Construction of Dihydro-1,4-dioxins: Synthesis of Dihydro-1,4-dioxin-3-carboxanilides

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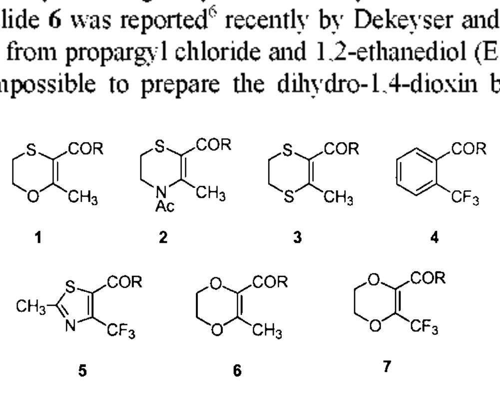
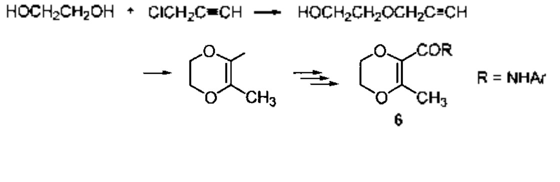
A new methodology for construction of dihydro-1,4-dioxin skeleton was described. Introduction of thio group at the α-position of **8** followed by chlorination gave **11**, which was to prevent an enolization as well as to promote the facile nucleophilic substitution reaction of ethylene glycol giving **16** in equilibrium with cyclic ether **19**. Removal of thio group of **19** and dehydration in the presence of an acid catalyst gave dihydro-1,4-dioxin **21**. In case of electron withdrawing trifluoromethyl group is subsituted in C-2, **18** was converted to the corresponding dihydro-1,4-dioxin **20** by the halogenation of hydroxy followed by treatment of triethylamine.

Keywords : Agrochemical, Fungicide, Pesticide, Dihydro-1,4-dioxin, α, β-Unsaturated carboxanilide.

Introduction

5,6-Dihydro-1,4-oxathiin-3-carboxanilide (**1**, carboxin) is an agrochemical systemic fungicide used for seed treatment and its fungi toxicity arises from *α,β*-unsaturated carboxanilide with methyl group in *cis* relationship.[1] As part of programs of synthesis and prospect of fungicidal activity of carboxin analogues we reported the syntheses of nitrogen **2** and sulfur **3** analogues[2] by replacing of oxygen in the oxathiin ring by a nitrogen or a sulfur atom respectively. Trifluoromethylated 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.[3] For example, commercialized fungicides, flutolanil[4] **4** and thifluzamide[5] **5** have trifluoromethyl group adjacent to the carboxanilide in the molecule. Our interest in carboxin analogue was aroused by the evaluation of fungicidal activity of the compound **6** and **7** by replacing the sulfur atom and the methyl group in the oxathiin ring by an oxygen atom and trifluoromethyl group respectively. Although a synthesis of dihydro-1,4-dioxin carboxanilide **6** was reported[6] recently by Dekeyser and Davis started from propargyl chloride and 1,2-ethanediol (Eq. 1) it was impossible to prepare the dihydro-1,4-dioxin bearing





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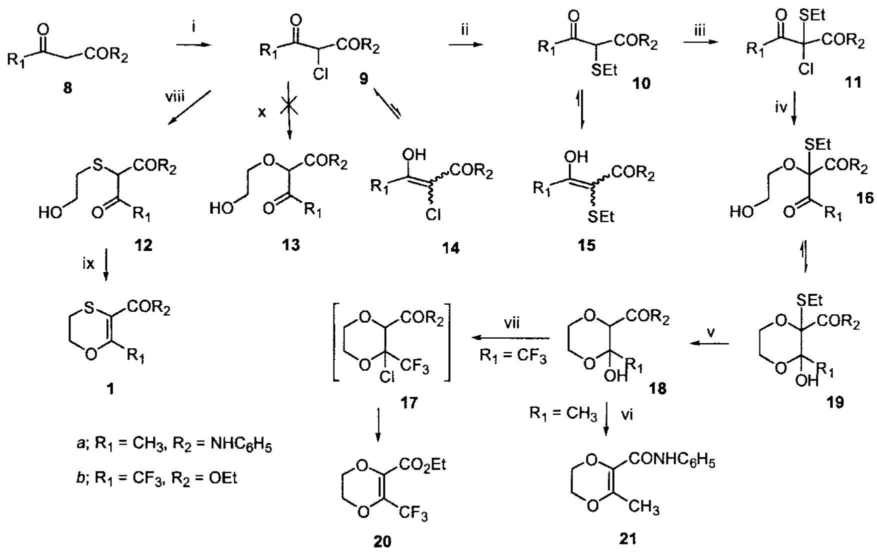
trifluoromethyl group in the molecule by application of the method. In this paper, we describe a new method for the construction of dihydro-1,4-dioxin skeleton.

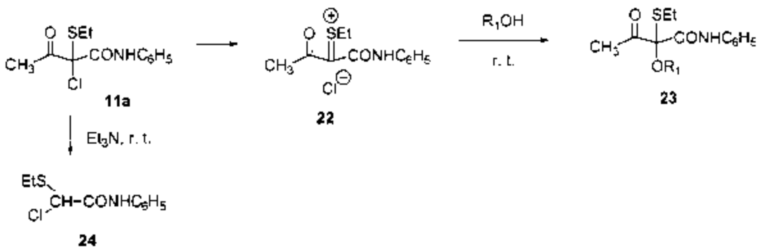
Results and Discussion

Synthesis of the title compounds was achieved according to method outlined in Scheme 1.

Chlorination of starting *β*-keto acid derivative **8a** was carried out by sulfuryl chloride to provide **9a** in good yield (85%). Similarly, treatment of **8b** with sulfuryl chloride yielded **9b** in low yield (< 10%). Satisfactory yield (85%) was obtained by chlorination of **8b** by chlorine at low temperature (10-15 °C).[7] Interestingly, **9a** was in equilibrium with its enol **14**, shown by the ^{1}H NMR spectroscopy. As reported previously,[8] the reaction of **9** with 2-mercaptoethanol in the presence of triethylamine at room temperature gave *β*-hydroxy sulfide **12**. No reaction was took place in treatment of **9** with ethylene glycol in the same reaction conditions and the similar reaction in the presence of sodium hydride instead of triethylamine failed, recovering the starting material. Enolization involving acidic α-proton of **9** and low nucleophilicity of oxygen of ethylene glycol would prevent the nucleophilic substitution reaction. Therefore, we considered an introduction of thio group at the α-position of **9** as a protecting group to prevent an enolization and to promote the facile nucleophilic substitution reaction. The lone pair electron of the sulfur might enhance the reaction. Reaction of **9** with ethanethiol gave sulfide **10** in quantitative yield, which was exist its enol **15** by the ^{1}H NMR spectroscopy. Chlorination of **10** with sulfuryl chloride followed by treatment of ethylene glycol afforded *β*-hydroxy ether **16** in equilibrium with cyclic ether 19, which was a diasteromeric mixture as indicated by the ^{1}H NMR spectroscopy. The facile nucleophilic displacement of the tertiary chloride by ethylene glycol would be attributed to the neighboring sulfur. The intermediate may be stabilized by formation of the probable thiiranium ion **22** (see Scheme 2) involving the lone pair electrons of the sulfur to facilitate nucleophilic sub-

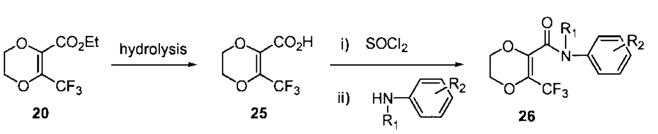


Scheme 1. Reagents and conditions: i) *for a*: SO_2Cl_2 25-30 °C, 2 h, *for b*: Cl_2, 10-15 °C, 1 h; ii) ethanethiol, Et_3N, C_6H_6, r.t., 4 h; iii) *for a*: SO_2Cl_2, CH_2Cl_2, r.t., 20 min, *for b*: SO_2Cl_2, C_6H_6, r.t., 1 h; iv) *for a*: ethylene glycol (10 equiv wt), r.t., 16 h, *for b*: ethylene glycol (4 equiv wt), r.t., 38 h; v) *for a*: Raney Ni (4 equiv wt), EtOH, reflux, 1 h; *for b*: Raney Ni (4 equiv wt), EtOH, reflux, 17 h; vi) *p*-TSA, C_6H_6, Dean-Stark reflux, 2.5 h; vii) $SOCl_2$, C_6H_6, r.t., 1 h and then Et_3N, C_6H_6, reflux, 16 h; viii) 2-mercaptoethanol, Et_3N, C_6H_6, 2 h; ix) *p*-TSA, C_6H_6, Dean-Stark reflux, 3 h; x) ethylene glycol, Et_3N or NaH, r.t., 20 h.



Scheme 2

stitution. The fact that an independent reaction of **11** in the presence of an excess amount of triethylamine at room temperature resulted in decomposition to yield **24**[9] suggested that the addition of triethylamine was disadvantage in this reaction. Similarly, solvolysis of **11** in methyl or ethyl alcohol at room temperature gave the corresponding **23** in quantitative yield. The cyclic ether **19** protected by ethanethiol transformed smoothly to the desired 1,4-dioxane **18** by treatment of Raney Ni in refluxing ethanol. No increased yield was obtained if the propanethiol or thiophenol was used instead of ethanethiol for the protecting group. Dehydration of **18a** in the presence of acid catalyst (*p*-toluenesulfonic acid monohydrate, *p*-TSA) in refluxing benzene with Dean-Stark water separator gave the desired dihydro-1,4-dioxin-3-carboxanilide **21**. In the other hand, acid-catalyzed (*p*-TSA) dehydration of **18b** in refluxing benzene as the same manner described above was not successful, probably due to the strong electron withdrawing character of the trifluoromethyl group.[10] Substitution of hydroxy in **18b** for a better leaving chlorine by treatment with thionyl chloride followed by exposure to triethylamine in refluxing benzene afforded dihydro-1,4-dioxin **20** (62% yield from **18b**) through plausible intermediate **17**.



Scheme 3

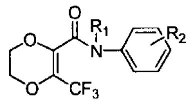
According to our synthetic program, the next step was a synthesis of trifluoromethylated dihydro-1,4-dioxin carboxanilide derivatives (Scheme 3). Hydrolysis of the ethyl ester **20** gave trifluoromethylated dihydro-1,4-dioxin carboxylic acid **25**. Reaction of **25** with thionyl chloride followed by treatment of aniline derivatives yielded the corresponding trifluoromethylated dihydro-1,4-dioxin carboxanilides **26**.

Table 1 shows a list of dihydro-1,4-dioxin carboxanilides prepared, yields, melting points and ^{1}H NMR spectra.

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 (300 MHz) in $CDCl_3$. 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}. Electron impact high-resolution mass spectra (HRMS)

Table 1. A list of dihydro-1,4-dioxin carboxanilides prepared, yields, melting points, ^{1}H NMR and IR spectral data



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No	R_1	R_2	yields (%)	mp (°C)	^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) and FT-IR (KBr, cm^{-1})
1	H	H	95	140	4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.10-7.60 (m, 5H, ArH), 8.01 (s, 1H, NH); 3264, 1638.
2	H	2-Cl	84	138-139	4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.03-8.49 (m, 4H, ArH), 8.69 (s, 1H, NH); 3376, 1638.
3	H	3-CF_3	88	130	4.30 (s, 4H, 5-CH_2 and 6-CH_2), 7.38-7.84 (m, 4H, ArH), 8.15 (s, 1H, NH); 3314, 1652.
4	H	3-CF_2CHF_2	96	77-78	4.29 (s, 4H, 5-CH_2 and 6-CH_2), 5.70-7.59 (m, 4H, ArH), 8.10 (s, 1H, NH); 3320, 1676
5	H	2-OCH_3	90	125-126	3.90 (s, 3H, ArOCH_3), 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 6.87-8.45 (m, 4H, ArH), 8.66 (s, 1H, NH); 3392, 1644.
6	H	2-CH_3	91	145	2.28 (s, 3H, ArCH_3), 4.29 (s, 4H, 5-CH_2 and 6-CH_2), 7.05-8.00 (m, 4H, ArH), 7.91 (s, 1H, NH); 3328, 1654.
7	H	3-$OCH(CH_3)_2$	89	97-98	1.31 (d, *J* = 6.6 Hz, 6H, 2xCH_3), 4.27 (s, 4H, 5-CH_2 and 6-CH_2), 4.52-4.60 (m, 1H, OCH), 6.64-7.31 (m, 4H, ArH), 7.96 (s, 1H, NH); 3264, 1644.
8	H	4-$OCH(CH_3)_2$	88	92	1.31 (d, *J* = 6.6 Hz, 6H, 2xCH_3), 4.27 (s, 4H, 5-CH_2 and 6-CH_2), 4.52-4.60 (m, 1H, OCH), 6.83-7.48 (m, 4H, ArH), 7.90 (s, 1H, NH); 3302, 1650.
9	H	2-Cl, 4-Cl	93	152-153	4.31 (s, 4H, 5-CH_2 and 6-CH_2), 7.24-8.47 (m, 3H, ArH), 8.66 (s, 1H, NH); 3384, 1638.
10	H	2-Cl, 4-CH_3	87	175-176	2.33 (s, 3H, ArCH_3), 4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.15-7.70 (m, 3H, ArH), 7.98 (s, 1H, NH); 3296, 1676.
11	H	2-CH_3, 4-CH_3	93	125-127	2.23 and 2.28 (2s, 6H, 2xArCH_3), 4.29 (s, 4H, 5-CH_2 and 6-CH_2), 7.00-7.79 (m, 3H, ArH), 7.82 (s, 1H, NH); 3402, 1638.
12	H	3-OC_6H_5	94	104-105	4.26 (s, 4H, 5-CH_2 and 6-CH_2), 6.75-7.42 (s, 9H, ArH), 8.00 (s, 1H, NH); 3258, 1640, 1672.
13	H	2-Cl, 4-Cl, 6-Cl	99	152	4.28 (s, 4H, 5-CH_2 and 6-CH_2), 7.40 (s, 2H, ArH), 7.75 (s, 1H, NH); 3278, 1656.
14	Et	3,4-methylenedioxy	79	not determined	1.14 (t, *J* = 6.9 Hz, 3H, CH_3), 3.69-3.94 (m, 6H, N-CH_2 and 5-CH_2 and 6-CH_2), 6.01 (s, 2H, CH_2), 6.67-7.24 (m, 3H, ArH); 3448, 1662.

were obtained on a Finnigan MAT95S.

Preparation of 2-chloro-3-oxo-*N*-phenylbutanamide (9a). To a suspension of acetoacetanilide **8a** (88.5 g, 0.5 mol) in benzene (600 mL) was added dropwise sulfuryl chloride (44 mL, 0.5 mol) at 25-30 °C under cold water bath while stirring. Stirring was continued at room temperature for 2 h. The white precipitates were filtered and the filter cake was washed with cold water. Crystallization from ethanol (500 mL) gave **9a** as a white needle (85.5 g, 81%).

mp 138-139 °C; ^{1}H NMR 2.20 (s, 0.9H, CH_3)*a*, 2.48 (s, 2.1H, CH_3)*b*, 4.96 (s, 0.7H, methine), 7.16-7.74 (m, 5H, ArH), 7.96 (br s, 0.3H, NH)*a*, 8.17 (br s, 0.7H, NH)*b*, 13.5 (s, 0.3H, enolic OH); IR (KBr) 3256 (NH), 1750 (C=O), 1671 (anilide C=O) cm^{-1}; MS (relative intensity) m/e 211 (M^+, 38), 134 (M^+- C_6H_5, 33), 119 (M^+- NHC_6H_5, 19).

a/*b* = enol form/keto form

Preparation of ethyl *α*-chloro-γ,γ,γ-trifluoroacetoacetate (9b). Ethyl 4,4,4-trifluoro-3-oxobutyrate (**8b**) (98.35 g, 0.45 mol) was treated with chlorine while stirring at 20 °C until the weight of the reaction mixture reaches to 15% increase. Nitrogen gas was purged to remove excess chlorine and HCl formed, and then fractional vacuum distillation gave **9b** as a transparent oil (83.9 g, 84%).

bp 92 °C/30 mmHg; ^{1}H NMR 1.35 (t, *J* = 7.2, 3H, CH_3), 4.35 (q, *J* = 7.2, 2H, CH_2), 5.22 and 12.52 (2s, 1H, CH and OH).

Preparation of 2-ethylthio-3-oxo-*N*-phenylbutanamide (10a). To a suspension of **9a** (29.8 g, 0.141 mol) in benzene (300 mL) was added dropwise a mixture of ethanethiol (11.0 mL, 0.148 mol) and triethylamine (20.6 mL, 0.15 mol) over 8 min. The reaction mixture was stirred at room temperature over 70 min. The reaction mixture was washed with saturated sodium bicaronate solution and cold water and then dried ($MgSO_4$). Evaporation of the solvent gave **10a** as a light yellow oil (33.4 g, 100%).

^{1}H NMR 1.27 (t, *J* = 7.4, 3H, SCH_2CH_3), 2.37 (s, 3H, CH_3), 2.58 (q, *J* = 7.4, 2H, SCH_2CH_3), 7.11-7.75 (m, 5H, ArH), 9.13 (s, 1H, NH), 15.25 (s, 1H, OH); IR (KBr) 1592 (C=C) cm^{-1}; MS (relative intensity) m/e 237 (M^-, 65), 207 (39), 135 (100).

Preparation of ethyl *α*-ethylthio-γ,γ,γ-trifluoroacetoacetate (10b). To a solution of **9b** (51.6 g, 0.236 mol) and triethylamine (34.6 mL, 0.248 mol) in benzene (600 mL) under the cold water bath was added dropwise ethanethiol (18.4 mL, 0.248 mol) over 10 min. Stirring was continued for 4 h at room temperature. The reaction mixture was washed with cold water twice and dried ($MgSO_4$). Evaporation of the solvent gave ethylthio ethyl ester **10b** as a yellow liquid (44.8 g, 78%).

^{1}H NMR 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, 1.2H, OCH_2 (enol)), 4.41 (q, *J* = 7.1, 0.8H, OCH_2 (keto)), 4.48 (s, 0.4H, methine), 13.68 (s, 0.6H, enolic OH); IR (KBr) 3446 (enolic OH), 1734 (C=O); HRMS Cacld. for $C_8H_{11}F_3O_3S$: 244.0381. Found: 244.0353.

Preparation of 2-chloro-2-ethylthio-3-oxo-*N*-phenyl-

butanamide (11a). To a solution of **10a** (26 g, 0.11 mol) in methylene chloride (26 mL) was added sulfuryl chloride (8.9 mL, 0.11 mol) over 2 min. The reaction mixture was stirred at room temperature for 20 min. Evaporation of the solvent gave **11a** as a light red oil (29.8 g, 100%).

^{1}H NMR 1.13 (t, J = 7.5, 3H, SCH_2CH_3), 2.33 (s, 3H, CH_3), 2.60 (q, J = 7.5, 2H, SCH_2CH_3), 7.00-7.39 (m, 5H, ArH), 8.26 (br s, 1H, NH); IR (KBr) 3434 (NH), 1599 (C=C) cm^{-1}; MS (relative intensity) m/e 271 (M^+, not found), 235 (M^+-Cl, 100).

Solvolysis of 2-chloro-2-ethylthio-3-oxo-*N*-phenylbutanamide (11a) in alcohol, *General Procedure*. A solution of **11a** (1 g, 3.7 mmol) in alcohol (10 mL) was stirred at room temperature for 17 h. Evaporation of the solvent gave an oily residue, which was dissolved in methylene chloride, washed with saturated sodium bicarbonate solution and water twice. Drying ($MgSO_4$) and evaporation of the solvent gave a light yellow solid (0.765 g). Crystallization from benzene and *n*-hexane afforded the desired compound as a white needle.

2-Ethylthio-2-methoxy-3-oxo-*N*-phenylbutanamide (23a). yield 78%, mp 93-95 °C; ^{1}H NMR 1.24 (t, J = 7.7, 3H, SCH_2CH_3), 2.37 (s, 3H, CH_3), 2.43-2.55 (m, 2H, SCH_2CH_3), 3.50 (s, 3H, OCH_3), 7.16-7.59 (m, 5H, ArH), 8.37 (br s, 1H, NH); IR (KBr) 3360 (NH), 1726 (C=O), 1626 (anilide C=O) cm^{-1}; MS, m/e 267 (M^+, 27), 73 (100), 60 (87).

2-Ethoxy-2-ethylthio-3-oxo-*N*-phenylbutanamide (23b). yield 79%, mp 90-91 °C; ^{1}H NMR 1.25 (t, J = 7.5, 3H, SCH_2CH_3), 1.38 (t, J = 7, 3H, OCH_2CH_3), 2.37 (s, 3H, CH_3), 2.42-2.60 (m, 2H, SCH_2CH_3), 3.57-3.90 (m, 2H, OCH_2CH_3), 7.15-7.60 (m, 5H, ArH), 8.45 (br s, 1H, NH); IR (KBr) 3356 (NH), 1725 (C=O), 1686 (anilide C=O) cm^{-1}; MS, m/e (relative intensity) 281 (M^+, 61), 85 (37).

Preparation of 3-ethylthio-2-hydroxy-2-methyl-*N*-phenyl-1,4-dioxane-3-carboxamide (19a). A mixture of **11a** (20 g, 73.7 mmol) in excess amount of ethylene glycol (41 mL, 737 mmol) was stirred at room temperature for 16 h. The reaction mixture was diluted with benzene (200 mL) and washed with brine (50 mL × 4), and then dried ($MgSO_4$). Evaporation of the solvent gave light yellow oily residue (22 g, 100%). Crystallization from ethyl acetate and *n*-hexane afforded **19a** as a white needle.

mp 112-114 °C; ^{1}H NMR 1.27 (t, J = 7.5, 2.3H, SCH_2CH_3), 1.37 (t, J = 7.3, 0.7H, SCH_2CH_3), 1.71 (s, 2.3H, t-CH_3), 1.73 (s, 0.7H, t-CH_3), 2.51-2.76 (m, 2H, SCH_2), 3.69-4.69 (m, 5H, OCH_2CH_2O and OH), 7.15-7.64 (m, 5H, ArH), 8.57 (br s, 1H, NH); 3436 (OH), 3296 (NH), 1676 (C=O) cm^{-1}; MS, m/e (relative intensity) 297 (M^+, 28), 281 (37), 163 (100).

Preparation of ethyl 3-ethylthio-2-hydroxy-2-trifluoromethyl-1,4-dioxane-3-carboxylate (19b). To a solution of ethylthio ethyl ester **10b** (43.8 g, 0.18 mol) in benzene (40 mL) under the cold water bath was added dropwise sulfuryl chloride (15.2 mL, 0.188 mmol) over 10 min. The reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated to give **11b** as an oily residue. Without purification of **11b**, a mixture of this oil and excess amount of ethylene glycol (39.4 mL, 0.75 mol) was stirred for 38 h at room temperature. The reaction mixture diluted with methylene chloride (600 mL) and washed with water twice and dried ($MgSO_4$). Evaporation of the solvent gave dioxane **19b** as a white solid (39 g, 82.1%).

mp 92-94 °C; ^{1}H NMR 1.27 (t, J = 7.5, 3H), SCH_2CH_3), 1.36 (t, J = 7.2, 3H, OCH_2CH_3), 2.57 (q, J = 7.5, 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 (KBr) 3374 (OH), 1734 (C=O); HRMS Cacld. for $C_{10}H_{15}F_3O_5S$: 304.0592. Found: 304.0591.

Preparation of 2-hydroxy-2-methyl-*N*-phenyl-1,4-dioxane-3-carboxamide (18a). To a suspension of Raney Ni prepared[11] freshly from nickel-aluminum alloy (11.2 g, 0.1 mol) in ethanol (50 mL) was added **19a** (3.0 g, 10 mmol). The reaction mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to give oily residue, which was dissolved in methylene chloride (100 mL) and washed with 1 *N* hydrochloric acid, water, and then dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **18a** as a colorless oil (2.3 g, 98%).

^{1}H NMR 1.50 and 1.60 (2s, 3H, CH_3), 3.61-4.20 (m, 6H, OCH_2CH_2O, methine and OH), 7.12-7.59 (m, 5H, ArH), 8.30 and 8.36 (2s, 1H, NH); IR (KBr) 3406 (OH), 1701 (C=O) cm^{-1}; MS, m/e (relative intensity) 237 (M^+, not found), 219 (M^+-H_2O, 55), 127 (M^+- H_2O-NHC_6H_5, 100).

Preparation of ethyl 2-hydroxy-2-trifluoromethyl-1,4-dioxane-3-carboxylate (18b). A suspension of ethylthio dioxane **19b** (30 g, 96 mmol) and Raney Ni (113 g) in ethanol (600 mL) was refluxed for 17 h. 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 ($MgSO_4$). Evaporation of the solvent gave hydroxy-1,4-dioxane **18b** as a white solid (16.5 g, 70%).

mp 40-41 °C; ^{1}H NMR 1.32 (t, J = 7.1, 3H, CH_3), 3.70-4.52 (m, 7H, CH_2CH_3, 3-CH, 5-CH_2 and 6-CH_2), 5.61 (s, 1H, OH); IR (KBr) 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 (20). To a solution of hydroxy 1,4-dioxane **18b** (16 g, 66 mmol) in benzene (300 mL) cooled in an ice bath under the nitrogen atmosphere was added sequentially pyridine (5.44 mL, 66 mmol) and thionyl chloride (5.12 mL, 66 mmol). The reaction mixture was stirred for 2 h 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 mol) in benzene (40 mL) was refluxed for 16 h. 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 ($MgSO_4$). Evaporation of the solvent gave brown oily residue, which was purified by chromatography (*n*-hexane : ethyl acetate = 4 : 1) to give 1,4-dioxin **20** as a yellow oil (8.5 g, 62.1%).

^{1}H NMR 1.33 (t, J = 7.1, 3H, CH_3), 4.20-4.26 (m, 4H, 5-

CH_2 and 6-CH_2), 4.31 (q, J = 7.1, 2H, CH_2CH_3); IR (KBr) 1730 (C=O); HRMS Cacld. for $C_8H_9F_3O_4$: 226.0453. Found: 226.0453.

Preparation of 2-methyl-*N*-phenyl-1,4-dioxin-3-carboxamide (21). A solution of 1,4-dioxane **18a** (3.5 g, 15 mmol) and *p*-toluenesulfonic acid monohydrate (0.14 g) in benzene (35 mL) was refluxed with Dean-Stark water trap for 2.5 h. The reaction mixture was cooled to room temperature and washed with saturated sodium bicarbonate solution, water, and then dried ($MgSO_4$). Evaporation of the solvent gave light yellow solid (3.0 g), which was crystallized form ethyl acetate and *n*-hexane afforded **21** as a light yellow needle (1.76 g, 54%).

mp 92-94 °C; ^{1}H NMR 2.34 (s, 3H, CH_3), 4.12-4.20 (m, 4H, OCH_2CH_2O), 7.05-7.58 (m, 5H, ArH), 8.19 (s, 1H, NH); IR (KBr) 3286 (NH), 1676 (C=O) cm^{-1}; MS, m/e (relative intensity) 219 (M^+, 48), 127 (M^+-NHC_6H_5, 100).

Preparation of 5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carboxylic acid (25). A solution of dihydro-1,4-dioxin ethyl ester **20** (8.0 g, 34 mol) and sodium hydroxide (2.1 g, 51 mol) in water (20 mL) was refluxed for 1 h. The reaction mixture was cooled, washed with methylene chloride. The aqueous solution was acidified with 6 *N* hydrochloric acid until the pH reaches 3. The reaction mixture was extracted with ethyl ether twice. Evaporation of the solvent gave solid residue, which was crystallized from ethyl acetate and *n*-hexane to afford dihydro-1,4-dioxin carboxylic acid **25** (4.7 g, 67%).

mp 120-122 °C; ^{1}H NMR 4.21-4.29 (m, 4H, 5-CH_2 and 6-CH_2), 10.35 (s, 1H, OH); IR (KBr) 1714 (C=O); HRMS Cacld. for $C_6H_5F_3O_4$: 198.0140. Found: 198.0138.

Preparation of 5,6-dihydro-2-trifluoromethyl-1,4-dioxin-3-carbxanilides (26), *General Procedure*. A solution of dihydro-1,4-dioxin carboxylic acid **25** (0.53 g, 2.7 mmol) and thionyl chloride (0.21 mL, 2.8 mmol) in benzene (10 mL) was refluxed for 1 h. Evaporation of the solvent gave a light yellow oily residue, which was diluted with benzene (10 mL) and treated with aniline (5.4 mmol). Stirring was continued for 2 h at room temperature. The reaction mixture was washed with 1 *N* hydrochloric acid, saturated sodium hydrogen bicarbonate solution, and cold water. Drying ($MgSO_4$) and evaporation of the solvent gave the corresponding carboxanilide **26** (yield 79-99%).

References and Notes

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9. We isolated 2-chloro-2-ethylthio-*N*-phenylethanamide (**24**) in 77% yields from the reaction of **11** in the presence of an excess amount of triethylamine for 17 h at room temperature; viscose red oil; ^{1}H NMR 1.26 (t, J = 7.4, 3H, SCH_2CH_3), 2.63 (q, J = 7.4, 2H, SCH_2), 4.74 (s, 1H, methine), 7.19-7.42 (m, 5H, ArH), 7.67 (s, 1H, NH); IR (KBr) 3253 (NH), 1683 (C=O) cm^{-1}; MS, m/e 229.7 (M^+, not found).
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