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Preliminary note

gem-Difluorination of 1,3-dithiolanes with the hexafluoropropene-diethylamine reagent and N-iodosuccinimide or 1,3-dibromo-5,5-dimethylhydantoin

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Abstract

gem-Difluoro compounds are readily prepared from 1,3-dithiolanes in good yield on treatment with hexafluoropropene-diethylamine/1,3-dibromo-5,5-dimethylhydantoin or /N-iodosuccinimide/water.

Keywords: gem-Difluorination; 1,3-Dithiolanes; NMR spectroscopy; Mass spectrometry

1. Introduction

The intriguing biological and physical properties of *gem*-difluorides [1] coupled with difficulties associated with the preparation of such compounds have prompted a convenient procedure for the preparation of *gem*-difluorides from derivatives of carbonyl compounds. Although there have been several procedures for *gem*-

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difluorides, only a few possess diverse applicability [2]. Difficulties reported in the literature concern low selectivities, the laborious preparation of the reagents and tedious experimental procedures involving the need for special reaction vessels; for these reasons, an easy procedure for the preparation of *gem*-difluorides has been highly desirable.

During an investigation into a new selective procedure for mono-fluoro compounds [3], we have found that the combined use of hexafluoropropene-diethylamine



^a Reactions carried out in dichloromethane under the conditions listed in the table. ^b Isolated yield.

Table 2		
Preparation	of gem-difluoro	compounds *

Entry	Substrate	X ⁺ source (equiv.)	H ₂ O (equiv.)	Product ^b	Yield (%) °	Ref.
7		DBH (2.0)	4.0		72	[2k]
	Ph S			Ph Ph		
8 9 10		DBH (3.0) DBH (3.0) NIS (3.0)	1.0 4.0 2.0	(0:100) (21:79) (100:0)	63 90 37	[2s]
11 12	S Ph	DBH (2.5) nis (3.0)	4.0 4.0	F F Br	81 76	[2s]
13	S S S S	DBH (3.0)	4.0	Ph Ph	45 ^d	
14	s,s	DBH (3.0)	4.0	CHF ₂	58	[2r]
15	S-S-C8H17	DBH (3.0)	4.0	F-F-F	88	[2k,s]

* Reactions run in dichloromethane with HFP-DA (4.0 equiv.) and other reagents shown in the table.

^b All products had spectroscopic properties identical to those reported in the literature.

^c Isolated yield.

Scheme 1.

^d HRMS *m/z*: Calc. for C₁₀H₉F₂Br: 245.9858. Found: 245.9865.



(i) HFP-DA (4.0 equiv.), DBH (3.0 equiv.), H_2O (4.0 equiv.), CH_2Cl_2 , 84%; (ii) MCPBA, CH_2Cl_2 , 75%; (iii) Al-Hg, THF/H₂O, 54%.

reagent (HFP-DA) [4] and N-iodosuccinimide (NIS) or 1,3-dibromo-5,5-dimethyl-hydantoin (DBH) provides an excellent system for the halofluorination of double bonds as well as for the activation of carbon-sulfur bonds ¹. When this system was applied to the fluorination of *gem*-bis(sulfide) ², *gem*-difluorinated compounds were obtained in good yield.

¹ It has been reported that C-S bonds can be replaced by fluorine. See, for example, Ref. [5].

 $^{^{2}}$ For pioneering work on the conversion of bis(sulfide) to diffuoride, see Ref. [6].



Scheme 2.

2. Experimental details

2.1. General procedure for the gem-difluorination of dithiolanes

To a solution of NIS (202 mg, 0.9 mmol) in dichloromethane (1 ml) was added a solution of HFP-DA (512 mg, 1.2 mmol) in dichloromethane (2 ml) and H_2O (22 µl, 1.2 mmol), successively at -78 °C, and the mixture was warmed to room temperature. After being stirred at room temperature for 5 min, the orange mixture was re-cooled to -78 °C and a solution of 2,2-di-n-pentyl-1,3-dithiolane (74 mg, 0.3 mmol) in 2 ml of dichloromethane was added. The resulting mixture was gradually warmed to -20 °C during 1 h. Saturated aq. NaHCO₃ (5 ml) was added and the entire mixture extracted with ether. After normal work-up, the crude oil was purified by flash silica gel column chromatography to give 6,6-difluoroundecane (41 mg, 71%) as a colorless oil. The spectroscopic properties were identical with reported data [2k]. ¹H NMR (CCl₄) δ: 0.67-1.17 (6H, m); 1.17–2.26 (16H, m) ppm. ¹⁹F NMR (CCl₄) δ: -99.0 (quintet, J = 16.0 Hz) ppm. IR (neat) (cm⁻¹): 2950; 2850; 1740; 1730; 1460; 930.

3. Results and discussion

The optimum reaction conditions were examined using 2,2-dipentyl-1,3-dithiolane as the substrate. As shown in Table 1, satisfactory results were obtained when the reaction was carried out with NIS (3.0 equiv.) or DBH (2.0 equiv.), HFP-DA (4.0 equiv.) and H₂O (4.0 equiv.), and 5,5-difluoroundecane was formed in 71% to 80% yield (entries 3 and 5) with the use of HFP-DA (4.0 equiv.) and H₂O (4.0 equiv.) being crucial for the best results. The effects of the reaction temperature were also important: the reaction occurred most efficiently at an initial temperature of -78 °C and then allowing the system to gradually warm to -20 °C. Under the optimum reaction conditions, various 1,3-dithiolanes were converted into the corresponding gem-difluorides in good yield as listed in Table 2.

In general, 1,3-dithiolanes derived from ketones gave better results than those from aldehydes, whereas 1,3dithiolanes from aliphatic aldehydes did not give the desired gem-difluorides probably because of the instability of the carbonium ion intermediate 7 (Scheme 2). A similar phenomenon was observed with the substrate possessing a carbonyl group adjacent to the gembis(sulfide) (Scheme 1). Ethyl 2,2-bis(phenylthio)hexanoate (3), prepared readily from the corresponding ester [7], was treated under similar conditions to give the monofluorinated compound 4 exclusively in good yield, implying that the ability of the carbon-bearing sulfur groups to stabilize the carbonium ion intermediate 7 determines the pathway of the present fluorination. The monofluorinated compound 4 was readily converted into the sulfur-free fluoro ester 5 via oxidation to sulfoxide followed by reductive removal with aluminum amalgam in good overall yield, demonstrating that this may be applied to the synthesis of a fluoro analog of the side-chain of prostaglandin (PG) derivatives [8].

An intriguing behavior of the dithiolane derived from propiophenone is noteworthy (entries 8, 9 and 10). Under the influence of DBH (3.0 equiv.) and H₂O (1.0 equiv.), the reaction gave a vinylic fluoride of type 10 [9] exclusively in good yield, whereas with NIS gemdifluoride 9 was obtained as the sole product, albeit in low yield. With the tetralone derivative (entry 13), the product was brominated at the α -position ³. This intrinsic nature of the tetralone derivative is best explained in terms of the initial formation of the vinylic sulfide 8 or the vinylic fluoride 10 followed by bromofluorination [10], as described by the following equa-

³ α -Bromodifluoride was readily reduced to the *gem*-difluoride on treatment with "Bu₃SnH in refluxing benzene.

tions for the possible reaction pathways in the present fluorination (Scheme 2).

A variety of 1,3-dithiolanes may be readily prepared via several standard procedures [11], the reagents are all commercially available, the reaction can also be conducted in ordinary glassware apparatus, and for these reasons the present *gem*-difluorination reaction offers a rapid and flexible approach to a biologically and physically interesting class of compounds.

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