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PRELIMINARY NOTE

A Facile Synthesis of 1-Fluoro-1-halogenoalka-1,3-dienes

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SUMMARY

1-Fluoro-1-halogenoalka-1,3-dienes are synthesized in good yields by treatment of 2,2-dihalogenocyclopropyl carbinols with $(HF)_n$.Py in the presence of diisopropylamine and NaF followed by dehydrohalogenation with potassium *t*-butoxide.

Although 1-fluoro-1-halogenoalka-1,3-dienes are attractive synthons for synthesis of potential bioactive compounds with the stable fluorohalogenated double bond [1], little has been published to date on synthesis of the dienes, and there are only a few methods published even on the preparation of 1-fluoro-1-halogeno-1-alkenes, which require either a 1-chloro-1-fluorovinyl transfer reagent of the Wittig type [2] or perchloryl fluoride for fluorination of 1-chloro-1-lithioalkenes [3].

We reported previously the regiospecific fluorination of cyclopropyl carbinols with $(HF)_n$.Py-additives [4]. We have now found that an extended application of this procedure to 2,2-dihalocyclopropyl carbinol [5], in which diisopropylamine and KHF_2 or NaF were also crucial additives, and the subsequent dehydrohalogenation leads to a facile synthesis of 1-fluoro-1-halogenoalka-1,3-dienes.

A typical procedure is as follows: To a solution of the cyclopropyl carbinol **1** (X = Cl, R^1 = R^2 = H, R^3 = Ph, 217 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) in the presence of diisopropylamine (0.6 ml) and NaF (200 mg, 4.8 mmol) was added $(HF)_n$.Py (1.5 ml, 70% HF in Py) at 5 °C, and the reaction mixture was stirred at that temperature for 1 hr. An aqueous KF (20%, 3 ml) was added

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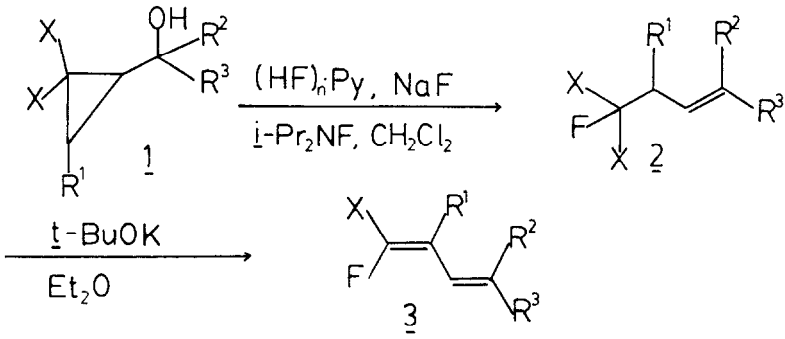


and the entire mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml x 3) and saturated aqueous NaCl (10 ml x 2). The crude oil obtained after drying and concentration of the extract was purified on preparative TLC (eluent: *n*-Hexane) to give **2** (134 mg, 61%) as a colorless oil. To a suspension of *t*-BuOK (103 mg, 0.92 mmol) in ether (10 ml) was added a solution of **2** (102 mg, 0.46 mmol) in ether (5 ml) at 0 °C, and the mixture was stirred at that temperature for 2 hr. Afte normal workup followed by purification on preparative TLC (eluent: *n*-hexane), **3** (74 mg, 87%) was obtained as a colorless oil. Examples of fluorination and dehydrohalogenation are summarized in Table I.

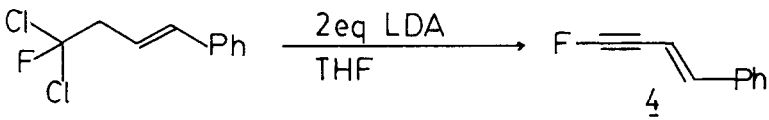
TABLE I

Synthesis of 1-Fluoro-1-halogenoalka-1,3-dienes[a]

Entry	Substrate	Yield of 2/%[b]	(*E*:*Z*)[c]	3/%[b]	(*E*,*E*:*Z*,*E*)[c]
1	X = Cl, R^1 = R^2 = H, R^3 = Ph	61	(>99:1)	87	(56:44)
2	X = Br, R^1 = R^2 = H, R^3 = Ph	51	(>99:1)	69	(>99:1)
3	X = Cl, R^1 = Me, R^2 = H, R^3 = Ph	16	(>99:1)	77	(49:51)
4	X = Cl, R^1 = H, R^2 = Me, R^3 = Ph	64	(>99:1)	88	(60:40)
5	X = Cl, R^1 = H, R^2 = R^3 = Me	22	(----)	--	
6	X = Cl, R^1 = R^2 = H, R^3 = PhC-C	65	(67:37)	80	(N.D.)[d]

[a] Fluorination and dehydrohalogenation were carried out on 0.5--1.0 mmol scale. All the compounds gave satisfactory spectroscopic data. [b] The yields refer to isolated pure materials. [c] Determined by ^1H and ^{19}F NMR. [d] Inseparable products were obtained.

As for the first fluorination step, almost all the carbinols examined here underwent regio- and stereoselective fluorination to give predominantly the (*E*)-isomer in good yield. In contrast to the previous results with cyclopropyl carbinols not containing halogens[4], an alkyl substituent on the cyclopropane ring considerably decreased the reactivity and the dihalofluoroalkene was obtained in poor yield (entry 3). When R^2 and R^3 are methyls, the reaction proceeded sluggishly, leaving the starting material even after 60 hr (entry 5). The subsequent dehydrohalogenation was stereospecific with the dibromo compound (entry 2), whereas the other substrates gave the diene as a mixture of isomers. On the other hand, dehydrohalogenation of 2 (X = Cl, R^1 = R^2 = H, R^3 = Ph) with lithium diisopropylamide (2 eq) in THF leads to 1-fluoro-enyne of type **4** in 62% yield.



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Since the starting materials, 2,2-dihalogenocyclopropyl carbinols are readily prepared via the dihalogenocarbene addition [5], fluorination-dehydrohalogenation as used in the present work offers a convenient approach to 1-fluoro-1-halogenoalka-1,3-dienes.

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5 Prepared via the dichlorocarbene addition to acrolein diethylacetal or crotonaldehyde diethyl acetal followed by hydrolysis and Grignard addition, or the dibromocarbene addition to 1,3-butadiene followed by oxidation and Grignard addition. See, K. Khusid, G. V. Kryshtal, V. A. Dombrousky, V. F. Kucherov, L. A. Yanovskaya, V. I. Kadentsen, and O. S. Chizhov, *Tetrahedron*, **33** (1977) 77; K. H. Holm, D. G. Lee, and L. Skattebal, *Acta Chem. Scand.*, **B32** (1978) 694.