Stereoselective synthesis of 1-bromo-1-fluorostyrenes

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DOI: 10.1070/MC2006v016n03ABEH002282

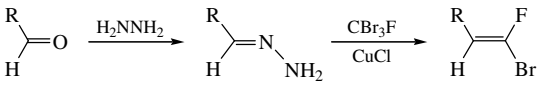
The effective and stereoselective one-pot synthesis of 1-bromo-1-fluorostyrenes from aromatic aldehydes based on a catalytic olefination reaction was elaborated.

Organofluorine compounds are of interest due to their biological activity.[1] For example, monofluorostilbenes ArCH=CFAr are the analogues of the natural polyhydroxylated stilbene resveratrol and are very interesting as potential enzyme inhibitors.[2] An approach to the synthesis of such stilbenes is the palladium-catalysed cross-coupling reaction of 1-bromo-1-fluorostyrenes with organoboron and organotin compounds.[3] The general methods for the synthesis of 1-bromo-1-fluorostyrenes include the decarboxylation of 2,3-dibromo-2-fluoro-3-arylpropanoic acids,[4] modifications of Wittig reaction[2,5–7] and a method suggested by Hiyama[8] who used $LiCFBr_2$ and carbonyl compounds.

We propose a new reaction of the catalytic olefination of carbonyl compounds.[9] It was found that N-unsubstituted hydrazones of carbonyl compounds can be converted to the corresponding olefins when treated with polyhaloalkanes in the presence of a catalytic amount of CuCl.

This reaction was used for the synthesis of 1-bromo-1-fluorostyrenes. Hydrazone of 4-nitrobenzaldehyde was used as the model substrate to find optimum reaction conditions. The highest yields of the target alkenes were obtained when ethanol was used as the solvent and ethylenediamine was used as the base, like in the synthesis of alkenes from Freons.[10] It is sufficient to use 1.5 equiv. of CBr_3F and 1 mol% CuCl. The high activity of this compound compared to CCl_4 is in agreement with quantum calculation global electrofilicity index for CBr_3F (the measure of polyhaloalkane olefination activity[11]) and with experimental data. Competitive reactions of 4-chlorobenzaldehyde hydrazone with a mixture of CCl_4 and CBr_3F give corresponding 1-bromo-1-fluorostyrene and 1,1-dichlorostyrene in a 5.9:1 ratio.

Under optimal reaction conditions, we investigated conversion of aromatic aldehydes **1** containing electron-donating and electron-withdrawing groups (one-pot method[12]) into 1-bromo-1-fluorostyrenes. We found that the reaction products can be prepared in high yields (Scheme 1, Table 1).†



1 **2** **3**

Scheme 1

Table 1 Synthesis of 1-bromo-1-fluorostyrenes **3a–m**.

Compound	R	Yield of alkenes **3** (%)	E/Z
3a	4-$NO_2C_6H_4$	87	3.5
3b	2-$NO_2C_6H_4$	86	3.3
3c	4-ClC_6H_4	86	6
3d	2-ClC_6H_4	86	4
3e	4-BrC_6H_4	85	5
3f	2-BrC_6H_4	85	4
3g	4-IC_6H_4	86	4
3h	4-MeC_6H_4	90	5.5
3i	4-$MeOC_6H_4$	85	5
3j	4-$MeO_2CC_6H_4$	95	3.5
3k	3,4-$(MeO)_2C_6H_3$	60	4.5
3l	2-Py	95	1.8
3m	2,6-$Cl_2C_6H_3$	48	21

Note that the reaction proceeds stereoselectively and the most unhindered (*E*)-isomer is obtained: for example, in the case of

† IR spectra were recorded on a UR 20 spectrophotometer (Nujol). ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. TLC was carried out with Merck 60 F254 plates; Merck silica gel (63–200 mesh) was used for column chromatography.

Synthesis of bromofluorostyrenes (general procedure). A solution of 2 mmol of the corresponding aldehyde in 8 ml of ethanol was added dropwise to the solution of 0.11 ml (2.1 mmol) of hydrazine hydrate in 4 ml of ethanol with intense stirring. After completion of hydrazone formation (TLC monitoring), 0.2 ml (1.5 equiv.) of ethylenediamine and 0.002 g (1 mol%) of CuCl were added. The reaction mixture was cooled to 0 °C and 0.3 ml (1.5 equiv.) of CBr_3F was added dropwise with stirring. The reaction mixture was stirred for 4–48 h at room temperature to the completion (TLC monitoring) and 50 ml of a 5% aqueous HCl solution was added (in the cases of pyridine-2-carbaldehyde, only water was added). The reaction products were extracted with CH_2Cl_2 (3×30 ml) and the extract was dried with Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on SiO_2 (hexane–CH_2Cl_2 mixture as an eluent). The (*E*)- and (*Z*)-alkene isomers cannot be separated by column chromatography.

^1H NMR spectra of compounds **3a**,**b**,**e**,**i**,**j**,[6] **3c**,[4(a)] **3d**[7] are in agreement with published data.

1-(2-Bromo-2-fluorovinyl)-2-bromobenzene **3f**: colourless oil, obtained as a mixture of *Z*/*E* isomers, 1:4. IR (ν/cm^{-1}): 1650 (C=C). (*E*)-isomer: ^1H NMR ($CDCl_3$) δ: 6.41 (d, 1H, ArC*H*=C, $^3J_{HF}$ 31.69 Hz), 7.16 (t, 1H, CH-5, ^3J 7.83 Hz), 7.33 (t, 1H, CH-4, ^3J 7.83 Hz), 7.60 (d, 1H, CH-6, ^3J 7.83 Hz), 7.68 (d, 1H, CH-3, ^3J 7.83 Hz). ^{13}C NMR ($CDCl_3$) δ: 111.86 (d, Ar*C*H=C, ^2J 5.13 Hz), 127.60 (C-5), 129.27 (C-4), 130.02 (C-2), 130.34 (d, C-6, J 2.19 Hz), 132.2 (d, C-1, ^3J 5.12 Hz), 132.91 (C-3), 135.32 (d, C–F, ^1J 331.5 Hz). (*Z*)-isomer: ^1H NMR ($CDCl_3$) δ: 6.78 (d, 1H, ArC*H*=C, $^3J_{HF}$ 13.69 Hz), 7.21 (t, 1H, CH-5, ^3J 8.21 Hz). Other signals are identical to those for (*E*)-isomer. ^{13}C NMR ($CDCl_3$) δ: 111.69 (d, Ar*C*H=C, ^2J 25.62 Hz), 127.23 (C-5), 129.56 (C-4), 132.68 (C-3), 137.17 (d, C–F, ^1J 317.0 Hz). Other signals are identical to those for (*E*)-isomer. Found (%): C, 34.20; H, 1.70; Calc. for $C_8H_5Br_2F$ (%): C, 34.32; H, 1.80.

1-(2-Bromo-2-fluorovinyl)-4-iodobenzene **3g**: yellowish crystals, obtained as a mixture of *Z*/*E* isomers, 1:4. IR (ν/cm^{-1}): 1650 (C=C). (*E*)-isomer: ^1H NMR ($CDCl_3$) δ: 5.93 (d, 1H, ArC*H*=C, $^3J_{HF}$ 32.47 Hz), 7.15 (d, 2H, CH-3,5, ^3J 8.22 Hz), 7.69 (d, 2H, CH-2,6, ^3J 8.22 Hz). ^{13}C NMR ($CDCl_3$) δ: 93.53 (C-4), 112.27 (d, Ar*C*H=C, ^2J 5.85 Hz), 129.67 (d, C-2,6, ^4J 7.32 Hz), 131.96 (d, C-1, ^3J 4.39 Hz), 134.62 (d, C–F, ^1J 332.2 Hz), 137.85 (C-3,5). (*Z*)-isomer: ^1H NMR ($CDCl_3$) δ: 6.60 (d, 1H, ArC*H*=C, $^3J_{HF}$ 14.67 Hz) 7.24 (d, 2H, CH-3,5, ^3J 8.61 Hz) 7.71 (d, 2H, CH-2,6, ^3J 8.61 Hz). ^{13}C NMR ($CDCl_3$) δ: 110.97 (d, Ar*C*H=C, ^2J 24.88 Hz), 130.09 (d, C-2,6, ^4J 3.66 Hz), 137.63 (C-3,5). Other signals are identical to those for (*E*)-isomer. Found (%): C, 29.55; H, 1.63. Calc. for C_8H_5BrFI (%): C, 29.39; H, 1.54.

1-(2-Bromo-2-fluorovinyl)-4-methylbenzene **3h**: colourless oil, obtained as a mixture of *Z*/*E* isomers, 1:5.5. IR (ν/cm^{-1}): 1650 (C=C). (*E*)-isomer: ^1H NMR ($CDCl_3$) δ: 2.40 (s, 3H, Me), 6.0 (d, 1H, ArC*H*=C, $^3J_{HF}$ 33.06 Hz), 7.21 (d, 2H, CH-3,5, ^3J 8.02 Hz), 7.35 (d, 2H, CH-2,6, ^3J 8.02 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.37 (Me), 113.12 (d, Ar*C*H=C, ^2J 6.59 Hz), 128.10 (d, C-2,6, ^4J 7.32 Hz), 129.50 (C-3,5), 129.86 (d, C-1, ^3J 4.39 Hz), 133.29 (d, C–F, ^1J 330.06 Hz), 137.93 (d, C-4, ^6J 2.19 Hz). (*Z*)-isomer: ^1H NMR ($CDCl_3$) δ: 2.41 (s, 3H, Me), 6.68 (d, 1H, ArC*H*=C, $^3J_{HF}$ 15.26 Hz), 7.23 (d, 2H, CH-3,5, ^3J 8.22 Hz), 7.44 (d, 2H, CH-2,6, ^3J 8.22 Hz). ^{13}C NMR ($CDCl_3$) δ: 111.67 (d, Ar*C*H=C, ^2J 23.42 Hz), 128.39 (d, C-2,6, ^4J 2.93 Hz), 129.29 (C-3,5), 134.47 (d, C–F, ^1J 314.70 Hz), 138.05 (C-4). Other signals are identical to those for (*E*)-isomer. Found (%): C, 50.38; H, 3.84. Calc. for C_9H_8BrF (%): C, 50.26; H, 3.75.

2,6-dichlorobenzaldehyde, the amount of a minor isomer is less than 5%. It is in good agreement with the earlier proposed reaction mechanism.[10,12] It was shown previously that the formation of the most unhindered isomer is preferable. High *E*/*Z* ratio of isomers is a significant advantage of our approach to 1-bromo-1-fluorostyrenes in comparison with the Wittig reaction. In the case of CBr_3F, Wittig olefination proceeds nonstereoselectively to give target alkenes as a mixture of almost equal amounts of (*E*)- and (*Z*)-isomers.[2,5–7] Moreover, an inert atmosphere and an excess of phosphorus or organometallic compounds are not required for the catalytic olefination.

Thus, we elaborated a new stereoselective one-pot method for the synthesis of 1-bromo-1-fluorostyrenes using commercially available starting materials. The target alkenes are formed in high yields and stereoselectively.

This work was supported by the Russian Foundation for Basic Research (project nos. 03-03-32052a and 06-03-32303) and the Russian Science Support Foundation.

1-(2-Bromo-2-fluorovinyl)-3,4-dimethoxybenzene **3k**: colourless oil, obtained as a mixture of *Z*/*E* isomers, 1:4.5. IR (ν/cm^{-1}): 1650 (C=C). (*E*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 3H, MeO), 3.88 (s, 3H, MeO), 5.90 (d, 1H, ArC*H*=C, $^3J_{HF}$ 33.06 Hz), 6.81 (d, 1H, CH-5, ^3J 8.21 Hz), 6.92 (dd, 1H, CH-6, ^3J 8.21 Hz, ^4J 1.96 Hz), 6.97 (d, 1H, CH-2, ^4J 1.96 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.77 (2MeO), 110.93 (C-2), 111.03 (d, Ar*C*H=C, ^2J 5.13 Hz), 112.75 (d, C-6, ^4J 5.89 Hz), 121.47 (d, C-5, ^5J 6.59 Hz), 125.44 (d, C-1, ^3J 4.39 Hz), 132.32 (d, C–F, ^1J 329.34 Hz), 148.79 (C-4), 148.84 (C-3). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H, MeO), 3.89 (s, 3H, MeO), 6.60 (d, 1H, ArC*H*=C, $^3J_{HF}$ 15.46 Hz), 6.85 (d, 1H, CH-5, ^3J 8.42 Hz), 7.02 (dd, 1H, CH-6, ^3J 8.42 Hz, ^4J 1.96 Hz), 7.08 (d, 1H, CH-2, ^4J 1.96 Hz). ^{13}C NMR ($CDCl_3$) δ: 121.47 (d, C-5, ^5J 3.66 Hz), 123.82 (d, C-1, ^3J 8.05 Hz), 133.67 (d, C–F, ^1J 313.96 Hz), 148.71 (*C*–OMe). Other signals are identical to those for (*E*)-isomer. Found (%): C, 45.85; H, 3.78. Calc. for $C_{10}H_{10}O_2BrF$ (%): C, 46.00; H, 3.86.

2-(2-Bromo-2-fluorovinyl)pyridine **3l**: colourless oil, obtained as a mixture of *Z*/*E* isomers, 1:1.8. IR (ν/cm^{-1}): 1650 (C=C). (*E*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 6.20 (d, 1H, PyC*H*=C, $^3J_{HF}$ 32.47 Hz), 7.06–7.09 (m, 1H, CH-5), 7.46 (d, 1H, CH-3, ^3J 8.02 Hz), 7.55–7.60 (m, 1H, CH-4), 8.48–8.49 (m, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ: 114.51 (d, Py*C*H=C, ^2J 4.59 Hz), 122.21 (C-5), 123.23 (d, C-3, ^3J 11.71 Hz), 136.48 (C-4), 137.13 (d, C–F, ^1J 332.99 Hz), 149.46 (C-6), 151.66 (d, C-2, ^3J 5.86 Hz). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 6.74 (d, 1H, ArC*H*=C, $^3J_{HF}$ 15.06 Hz), 7.09–7.12 (m, 1H, CH-5), 7.53 (d, 1H, CH-3, ^3J 8.02 Hz), 7.57–7.61 (m, 1H, CH-4), 8.52–8.54 (m, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ: 112.54 (d, Py*C*H=C, ^2J 24.15 Hz), 122.39 (C-5), 123.07 (d, C-3, ^3J 3.66 Hz), 136.11 (C-4), 135.78 (d, C–F, ^1J 318.35 Hz), 149.54 (C-6), 151.27 (d, C-2, ^3J 12.44 Hz). Found (%): C, 41.83; H, 2.62. Calc. for C_7H_5NBrF (%): C, 41.62; H, 2.49.

1-(2-Bromo-2-fluorovinyl)-2,6-dichlorobenzene **3m**: colourless oil, obtained as a mixture of *Z*/*E* isomers, 1:21. IR (ν/cm^{-1}): 1660 (C=C). (*E*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 6.09 (d, 1H, ArC*H*=C, $^3J_{HF}$ 31.35 Hz), 7.22 (t, 1H, CH-4, ^3J 8.21 Hz), 7.36 (d, 2H, CH-3,5, ^3J 8.21 Hz). ^{13}C NMR ($CDCl_3$) δ: 107.69 (d, Ar*C*H=C, ^2J 11 Hz), 128.01 (C-3,5), 129.68 (C-4), 129.99 (C-1), 134.99 (C-2,6), 135.2 (d, C–F, ^1J 330.06 Hz). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$) δ: 6.52 (d, ArC*H*=C, $^3J_{HF}$ 10.0 Hz). Other signals are identical to those for (*E*)-isomer. All ^{13}C NMR signals are identical to those for (*E*)-isomer. Found (%): C, 35.74; H, 1.55. Calc. for $C_8H_4BrCl_2F$ (%): C, 35.60; H, 1.49.

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Received: 29th November 2005; Com. 05/2624