Synthesis of 5,6-Dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxanilides through Polymer-bound Activated Ester: Construction of Dihydro-1,4-dioxin

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This work is dedicated to the memory of Professor Raymond N. Castle

A new construction of dihydro-1,4-dioxin and a synthesis of 5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxanilides **22** through polymer-bound activated ester are described. An intermediate β-hydroxy ether **18** was prepared from the substitution reaction of α-thio-α-chloro compound **8** with ethylene glycol followed by treatment with Raney Ni. Replacement of hydroxy by chlorine and then dehydrochlorination afforded trifluoromethyl dihydro-1,4-dioxin ester **15**. The polymer-bound trifluoromethyl dihydro-1,4-dioxin-3-carboxylic acid, 4-hydroxy-3-nitrobenzophenone ester (**21**) was prepared through the reaction of polystyrene-bound 4-hydroxy-3-nitrobenzophenone (**19**) with the trifluoromethyl dihydro-1,4-dioxin-3-carbonyl chloride (**20**). Refluxing of **21** with substituted aniline in acetonitrile gave the corresponding carboxanilide **22**. The reaction rate depended on the nucleophilicity of nitrogen of the aniline.

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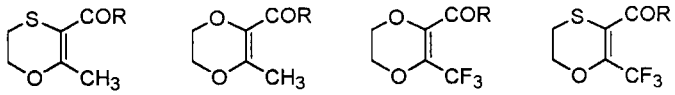
Introduction.

The design and synthesis of new fungicide are a continuing challenge in the field of agricultural chemistry because of the persistent problem of resistance development, and as a result of economic and environmental pressures to find compounds with high activity as well as low toxicity. Since an agrochemical systemic fungicide, 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (**1**) or carboxin was used for seed treatment [1], a large number of heterocycles containing α,β-unsaturated carboxanilide in which carboxanilide is *cis* to methyl group have been synthesized [2]. Trifluoromethyl heterocycles are also of considerable interests in these areas on account of the acid-strengthening/base-weakening electronic effects of the trifluoromethyl group and in view of the increased lipophilicity of compounds bearing this functionality. As part of a program of synthesis and evaluation of trifluoromethyl heterocycles for the development of new agrochemical fungicide, the fungicidal activity of the oxygen analogue of **1** bearing trifluoromethyl moiety is of great interest. A previous synthesis of **2**, developed by Dekeyser *et al.* [3], involves the reaction of 2,3-dihydro-5-methyl-1,4-dioxin with trifluoroacetic anhydride followed by hydrolysis. For the synthesis of **3** bearing trifluoromethyl moiety, we considered another synthetic pathway from the commercially available reagents.

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 the pharmaceutical discovery research fields [4]. However, only a few papers reported its use in generation of leads for the agrochemical purpose [5]. While the solid-phase methodology offers a number of inherent advantages over the solution phase methods, its practical implementation frequently poses a number of challenges. Polymer-bound



1 **2** **3** **4**

R = NHC_6H_5

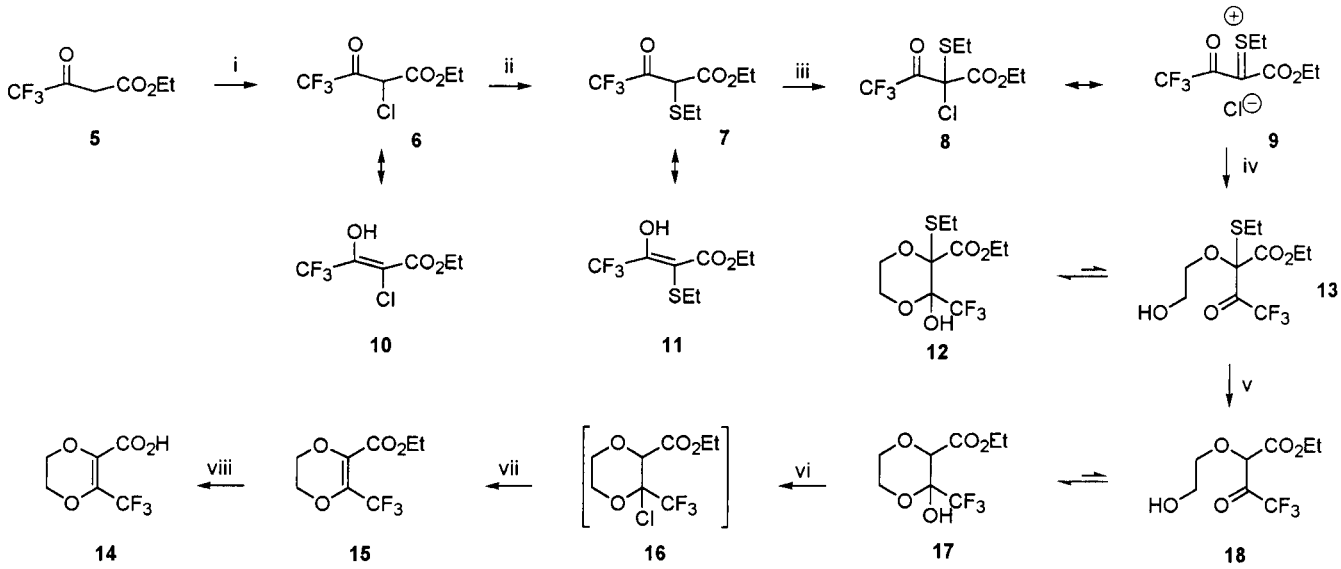
active esters have been found to be useful as acylating reagents in peptide synthesis [6]. In our previous paper, we reported a synthesis of dihydro-1,4-oxathiin-3-carboxanilides **4** through polymer-bound activated ester [7]. Here we describe a synthesis of 5,6-dihydro-1,4-dioxin **3** and compare the results with those reported previously [7].

Result and Discussion.

Our synthesis of **3** required β-hydroxy ether **18** as the key intermediate (Scheme 1). Chlorination of starting trifluoromethyl β-keto ester **5** was carried out by the known method [8] to provide **6** in satisfactory yield (85%) [9]. An attempt to prepare **18** by reaction of **6** with ethylene glycol in the presence of either triethylamine or sodium hydride failed, recovering the starting material unchanged. The enolization involving the methine hydrogen activated by neighboring carbonyls to form enol **10** and lower nucleophilic character of oxygen in comparison with sulfur would inhibit the formation of ether bond. Thus, we decided to introduce a protecting group in **6** to prevent enolization.

Treatment of α-chloride **6** with ethanethiol in the presence of triethylamine in benzene at room temperature gave an equilibrium mixture of α-sulfide **7** and its enol **11** as indicated by ^1H nmr spectroscopy in 78% yields. Chlorination of **7** with sulfuryl chloride in methylene chloride at room temperature afforded the α-thio-α-chloro compound **8**.

Scheme 1



Reagent and condition: i) Cl_2, 15-20°, 16 hours, 85%; ii) ethanethiol Et_3N, C_6H_6, r. t., 4 hours, 78%; iii) SO_2Cl_2, CH_2Cl_2, r. t., 1 hour; iv) ethylene glycol (4 equiv wt), r. t., 38 hours, 82% from **6**; v) Raney Ni (4 equiv wt), EtOH, reflux, 17 hours, 70%; vi) $SOCl_2$, C_6H_6, 1hour, r. t.; vii) Et_3N, reflux, 62% from **15**; viii) NaOH, H_2O, reflux 1 hour, and then 6 *N* HCl, 67%

Without isolation of **8**, solvolysis in ethylene glycol at room temperature gave β-hydroxy ether **13**, which existed as cyclic form **12** shown by ^1H nmr spectroscopy. The facile nucleophilic displacement of the tertiary chloride by ethylene glycol would be attributed to the neighboring sulfur. The carbocation may be stabilized by formation of the probable thiiranium ion **9** involving the lone pair electrons of the sulfur to facilitate nucleophilic substitution. The β-hydroxy ether **13** was subjected to Raney Ni in ethanol solution to afford a desired intermediate **18** which was in equilibrium with hydroxy 1,4-dioxane **17** as shown by ^1H nmr spectroscopy. Acid-catalyzed (*p*-toluenesulfonic acid) dehydration of **17** in refluxing benzene with Dean-Stark water separator was not successful probably due to the strong electron withdrawing character of the trifluoromethyl group [10]. Substitution of the hydroxy group in **17** for a better leaving chlorine by treatment with thionyl chloride followed by exposure to triethylamine in benzene at reflux afforded dihydro-1,4-dioxin **15** (60% yield) through plausible intermediate **16**. Hydrolysis of **15** gave the dihydro-1,4-dioxincarboxylic acid **14**, which was converted to its acid chloride **20** by treating with thionyl chloride.

Our next step was a synthesis of the dihydro-1,4-dioxin-3-carboxanilides. The attempted preparation of carboxanilides through the reaction of acid chlorides with anilines using solution-phase techniques resulted in mixtures containing some type of acid anhydride, which may be contaminated with the unreacted starting materials. Therefore, we chose a solid-phase approach for preparation of the carboxanilide derivatives to overcome the disadvantages of solution-phase techniques. Polymer-bound 4-hydroxy-3-nitrobenzophenone **19** 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 [6b].

As shown in Scheme 2, the resin **19** prepared by the previously reported method [6b] was reacted with acyl

Scheme 2

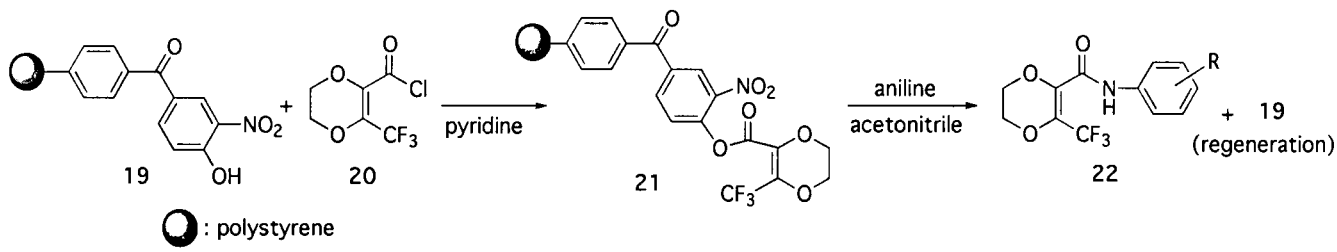


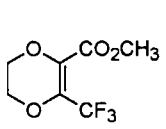
Table 1

Conversion of polymer-bound activated ester **21** to dihydro-1,4-dioxin-3-carboxanilides **22**

Entry	R	Reaction Time (hours)	Yields (%)	mp (∞) [a]	Reagents and conditions
1	H	1.2	100	140	CH_3CN, reflux
2	"	20	100		CH_2Cl_2, Et_3N, r. t.
3	2,4,6-trimethyl	14	100	166	CH_3CN, reflux
4	2-methyl	5	100	145	CH_3CN, reflux
5	3-methyl	1.5	100	156	CH_3CN, reflux
6	4-methyl	0.5	100	136	CH_3CN, reflux
7	2-methoxy	2.5	100	125	CH_3CN, reflux
8	3-methoxy	2.5	100	122	CH_3CN, reflux
9	4-methoxy	0.3	100	106	CH_3CN, reflux
10	"	5	85.6		CH_3CN, r. t.
11	2-nitro	72	66	164	CH_3CN, reflux
12	3-nitro	<24	100	182	CH_3CN, reflux
13	4-nitro	92	61.5	213	CH_3CN, reflux
14	"	48	41.3		DMF, 80∞
15	"	2	0		CH_3CN, reflux [b]
16	2-chloro	24	100	138	CH_3CN, reflux
17	3-chloro	14	100	147	CH_3CN, reflux
18	4-chloro	9	100	114	CH_3CN, reflux
19	2,4,6-trichloro	70	0	-	CH_3CN, reflux

a) In case that the reaction was incomplete, the melting points was measured after purification by flash chromatography.
b) The reaction was carried out in the presence of triethylamine (1.4 equiv wt).

chloride **20** (1.5 equivalent weight) in the presence of excess (3 equivalent) pyridine to give polymer-bound activated ester **21** in 70.5% yield [11]. Its ir spectrum showed a strong absorption at 1768 cm^{-1} for the ester carbonyl. Next, the conversions of the ester to the amide were set up using an excess of polymer-bound activated ester **21** over the nucleophilic anilines in acetonitrile solution. This allows addition without precise measurement of the polymer for each reaction and ensures complete consumption of the nucleophile. Typically, 1 equivalent of polymer reacted with 0.63 equivalent of nucleophile in refluxing acetonitrile. Table 1 provides a list of the various carboxanilides that were prepared, yields, reaction time and melting points of the products. The reaction progress was quantitatively monitored by GC/MS. The same melting points and ^1H nmr spectra of the products were obtained with those prepared by the independent reaction of acyl chloride **20** and the 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 **22**.



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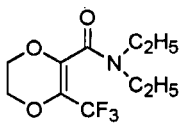

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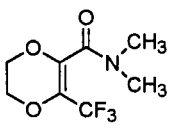

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Table 1 attests that the electronic effect of the substituent in the aniline is more important than the steric factor in the reaction. The reaction proceeded more smoothly where an electron-donating substituent was present at the benzene ring. For instance, in the case of *p*-methoxyaniline (entry 9) the reaction proceeded quantitatively in 0.3 hour. In contrast, a much longer reaction time was required when an electron withdrawing group such as nitro was substituted either at ortho (entry 11) or para (entry 13) position of the phenyl. Addition of triethylamine for the enhancement of the reaction led to unexpected products. Thus, the reaction of **21** with *p*-nitroaniline (entry 15) in the presence of triethylamine (1.4 equivalent weight) gave dihydro-1,4-dioxin methyl ester **23** as a major product in 2 hours accompanied by a trace amount of diethylamide **24** (<1%) without formation of carboxanilide. The formation of **23** and **24** was attributed to the methanol confined in the resin [12,13] and nucleophile attack of diethylamine contaminated in the triethylamine respectively.

No significantly higher yield was obtained when the reaction was carried out in *N,N*-dimethylformainde (entry 14). Instead, a small amount of dimethyl amide **25** (7%) and the carboxylic acid **14** (3%) were produced as by-products. The same reaction under the drastic condition (reflux in *N,N*-dimethylformamide) afforded the dimethyl amide **25** quantitatively without formation of the corresponding carboxanilide **22** in 2 hours, from which possibly arose the decomposition of *N,N*-dimethylformainde. In addition, when a longer time was required for the reaction (entry 13) hydrolysis of activated ester **21** took place to

give the carboxylic acid **14** in very low yield (<1%). No reaction occurred for the 2,4,6-trichloroaniline (entry 19).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. All ^1H nmr spectra were recorded on either a Varian Gemini 300 (300 MHz) or Bruker Avance 300 (300 MHz) spectrometer. Chemical shift (δ) are given in ppm and the coupling constants (J) are in Hz. Infrated (ir) spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm^{-1}. Mass spectra (ms) were recorded on a Hewlett Packard 5890 series GC/MSD. Electron impact high-resolution mass spectra (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-Ethylthio-γ,γ,γ-trifluoroacetoacetate (**7**).

To a solution of α-chloride **6** (51.6 g, 0.236 mole) [8] and triethylamine (34.6 ml, 0.248 mole) in benzene (600 ml) under the cold water bath was added dropwise ethanethiol (18.4 ml, 0.248 mole) over 10 minutes. Stirring was continued for 4 hours at room temperature. The reaction mixture was washed with cold water twice and dried (Magnesium sulfate). Evaporation of the solvent gave ethylthio ethyl ester **7** (44.8 g, 78%) as an yellow liquid, ^1H nmr (deuteriochloroform): δ 1.18-1.42 (m, 6H, SCH_2CH_3 and OCH_2CH_3), 2.57-2.81 (m, 2H, SCH_2), 4.28 (q, J = 7.1 Hz, 1.2H, OCH_2 (enol)), 4.41 (q, J = 7.1 Hz, 0.8H, OCH_2 (keto)), 4.48 (s, 0.4H, methine), 13.68 (s, 0.6H, enolic OH); ir (potassium bromide): 3446 (enolic OH), 1734 (C=O); hrms: Cacld. for $C_8H_{11}F_3O_3S$: 244.0381. Found: 244.0353.

Preparation of Ethyl 3-Ethylthio-2-hydroxy-2-trifluoromethyl-1,4-dioxane-3-carboxylate (**12**).

To a solution of ethylthio ethyl ester **7** (43.8 g, 0.18 mole) in benzene (40 ml) under the cold water bath was added dropwise sulfuryl chloride (15.2 ml, 0.188 mmole) over 10 minutes. The reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated to give **8** as an oily residue. A mixture of this oil and ethylene glycol (39.4 ml, 0.75 mole) was stirred for 38 hours at room temperature. The reaction mixture diluted with methylene chloride (600 ml) and washed with water twice and dried (Magnesium sulfate). Evaporation of the solvent gave dioxane **12** (39 g, 82.1%) as a white solid, mp 92-94°; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7.5 Hz, 3H), SCH_2CH_3), 1.36 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.57 (q, J = 7.5 Hz, 2H, SCH_2), 3.69-4.53 (m, 6H, OCH_2CH_3, 5-CH_2, and 6-CH_2), 5.38 (s, 1H, OH); ir (potassium bromide): 3374 (OH), 1734 (C=O); hrms: Cacld. for $C_{10}H_{15}F_3O_5S$: 304.0592. Found: 304.0591.

For **8**: colorless oil, ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7.6 Hz, 3H, SCH_2CH_3), 1.33 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.56 and 2.70 (2 d x q, J = 7.6 Hz, 11.7 Hz, SCH_2CH_3), 4.38 (q, J = 7.2 Hz, 2H, OCH_2CH_3).

Preparation of Ethyl 2-Hydroxy-2-trifluoromethyl-1,4-dioxane-3-carboxylate (**17**).

A suspension of ethylthio dioxane **12** (30 g, 96 mmoles) and Raney Ni (113 g) in ethanol (600 ml) was refluxed for 17 hours. The reaction mixture was cooled, filtered and then evaporated to give an brown oily residue, which was dissolved in methylene chloride. The reaction mixture was washed with 1 *N* hydrochloric acid, water and then dried (Magnesium sulfate). Evaporation of the solvent gave hydroxy-1,4-dioxane **17** (16.5 g, 70%) as a white solid, mp 40-41°; ^1H nmr (deuteriochloroform): δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 3.70-4.52 (m, 7H, ethyl CH_2, 3-CH, 5-CH_2 and 6-CH_2), 5.61 (s, 1H, OH); ir (potassium bromide): 3420 (OH), 1756 (C=O); hrms: Cacld. for $C_8H_{11}F_3O_5$: 244.0559. Found: 244.0563.

Preparation of Ethyl 5,6-Dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxylate (**15**).

To a solution of hydroxy1,4-dioxane **17** (16 g, 66 mmoles) in benzene (300 ml) cooled in the ice bath under a nitrogen atmosphere was added sequentially pyridine (5.44 ml, 66 mmoles) and thionyl chloride (5.12 ml, 66 mmoles). The reaction mixture was stirred for 2 hours at room temperature. The precipitates were filtered off and the filtrate was evaporated to give an oily residue (16.0 g). A solution of this oily residue and triethylamine (1.07 ml, 122 moles) in benzene (40 ml) was refluxed for 16 hours. The reaction mixture was cooled and washed sequentially with 1 *N* sodium hydroxide and 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, water and then dried (Magnesium sulfate). Evaporation of the solvent gave a brown oily residue, which was chromatographied using *n*-hexane:ethyl acetate = 4:1 to give 1,4-dioxin (**15**) (8.5 g, 62.1%) as an yellow oil, ^1H nmr (deuteriochloroform): δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 4.20-4.26 (m, 4H, 5-CH_2 and 6-CH_2), 4.31 (q, J = 7.1 Hz, 2H, ethyl CH_2); ir (potassium bromide): 1730 (C=O); hrms: Cacld. for $C_8H_9F_3O_4$: 226.0453. Found: 226.0453.

Preparation of 5,6-Dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxylic acid (**14**).

A solution of 1,4-dioxin ethyl ester **15** (8.0 g, 34 moles) and sodium hydroxide (2.1 g, 51 moles) in water (20 ml) was refluxed for 1 hour. The reaction mixture was cooled, washed with methylene chloride. The aqueous solution was acidified with 6 *N* hydrochloric acid until the *p*H reaches 3. The reaction mixture was extracted with ethyl ether twice. Evaporation of the solvent gave a solid residue, which was crystallized from ethyl acetate and *n*-hexane to afford dihydro-1,4-dioxin carboxylic acid **14** (4.7 g, 67%), mp 120-122°; ^1H nmr (deuteriochloroform): δ 4.21-4.29 (m, 4H, 5-CH_2 and 6-CH_2), 10.35 (s, 1H, OH); ir (potassium bromide): 1714 (C=O); hrms: Cacld. for $C_6H_5F_3O_4$: 198.0140. Found: 198.0138.

Preparation of Polymer-bound Activated Ester (**21**).

A suspension of carboxylic acid **14** (3.85 g, 19.4 mmoles) and thionyl chloride (1.57 ml, 21.3 mmoles) in benzene (100 ml) was refluxed for 5 hours. The solvent and excess thionyl chloride were removed by evaporation to give the corresponding acyl chloride **20** as an oily residue. To a solution of polymer-bound 4-hydroxy-3-nitrobenzophenone (5.0 g, 2.59 mmoles/g, 13 mmoles) [14] and pyrdine (3.1 ml, 38.9 mmoles) swelled at room temperature for 2 hours in methylene chloride was added a solution of acyl chloride in methylene chloride (15 ml) at the same temperature over 1 hour. Stirring was continued at room temperature for 24 hours. The solid was filtered, washed sequentially with methylene chloride, a 2:1 mixture of methylene chloride and methanol, methylene chloride and then dried in air. The resin was dried under high vacuum for 3 days to give yellow resin **21** (6.65 g, 70.5%), ir (potassium bromide): 1768 (ester C=O).

Anal. C, 61.7, H, 4.63, N, 3.08.

Preparation of 5,6-Dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxanilides **22** (General Procedure).

A suspension of active ester resin **21** (1.32 mmoles/g, 0.5 g, 0.66 mmole), aniline (49 mg, 0.53 mmole) and triethylamine (107 mg, 1.06 mmoles) 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 **22**.

5,6-Dihydro-*N*-phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = H) (**22**).

This compound was obtained by the general procedure above; mp 140°; ^{1}H nmr (deuteriochloroform): δ 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.11-7.61 (m, 5H, ArH), 8.05 (br s, NH); ir (potassium bromide): 3264 (NH), 1672 (C=O); hrms: Cacld. for $C_{12}H_{10}F_3NO_3$: 273.0613. Found: 273.0599.

5,6-Dihydro-2-trifluoromethyl-*N*-(2,4,6-trimethyl)phenyl-1,4-dioxin-3-carboxamide) (R = 2,4,6-tri-CH_3) (**22**).

This compound was obtained by the general procedure above; mp 166°; ^{1}H nmr (deuteriochloroform): δ 2.19 and 2.26 (2s, 9H, 2'-CH_3, 6'-CH_3 and 4'-CH_3), 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 6.89 (s, 2H, ArH), 7.40 (br s, NH); ir (potassium bromide): 3316 (NH), 1674 (C=O); hrms: Cacld. for $C_{15}H_{16}F_3NO_3$: 315.1082. Found: 315.1086.

5,6-Dihydro-*N*-(2-methyl)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 2-CH_3) (**22**).

This compound was obtained by the general procedure above; mp 145°; ^{1}H nmr (deuteriochloroform): δ 2.28 (s, 3H, 2'-CH_3) 4.29 (s, 4H, 5-CH_2 and 6-CH_2), 7.05-8.00 (m, 4H, ArH), 7.91 (br s, NH); ir (potassium bromide): 3328 (NH), 1674 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0765.

5,6-Dihydro-*N*-(3-methyl)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 3-CH_3) (**22**).

This compound was obtained by the general procedure above; mp 156°; ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, 3'-CH_3) 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 6.93-7.51 (m, 4H, ArH), 7.97 (br s, NH); ir (potassium bromide): 3328 (NH), 1676 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0762.

5,6-Dihydro-*N*-(4-methyl)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 4-CH_3) (**22**).

This compound was obtained by the general procedure above; mp 136°; ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H, 4'-CH_3) 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.13-7.49 (m, 4H, ArH), 7.98 (br s, NH); ir (potassium bromide): 3364 (NH), 1673 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_3$: 287.0769. Found: 287.0764.

5,6-Dihydro-*N*-(2-methoxy)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 2-OCH_3) (**22**).

This compound was obtained by the general procedure above; mp 125-126°; ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 3H, 2'-OCH_3) 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 6.88-8.46 (m, 4H, ArH), 8.67 (br s, NH); ir (potassium bromide): 3392 (NH), 1692 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_4$: 303.0718. Found: 303.0724.

5,6-Dihydro-*N*-(3-methoxy)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 3-OCH_3) (**22**).

This compound was obtained by the general procedure above; mp 122°; ^{1}H nmr (deuteriochloroform): δ 3.80 (s, 3H, 3'-OCH_3) 4.26 (s, 4H, 5-CH_2 and 6-CH_2), 6.66-7.34 (m, 4H, ArH), 8.06 (br s, NH); ir (potassium bromide): 3356 (NH), 1676 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_4$: 303.0718. Found: 303.0727.

5,6-Dihydro-*N*-(4-methoxy)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 4-OCH_3) (**22**).

This compound was obtained by the general procedure above; mp 106°; ^{1}H nmr (deuteriochloroform): δ 3.79 (s, 3H, 2'-OCH_3) 4.27 (s, 4H, 5-CH_2 and 6-CH_2), 6.85-7.51 (m, 4H, ArH), 7.93 (br s, NH); ir (potassium bromide): 3300 (NH), 1674 (C=O); hrms: Cacld. for $C_{13}H_{12}F_3NO_4$: 303.0718. Found: 303.0724.

5,6-Dihydro-*N*-(2-nitro)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 2-NO_2) (**22**).

This compound was obtained by the general procedure above; mp 164°; ^{1}H nmr (deuteriochloroform): δ 4.35 (s, 4H, 5-CH_2 and 6-CH_2), 7.20-8.88 (m, 4H, ArH), 11.28 (br s, NH); ir (potassium bromide): 3322 (NH), 1710 (C=O); hrms: Cacld. for $C_{12}H_9F_3N_2O_5$: 318.0464. Found: 318.0468.

5,6-Dihydro-*N*-(3-nitro)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 3-NO_2) (**22**).

This compound was obtained by the general procedure above; mp 182°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 4.30 (s, 4H, 5-CH_2 and 6-CH_2), 7.58-8.04 (m, 4H, ArH), 10.75 (br s, NH); ir (potassium bromide): 3360 (NH), 1704 (C=O); hrms: Cacld. for $C_{12}H_9F_3N_2O_5$: 318.0464. Found: 318.0470.

5,6-Dihydro-*N*-(4-nitro)phenyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 4-NO_2) (**22**).

This compound was obtained by the general procedure above; mp 213°; ^{1}H nmr (dimethyl-d_6 sulfoxide:deuteriochloroform = 1:4): δ 4.06 (s, 4H, 5-CH_2 and 6-CH_2), 7.64-7.95 (m, 4H, ArH), 9.64 (br s, NH); ir (potassium bromide) 3340 (NH), 1702 (C=O); hrms: Cacld. for $C_{12}H_9F_3N_2O_5$: 318.0464. Found: 318.0468.

N-(2-Chloro)phenyl-5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 2-Cl) (**22**).

This compound was obtained by the general procedure above; mp 138-139°; ^{1}H nmr (deuteriochloroform): δ 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.03-8.49 (m, 4H, ArH), 8.69 (br s, NH); ir (potassium bromide): 3376 (NH), 1702 (C=O); hrms: Cacld. for $C_{12}H_9ClF_3NO_3$: 307.0223. Found: 307.0225.

N-(3-Chloro)phenyl-5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 3-Cl) (**22**).

This compound was obtained by the general procedure above; mp 147-148°; ^{1}H nmr (deuteriochloroform): δ 4.29 (s, 4H, 5-CH_2 and 6-CH_2), 7.09-7.75 (m, 4H, ArH), 8.04 (br s, NH); ir (potassium bromide) 1680 (C=O), 3312 (NH); hrms: Cacld. for $C_{12}H_9ClF_3NO_3$: 307.0223. Found: 307.0230.

N-(4-Chloro)phenyl-5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxamide (R = 4-Cl) (**22**).

This compound was obtained by the general procedure above; mp 114°; ^{1}H nmr (deuteriochloroform) δ 4.26 (s, 4H, 5-CH_2 and 6-CH_2), 7.28-7.57 (m, 4H, ArH), 8.06 (br s, NH); ir (potassium bromide): 3400 (NH), 1702 (C=O); hrms: Cacld. for $C_{12}H_9ClF_3NO_3$: 307.0223. Found: 307.0232.

Methyl 5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxylate (**23**).

^{1}H NMR (deuteriochloroform): δ 3.84 (s, 3H, -OCH_3), 4.19-4.26 (m, 4H, 5-CH_2 and 6-CH_2); ir (potassium bromide): 1674 (C=O); ms: m/z (relative intensity) 212 (M^+, 35), 181 (M^+ - OCH_3, 28); hrms: Cacld. for $C_7H_7F_3O_4$: 212.0296. Found: 212.0287.

N,N-Diethyl-5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxamide (**24**).

^{1}H NMR (deuteriochloroform): δ 1.14, 1.18 (2t, J = 7.14, 6H, $N(CH_2CH_3)_2$), 3.33, 3.42 (2q, J = 7.14, 4H, $(CH_2CH_3)_2$), 4.12 (s, 4H, 5-CH_2 and 6-CH_2); ir (potassium bromide): 1644 (C=O); ms: m/z (relative intensity) 253 (M^+, 14), 181 (M^+ - $N(CH_2CH_3)_2$, 100); hrms: Cacld. for $C_{10}H_{14}F_3NO_3$: 253.0926. Found: 253.0928.

5,6-Dihydro-*N,N*-dimethyl-2-trifluoromethyl-1,4-dioxin-3-carboxamide (**25**).

^{1}H NMR (deuteriochloroform): δ 3.00, 3.03 (2s, 6H, $N(CH_3)_2$), 4.23(s, 4H, 5-$_2$ and 6-CH_2); ir (potassium bromide): 1654 (C=O); ms: m/z (relative intensity) 225 (M^+, 28), 181 (M^+ - $N(CH_3)_2$, 26); hrms: Cacld. for $C_8H_{10}F_3NO_3$: 225.0613. Found: 225.0618.

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

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[11] The yield was calculated by increase of the weight.

[12] The polymer-bound activated ester **21** was washed with methanol in the work-up when the **21** was prepared.

[13] Dihydro-1,4-dioxin methyl ester **23** was obtained in 92% yield when the activated ester **21** was heated in the presence of triethylamine (1.4 equiv wt) in acetonitrile for 10 hours.

[14] Elemental analysis data of the resin **19**: C, 69.34; H, 4.69; N, 3.63.