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A CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 4-ALKOXYDIHYDROBENZO[*b*][1,4]DIAZEPINOLS AND 3*H*-BENZO[*b*][1,4]DIAZEPINES BY THE REACTION OF β -TRIFLUOROACETYLKETENE ACETALS WITH 1,2-PHENYLENE-DIAMINES

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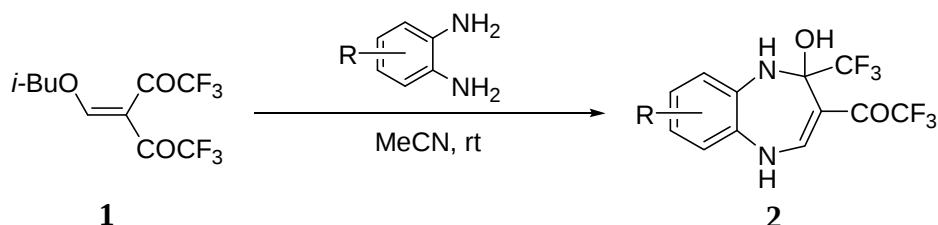
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Abstract – β -Trifluoroacetylketene dialkyl acetals (**3** and **5**) reacted easily with various 1,2-phenylenediamines to give novel 4-alkoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**) in moderate to high yields. Dehydration of **6** and **8** proceeded thermally under reduced pressure to afford the corresponding fluorine-containing 3*H*-benzo[*b*][1,4]diazepines (**7** and **9**).

INTRODUCTION

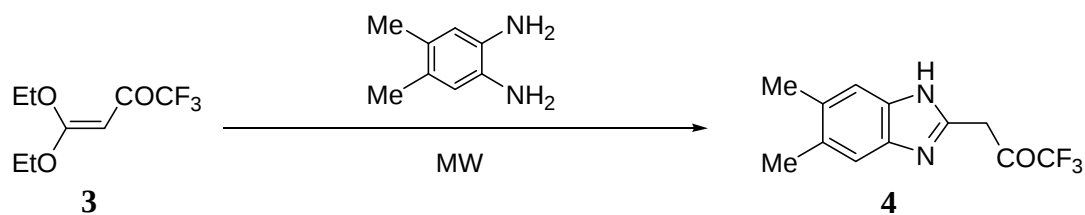
Benzo[*b*][1,4]diazepines have attracted much attention as an important class of heterocycles in the field of medicinal and agricultural chemistries.¹ These compounds are widely used as powerful agents, especially for the antipsychotic therapy.² Very recently, we have reported the facile synthesis of novel fluorine-containing dihydrobenzo[*b*][1,4]diazepinols (**2**),³ some of which showed remarkable antineoplastic efficacy,⁴ by the reaction of β,β -bis(trifluoroacetyl)vinyl ethers (**1**) with various 1,2-phenylenediamines (Scheme 1). In our previous studies, it was found that ketene dithioacetals⁵ and orthoacetates⁶ reacted with trifluoroacetic anhydride quite easily to afford the corresponding β -trifluoroacetylated ketene *S,S*- and *O,O*-acetals, respectively, and that these acylated compounds

cleanly underwent nucleophilic *S-N* and *O-N* exchange reactions^{7,8} with aliphatic and aromatic amines to give β -trifluoroacetylated ketene *S,N*-, *O,N*-, and *N,N*-acetals. Thereafter, these β -trifluoroacetyl-



Scheme 1

ketene acetals were found to be convenient building blocks which are applicable to the syntheses of a variety of novel fluorine-containing heterocyclic compounds by the reactions with bifunctional nucleophiles. For instance, fluorine-containing isoxazolines, 1*H*-pyrazolines, and imidazolines were easily obtained by the reactions with hydroxylamine, hydrazines, and 1,2-ethylenediamine, respectively.^{9,10} Additionally, Reddy *et al.* reported the interesting reaction of β -trifluoroacetylketene acetal (**3**) with 4,5-dimethyl-1,2-phenylenediamine under microwave irradiation to give solely benzimidazoles (**4**) without any formation of benzodiazepines (Scheme 2).¹¹ These studies and our



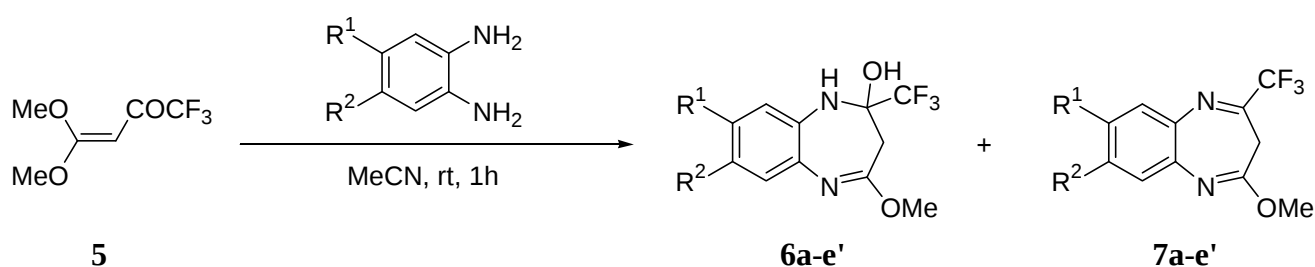
Scheme 2

continuing interest in the synthesis of trifluoromethyl-containing benzodiazepines, a new potential pharmacophore of antineoplastic efficacy, prompted us to explore the feasibility of the benzodiazepine-ring construction by the non-microwave assisted cyclization reaction of β -trifluoroacetylketene acetals with 1,2-phenylenediamines. In this paper we wish to report the annulation reaction of β -trifluoroacetylketene acetals (**3** and **5**) with various 1,2-phenylenediamines under very mild conditions without microwave irradiation to afford the desired fluorine-containing 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**) having an alkoxy group at the C-4 position. In addition, the

thermally induced dehydration of **6** and **8** under reduced pressure leading to the formation of the corresponding 2-alkoxy-3*H*-benzo[*b*][1,4]diazepines (**7** and **9**) is presented.

RESULTS AND DISCUSSION

β -Trifluoroacetylketene dimethyl acetal (**5**) was easily prepared in 92% yield by the acylation of trimethyl orthoacetate with trifluoroacetic anhydride according to our method reported previously.^{6,12} The results of the annulation reaction of **5** with 1,2-phenylenediamines are depicted in Scheme 3 and summarized in Table 1. Reaction of **5** with slightly excess amounts of 1,2-phenylenediamine readily occurred at room



Scheme 3

Table 1. Reaction of β -trifluoroacetylketene dimethyl acetal (**5**) with 1,2-phenylenediamines.^a

Entry	R ¹	R ²	Product	Yield (%) ^b
1	H	H	6a	68
			7a	5
2	Me	Me	6b	63
			7b	13
3	Cl	Cl	6c	78
			7c	5
4	COPh or H	H or COPh	6d and 6d' ^c	81 ^d
			7d and 7d' ^c	2 ^d
5	NO ₂ or H	H or NO ₂	6e and 6e' ^c	65 ^d
			7e and 7e' ^c	11 ^d

^a 1.1 equiv of 1,2-phenylenediamines was used.

^b Isolated yield after chromatography.

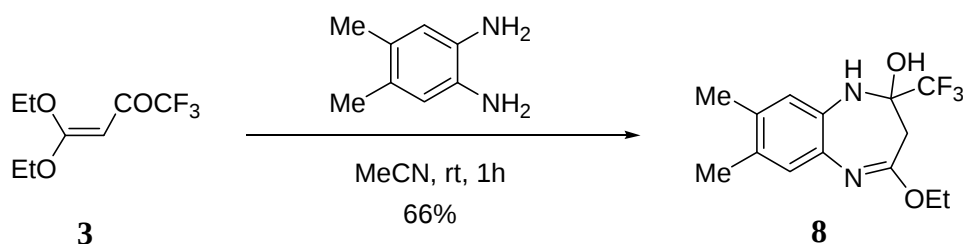
^c The mixture of the two regioisomers was placed on the column. The regio-chemistry and the ratio are not determined yet.

^d Combined yield of two regioisomers.

temperature in acetonitrile to give the desired 4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**6a**) in 68% yield with the formation of its dehydrated product,

2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (**7a**), in 5% yield (Entry 1). Similarly, 4,5-dimethyl- and 4,5-dichloro-1,2-phenylenediamines reacted with **5** to afford the corresponding dihydrobenzodiazepinols (**6b,c**) - benzodiazepines (**7b,c**) mixtures in high combined yields (Entries 2 and 3). The annulation with unsymmetrical 1,2-phenylenediamines such as 4-benzoyl- and 4-nitro-1,2-phenylenediamines also proceeded cleanly to afford the mixtures of the four components, the two regioisomers of dihydrobenzodiazepinols (**6d,d'** and **6e,e'**) and those of benzodiazepines (**7d,d'** and **7e,e'**), in excellent combined yields (Entries 4 and 5). Although the attempted separation of mixtures of the two regioisomers was unsuccessful, all of the separation of the mixtures into **6a-e'** and **7a-e'** was easily performed by column chromatography.

These results of our approaches on the reactions of **5** with 1,2-phenylenediamines show sharp contrast with those reported by Reddy *et al* (see Scheme 2).¹¹ As shown in Scheme 3, dihydrobenzodiazepinols (**6**) were obtained predominantly, together with the small amounts of the corresponding benzodiazepines (**7**) under very mild conditions in the absence of microwave irradiation in acetonitrile without any formation of the corresponding benzimidazoles (**4**). To verify no difference in reactivities between dimethyl derivative (**5**) and diethyl one (**3**), we then examined the reaction of **3** with 4,5-dimethyl-1,2-phenylenediamine, in which 4-ethoxy derivative of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**8**) was obtained solely in 66% yield without corresponding benzimidazoles (**4**) as depicted in Scheme 4.



Scheme 4

Next we attempted the acid-catalyzed dehydration of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ols (**6a-e'** and **8**) to 3*H*-benzo[*b*][1,4]diazepines (**7a-e'** and **9**), but this resulted in failure to give complex mixtures. So, we tried to carry out the present dehydration with the use of Kugelrohr distillation apparatus, namely, by heating under reduced pressure, as depicted in Scheme 5 and summarized in Table 2. All dihydrobenzodiazepinols (**6a-e'** and **8**) was thoroughly dehydrated at 110-150 °C under reduced pressure (3 mmHg) within 1.5 h to provide the corresponding benzodiazepines (**7a-e'** and **9**) in high yields except for the cases of **7a** and **7e,e'** with formation of large amounts of decomposition products.



Scheme 5

Table 2. Dehydration of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6a-e'** and **8**).

Entry	R ¹	R ²	R ³	Temp (°C) ^a	Product	Yield (%) ^b
1	H	H	Me	110	7a	24
2	Me	Me	Me	120	7b	91
3	Cl	Cl	Me	120	7c	75
4 ^c	COPh or H	H or COPh	Me	110	7d and 7d' ^d	89 ^e
5 ^c	NO ₂ or H	H or NO ₂	Me	150	7e and 7e' ^d	48 ^e
6	Me	Me	Et	120	9	85

^a Oven temperature (3 mmHg).^b Isolated yield after distillation.^c A mixture of two regioisomers (**6d,d'** or **6e,e'**) was used as a starting material.^d The mixture of two regioisomers was distilled. The regiochemistry and the ratio are not determined yet.^e Combined yield of two regioisomers.

In summary, we have developed a facile and convenient synthetic method for 4-alkoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**), which are not easily obtained by other methods. Moreover, the thermal dehydration of **6** and **8** was successfully carried out under reduced pressure to give 2-alkoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepines (**7** and **9**). Evaluation of biological activities, especially of antineoplastic efficacy, is now under way for novel fluorine-containing benzodiazepines (**6-9**).

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. The ¹H NMR spectra were recorded on a Bruker AVANCE500 spectrometer using TMS as an internal standard. IR spectra were taken with a PerkinElmer Spectrum ONE FT-IR spectrometer. Microanalyses were taken with a YANACO CHN-Corder MT-5 analyzer.

Synthesis of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (**5**).¹²

To an ice-cooled stirred solution of 1,1,1-trimethoxyethane (4.81 g, 40 mmol) and pyridine (6.33 g, 80 mmol) in CHCl₃ (40 mL) was added dropwise trifluoroacetic anhydride (16.80 g, 80 mmol) and the

mixture was stirred for 3 h at rt. Then, CH₂Cl₂ (100 mL) was added and the whole mixture was washed with 10 % aq. Na₂CO₃ (50 mL) and with water (50 mL), and dried over Na₂SO₄. The solvent and pyridine was removed in vacuo to give **5** (6.76 g, 92%). **5**: mp 67-68 °C (*n*-hexane-EtOAc); ¹H NMR (CDCl₃): δ 4.98 (s, 1H, =CH), 3.98 (s, 3H, CH₃), 3.92 (s, 3H, CH₃); IR (KBr): 1675 (C=O) cm⁻¹. Anal. Calcd for C₆H₇F₃O₃: C, 39.14; H, 3.83. Found: C, 39.16; H, 3.82.

General procedure for the synthesis of 4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-2-ols (6a-e'**) and 4-methoxy-2-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepines (**7a-e'**).**

To a solution of **5** (184 mg, 1.0 mmol) in MeCN (4 mL) was added 1,2-phenylenediamines (1.1 mmol) and the mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane-EtOAc (9:1) as eluent to give **6a-e'** and **7a-e'**. In the case with 4-benzoyl-1,2-phenylenediamine, a mixture of **6d** and **6d'** and a mixture of **7d** and **7d'** were eluted respectively. Similarly, a mixture of **6e** and **6e'** and a mixture of **7e** and **7e'** were eluted respectively in the case with 4-nitro-1,2-phenylenediamine.

4-Methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6a**):** mp 126-127 °C (*n*-hexane-EtOAc); ¹H NMR (CDCl₃): δ 7.10-6.81 (m, 4H, H_{arom}), 4.11 (s, 1H, OH or NH), 3.91 (s, 3H, OCH₃), 3.27 (s, 1H, OH or NH), 2.82 (d, 1H, *J* = 14.0 Hz, CH₂), 2.61 (d, 1H, *J* = 14.0 Hz, CH₂); IR (KBr): 3326, 3112, 1652 cm⁻¹. Anal. Calcd for C₁₁H₁₁F₃N₂O₂: C, 50.77; H, 4.26; N, 10.77. Found: C, 50.72; H, 4.43; N, 10.65.

4-Methoxy-7,8-dimethyl-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6b**):** mp 122-123 °C (*n*-hexane-EtOAc); ¹H NMR (CDCl₃): δ 6.89 (s, 1H, H_{arom}), 6.62 (s, 1H, H_{arom}), 4.05 (s, 1H, OH or NH), 3.88 (s, 3H, OCH₃), 3.14 (s, 1H, OH or NH), 2.81 (d, 1H, *J* = 14.0 Hz, CH₂), 2.59 (d, 1H, *J* = 14.0 Hz, CH₂), 2.20 (s, 3H, CH₃), 2.19 (s, 3H, CH₃); IR (KBr): 3321, 3082, 1652 cm⁻¹. Anal. Calcd for C₁₃H₁₅F₃N₂O₂: C, 54.16; H, 5.24; N, 9.72. Found: C, 54.10; H, 5.01; N, 9.47.

7,8-Dichloro-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6c**):** mp 117-118 °C (*n*-hexane-EtOAc); ¹H NMR (CDCl₃): δ 7.21 (s, 1H, H_{arom}), 6.97 (s, 1H, H_{arom}), 4.21 (s, 1H, OH or NH), 3.89 (s, 3H, OCH₃), 3.17 (s, 1H, OH or NH), 2.84 (d, 1H, *J* = 14.0 Hz, CH₂), 2.63 (d, 1H, *J* = 14.0 Hz, CH₂); IR (KBr): 3315, 3071, 1648 cm⁻¹. Anal. Calcd for C₁₁H₉Cl₂F₃N₂O₂: C, 40.14; H, 2.76; N, 8.51. Found: C, 40.28; H, 2.74; N, 8.40.

A mixture of (2-hydroxy-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-8-yl)phenylmethanone (6d**) and (2-hydroxy-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (**6d'**):** ¹H NMR (CDCl₃): δ 7.74-6.82 (m, 8H, H_{arom}), 4.61 (s, 1H, OH or NH), 4.50 (s, 1H, OH or NH), 3.92, 3.86 (s, 3H, OCH₃), 2.89 (d, 1H, *J* = 14.0 Hz, CH₂), 2.73 (d, 1H, *J* = 14.0 Hz, CH₂); IR (KBr): 3372, 3324, 1662, 1646 cm⁻¹. Anal. Calcd for C₁₈H₁₅F₃N₂O₃: C, 59.34; H, 4.15; N, 7.69. Found: C, 59.49; H, 4.41; N, 8.02.

A mixture of 4-methoxy-8-nitro-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6e) and 4-methoxy-7-nitro-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6e'): ^1H NMR ($\text{CDCl}_3 + \text{CD}_3\text{CN}$): δ 8.20-7.73 (m, 2H, H_{arom}), 7.23-7.07 (m, 1H, H_{arom}), 5.60 (s, 1H, NH or OH), 5.50 (s, 1H, NH or OH), 4.00, 3.90 (s, 3H, OCH_3), 2.89 (d, 1H, $J = 14.0$ Hz, CH_2), 2.73 (d, 1H, $J = 14.0$ Hz, CH_2); IR (KBr): 3487, 3300, 3170, 1649 cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_4$: C, 43.29; H, 3.30; N, 13.77. Found: C, 43.38; H, 3.33; N, 13.65.

2-Methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7a): bp (oven temperature) 110 °C / 3 mmHg; ^1H NMR (CDCl_3): δ 7.63-7.13 (m, 4H, H_{arom}), 3.87 (s, 3H, OCH_3), 3.10 (s, 2H, CH_2); IR (KBr): 1646 cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_2\text{O}$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.79; H, 3.71; N, 11.37.

2-Methoxy-7,8-dimethyl-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7b): bp (oven temperature) 120 °C / 3 mmHg; ^1H NMR (CDCl_3): δ 7.32 (s, 1H, H_{arom}), 7.16 (s, 1H, H_{arom}), 3.90 (s, 3H, OCH_3), 3.08 (s, 2H, CH_2), 2.30 (s, 6H, CH_3); IR (KBr): 1648 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_2\text{O}$: C, 57.78; H, 4.85; N, 10.37. Found: C, 57.96; H, 4.94; N, 10.10.

7,8-Dichloro-2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7c): mp 98-99 °C (*n*-hexane-EtOAc); ^1H NMR (CDCl_3): δ 7.66 (s, 1H, H_{arom}), 7.49 (s, 1H, H_{arom}), 3.93 (s, 3H, OCH_3), 3.16 (s, 2H, CH_2); IR (KBr): 1648 cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_7\text{Cl}_2\text{F}_3\text{N}_2\text{O}$: C, 42.47; H, 2.27; N, 9.01. Found: C, 42.87; H, 2.36; N, 8.68.

A mixture of (2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (7d) and (4-methoxy-2-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (7d'): bp (oven temperature) 140 °C / 3 mmHg; ^1H NMR (CD_3CN): δ 8.07-7.35 (m, 8H, H_{arom}), 3.94, 3.91 (s, 3H, OCH_3), 3.29 (s, 2H, CH_2); IR (KBr): 1657, 1642 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.39; H, 3.98; N, 7.93.

A mixture of 2-methoxy-7-nitro-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7e) and 4-methoxy-7-nitro-2-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7e'): bp (oven temperature) 150 °C / 3 mmHg; ^1H NMR (CDCl_3): δ 8.27-8.00 (m, 2H, H_{arom}), 7.73-7.57 (m, 1H, H_{arom}), 3.81 (br s, 3H, OCH_3), 3.24 (s, 2H, CH_2); IR (KBr): 1646 cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{N}_3\text{O}_3$: C, 46.00; H, 2.81; N, 14.63. Found: C, 46.02; H, 2.98; N, 14.44.

Synthesis of 4-ethoxy-7,8-dimethyl-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (8).

To a solution of **3**⁶ (214mg, 1.0 mmol) in MeCN (4 mL) was added 4,5-dimethyl-1,2-phenylenediamine (150 mg, 1.1 mmol) and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane-EtOAc (4:1) as eluent to give **8** (200 mg, 66%). **8**: mp 117-118 °C (*n*-hexane-EtOAc); ^1H

NMR (CDCl₃): δ 6.79 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}), 4.35 (s, 1H, OH or NH), 4.24 (q, 2H, J = 7.0 Hz, CH₂CH₃), 4.12 (s, 1H, OH or NH), 2.71 (d, 1H, J = 14.0 Hz, CH₂), 2.48 (d, 1H, J = 14.0 Hz, CH₂), 2.16 (s, 6H, CH₃), 1.30 (t, 3H, J = 7.0 Hz, CH₂CH₃); IR (KBr): 3332, 3095, 1648 cm⁻¹. Anal. Calcd for C₁₄H₁₇F₃N₂O₂: C, 55.62; H, 5.67; N, 9.27. Found: C, 55.66; H, 5.66; N, 9.22.

General procedure for the dehydration of dihydrobenzodiazepinols (6 and 8) to benzodiazepines (7 and 9).

The dehydration of **6** and **8** was successfully carried out with the use of Kugelrohr distillation apparatus. The conditions are as follows: oven temperature, see Table 2; heating time, 1.5 h; reduced pressure, 3 mmHg.

2-Ethoxy-7,8-dimethyl-4-trifluoromethyl-3H-benzo[b][1,4]diazepine (9): mp 82-83 °C (*n*-hexane-EtOAc); ¹H NMR (CDCl₃): δ 7.26 (s, 1H, H_{arom}), 7.09 (s, 1H, H_{arom}), 4.30 (q, 2H, J = 7.0 Hz, CH₂CH₃), 3.07 (s, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 1.32 (t, 3H, J = 7.0 Hz, CH₂CH₃); IR (KBr): 1642, 1615 cm⁻¹. Anal. Calcd for C₁₄H₁₅F₃N₂O: C, 59.15; H, 5.32; N, 9.85. Found: C, 59.20; H, 5.36; N, 10.04.

REFERENCES

1. D. Lloyd and H. MacNab, *Adv. Heterocycl. Chem.*, 1998, **71**, 1.
2. (a) H. Schutz, 'Benzodiazepines,' Springer, Heidelberg, 1982. (b) R. I. Fryer, 'Comprehensive Heterocyclic Chemistry,' Wiley, New York, 1991. (c) L. Randall and B. Kappel, 'Benzodiazepines,' Raven Press, New York, 1973.
3. N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, 2008, **76**, 1205.
4. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-273844, 2006.
5. M. Hojo, R. Masuda, and Y. Kamitori, *Tetrahedron Lett.*, 1976, **17**, 1009.
6. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
7. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
8. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
9. M. A. P. Martins, C. M. P. Pereira, N. E. K. Zimmermann, W. Cunico, S. Moura, P. Beck, N. Zanatta, and H. G. Bonaccorso, *J. Fluorine Chem.*, 2003, **123**, 261.
10. B. Narsaiah, A. Sivaprasad, and R. V. Venkataratnam, *J. Fluorine Chem.*, 1994, **66**, 47.
11. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
12. Very recently, the synthesis of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (**5**) was reported: M. Lubbe, A. Bunescu, M. Sher, A. Villinger, and P. Langer, *Synlett*, 2008, 1862.