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SYNTHESIS OF α-(TRIFLUOROMETHYL)PYRROLIDINES BY CYCLIZATION OF *N*-TOSYL-α-(TRIFLUOROMETHYL)HOMO-ALLYLAMINE DERIVATIVES

Itsumaro Kumadaki,* Shuichi Jonoshita, Kazuyuki Sato, Masaaki Omote, and Akira Ando

Faculty of Pharmaceutical Sciences, Setsunan University
45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

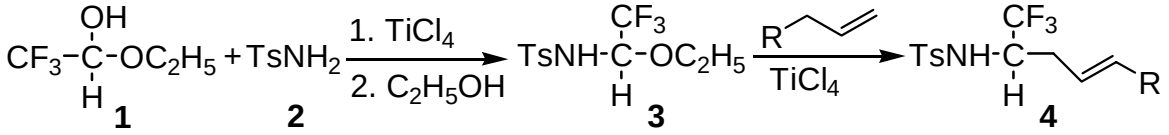
This is dedicated to 77th birthday of Professor Sho Itoh.

Abstract:– Treatment of *N*-tosyl-α-(trifluoromethyl)homoallylamines (**4**), obtained by the ene type reaction of *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**3**), with a protic acid afforded *N*-tosyl- α -(trifluoromethyl)pyrrolidine derivatives (**5** and **6**). For example, 4-phenyl-*N*-tosyl-1-(trifluoromethyl)-3-butenylamine (**4a**) gave *cis*- and *trans*-2-phenyl-*N*-tosyl-5-(trifluoromethyl)pyrrolidines (**5a** and **6a**). Interestingly, **6a** was a major product in a moderate reaction condition, while **5a** was a major product in more drastic conditions. The mechanism of these reactions is speculated. Treatment of **4a** with iodine in the presence of sodium hydrogencarbonate brought about iodocyclization to give 3-iodo-2-phenyl-5-(trifluoromethyl)-*N*-tosylpyrrolidines (**7** and **8**).

In the course of our study to develop a new synthon for synthesis of organofluorine compounds, trifluoroacetaldehyde ethyl hemiacetal (**1**) was found to react with ene compounds as an enophile in the presence of a Lewis acid.[1] Further, **1** reacted with *p*-toulenesulfonamide (**2**) in the presence of $TiCl_4$, followed by treatment with ethanol to give *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**3**). Reaction of **3** with ene compounds in the presence of $TiCl_4$ gave much better yields of ene reaction products (**4**) than did the reaction of *N*-tosyltrifluoroacetaldehyde imine itself with ene compounds,[2] as shown Scheme 1.

On the other hand, the ene products from the reaction of *N*-tosylhexafluoroacetone imine cyclized to α, α -bis(trifluoromethyl)pyrrolidine derivatives by treatment with *p*-toluenesulfonic acid.[3] Here, we

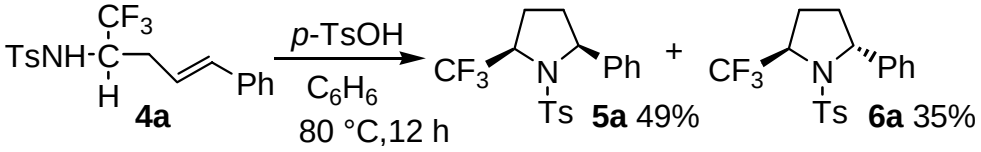
Scheme 1



would like to report cyclization of **4** in the presence of protic acids to α-(trifluoromethyl)pyrrolidine derivatives. In this reaction, two stereoisomers were obtained depending on the reaction conditions. Further iodoamination cyclization will be presented.

First, cyclization of *N*-tosyl-4-phenyl-1-(trifluoromethyl)-3-butenylamine (**4a**) was examined in the presence of *p*-toluenesulfonic acid.[4] The cyclization proceeded as expected, and gave two diastereo-isomers of -(trifluoromethyl)pyrrolidine, as shown in Scheme 2.

Scheme 2



One isomer showed n.O.e. between the 2- and 5-protons, and was assigned to be a *cis* isomer (**5a**), and the other as a *trans* isomer (**6a**). A characteristic point is that in the milder conditions, the *trans* isomer (**6a**) was obtained as a major product. Namely, **6a** must be a product of rate control, and **5a** of equilibrium control. We estimated the difference in stability using the molecular models. If **5a** took an envelope form, phenyl, trifluoromethyl and tosyl groups could occupy quasi-equatorial positions, while in **6a** one of these must be in quasi-axial position, as shown in Figure 1. In this figure, the phenyl group

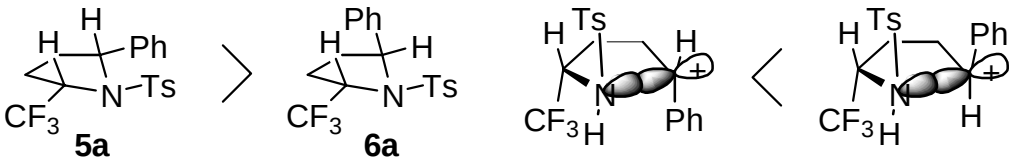


Figure 1 Speculation of differences in stability of products and transition states

was shown in quasi-axial position.

Protonation on the double bond would give a benzylic cation intermediate, which would be attacked by the lone pair on the nitrogen in the transition states, where the five membered ring must be planar. In the transition state to **5a**, the trifluoromethyl and the phenyl groups are *cis*, and there should be a significant repulsion between both groups. On the other hand, no such repulsion is evident for **6a**. This explains that **6a** is a product of kinetic control (see Figure 1).

Next, we examined the reaction using other protic acids and solvents. Results are shown in Table 2.

p-Toluenesulfonic acid was the least effective acid of the examined ones. Benzene is less polar than dichloromethane. In the former solvent, significant amount of the rate controlled product (**6a**) was obtained with the equilibrium controlled product (**5a**), while in the latter solvent, only **5a** was obtained in

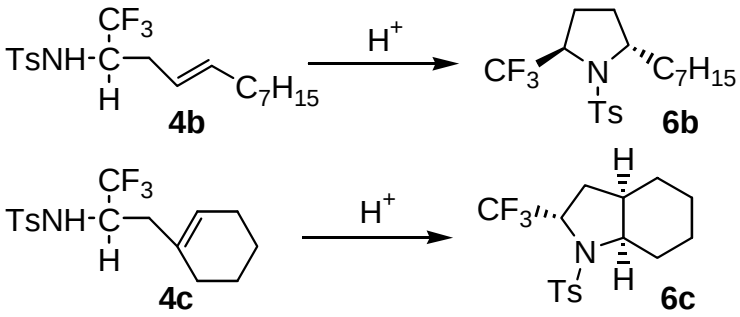
a quantitative yield even at –30˚C. When **6a** was treated with trifluoromethanesulfonic acid at room temperature in dichloromethane, it was converted to **5a** completely. These results support that **5a** is more stable than **6a** and that the isomerization occurred through a benzylic cation intermediate.

Table 2. Effects of acids and solvents on the cyclization.

Run	Acid (eq)	Solvent	Temp (˚C)	Time (h)	Yield (%)		
					5a (*cis*)	**6a** (*trans*)	**4a** (recovered)
1	*p*-TsOH (1)	C_6H_6	20	96	–	–	100
2	CF_3SO_3H (1)	C_6H_6	20	96	59	23	18
3	70% $HClO_4$ (1)	C_6H_6	35	48	27	43	30
4	*p*-TsOH (1)	CH_2Cl_2	20	48	–	–	quant.
5	CF_3SO_3H (1)	CH_2Cl_2	0	0.1	quant.	–	–
6	CF_3SO_3H (1)	CH_2Cl_2	–30	1.5	quant.	–	–
7	70% $HClO_4$ (2)	CH_2Cl_2	20	48	quant.	–	–

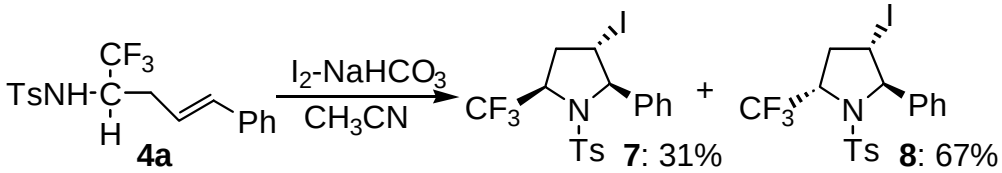
Cyclization of other ene products proceeded similarly. Treatment **4b** with *p*-toluenesulfonic acid in boiling benzene for 14 h gave a cyclization product (**6b**) only in 22 % yield. Using xylene in the place of benzene as solvent at 150 °C afforded a 68 % yield of **6b**. Trifluoromethanesulfonic acid at room temperature in dichloromethane improved the yield of **6b** to 78 %.[5] In these reactions, any stereoisomers of **6b** were not observed. We tentatively assigned this as **6b**, a kinetic controlled product. Namely, this could not form any stabilized cation intermediate, and any isomerization was not observed. The ene product (**4c**) gave a cyclization product (**6c**) in a 99 % yield by treatment with trifluoromethane-sulfonic acid.[6] These results show that ene products from trifluoroacetaldehyde imine cyclize to give α-trifluoromethylpyrrolidine derivatives.

Scheme 3



Treatment of **4a** with iodine in the presence of a base afforded cyclized iodo compounds, 2α,3β,5α– and 2α,3β,5β-3-iodo-2-phenyl-*N*-tosyl-5-(trifluoromethyl)pyrrolidines (**7** and **8**) as shown in Scheme 4.

Scheme 4



The stereochemistry of both compounds was assigned from the following NMR spectral data. The coupling constants between 2- and 3-protons of both compounds are about 10 Hz, which suggests that the iodine and the phenyl group are *trans*. The 5-H of **8** appeared at 5.09 ppm probably due to the anisotropic effect of the phenyl group, while that of **7** at 4.78 ppm. A larger n.O.e. was observed

between the 3- and 5-protons of **8** than of **7**.

If the base was absent in the above reaction, non-iodinated product (**5a**) was obtained beside **7**. Hydrogen iodide formed from iodocyclization must have promoted the acid-catalyzed cyclization.

In conclusion, the ene reaction products of *N*-tosyltrifluoroacetaldehyde imine cyclized to α-(trifluoromethyl)pyrrolidine derivatives on treatment with protic acids or iodine-base. These reactions will provide new routes for fluorine compounds.

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4. A typical experiment is as follows. A solution of **4a** (20 mg, 0.054 mmol) and *p*-toluenesulfonic acid (10 mg, 0.06 mmol) in C_6D_6 (0.8 mL) was stirred at 80 °C for 14 h. After 1,4-dioxane was added as an internal standard, the solution was analyzed by ^{1}H-NMR and found to contain **5a** (49%), **6a** (35%) and **4a** (16%). The mixture was separated by column chromatography (SiO_2, hexane-CH_2Cl_2), and the structures were determined by spectral data. **5a**: colorless crystals. mp 107-108 °C (CH_2Cl_2-hexane). **6a**. colorless crystals. mp 103-105 °C (CH_2Cl_2-hexane).
5. Reaction of **4b** (100 mg, 0.25 mmol) with CF_3SO_3H(24 μL, 0.26 mmol) in CH_2Cl_2 (5 mL) for 12 h at rt gave **6b** (colorless oil, 78 mg, 78%), the structure of which was assigned by spectral data.
6. A similar reaction of **4c** (70 mg, 0.2 mmol) with trifluoromethanesulfonic acid (20 μL, 0.22 mmol) in CH_2Cl_2 (1 mL) at rt for 24 h gave 7-tosyl-8-(trifluoromethyl)-7-azabicyclo[4.3.0]nonane (**6c**, 69 mg, 99%). **6c**: colorless crystals. mp 74-76 °C (CH_2Cl_2-hexane).
7. Reaction of **4a** (100 mg, 0.27 mmol) with I_2 (282 mg, 1.1 mmol) and $NaHCO_3$ (62 mg, 0.76 mmol) in CH_3CN (1.0 mL) gave 3-iodo-2-phenyl-5-(trifluoromethyl)-*N*-tosylpyrrolidines (**7**, 41 mg, 31%) and (**8**, 90 mg, 67%). **7**: colorless crystals. mp 98-99 °C (CH_2Cl_2-hexane). **8**: colorless crystals. mp 158 °C (CH_2Cl_2-hexane). Structures of both compounds were determined by their spectral data.