5-*endo*-Trigonal cyclization of *o*-substituted *gem*-difluorostyrenes: syntheses of 2-fluorinated indoles, benzo[*b*]furans and benzo[*b*]thiophenes

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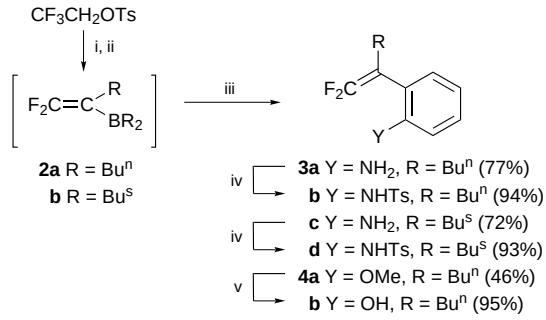
β,β-Difluorostyrenes bearing tosylamido, hydroxy or methylsulfinyl groups at the *o*-position undergo intramolecular substitution of the nitrogen, oxygen or sulfur with loss of fluorine *via* a 5-*endo*-trigonal process leading to 2-fluorinated heterocyclic systems in high yields.

gem-Difluoroalkenes possess remarkable reactivity toward nucleophilic substitution for their fluorine atoms *via* addition–elimination processes.[1] This reactivity is due to (i) the electrophilic activation of the carbon–carbon double bond by the two fluorines and (ii) the leaving-group ability of the fluoride ion. This chemical reactivity renders these alkenes valuable as synthetic building blocks[2] as well as mechanism-based enzyme inhibitors.[3] We have recently reported the reactions of 2,2-difluorovinyl ketones with external nucleophiles leading to facile syntheses of α,β-unsaturated ketones,[4] α-oxo ketene derivatives[5] and 3- or 5-fluoropyrazoles.[6] Our interest in the further application of *gem*-difluoroalkene chemistry led us to explore an intramolecular version of such vinylic fluorine substitution reactions. Here we report the construction of ring-fluorinated heterocyclic systems starting from *o*-substituted β,β-difluorostyrenes.[7]

β,β-Difluorostyrenes **1** bearing nucleophilic *ortho* nitrogen, oxygen or sulfur heteroatoms were designed as substrates for the intramolecular substitution. We sought to effect the 5-*endo*-trigonal ring closure of **1** to afford 5-membered 2-fluoro heterocycles despite this cyclization being disfavoured in Baldwin's rules.[8] Among 5-*endo*-trigonal cyclizations, such nucleophile-driven ring closures have only rarely been observed in synthetic chemistry,[9] in contrast with electrophile-driven[10]‡ and radical-initiated ring closures.[11] We expected that the unique properties of *gem*-difluoroalkenes could make a nucleophilic approach feasible. Specifically, we thought that (i) the highly polarized difluorovinylidene alkenic bond displays significant single bond character (^{13}C NMR: *ca.* δ 150 and 90 for CF_2=C) and would allow initial ring formation, and (ii) the successive elimination of fluoride ion could suppress the reverse ring opening. Such a process would provide an efficient access to 2-fluorinated indoles, benzo[*b*]furans, and benzo[*b*]-thiophenes, of which synthetic methods are quite limited in spite of the potential uses of 2-fluoro heterocycles as components of agrochemicals, pharmaceuticals and dyestuffs.[12] On the basis of these considerations, we investigated the cyclization of **1**.

The starting materials were easily prepared as outlined in Scheme 1 by using the one-pot sequence which we have previously developed for the preparation of *gem*-difluorostyrenes.[13] The coupling reactions of 2,2-difluorovinylboranes **2a** and **2b** (generated *in situ* from 2,2,2-trifluoroethyl toluene-*p*-sulfonate) with *N*-butylmagnesio-*o*-iodoaniline were effected in the presence of CuI with palladium catalysis to prepare *o*-amino-β,β-difluorostyrenes **3a** and **3c** as precursors of 2-fluoroindoles. *o*-Hydroxy-β,β-difluorostyrene **4b**, a precursor of 2-fluorobenzo[*b*]furan, was similarly obtained by the coupling of **2a** with *o*-iodoanisole, followed by demethylation with BBr_3.

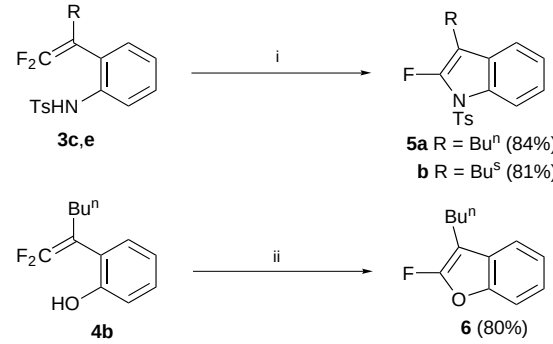
The attempted cyclization of **3a** by treatment with 1.2 equiv. of Bu^{n}Li failed, while treatment of toluene-*p*-sulfonamide **3b** with 1.2 equiv. of NaH in DMF successfully promoted the



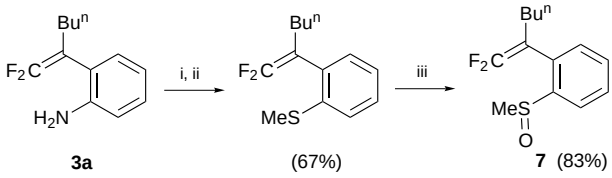
Scheme 1 *Reagents and conditions*: i, Bu^{n}Li (2.1 equiv.), THF, −78 °C, 0.5 h; ii, BR_3 (1.1 equiv.), THF, −78 °C, 1 h then room temp., 3 h; iii, ArI (0.9 equiv.), CuI (1.0 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (0.02 equiv.), PPh_3 (0.08 equiv.), THF–HMPA (4 : 1), room temp. 1 h; iv, TsCl (1.1 equiv.), pyridine, 0 °C to room temp., 11 h; v, BBr_3 (1.1 equiv.), CH_2Cl_2, −15 °C to room temp., 2 h

'disfavoured' 5-*endo*-trigonal cyclization to afford 2-fluoroindole **5a** in 84% yield (Scheme 2).[14]§ Successful ring closure did not necessitate the use of high-dilution conditions, and proceeded smoothly even in the case of the starting styrene **3d** which bore a secondary alkyl group at the α-position. Moreover, when the hydroxystyrene **4b** was treated under similar conditions, 5-*endo*-trigonal cyclization of the corresponding alkoxide occurred leading to 2-fluorobenzo[*b*]furan **6** in 80% yield (Scheme 2).[15]¶

As a further example of the cyclization we next tried the intramolecular substitution utilizing a sulfur nucleophile. For the purposes of generating a thiolate moiety, the methlysulfinyl group was selected as an *ortho* substituent of β,β-difluorostyrene. The Pummerer rearrangement of *o*-methylsulfinyl-β,β-difluorostyrene **7** followed by solvolysis would allow the cyclization *via* the unisolated intermediate, hemiacetal trifluoroacetate **8**.[16] Thus, **7** was readily derived from **3a** *via* diazotization as depicted in Scheme 3. Successive treatment of **7** with (i) trifluoroacetic anhydride and Et_3N and (ii) K_2CO_3 in MeOH provided 2-fluorobenzo[*b*]thiophene **9** in 82% yield as expected (Scheme 4).[17]‖

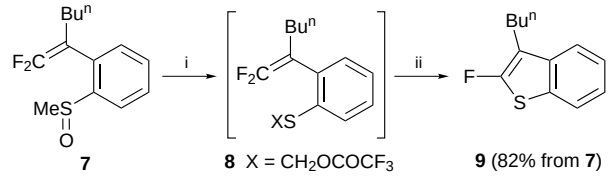


Scheme 2 *Reagents and conditions*: i, NaH (1.2 equiv.), DMF, 80 °C, 7 h; ii, NaH (1.2 equiv.), DMF, 0 to 60 °C, 2 h



3a (67%) **7** (83%)

Scheme 3 *Reagents and conditions*: i, CF_3CO_2H (2 equiv.), $Me_2CHCH_2CH_2ONO$ (2 equiv.), MeCN, 0 °C, 0.5 h; ii, aq. NaSMe (3 equiv.), MeCN, 0 °C to room temp., 1.5 h; iii, aq. $TiCl_3$ (2 equiv.), aq. H_2O_2 (3 equiv.), MeOH–H_2O, room temp., 2 h



7 **8** X = CH_2OCOCF_3 **9** (82% from **7**)

Scheme 4 *Reagents and conditions*: i, $(CF_3CO)_2O$ (3 equiv.), Et_3N (3 equiv.), CH_2Cl_2, 0 °C, 0.5 h; ii, K_2CO_3 (6 equiv.), MeOH, 0 °C to reflux, 2 h

In conclusion, nucleophilic addition–elimination reactions with the β,β-difluorovinylidene moiety allows normally 'disfavoured' 5-*endo*-trigonal cyclizations to occur. This cyclization process affords ring-fluorinated indoles, benzo[*b*]furans, and benzo[*b*]thiophenes in high yields. These 'anti-Baldwin' results indicate that some of the unique reactivity of *gem*-difluoroalkenes may be derived from a partial single bond character of the alkene.

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Footnotes and References

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‡ Electrophile-driven cyclizations refer to ring closure initiated by the coordination of the double bond in a substrate to an external electrophile such as I_2 and PhSeCl. Strictly speaking, this type of cyclization does not seem likely to be an exception to Baldwin's rules.

§ **5a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* 7.4 Hz), 1.21 (2H, tq, *J* 7.4, 7.4 Hz), 1.53 (2H, tt, *J* 7.4, 7.4 Hz), 2.34 (3H, s), 2.52 (2H, td, *J* 7.4 Hz, J_{HF} 0.8 Hz), 7.20 (2H, d, *J* 8.4 Hz), 7.23 (1H, ddd, *J* 7.7, 7.7, 1.2 Hz), 7.28 (1H, ddd, *J* 7.7, 7.7, 1.4 Hz), 7.33 (1H, dd, *J* 7.7, 1.2 Hz), 7.73 (2H, d, *J* 8.4 Hz), 8.08 (1H, d, *J* 7.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.6, 21.3 (d, J_{CF} 3 Hz), 21.5, 22.1, 30.5, 99.7 (d, J_{CF} 11 Hz), 114.4, 118.9 (d, J_{CF} 7 Hz), 124.0, 124.0 (d, J_{CF} 4 Hz), 126.8, 128.1 (d, J_{CF} 6 Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, J_{CF} 276 Hz). ^{19}F NMR (470 MHz, $CDCl_3$–C_6F_6): δ 29.1 (1F, s). ν_{max}(neat)/cm^{-1} 2960, 2930, 2860, 1660, 1455, 1395, 1190, 1180, 745, 690, 665. *m/z* (20 eV) 345 (M^+, 100%), 190 (68), 148 (92). HRMS: calc. for $C_{19}H_{20}O_2SNF$, 345.1199 (M^+). Found, 345.1188.

¶ *Selected data* for **6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* 7.4 Hz), 1.39 (2H, tq, *J* 7.4, 7.4 Hz), 1.66 (2H, tt, *J* 7.4, 7.4 Hz), 2.57 (2H, td, *J* 7.4 Hz, J_{HF} 1.0 Hz), 7.19–7.25 (2H, m), 7.32–7.36 (1H, m), 7.40–7.45 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.8, 21.0 (d, J_{CF} 3 Hz), 22.4, 30.7 (d, J_{CF} 2 Hz), 90.6 (d, J_{CF} 12 Hz), 110.8, 119.2 (d, J_{CF} 6 Hz), 123.1 (d, J_{CF} 4 Hz), 123.2, 129.3 (d, J_{CF} 3 Hz), 147.1, 157.1 (d, J_{CF} 278 Hz). ^{19}F NMR (470 MHz, $CDCl_3$–C_6F_6): δ 42.0 (1F, s). ν_{max} (neat)/cm^{-1} 2960, 2940, 2860, 1675, 1455, 1380, 1295, 1260, 1185, 1140, 740. *m/z* (20 eV) 192 (M^+, 43%), 149 (100). HRMS: calc. for $C_{12}H_{13}OF$, 192.0950 (M^+). Found, 192.0918.

‖ This formation of benzothiophenes is favoured by Baldwin's rules since second-row elements are permitted 5-*endo*-trigonal processes [ref. 8(*b*)]. *Selected data* for **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* 7.5 Hz), 1.39 (2H, tq, *J* 7.5, 7.5 Hz), 1.64 (2H, tt, *J* 7.5, 7.5 Hz), 2.75 (2H, td, *J* 7.5 Hz, J_{HF} 1.3 Hz), 7.28 (1H, ddd, *J* 7.6, 7.6, 1.4 Hz), 7.35 (1H, ddd, *J* 7.6, 7.6, 0.9 Hz), 7.58 (1H, d, *J* 7.9 Hz), 7.64 (1H, d, *J* 7.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.8, 22.5, 23.6, 31.0 (d, J_{CF} 2 Hz), 115.5 (d, J_{CF} 10 Hz), 121.5 (d, J_{CF} 6 Hz), 122.6, 124.0 (d, J_{CF} 4 Hz), 124.6, 131.3 (d, J_{CF} 2 Hz), 136.8 (d, J_{CF} 6 Hz), 159.2 (d, J_{CF} 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$–C_6F_6): δ 29.1 (1F, s). ν_{max}(neat)/cm^{-1} 2960, 2930, 2860, 1610, 1460, 1435, 1265, 1190, 1065, 755, 730. *m/z* (20 eV) 208 (M^+, 50%), 165 (100). HRMS: calc. for $C_{12}H_{13}SF$, 208.0722 (M^+). Found 208.0694.

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