# SYNTHESIS OF TRIFLUOROMETHYLATED DIHYDRO-1,4-OXATHIIN-3-CARBOXANILIDES THROUGH POLYMER-BOUND ACTIVATED ESTER

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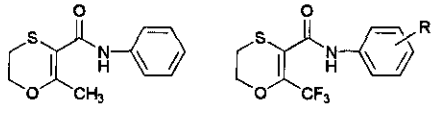
**Abstract** - A synthesis of new trifluoromethylated dihydro-1,4-oxathiin-3-carboxanilids (**2**) through polymer-bound activated ester is described. Chlorination of ethyl γ,γ,γ–trifluoroacetoacetate (**3**) followed by treatment of 2-mercaptoethanol gave hydroxyoxathianes isomers (*cis*-**10** and *trans*-**11**). Replacement of hydroxy to chlorine and then dehydrochlorination afforded trifluoromethyl dihydro-1,4-oxathiin ester (**7**). The polymer-bound trifluoromethylated dihydro-1,4-oxathiin-3-carboxylic acid, 4-hydroxy-3-nitrobenzophenone ester (**16**) was prepared through the reaction of polystyrene-bound 4-hydroxy-3-nitrobenzophenone (**14**) with the trifluoromethylated dihydro-1,4-oxathiin-3-carbonyl chloride (**15**). Refluxing of **16** with anilines in acetonitrile gave the corresponding carboxanilide (**2**). The reaction rate depended on the nucelophilicity of nitrogen in aniline.

## INTRODUCTION

5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (**1**) or carboxin is a well-known systemic fungicide used for seed treatment, and its toxicity arises from the α,β-unsaturated carboxanilide group *cis* to methyl group.[1] Trifluoromethyl group has received increasing interest owing to its unique nature for material sciences and potential biological activities for pharmaceuticals and agrochemicals. In the course of our studies of the development of new agrochemical fungicides, we became interested in the synthesis of a dihydro-1,4-oxathiin-3-carboxanilides (**2**) bearing trifluoromethyl group at C-2. The development of solid-phase organic synthesis methods as well as screening in high-throughput assays for the preparation of combinatorial libraries is a rapidly growing area in pharmaceutical discovery research fields.[2] However, only a few papers reported its use in generation of leads for the agrochemical purpose.[3] While the solid-

phase methodology offers a number of inherent advantages over solution phase methods, its practical implementation frequently poses a number of challenges. The preparation of carboxanilides through the reaction of acid chlorides with anilines using employed solution-phase techniques resulted in produce mixtures containing some type of acid anhydride, which may be contaminated with unreacted starting materials. For the preparation of the carboxanilide derivatives, we chose to utilize a solid-phase approach to overcome the disadvantages of solution-phase techniques. Polymer-bound active esters have been found to be of considerable use as acylating reagents in peptide synthesis.[4] Here we describe a synthesis of new trifluoromethylated dihydro-1,4-oxathiin-3-carboxanilides using a polymer-bound activated ester.



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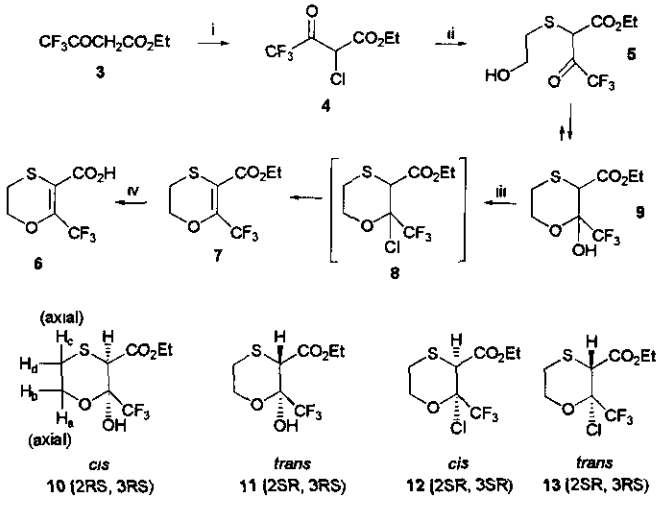
## RESULTS AND DISCUSSION

In order to construct dihydro-1,4-oxathiin heterocycles, we used β-keto ester (**3**) bearing trifluoromethyl group as shown in Scheme 1.

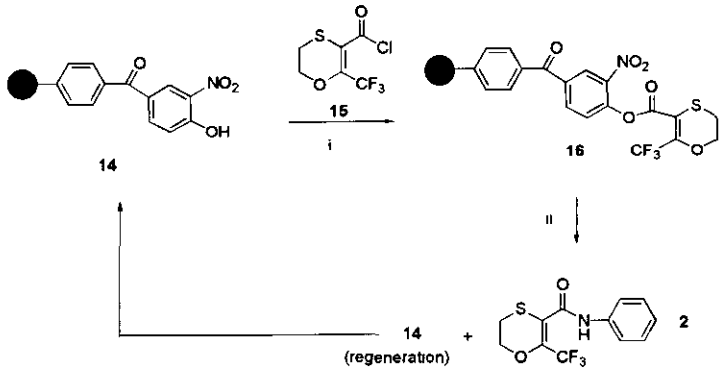



Reagents and conditions: i. $Cl_2$, 15-20°C, 1 h, 84%; ii. 2-mercaptoethanol, $Et_3N$, $C_6H_6$, 15-20°C, 2 h, 97%; iii. $SOCl_2$, pyridine, $C_6H_6$, 5 h rt, and then $Et_3N$, 48 h, rt, 58%; iv. aq. 6% sodium hydroxide, reflux, and then 6N hydrochloric acid, 63%.

Scheme 1

Chlorination of β-keto ester (**3**) was carried out by the known method[5] to provide **4** in satisfactory yield (84% isolated).[6] The reaction of **4** with 2-mercaptoethanol in the presence of triethylamine afforded β-hydroxy sulfide (**5**), which existed in 1,4-oxathiane (**9**) as a 5:12 disterostreomeric mixture of *cis*-**10** and *trans*-**11** by the $^1H$ NMR spectroscopy. Without separation of the mixture, dehydration of **9** in the

presence of an acid catalyst (*p*-toluenesulfonic acid) in refluxing benzene with Dean-Stark water separator by the application[7] of the synthesis of dihydro-1,4-oxathiin (**1**) was not successful, probably due to the strong electron withdrawing character of trifluoromethyl moiety. For the introduction of a better leaving group at C-2 the 1,4-oxathiane (**9**) was treated with thionyl chloride in the presence of pyridine in benzene solution to give a 2:3 diastereomeric mixture of tertiary chloride (*cis*-**12** and *trans*-**13**) We assigned the isomers as *trans*-**13**, which is converted to dihydro-1,4-oxathiin (**2**) with loss of hydrogen chloride spontaneously at room temperature and the isomers as *cis*-**12**, which is unreacted unchanged. Since the *cis* isomer (**12**) was transformed to **7** by treatment of triethylamine, the reaction mixture was subjected to triethylamine in benzene for 2 days without separation of the isomers to give desired dihydro-1,4-oxathiin (**7**) in moderate yield. The structure of **7** was confirmed by $^1$H NMR, $^{13}$C NMR, IR and MS spectrometries. Hydrolysis of the ester (**7**) gave a corresponding carboxylic acid (**6**). The next step was a synthesis of dihydro-1,4-oxathiin-3-carboxanilides (**2**) by the coupling of the carboxylic acid (**6**) and anilines. The prudent anhydrous reaction conditions as well as the tedious work-up process have been employed to remove the contaminated unreacted starting materials and acid anhydride in the preparation of carboxanilides through the reaction of acid chloride with anilines in solution-phase techniques. To overcome these disadvantages, we synthesized the dihydro-1,4-oxathiin-3-carboxanilides through the polymer-bound activated ester (Scheme 2).




Reagents and conditions: i. pyridine (1 8 eq), $CH_2Cl_2$, rt, 72 h, ii. aniline (0 8 eq), $Et_3N$ (1.6 eq), reflux, MeCN.

Scheme 2

Polymer-bound 4-hydroxy-3-nitrobenzophenone (**14**) has been reported to possess desirable acylating reactivity, to be insensitive to moisture in the solvent, to be stable at room temperature for several months, and to have the capability of being recycled.[4b] The resin (**14**) prepared by the previously reported method[4b] was reacted with acyl chloride (**15**)(0.88 equivalent) synthesized from the dihydro-1,4-oxathiin-carboxylic acid (**6**) by the treatment of thionyl chloride in the presence of excess (1.8 equivalent) pyridine to give

polymer-bound activated ester (**16**). Its IR spectrum showed a strong absorption at 1762 $cm^{-1}$ for ester carbonyl. An elemental analysis of sulfur (4.24%) suggested that 74% conversion of the reaction and it had 1.32 mmol of dihydro-1,4-oxathiin moiety per gram of the resin. Next, the nucleophilic reactions were set up so that an excess of polymer-bound activated ester (**16**) was used over the nucleophilic anilines in acetonitrile solution. This allows addition without precise measurement of polymer for each reaction and ensures complete consumption of the nucleophile. Typically, 1.26 equivalent of polymer reacted with 1 equivalent of nucleophile in the presence of 2 equivalent of triethylamine in refluxing acetonitrile. Table 1 provides a list of the various carboxanilies that were prepared, the yields and melting points. The reaction progress was quantitatively monitored by GC/MS spectrometer. The same melting points and $^1H$ NMR spectra of the products were obtained with those prepared by the independent reaction of acyl chloride (**15**) and corresponding anilines respectively. Upon completion, filtration of the reaction mixture yielded a solution containing a product, while the excess activated esters remained on the resin and were easily filtered away. Evaporation of the solvent without work-up process afforded the corresponding **2**

Table 1. Conversion of polymer-bound activated ester (**16**) to dihydro-1,4-oxathiin-3-carboxanilides (**2**) in presence of triethylamine in refluxing acetonitrile.

| Entry | anilines (R) | reaction time (h) | yields(%) | mp (°C)[8] |
|---|---|---|---|---|
| 1 | H | 2 | 50 | - |
| | " | 18 | 95 | - |
| | " | 84 | 100 | 109 |
| 2 | 2-methyl | 80 | 65 | 117 |
| 3 | 3-methyl | 36 | 88 | 106 |
| | | 72 | 90 | - |
| 4 | 4-methyl | 1 | 100 | 169 |
| 5 | 2,4,6-trimethyl | 72 | 65 | 210 |
| 6 | 2-methoxy | 1 | 100 | 117 |
| 7 | 4-methoxy | 96[a] | 100 | 139 |
| | | 1 | 100 | - |
| 8 | 3,4,5-trimethoxy | 105 | 97 | 167 |
| 9 | 2-acetyl | 105 | 9 | - |
| 10 | 3-acetyl | 105 | 53 | - |
| 11 | 4-acetyl | 105 | 10 | - |
| 12 | 2-nitro | 96 | 0 | - |
| 13 | 3-nitro | 96 | 5 | - |
| 14 | 4-nitro | 96 | 0 | - |
| 15 | 2-chloro | 80 | 0 | - |
| 16 | 3-chloro | 80 | 33 | - |
| 17 | 2,4,6-trichloro | 96 | 0 | - |

[a] Performed at room temperature

Table 1 attests that the electronic effect of the substituent in the aniline is more important than the steric factor in the reaction. The reaction proceeded more smoothly where an electron-donating substituent is present at the benzene ring. For instance, in case of *para* methoxy aniline (entry 7) the reaction proceeded quantitatively at room temperature. In contrast, electron-withdrawing substituents resulted in disadvantageous for the reaction. No reaction occurred where nitro group is substituted either at ortho or at para in aromatic nucleus (entries 12 and 14) either under the same reaction conditions or even under the drastic reaction conditions (in the presence of catalytic amount of *N,N*-dimethylaminopyridine in dimethylformamide at 100 °C)

The resin (**14**) is recyclable As shown in Scheme 2 the recovered resin could be reused for the preparation of active ester (**16**). Elemental analysis of sulfur (3.62%) of the regenerated resin (**16**) prepared from the recovered resin demonstrated that about 85% efficiency of reproduction of the resin (compared to the analytical data of sulfur in 4.24% described above).

## EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. All $^1$H NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shift (δ) are given in ppm and the coupling constants (*J*) in Hz. IR spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm$^{-1}$. MS spectra were recorded on a Hewlet Packard 5890 series GC/MSD. HRMS were obtained on a Finnigan MAT95S. Elemental analysis was performed using a Fisons EA1108 analyzer. All chromatographic isolation was accomplished on silica gel GF254 (230-400 mesh)

### Preparation of ethyl α-(2-hydroxyethylthio)-γ,γ,γ−trifluoroacetoacetate (5).

To a solution of ethyl α-chloride (**4**)[5] (22.3 g, 0.102 mol) and triethylamine (15.69 mL, 0.112 mol) in benzene (110 mL) cooled in the cold water bath (5 °C) was added dropwise 2-mercaptoethanol over 1 h. Stirring was continued for 2 h at the same temperature and the insoluble precipitate was filtered off. The organic layer was washed sequentially with 1N hydrochloric acid, aqueous saturated sodium bicarbonate solution, water, and then dried ($MgSO_4$). Evaporation of solvent gave **5** (25.9 g, 97%) as a 5:12 mixture of 1,4-oxathianes (*cis*-**10** and *trans*-**11**).

For *cis* isomer (**10**)· viscose oil; $^1$H NMR 1.36 (t, $J$ = 7 1, $CH_3$), 2.17 (ddd, $J_{ad}$ = 2.5, $J_{bd}$ = 1.5, $J_{cd}$ = 13.6, 5-CH (equatorial)), 3.35 (*s, methine*), 3.79 (ddd, $J_{ac}$ = 12.6, $J_{bc}$ = 4.0, $J_{cd}$ = 13.6, 5-CH (axial)), 4.16 (ddd, $J_{ab}$ = 12.4, $J_{bc}$ = 4.0, $J_{bd}$ = 1.5, 6-CH (equatorial)), 4.23 (q, $J$ = 7.1, ester $CH_2$), 4.37 (ddd, $J_{ab}$ = 12.4, $J_{ac}$ = 12.6, $J_{ad}$ = 2.5, 6-CH (axial)).

For *trans* isomer (**11**): viscose oil, $^1$H NMR 1.30 (t, $J$ = 7.1, $CH_3$), 2.42 (ddd, $J_{ad}$ = 2.2, $J_{bd}$ = 2.0, $J_{cd}$ = 13 8, 5-CH (equatorial)), 3.07 (ddd, $J_{ac}$ = 12.4, $J_{bc}$ = 3 4, $J_{cd}$ = 13.8, 5-CH(axial)), 4.02 (ddd, $J_{ab}$ =12.1, $J_{bc}$ = 3.4, $J_{bd}$ = 2 0, 6-CH (equatorial)), 4.04 (s, methine), 4.27 (q, $J$ = 7.1, ester $CH_2$), 4 42 (ddd, $J_{ab}$ =12.1, $J_{ac}$ = 12.4, $J_{ad}$ = 2.2, 6-CH (axial)), 5.54 (s, OH, exchangable wih $D_2O$).

**Preparation of ethyl 5,6-dihydro-2-trifluoromethyl-1,4-oxathiin-3-carboxylate (7).**

To a solution of a 5:12 mixture 1,4-oxathiane (*cis*-**10** and *trans*-**11** (24.32 g, 93.3 mmol)) and pyridine (8.33 mL, 103 mmol) in benzene (60 mL) was added a thionyl chloride (12.0 mL, 103 mmol) over 30 min at 20 °C. Stirring was continued for 5 h at rt. The insoluble precipitates were filtered off. To the reaction mixture was added dropwise triethylamine (19.5 mL, 140 mmol) over 1 h at 10 °C. The cooling bath was removed and the reaction mixture was stirred for 48 h at rt. The insoluble precipitates were filtered off and the organic solution was washed sequentially with 1N hydrochloric acid, aqueous saturated sodium bicarbonate solution, water, and then dried ($MgSO_4$). Evaporation of the solvent gave a dark brown oily residue, which was chromatographied using n-hexane: ethyl acetate = 4:1 as eluent to give **7** (13.02 g, 58%). $R_f$ = 0 47; bp 68-76 °C (3 mmHg); $^1$H NMR 1.32 (t, $J$ = 7.1, $CH_3$), 3.00-3.03 (m, $CH_2S$), 4.27 (q, $J$ = 7.1, ester $CH_2$), 4.40-4.43 (m, $CH_2O$); IR (KBr) 1730 (C=O), 1618 (C=C); MS, m/z (relative intensity), 242 ($M^+$, 100), 214 ($M^+$ - $CH_2$=$CH_2$, 17), 197 ($M^+$ - $CH_3CH_2O$, 77).

The reaction mixture was partially quenched before the treatment of triethylamine in above reaction, and then separation by flash chromatography using n-hexane· ethyl acetate = 4:1 as eluent to give *cis* isomer **12**. For *cis* isomer (**12**): $R_f$=0.64; viscose oil, $^1$H NMR 1.31 (t, $J$ = 7.1, $CH_3$), 2.31 (ddd, $J_{ad}$ = 2.64, $J_{bd}$ = 2.14, $J_{cd}$ = 13.9, 5-CH (equatorial)), 3.49 (s, methine), 3 82 (ddd, $J_{ac}$ = 12.6, $J_{bc}$ = 4 1, $J_{cd}$ = 13.9, 5-CH (axial)), 4.25 (q, $J$ = 7.1, ester $CH_2$), 4.34 (ddd, $J_{ab}$ = 12.1, $J_{bc}$ = 4.1, $J_{bd}$ = 2.14, 6-CH (equatorial)), 4.47 (ddd, $J_{ab}$ = 12.1, $J_{ac}$ = 12 6, $J_{ad}$ = 2.64, 6-CH (axial)); IR (NaCl) 1740 (C=O); MS, m/z (relative intensity), 278 ($M^+$, 79), 205 ($M^+$ - $CH_3CH_2OCO$, 100).

**Preparation of 5,6-dihydro-2-trifluoromethyl-1,4-oxathiin-3-carboxylic acid (6).**

A suspended solution of the ethyl ester (**7**) (10.5 g, 43 mmol) and sodium hydroxide (2.6 g) in water (40 mL) was refluxed for 1 h. The reaction mixture was cooled to rt, washed with methylene chloride. The aqueous layer was acidified with 6N hydrochloric acid (pH 2-3). The yellow precipitates were collected by filtering and dried in air. The aqueous layer was extracted with ether twice The organic layer was dried ($MgSO_4$), evaporated to give an yellow solid. The precipitates and the solid were combined and crystallized from ethyl acetate and n-hexane to give **6** (5.82 g, 63%) as a white solid. mp 143-144 °C (crystallized from ethyl acetate and *n*-hexane); $^1$H NMR 3.08-3.11 (m, 5-$CH_2$), 4.42-4.45 (m, 6-$CH_2$), 5.35 (br s, OH). IR (KBr) 1700 (C=O); MS, m/z (relative intensity), 214 ($M^+$, 100), 142 (70).

**Preparation of polymer-bound activated ester (16).**

A suspension of the carboxylic acid (**6**) (4.5 g, 21 mmol) and thionyl chloride (1.70 mL, 23 mmol) in benzene (100 mL) was refluxed for 1 h. The solvent and excess thionyl chloride were removed by evaporation to give the corresponding acyl chloride (**15**) (5.4 g) as an oily residue. A suspension of polymer-bound 4-hydroxy-3-nitrobenzophenone (**14**)(2.34 mmol/g, 10.2 g, 23.9 mmol),[9] the acyl chloride (**15**) (5.4 g, 21 mmol), and pyridine (3 mL, 38 mmol) in methylene chloride (30 mL) was stirred for 72 h at rt. The reaction mixture was filtered, washed sequentially with a 2:1 mixture of methylene chloride and methanol, dimethylformamide, a 2:1 mixture of methylene chloride and methanol again, and then dried in air. The resin was dried under the high vacuum for 2 days to give yellow resin (**16**) (1.32 mmol/g, 13.4 g, 17 7 mmol).[10]

**Preparation of 5,6-dihydro-2-trifluoromethyl-1,4-oxathiin-3-carboxanilides (2)(General Procedure).**

A suspension of active ester resin (**16**) (1.32 mmol/g, 0.5 g, 0.66 mmol), aniline (49 mg, 0.53 mmol) and triethylamine (107 mg, 1.06 mmol) in acetonitrile (5 mL) was refluxed in oil bath. The reactions were monitored by GC/MS during the reaction. The reaction mixture was filtered and the filter cake was washed with a 2·1 mixture of methylene chloride and methanol. Evaporation of the filtrate gave the corresponding *dihydro-1,4-oxathiin-3-carboxanilides* (**2**).

5,6-Dihydro-2-trifluoromethyl-*N*-phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = H): mp 109 °C (crystallized from ethyl acetate and *n*-hexane); $^1$H NMR 3.12-3.15 (m, 5-$CH_2$), 4.41-4.44 (m, 6-$CH_2$), 7.13-7.53 (m, ArH), 7.46 (br s, NH) IR (KBr) 1660 (C=O), 3296 (NH); MS, m/z (relative intensity), 289 ($M^+$, 23), 220 ($M^+$ - $CF_3$, 21), 197 ($M^+$ - $NHC_6H_5$, 100), 141 (37), HRMS for $C_{12}H_{10}NO_2F_3S$: Calcd 289.0384. Found 289.0386. *Anal.* Calcd $C_{12}H_{10}NO_2F_3S$· C, 49 7, H, 3.42, N, 4.77 Found, C, 49.75, H, 3.43, N, 4.83.

5,6-Dihydro-2-trifluoromethyl-*N*-(2-methyl)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 2-$CH_3$): mp 117 °C (crystallized from ethyl acetate and *n*-hexane); $^1$H NMR 2.28 (s, $CH_3$), 3.16-3.19 (m, 5-$CH_2$), 4 44-4.47 (m, 6-$CH_2$), 7.12-7.83 (m, NH and ArH); IR (KBr) 1648 (C=O), 3240 (NH); MS, m/z (relative intensity), 303 ($M^+$, 17), 234 ($M^+$ - $CF_3$, 24), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (61); HRMS for $C_{13}H_{12}NO_2F_3S$: Calcd 303.0541 Found, 303.0542.

5,6-Dihydro-2-trifluoromethyl-*N*-(3-methyl)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 3-$CH_3$): mp 106 °C (crystallized from ethyl acetate and *n*-hexane); $^1$H NMR 2.35 (s, 3H, $CH_3$), 3.13-3.16 (m, 2H, 5-$CH_2$), 4.42-4.45 (m, 2H, 6-$CH_2$), 6.96-7.41 (m, 5H, NH and ArH); IR (KBr) 1658 (C=O), 3230 (NH) ; MS, m/z (relative intensity), 303 ($M^+$, 31), 234 ($M^+$ - $CF_3$, 31), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (80); HRMS for $C_{13}H_{12}NO_2F_3S$: Calcd 303.0541. Found, 303.0542.

5,6-Dihydro-2-trifluoromethyl-*N*-(4-methyl)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 4-$CH_3$)· mp 169 °C (crystallized from ethyl acetate and *n*-hexane); $^1$H NMR 2.32 (s, $CH_3$), 3.13-3.16 (m, 5-$CH_2$), 4.42-4.45 (m, 6-$CH_2$), 7.13-7.41 (m, NH and ArH); IR (KBr) 1658 (C=O), 3302 (NH) ; MS, m/z (relative intensity),

303 ($M^+$, 37), 234 ($M^+$ - $CF_3$, 20), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (68); HRMS for $C_{13}H_{12}NO_2F_3S$: Calcd 303.0541. Found, 303.0549.

5,6-Dihydro-2-trifluoromethyl-*N*-(2,4,6-trimethyl)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 2,4,6-tri-$CH_3$): mp 210 °C (crystallized from ethyl acetate and *n*-hexane); $^1H$ NMR 2.21(s, 3x$CH_3$), 2.26 (s, $CH_3$), 3.16-3.19 (m, 5-$CH_2$), 4.42-4.45 (m, 6-$CH_2$), 6.90 (s, ArH), 6.97 (br s, NH); IR (KBr) 1674 (C=O), 3228 (NH) ; MS, m/z (relative intensity), 331 ($M^+$, 30), 262 ($M^+$ - $CF_3$, 5), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (41); HRMS for $C_{15}H_{16}NO_2F_3S$: Calcd 331.0854. Found, 331.0858.

5,6-Dihydro-2-trifluoromethyl-*N*-(2-methoxy)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 2-$OCH_3$): mp 117 °C (crystallized from ethyl acetate and *n*-hexane); $^1H$ NMR 3.13-3.16 (m, 5-$CH_2$), 3.90 (s, $OCH_3$), 4.43-4.46 (m, 6-$CH_2$), 6 88-8.36 (m, ArH), 8.12 (br s, NH); IR (KBr) 1681 (C=O), 3325 (NH) ; MS, m/z (relative intensity), 319 ($M^+$, 44), 250 ($M^+$ - $CF_3$, 27), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (76); HRMS for $C_{13}H_{12}NO_3F_3S$· Calcd 319.0490. Found, 319.0484.

5,6-Dihydro-2-trifluoromethyl-*N*-(4-methoxy)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 4-$OCH_3$): mp 139 °C (crystallized from ethyl acetate and *n*-hexane); $^1H$ NMR 3.13-3.16 (m, 5-$CH_2$), 3.79 (s, $OCH_3$), 4.42-4.45 (m, 6-$CH_2$), 6.86-7.44 (m, ArH), 7.34 (br s, NH); IR (KBr) 1660 (C=O), 3302 (NH) ; MS, m/z (relative intensity), 319 ($M^+$, 72), 250 ($M^+$ - $CF_3$, 8), 197 ($M^+$ - $NHC_6H_4CH_3$, 100), 141 (70); HRMS for $C_{13}H_{12}NO_3F_3S$: Calcd 319.0490. Found, 319.0490.

5,6-Dihydro-2-trifluoromethyl-*N*-(3,4,5-trimethoxy)phenyl-1,4-oxathiin-3-carboxanilide (**2**) (R = 3,4,5-tri-$OCH_3$): mp 167 °C (crystallized from ethyl acetate and *n*-hexane); $^1H$ NMR 3.14-3.17 (m, 5-$CH_2$), 3.82 (s, Ar$OCH_3$ (4-)), 3.86 (s, 2xAr$OCH_3$ (3,5-)), 4.43-4.46 (m, 6-$CH_2$), 6.83 (s, ArH), 7.44 (br s, NH); IR (KBr) 1660 (C=O), 3290 (NH) ; MS, m/z (relative intensity), 379 ($M^+$, 36), 197 ($M^+$ - $NHC_6H_2(OCH_3)_3$, 100), 141 (41); HRMS for $C_{15}H_{16}NO_5F_3S$: Calcd 379.0701. Found, 379.0699

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6. Chlorination by sulfuryl chloride gave α-chloride (**4**) in low yield (10%).

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8. In case that the reaction was incomplete, the melting points were measured after purification by flash chromatography.
9. Elemental analysis data of the resin (**14**): C, 73.08, H, 5.40, N, 3.28.
10. Its IR spectrum (KBr) showed at 1762 $cm^{-1}$ for ester carbonyl. The conversion ratio (74%) of the reaction was calculated by the elemental analysis data of the polymer-bound activated ester (**16**): C, 62.09, H, 4.26, N, 2.22, S, 4.24.

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