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Synthesis of (*E*)- and (*Z*)-α,β-difluorourocanic acid

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Abstract

Horner–Emmons fluoroolefination of an aryl aldehyde followed by introduction of a second fluorine via "FBr" addition provides an original approach to the preparation of 1-alkyl-2-aryl-1,2-difluoroethenes. The utility of this procedure is demonstrated by the preparation of (*E* and *Z*)-α,β-difluorourocanic acid.
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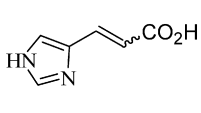
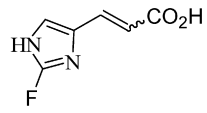
Keywords: Fluoroimidazole; Urocanic acid; Fluoroolefins; FBr addition; Regiochemistry

1. Introduction

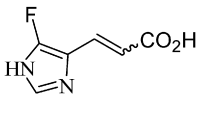
(*E*)-Urocanic acid **1a** is elaborated in vivo by histidine ammonia lyase-catalyzed loss of ammonia from histidine. The photochemistry and biological properties of urocanic acid continue to receive attention, in part because of evidence that (*Z*)-urocanic acid (**1b**), formed in the body by photo-isomerization of the *E* isomer, is a mediator of photo-immunosuppression [1]. As part of our program to prepare fluorinated analogues of biologically important imidazoles, we have reported the synthesis of (*E*)- and (*Z*)-2- and 4-fluorourocanic acid (**2a**,**b** and **3a**,**b**, respectively) [2], (*E*)- and (*Z*)-α-fluorourocanic acid (**4a**,**b**) [3] and (*E*)- and (*Z*-β)-fluorourocanic acid (**5a**,**b**) [4]. Ring-fluorinated analogues **2** and **3** were prepared from ring-fluorinated aldehyde precursors using a Horner–Emmons olefination with triethyl phosphonoacetate [2]. A similar olefination of 1-trityl-(1H)imidazole-4-carboxaldehyde with triethyl flourophosphonoacetate was the key step in the synthesis of **4a**,**b** [3]. To access the β-fluoroanalogues **5a**,**b**, addition of "FBr" to a vinyl imidazole derivative to place fluorine adjacent to the imidazole ring was the key step [4]. Missing from the inventory of side-chain fluorinated analogues of urocanic acid is α,β-difluorourocanic acids (**6a**,**6b**), compounds that should have interesting chemical and biological behavior by virtue of the difluoroacrylate functionality.



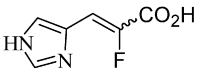
1a *E* (trans)
1b *Z* (cis)



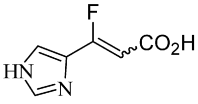
2a *E* (trans)
2b *Z* (cis)



3a *E* (trans)
3b *Z* (cis)



4a *Z* (trans)
4b *E* (cis)



5a *Z* (trans)
5b *E* (cis)

6a *E* (trans)
6b *Z* (cis)

Published routes to compounds of the general structure Aryl-CF=CF-Alkyl would not seem readily applicable to the synthesis of **6a** and **6b**. One approach based on reaction of CF_2=CF_2 or R–CF=CFX (where X is H or halogen) with ArLi has been applied to heteroaryl compounds [5]. However, in general, this method would not readily tolerate functional groups. A second approach that involves elimination of "X–X" from R–CFX–CFX–R [6] requires lengthy and, in our case, problematic preparation of precursors. A third approach would be direct addition of F_2 diluted with N_2 to a triple bond. In one example, addition of F_2 to a series of tolanes give mixtures of products, including α,α′-difluorostilbenes [7]. We did not consider this approach because of the complex reaction products and requirement for special equipment.

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We have approached the synthesis of **6a**,**b** by combining chemistry we used for the preparation of **4** and **5**. In a key reaction in our synthesis of α-fluorourocanic acids, Horner–Emmons olefination of 1-trityl-(1H)imidazole-4-carboxaldehyde with triethyl fluorophosphonoacetate produces α-fluoropropenoates **7** [3]. In our synthesis of β-fluorourocanic acids, we took advantage of regiospecific ''FBr'' addition to a vinyl imidazole derivative followed by HBr elimination to install fluorine in the β-position [4]. In contemplating a combination of these two approaches in order to place fluorine at both the α- and β-positions, a critical question involves regioselectivity of the ''FBr'' addition to 1-alkyl-2-aryl-1-fluoroalkenes. If the directive effect of fluorine (resulting in stabilization of an α-carbonium ion) is strong enough to take precedence over aryl carbonium ion stabilization, ''FBr'' addition would be predicted to lead to the geminal instead of the desired vicinal difluoro compounds. Indeed, this is the observed product of addition of FBr to vinyl fluorides where an aryl group is not present [8] or when the aryl group and fluorine are on the same carbon [9]. To our surprise, we have found no examples of electrophilic additions to 1-alkyl-2-aryl-1-fluoroalkenes.

Having found no precedent wherein addition of ''FBr'' to a vinyl monofluoride produces the vicinal difluoride, we were pleased to find that addition of ''FBr'' to 3-(1-trityl-1(H)-imidazol-4-yl)-1-hydroxymethyl-2-fluoro-2-propene (**8**) in fact proceeds with regioselectivity to produce the vicinal difluoride. This somewhat unexpected direction of addition provides a convenient route to α,β-difluorourocanic acids. In addition, this discovery should make possible the synthesis of other 1-aryl-1,2-difluoroalkenes by the same route.

2. Chemistry

(*E*)- and (*Z*)-Ethyl 2-fluoro-3-(1-trityl-1-H-imidazol-4-yl)-prop-2-enoate (**7a**,**b**) were prepared as described [4]. Based on our experience with the preparation of **5**, we were aware that reduction of the ester to alcohol was necessary to achieve the desired chemoselectivity of halide elimination (bromide vs. fluoride) in the sequence [4]. Previously, we also found that the carboxyl function of urocanic acid deactivates the double bond to the extent that ''FBr'' addition via $Et_3N{\cdot}3HF$ and NBS becomes a sluggish process [4]. In a related example, we were unable to effect ''FBr'' addition to ethoxycabonylalkynylimidazole [10]. Consistent with these results, we found that no FBr-adducts are formed from α-bromourocanate or α-fluorourocanate **7** using our usual conditions. Therefore, we reduced the deactivating ester function to the hydroxymethyl electron donating group to obtain 2-fluoropropenols **8a** and **8b**. These were then used as substrates to study FBr adduct formation. In subsequent reactions, since addition of ''FBr'' to either olefin produced diasteromeric mixtures of products that were extremely difficult to separate, it was convenient to carry out addition of ''FBr'' and elimination of HBr on mixtures of **8a/8b**.

The reactivity of the 2-fluoropropenols **8a**,**b** proved to be lower in comparison to their nonfluorinated analogs [4] or isomeric 3-fluoropropenols [9], where the conversion is about 100%. Under the usual conditions, the conversion of 2-fluoropropenols to products **9a** and **9b** was only 84% of **8a** and 52% of **8b**. As is usual in the cases of poorly reactive olefins, in addition to the desired FBr adducts, the dibromo adducts **10** were also formed in about 25% yield. Thus the reactivity is similar to trityl urocanic methyl ester (conversion 62%) [4]. As in that case, the conversion of **8** can be increased by increasing the reagent amounts (see Table 1). We found no evidence (^1H and ^{19}F NMR) of reversed regioselectivity with formation of geminal difluoro compound.

Table 1
Results of addition of ''FBr'' on **6a** or **6b**

Starting isomer	Reaction conditions[a]			Products molar ratio (%)				
	''HF''	NBS	Time	**9a**	**9b**	**10a**	**10b**	**8**[b]
(a) **8a**	1.5	1.1	2	41	17	13	13	16
(b) **8a**	1.5	1.1	5	51	18	6	6	19
(c) **8b**	1.5	1.1	14	3	24	12	13	48
(d) **8b**	2.5	1.8	44	6	41	11	15	27
(e) **8b**	3.2	2.2	19	8	59	15	18	0

[a] Content of columns is as follows: equivalents of $Et_3N{\cdot}3HF$, equivalents of NBS, reaction time in hours.
[b] Starting isomer **8a** or **8b**.

It is well documented that in these reactions, *trans* alkenes give mainly the product of *anti* addition, but *cis* alkenes give mixture of *anti* and *syn* addition [4]. However, there are few precedents for reactions of alkenes having a halogen substituent in place of hydrogen on the double bond. We found that isomer **8b**, where the carbon substituents are *trans* to each other, gives diastereoisomeric adducts in a ratio of 88:12, tentatively assigned as products from *anti* (**9b**, $2R^*,3S^*$-configuration) and *syn* (**9a**, $2R^*,3R^*$-configuration) additions, respectively. This is slightly lower diastereoselectivity than found with the nonfluorinated analog (95:5) [4]. Isomer **8a**, where the carbon substituents are in a *cis* orientation, gives a diastereoisomeric mixture in a ratio of 75:25, tentatively assigned as products from *anti* (**9a**) and *syn* (**9b**) additions. This is significantly higher *anti* diastereoselectivity than found with the *cis*-configured nonfluorinated analog, which gave an *anti*/*syn* addition ratio of 20:80 [4]. It is interesting to note that byproduct Br_2-adducts, two diastereoisomers **10a** and **10b** are formed in ratio of about 1:1 in both cases. These results are summarized in Table 1.

Dehydrobromination of mixture **9a** and **9b** gives corresponding difluoropropenols **11a** and **11b** in the usual yields of 60–70%. Double bond configuration was readily assigned to the two geometrical isomers based on ^{19}F NMR data. The (*E*)-isomer **11a** has a significantly higher F–F coupling constant (126 Hz) than does the (*Z*)-isomer **11b** (21 Hz). The oxidation to aldehyde **12a** and **12b** by MnO_2 surprisingly proceeds with formation of byproduct **13**, the yield of which increases with longer reaction times or increased reaction temperature. The isomer **11b** is significantly less reactive than **11a** and compound **13** becomes the main product of the oxidation (see Section 4.8). We have found no precedent for this conversion and any mechanistic proposals would be entirely speculative. For acceptable yield of the aldehydes **12** (30–50%), it is necessary