-cyclopentanedione (**2l**), a low yield was obtained for the reaction of 2-phenyl 1,3-cyclohexanedione (**2c**). This *O*-difluoromethylation protocol cannot be well applied to 1,3-cycloheptanedione (**2n**) or acyclic 1,3-dione (**2o**).

On the basis of above results, we propose that the reaction mechanism shown in Scheme 2 is plausible. The decarboxylation of PDFA followed by the dissociation of P-CF_2 bond would readily generate difluorocarbene [18]. Substrate 1,3-dione is in equilibrium with its enolate form **1'**. Both 1,3-dione **1** and enolate **1'** can easily trap difluorocarbene to produce intermediates **Int** and **Int'**, respectively. The subsequent proton migration in **Int** and **Int'** affords the final product **2**.

3. Conclusions

In summary, we have described the base-free *O*-difluoromethylation of 1,3-diones with difluorocarbene generated from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) to give difluoromethyl enol ethers in moderate to high yields. This work represents a mild and efficient protocol for the construction of OCF_2H moiety since simply heating the mixture of 1,3-diones with difluorocarbene reagent can furnish the desired products.

4. Experimental section

4.1. General Information

^1H, ^{13}C and ^{19}F NMR spectra were detected on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS. High resolution mass data were recorded on a high resolution mass spectrometer in the EI. All starting materials were commercially available except **1c** [34] and **1d** [34], **1l** [35] and **1m** [35]**,** which were prepared according to literature. PDFA was prepared according to our previous work [25].

4.2 General procedure for *O*-difluoromethylation of 1,3-diones:

Into a mixture of substrate **1** (0.2 mmol, 1.0 equiv.) and PDFA (0.4 mmol, 142 mg, 2.0 equiv.) in a dry 10 mL Schlenk tube, dry *p*-xylene (2 mL) was added under N_2 atmosphere. The reaction mixture was stirred at 60 ^oC for 3 hours. After being cooled to room temperature, the mixture was directly subjected to flash column chromatography (PE/EA = 5:1 to 3:1 as eluent) to afford the desired product.

3-(Difluoromethoxy)cyclohex-2-en-1-one (**2a**) [37]: 84%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (t, *J* = 72.0 Hz, 1H), 5.51 (s, 1H), 2.49 (t, *J* = 6.2 Hz, 2H), 2.39 - 2.33 (m, 2H), 2.07 - 1.98 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.29 (d, *J* = 72.0 Hz, 2F).

3-(Difluoromethoxy)-2-methylcyclohex-2-en-1-one (**2b**) [37]: 87%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.52 (t, *J* = 73.4 Hz, 1H), 2.64 - 2.56 (m, 2H), 2.43 - 2.31 (m, 2H), 2.07 - 1.91 (m, 2H), 1.73 (s, 3H).^{19}F NMR (376 MHz, $CDCl_3$) δ -80.20 (d, *J* = 73.4 Hz, 2F).

6-(Difluoromethoxy)-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one (**2c**): 30%. Colourless oil. ^1H NMR

(400 MHz, $CDCl_3$) δ 7.43 - 7.31 (m, 3H), 7.21 - 7.17 (m, 2H), 6.35 (t, *J* = 73.4 Hz, 1H), 2.80 (t, *J* = 6.2 Hz, 2H), 2.59 - 2.55 (m, 2H), 2.20 - 2.11 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.71 (d, *J* = 73.4 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.51 (s), 163.70 (s), 131.34 (s), 130.17 (s), 128.00 (s), 127.76 (s), 127.08 (s), 114.36 (t, *J* = 264.3 Hz), 37.15 (s), 28.10 (s), 20.57 (s). IR (neat) ν = 3057, 2956, 1670, 1634, 1599, 1495, 1428, 1352, 1334, 1301, 1211, 1190, 1104, 1057, 1003, 985, 965, 761, 699 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{12}F_2O_2$ $[M]^+$: 238.0805, Found: 238.0799.

2-Benzyl-3-(difluoromethoxy)cyclohex-2-en-1-one (**2d**) [37]: 74%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.01 (m, 5H), 6.53 (t, *J* = 73.3 Hz, 1H), 3.64 (s, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.40 (t, *J* = 6.2 Hz, 2H), 2.07 - 1.97 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.34 (d, *J* = 73.3 Hz, 2F).

3-(Difluoromethoxy)-5-methylcyclohex-2-en-1-one (**2e**) [37]: 59%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (t, *J* = 72.0 Hz, 1H), 5.50 (s, 1H), 2.52 - 2.41 (m, 2H), 2.30 - 2.18 (m, 2H), 2.09 - 2.00 (m, 1H), 1.09 (d, *J* = 6.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.71 (dd, *J* = 173.7, 72.0 Hz, 1F), -85.98 (dd, *J* = 173.7, 72.0 Hz, 1F).

3-(Difluoromethoxy)-5,5-dimethylcyclohex-2-en-1-one (**2f**) [36]: 58%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (t, *J* = 72.1 Hz, 1H), 5.52 - 5.48 (m, 1H), 2.34 (s, 2H), 2.21 (s, 2H), 1.07 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.33 (d, *J* = 72.1 Hz, 2F).

5-(Difluoromethoxy)-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (**2g**) [37]: 85%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.21 (m, 5H), 6.55 (dd, *J* = 72.6, 71.2 Hz, 1H), 5.63 (s, 1H), 3.48 - 3.33 (m, 1H), 2.83 - 2.49 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.56 (dd, *J* = 173.5, 72.6 Hz, 1F), -86.12 (dd, *J* = 173.3, 71.2 Hz, 1F).

3-(Difluoromethoxy)-5-isopropylcyclohex-2-en-1-one (**2h**) [37]: 79%. Colourless oil.^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 72.9, 71.2 Hz, 1H), 5.53 (s, 1H), 2.54 - 2.44 (m, 2H), 2.38 - 2.28 (m, 1H), 2.15 - 2.04 (m, 1H), 2.00 - 1.88 (m, 1H), 1.69 - 1.59 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).^{19}F NMR (376 MHz, $CDCl_3$) δ -84.57 (ddd, *J* = 173.8, 72.9, 0.8 Hz, 1F), -86.20 (dd, *J* = 173.8, 71.2 Hz, 1F).

3-(Difluoromethoxy)cyclopent-2-en-1-one (**2i**) [37]: 81%. Colourless oil.^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (t, *J* = 71.7 Hz, 1H), 5.54 (s, 1H), 2.75 - 2.71 (m, 2H), 2.51 - 2.46 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -86.85 (d, *J* = 71.7 Hz, 2F).

3-(Difluoromethoxy)-2-methylcyclopent-2-en-1-one (**2j**) [37]: 85%. Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (t, *J* = 72.2, 1H), 2.81 - 2.75 (m, 2H), 2.65 - 2.42 (m, 2H), 1.68 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.30 (d, *J* = 72.2 Hz, 2F).

3-(Difluoromethoxy)-2-ethylcyclopent-2-en-1-one (**2k**) [37]: 67%. Colourless oil.^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (t, *J* = 72.3 Hz, 1H), 2.78 - 2.73 (m, 2H), 2.50 - 2.46 (m, 2H), 2.15 (q, *J* = 7.6

Hz, 2H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.57 (d, *J* = 72.3 Hz, 2F).

3-(Difluoromethoxy)-2-phenylcyclopent-2-en-1-one (**2l**): 83%. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.31 (tt, *J* = 7.6, 1.3 Hz, 1H), 6.71 (t, *J* = 71.9 Hz, 1H), 2.94 - 2.88 (m, 2H), 2.66 - 2.62 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.84 (d, *J* = 71.9 Hz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.57 (s), 174.31 (s), 128.69 (s), 128.64 (s), 128.29 (s), 128.24 (s), 124.35 (s), 114.23 (t, *J* = 266.9 Hz), 34.25 (s), 25.73 (s). IR (neat) ν = 3058, 2926, 2854, 1701, 1647, 1600, 1497, 1446, 1437, 1365, 1334, 1303, 1280, 1220, 1104, 1057, 983, 925, 836, 765, 697, 655, 578, 478 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{10}F_2O_2$ $[M]^+$: 224.0649, Found: 224.0642.

2-Benzyl-3-(difluoromethoxy)cyclopent-2-en-1-one (**2m**) [37]: 79%. Colourless oil. ^{1}H NMR (400 MHz, CDCl3)δ 7.27 - 7.13 (m, 5H), 6.65 (t, *J* = 72.1 Hz, 1H), 3.50 (s, 2H), 2.87 - 2.73 (m, 2H), 2.56 - 2.42 (m, 2H). ^{19}F NMR (376 MHz, CDCl3) δ -81.48 (d, *J* = 72.1 Hz, 2F).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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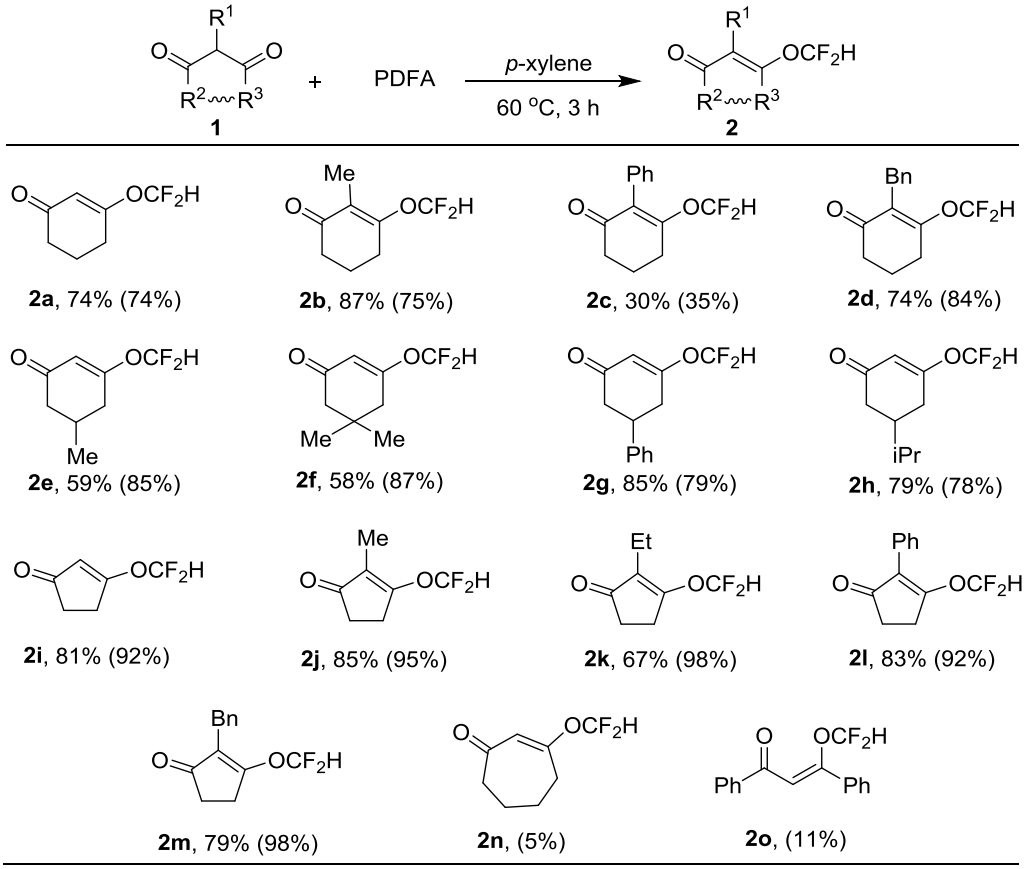
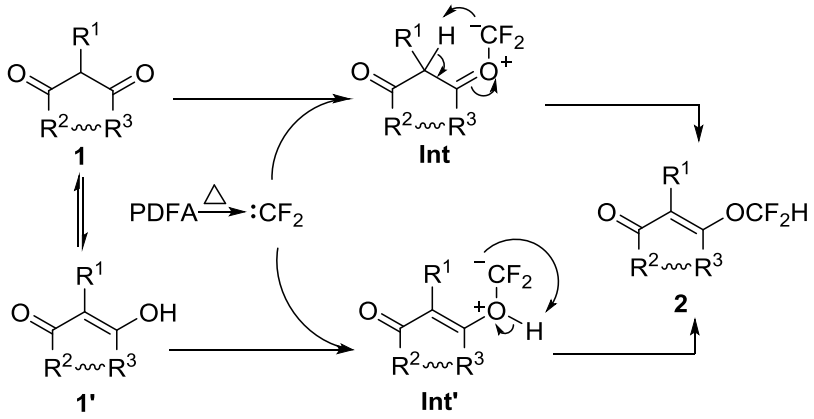
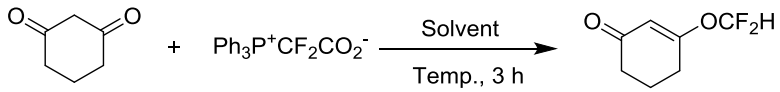


Scheme 1. Substrate scope for *O*-difluoromethylation. Isolated yields. Values in parentheses are the yields determined by ^{19}F NMR.



Scheme 2. The plausible reaction mechanism

Table 1 Optimization of the reaction conditions



1a PDFA **2a**

Entry	Ratio[b]	Solvent	Temp. (°C)	Yeild (%)[c]
1	1:2	*p*-Xylene	60	74
2	1:2	Toluene	60	73
3	1:2	1,4-Dioxane	60	69
4	1:2	THF	60	68
5	1:2	Acetonitrile	60	53
6	1:2	DMF	60	32
7	1:2	*p*-Xylene	50	68
8	1:2	*p*-Xylene	70	72
9	1:2	*p*-Xylene	80	71
10	1:1	*p*-Xylene	60	49
11	1:3	*p*-Xylene	60	72
12	1:4	*p*-Xylene	60	75
13[d]	1:2	*p*-Xylene	60	74

[a]Reaction conditions: **1a** (0.2 mmol) and PDFA in solvent (2 mL); [b]Molar ratio of **1a**:PDFA; [c]Determined by ^{19}F NMR; [d]The reaction time was prolonged to 10 h.