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Novel synthesis of perfluoroalkylated heterocyclic compounds from α-chlorostyrenes via perfluoroalkylated α,β-unsaturated ketones

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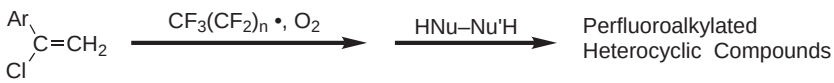
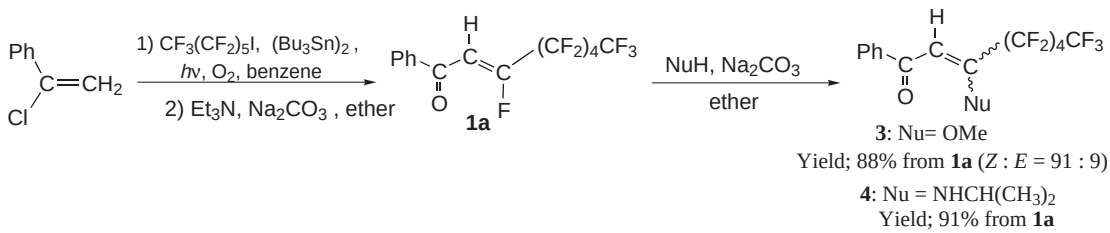
Abstract—A convenient method for the one-pot synthesis of heterocyclic compounds bearing a perfluoroalkyl group from α-chlorostyrenes via perfluoroalkylated α,β-unsaturated ketones has been developed.

Development of an efficient method for the synthesis of perfluoroalkylated heterocyclic compounds is currently an important subject, especially in agrochemical and pharmaceutical fields,[1] because the fluoroalkylated heterocyclic compounds have high potential as herbicides, fungicides, drugs and pesticides, etc.[2] Among the various methods, the building-block strategy is the most popular and attractive. In our continuous work on oxygenative perfluoroalkylation of olefins,[3,4] we now report a novel one-pot synthetic route to heterocyclic compounds bearing a perfluoroalkyl group from α-chlorostyrene as shown in Scheme 1.

As reported previously, fluoroalkylated ketones were obtained as a mixture of the unsaturated ketone (ArCOCH=CF$(CF_2)_{n-1}CF_3$: **1**) and the saturated ketone (ArCOCH$_2(CF_2)_nCF_3$: **2**) in the photochemical reaction of α-chlorostyrene with perfluoroalkyl iodide in the presence of hexabutylditin under oxygen atmosphere.[4] The saturated ketone **2** was produced initially, and then the elimination of HF gave the unsaturated ketone **1** under basic conditions. The ketone **1** is expected to be very reactive for various types of nucleophiles.[4–6] When the ketone **1a**, thus produced, was treated with methanol or isopropylamine, the corresponding substitution products (**3** and **4**) were obtained in high yields (Scheme 2). The more thermodynamically stable *Z* isomer was formed selectively in **3**. The structure of **3**



Scheme 1.



Scheme 2. Reaction of **1a** with nucleophiles.

Keywords: oxygenation; fluorine and compounds; ketones; nitrogen heterocycles.

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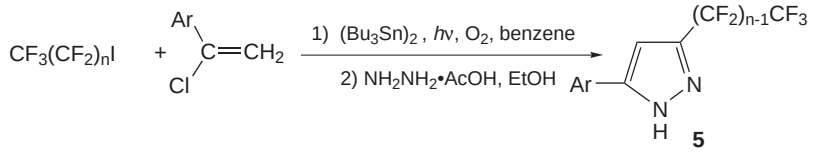
was characterized by examination of the spectroscopic data in comparison with those of *E* and *Z*-**1a**.[4] In **4**, one isomer was obtained selectively, and the structure was assigned to the *Z* isomer based on the N–H···O hydrogen bond.

Since an attempted photochemical reaction produced a mixture of **1** and **2**, we planned the synthesis of heterocyclic compounds starting from the mixture of **1** and **2**. By using the new methodology, a variety of perfluoroalkylated heterocyclic compounds hitherto unknown can be expected to be prepared in very short steps. When the reaction mixture consisting of **1** and **2** was treated with hydrazine acetate, the fluoroalkylated pyrazole **5** was obtained (Scheme 3).[7] Although the two tautomers, 5-aryl-3-perfluoroalkyl- and 3-aryl-5-perfluoroalkylpyrazoles are possible, the NMR spectra showed one set of signals even at −80°C. The observed ^{13}C NMR chemical shifts were consistent with those of 5-aryl-3-perfluoroalkylpyrazole (**5**) in the comparison with those of 3- and 5-phenylpyrazoles and *N*-methylpyrazole reported in the literature.[8] The length of the fluoroalkyl chains and the substituents on the benzene ring (*p*-Me and *p*-Cl) had little effect on the yields of the pyrazoles **5** (Table 1).

Similarly, dihydrodiazepines **6** and pyrimidines **7** were obtained in moderate yields by the reactions with ethylene diamine ($NH_2CH_2CH_2NH_2$) and formamidine acetate ($NH{=}CHNH_2{\cdot}AcOH$), respectively (Scheme 4, Table 1).[9] In the diazepine, one tautomer (7-aryl-5-perfluoroalkyl-2,3-dihydro-1,4-diazepine: **6**) was observed; the structure was determined by the comparison of the ^{13}C NMR spectra with those of 5-trifluoromethy-2,3-dihydro-1,4-diazepine.[10]

Interestingly, in the reaction with cyclic hydrazine like piperidazine, bicyclic iminium salts **8** were obtained (Scheme 5). As the reaction was carried out in one-pot, Bu_3SnI formed by the iodine abstraction from perfluoroalkyl iodide with a stannyl radical in the photochemical reaction, remained in the reaction system, and the iodine became the counter anion of the salt. The structures of these compounds were characterized by examination of the spectroscopic and analytical data.[12] Thus, the method is also applicable to secondary amines to afford the *N*-alkylated pyrazoles.

Fluoroalkylated isoxazoles were obtained as a mixture of the regioisomers **9** and **10** by the direct reaction

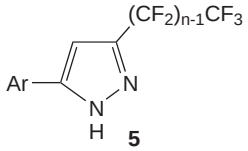


Scheme 3. Synthesis of **5**.

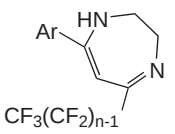
Table 1. One-pot synthesis of **5**–**7** from α-chlorostyrenes via **1**

Table 1

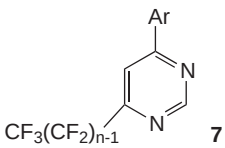
One-pot synthesis of **5** - **7** from α-chlorostyrenes via **1**



n	Ar	Yield / %[a]
a; 3	Ph[b]	59 (44)
b; 5	Ph[b]	65 (42)
c; 9	Ph	69 (48)
d; 5	*p*-ClC_6H_4	57 (40)
e; 5	*p*-MeC_6H_4	57 (47)

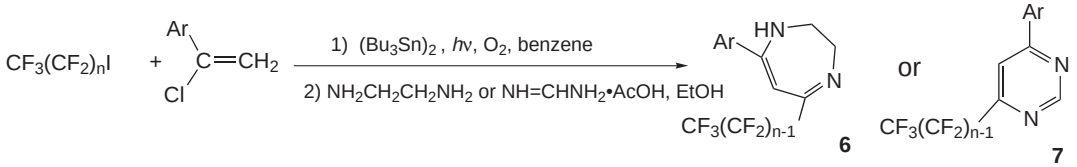


n	Ar	Yield / %[a]
a; 3	Ph	48 (40)
b; 5	Ph	48 (37)
c; 9	Ph	54 (47)
d; 5	*p*-ClC_6H_4	54
e; 5	*p*-MeC_6H_4	57

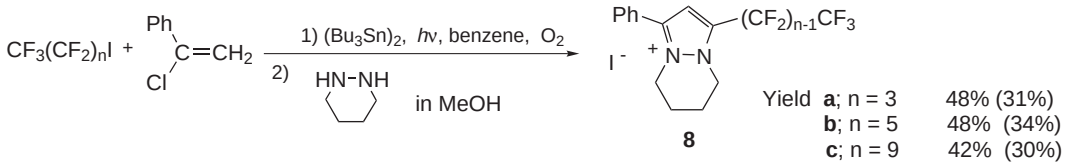


n	Ar	Yield / %[a]
a; 3	Ph	41 (35)
b; 5	Ph	43 (34)
c; 9	Ph	47 (39)
d; 5	*p*-ClC_6H_4	45
e; 5	*p*-MeC_6H_4	44

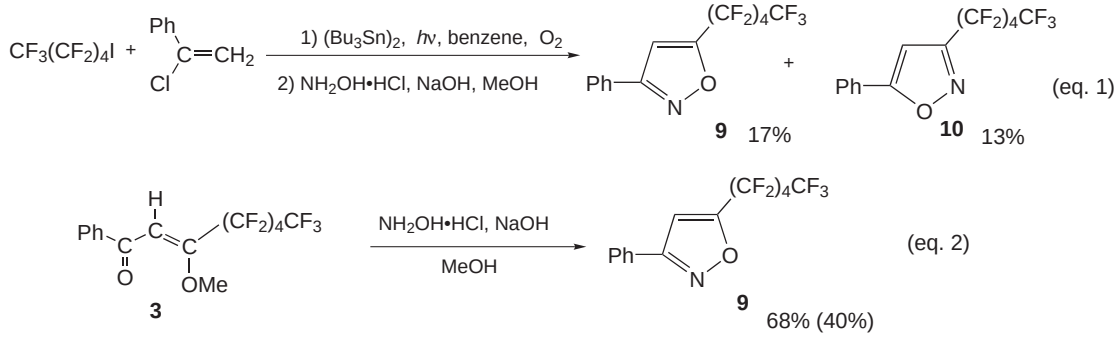
a) Yields (overall yields based on $CF_3(CF_2)_nI$) were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. Isolated yields are shown in parenthesis. b) Known compounds.[11]



Scheme 4. Synthesis of **6** and **7**.



Scheme 5. Synthesis of **8**. Overall yields were determined by ^{19}F NMR. Isolated yields are shown in parenthesis.



Scheme 6. Synthesis of **9** and **10**. Isolated yield is shown in parenthesis.

between the photochemical reaction mixture and hydroxylamine (Eq. (1), Scheme 6).[13] On the other hand, the ketone **3** was found to give the isoxazole **9** selectively by the reaction with hydroxylamine; the one-pot procedure for the regioselective synthesis of **9** was carried out as shown in Eq. (2) of Scheme 6.[14] The ^1H NMR chemical shift ($\delta_H = 7.07$) of the isoxazole **9** thus obtained was consistent with the reported shift,[15] and the C-5 carbon in the isoxazole ring was observed at $\delta = 158.83$ as a triplet due to the CCF coupling reflecting the existence of a perfluoroalkyl group on this carbon.[14]

In summary, the high potential of the ketone **1** as a building block for the synthesis of heterocyclic compounds was shown. As α-chlorostyrenes were readily prepared from styrenes with $PhSeCl_3$[16] or from acetophenone derivatives with PCl_5,[17] the method described here is very convenient and practical for the regioselective synthesis of various types of heterocyclic compounds bearing both perfluoroalkyl and aryl groups.

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7. Typical procedure for the synthesis of **5**. A solution of perfluoroalkyl iodide (0.40 mmol), α-chlorostyrene (1.20 mmol), and $(Bu_3Sn)_2$ (0.44 mmol) in 3 mL of benzene was irradiated using a metal halide lamp (National Sky-beam MT-70) in Pyrex tube under O_2 atmosphere for 5 h. After removal of benzene from the reaction mixture, ethanol and hydrazine acetate were added. The resultant solution was stirred under reflux for 2 h. The pyrazole **5** was isolated using column chromatography on silica gel with hexane/dichloromethane as eluent, followed by gel permeation chromatography. Compound **5b** (Ar = Ph, $n = 5$): colorless needles from hexane; mp 91.2–92.2°C; ^1H NMR (500 MHz: $CDCl_3$) δ 6.82 (s, 1H), 7.42-7.50 (m, 3H), 7.59 (m, 2H), 11.05 (brs, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 102.78, 125.61, 127.94, 129.28, 129.49, 142.52 (br), 145.24; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.44 (3F), −34.68 (2F), −47.05 (2F), −47.41 (2F), −50.90 (2F); EI-MS (m/z) 412 (M^+); HRMS 412.0430 (calcd for $C_{14}H_7F_{11}N_2$: 412.0433). Compound **5d** (Ar = p-ClC_6H_4, $n = 5$): colorless needles from hexane; mp 131.6–132.3°C; ^1H NMR (500 MHz: $CDCl_3$) δ 6.82 (s, 1H), 7.46 (d, $J = 8.7Hz$, 2H), 7.54 (d, $J = 8.7$ Hz, 2H), the NH proton did not appear in

$CDCl_3$; ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 103.22, 126.64, 126.97, 129.60, 135.62, 142.30 (br), 144.56;^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.43 (3F), −34.66 (2F), −47.03 (2F), −47.41 (2F), −50.88 (2F); EI-MS (m/z) 446 (M^+); HRMS 446.0036 (calcd for $C_{14}H_6ClF_{11}N_2$: 446.0043). Compound **5e** (Ar = p-MeC_6H_4, $n = 5$): colorless needles from hexane; mp 159.7–160.3°C; ^1H NMR (400 MHz: $CDCl_3$) δ 2.53 (s, 3H), 6.78 (s, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H) 11.63 (brs, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 21.27, 102.44, 125.18, 125.52, 129.95, 139.57, 142.54 (t, $J_{CCF} = 29$ Hz), 145.25; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.45 (3F), −34.65 (2F), −47.04 (2F), −47.38 (2F), −50.90 (2F); EI-MS (m/z) 426 (M^+); HRMS 426.0580 (calcd for $C_{15}H_9F_{11}N_2$: 426.0590).

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9. Compound **6b** (Ar = Ph, $n = 5$): yellow oil; ^1H NMR (500 MHz: $CDCl_3$) δ 3.39 (brs, 2H), 4.07 (brs, 2H), 5.31 (s, 1H), 5.61 (brs, 1H), 7.40 (m, 2H), 7.45 (m, 1H), 7.50 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 48.69, 57.42, 88.59, 127.19, 128.84, 130.34, 138.51, 156.79, 157.08 (br, t); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.46 (3F), −38.79 (2F), −46.16 (2F), −46.89 (2F), −50.81 (2F); EI-MS (m/z) 440 (M^+); HRMS 440.0755 (calcd for $C_{16}H_{11}F_{11}N_2$: 440.0746). Compound **7b** (Ar = Ph, $n = 5$): yellow oil; ^1H NMR (400 MHz: $CDCl_3$) δ 7.54–7.60 (m, 3H), 8.05 (s, 1H), 8.17 (m, 2H), 9.42 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 114.43, 127.47, 129.29, 132.15, 135.34, 156.44 (t, $J_{CCF} =$ 26 Hz), 159.20, 166.29; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.42 (3F), −40.57 (2F), −46.49 (2F), −46.82 (2F), −50,79 (2F); EI-MS (m/z) 424 (M^+); HRMS 424.0417 (calcd for $C_{15}H_7F_{11}N_2$: 424.0433).
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12. Iminium salt **8** was obtained as follows. The reaction mixture was dissolved in CH_3CN and the solution was washed with hexane. After removal of CH_3CN, the residue was purified by gel permeation chromatography. Compound **8** was isolated by recrystallization from hexane/dichloromethane. **8b** (Ar = Ph, $n = 5$): colorless plates; mp 163.7–164.5°C; ^1H NMR (400 MHz: $CDCl_3$) δ 2.42 (m, 2H), 2.53 (m, 2H), 4.89–4.95 (m, 4H), 7.08 (s, 1H), 7.58–7.64 (m, 3H), 7.80 (m, 2H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 18.88, 18.92, 50.46, 50.95, 110.78, 123.88, 129.62, 129.87, 132.19, 135.30 (t, $J_{CCF} = 28$ Hz), 149.81; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.22 (3F), −33.08 (2F), −44.97(2F), −46.68 (2F), −50.63 (2F); FAB-MS (m/z) 594 (M^+), 468 ($M^+ - 126$); calcd for $C_{18}H_{14}F_{11}N_2I$: C, 36.38; H, 2.37; N, 4.71; found: C, 36.41, H, 2.34; N, 4.72.
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14. The photochemical reaction mixture starting from 0.40 mmol of perfluorohexyl iodide and 1.2 mmol of α-chlorostyrene was treated with MeOH (40 mg) in the presence of Et_3N (0.1 mL) and Na_2CO_3 (130 mg) in ether (2 mL) for 2 h at room temperature. After the solvent was changed from ether to MeOH, NaOH (80 mg) was added, and the solution was heated at reflux for 4 h. After evaporation of MeOH, the organic product was extracted with benzene, and the isoxazole **9** was isolated using column chromatography on silica gel, followed by gel permeation chromatography. **9**: colorless needles from pentane; mp 58.5–60.4°C; ^1H NMR (400 MHz: $CDCl_3$) δ 7.07 (s, 1H), 7.51 (m, 3H), 7.83 (m, 2H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 105.45, 126.07, 126.97, 129.19, 130.95, 158.83 (t, $J_{CCF} = 32$ Hz), 162.74; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm down field from external CF_3COOH) −5.38 (3F), -36.43 (2F), −47.26 (4F), −50.84 (2F); EI-MS (m/z) 413 (M^+); HRMS 413.0287 (calcd for $C_{14}H_6F_{11}NO$: 413.0274).
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