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Difluoromethyl 2-Pyridyl Sulfone: A New *gem*-Difluoroolefination Reagent for Aldehydes and Ketones

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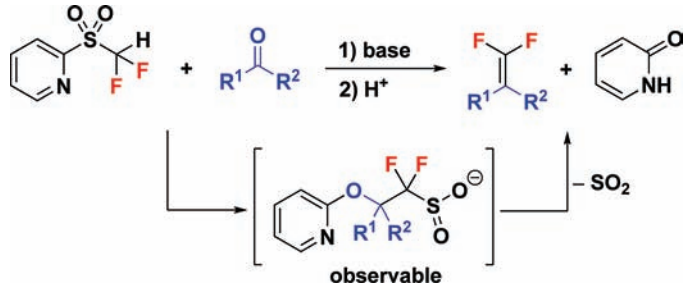
ABSTRACT



Difluoromethyl 2-pyridyl sulfone, a previously unknown compound, was found to act as a novel and efficient *gem*-difluoroolefination reagent for both aldehydes and ketones. It was found that the fluorinated sulfinate intermediate in the reaction is relatively stable, which can be observed by ^{19}F NMR and trapped with CH_3I.

Incorporation of fluorine atom(s) or fluorinated moieties into an organic molecule often results in profound changes of physical, chemical, and biological properties of the target molecule.[1] For instance, unlike other nonfluorinated alkenes, *gem*-difluoroalkene (*gem*-difluoroolefin) functionality is highly electrophilic and the fluorine atom(s) can be replaced by nucleophiles through an addition−elimination mechanism,[2,3] which enables *gem*-difluoroalkenes to act as valuable intermediates for the synthesis of other important molecules, such as 2-fluorinated indoles,[3a] monofluoroalkenes,[3b] esters, and carboxylic acids.[3c] Moreover, *gem*-difluorovinyl functionality is known to act as a bioisostere for carbonyl group,[4] and it is critical to many biologically active molecules such as mechanism-based enzyme inhibitors.[1,5] Owing to their important applications, various approaches have been developed for the preparation of *gem*-difluoroalkenes, among which the *gem*-difluoroolefination reaction with aldehydes or ketones is one of the most straightforward methods.[1,2] In

(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) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000.

(2) (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Biological Chemistry*; Wiley: New York, 1991. (c) *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer: New York, 1997. (d) Ichikawa, J. In *Current Fluoroorganic Chemistry*; Soloshonok, V. A., Mikami, K., Yamazaki, T., Welch, J. T., Honek, J. F., Eds.; ACS Symposium Series 949; American Chemical Society: Washington, DC, 2007. (e) Ichikawa, J. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005.

(3) (a) Ichikawa, J.; Wada, W.; Okauchi, T.; Minami, T. *J. Chem. Soc., Chem Commun.* **1997**, 1537. (b) Hayashi, S.; Nakai, T.; Ichikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983. (c) Hayashi, S.; Nakai, T.; Ichikawa, N. *Chem. Lett.* **1980**, 651. (d) Yokota, M.; Fujita, D.; Ichikawa, J. *Org. Lett.* **2007**, *9*, 4639. (e) Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4870.

(4) Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem.Commun.* **1989**, 1437.

(5) (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. (b) Altenburger, J. M.; Lassalle, G. Y.; Matrougui, M.; Galtier, D.; Jetha, J. C.; Bocskei, Z.; Berry, C. N.; Lunven, C.; Lorrain, J.; Herault, J. P.; Schaeffer, P.; O'Connor, S. E.; Herbert, J. M. *Biorg. Med. Chem.* **2004**, *12*, 1713. (c) Weintraub, P. M.; Holland, A. K.; Gates, C. A.; Moore, W. R.; Resvick, R. J.; Bey, P.; Peet, N. P. *Biorg. Med. Chem.* **2003**, *11*, 427.

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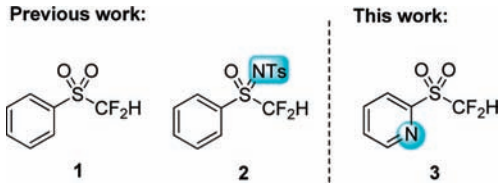
Wittig-type reactions developed by Silverstein and Burton, difluoromethylene ylide generated from the reaction of PPh_3 and $CF_2ClCOONa$ or CF_2Br_2 successfully difluoromethylenates aldehydes and activated ketones.[6] For unactivated ketones, reagents such as HMPT/CF_2Br_2[7a−c] or $(CF_3)_2Hg$/NaI/PPh_3[7d] are needed. Horner−Wadsworth−Emmons-type and Horner−Wittig-type *gem*-difluoroolefination reactions provide more general routes suitable for both aldehydes and ketones.[8] Alternatively, in classical Julia reaction, difluoromethyl phenyl sulfone is empolyed to achieve a three-step synthesis of *gem*-difluoroalkenes via a reduction−desulfonation protocol.[9] In these *gem*-difluoroolefination reactions, however, low-boiling or toxic reagents, strictly anhydrous reaction conditions, and/or mutistep procedures are often needed. Herein, we report a concise and efficient method for *gem*-difluoroolefination of both aldehydes and ketones via a Julia−Kocienski protocol.

Previously, we were interested in investigating the unique synthetic applications of fluorinated sulfones[10] and sulfoximines.[11] Difluoromethyl phenyl sulfone ($PhSO_2CF_2H$, **1**) was found to be a robust nucleophilic difluoromethylation reagent (via its deprotonated form $PhSO_2CF_2^-$), thanks to the excellent modulating ability of the phenylsulfonyl group on both the stability and nucleophilicity of the $PhSO_2CF_2^-$ anion species (Scheme 1).[10] Recently, we found that when one oxygen atom in

Scheme 1. Difluoromethyl Sulfones and Sulfoximines (Ts = *p*-Toluenesulfonyl Group)

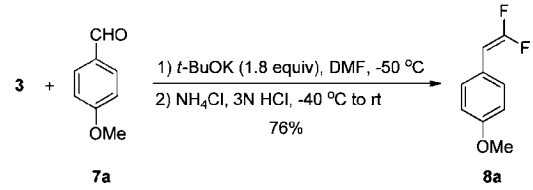


compound **1** was replaced by the NTs group (Ts = *p*-toluenesulfonyl), the chemical reactivity of the resulting compound *N*-tolyl-*S*-difluoromethyl-*S*-phenylsulfoximine **2** is significantly different from **1**. While compound **1** is a nucleophilic difluoromethylation agent, compound **2** behaves as an "electrophilic" difluoromethylation reagent through a difluorocarbene mechanism.[11a] Intrigued by these results, we envisioned that as another analogous compound of **1**, difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$, **3**[12]) may possess other interesting reactivities that are different from those of **1** and **2**. Furthermore, it would also be interesting to compare the reactivity of **3** with those of other difluoromethyl heteroaryl sulfones such as 1,3-benzothiazol-2-yl difluoromethyl sulfone (**4**), 1-phenyl-1*H*-tetrazol-5-yl difluoromethyl sulfone (**5**), and 1-*tert*-butyl-1*H*-tetrazol-5-yl difluoromethyl sulfone (**6**).

(6) (a) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. *Tetrahedron Lett.* **1964**, 1461. (b) Herkes, F. E.; Burton, D. J. *J. Org. Chem.* **1967**, *32*, 1311. (c) Naae, D. G.; Burton, D. J. *J. Fluorine Chem* **1971**, *1*, 123. (d) Burton, D. J.; Wheaton, G. A. *J. Org. Chem.* **1983**, *48*, 917.

With these considerations in mind, we attempted the reaction between **3**[12] and anisaldehyde (**7a**) using *t*-BuOK as a base (Scheme 2). Therefore, into an equimolar mixture

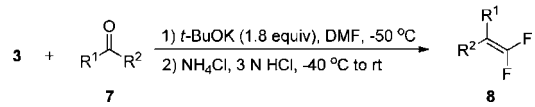
Scheme 2. Difluoromethylenation of Anisaldehyde with 2-$PySO_2CF_2H$ (**3**)

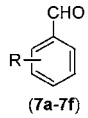
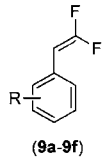
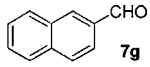
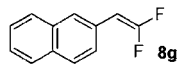
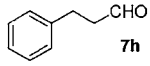
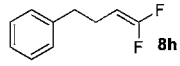
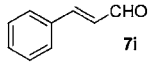
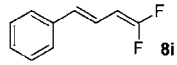
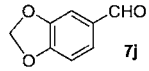
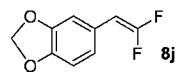
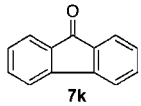
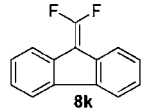
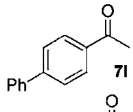
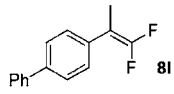
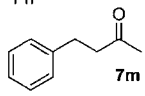
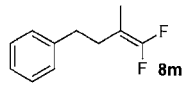
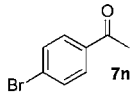
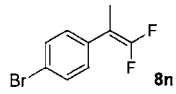
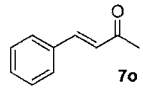
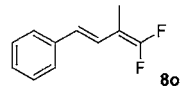
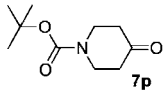
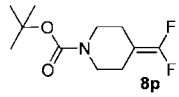


of sulfone **3** and aldehyde **7a** in DMF at −50 °C was slowly added a DMF solution of *t*-BuOK (2 equiv). The reaction mixture was subsequently warmed to −40 °C over a period of 15 min and then quenched with 3 N HCl. After routine workup and purification, we were able to isolate 1-(2,2-difluorovinyl)-4-methoxybenzene (**8a**) in 76% yield (Scheme 2). It became apparent that a Julia−Kocienski-type olefination[13] occurred under the present reaction conditions. After a quick optimization of the reactant ratio (**3**/**7a**/*t*-BuOK = 1.0:1.2:1.8), the product yield of **8a** was increased to 86% (Table 1, entry 1). It should be noted that, to the best of our knowledge, this is the first example of Julia−Kocienski-type one-step *gem*-difluoroolefination reaction.

With the optimized reaction condition (reactant molar ratio **3**/**7**/*t*-BuOK = 1.0:1.2:1.8), we examined the generality and substrate scope of this new *gem*-difluoroolefination reaction between **3** and carbonyl compounds **7**. As shown in Table 1, various aldehydes and ketones were treated with **3**, smoothly giving the corresponding *gem*-difluoroalkenes in good to excellent yields. This method tolerates various substituents on carbonyl compounds (entries 1−6, 9, 10, and 14−16), which is superior to Wittig-type *gem*-difluoroolefination reactions.[6,7] It was found that aldehydes with electron-donating groups gave slightly higher yield than those with electron-withdrawing groups (entries 1−6). For the enolizable aldehyde **7h** (entry 8), lower yield was observed even when LiHMDS was used as a base to suppress the undesired aldol reaction. The reaction was also amenable to both aliphatic and aromatic ketones, leading to the formation of structurally diverse *gem*-difluoroalkenes **8k**−**p** (entries 11−16). It was reported that difluoroalkenes **8i** and **8o** were previously prepared from **7i** and **7o** in low yields (≤41%) by using toxic $(CF_3)_2Hg$ reagent,[7d] but in our cases with reagent **3**, products **8i** and **8o** were obtained in 62% and 80% yield, respectively (entries 9 and 15). Furthermore, our method gave product **8p**, an intermediate for the synthesis of thrombin inhibitor SSR182289A, in 84% yield, which is also superior to the previously reported results (with 61% yield through a Wittig-type reaction using excess CF_2Br_2 and HMPT).[5b] It should be noted that reagent **3** is a stable and crystalline solid[12] and the organic byproduct of the reaction is pyridin-2-ol (water-soluble), both factors making the current difluoroolefination reaction easy to handle.

Table 1. *gem*-Difluoroolefination of Carbonyl Compounds with Reagent **3**

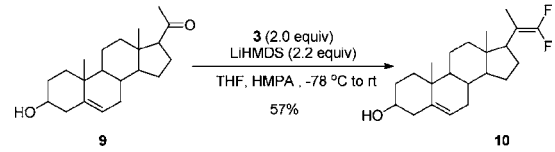


entry[a]	substrate	product	yield (%)[b]
1	 (**7a-7f**)	 (**9a-9f**)	**8a** R = p-MeO	86
2			**8b** R = *p*-*t*Bu	74
3			**8c** R = 2, 4-Cl	72
4			**8d** R = m-NO_2	72
5			**8e** R = *p*-NMe_2	91
6			**8f** R = *p*-Br	72
7	 **7g**	 **8g**	92
8[c]	 **7h**	 **8h**	40[d]
9	 **7i**	 **8i**	62[d]
10	 **7j**	 **8j**	93
11	 **7k**	 **8k**	87
12[e]	 **7l**	 **8l**	81
13[c]	 **7m**	 **8m**	72
14[e]	 **7n**	 **8n**	77
15	 **7o**	 **8o**	80
16	 **7p**	 **8p**	84

[a] For all cases, the molar ratio of reactants was **3**/**7**/*t*-BuOK = 1.0:1.2:1.8. [b] Isolated yield. [c] LiHMDS was used as a base. [d] Low yield is partially due to the high volatility of the product. [e] THF was added as a cosolvent due to the poor solubility of these substrates in DMF at low temperature.

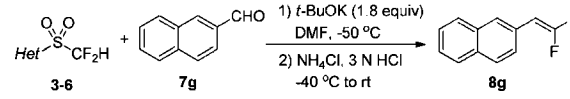
To further demonstrate the synthetic potency of our method with reagent **3**, we applied it in the synthesis of 21,21-difluoro-3-hydroxy-20-methylpregna-5,20-diene (**10**), a potential inhibitor of steroid $C_{17(20)}$-lyase.[5c] Compound **10** was previously prepared from pregnenolone acetate using (difluoromethyl)diphenylphospine oxide in low yield (20%).[5c] We found that by using **3**/LiHMDS/THF/HMPA system, **10** could be produced in 57% yield directly from unprotected pregnenolone **9** (with recycling of 30% unreacted **9**) (Scheme 3).

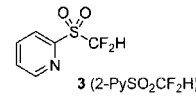
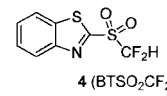
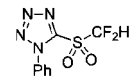
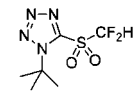
Scheme 3. Synthesis of **10**



Considering that in nonfluorinated Julia−Kocienski olefination reactions, 2-pyridyl sulfones generally give lower yield of olefins than other heteroaryl sulfones such as 1,3-benzothiazol-2-yl (BT), 1-phenyl-1*H*-tetrazol-5-yl (PT), and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfones,[13] we prepared other three difluoromethyl heteroaryl sulfones **4**−**6**[12] and investigated their reactivities in difluoroolefination reactions. As shown in Table 2, we were surprised to find that under

Table 2. *gem*-Difluoroolefination with Different Sulfones



entry	reagent	yield (%)[a]
1	 **3** (2-$PySO_2CF_2H$)	92
2	 **4** ($BTSO_2CF_2H$)	42
3	 **5** ($PTSO_2CF_2H$)	trace[b]
4	 **6** ($TBTSO_2CF_2H$)	0[b]

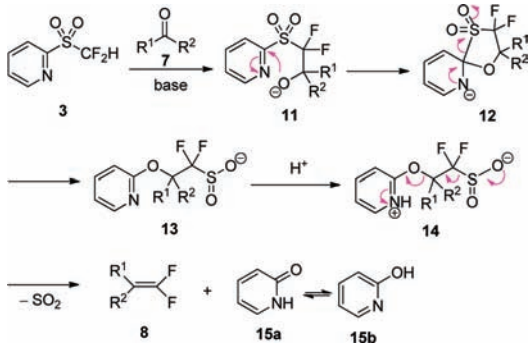
[a] Isolated yield. [b] Determined by ^{19}F NMR spectroscopy.

similar reaction conditions (as those for Table 1), sulfones **4**−**6** showed lower reactivity in the difluoroolefination reaction with 2-naphthaldehyde **7g**. The reaction with $BTSO_2CF_2H$ (**4**) gave product **8g** in 42% yield, while both $PTSO_2CF_2H$ (**5**) and $TBTSO_2CF_2H$ (**6**) did not show significant reactivity with aldehyde **7g**. However, the reaction with reagent **3** provided alkene **8g** in 92% isolated yield. The sharp contrast between the reactivities of nonfluorinated heteroaryl sulfones[13] and difluoromethyl sulfones **3**−**6** in Julia−Kocienski olefination was striking and never reported.[14] We speculate that the high reactivity of sulfone **3** (compared with other sulfones **4**−**6**) may be due to the fact that 2-$PySO_2CF_2^-$ anion possesses the best nucleophilicity

(among four $HetSO_2CF_2^-$ anions; Het = 2-Py, BT, PT, and TBT) toward carbonyl compounds.[15]

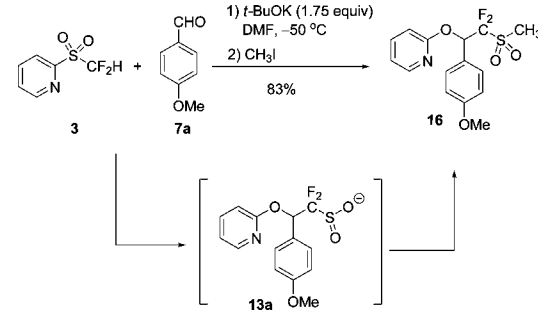
The reaction mechanism of the current difluoroolefinationwith **3** is proposed in Scheme 4, following the generally

Scheme 4. Proposed Reaction Mechanism



accepted mechanism of the Julia–Kocienski reaction.[13] First, sulfone **3** and carbonyl compound **7** condense under basic condition to afford the adduct **11**, which rearranges to a relatively stable sulfinate salt **13**. When protonated at pyridine, the leaving ability of the 2-pyridyloxyl group is enhanced, and the sulfinate salt **14** readily decomposes to the desired *gem*-difluoroalkene product **8**, sulfur dioxide, and 2-pyridone **15a** (or pyridin-2-ol **15b**). This mechanism is supported by our experimental observations: (a) species **13** was observed by ^{19}F NMR [−127.9 ppm (dd, $^2J_{F-F}$ = 230 Hz, $^3J_{F-H}$ = 12 Hz), 1F; −129.0 ppm (dd, $^2J_{F-F}$ = 230 Hz, $^3J_{F-H}$ = 15 Hz), 1F; relative to $CFCl_3$], (b) when we quenched the reaction mixture (from **3** and aldehyde **7a**) with CH_3I, methylated compound **16** was isolated in 83% yield via difluorinated sulfinate intermediate **13a** (Scheme 5).

Scheme 5. Trapping the Sulfinate Salt with Iodomethane



In conclusion, difluoromethyl 2-pyridyl sulfone **3**, a previously unknown compound that can be readily prepared from 2-mercaptopyridine,[12] was found to be a novel and efficient *gem*-difluoroolefination reagent for preparing *gem*-difluoroalkenes from both aldehydes and ketones. Our experimental data suggest that the intermediate sulfinate salt is relatively stable under basic conditions and decomposes after protonolysis. The remarkable feature of the present new difluoroolefination method is its practical simplicity and broad scope of applicability, which promises it to find many applications in organic synthesis. The unusual reactivity difference of sulfones **3**–**6** (as shown in Table 2) provides some insights into both fluorinated sulfone chemistry and Julia–Kocienski reaction. Further exploration of this chemistry is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Similar to $PhSO_2CF_2H$, difluoromethyl sulfone compounds **3**–**6** can be readily prepared by difluoromethylation of the corresponding thiols, followed by simple oxidation (see the Supporting Information). Compounds **3**, **5**, and **6** were previously unkown, and the chemical reactivities of compounds **3**–**6** have never been reported.

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