gem-Difluorination of 2,2-diaryl-1,3-dithiolanes by Selectfluor® and pyridinium polyhydrogen fluoride

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2,2-Diaryl-1,3-dithiolanes, readily obtainable from diaryl ketones, were transformed into the corresponding *gem*-difluoro compounds using a novel reagent combination involving Selectfluor® and pyridinium polyhydrogen fluoride (PPHF) under mild conditions in moderate to good yields.

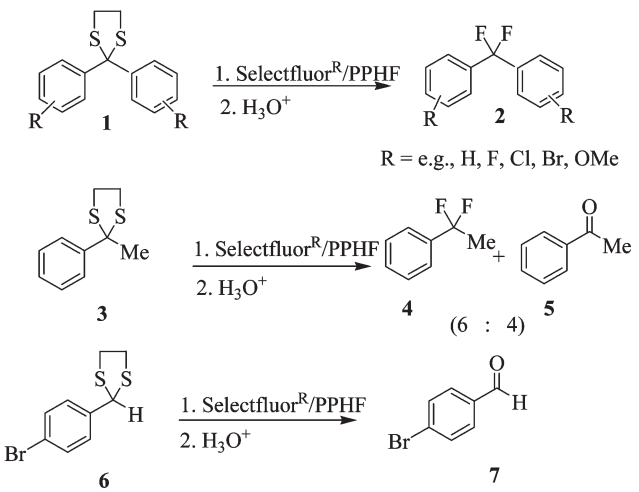
There has been growing interest in the applications of *gem*-difluorinated organic compounds in biological and medicinal chemistry.[1,2] These compounds are isosteric and isopolar analogues of the corresponding ethers, and have found a wide range of biological applications.[3] For example, they can be potentially used as enzyme inhibitors.[4] We have earlier reported synthetic methods for the preparation of the *gem*-difluoro compounds involving the reaction of hydrazones with *N*-bromosuccinimide in pyridinium polyhydrogen fluoride (PPHF).[5] The synthesis of *gem*-difluorinated compounds can also be achieved by the reaction of 1,3-dithiolanes with sulfuryl chloride fluoride (SO_2ClF) or sulfuryl chloride (SO_2Cl_2) in PPHF.[6] Katzenellenbogen and coworkers have reported the desulfurative *gem*-difluorinations of dithiolanes using 1,3-dibromo-5,5-dimethylhydantoin in PPHF.[7] Motherwell has transformed dithioketals to *gem*-difluoro compounds by reaction with 4-methyl(difluoroiodo)benzene.[8] Dithiolanes were also transformed to the *gem*-difluoro compounds by reaction with hexafluoropropene-diethylamine/1,3-dibromo-5,5-dimethylhydantoin,[9] tetrabutylammonium dihydrogen trifluoride and *N*-haloamides,[10] and by the anodic desulfurization in $Et_3N{\cdot}3HF$.[11]

The direct transformation of the carbonyl compounds into *gem*-difluoro compounds can also be achieved using SF_4 and diethylaminosulfur trifluoride (Et_2NSF_3), although these reactions require extreme conditions and give poor yields for deactivated carbonyl compounds.[12,13] Chambers and coworkers have found that the dithiolane derivatives of diaryl ketones react with elemental fluorine–iodine mixtures to give the corresponding *gem*-difluoro compounds.[14,15] The later reaction in aqueous medium resulted in the hydrolysis of the substrates to the corresponding carbonyl compounds.

We now disclose that the reactions of 2,2-diaryl-1,3-dithiolanes with Selectfluor® and PPHF readily give the corresponding *gem*-difluoro compounds under mild reaction conditions. Recently, there has been an enormous interest in the applications of Selectfluor® as an electrophilic fluorinating agent.[16] We also note the limitations of this reagent combination.

We have synthesized the 2-aryl-1,3-dithiolanes from the corresponding diaryl ketones using the reported methods.[7] The resulting dithiolanes were allowed to react with solutions of PPHF and Selectfluor® (Table 1). The reactions† were rapid even at 0 °C, and in about 5 to 10 min complete conversion of the substrate to the *gem*-difluoro compounds was observed. A variety of ring-halogenated and alkoxy substituted 2,2-diaryl-13-dithiolanes (**1**), gave the corresponding *gem*-difluoro compounds (**2**) as the only products, as shown by the GC/MS of the corresponding reaction mixtures at the end of the reaction. The reaction was, however, inefficient for the alkyl aryl ketones: acetophenone dithiolane (**3**) gave the corresponding *gem*-difluoromethylene compound, **4**, and acetophenone in a ratio of 6 : 4 under these conditions. The dithiolane derived from *p*-bromobenzaldehyde, **6**, gave *p*-bromobenzaldehyde (**7**) in quantitative yield after aqueous work up (Scheme 1).‡ The lower yields observed for compound **3**, and quantitative conversion of compound **6** and dithiolane derived from cyclododecanone to the corresponding carbonyl compounds may be explained in terms of the relatively unstable nature of the incipient carbocation intermediates involved in these reactions.

We have found that the reactions of these dithiolanes with Selectfluor® in aqueous acetonitrile or in aqueous PPHF give the corresponding carbonyl compounds as the only reaction products, in accordance with the observations of Wong and coworkers.[17] In anhydrous CH_2Cl_2, there was no noticeable reaction of dithiolanes with either HF or Selectfluor® alone under the reaction conditions used in our work. Thus the combination of Selectfluor® with PPHF has a synergistic effect in the formation of the *gem*-difluoromethylene compounds.



Scheme 1 Reactions of dithiolanes with Selectfluor®/PPHF.

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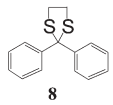
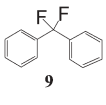
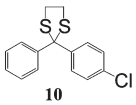
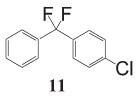
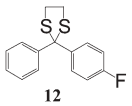
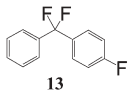
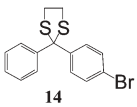
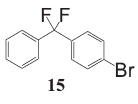
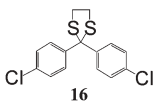
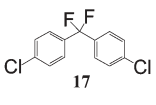
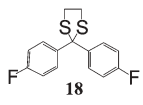
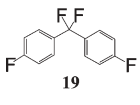
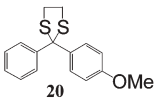
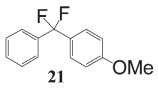
Table 1

Dithiolane	Product	Yield (%)	δ^{19}F	MS [*m*/*z*, (%)]
 **8**	 **9**	86[a]	−89.3 (s)	204 ($M^{+\cdot}$, 68), 183 (20) 127 (100), 107 (10) 77 (25)
 **10**	 **11**	76[b]	−89.2 (s)	238 ($M^{+\cdot}$, 100), 219 (10), 203 (79), 183 (26), 161 (33), 127 (27)
 **12**	 **13**	80[b]	−88.1 (s) and −111.5 (s)	222 ($M^{+\cdot}$, 100), 203 (19), 145 (87), 127 (77), 95 (18)
 **14**	 **15**	85[a]	−89.5(s)	282 ($M^{+\cdot}$, 41), 203 (60), 183 (84), 127 (93), 107 (30), 77 (100)
 **16**	 **17**	62[b]	−89.1(s)	272 ($M^{+\cdot}$, 50), 237 (67) 201 (18), 161 (100) 111 (27), 75 (41)
 **18**	 **19**	81[b]	−86.7 (s) and −111.5 (s)	240 ($M^{+\cdot}$, 100), 239 (29), 221 (17), 201 (7) 145 (78)
 **20**	 **21**	64[b]	−87.2(s)	234 ($M^{+\cdot}$, 100), 203 (13), 157 (74), 127 (10), 77 (7).

[a] Isolated yields. [b] Estimated by GC/MS

In summary, the currently developed reaction is very convenient and efficient for the preparation of 1,1-difluorodiarylmethanes.

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Notes and references

† Selectfluor® (0.71 g, 2 mmol) was dissolved in PPHF (HF:Py = 61:39 (wt%)) in a 50 mL polyethylene bottle and cooled to 0 °C. A solution of 2,2-diphenyl-1,3-dithiolane, **8**, (0.26 g, 1 mmol) in dichloromethane (10 mL) was added to the contents dropwise and allowed to stir for 10 min at room temperature. The reaction mixture was extracted with dichloromethane (3 × 30 mL), combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent: 2.0% diethyl ether in hexane) to give compound **9**:[18] yield 0.17 g (86%); ^{1}H NMR ($CDCl_3$) δ 7.85 (dd, 4H, J = 7 Hz, 1.1 Hz, C_3, C_5–H), 7.64 (tt, 2H, J = 7.4 Hz, 1.46 Hz, C_4–H), 7.54 (d, 4H, J = 7.87 Hz, C_2, C_6–H); ^{13}C NMR ($CDCl_3$) 128.16 (C_3, C_5), 129.9 (C_2, C_6), 132.3 (C_4), 137.5 (C_1). All the *gem*-difluoromethylene compounds have relatively lower GC retention times than the corresponding dithiolanes, and are well separated in GC/MS. The NMR, and GC/MS data for all the products are in accordance with those reported earlier.[5–11,14,15,19]

‡ The dithiolane derived from cyclododecanone similarly gave cyclododecanone in nearly quantitative yield. GC/MS analysis of the reaction mixture showed the formation of trace amounts of the *gem*-difluoromethylene compound. Interestingly, however, 2-adamantanone-derived dithiolane gave the 2,2-difluoroadamantane as the only product under these reaction conditions, as shown by GC/MS analysis.

Caution: PPHF is extremely corrosive and should be handled in a well ventilated hood with protective gloves, face mask and clothing. It should be considered as HF with higher boiling point.

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