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New approaches to side-chain fluorinated bioimidazoles: 4-alkynylimidazoles as substrates for fluorination

Bohumil Dolensky, Kenneth L. Kirk*

Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda, MD 20892, USA

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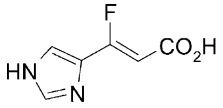
Abstract

4-Alkynylimidazoles have been prepared and their behavior as substrates for ''FBr'' addition (NBS + $Et_3N{\cdot}3HF$) have been studied. Facile Markownikov addition to ethylnylimidazole **2** gave fluorobromoolefin **9a**, a potential synthon for the 2-imidazolyl-2-fluoro-1-ethenyl moiety. Reaction of the lithium salt of **2** with diethyl oxalate produced imidazolylpropynoic ester **3b**. However, because of the deactivating effect of the ester functionality, all attempts to carry out addition of ''FBr'' to **3b** met with failure. Reduction of the ester gave the hydroxymethyl-substituted acetylene **4**. Addition of ''FBr'' to this substrate and reductive removal of bromine from the product produced fluoroolefins **12**, precursors to *E*- and *Z*-β-fluorourocanic acids. The same fluoroolefins can be used as intermediates in the synthesis of β-fluorohistidinols.

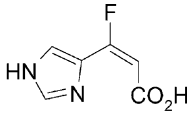
Keywords: Alkynes; ''FBr'' addition; Urocanic acid

1. Introduction

Interest in urocanic acid and derivatives has increased with the discovery that *Z*-urocanic, formed by photoisomerization of the initially formed *E*-isomer in the epidermis, functions systemically as an immunosupressive agent. We have had a long-standing interest in the chemistry and biology of fluorinated imidazole derivatives, including fluorinated analogues of urocanic acid. Thus, to study the possible consequences of side-chain fluorination on such properties as photoisomerization, we prepared *Z*- and *E*-α-fluorourocanic acids and we more recently have described preparation of *Z*- and *E*-β-fluorourocanic acid (**1a** and **1b**) [1]. The key to this latter synthesis was the addition of an FBr equivalent to the double bond of *Z*- and *E*-isomers of 1-trityl-4-(3-hydroxy-1-propenyl)imidazoles. Subsequent elimination of HBr gave fluoroolefins that were oxidized to the urocanic acid derivatives. A complicating factor in this approach was undesired isomerization during ''FBr'' addition to the *Z*-isomer of the olefin. For this reason, dehydrobromination of this adduct gave predominantly the *E*-fluoroolefin rather than the expected *Z*-fluoroolefin. Since no similar loss of stereochemistry occurred in the sequence starting with the *E*-starting olefin, this also produced the *E*-fluoroolefin. This complicated the synthesis of *Z*-β-fluorourocanic acid (**1a**). During the development of this synthesis, we had considered different approaches that would be more convenient for the synthesis of **1a** and had made significant progress to that end. This work was based on preparation and functional manipulation of alkynylimidazoles and involved the preparation of several imidazole intermediates that have potential for serving as synthons for additional targets. We herein report the details of the chemistry of alkynylimidazoles that was developed and the successful completion of this alternative approach to acids **1a** and **1b**.



1a



1b

2. Chemistry

2.1. Preparation of alkynylimidazoles

There are only limited reports of preparation of 4-alkynylimidazoles in the literature [2]. For the purposes of these studies, we prepared the four alkynylimidazoles **2**, **3a**, **3b** and **4**. Ethynylimidazole **2** was prepared by addition of

* Corresponding author. Tel.: +1-301-496-2610; fax: +1-301-402-4182.
E-mail address: kennethk@bdg8.niddk.nih.gov (K.L. Kirk).

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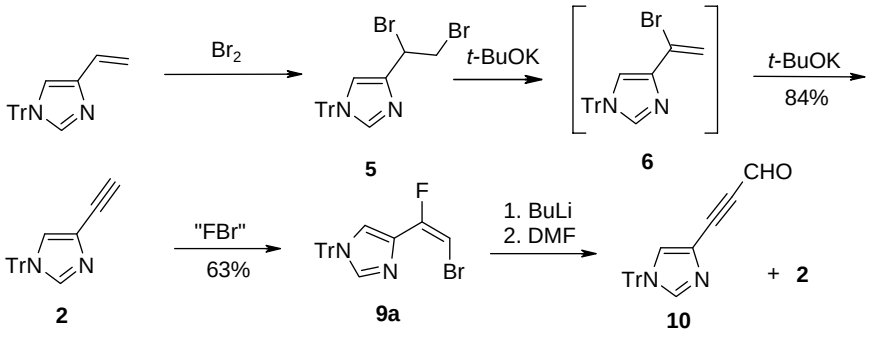
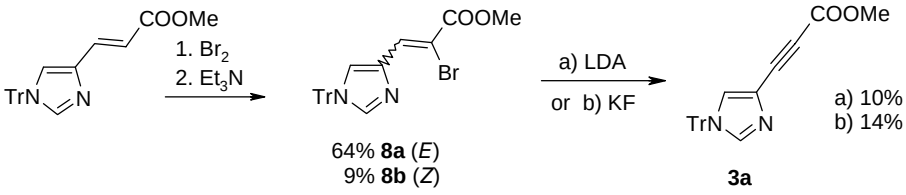


Scheme 1. Preparation of alkynylimidazoles from vinylimidazole.



Scheme 2. Preparation of alkynyl ester **3a** from methyl urocanate.

bromine to the double bond of 1-trityl-4-vinylimidazole [3] followed by elimination of two molecules of HBr from bromine addition product **5** using *t*-BuOK. This approach worked very well and ethynylimidazole **2** was obtained in an overall yield of 84%. In addition, when insufficient excess of *t*-BuOK was used, the intermediate α-bromovinylimidazole **6** could be isolated (Scheme 1).

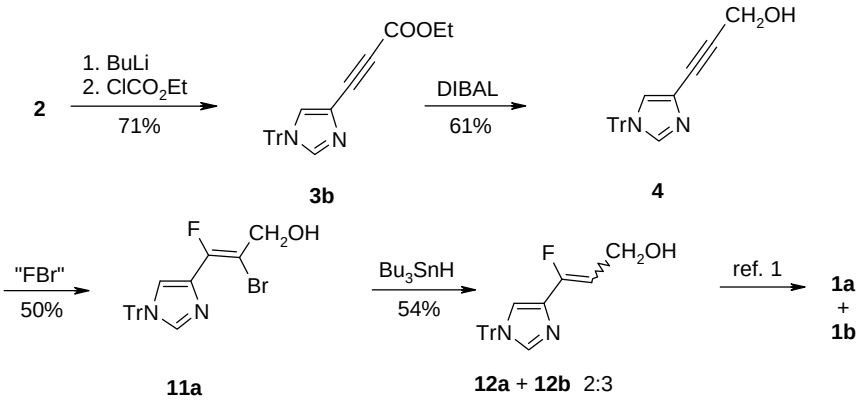
We tried a similar approach for the preparation of methyl ester of the 1-trityl-4-imidazoyl propynoic acid (**3a**) (Scheme 2). The addition of bromine to tritylated urocanic acid methyl ester takes place with no problem and the adduct **7** is formed in almost quantitative yield as a single diastereoisomer. The first molecule of HBr is eliminated readily by treatment with Et_3N to produce isomers **8a** and **8b** in a ratio of 88:12. The major isomer **8a** has the expected *E* configuration that would be predicted from *anti* addition of Br_2 and *anti* elimination of HBr. (This contrasts to the observed *syn* elimination of HF from the analogous FBr-adduct [1].) However, we met serious problems with elimination of the second HBr molecule. Use of bases such as *t*-BuOK or KOH/MeOH was unsuccessful, possibly because of nucleophilic attack on the ester carbonyl and/or triple bond, as suggested by crude NMR data. Warming in Et_3N causes only isomerization of **8a** to **8b**. Use of DBU also was unsuccessful. About 10% of alkynylimidazole **3a** is formed from **8a** or **8b** by treatment with LDA. A longer reaction time or bigger excess of LDA resulted in degradation of both starting bromoolefins **8** and alkynylimidazole **3a**.

It is also known that KF treatment can lead to HBr elimination from bromoethylenes [4]. However, in the literature we found no examples of this transformation wherein the substrate also contained an ester function. In our case, we found that treatment of bromoolefin **8a** with KF in DMF gives three products: isomer **8b**, the desired alkynylimidazol **3a** and, surprisingly, also ethynylimidazole **2**. The product ratios depend on reaction time and temperature. In general, a longer reaction time or higher temperature leads to a higher yield of ethynylimidazole **2** (Table 1, see Section 4) that suggests that formation of **2** is a result of decomposition of alkynylimidazole **3a**. Unfortunately, it is impossible to force

Table 1
Conditions vs. results for dehydrobromination of **8**

Starting compound	Reaction conditions			Product ratios			
	KF (eq.)	Temperature (°C)	Time (h)	**8a**	**8b**	**3a**	**2**
8a	2	125	15	47	44	9	Traces
8b	2	125	15	Traces	84	16	Traces
8a	10	80	40	26	73	1	0
8a	11	130	45	32	56	11	Traces
8b	9	140	14	Traces	63	16	21
8b	10	140	64	Traces	9	1	90

The preparative yield of **2** is about 25%.



Scheme 3. Preparation of fluoroolefins **12a** and **12b** from ethynylimidazole **2**.

the reaction to full conversion to **2**, and the separation of **3a** from **2** is difficult. Thus, this approach is not suitable for the preparation of either **2** or **3a**. This process nonetheless is intriguing because reported formation of propynes by decarbomethoxylation of methyl propynoates occurs only under condition of vacuum flash pyrolysis at 750 °C [5]. The fact that we observed no loss of the carbomethoxy group when alkynylimidazole **3b** was treated with KF suggests that HBr produced in an initial step may play an important role in loss of the carbomethoxy group.

With these largely negative results, we abandoned attempts to carry out direct conversion of *N*-tritylurocanate esters to the corresponding propynoates. Having a convenient method of preparation of ethynylimidazole **2** in hand, we used this as our source of imidazoylpropynoates. Treatment of **2** with butyllithium followed by reaction of the lithium salt with ethyl chloroformate produced **3b** in a yield of 71%. Reduction of ethyl ester **3b** with DIBAL-H produced the corresponding alcohol **4** (Scheme 3).

2.2. Introduction of fluorine

The most direct route to the target acids **1** would consist of HF addition to the triple bond of esters **3**. Indeed, facile HF addition to the triple bond of phenyl analogues by $Bu_4N^+H_2F_3^-$ gives the corresponding β-fluorocinnamates in high yields [6]. However, in the case of ester **3b** we observed destruction of starting material using published conditions [6] (120 °C, 4 h), and no reaction occurred at a lower reaction temperature (80 °C, 3 h).

We also explored the addition of an FBr equivalent to the triple bond of ester **3b** as a second approach to fluorine introduction. This addition to acetylenic compounds is known and typically gives products resulting from *anti* addition [7]. Reductive removal of bromine would provide a facile route to the target compounds. However, attempted ''FBr'' addition to ester **3b** gives no fluorinated products (^{19}F NMR). The lower reactivity of triple bonds in electrophilic reactions compared to olefins together with the electron-withdrawing effects of the carbonyl group obviously combines to block addition. This low reactivity can be overcome *via* using the authentic mixed halogen, FBr [8].

In contrast to the deactivated acetylenic ester **3b**, ''FBr'' addition to ethynylimidazole **2** occurs readily to produce the *E* adduct **9a** and *Z* adduct **9b** in a ratio of 96:4 (Scheme 1). We had hoped that lithiation of **9a** with BuLi followed by treatment with electrophiles (CO_2 or DMF) would produce the α-bromo-β-fluoropropenoic acid or aldehyde [9]. Subsequent reductive elimination of bromine would be provide a route to our target compounds. However, such reactions of bromofluoroalkene **9a** were unsuccessful. For example, the reaction of **9a** with *t*-BuLi followed by addition of DMF to the reaction mixture resulted in loss of both fluorine and bromine, and formation of aldehyde **10** and ethynylimidazole **2** (Scheme 1). Even under very short reaction times there were no traces of fluorinated compounds (^{19}F NMR), suggesting that no fluorinated intermediates capable of being intercepted are being formed. We are currently exploring substitution of bromine *via* transition metal catalyzed reactions of **9a** as an approach to the synthesis of imidazole-containing structures linked by the ethylene unit.

Turning next to a substrate that contains the necessary carbon skeleton, but is not deactivated by the ester function, we examined ''FBr'' addition to acetylenic alcohol **4**. We were pleased to find that addition occurs readily to give **11a**, the expected product of *trans* ''FBr'' addition, in 50% yield (Scheme 3). The bromine in **11a** was removed by Bu_3SnH reduction [10] to give a 2:3 mixture of the fluoropropenols **12a** [*E*-isomer] and **12b** [*Z*-isomer]. These are the same fluoropropenols we had prepared in our previous synthesis of β-fluorourocanic acids **1** [1]. Thus, the fluoropropenols **12a** and **12b** can be oxidized and deprotected to give the corresponding isomers of **1**, as we demonstrated in our previous work. The lack of stereochemical control in the reductive removal of bromine is actually very welcome because the isomers of **12** can be easily separated by chromatography and both isomers of β-fluorourocanic acids **1** thus can be prepared from a single precursor. In addition, the fluoropropenols **12** were key intermediates in the synthesis of β-fluoro- and β,β-difluoro-histidinols [11].

3. Summary

We have developed an alternative approach to the preparation of *E*- and *Z*-isomers of β-fluorourocanic acid. One advantage over the previous method [1] is that this approach overcomes the problem we experienced related to selectivity of "FBr" addition to the *cis* isomers of alkenes. Although this synthetic pathway has more steps than the previous one [1], the effort extended to make both isomers actually is less. This is because the same readily prepared starting compound can be used to make both isomers. From a practical point of view, we feel this is the superior approach. In addition, the work represents an alternative approach to other biologically important imidazoles, including β-fluorohistidinols. Finally, intermediates prepared in this work, such as the bromofluoroolefin **9a**, hold promise for additional synthetic applications. We are exploring these possibilities.

4. Experimental

The NMR spectra were recorded at frequencies of 300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282.2 MHz for ^{19}F spectra. The solvent is $CDCl_3$ unless otherwise specified. On selected carbons the interaction constants with hydrogen (J_{CH}), important for assignment, are given.

4.1. Preparation *2*, *5* and *6*

4.1.1. Procedure A

To a stirred solution of 250 mg (0.74 mmol) of vinylimidazole [3] in 8 ml of CH_2Cl_2 was added drop wise 38 μl (0.74 mmol) of bromine at 0 °C. After 15 min the light yellow solution was evaporated to dryness and crude dibromoimidazole **5** was obtained in quantitative yield. Dibromide **5** was suspended in a mixture of 20 ml of petroleum ether and 10 ml of 2-propanol and 502 mg (4.47 mol, 6 eq.) of *t*-BuOK was added. After 20 h of stirring at room temperature the mixture was evaporated to dryness and the resulting solid was partitioned between 20 ml of CH_2Cl_2 and a 1N aqueous solution of citric acid and brine. The organic portion was dried over $MgSO_4$ and evaporated to dryness. The solid that was obtained (287 mg) was separated by preparative TLC to give 48 mg (16%) of bromovinylimidazole **6** and 96 mg (39%) of ethynylimidazole **2**.

4.1.2. Procedure B

To a stirred solution of 250 mg (0.74 mmol) vinylimidazole [3] in 8 ml of CH_2Cl_2 was added by drop wise 38 μl (0.74 mmol) of bromine at 0 °C. After 15 min the light yellow solution was evaporated to dryness to give crude dibromoimidazole **5** in quantitative yield. Crude dibromide **5** suspended in a mixture of petroleum ether and isopropyl alcohol was treated with 6 eq. of *t*-BuOK at 40 °C for 3 h. The ethynylimidazole **2** was obtained in 84% yield as the only product.

4.2. 4-(Ethynyl)-1-trityl-1H-imidazole (*2*)

Melting point 186.5–187.0 °C. ^{1}H NMR: 7.40 (1H, d, 1.5), 7.36–7.30 (9H, m), 7.16–7.09 (6H, m), 7.08 (1H, d, 1.5), 3.03 (1H, s). ^{13}C NMR: 141.76 (3C, $\sum J_{CH}$ 18), 138.85 (J_{CH} 211.8 d, 7.1 d, $C2_{imi}$), 129.58 (6CH), 128.16 (3CH), 128.08 (6CH), 126.26 (J_{CH} 195.0 d, 8 m, $C5_{imi}$), 122.27 ($C4_{imi}$), 77.45 (J_{CH} 252.1 d, ≡CH), 77.44 (J_{CH} 50.5 d, –C≡), 75.66 (Tr). Anal. Calcd. for $C_{24}H_{18}N_2$: C, 86.20; H, 5.42; N, 8.38. Found: C, 85.79; H 5.60; N, 8.34.

4.3. 4-(1,2-Dibromoethyl)-1-trityl-1H-imidazole (*5*)

^{1}H NMR: 7.48 (1H, d, 1.5), 7.36–7.31 (9H, m), 7.16–7.10 (6H, m), 6.89 (1H, d, 1.2), 5.17 (1H, dd, 10.8, 4.8), 4.24 (1H, dd, 10.8, 9.9), 3.99 (1H, dd, 9.9, 4.8). ^{13}C NMR: 141.82 (3C), 139.34 ($C2_{imi}$), 137.96 ($C4_{imi}$), 129.65 (6CH), 128.19 (3CH), 128.08 (6CH), 120.61 ($C5_{imi}$), 75.66 (Tr), 44.54 (J_{CH} 160.7 d, CHBr), 34.40 (J_{CH} 158.4 t, CH_2Br). HRMS FAB^+ Calcd. for MH^+ e.i. $C_{24}H_{21}N_2Br_2$: 495.0071, 497.0053, 499.0037. Found: 495.0073, 497.0049, 499.0053.

4.4. 4-(1-Bromovinyl)-1-trityl-1H-imidazole (*6*)

^{1}H NMR: 7.43 (1H, d, 1.5), 7.37–7.31 (9H, m), 7.18–7.11 (6H, m), 7.04 (1H, d, 1.5), 6.50 (1H, d, 1.5), 5.45 (1H, d, 1.8). ^{13}C NMR: 141.98 (3C), 139.59 (J_{CH} 210.6 d, 7.5 d, $C2_{imi}$), 139.57 ($C4_{imi}$), 129.67 (6CH), 128.19 (3CH), 128.13 (6CH), 121.87 (J_{CH} 193.5 d, 3.3 d, $C5_{imi}$), 121.52 (J_{CH} 5.5 t, CBr), 114.15 (J_{CH} 166.8 d, 160.5 d, CH_2), 75.60 (Tr).

4.5. Preparation of *7*, *8a* and *8b*

To a solution of 5.67 g (14.4 mmol) of methyl urocanate [1] in 60 ml of CH_2Cl_2 was adding solution of bromine in CH_2Cl_2 (3 g in 10 ml) until an orange color persisted for 5 min. A small sample of the reaction mixture was evaporated to dryness to give a solid. The ^{1}H NMR of the solid showed that it was essentially pure dibromo adduct **7**. The sample was returned to the reaction mixture and 6 ml (43.0 mmol) of Et_3N was added. The mixture was stirred at room temperature for 3 days and then evaporated to dryness. Separation by column chromatography (100 g, CH_2Cl_2:Et_2O 1:0 → 8:2) gave 4.37 g (64%) of pure **8a** (*E*) and 0.58 g (9%) of pure **8b** (*Z*). All characteristics of compounds **7**, **8a** and **8b** were identical with values published previously [1].

4.6. (1-Trityl-1H-imidazol-4-yl)-propynoic acid methyl ester (*3a*)

4.6.1. Procedure A

To a solution of 100 mg (211 μmol) of **8a** in 5 ml of THF was added 105 μl (210 μmol) of LDA solution (2 M in heptane:THF:EtPh) at −68 °C. After 1 h, the mixture was allowed to warm to room temperature and after an additional

1 h evaporated to dryness. The resulting solid was partitioned between CH_2Cl_2 and brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The resulting solid was subjected to repeat preparative TLC to give a low yield (>10%) of **3a**.

4.6.2. Procedure B

To 854 mg (1.80 mmol) of **8b** dissolved in 25 ml of dry DMF was added 960 mg (16.5 mmol) of KF. The mixture was stirred at 140 °C for 15 h. Solvent was removed by evaporation and the residue was extracted with CH_2Cl_2. ^{1}H NMR indicated three compounds, **8b**, **3a** and **2**, in a ratio of 63:16:21. By repeated column chromatography (100 g, silica gel, petroleum ether:EtOAc 6:4) there was obtained **3a** in low yield (<15%). (For effects on variation of the reaction conditions on the dehydrobromination of **8a** and **8b** see Table 1.) ^{1}H NMR: 7.45 (1H, d, 1.2), 7.39–7.27 (10H, m), 7.16–7.10 (6H, m), 3.78 (3H, s). ^{13}C NMR: 154.42 (CO), 141.51 (3C), 139.87 ($C2_{imi}$), 129.97 ($C5_{imi}$), 129.60 (6CH), 128.42 (3CH), 128.27 (6CH), 120.32 ($C4_{imi}$) 81.51 (CC), 81.36 (CC), 76.15 (Tr), 52.60 (CH_3). HRMS DCI$^+$ Calcd. for M^+ e.i. $C_{26}H_{20}N_2O_2$: 392.1525. Found: 392.1518.

4.7. (1-Trityl-1H-imidazol-4-yl)-propynoic acid ethyl ester (3b)

To a stirred solution of ethynylimidazole **2** (0.75 g, 2.24 mmol) in 60 ml of THF at −65 °C was added a solution of *n*-BuLi (1.6 M in hexane, 2.1 ml, 3.36 mmol). After 30 min ethyl chloroformate (0.33 ml, 3.45 mmol) was added and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was evaporated to dryness and the resulting solid was separated by column chromatography (10 g silica gel, CH_2Cl_2:Et_2O 9:1) to give 0.65 g (71%) of **3b**. Melting point 212–215 °C (from petrol ether). ^{1}H NMR: 7.45 (1H, d, 1.4), 7.38–7.28 (10H, m), 7.16–7.09 (6H, m), 4.24 (2H, q, 7.2), 1.30 (3H, t, 7.2). ^{13}C NMR: 153.93 (CO), 141.50 (3C, Tr), 139.78 ($C2_{imi}$), 129.81 ($C5_{imi}$), 129.55 (6CH), 128.37 (3CH), 128.22 (6CH), 120.37 ($C4_{imi}$), 81.65 (C=), 80.95 (C=), 76.08 (Tr), 61.77 (CH_2), 13.99 (CH_3). HRMS DCI$^+$ Calcd. for M^+ e.i. $C_{27}H_{22}N_2O_2$: 406.1681. Found: 406.1669.

4.8. 3-(1-Trityl-1H-imidazol-4-yl)-prop-2-yn-1-ol (4)

To solution of 390 mg of **3b** (0.96 mmol) in 60 ml of CH_2Cl_2 was added 5 ml of DIBAL-H (1.0 M in THF, 5 mmol) at −65 °C. The reaction was stirred for 4 h at the same temperature. Then 20 ml of aqueous solution NH_4Cl was added, the mixture was allowed to warm to room temperature and was partitioned between CH_2Cl_2 and water with brine. The organic fraction was dried over $MgSO_4$ and evaporated to dryness. The resulting solid was separated by column chromatography (20 g silica gel, CH_2Cl_2:Et_2O 99:1 → 0:1) to give 215 mg (61%) of propynol **4**. ^{1}H NMR: 7.40 (1H, d, 1.4), 7.37–7.31 (9H, m), 7.15–7.09 (6H, m), 7.02 (1H, d, 1.4), 4.45 (2H, br d, 4.9, CH_2), 2.00 (1H, br t, 4.9, OH).

4.9. (Z)-4-(2-Bromo-1-fluoroethenyl)-1-trityl-1H-imidazole (9a)

To a stirred solution of 999 mg (2.99 mmol) of ethynylimidazole **2** and 750 μl (4.60 mmol) of $Et_3N{\cdot}3HF$ in 20 ml of CH_2Cl_2 was added 585 mg (3.28 mmol) of NBS at 0 °C. After 30 min, the mixture was allowed to come to room temperature and stirred an additional 2 h. The mixture was then partitioned between CH_2Cl_2 and water/brine. The organic fraction was dried over $MgSO_4$ and evaporated to dryness. The solid that was obtained (1.233 g) was separated by column chromatography (100 g silica gel, CH_2Cl_2 → CH_2Cl_2:Et_2O 100:1) and to give 817 mg (63%) of *Z*-fluorobromoimidazole **9a**, 99 mg (10%) of starting ethynylimidazole **2**, and 37 mg (3%) of *E*-fluorobromoimidazole **9b**[3]. Attempts to recrystalization of **9a** from methanol led to loss of trityl group to give unprotected derivative **13** together with tritylmethylether. The unprotected derivative **13** was re-tritylated to **9a** under the usual conditions.

4.10. (Z)-4-(2-Bromo-1-fluoroethenyl)-1-trityl-1H-imidazole (9a)

Melting point 139 °C (decomp.). ^{1}H NMR: 7.53 (1H, t, 1.4), 7.45 (1H, d, 1.5), 7.36–7.32 (9H, m), 7.17–7.10 (6H, m), 6.06 (1H, d, 15.4). ^{13}C NMR: 153.78 (d, 243.0, CF), 141.78 (3C), 139.13 (d, 0.9, $C2_{imi}$), 131.66 (d, 33.1, $C4_{imi}$), 129.60 (6CH), 128.23 (3CH), 128.13 (6CH), 123.34 (d, 5.9, $C5_{imi}$), 84.73 (d, 51.7, CHBr), 75.82 (Tr). ^{19}F NMR: −107.5 (d, 15.4). Anal. Calcd. for $C_{24}H_{18}BrFN_2$: C, 66.52; H, 4.19; N, 6.46. Found: C, 67.30; H, 4.18; N, 6.49.

4.11. (Z)-4-(2-Bromo-1-fluoroethenyl)-1H-imidazole (13)

^{1}H NMR (CD_3OD): 7.82 (1H, s), 7.79 (1H, s), 6.30 (1H, d, 15.0).

4.12. 3-(1-Trityl-1H-imidazol-4-yl)propynal (10)

Bromofluoroolefin **9a** (179 mg, 413 μmol) was dissolved in 16 ml of dry THF and chilled to −65 °C and 1.7 M *t*-BuLi in pentane (0.41 ml, 697 μmol) was added dropwise. After 5 min 0.6 ml of DMF (7.75 mmol) in 2 ml of dry THF was added. After 10 min was mixture allowed to warm to room temperature and then kept at this temperature for 1 h. The reaction mixture was partitioned between water and CH_2Cl_2, the organic layer part was separated and evaporated to dryness. The residue was subjected to preparative TLC (CH_2Cl_2:Et_2O 95:5) to give 60 mg (34%) of starting olefin **9a** and 79 mg of a mixture of ethynylimidazole **2** and aldehyde **10** in ratio of about 1:1. This mixture was separated on by a second preparative TLC (CH_2Cl_2:Et_2O 95:5) to give a low yield (<20% based on ^{1}H NMR) of aldehyde **10**.

^{1}H NMR: 9.36 (1H, s), 7.50 (1H, d, 1.5), 7.40–7.32 (10H, m), 7.14–7.07 (6H, m). ^{13}C NMR: 176.27 (J_{CH} 192.7 d, CHO), 141.40 (3C, J_{CH} 17 m), 140.40 (J_{CH} 213.4 d, 7.3 d, $C2_{Imi}$), 130.86 (J_{CH} 190.8 d, 3.7 d, $C5_{Imi}$), 129.55 (6CH), 128.40 (3CH), 128.30 (6CH), 120.16 (J_{CH} 13.0 d, 8.5 d), 90.48 (J_{CH} 5.7 d), 90.33 (J_{CH} 32.3 d), 76.36. HRMS DCI$^+$ Calcd. for M^+ e.i. $C_{25}H_{18}N_2O$: 362.1419. Found: 362.1425.

*4.13. E-2-Bromo-3-fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**11a**)*

The same procedure described for the preparation of **9** was used, employing 100 mg (274 μmol) of alcohol **4**, 70 μl (429 μmol) of $Et_3N{\cdot}3HF$, 54 mg (303 μmol) of NBS and 4 ml of CH_2Cl_2. The crude product was separated on preparative TLC (CH_2Cl_2:Et_2O 3:2) to give the FBr-adduct **11a** (63 mg, 50%) as a waxy white solid. No formation of *Z*-isomer **11b** was observed. ^{1}H NMR: 9.58 (1H, br s), 7.52 (1H, dd, 1.4, 1.0), 7.47 (1H, d, 1.4), 7.37–7.31 (9H, m), 7.17–7.10 (6H, m), 4.56 (2H, d, 4.1). ^{13}C NMR: 149.99 (d, 246.4, J_{CH} 3.1 t, CF), 141.71 (3C), 138.91 (J_{CH} 212.8 d, 7.4 d, $C2_{imi}$), 131.56 (d, 32.8, $C4_{imi}$), 129.61 (6CH), 128.28 (3CH), 128.18 (6CH), 124.3 (d, 6.6, J_{CH} 196.0 d, 12.9 m, $C5_{imi}$), 106.46 (d, 38.3, J_{CH} 2.8 t, =CBr–), 75.93 (Tr), 61.24 (d, 6.9, J_{CH} 147.2 t, CH_2OH). ^{19}F NMR: −106.7 (t, 4.1). HRMS FAB$^+$ Calcd. for MH^+ e.i. $C_{26}H_{23}BrFN_2O_2$: 493.0927, 495.0906. Found: 493.0935, 495.0931.

*4.14. E- and Z-3-Fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**12a** and **12b**)*

A pressure tube containing 63 mg (0.14 mmol) of FBr-adduct **11a**, 44 μl (0.16 mmol) of Bu_3SnH, 4 ml of dry benzene, and 1 mg (7 μmol) of 1,1′-azobis(cyclohexanecarbonitrile) were placed under N_2 and warmed in an oil bath at 90 °C for 2.5 h. A small sample of the mixture (0.1 ml) was evaporated to dryness and ^{1}H and ^{19}F NMR indicated four fluorinated compounds **11a**:**11b**:**12a**:**12b** in a ratio 83:10:1:6. The mixture was stirred additional 9 h at 110 °C, after which time the NMR spectrum indicated full conversion of **11a** (and formed **11b**). After evaporation to dryness there was obtained 11 mg (21%) of **12a** and 17 mg (33%) of **12b**, isolated by preparative TLC (CH_2Cl_2:Et_2O 7:3). Physical and spectral data of **12a** and **12b** were identical to the values for **19a** and **19b**, respectively, prepared and reported in our previously published work [1]. Evidence for the formation of the *Z*-isomer **11b** is based only on a signal at −108.0 ppm (t, 4.5) in ^{19}F NMR spectrum.

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