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**5-endo-trig Cyclization**

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Disfavored ring formation: 5-endo-trig Cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular Sn2' reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group.
A New Class of Substrates for Nucleophilic 5-endo-trig Cyclization, 2-Trifluoromethyl-1-alkenes: Synthesis of Five-Membered Hetero- and Carbocycles Bearing Fluorinated One-Carbon Units

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The present work is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

Abstract: Disfavored 5-endo-trig cyclizations are achieved in 2-trifluoromethyl-1-alkenes with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom via (i) intramolecular SN2 reaction with loss of a fluoride ion or (ii) intramolecular nucleophilic addition to the vinylic group. This reaction manifold provides a versatile method for the synthesis of indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[b]thiophenes, tetrahydrothiophenes, and cyclopentanes bearing a fluorinated one-carbon unit such as a difluoromethylene, difluoromethyl, or trifluoromethyl group.

Keywords: 5-endo-trig cyclization, fluorine, heterocycles, carbocycles, synthetic methods

Introduction

The 5-endo-trig cyclization has long been considered to be a geometrically disfavored process according to Baldwin’s rules. Reported examples of this disfavored ring closure are classified into three categories: nucleophile-driven,2,3 electrophile-driven,4 and radical-initiated cyclizations. Among these, nucleophile-driven 5-endo-trig cyclizations have rarely been observed in synthetic chemistry, compared with the two other types of cyclization.

In our recent studies, we have accomplished the normally disfavored nucleophilic 5-endo-trig cyclizations with 1,1-difluoro-1-alkene substrates (2,2-difluorovinylic compounds) bearing a functional group such as NHTs, OH, SH, or CH2I (Scheme 1a).2 Deprotonation or lithium–iodine exchange of these groups generates N-, O-, S-, and C-nucleophiles, which successfully undergo a vinylic addition–elimination (SNV) process to construct five-membered ring-fluorinated heterocycles and carbocycles such as indoles, pyrrolines, benzo[b]furans, 2,3-dihydrofurans, benzo[b]thiophenes, 2,3-dihydrothiophenes, and cyclopentenes. Such unique reactivities of 1,1-difluoro-1-alkenes are presumably the result of (i) the highly polarized C=C double bond, which allows the initial five-membered ring formation by electrostatic attraction of the positive CF2 carbon for the nucleophiles, and (ii) the subsequent elimination of fluoride ion, which suppresses the reverse ring opening.

Among fluoroalkenes, 2-trifluoromethyl-1-alkenes are also known to possess an interesting reactivity in nucleophilic reaction, resulting from (i) the highly electrophilic double bond with a strong electron-withdrawing CF3 group and (ii) the good leaving group ability of allylic fluorine atoms. The nucleophilic reaction of 2-trifluoromethyl-1-alkene substrates [1-(trifluoromethyl)vinyl compounds] proceeds with the accompanying elimination of an allylic fluorine (SN2-type process), which provides a potential method for the preparation of 1,1-difluoro-1-alkenes.6 We have recently conducted the SN2-type reaction with nitrogen and carbon...
nucleophiles in an intramolecular fashion to construct six-membered rings. Furthermore, we have observed them to undergo addition and substitution in the presence and absence of a proton source, respectively. These reactions readily provided quinoline and isoquinoline derivatives bearing a CF₃, CHF₂, or =CF₂ group under mild reaction conditions.⁷

Such a high reactivity of that 1-(trifluoromethyl)vinyl moiety prompted us to examine the geometrically disfavored 5-endo-trig cyclization, which might allow the development of a new synthetic route to five-membered ring systems bearing fluorinated one-carbon units (Scheme 1b). Indeed, the presence of nucleophilic centers on the position β to the 1-(trifluoromethyl)vinyl group might lead to either an intramolecular Sn₂-type process or an addition reaction, depending on the conditions, and thus deliver five-membered cycles.

Five-membered heterocycles and carbocycles constitute important classes of compounds in pharmaceuticals, agrochemicals, materials, and catalysts. In these fields of science, the introduction of a fluorine atom or fluorocarbon substituents has come into wide use as one of the most efficient methods for modification of biological activity as well as of physical and chemical properties.⁸ Among fluorocarbon substituents, fluorinated one-carbon units (CF₃, CHF₂, =CF₂, and CH₂F) are quite attractive:⁹ (i) the incorporation of a trifluoromethyl (CF₃) group into organic molecules increases lipophilicity and affects electron density,¹⁰ (ii) a difluoromethyl (CHF₂) group has hydrogen bond donor ability without nucleophilicity and with high lipophilicity,¹¹ which makes it a special mimic of a hydroxy group,¹² and (iii) a difluoromethylene (=CF₂) group acts as a reactive site towards nucleophiles¹³ and a potential isostere of carboxylic groups,¹⁴ and provides a CHF₂ group via its reduction.¹⁵ Nevertheless, synthetic methods for heterocycles and carbocycles with these fluorinated one-carbon units are limited and remain to be developed.

The preliminary results of the 5-endo-trig cyclizations of 1-(trifluoromethyl)vinyl compounds have been briefly reported in our previous communication, where we focused on those with intramolecular nitrogen nucleophiles.¹⁶ Combining the results of those obtained with other nucleophiles such as oxygen, sulfur, and carbon resulted in this full account of our studies on the 5-endo-trig cyclizations of 1-(trifluoromethyl)vinyl compounds, yielding difluoromethylene-, difluoromethyl-, and trifluoromethyl-substituted indoline, indole, pyrrolidine, tetrahydrofuran, benzo[b]thiophene, tetrahydrothiophene, and cyclopentanone derivatives.

Results and Discussion

Preparation of the Cyclization Precursors

We first selected α-(trifluoromethyl)styrenes bearing a nucleophilic nitrogen or sulfur at the o-position as 2-trifluoromethyl-1-alkene substrates for 5-endo-trig cyclization, because of the previously reported favorable effect of a 1-aryl group in 1-(trifluoromethyl)vinyl compounds undergoing Sn₂ reaction.⁴⁶ 2-(3,3,3-Trifluoroprop-1-en-2-yl)-substituted anilines 1 were prepared by the palladium-catalyzed coupling reaction of o-iodoaniline with (3,3,3-Trifluoroprop-1-en-2-yl)boration acid, obtained from the magnesium-mediated Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with trimethyl borate, following a literature procedure.⁴⁷a,⁴⁷b Sulfonylation of the amino group of 1 gave anilides 2 (Scheme 2). Introduction of an S-functionality was effected via diazotization of the amino group. Treatment of 1a with i-AmONO and CF₂CO₂H, followed by the addition of sodium thioacetate, gave thiophenol ester 3 (Scheme 3).

In addition, we designed nonconjugated substrates lacking a phenylene tether, 3-(trifluoromethyl)homoallyl sulfonamides, alcohols, thiols, and malonic acid derivatives, as second-type precursors of hetero- and carbocycles. Two methods were employed for the construction of these skeletons: (i) addition of 2-trifluoromethyl-substituted allylsilane to aldehydes¹⁸ and (ii) ring opening of oxiranes with 1-trifluoromethyl-substituted vinyl lithium,¹⁹ prepared by treatment of 2-bromo-3,3,3-trifluoropropene with n-BuLi, both of which provided 3-(trifluoromethyl)homoallyl alcohols 4. The Mitsunobu reaction of 4 with BocNHTs,²⁰ followed by deprotection of the Boc group afforded the cyclization precursors 5 (Scheme 4). 3-(Trifluoromethyl)homoallyl alcohol 4a was also adopted as a cyclization precursor featuring a nucleophilic oxygen. α-Alkylated ketones 6, prepared from 4 via oxidation and alkylation, were reduced to give homoallyl alcohols 7 bearing 2,2-dialkyl substituents (Scheme 5). S-[3-(Trifluoromethyl)homoallyl] thioacetates 8 were prepared by the Mitsuobu reaction of homoallyl alcohols 4.²⁰ Treatment with AcSH, DEAD, and PPh₃ afforded 8a,b in moderate yields (Scheme 6).

3-(Trifluoromethyl)homoallyl-substituted malonate and malononitrile 10 and 11 were prepared for carbocycle synthesis. Conjugate addition of 2-(trifluoromethyl)allylsilane¹⁸ to diethyl

Abstract in Japanese:
分子に塩素、酸素、窒素、炭素求核極を有する2-トリフルオロオルメチル-1-アルケンにおいて、これまで困難とされてきた求核的5-endo-trig環化を達成した。この5員環形成反応は、(i) フッ素化イオンの観点を伴う分子内Sn2反応、もしくは(ii) ピリニウム基への分子内求核付加を経て進行する。これら一連の反応により、ジフルオロオルメチル基、ジフルオロメチル基、トリフルオロメチル基のような含フッ素1炭素ユニットを有するインドリン、インドメール、ピロリンジ、テトラヒドロフラン、2,3-ジヒドロペンゾ[b]チオフェン、テトラヒドロチオフェン、およびシクロペタンを合成することができる。
benzylidenemalonate 9 and a modified Mitsunobu reaction\textsuperscript{21} of 4a with malononitrile gave 10 and 11, respectively (Scheme 7).
occurred to give 3-(trifluoromethyl)indole 14 in 90% yield. Similarly, treatment of 12a with 1.3 equiv of Br2 gave 3-(bromodifluoro)methylindole 15 in 96% yield. Furthermore, when HI [generated from NaI (1.6 equiv), TMSCl (1.6 equiv), and H2O (0.8 equiv)]17 was added to 12a, 3-(difluoromethyl)indole 16 was obtained in 96% yield.28 While the opposite regioselectivity in the HI addition of 12a would be kinetically favorable because of the -cation-stabilizing effect of fluoride,29 the addition product with that regiochemistry underwent elimination of HI to regenerate 12a. Consequently, the synthesis of indoles 14–16 with a variety of fluorinated one-carbon units is readily accomplished from a common starting material, 12a.

Scheme 9. Synthesis of Indoles 14–16 Bearing Fluorinated One-Carbon Units. Reagents and conditions: (a) NIS (2.4 equiv), Et3N•3HF (2.5 equiv), –10 °C, 2 h, CH2Cl2. (b) Br2 (1.3 equiv), rt, 3 h, CCl4. (c) NaI (1.6 equiv), TMSCl (1.6 equiv), H2O (0.8 equiv), rt, 10 h, CH3CN.

Synthesis of 2,3-Dihydrobenzo[b]thiophenes Bearing Fluorinated One-Carbon Units

As a further example of the intramolecular cyclization, we examined a sulfur nucleophile, although 5-endo-trig cyclizations with sulfur nucleophiles are not a disfavored process by Baldwin’s rules because of the large atom size of sulfur.1 A solution of a thiophenolate, generated in situ by treatment of thiophenol ester 3 with 1.1 equiv of potassium tert-butoxide (KOH-Bu) in THF, was heated at reflux to afford 3-difluoromethylene-2,3-dihydrobenzothiophene 17 in 65% yield (Scheme 10). The intramolecular addition process of the sulfur nucleophile under protic conditions was also examined. On treatment of 3 with 1.1 equiv of K2CO3 in MeOH, the desired 3-trifluoromethyl-2,3-dihydrobenzothiophene 18 was obtained in 61% yield (Scheme 10).30 These cyclizations of sulfur nucleophiles proceeded under milder conditions than those required for nitrogen nucleophiles.

Scheme 10. Synthesis of 3-Difluoromethylene and 3-Trifluoromethyl 2,3-Dihydrobenzo[b]thiophenes 17 and 18. Reagents and conditions: (a) KOt-Bu (1.1 equiv), reflux, 2 h, THF. (b) K2CO3 (1.1 equiv), reflux, 1 h, MeOH.

Synthesis of Pyrrolidines Bearing Fluorinated One-Carbon Units

Substrates 2 and 3 have a benzene ring tethering the nucleophilic heteroatom and the 1-(trifluoromethyl)vinyl group, which could allow a 6a-electrocyclization process to operate. To rule out the possibility of the 6b-electrocyclization mechanism and to broaden the scope for these types of 5-endo-trig cyclizations, we investigated the reaction of a nonconjugated system, N-[3-(trifluoromethyl)homoallyl] sulfonamides 5 bearing a two-sp3 carbon tether. Whereas the 1-(trifluoromethyl)vinyl system without a 1-aryl group is known to possess a reduced SN2 reactivity,68 we expected activation of the substrates by conducting the reactions in an intramolecular fashion.

Treatment of 5a with 1.3 equiv of NaH in DMF successfully promoted a similar cyclization to afford 4-(difluoromethylene)pyrrolidine 19a in 91% yield (Scheme 11).15,16,31 In contrast, the intermolecular reaction of 5-phenyl-2-(trifluoromethyl)pent-1-ene with 4-methyl-N-propylenesulfonamide gave only 2% yield of the corresponding Sn2’ product under similar reaction conditions. These results clearly indicate that (i) the reactions proceed via the nucleophilic 5-endo-trig cyclization, not via the electrocyclization, and (ii) substrate 5a preserves good Sn2’ reactivity due to the intramolecular nature of the reaction. We further examined the intramolecular Sn2’ reaction of several other N-[3-(trifluoromethyl)homoallyl] sulfonamides 5b–f bearing a 1-aryl, 1-alkyl, or 2-aryl group, and 1,2-unsubstituted homoallyl sulfonamide 5f. The reactions afforded good to excellent yields of the desired 4-difluoromethylene-substituted pyrrolidines 19b–f.

Cyclization of 5 in the presence of a proton source was attempted for the synthesis of (trifluoromethyl)pyrrolidines. In contrast to (trifluoromethyl)indoline synthesis, treatment of 5a with DBU in DMF promoted the Sn2’ reaction and not the addition reaction. When the reaction was conducted with 5 equiv of KOH in ethylene glycol or ethylene glycol–THF (10:1), the desired addition product, 4-(trifluoromethyl)pyrrolidine 20a, was obtained in 85% yield with high 2,4-trans selectivity (trans : cis = 92 : 8) (Scheme 11).15,16,32 We conducted the intramolecular addition reaction of other sulfonamides 5b–e, which afforded good to high yields of the desired 4-(trifluoromethyl)pyrrolidines 20b–e with 2,4-trans selectivity (20b–d)33 or 3,4-trans selectivity (20e).34 Under the cyclization conditions, neither the cis nor the trans isomer of 20b underwent cis/trans isomerization, which indicates that the ratios represent the kinetic selectivity of the cyclization.

Scheme 11. Intramolecular cyclization of 5a. Reagents and conditions: (a) KOt-Bu (1.1 equiv), reflux, 2 h, THF. (b) K2CO3 (1.1 equiv), reflux, 1 h, MeOH.
Synthesis of 4-Difluoromethylene- and 4-Trifluoromethyl Pyrrolidines 19 and 20. Reagents and conditions: (a) NaH (1.3 equiv), 120–130 °C, 0.5–4 h, DMF. (b) KOH (5 equiv), 130 °C, 20 h, (CH₂OH)₂ (for 20a-e and 20f), (c) KOH (5 equiv), 130 °C, 20 h, (CH₂OH)₂-THF (10:1) (for 20d).

Synthesis of Tetrahydrofurans Bearing a Difluoromethylene Group

We then focused on the construction of oxygen heterocycles. An attempted 2'-type cyclization of homoallyl alcohol 4a resulted in its intramolecular dehydration without accompanying cyclized products. Thus, we examined substrates 7 bearing two alkyl groups at the allylic position to prevent dehydration and to take advantage of the gem-dialkyl effect in cyclization. 35 On treatment with KOt-Bu in THF at 70 °C, homoallyl alcohols 7a-c underwent an Sn2'-type reaction, leading to 4-difluoromethylene-substituted tetrahydrofurans 21a-c in high yields (Scheme 12). 36 The 1-styryl-substituted substrate 7d [R1 = R2 = Me, R1 = CH=CHPh(E)], however, gave a complex mixture presumably due to 3,3-sigmatropic rearrangement. The reaction of 7a with KOt-Bu, even when conducted in t-BuOH, gave 21a as well as 4-(trifluoromethyl)tetrahydrofuran.

Synthesis of Tetrahydrothiophenes Bearing Fluorinated One-Carbon Units

A sulfur nucleophile was employed in the cyclizations for the construction of the tetrahydrothiophene ring. Treatment of thiaoacetates 8a,b with 1.3 equiv of NaOMe in DMF generated the corresponding thiolate, which underwent an Sn2'-type reaction to afford 4-(difluoromethylene)tetrahydrothiophenes 22a,b in 82% and 75% yield, respectively (Scheme 13). 37 The addition reaction of 8a,b was also readily effected on treatment with 1.1 equiv of K₂CO₃ in MeOH as a proton source (Scheme 13). The desired 4-(trifluoromethyl)tetrahydrothiophenes 23a,b were obtained in 90% and 82% yield, respectively. 38

Synthesis of Cyclpentanes Bearing a Difluoromethylene Group

Having accomplished heterocycle synthesis, we turned our attention to the 5-endo-trig cyclization of 1-(trifluoromethyl)vinyl compounds with carbon nucleophiles, which would allow the construction of five-membered carbocycles with a fluorinated one-carbon unit. When 3-(trifluoromethyl) homoallyl-substituted malonate and malononitrile 10 and 11 were treated with 1.3 equiv of NaN₃ in DMF, the Sn2'-type cyclization successfully proceeded to give difluoromethylene-substituted cyclopentanes 24 and 25 in 77% and 61% yield, respectively (Scheme 14). 39

Conclusion

In conclusion, we have found that the 1-(trifluoromethyl)vinyl system with a nucleophilic moiety constitutes a new class of compounds that undergoes the normally disfavored 5-endo-trig cyclization. These ‘anti-Baldwin’ results, based on the intramolecular substitution and addition concept, provide a high-yielding process for a variety of five-membered heterocycles and carbocycles. The resulting indolines, indoles, pyrrolidines, tetrahydrofurans, 2,3-dihydrobenzo[b]thiophenes, tetrahydrothiophenes, and cyclopentanes bearing fluorinated one-carbon units (=CF₂, CF₃, CHF₂, and CBrF₂) have so far been less accessible, despite their increasing and potential utility as agrochemicals, pharmaceuticals, and other materials. The
4-Methyl-N-[1-(3-trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5a): Colorless crystals; yield 89%; m.p. 78.6–81.0°C (IR: neat) 3269, 3064, 3030, 2932, 2856, 1532, 1159, 1129, 912 cm⁻¹; 1H NMR: δ = 2.37 (3H, s), 2.58 (4H, dd, J = 15.3, 7.2 Hz), 2.71 (1H, dd, J = 15.3, 7.8 Hz), 4.49 (4H, dd, J = 7.3, 7.8, 7.3 Hz), 4.91 (4H, br, s), 5.19 (5H, s), 6.03 (3H, s), 7.02 (2H, s), 7.14 (2H, d, J = 8.2 Hz), 7.17 (2H, s), 7.39 (2H, d, J = 8.4 Hz); 19F NMR: δ = 272.3 (q, J = 2.3 Hz, J = 277 Hz), 126.1, 127.1, 128.6, 129.3, 133.4 (q, J = 30.2 Hz), 137.2, 139.5, 143.2; 3F NMR: δ = 93.4 (br s); elemental analysis: calcld (% for C₂₁H₁₇F₃NO₂S: C 48.23, H 3.82, N 3.12, found: C 48.71, H 3.77, N 3.06; Mass spectrum: HRMS (FAB): calcld for C₂₁H₁₇F₃NO₂S·H⁺ [M + H]⁺ 368.08, found 368.07;

N-[4-(4-methylbenzenesulfonyl)-3-(trifluoromethyl)but-3-en-1-yl]benzenesulfonamide (5b): Colorless crystals; yield 65%; m.p. 113–113.5°C (IR: neat) 3263, 3066, 3030, 2924, 1469, 1151, 1115, 957 cm⁻¹; 1H NMR: δ = 2.16 (3H, s), 2.34 (2H, s), 4.55 (2H, d, J = 7.8 Hz), 5.19 (5H, s), 5.63 (1H, s), 7.02 (2H, d, J = 8.2 Hz), 7.18 (2H, s), 7.29 (2H, d, J = 8.4 Hz); 19F NMR: δ = 21.4, 35.0, 50.2, 107.8, 110.0, 121.9 (q, J = 6 Hz), 123.3 (q, J = 272 Hz), 127.0, 129.4, 131.5 (J = 30 Hz), 136.9, 138.4, 143.6; 3F NMR: δ = 93.5 (br s); elemental analysis: calcld (% for C₂₁H₁₇F₃NO₂S·H⁺ [M + H]⁺ 368.08, found 368.07;
4.1 mL, 23 mmol) dropwise, and the reaction mixture was stirred for 40 min at 78 °C. Methyl trifluoromethanesulfonate (0.26 mL, 2.3 mmol) was added at that temperature, and the reaction mixture was stirred for 10 min at 78 °C. After being allowed to warm up to rt, the reaction mixture was stirred for 2 h. Reaction was quenched with phosphate buffer (pH 7, 30 mL), and organic materials were extracted with EtOAc (30 mL). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 20:1 to 5:1) to give a mixture of 1-phenyl-3-(trifluoromethyl)but-3-en-1-one (4a, 17% yield for 2 steps). The combined extracts were washed with brine (30 mL), and organic materials were extracted with EtOAc (30 mL x 3). The combined extracts were washed with brine (30 mL), and dried over MgSO4. After removal of the solvent under reduced pressure, the crude silylether was isolated as pale brown liquid. Then, the crude product was dissolved in CH2CN (20 mL), and the solution was added to a solution of Pd(OAc)2 (0.91 mmol) in CH2CN (20 mL) at rt. After stirring for 12 h at rt, the reaction mixture was stirred for 3 h at –78 °C. To a solution of methyl trifluoromethanesulfonate (5.05 mL, 44.6 mmol) was added at –105 °C, and the mixture was quenched with phosphate buffer (pH 7, 30 mL) and organic materials were extracted with EtOAc (30 mL). The combined extracts were washed with brine (30 mL), and organic materials were extracted with EtOAc (30 mL x 3). The combined extracts were washed with brine (30 mL), and dried over MgSO4. After removal of the solvent under reduced pressure, the crude silylether was isolated as pale brown liquid. Then, the crude product was dissolved in CH2CN (20 mL), and the solution was added to a solution of Pd(OAc)2 (0.91 mmol) in CH2CN (20 mL) at rt. After stirring for 12 h at rt, the reaction mixture was stirred for 3 h at –78 °C. To a solution of methyl trifluoromethanesulfonate (5.05 mL, 44.6 mmol) was added at –105 °C, and the mixture was quenched with phosphate buffer (pH 7, 30 mL) and organic materials were extracted with EtOAc (30 mL). After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (hexane–EtOAc, 5:1) to give 4a (260 mg, 55% yield) as a colorless liquid.
(40% in toluene solution; 3.45 mL, 6.81 mmol) at –10 °C. The reaction mixture was stirred at 0 °C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:1) to give 1 (226 mg, 0.704 mmol) in CH2Cl2 (3 mL) was added Et3N·3HF (285 mg, 1.77 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 mg, 0.010 mmol) at rt. After the reaction mixture was stirred at rt for 2.5 h, the reaction was quenched with water (10 mL), and organic materials were extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine and dried over Na2SO4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give 1-(4-methylbenzenesulfonyl)-3-trifluoromethyl)indoline (11a): Colorless crystals; yield 69%; IR: νmax (neat): 3250, 3092, 2931 cm−1; 1H NMR: δ 7.19 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7.4 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 129.0, 129.8, 133.7, 144.1, 144.9, 145.0, 146.2 (q, JCF = 287, 287 Hz); 19F NMR: δ 90.0 (d, JFF = 28 Hz); HRMS (FAB): calcd for C17H16FNO2S ([M + H]+) 340.0619, found 340.0617. 3-Chloro-1-(4-methylbenzenesulfonyl)-3-trifluoromethyl)indoline (11b): Colorless crystals; yield 71%; IR: νmax (neat): 3250, 3092, 2931 cm−1; 1H NMR: δ 7.19 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7.4 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 129.0, 129.8, 133.7, 144.1, 144.9, 145.0, 146.2 (q, JCF = 287, 287 Hz); 19F NMR: δ 90.0 (d, JFF = 28 Hz); HRMS (FAB): calcd for C17H15ClFNO2S ([M + H]+) 356.0932, found 356.0947. 6-Chloro-1-(4-methylbenzenesulfonyl)-3-trifluoromethyl)indoline (13a): Colorless crystals; yield 69%; IR: νmax (neat): 3250, 3092, 2931 cm−1; 1H NMR: δ 7.19 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7.4 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 129.0, 129.8, 133.7, 144.1, 144.9, 145.0, 146.2 (q, JCF = 287, 287 Hz); 19F NMR: δ 90.0 (d, JFF = 28 Hz); elemental analysis: calcd (% for C17H15ClFNO2S: C 56.88, H 4.46, found: C 56.78, H 4.50. 6-Chloro-1-(4-methylbenzenesulfonyl)-3-trifluoromethyl)indoline (13b): Colorless crystals; yield 69%; IR: νmax (neat): 3250, 3092, 2931 cm−1; 1H NMR: δ 7.19 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7.4 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 129.0, 129.8, 133.7, 144.1, 144.9, 145.0, 146.2 (q, JCF = 287, 287 Hz); 19F NMR: δ 90.0 (d, JFF = 28 Hz); elemental analysis: calcd (% for C17H16FNO2S: C 58.00, H 3.40, found: C 57.86, H 3.36. 7-Chloro-1-(4-methylbenzenesulfonyl)-3-trifluoromethyl)indoline (13d): Colorless crystals; yield 71%; IR: νmax (neat): 3250, 3092, 2931 cm−1; 1H NMR: δ 7.19 (1H, d, J = 7.4 Hz), 7.06 (1H, d, J = 7.4 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.82 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 7.4 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.07 (1H, d, J = 7.4 Hz); 13C NMR: δ 129.0, 129.8, 133.7, 144.1, 144.9, 145.0, 146.2 (q, JCF = 287, 287 Hz); 19F NMR: δ 90.0 (d, JFF = 28 Hz); elemental analysis: calcd (% for C17H16FNO2S: C 58.00, H 3.40, found: C 57.86, H 3.36.
Colorless crystals; yield 85% (trans,cis = 92:8); m.p. 90–91 °C (IR: neat; 300±2, 2881, 1450, 1348, 1157, 1120 cm−1; 1H NMR: δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 6.78 (1H, br s, J = 7.7 Hz), 7.38 (2H, dd, J = 8.4, 8.4 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.53 (1H, d, J = 10.3, 8.5 Hz), 4.94 (1H, dd, J = 5.4, 4.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); αδ = 2.42 (2H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, d, J = 7.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.66 (2H, d, J = 8.2 Hz), 8.50 (1H, d, J = 10.0 Hz)).

3,5-Difluoromethylene-1-(4-methylbenzenesulfonyl)-4-phenylpyrrolidine (20a): Colorless crystals; yield 85% (trans,cis = 92:8); m.p. 90–91 °C (IR: neat; 300±2, 2881, 1450, 1348, 1157, 1120 cm−1; 1H NMR: δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 6.78 (1H, br s, J = 7.7 Hz), 7.38 (2H, dd, J = 8.4, 8.4 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.53 (1H, d, J = 10.3, 8.5 Hz), 4.94 (1H, dd, J = 5.4, 4.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); αδ = 2.42 (2H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, d, J = 7.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.66 (2H, d, J = 8.2 Hz), 8.50 (1H, d, J = 10.0 Hz)).

3,5-Difluoromethylene-1-(4-fluorobenzensulfonyl)-4-phenylpyrrolidine (20b): Colorless crystals; yield 85% (trans,cis = 92:8); m.p. 90–91 °C (IR: neat; 300±2, 2881, 1450, 1348, 1157, 1120 cm−1; 1H NMR: δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 6.78 (1H, br s, J = 7.7 Hz), 7.38 (2H, dd, J = 8.4, 8.4 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.53 (1H, d, J = 10.3, 8.5 Hz), 4.94 (1H, dd, J = 5.4, 4.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); αδ = 2.42 (2H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, d, J = 7.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.66 (2H, d, J = 8.2 Hz), 8.50 (1H, d, J = 10.0 Hz)).

3,5-Difluoromethylene-1-(4-chlorobenzensulfonyl)-4-phenylpyrrolidine (20c): Colorless crystals; yield 85% (trans,cis = 92:8); m.p. 90–91 °C (IR: neat; 300±2, 2881, 1450, 1348, 1157, 1120 cm−1; 1H NMR: δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 6.78 (1H, br s, J = 7.7 Hz), 7.38 (2H, dd, J = 8.4, 8.4 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.53 (1H, d, J = 10.3, 8.5 Hz), 4.94 (1H, dd, J = 5.4, 4.4 Hz), 7.23–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); αδ = 2.42 (2H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, d, J = 7.3, 7.3 Hz), 7.23–7.48 (7H, m), 7.66 (2H, d, J = 8.2 Hz), 8.50 (1H, d, J = 10.0 Hz)).

3,5-Difluoromethylene-1-(4-bromobenzensulfonyl)-4-phenylpyrrolidine (20d): Colorless crystals; yield 85% (trans,cis = 92:8); m.p. 90–91 °C (IR: neat; 300±2, 2881, 1450, 1348, 1157, 1120 cm−1; 1H NMR: δ = 2.05 (2H, dd, J = 8.6, 5.4 Hz), 6.78 (1H, br s, J = 7.7 Hz), 7.38 (2H, dd, J = 8.4, 8.4 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.52 (1H, d, J = 10.3, 8.5 Hz), 4.92 (1H, dd, J = 5.4, 4.4 Hz), 7.21–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz); αδ = 2.42 (2H, s), 2.48–2.53 (2H, m), 2.58–3.68 (1H, m), 3.58 (1H, dd, J = 11.5, 9.8 Hz), 3.96 (1H, dd, J = 11.5, 8.1 Hz), 4.71 (1H, d, J = 7.3, 7.3 Hz), 7.21–7.48 (7H, m), 7.67 (2H, d, J = 8.2 Hz), 8.49 (1H, dd, J = 8.2, 3.3 Hz), 7.17 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 8.5 Hz).
4-Di fluoromethylene-1-phenyl-2-oxa zoplano (4Jnonane: A colorless liquid; yield 70%: IR (neat): 3023, 2956, 2870, 1765, 1715, 1051, 985, 729, 702 cm (DMF) was added at 100 °C for 15 h. Purification by column yield 70%: IR (neat): 3023, 2956, 2870, 1765, 1715, 1051, 985, 729, 702 cm (%). 1H NMR: 7.02–7.10 (5H, m); 13C NMR: 128.2, 128.6, 129.3, 129.9 (q, 1F, d, J = 2.9 Hz), 62.9, 63.7 (dd, J = 7.5, 4.0 Hz); 19F NMR: 71.7 (1F, d, J = 8.2 Hz); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-2-phenyl-2,3,4,5-tetrahydrothiophene (22a): A solution of 8a (80 mg, 0.29 mmol) in DMF (1 mL) was added. NaOMe (19 mg, 0.36 mmol) at 0 °C of water was added and reacted. After the reaction mixture was stirred at 0 °C for 2 h, the column chromatography (hexane-EtOAc, 5:1) gave 22a (50 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

2-Phenyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (23a): A solution of 8a (87 mg, 0.32 mmol) in MeOH (3 mL) was added KCO3 (47 mg, 0.34 mmol) at rt. After the reaction mixture was reacted at reflux for 2h, the column chromatography (hexane-EtOAc, 1:0.25) to give 23a (48 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-1-phenyl-2-oxa zoplano (4Jnonane: A colorless liquid; yield 70%: IR (neat): 3023, 2956, 2870, 1765, 1715, 1051, 985, 729, 702 cm (%). 1H NMR: 7.02–7.10 (5H, m); 13C NMR: 128.2, 128.6, 129.3, 129.9 (q, 1F, d, J = 2.9 Hz), 62.9, 63.7 (dd, J = 7.5, 4.0 Hz); 19F NMR: 71.7 (1F, d, J = 8.2 Hz); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-2-phenyl-2,3,4,5-tetrahydrothiophene (22a): A solution of 8a (80 mg, 0.29 mmol) in DMF (1 mL) was added. NaOMe (19 mg, 0.36 mmol) at 0 °C of water was added and reacted. After the reaction mixture was stirred at 0 °C for 2 h, the column chromatography (hexane-EtOAc, 5:1) gave 22a (50 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

2-Phenyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (23a): A solution of 8a (87 mg, 0.32 mmol) in MeOH (3 mL) was added KCO3 (47 mg, 0.34 mmol) at rt. After the reaction mixture was reacted at reflux for 2h, the column chromatography (hexane-EtOAc, 1:0.25) to give 23a (48 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-1-phenyl-2-oxa zoplano (4Jnonane: A colorless liquid; yield 70%: IR (neat): 3023, 2956, 2870, 1765, 1715, 1051, 985, 729, 702 cm (%). 1H NMR: 7.02–7.10 (5H, m); 13C NMR: 128.2, 128.6, 129.3, 129.9 (q, 1F, d, J = 2.9 Hz), 62.9, 63.7 (dd, J = 7.5, 4.0 Hz); 19F NMR: 71.7 (1F, d, J = 8.2 Hz); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-2-phenyl-2,3,4,5-tetrahydrothiophene (22a): A solution of 8a (80 mg, 0.29 mmol) in DMF (1 mL) was added. NaOMe (19 mg, 0.36 mmol) at 0 °C of water was added and reacted. After the reaction mixture was stirred at 0 °C for 2 h, the column chromatography (hexane-EtOAc, 5:1) gave 22a (50 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

2-Phenyl-4-trifluoromethyl-2,3,4,5-tetrahydrothiophene (23a): A solution of 8a (87 mg, 0.32 mmol) in MeOH (3 mL) was added KCO3 (47 mg, 0.34 mmol) at rt. After the reaction mixture was reacted at reflux for 2h, the column chromatography (hexane-EtOAc, 1:0.25) to give 23a (48 mg, 82%) as a colorless liquid. 1H NMR: 0.83, 0.89, 2.09 (3H, s), 4.01, 4.09 (2H, s); 13C NMR: 251.406, found 253.184.

4-Di fluoromethylene-1-phenyl-2-oxa zoplano (4Jnonane: A colorless liquid; yield 70%: IR (neat): 3023, 2956, 2870, 1765, 1715, 1051, 985, 729, 702 cm (%). 1H NMR: 7.02–7.10 (5H, m); 13C NMR: 128.2, 128.6, 129.3, 129.9 (q, 1F, d, J = 2.9 Hz), 62.9, 63.7 (dd, J = 7.5, 4.0 Hz); 19F NMR: 71.7 (1F, d, J = 8.2 Hz); 13C NMR: 251.406, found 253.184.


For recent reports on 3-(difluoromethylene)pyrrolidines, see: a) J. Ichikawa, R. Hidai, T. Kan, Synlett 2000, 105, 25.


There are no reports on 3-(difluoromethylen)indoles to our knowledge. For recent papers on 2-(difluoromethylen)indoles, see: a) F. Ge, Z. Wang, W. Wan, J. Hao, Synlett 2007, 447; b) ref. 24b.


For a recent review on the trans/cis stereochemistry of 1-(4-methylbenzenesulfonyl)-3-phenyl-4-(trifluoromethyl)pyrroline (20e), it was determined by a NOESY experiment. A cross peak between the C-4 proton of the pyrroline ring and the α-protons of the 3-phenyl group was observed in the major product, but not in the minor product.

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