ELSEVIER

Journal of Fluorine Chemistry 71 (1995) 9–12

JOURNAL OF FLUORINE CHEMISTRY

Preliminary note

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

Makoto Shimizu, Takashi Maeda, Tamotsu Fujisawa *

Department of Chemistry for Materials, Mie University, Tsu, Mie 514, Japan

Received 6 July 1994; accepted 1 October 1994

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

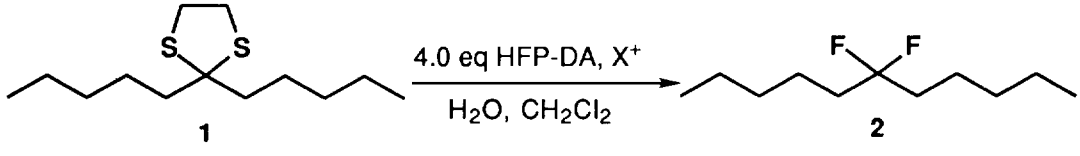
1. Introduction

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*-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

* Corresponding author.

Table 1
Comparison of reaction conditions [a]



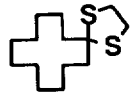
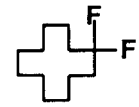
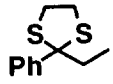
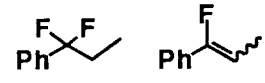
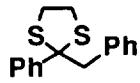
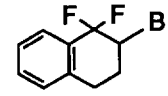
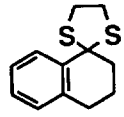
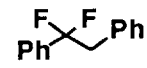
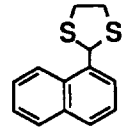
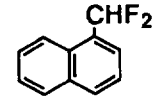
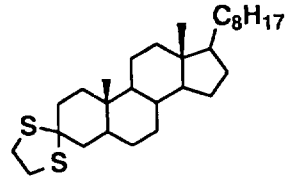
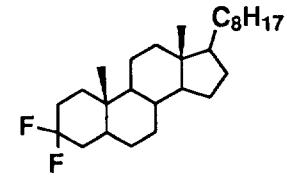
1 2

Entry	X^+ source (equiv.)	H_2O (equiv.)	Temp. (°C)	Yield of 2 (%) [b]
1	DBH (2.0)	1.0	−78 to −20	31
2	DBH (2.0)	2.0	−78 to 0	50
3	DBH (2.0)	4.0	−78 to −25	80
4	DBH (3.0)	4.0	−78 to −20	68
5	NIS (3.0)	4.0	−78 to −20	71
6	NIS (2.5)	4.0	−78 to 0	0

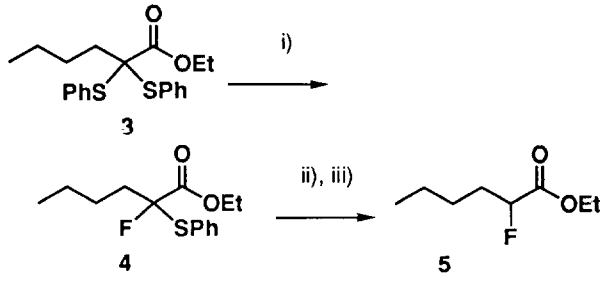
[a] Reactions carried out in dichloromethane under the conditions listed in the table.
[b] Isolated yield.

SSDI 0022-1139(94)03187-8

Table 2
Preparation of *gem*-difluoro compounds [a]

Entry	Substrate	X^+ source (equiv.)	H_2O (equiv.)	Product [b]	Yield (%) [c]	Ref.
7		DBH (2.0)	4.0		72	[2k]
8		DBH (3.0)	1.0	 (0:100)	63	[2s]
9		DBH (3.0)	4.0	(21:79)	90	
10		NIS (3.0)	2.0	(100:0)	37	
11		DBH (2.5)	4.0		81	[2s]
12		nis (3.0)	4.0		76	
13		DBH (3.0)	4.0		45[d]	
14		DBH (3.0)	4.0		58	[2r]
15		DBH (3.0)	4.0		88	[2k,s]

[a] 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.
[d] HRMS *m/z*: Calc. for $C_{10}H_9F_2Br$: 245.9858. Found: 245.9865.

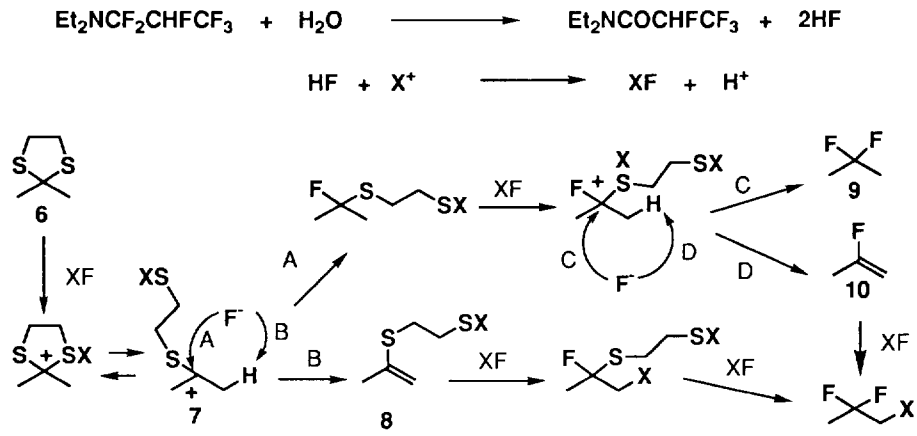


(i) HFP–DA (4.0 equiv.), DBH (3.0 equiv.), H_2O (4.0 equiv.), CH_2Cl_2, 84%; (ii) MCPBA, CH_2Cl_2, 75%; (iii) Al–Hg, THF/H_2O, 54%.

Scheme 1.

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 difluoride, 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. $NaHCO_3$ (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 (CCl_4) δ: 0.67–1.17 (6H, m); 1.17–2.26 (16H, m) ppm. ^{19}F NMR (CCl_4) 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 H_2O (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 H_2O (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 1,3-dithiolanes 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 *gem*-bis(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 H_2O (1.0 equiv.), the reaction gave a vinylic fluoride of type **10** [9] exclusively in good yield, whereas with NIS *gem*-difluoride **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 $^nBu_3SnH$ 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.

References

[1] N. Ishikawa (ed.), *Synthesis and Function of Fluorinated Compounds*, CMC, Tokyo, 1987; J.T. Welch, *Tetrahedron, 43* (1987) 3123.

[2] (a) A.L. Henne, *Org. React., 2* (1944) 49; (b) T.E. Stevens, *J. Org. Chem., 26* (1961) 1627; (c) D.G. Martin and F. Kagan, *ibid., 27* (1962) 3164; (d) F.S. Fawcett, C.W. Tullock and D.D. Coffmann, *J. Am. Chem. Soc., 84* (1962) 4275; (e) F. Mathey and J. Bensoan, *Tetrahedron, 27* (1971) 3965; (f) G.A. Olah, M. Nojima and F. Kerekes, *J. Am. Chem. Soc., 96* (1974) 925; (g) S. Rozen, M. Brand, D. Zamir and D. Hebel, *J. Am. Chem. Soc., 109* (1987) 896; (h) T.B. Patreich, J.J. Scheibel and G.L. Lantrell, *J. Org. Chem., 46* (1981) 3917; (i) E.A. Hallinan and J. Fried, *Tetrahedron Lett., 25* (1984) 2301; (j) C.J. Wang, *Org. React., 34* (1985) 319; (k) S.C. Sondej and I.A. Katzenellenbogen, *J. Org. Chem., 51* (1986) 3508; (l) A.J. Bloodworth and K.J. Bowyer, *Tetrahedron Lett., 28* (1987) 5347; (m) R.J. Linderman and D.M. Graves, *J. Org. Chem., 54* (1989) 661; (n) W.H. Bunnelle, B.R. McKinnis and B.A. Norayanan, *ibid., 55* (1990) 768); (o) G.K.S. Prakash, V.P. Reddy, X.-Y. Li and G.A. Olah, *Synlett,* (1990) 594; (p) H. Suga, T. Hanatani, Y. Guggisberg and M. Schlosser, *Tetrahedron, 46* (1990) 4255; (q) W.B. Motherwell and J.A. Wilkinson, *Synlett,* (1991) 191; (r) M. Kuroboshi and T. Hiyama, *Synlett,* (1991) 909); (s) S. Rozen and D. Zamir, *J. Org. Chem., 56* (1991) 4695; (t) G.K. Prakash, S.D. Hoole, V.P. Reddy and G.A. Olah, *Synlett,* (1993) 691; (u) M. Kuroboshi and T. Hiyama, *Synlett,* (1994) 251; (v) for a review, see M. Kuroboshi and T. Hiyama, *J. Synth. Org. Chem. Jpn., 51* (1993) 1124.

[3] M. Shimizu, M. Okamura and T. Fujisawa, *Bull. Chem. Soc. Jpn., 64* (1991) 2596; M. Shimizu, O. Morita, S. Ito and T. Fujisawa, *Tetrehedron Lett., 33* (1992) 7003.

[4] A. Takaoka, H. Iwakiri and N. Ishikawa, *Bull. Chem. Soc. Jpn., 52* (1979) 3377.

[5] K.C. Nicolaou, R.E. Dolle, D.P. Papahatjis and J.L. Randall, *J. Am. Chem. Soc., 106* (1984) 4189.

[6] J. Kollonitsch, S. Marburg and L.M. Perkins, *J. Org. Chem., 41* (1976) 3107.

[7] B.M. Trost, T.N. Saltzmann and K. Hiroi, *J. Am. Chem. Soc., 98* (1975) 4887.

[8] B.J. Magerlein and W.L. Miller, *Prostaglandins, 9* (1975) 527.

[9] (a) G. Boche and U. Fahrmann, *Chem. Ber., 114* (1981) 4005; (b) S.H. Lee and J. Swartz, *J. Am. Chem. Soc., 108* (1986) 2445; (c) M. Shimizu and H. Yoshioka, *Tetrahedron Lett., 30* (1989) 967; (d) M. Kuroboshi and T. Hiyama, *ibid., 32* (1991) 1215; (e) M.A. Tius and J.K. Kawanami, *Synth. Commun., 22* (1992) 1461.

[10] M. Shimizu, Y. Nakahara and H. Yoshioka, *J. Chem. Soc., Chem. Commun.,* (1989) 1881, and references cited therein.

[11] E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, 1978; B.M. Trost, *Chem. Rev., 78* (1978) 363.