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Selective *O*-Difluoromethylation of 1,3-Diones by Bromodifluoromethylating Reagents

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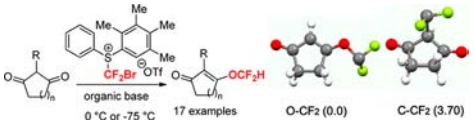
ABSTRACT



The regioselective *O*-difluoromethylation of 1,3-diones was achieved via *in situ* generation of difluorocarbene from bromodifluoromethylating reagents in the presence of an organic base. A wide variety of difluormethyl enol ethers were obtained in good to excellent yields. The reaction mechanism is discussed based on *ab initio* calculations (kcal/mol).

Fluoro-organic compounds play an important role in the development of pharmaceuticals, agrochemicals, and advanced materials.[1] In particular, compounds having a difluoromethyl group (CF_2H) have attracted much attention recently, since the CF_2H moiety could act as an isostere to the unit of methanol (CH_2OH) with improved lipophilicity and resistance to oxidation.[2] Thus, the difluoromethylated variants of biologically active molecules having a CH_2OH group are highly likely to show increased membrane permeability with metabolic stability, which might be potential candidates in the future drug market.[3] Direct introduction of a difluoromethyl group into target molecules is an ideal strategy for the synthesis of CF_2H compounds. The building strategy is not often suitable since the acidic CF_2H moiety might not be tolerated during the overall synthetic process. Despite the success of direct trifluoromethylation,[4] methodologies for the introduction of a CF_2H unit into molecules is still under development.[5−7] With this background in mind, we were interested in so-called self-stable electrophilic difluoromethylating reagents ($^+CF_2H$-reagents) for this purpose and selected successful examples are shown in Figure 1 including the reagents by Prakash and Hu.[6f,i,k]

Xiao et al. recently reported the synthesis of symmetrical *S*-(bromodifluoromethyl)diarylsulfoniumsal-ts ($ArS^+(CF_2Br)Ar$) and their utility in the electrophilic bromodifluoromethylation reaction ($^+CF_2Br$).[6j] Shortly afterwards, we also disclosed the synthesis of a series of

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(1) (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (c) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777. (d) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15–24. (e) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.

(2) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626–1631. (b) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882–5886.

(3) (a) Furuya, T.; Kuttruff, C.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803–819. (b) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Sheperd, P. R. *J. Med. Chem.* **2011**, *54*, 7105–7126.

(4) For trifluoromethylation, see: (a) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465–3468. (b) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324–6327. (c) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 572–576. (d) Allen, A. E.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986–4987. (e) Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7803–7806. (f) Pham, P. V.; Nagib, D. A.; Macmillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119–6122. (g) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1059–1063. (h) Deng, Q.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769–10772.

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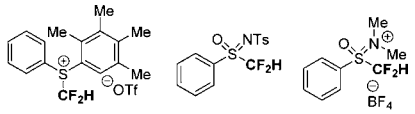
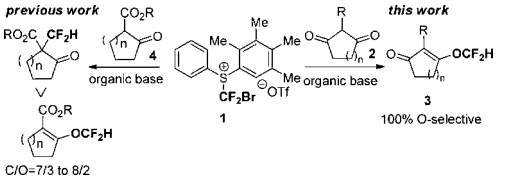


Figure 1. Selected examples of electrophilic difluoromethylating reagents having a CF_2H moiety.

unsymmetrical *S*-(bromodifluoromethyl)-diarylsulfonium salts ($ArS^+(CF_2Br)Ar'$, **1**) as $^+CF_2Br$-reagents of terminal alkynes in response to *n*-BuLi.[8] Interestingly, we observed a phenomenon in which **1** acts as efficient $^+CF_2H$-reagents rather than $^+CF_2Br$-reagents for sp^3-C nucleophiles, including β-ketoesters, by using organic bases in high to excellent yields.[9] In situ generation of difluorocarbene (CF_2 carbene) from **1** under low reaction temperature is responsible for the transfer of CF_2H. The use of CF_2Br-reagents **1** as a source of CF_2H is advantageous since **1** are more stable than CF_2H-type reagents due to the lack of an acidic H-atom. As a part of our research toward the development of efficient methodologies for the synthesis of fluoro-organic compounds, we disclose herein the difluoromethylation of 1,3-diketones **2** with **1** mediated by DBU or P_2-Et to provide difluoromethyl enol ethers **3** in high yields with complete oxygen selectivity.[10] It is noteworthy that the *O*-selective difluoromethylation of **2** was observed, while *C*-difluoromethylation predominated on the β-ketoesters **4** under the same conditions (Scheme 1).

Scheme 1. Electrophilic Difluoromethylation of 1,3-Dicarbonyl Compounds with CF_2Br-Reagents **1**



2-Methyl-1,3-cyclopentanedione **2a** was chosen as a model substrate for optimization of the reaction conditions (Table 1). First, treatment of **2a** with **1** (1.0 equiv) and DBU (1.2 equiv) at −75 °C in CH_2Cl_2 was carried out. Despite our expectation, a regioselective *O*-difluoromethylation product (*O*-CF_2H, **3a**) was solely obtained in 45% yield without any *C*-CF_2H product (entry 1). Enthused by this outcome, we further optimized the reaction conditions to improve the yield of **3a**. Increasing the equivalence of DBU showed no influence on the yield of **3a** (entry 2), but excess **2a** (2.0 equiv) with 1.0 equiv of DBU gave 69% of **3a** based on the use of reagents **1** (entry 3). The yield of **3a** was further improved to 84% under the conditions of **2a**/DBU/**1** at a ratio of 2.2/2.0/1.0 (entry 4). We next investigated the effect of base, and the most organic bases performed well with good yields (entries 5−9). P_2-Et reacted slightly better than DBU to give **3a** in 88% yield (entry 7). Reaction temperature was also investigated (entries 10 and 11). The reaction was unresponsive to temperature, and **3a** was obtained in excellent yields at both rt and 0 °C. Solvent screening showed dichloromethane to be the best choice (entries 12−14). In all cases, *O*-CF_2H product **3a** was selectively observed.

With the optimum conditions in hand, we explored the generality of this *O*-regioselective difluoromethylation using various 1,3-dione substrates (Table 2). A series of 1,3-cyclopentanediones **2a**−**e** and 1,3-cyclohexanediones **2f**−**i** with different substituents at the C-2 position provided the corresponding difluoromethyl enol ethers **3a**−**e** (entries 1−5) and **3f**−**i** (entries 6−9) in good to high yields. 1,3-Cyclohexanediones **2j**−**o** with substituents at the C-5 position also gave high to excellent yields for **3j**−**o** (entries 10−15). The reaction of 1,3-indandiones **2p** and **2q**

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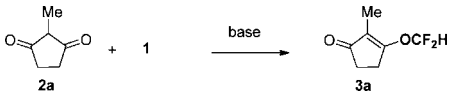
(8) Liu, G.; Mori, S.; Wang, X.; Noritake, S.; Tokunaga, E.; Shibata, N. *New J. Chem.* **2012**, *36*, 1769–1773.

(9) Liu, G.; Wang, X.; Lu, X.; Xu, X.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2012**, *1*, 227–231.

(10) Xiao et al. observed a single example of *O*-difluoromethylation of 1,3-dicyclopentane dione (not bromodifluoromethylation) with NaH during their study of bromodifluoromethylation by $PhS^+(CF_2Br)Ph$, although the generality of the reaction was not discussed. See ref 6j.

Table 1. Optimization of Reaction Conditions[a]



entry	base	temp (°C)	**2a**/base/**1**	**3a** yield (%)[b]
1	DBU	−75	1.0/1.2/1.0	45
2	DBU	−75	1.0/2.0/1.0	43
3	DBU	−75	2.0/1.0/1.0	69
4	DBU	−75	2.2/2.0/1.0	84
5	P_1-*t*-Oct	−75	2.2/2.0/1.0	76
6	P_1-*t*-Bu	−75	2.2/2.0/1.0	80
7	P_2-Et	−75	2.2/2.0/1.0	88
8	Et_3N	−75	2.2/2.0/1.0	39
9	Cs_2CO_3	−75	2.2/2.0/1.0	20
10	P_2-Et	rt	2.2/2.0/1.0	85
11	P_2-Et	0	2.2/2.0/1.0	93
12[c]	P_2-Et	0	2.2/2.0/1.0	77
13[d]	P_2-Et	0	2.2/2.0/1.0	78
14[e]	P_2-Et	0	2.2/2.0/1.0	57

[a] The reaction was carried out with 0.1 mmol of **2a** in dichloromethane. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, P_1-*t*-Oct: *ter*-Octylimino-tris-(dimethylamino)phosphorane, P_1-*t*-Bu: *tert*-butylimino-tri(pyrrolidino)-phosphorane, P_2-Et: tetramethyl-(tris(dimethylamino) phosphoranylidene)-phosphorictriamid-Et-imin, Et_3N: triethylamine. [b] Determined by ^{19}F NMR. [c] THF was used as the solvent. [d] CH_3CN was used as the solvent. [e] DMF was used as the solvent.

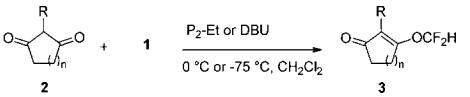
with **1** also proceeded successfully to furnish corresponding *O*-CF_2H products **3p** and **3q** in 55% and 66% yields, respectively (entries 16 and 17). However, acyclic 1,3-dione **2f** gave a complex mixture (entry 18). DBU performed more effectively in some cases (entries 6, 9, 10, 12, 13, and 15), and in some cases it proceeded even at −75 °C (entries 6−7, 9−10, 12−13, 15−17).

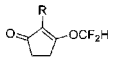
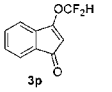
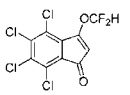
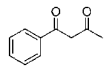
To demonstrate the further utility of difluoromethyl enol ethers, the transformation of **3** was examined. Difluoromethyl enol ether **3p** was selectively reduced into compound **5** by 6 equiv of $NaBH_4$ quantitatively in 30 min (Scheme 2).

A plausible mechanism for *O*-difluoromethylation of 1,3-diones **2** with **1** is shown in Scheme 3. Initially, diketones **2** react with a base to provide enolates **A**, which attack at the Br-atom in **1** to furnish CF_2 carbene, $PhSC_6HMe_4$, brominated products **B**, and $TfO^-[Base\text{-}H]^+$. Although we did not detect **B**, some structurally unidentified complex mixtures were observed after the completion of the reaction. The generated CF_2 carbene reacted with enolates **A** to furnish *O*-difluoromethyl anions **C**, and the latter should be protonated by $[Base\text{-}H]^+$to give **3** with a base. The last protonation step from C to **3** and base may be reversible due to the acidity of the CF_2H moiety, and this hypothesis is supported by the fact that 2 equiv of base are desirable for better yields (see entries 3 and 4, Table 1).

Finally, we discuss the complete *O*-regioselectivity. As mentioned in the introduction part of this manuscript, β-ketoesters **4** furnish *C*-CF_2H products predominantly (8:2 ratio),[9] while 1,3-diketones **2** afford *O*-CF_2H products

Table 2. *O*-Difluoromethylation of 1,3-Diones **2a**−**q**[a]



entry	1	product 3	yield (%)[c]
1			90 (**3a**)
2[b]			85 (**3b**)
3	**2a** (R =Me) **2b** (R = H) **2c** (R = Et) **2d** (R =Br) **2e**(R = Bn)	**3a** (R =Me) **3b** (R = H) **3c** (R = Et) **3d** (R =Br) **3e**(R = Bn)	82 (**3c**)
4			73 (**3d**)
5			84 (**3e**)
6[b,c,d]			83 (**3f**)
7[d]			80 (**3g**)
8	**2f** (R = H) **2g** (R = Me) **2h** (R = Br) **2i** (R = Bn)	**3f** (R = H) **3g** (R = Me) **3h** (R = Br) **3i** (R = Bn)	75 (**3h**)
9[c,d]			75 (**3i**)
10[b,c,d]			79 (**3j**)
11			82 (**3k**)
12[c,d]	**2j** (R = H) **2k**(R = Br) **2l** (R = Bn)	**3j** (R = H) **3k**(R = Br) **3l** (R = Bn)	75 (**3l**)
13[b,c,d]			80 (**3m**)
14			82 (**3n**)
15[c,d]	**2m** (R = H) **2n** (R = Br) **2o** (R = Bn)	**3m** (R = H) **3n** (R = Br) **3o** (R = Bn)	75 (**3o**)
16[d]	 **2p**	 **3p**	55 (**3p**)
17[d]	 **2q**	 **3q**	66 (**3q**)
18	 **2r**	Complex	

[a] The reaction was carried out with 2.2 equiv of **2**, 1.0 equiv of **1** (0.1 mmol), and 2.0 equiv of base in CH_2Cl_2 at 0 or −75 °C. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, P_2-Et: tetramethyl-(tris(dimethylamino)phosphoranylidene)phosphorictriamid-Et-imin. For detailed reaction conditions, see Supporting Information. [b] Small amounts of 2-bromo-*O*-difluoromethyl enol ethers were separated as byproducts. [c] DBU was used as the base. [d] The reaction was carried out at −75 °C. [e] Isolated yields were calculated based on **1**.

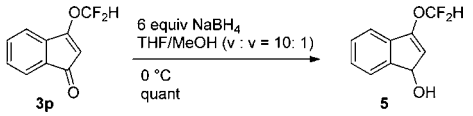
3 (100% selectivity) under the same reaction conditions.[11,12] Molecular orbital calculations were therefore carried out to study the reaction of anions **6** and **7** with CF_2 carbene providing *O*-CF_2H or *C*-CF_2H products (Scheme 4).

The interactions between CF_2 carbene with anion **6** or **7** were studied by *ab initio* molecular orbital calculations.[13] The geometry of the complex of **6** with a singlet CF_2 carbene was optimized from 24 initial geometries. The

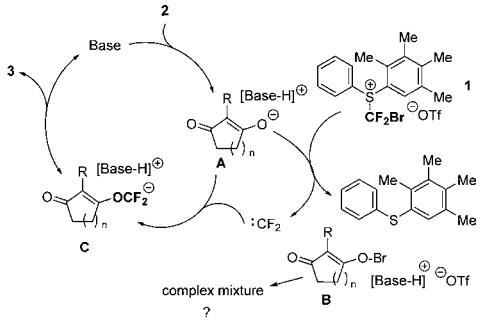
(11) *O*-Difluoromethylation of ketones is often observed (see refs 6d and 6m); however, as far as we know, the reason for the oxygen preference has not actively been discussed except by us (see refs 6q and 12).

(12) We previously discussed the *C*- and *O*-selectivity for electrophilic or radical fluoromethylations of β-ketoesters, but not for carbene-mediated fluoromethylations (see ref 6q).

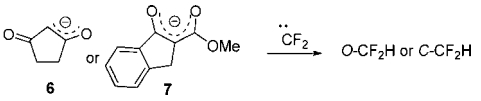
Scheme 2. Selective Reduction of **3p**



Scheme 3. Proposed Reaction Mechanism



Scheme 4. Models of Anions **6** and **7**with the Reaction of CF_2 Carbene for Caluculations



O- or *C*-CF_2H products were spontaneously produced by geometry optimizations of the complex. The optimized geometries of the most stable *O*- or *C*-CF_2H products with their relative energies are shown in Figure 2a. The calculated relative energies show that the *O*-CF_2H product is more stable than the *C*-CF_2H product by 3.7 kcal/mol. The reaction of β-ketoester was investigated next (Figure 2b). The geometry of the complex of **7** with a singlet CF_2 carbene was optimized from 19 initial geometries. The most stable *O*- and *C*-CF_2H products are shown in Figure 2b. In contrast to **6**, the calculated relative energies show that the *C*-CF_2H product is more stable than the *O*-CF_2H product by 4.18 kcal/mol. The difluoromethylation of an O-atom of the ester group did not occur after the geometry optimizations. The complex of **7** with CF_2 carbene was also obtained by the geometry optimizations. The complex is substantially less stable (10.97 kcal/mol) than the *C*- and *O*-CF_2H products. These calculated relative energies of the CF_2H products explain well the experimentally observed selectivity of the difluoromethylation reaction of diketones **2** (*O*-difluoromethylation) and β-ketoesters **4** (*C*-difluoromethylation).

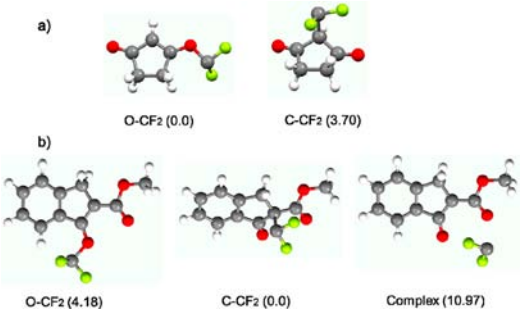


Figure 2. (a) Geometries and relative energies of CF_2H products of **6**; (b) Geometries and relative energies of CF_2H products of **7** and complex of **7** with CF_2 carbene. Energy in kcal/mol.

In conclusion, we developed selective *O*-difluoromethylation of 1,3-diones **2** by *S*-(bromodifluoromethyl)diaryl sulfonium salts **1** in the presence of an organic base. A wide variety of difluoromethyl enol ethers **3** were synthesized nicely in good to excellent yields by **1**. This approach provides a synthetic entry to biologically relevant difluoromethyl ethers of interest to the pharmaceutical and agrochemical industries.[1a,b,e] The further application of *S*-(bromodifluoromethyl)diaryl sulfonium salt **1** is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet http://pubs.acs.org.

The authors declare no competing financial interest.

(13) The Gaussian 03 program was used for the *ab initio* molecular orbital calculations. The 6-311G** basis set was used for the calculations. Electron correlation was accounted for by the second-order Møller–Plesset perturbation (MP2) method. See: *Gaussian 03*, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Wallingford, CT, 2004.