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Difluorophenylsulfanylmethyl Radical and Difluoromethylene Diradical Synthons: *gem*-Difluoromethylene Building Block

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Abstract: Bromodifluorophenylsulfanylmethane has been demonstrated to be a highly versatile *gem*-difluoromethylene (CF_2) building block via the reaction of difluorophenylsulfanylmethyl radical with olefins. *gem*-Difluoroalkenes and products containing a midchain CF_2 group and with manipulatable functionality can be readily synthesized. The first example of a *gem*-difluoromethylene radical synthon is also reported.

The ability of the fluorine atom to enhance biological and therapeutic activity has led to widespread interest in the selective introduction of either one or two fluorine atoms into organic molecules. Organofluorine chemistry is receiving remarkable interest due to the enormous utility of organofluorine compounds in several fields such as medicinal, biological, agricultural, and analytical chemistry.[1] The replacement of hydrogen atoms by fluorine atoms in biological molecules causes a relatively small steric perturbation but leads to major changes in lipophilicity and polarity factors.[2] Of particular interest is the introduction of a *gem*-difluoromethylene moiety into organic molecules.[3] It has been reported that the CF_2 group has a steric profile similar to that of the CH_2 group, but since it has both a very different polarity and reactivity, it can be regarded as an isopolar and isosteric replacement for oxygen.[1g,4] Certain molecules incorporating a difluoromethylene unit have been shown to act as potent antitumor agents,[5] broad spectrum antibiotics,[6] inhibitors of HIV-1 reverse transcriptase,[7] and potent inhibitors of various proteolytic enzymes.[8] Limited examples have been reported on the introduction of the *gem*-difluoromethylene moiety.[3] Radical,[9] carbene,[10] and ionic[11] reactions involving *gem*-difluorinated carbon species have been utilized. New and convenient methods for the synthesis of *gem*-difluoromethylene compounds, involving readily available sources of *gem*-difluorinated compounds, are still highly desirable.

As part of our ongoing effort in the synthesis of new fluorinated compounds with potential biological and synthetic applications, we wish to report the novel use of bromodifluorophenylsulfanylmethane **1** as a CF_2 "building block" via the carbon−carbon bond formation between the previously unknown difluorophenysulfanylmethyl radical **2** and olefins.[3] It is anticipated that the presence of the phenylsulfanyl group will exert a stabilizing effect on the radical and will provide a functional group in the adducts for further chemical manipulation.

Compound **1** was readily synthesized by the reaction of sodium phenylthiolate with dibromodifluoromethane.[12] After considerable experimentation on various reagents for the generation[13] of the radical **2**, it was found that the three procedures are complementary to each other;

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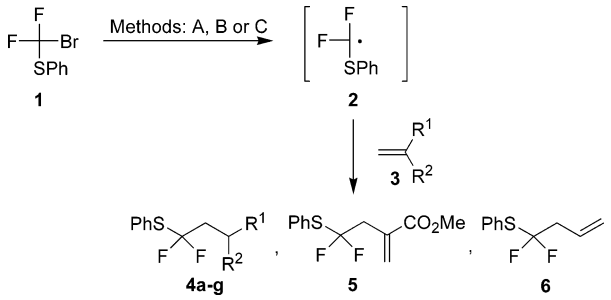
TABLE 1. Results of Trapping the Radical 2 with Olefins

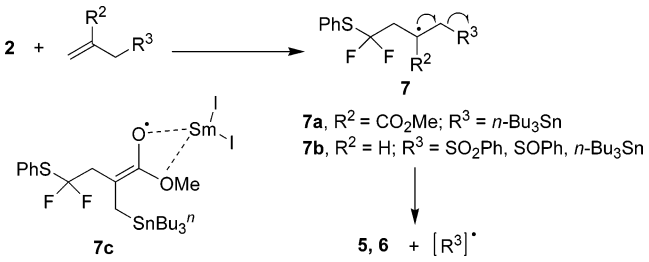
	olefins **3**			% yield of **4**, **5** or **6**		
entry	R^1	R^2		method A[a]	method B[a]	method C[a]
1	Ph	H	**4a**	53	46	46
2	CN	Me	**4b**	59	53	50
3	$CO_2CH_2CH{=}CH_2$	Me	**4c**	47	39	37
4	SO_2Ph	H	**4d**	34	49	12
5	CH_2SnBu_3	CO_2Me	**4e**	62	47 and 12 of **5**	12 and 12 of **5**
6	CH_2SnBu_3	CO_2Me	**4e**	57[b]	40[b] of **5**	32[b] of **5**
7	CH_2SO_2Ph	H	**6**	71[b]	70[b]	67[b]
8	CH_2SOPh	H	**6**	64[b]	60[b]	56[b]
9	CH_2SnBu_3	H	**6**	72[b]	70[b]	61[b]
10	3,4-$(MeO)_2C_6H_3CH_2$	H	**4f**	8	12	12
11	$(CH_2)_9OH$	H	**4g**	8	10	8

[a] Methods: (A) 1.5 equiv of SmI_2/THF/*i*-PrOH, 0 °C 20 min and then rt, 2 h; (B) 1.0 equiv of AIBN/2.0 equiv of *n*-Bu_3SnH/benzene/reflux, 10 h; C 1.2 equiv of Et_3B/1.5 equiv of *n*-$Bu_3SnH/O_2/CH_2Cl_2$, rt, overnight. [b] Without *i*-PrOH (method A) and without *n*-Bu_3SnH (methods B and C) (see text).

SCHEME 1



SCHEME 2

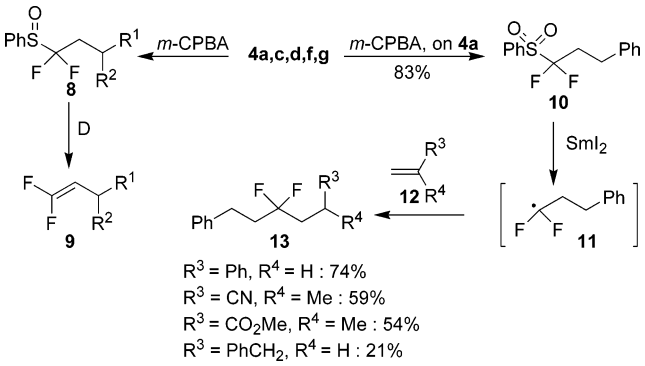


i.e., method A (SmI_2/THF), method B (*n*-Bu_3SnH/AIBN/benzene), and method C (Et_3B/*n*-Bu_3SnH/O_2) gave moderate to high yields of the adducts **4** depending on the olefinic substrates **3** (Scheme 1). The results are summarized in Table 1.

Electrophilic olefins, entries 1−6, gave moderate to good yields of adducts **4a**−**e**. In entry 5, product **4e** together with a small yield (12%) of compound **5**, arising from the elimination of tri-*n*-butyltin radical (Scheme 2), was isolated when methods B and C were employed.

These results can be explained by the competitive rate of tri-*n*-butyltin radical elimination versus the hydrogen radical abstraction from *n*-Bu_3SnH of the stabilized radical **7a**. The formation of product **4e** only, in entries 5 and 6 when method A with or without the hydrogen radical source was employed, can be explained by the chelation of Sm(III) ion (**7c**) with the stabilized radical **7a**, which prevents the elimination of the tri-*n*-butyltin radical. In entry 6, when methods B and C were employed without *n*-Bu_3SnH, only product **5** was isolated in moderate yield in both cases (40 and 32%, respectively), indicating fast elimination of tri-*n*-butyltin radical in the absence of chelation. In the reactions in entries 7−9, compound **6** was isolated in high yield in the absence of hydrogen radical sources. Under the same reaction conditions but with hydrogen radical sources, compound **6** was still the only product isolated but in a much lower yield (31−38%). These results suggested that the elimination process of radical **7b** was fast compared with its ability to undergo hydrogen radical abstraction.

SCHEME 3



Nonactivated olefins, entries 10 and 11, gave low yields of the products **4f** and **4g**. These results suggest the nucleophilic character of the radical **2**.[9b]

The synthetic utility of the reactions described in Scheme 1 for the synthesis of *gem*-difluoromethylene compounds is further demonstrated by the transformations of selected adducts **4** to *gem*-difluoroalkenes and more complex *gem*-difluoromethylene compounds **13** (Scheme 3).

The sulfoxides **8a**−**e** could be prepared in high yields (75 to 92%) by oxidation of **4a**,**c**,**d**,**f**,**g**, respectively, with 1.1 equiv of *m*-CPBA. Vacuum pyrolysis gave the corresponding *gem*-difluoroalkenes[14] **9a**−**e** in high yields (68−81%) (Table 2). The reaction of the sulfone **10**, readily prepared by oxidation of **4a** with 2.1 equiv of *m*-CPBA in 83% yield, with 5.0 equiv of SmI_2/THF/HMPA followed

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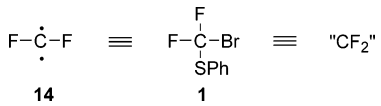
TABLE 2. Synthesis of *gem*-Difluoroalkenes 9

adduct **4**	sulfoxide **8**, %	*gem*-difluoroalkene **9**, %
4a	**8a**, 92	**9a**, 81
4c	**8b**, 79	**9b**, 71
4d	**8c**, 77	**9c**, 68
4f	**8d**, 75	**9d**, 80
4g	**8e**, 81	**9e**, 62

by the trapping of the radical **11** with olefins **12** gave the *gem*-difluoroalkanes **13a**−**d** in moderate to good yields. These reactions provide a novel method for the synthesis of products containing a midchain CF_2 moiety and with a functional group for further chemical manipulation.[15]

In conclusion, our preliminary results clearly demonstrate, for the first time, the synthetic potential of bromodifluorophenylsulfanylmethane **1** as a *gem*-difluoro methylene (CF_2) building block through the reaction of difluorophenylsulfanylmethyl radical **2** and as the synthetic equivalent of a *gem*-difluoromethylene diradical **14** synthon.



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Supporting Information Available: General experimental details and $^1H/^{13}C$NMR spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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