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Short communication

Synthesis of organofluorine compounds using ene type reaction of *N*-(*p*-toluenesulfonyl)trifluoroacetaldehyde imine

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Dedicated to Prof. Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

N-Tosyltrifluoroacetaldehyde imine (**4**) reacted as an enophile, but it is very sensitive to moisture and the yields of ene products were low. *N*-(2,2,2-Trifluoro-1-ethoxyethyl)tosylamide (**11**), obtained by the reaction of trifluoroacetaldehyde ethyl hemiacetal (**1**) with tosylamide (**3**) in the presence of $TiCl_4$ followed by addition of ethanol, was found to react as a good substitute for **4** to give the same products from the ene reaction of **4** in much better yields. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Trifluoroacetaldehyde; Imine; Ene reaction; Amidoacetal; Titanium tetrachloride

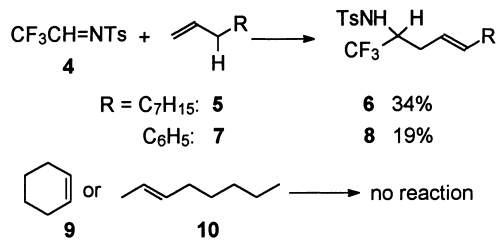
Nowadays, organofluorine compounds are attracting much attention in biomedicinal fields, and some new medicines containing fluorine substituents have been developed [1]. New methodologies for fluorine compounds have been developed, too. However, new methods for syntheses of new types of fluorine compounds are still required. We are engaged in finding new synthones for synthesis of trifluoromethyl compounds, and reported that trifluoromethyl carbonyl compounds reacted as a good enophile in the presence or absence of a Lewis acid and gave a wide range of α-(trifluoromethyl)homoallyl alcohols [2].

In this paper, we would like to present the ene reaction of *N*-tosyltrifluoroacetaldehyde imine (**4**) and related reactions.

To compare the ene reaction of trifluoromethyl carbonyl compounds with that of imine with a trifluoromethyl group, *N*-tosyltrifluoroacetaldehyde imine (**4**) was synthesized. Thus, trifluoroacetaldehyde (**2**), generated from trifluoroacetaldehyde ethyl hemiacetal (**1**), was treated with *p*-toluenesulfonamide (**3**), and the intermediate was treated with thionyl chloride to give the imine (**4**) (Eq. (1)). This imine was very sensitive to moisture and used for ene reaction without purification.[1]

$$\underset{\mathbf{1}}{CF_3CH(OH)OC_2H_5} \xrightarrow{H_2SO_4} \underset{\mathbf{2}}{CF_3CHO} \xrightarrow[SOCl_2]{TsNH_2\ \mathbf{3}} \underset{\mathbf{4}}{CF_3CH{=}NTs} \qquad (1)$$

Reaction of **4** with terminal ene compounds, 1-decene (**5**) and allylbenzene (**7**), proceeded in boiling xylene to give *E*-*N*-[1-(trifluoromethyl)-3-undecenyl]tosylamide (**6**) and



Scheme 1.

[1] CF_3CHO (**2**), generated from $CF_3CH(OH)OEt$ (**1**, 3 ml) and concentrated H_2SO_4 at 80°C, was introduced to a solution of *p*-toluenesulfonamide (**3**, 2.00 g, 11.7 mmol) in anhydrous THF (10 ml) containing pyridine (45 μl, 5 mol%). After standing in a sealed tube at room temperature for two days, the mixture was concentrated using a vacuum-line. The residue was refluxed with thionyl chloride (2 ml) in C_6H_6 (5 ml) for 5 h, and the mixture was concentrated using a vacuum line. The residue, *N*-tosyltrifluoroacetaldehyde imine (**4**), was used for the ene reaction.

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E-*N*-[4-phenyl-1-(trifluoromethyl)-3-butenyl]tosylamide (**8**), respectively, while non-terminal ene compounds, cyclohexene (**9**) and *trans*-2-octene (**10**), hardly reacted (Scheme 1).[2]

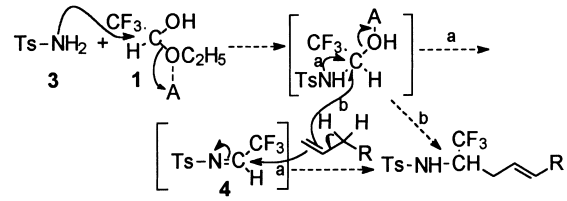
The ene reaction of trifluoroacetaldehyde itself does not proceed thermally [3]. This means that a tosylimino group is a better substituent as an enophile than a carbonyl group, while the two large substituents of **4**, a trifluoromethyl and a *p*-toluenesulfonyl groups, make non-terminal disubstituted olefins unreactive. Thus, **4** was found to be useful as an enophile in the reaction with terminal olefins. However, synthesis of **4** needs multistep and it is highly sensitive to moisture and difficult to do with. This could be the reason why the yields of the reaction were not satisfactory.

If our previous finding that **1** reacted with ene compounds in the presence of Lewis acids [4] could be applied here, the above difficulties would be removed (Scheme 2).

Namely, if **1** reacts with **3** in the presence of a Lewis acid to give α-tosylamidoalcohol and this forms the imine **4** (a) or the amidoalcohol reacts directly with an ene compound in the presence of the Lewis acid (b), the same product from the ene reaction will be obtained.

In practice, the best result was obtained when **1**, **3** and two equivalents of **5** were treated in the presence of about two equivalents of titanium chloride in methylene chloride. By this reaction the ene product **6** was obtained in 66% yield with 19% of *N*-(2,2,2-trifluoro-1- ethoxyethyl)tosylamide (**11**). This reaction is superior to the former ene reaction of the imine (**4**), since this procedure needs not preliminary formation of trifluoroacetaldehyde **2** and its imine **4**.

The same reaction of allylbenzene (**7**) gave the ene product (**8**) and *N*-(2,2,2-trifluoro- 1-ethoxyethyl)tosylamide (**11**) in 34% and 25% yields, respectively.[3] These results showed that the same products from the ene reaction



Scheme 2.

of **4** were obtained from monosubstituted olefins by a much more simple procedure. However, this procedure was not effective for disubstituted olefins. These results are shown in Scheme 3.

The above results suggest that disubstituted olefins are much less reactive than monosubstituted ones. This may be due to the larger steric hindrance of the reactive intermediate of this reaction than those in the reaction of trifluoromethyl carbonyl compounds.

The above method made the procedure for the ene products much simpler, but the yields were not satisfactory, and the reaction hardly proceeded with disubstituted ene compounds. The byproduct of the above reaction, *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**11**), seemed to be a good intermediate for the ene products. We could obtain **11** in a high yield by reaction of **1** and **3** in the presence of $TiCl_4$, followed by treatment with ethanol.[4]

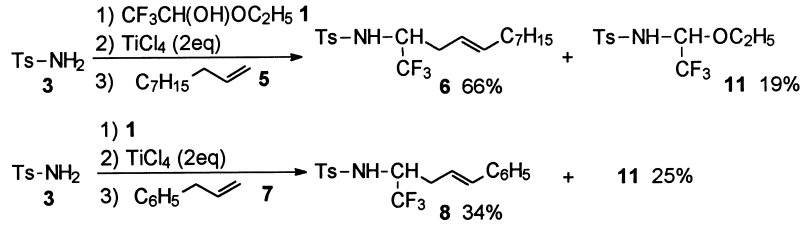
Treatment of **5** and **11** with $TiCl_4$ gave **6** in 29% yield after 20 h. Namely, the reaction proceeded very slowly. We presumed that the reaction could be accelerated, if an intermediate like the imine **4** was formed. Thus, **11** was treated with sodium hydride then $TiCl_4$ followed by addition of **5** to the mixture. Remarkably, **6** was obtained in 86% by this procedure.[5] Investigation of the mixture by ^{19}F-NMR showed no signal of **4** but a new peak at −14.1 ppm from benzotrifluoride temporarily assigned to the intermediate **12** (Scheme 4).

[2]A typical procedure for the ene reaction: 1-Decene (**5**, 1.35 ml, 7.1 mmol) and xylene (10 ml) was added to **4** obtained as above, and the mixture was refluxed for 16 h. The mixture was worked up the usual way, and the product was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 7:3) to give *N*-[1-(trifluoromethyl)-3-undecenyl]tosylamide (**6**, 0.992 g, 34%). **6**: Colorless crystals. Mp 46–47°C. Mass spectrum (MS) *m/z*: 391 (M^+). HRMS Calcd $C_{19}H_{28}F_3NO_2S$: 391.179. Found: 391.179. IR (KBr) cm^{-1}: 3292 (N–H), 1338, 1180 (SO). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=6.7 Hz), 1.13 (10H, m), 1.91 (2H, dt, *J*=6.7, 6.7 Hz), 2.27 (1H, ddd, *J*=7.3, 7.3, 14.7 Hz), 2.35 (1H, ddd, *J*=5.2, 7.3, 14.7 Hz), 2.43 (3H, s), 3.91 (1H, m, ddq on treatment with D_2O (*J*=5.2, 7.3, 7.3 Hz)), 5.04 (1H, d, *J*=9.2 Hz, disappeared on treatment with D_2O), 5.10 (1H, ddd, *J*=7.3, 7.3, 15.2 Hz), 5.47 (1H, dtt, *J*=15.2, 6.7, 1.2 Hz), 7.30 (2H, d, *J*=8.2 Hz), 7.73 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm (from $C_6H_5CF_3$): −11.2 (3F, d, *J*=7.3 Hz). All the spectral data of other products support the assigned structures.

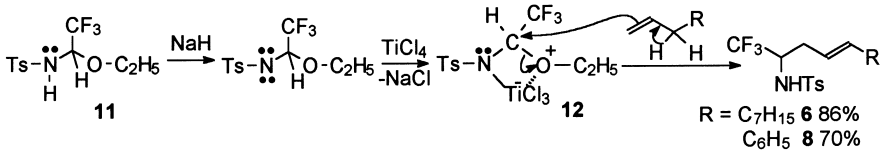
[3]The typical procedure of the reaction of **1**, **3** and an ene compound in the presence of $TiCl_4$: In a stream of Ar, $CF_3CH(OH)OEt$ (**1**, 132 μl, 1.1 mmol) and $TiCl_4$ (218 µl, 2.0 mmol) was added to a solution of $TsNH_2$ (**3**, 0.171 g, 1.0 mmol) in CH_2Cl_2 (2 ml) dropwise, then the mixture was stirred for 4 h. Allylbenzene (**7**, 300 μl, 2.3 mmol) was added to the mixture, and the whole was stirred for 6 h in a sealed condition. The mixture was worked up the usual way, and the product was separated by column chromatography (SiO_2, hexane–AcOEt–Et_2O, 8:1:1) to give **8** (124 mg, 34%) and 11 (74 mg, 25%).

[4]Preparation of **11**: In a stream of Ar, **1** (1.32 ml, 11 mmol) and $TiCl_4$ (2.18 ml, 20 mmol) was added dropwise to a solution of **3** (1.71 g, 10 mmol) in CH_2Cl_2 (20 ml), and the mixture was stirred at room temperature for 14 h, followed by treatment with EtOH (3.50 ml, 60 mmol), to give **11** (2.49 g, 84%) after separation by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7:2:1). **11**: Colorless crystals. MS *m/z*: 349 (M^+). HRMS Calcd $C_{16}H_{22}F_3NO_2S$: 349.132. Found: 349.132. IR (KBr) cm^{-1}: 3292 (N–H), 1330, 1166 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.26 (4H, m), 1.42 (2H, m), 2.42 (3H, s), 2.52 (1H, m), 3.97 (1H, ddq, *J*=2.8, 12.5, 8.0 Hz), 4.71 (1H, d, *J*=12.5 Hz), 5.16 (1H, ddd, *J*=0.9, 1.2, 17.1 Hz), 5.27 (1H, dd, *J*=1.2, 10.7 Hz), 5.62 (1H, dddq, *J*=8.2, 10.7, 17.1, 0.9 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.74 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.78 (3F, d, *J*=8.0 Hz).

[5]In a stream of Ar, a solution of **11** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) and $TiCl_4$ (218 µl, 2.0 mmol) were added in this order to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1.5 h, then 1-decene (**5**, 190 μl, 1.0 mmol) was added. After stirring for 4 h, the mixture was worked up as usual and the product was separated by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7:2:1) to give 6 (0.339 g, 86%).



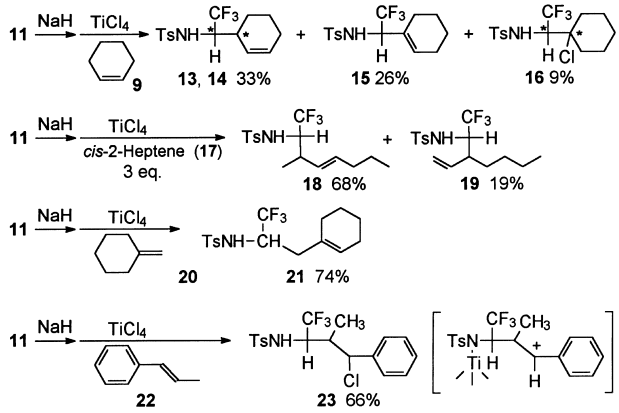
Scheme 3.



Scheme 4.

This method can be applied to other ene compounds. Allylbenzene (**7**) gave **8** in 70% yield. Surprisingly, non-terminal olefins gave products from the ene reaction. Thus, cyclohexene (**9**) gave a mixture of ene products (**13** and **14**), their isomerization product (**15**) and an HCl adduct of **15** (**16**) in 33%, 26% and 9% yields, respectively (Scheme 5). The same reaction of *cis*-2-heptene (**17**) gave two ene products (**18** and **19**) in 68% and 19% yields, respectively. Methylenecyclohexane (**20**) gave the ene type product (**21**) in 74% yield. β-Methylstyrene (**22**) did not give the ene type product but an adduct of the cation from **12** and chloride ion. These results are shown in Scheme 5.

These results suggest that the above reaction is not a concerted ene reaction but a stepwise reaction with cation intermediates. Namely, a cationic carbon from **12** attacks the double bond of the ene compounds. In the last example, a stable benzyl cation, shown in the bracket was formed and reacted with chloride ion to give **23**. Formation of other ene type products in the above reaction seems to be explained by similar cationic intermediates.



Scheme 5.

In conclusion, *N*-tosyltrifluoroacetaldehyde imine (**4**) reacts as an enophile to give ene reaction products, but it is so sensitive to moisture that it must be synthesized just before use and the yields of the ene products are unsatisfactory. Non-terminal olefins do not react with **4** at all. *N*-(2,2,2-Trifluoro-1-ethoxyethyl)tosylamide (**11**), which is obtained by the reaction of the hemiacetal (**1**) and tosylamide (**3**) in the presence of $TiCl_4$ followed by addition of ethanol, serves as a good substitute for **4** to obtain the ene products. Treatment of **11** with sodium hydride and $TiCl_4$, followed by addition of ene compounds at room temperature, gives high yields of the ene reaction products even from non-terminal olefins. This reaction would serve for synthesis of new type of fluorine compounds.

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References

[1] R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), in: Organic Compounds in Medicinal Chemistry and Biomedicinal Applications, Elsevier, Amsterdam, 1993.
[2] I. Kumadaki, Reviews Heteroatom Chem. 9 (1993) 183 and references therein.
[3] K. Ogawa, T. Nagai, M. Nonomura, T. Takagi, M. Koyama, A. Ando, T. Miki, I. Kumadaki, Chem. Pharm. Bull. 39 (1991) 1707.
[4] K. Sakumo, N. Kuki, T. Kuno, T. Takagi, M. Koyama, A. Ando, I. Kumadaki, J. Fluorine Chem. 93 (1999) 165.