A New Class of Substrates for the Nucleophilic 5-*endo-trig* Cyclization, 1-Trifluoromethylvinyl Compounds: Syntheses of Indoline and Pyrrolidine Derivatives

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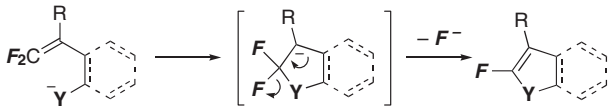
Disfavored 5-*endo-trig* cyclizations were achieved in 1-trifluoromethylvinyl compounds with a sulfonamido group via (i) intramolecular SN2′ reaction with loss of a fluoride ion or (ii) intramolecular addition to the vinylic group. These reactions provided indoline and pyrrolidine derivatives bearing fluorinated one-carbon units such as difluoromethylene and trifluoromethyl groups.

The 5-*endo-trig* cyclization has long been considered to be a geometrically disfavored process according to Baldwin's rules.[1] Reported examples of this disfavored ring closures are classified into three categories: nucleophile-driven,[2,3] electrophile-driven,[4] and radical-initiated cyclizations.[5] Among them, nucleophile-driven 5-*endo-trig* cyclizations have still rarely been observed in synthetic chemistry, compared to the other two types of cyclization.

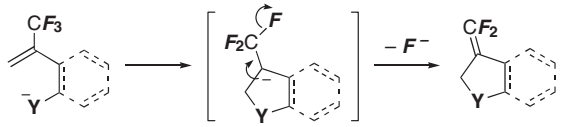
In our recent studies, we have accomplished the normally disfavored nucleophilic 5-*endo-trig* cyclizations with 1,1-difluoro-1-alkene substrates (2,2-difluorovinylic compounds) bearing functional groups such as NHTs, OH, SH, or CH_2I (Scheme 1a). In situ generated *N*-, *O*-, *S*-, and *C*-nucleophiles successfully undergo a vinylic addition–elimination (SNV) process to construct 5-memberd ring-fluorinated heterocycles and carbocycles, due to the unique reactivity of 1,1-difluoro-1-alkenes.[2,6]

(a) SNV process of 2,2-difluorovinylic compounds



Y = NTs, O, S, or CH_2

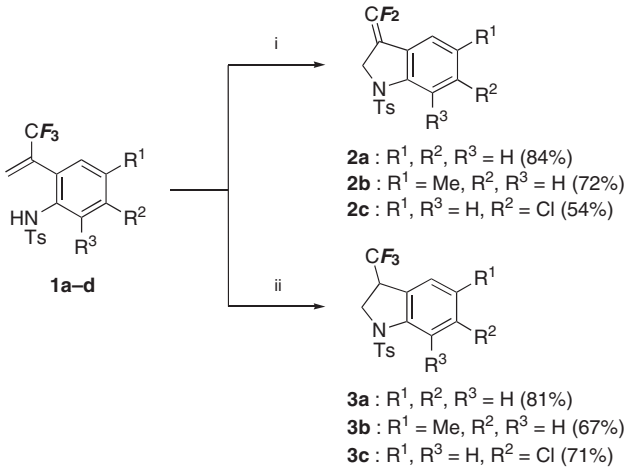
(b) SN2′ process of 1-trifluoromethylvinyl compounds



Scheme 1. Nucleophilic 5-*endo-tirg* cyclizations.

In terms of nucleophilic substitution for fluorine, 2-trifluoromethyl-1-alkenes (1-trifluoromethylvinyl compounds) bear a similarity to 1,1-difluoro-1-alkenes. They tend to react with nucleophiles accompanying loss of a fluoride ion in a SN2′ fashion to afford 1,1-difluoro-1-alkenes.[7] This fact prompted us to investigate an intramolecular version of their SN2′ reaction (Scheme 1b). Recently, we have reported the synthesis of 6-membered heterocycles, 4-difluoromethylquinolines via cyanide-ion-catalyzed intramolecular cyclization of *o*-methyleneamino-substituted α-trifluoromethylstyrenes.[8] In continuation of our research on the cyclization of 1-trifluoromethylvinyl compounds, we sought to apply the "intramolecular SN2′ reaction" concept to the construction of 5-membered rings. Herein we wish to report such 5-*endo-trig* cyclizations yielding 3-difluoromethylene- and 3-trifluoromethyl-substituted indoline and pyrrolidine derivatives.

We first designed α-trifluoromethylstyrene substrates **1** as precursors of indoline derivatives, since an aryl group at this position in 1-trifluoromethylvinyl compounds is known to raise their SN2′ reactivity.[7b] Styrene **1** was easily prepared by the coupling reaction of 2-bromo-3,3,3-trifluoro-1-propene and *o*-iodoaniline via 1-trifluoromethylvinyl boronic acid according to a modified literature procedure,[8,9] followed by tosylation of the nitrogen. The cyclization of **1a** was attempted by treatment with 1.2 molar amounts of NaH in several solvents. While the reaction in THF or 1,4-dioxane gave no cyclized products, the use of DMF successfully promoted the desired 5-*endo-trig* cyclization via the SN2′ reaction to afford 3-difluoromethyleneindoline **2a** in 84% yield (Scheme 2).[10]



Scheme 2. Reagents and conditions: i, NaH (1.2 ma), 80 °C, 5–8 h, DMF. ii, DBU (0.3 ma), 120 °C, 0.5–1 h, DMF. ma: molar amount.

On the other hand, a similar reaction of **1** conducted in the presence of proton source was expected to allow intramolecular addition without elimination of a fluoride ion, leading to a trifluoromethylated product. The cyclization was attempted by employing DBU instead of NaH, where the sulfonamide group of **1** and/or DBU·H^+ acted as a proton donor. Whereas the use of 1 molar amount of DBU gave 3-trifluoromethylindoline **3a** only in low yield (18%), treatment of **1a** with 0.3 molar amounts of DBU interestingly provided **3a** in 81% yield (Scheme 2).[11,12]

These two types of 5-*endo-trig* cyclizations, the SN2′ or the

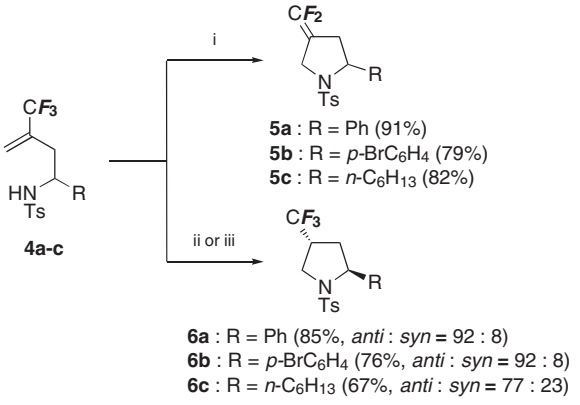
addition reactions similarly proceeded with other sulfonamides **1b**, **1c** bearing a methyl group or a chlorine on the benzene ring. Each indoline **2** or **3** was selectively obtained from a common substrate **1** simply by choosing the base and the conditions (Scheme 2).

Substrates **1** had a benzene ring as a tether connecting the nucleophilic nitrogen atom and the 1-trifluoromethylvinyl group, which could allow a 6π-electrocyclization process to work. In order to rule out the possibility of the 6π-electrocyclization mechanism and to broaden the scope for this type of 5-*endo-trig* cyclization, we investigated the reaction of a nonconjugated system, 3-trifluoromethyl-3-butenamides **4** bearing a two-sp^3 carbon tether. Whereas the trifluoromethylvinylic system without an aryl group at the vinylic position is known to possess a reduced S$_N$2′ reactivity,[7b] we expected activation of the substrates by conducting an intramolecular reaction.

Sulfonamides **4** were easily prepared via trifluoromethylallylation of aldehydes[13] and the Mitsunobu reaction of the resulting alcohols with BocNHTs,[14] followed by deprotection of the Boc group. The cyclization of **4** was attempted to construct pyrrolidine framework. Treatment of **4** with 1.3 molar amounts of NaH in DMF successfully promoted a similar cyclization to afford 3-difluoromethylenepyrrolidines **5** in high yield (Scheme 3).[15] These results clearly indicate that (i) the reactions proceed via the nucleophilic 5-*endo-trig* cyclization, not via the electrocyclization and (ii) substrates **4** preserve the S$_N$2′ reactivity due to intramolecular reaction.

The cyclization of **4** in the presence of proton source was also examined for the synthesis of trifluoromethylated pyrrolidines.[16] On treatment of **4** with 5 molar amounts of KOH in $(CH_2OH)_2$ or $(CH_2OH)_2$–THF (10:1), the desired 3-trifluoromethylpyrrolidines **6** were obtained in good to high yield with good *anti* selectivity (Scheme 3).[17,18]

In conclusion, we have found that 1-trifluoromethylvinylic system with a nucleophilic part constitutes a new class of compounds that undergo the normally disfavored 5-*endo-trig* cyclization. This methodology provides a versatile process for 5-membered nitrogen heterocycles such as indolines and pyrrolidines bearing fluorinated one-carbon units (CF_2= and CF_3– group), which have potential uses as agrochemicals, pharmaceuticals, and other materials.[19] The difluoromethylene group functions as a reactive site and a potential isostere of carbonyl groups.[20] Studies on the cyclization by using other intramolecular nucleophiles including carbanions are currently under progress in our laboratory.



Scheme 3. Reagents and conditions: i, NaH (1.3 ma), 120 °C, 2–4 h, DMF. ii, KOH (5 ma), 130 °C, 10–20 h, $(CH_2OH)_2$ for **6a**, **6b**. iii, KOH (5 ma), 130 °C, 20 h, $(CH_2OH)_2$–THF (10:1) for **6c**.

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17 The stereochemistry of the *syn* and the *anti* isomers of **6b** was determined by the NOESY cross-peak between the C-2 and C-4 protons. The configuration of the other isomers **6a**, **6c** was assigned by comparing their ^{1}H NMR spectra with that of **6b**.

18 Under the cyclization conditions, neither the *syn* nor the *anti* isomer of **6b** underwent *syn*/*anti* isomerization.

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