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

Junji Ichikawa,*† Yukinori Wada, Tatsuo Okauchi and Toru Minami*

Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804, Japan

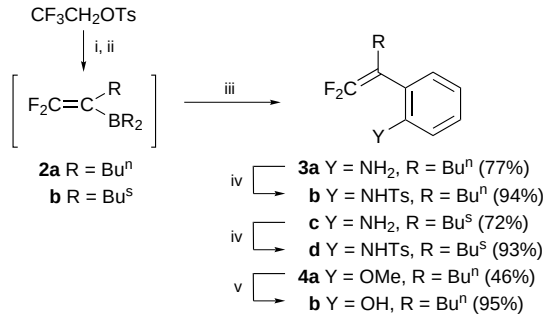
β,β-Difluorostyrenes bearing tosylamido, hydroxy or methylsulfinyl groups at the *o*-position undergo intramolecular substitution of the nitrogen, oxygen or sulfur with loss of fluorine *via* a 5-*endo*-trigonal process leading to 2-fluorinated heterocyclic systems in high yields.

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.

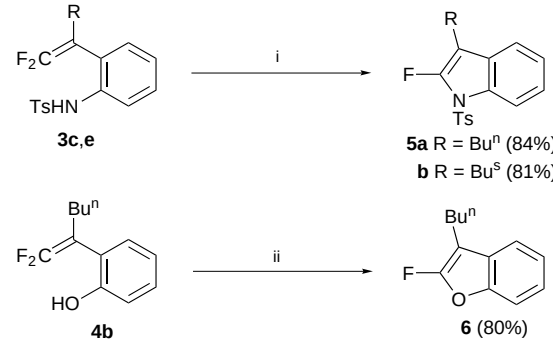
The attempted cyclization of **3a** by treatment with 1.2 equiv. of Bu^{n}Li failed, while treatment of toluene-*p*-sulfonamide **3b** with 1.2 equiv. of NaH in DMF successfully promoted the



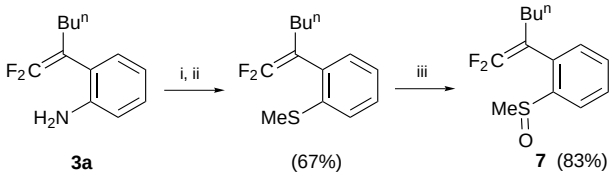
Scheme 1 *Reagents and conditions*: i, Bu^{n}Li (2.1 equiv.), THF, −78 °C, 0.5 h; ii, BR_3 (1.1 equiv.), THF, −78 °C, 1 h then room temp., 3 h; iii, ArI (0.9 equiv.), CuI (1.0 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (0.02 equiv.), PPh_3 (0.08 equiv.), THF–HMPA (4 : 1), room temp. 1 h; iv, TsCl (1.1 equiv.),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

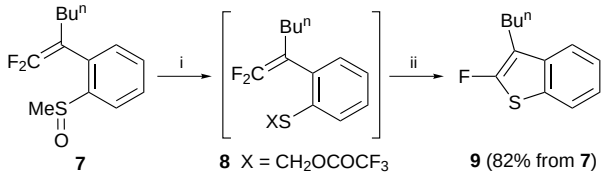
As a further example of the cyclization we next tried the intramolecular substitution utilizing a sulfur nucleophile. For the purposes of generating a thiolate moiety, the methlysulfinyl group was selected as an *ortho* substituent of β,β-difluorostyrene. The Pummerer rearrangement of *o*-methylsulfinyl-β,β-difluorostyrene **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



Scheme 3 *Reagents and conditions*: i, CF_3CO_2H (2 equiv.), Me_2CHCH_2-CH_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



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.

We gratefully acknowledge financial support for this research in the form of a grant from the Ministry of Education, Science, Sports, and Culture, Japan (Grant-in-Aid for Scientific Research No. 09640641), and Central Glass Co. Ltd. to J. I. We also thank the Center for Instrumental Analysis KIT for the measurement of analytical data.

Footnotes and References

† E-mail: ichikawa@che.kyutech.ac.jp

‡ 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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Received in Cambridge, UK, 7th May 1997; 7/03110F