HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1205 - 1217. © The Japan Institute of Heterocyclic Chemistry
Received, 31st March, 2008, Accepted, 19th May, 2008, Published online, 22nd May, 2008. COM-08-S(N)82

A CONVENIENT SYNTHESIS OF FLUORINE-CONTAINING DIHYDROBENZO[*b*][1,4]DIAZEPINOLS AND ITS APPLICATION TO A SYNTHESIS OF NOVEL *N*-SULFINYLANILINES

**Norio Ota,[a] Takehisa Tomoda,[a] Naoya Terai,[a] Yasuhiro Kamitori,[a*]
Dai Shibata,[a] Maurice Médebielle,[b] and Etsuji Okada[a*]**

[a]Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan
Fax: +81(78)8036163; E-mail: kamitori@kobe-u.ac.jp
[b]Université Claude Bernard Lyon 1 (UCBL), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), UMR CNRS-UCBL 5246, Laboratoire de Synthèse de Biomolécules, Bâtiment Chevreul, 5ème étage, 43 bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

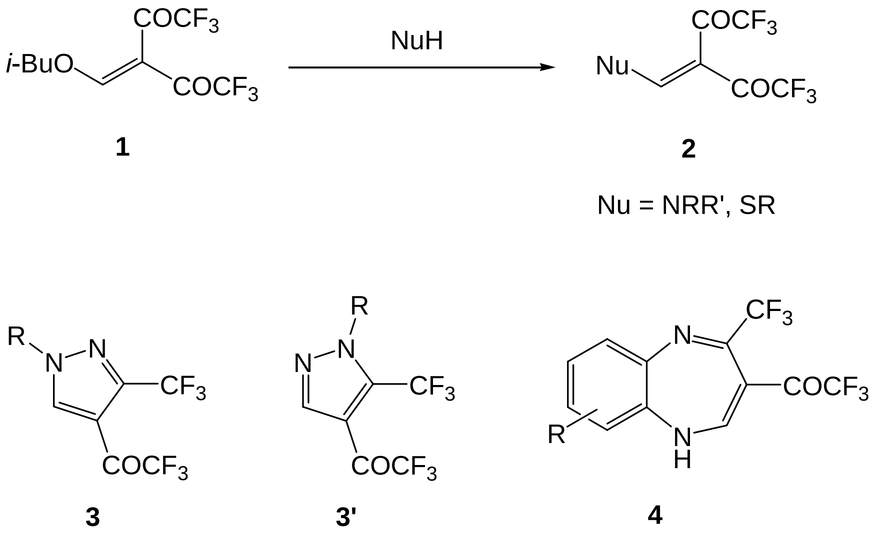
Abstract – The reactions of 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)-pentane-2,4-dione (**1**) with various benzene-1,2-diamines gave 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepines (**5**) in moderate to high yields under very mild conditions. Also, 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepines (**7**) were synthesized successfully by quite similar manner. Reactions of thus obtained dihydrobenzo[*b*][1,4]-diazepinols (**5**) with thionyl chloride gave unexpected novel fluorine-containing *N*-sulfinylanilines (**9**).

INTRODUCTION

Benzo[*b*][1,4]diazepines are attractive and important heterocycles because of being applicable to the creation of useful biologically active substances. In medicinal scientific fields, certain benzo[*b*][1,4]diazepines are useful for the antipsychotic therapy. For example, 2-amino-4-phenyl and 2-(*p*-fluorophenyl)-4-phenyl-8-chloro derivatives are known as tranquilizers[1] and antidepressants[2] respectively. It has been also reported that some 2-amino-4-methylthiobenzo[*b*][1,4]diazepines act as depressants of the central nervous system and anti-convulsants, whereas 2,4-diamino derivatives showed effects as stimulants and convulsants.[3] Moreover, some benzo[*b*][1,4]diazepines, in particular 2-thio derivatives, show antibacterial activity,[4-6] while 2,4-dimethyl derivatives are known as anti-sarcoma.[7] In agricultural scientific fields, new herbicidal agents bearing a benzo[*b*][1,4]diazepine unit have been developed.[8]

On the other hand, much attention in recent years has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities useful in medicinal and agricultural fields.[9-12]

In the course of our investigations on the nucleophilic substitutions at olefinic carbon atoms,[13-18] it was found that 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione **1**[19] readily reacted with various amines and thiols under very mild conditions to give the corresponding *O*-*N* and *O*-*S* exchanged products **2** in high yields.[18] These findings prompted us to investigate about the application of above nucleophilic substitutions with the use of bifunctional nucleophiles to the syntheses of a variety of novel fluorine-containing heterocycles which have high potential leading to pharmacophores. For instance, using the reaction of **1** with hydrazines, we succeeded in the synthesis of 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles (**3** and **3'**) which are hardly obtainable by other methods.[20] As for the synthesis of fluorine-containing benzo[*b*][1,4]diazepines, Reddy *et al*. reported the reaction of **1** with benzene-1,2-diamines under microwave irradiation to give 1*H*-benzo[*b*][1,4]diazepines (**4**) (Scheme 1).[21,22]



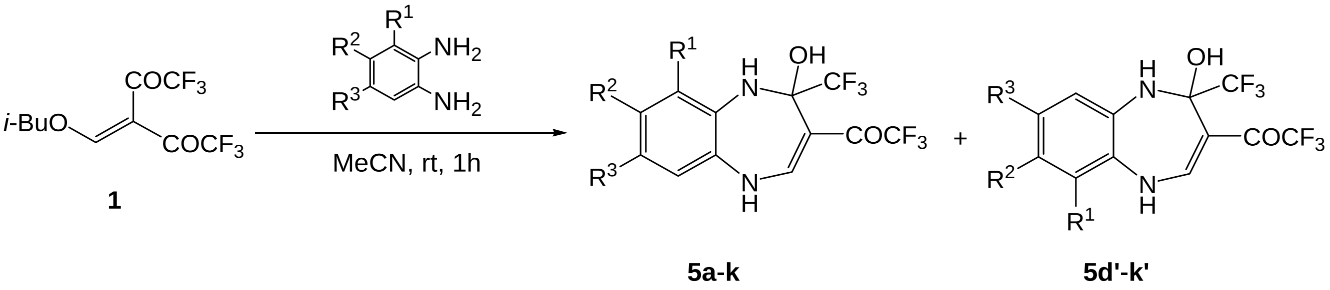
Scheme 1

In contrast to their results, we found the reaction of β,β-bis(perhaloalkanoyl)vinyl ethers including **1** with benzene-1,2-diamines without microwave irradiation gave novel 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepinols (**5** and **7**) selectively under very mild conditions. We here report an efficient and convenient synthetic method for these dihydrobenzo[*b*][1,4]diazepinols which are expected to have remarkable anti-tumor activities.

Moreover, we describe in this report a facile synthesis of novel fluorine-containing *N*-sulfinylanilines (**9**), which were obtained unexpectedly from dihydrobenzo[*b*][1,4]diazepinols (**5**) by treatment with thionyl chloride. These *N*-sulfinylanilines (**9**) are also expected to have noticeable anti-tumor activities.

RESULTS AND DISCUSSION

We examined the reaction of β,β-bistrifluoroacetylvinyl ether (**1**) with various benzene-1,2-diamines (Scheme 2 and Table 1). The reaction of **1** with slightly excess amounts of benzene-1,2-diamine in acetonitrile readily occurred at ambient temperature to give dihydrobenzo[*b*][1,4]diazepinol (**5a**) in 85% yield (entry 1). Under the same conditions, the reaction of **1** with 4,5-dimethylbenzene-1,2-diamine and 4,5-dichlorobenzene-1,2-diamine afforded the corresponding diazepinols **5b** and **5c** in high yields (entry 2 and 3). In the ^{13}C NMR spectra of **5b**, the ring carbon (C-2') substituted by a CF_3 group appeared at 86.4 ppm as a quartet signal due to C-F geminal coupling ($^2J_{CF}$ = 28.2 Hz) and a signal of the carbonyl carbon was observed at 178.7 ppm as quartet ($^2J_{CF}$ = 34.3 Hz).



Scheme 2

The annulation reaction of **1** with mono-substituted benzene-1,2-diamine gave a mixture of two regioisomers of the corresponding diazepinol. Thus a mixture of two regioisomers (**5d**, **d'**) was obtained in 69% yield when **1** was reacted with 3-methylbenzene-1,2-diamine (entry 4). Quite similarly, the reactions of **1** with other benzene-1,2-diamines bearing various substituents on benzene ring proceeded successfully. The reaction of **1** with 4-chlorobenzene-1,2-diamine, 4-methylbenzene-1,2-diamine, 4-nitrobenzene-1,2-diamine, 3,4-diaminophenyl(phenyl)methanone, 3,4-diaminobenzoic acid, methyl 3,4-diaminobenzoate and *n*-butyl 3,4-diaminobenzoate gave mixtures of the corresponding 7-substituted and 8-substituted dihydrobenzo[*b*][1,4]diazepinols (**5e-k'**) in 71-89% yields (entry 5-11).

The results of our approaches on the reactions of **1** with benzene-1,2-diamines show sharp contrast with those reported by Reddy *et al.*[21,22] In all cases in Table 1, dihydrobenzo[*b*][1,4]diazepinols (**5a-k'**) were obtained selectively under very mild conditions in the absence of microwave irradiation without any formation of the corresponding 1*H*-benzo[*b*][1,4]diazepines (**4**).

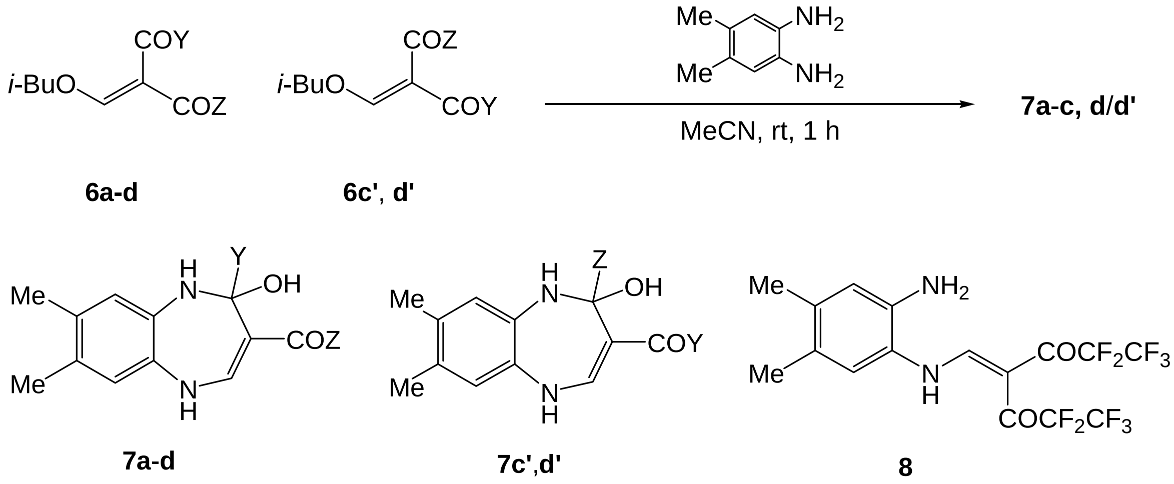
Table 1. Synthesis of 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]-diazepinols **5a-k’** form **1** and benzene-1,2-diamines.[a]

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	H	H	**5a**	85
2	H	Me	Me	**5b**	87
3	H	Cl	Cl	**5c**	82
4	Me	H	H	**5d**, **5d’**[c]	69[d]
5	H	Cl	H	**5e**, **5e’**[e]	71[d]
6	H	Me	H	**5f**, **5f’**[e]	80[d]
7	H	NO_2	H	**5g**, **5g’**[c]	76[d]
8	H	COPh	H	**5h**, **5h’**[e]	78[d]
9	H	CO_2H	H	**5i**, **5i’**[e]	74[d]
10	H	CO_2Me	H	**5j**, **5j’**[e]	82[d]
11	H	CO_2Bu-*n*	H	**5k**, **5k’**[e]	89[d]

[a] Benzene-1,2-diamines (1.1 times molar amounts) were used.
[b] Isolated yield.
[c] Ratio of regioisomers calculated by ^1H NMR spectra were 3.3/1 (**5d**/**5d’** or **5d’**/**5d**) and 2.5/1 (**5g**/**5g’** or **5g’**/**5g**) respectively.
[d] Combined yield of two regioisomers.
[e] Ratio of regioisomers could not be determined.

Our method was applicable to the synthesis of fluorine-containing dihydrobenzo[*b*][1,4]diazepinols from several β,β-bisperhaloalkanoylvinyl ethers (**6a-d’**). As shown in Scheme 3 and Table 2, we attempted the reactions of **6a-d’** with 4,5-dimethylbenzene-1,2-diamine employing the same reaction condition for the synthesis of diazepinols **5a-k’** from **1**. The annulation reaction of β,β-bis(chlorodifluoroacetyl)vinyl ether (**6a**) with 4,5-dimethylbenzene-1,2-diamine easily proceeded at room temperature to give the corresponding diazepinol **7a** in 79% yield (entry 1). In contrast to this, the reaction of β,β-bis(pentafluoropropanoyl)vinyl ether (**6b**) with 4,5-dimethylbenzene-1,2-diamine afforded enamine **8** which is thought to be a precursor of **7b** together with equimolar amounts of the corresponding diazepinol **7b** (entry 2). Unfortunately, the ratio of **7b** and **8** almost unchanged by prolongation of reaction time, and **7b** could not be isolated from the mixture in spite of any our effort. The formation of diazepinol **7b** was confirmed by ^{13}C NMR measurement of a mixture of **7b** and **8**. The ring carbon (C-2’) binding a CF_2CF_3 group of **7b** appeared at 87.6 ppm as a triplet signal ($^2J_{CF}$ = 24.3 Hz). This chemical shift of C-2’ is compatible with that (86.4 ppm) of diazepinol **5b** described above.

The structures of **7c**, **7d** and **7d’** were also confirmed by ^{13}C NMR spectra. In the spectra of **7c**, the ring carbon (C-2’) binding a CF_3 group appeared at 85.7 ppm as a quartet signal ($^2J_{CF}$ = 29.8 Hz), while the carbonyl carbon gave a triplet signal ($^{2}J_{CF}$ = 23.7 Hz) at 180.7 ppm. In the spectra of **7d**, the ring carbon (C-2') appeared at 86.7 ppm as a quartet signal ($^{2}J_{CF}$ = 29.8 Hz), while the carbonyl carbon was observed at 182.4 ppm as a singlet signal. Although **7d'** could not be isolated, in the spectra of a mixture of **7d** and **7d'**, the ring carbon (C-2') of **7d'** appeared at 100.3 ppm as a singlet signal, and the carbonyl carbon of **7d'** gave a quartet signal ($^{2}J_{CF}$ = 32.0 Hz) at 179.0 ppm.



Scheme 3

Table 2. Synthesis of 2,5-dihydro-7,8-dimethyl-1*H*-benzo[*b*][1,4]diazepinols **7a-d'** from **6a-d'** and 4,5-dimethylbenzene-1,2-diamines.[a]

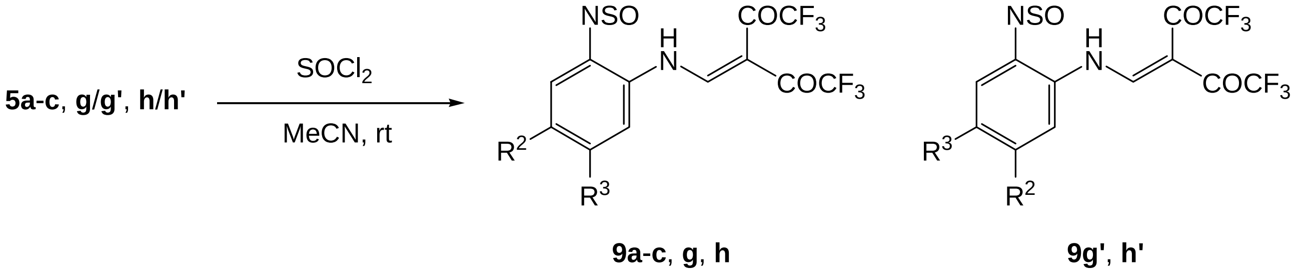
Entry	Substrate	Y	Z	Product	Yield (%)
1	**6a**	CF_2Cl	CF_2Cl	**7a**	79[b]
2	**6b**	CF_2CF_3	CF_2CF_3	**7b**[c]	46[d]
3	**6c**, **6c'**[e]	CF_3	CF_2CF_3	**7c**	73[b]
4	**6d**, **6d'**[e]	CF_3	CCl_3	**7d**, **7d'**	78[f]

[a] 4,5-Dimethylbenzene-1,2-diamines (1.1 times molar amounts) were used.
[b] Isolated yield.
[c] **7b** was obtained as a mixture with enamine **8** (**7b**/**8**= 1/1).
[d] The yield of **7b** was calculated from signal intensity in ^{1}H NMR spectra.
[e] A mixture of **6c** and **6c'** (**6c**/**6c'**= 1/4 or 4/1) or **6d** and **6d'** (**6d**/**6d'**= 1/1) was used as a substrate.
[f] Combined yield of two regioisomers.

Our attempts to dehydrate dihydrobenzo[*b*][1,4]diazepinol (**5a**) to the corresponding 1*H*-benzo[*b*][1,4]-diazepine (**4**: R= H) by acid catalysis resulted in failure to give a complex mixture. So, we tried dehydration of **5a** with the use of thionyl chloride.

As shown in Scheme 4 and Table 3, the reaction of **5a** with equimolar amounts of thionyl chloride in acetonitrile completed within 5 min at ambient temperature to afford unexpected *N*-sulfinylaniline **9a** in

86% yield (entry 1), and neither expected 1*H*-benzo[*b*][1,4]diazepine (**4**: R= H) nor its precursor, 2-chloro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine, was obtained. Similarly 7,8-dimethyl- and 7,8-dichlorodihydrobenzo[*b*][1,4]diazepinols (**5b**, **c**) treated with thionyl choloride to give the corresponding *N*-sulfinylanilines (**9b**, **c**) in high yields (entry 2 and 3). In the cases of the reactions using a mixture of 7- and 8-nitrodihydrobenzo[*b*][1,4]diazepinol (**5g**, **g'**) and a mixture of 7- and 8-benzoyldihydrobenzo[*b*][1,4]diazepinol (**5h**, **h'**), prolonged reaction time and, in the latter case, use of 2 times molar amounts of thionyl chloride were necessary to obtain the corresponding *N*-sulfinylanilines (**9g**, **g'** and **9h**, **h'**) in high yields (entry 4 and 5).



Scheme 4

Table 3. Synthesis of *N*-sulfinylanilines **9a-c**, **g/g'** and **h/h'** from **5a-c**, **g/g'** and **h/h'**.

Entry	Substrate	R^2	R^3	$SOCl_2$ (mol equiv)	Time (min)	Product	Yield (%)[a]
1	**5a**	H	H	1	5	**9a**	86
2	**5b**	Me	Me	1	5	**9b**	100
3	**5c**	Cl	Cl	1	5	**9c**	79
4	**5g**, **5g'**[b]	NO_2	H	1	30	**9g**, **9g'**[c]	98[d]
5	**5h**, **5h'**[b,c]	COPh	H	2	30	**9h**, **9h'**[c]	94[d]

[a] Isolated yield.
[b] A mixture of **5g** and **5g'** (**5g**/**5g'**= 1/2.5 or 2.5/1) or **5h** and **5h'** was used as a substrate.
[c] Ratio of regioisomers could not be determined.
[d] Combined yield of two regioisomers.

In conclusion, we present here an efficient and convenient synthetic method accessing novel fluorine-containing dihydrobenzo[*b*][1,4]diazepinols which are not easily obtainable by other methods. Moreover, we can provide a facile and convenient method to synthesize novel *N*-sulfinylanilines via fluorine-containing dihydrobenzo[*b*][1,4]diazepinols.

In addition, we have found that dihydrobenzo[*b*][1,4]diazepinol (**5b**) and *N*-sulfinylaniline (**9b**) exert fine anti-tumor potency on carcinomas of lung, colon and ovary.[23] On the basis of our results, further biological evaluation of these novel dihydrobenzo[*b*][1,4]diazepinols (**5** and **7**) and *N*-sulfinylanilines (**9**) is now under way to fulfill our expectations for discovery of a new pharmacophore with antineoplastic efficacy.

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. The ^{13}C NMR spectra were recorded on a VARIAN Unity INOVA 400 spectrometer using TMS as an internal standard. ^{1}H NMR spectra were obtained with a JEOL PMX 60SI spectrometer. IR spectra were taken with a PerkinElmer Spectrum ONE FT-IR spectrometer. Microanalyses were taken with a YANACO CHN-Corder MT-5 analyzer.

General procedure for the synthesis of 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepinols (5a-k') from 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (1).

To a solution of **1**[19] (293 mg, 1.0 mmol) dissolved in MeCN (4 mL) was added benzene-1,2-diamines (1.1 mmol) and the mixture was stirred for 1 h at ambient temperature. After evaporation of the solvent, purification of a residue by silica gel column chromatography using *n*-hexane-EtOAc (10:1) afforded **5a-k'**. In the cases of **5d**, **5d'**, and **5f-k'**, small amount of single isomer could be isolated, while the other isomer could not be separated from the mixture of two isomers by silica gel column chromatography. Neither **5e** nor **5e'** could be isolated from the mixture of two isomers by silica gel column chromatography.

2,2,2-Trifluoro-1-(2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-ethanone (5a): mp 86-87 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.60-9.05 (br, 1H, NH), 8.55 (br s, 1H, OH), 7.92 (d, J = 10.0 Hz, 1H, H-4'), 7.37-7.02 (m, 4H, H_{arom}), 4.98 (br s, 1H, NH); IR (KBr): 1551 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_8F_6N_2O_2$: C, 44.18; H, 2.47; N, 8.59. Found: C, 44.08; H, 2.63; N, 8.60.

2,2,2-Trifluoro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5b): mp 126-127 °C (*n*-hexane-EtOAc); ^{13}C NMR (CD_3COCD_3) δ 18.8, 19.3 (CH_3), 86.4 ($^{2}J_{CF}$ = 28.2 Hz, C-2'), 102.9 (C-3'), 118.7 ($^{1}J_{CF}$ = 290.7 Hz, CO**C**F_3), 125.8 ($^{1}J_{CF}$ = 294.5 Hz, 2'-CF_3), 122.6, 123.3, 127.0, 131.3, 132.9, 136.7 (C_{arom}), 149.1 (C-4'), 178.7 ($^{2}J_{CF}$ = 34.3 Hz, **C**OCF_3); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.32-8.73 (br, 1H, NH), 8.55 (br s, 1H, OH), 7.82 (d, J = 10.0 Hz, 1H, H-4'), 6.78 (s, 2H, H_{arom}), 4.65-4.37 (br, 1H, NH), 2.22 (s, 6H, CH_3); IR (KBr): 1583 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_6N_2O_2$: C, 47.47; H, 3.41; N, 7.91. Found: C, 47.24; H, 3.14; N, 7.90.

1-(7,8-Dichloro-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5c): mp 163-164 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.65-9.05 (br, 1H, NH), 8.35 (br s, 1H, OH), 7.83 (d, *J* = 9.0 Hz, 1H, H-4'), 7.22 (s, 2H, H_{arom}), 5.18 (br s, 1H, NH); IR (KBr): 1544 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_2F_6N_2O_2$: C, 36.48; H, 1.53; N, 7.09. Found: C, 36.18; H, 1.79; N, 7.13.

2,2,2-Trifluoro-1-(2-hydroxy-6-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5d) or 2,2,2-trifluoro-1-(2-hydroxy-9-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5d'): mp 131-132 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.48-8.82 (br, 1H, NH), 8.57 (br s, 1H, OH), 7.85 (d, *J* = 10.0 Hz, 1H, H-4'), 7.28-6.80 (m, 3H, H_{arom}), 4.52 (br s, 1H, NH), 2.33 (s, 3H, CH_3); IR (KBr): 1610 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; N, 8.23. Found: C, 45.62; H, 3.00; N, 8.23.

A mixture of 1-(7-chloro-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5e) and 1-(8-chloro-2-hydroxy-2-trifluormethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5e'): ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.40-8.90 (br, 1H, OH), 8.63-8.28 (br, 1H, NH), 7.85 (d, *J* = 9.0 Hz, 1H, H-4'), 7.37-6.87 (m, 3H, H_{arom}), 4.87, 4.20 (br s, 1H, NH of two regioisomers); IR (KBr): 1555 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_7ClF_6N_2O_2$: C, 39.96; H, 1.96; N, 7.77. Found: C, 39.93; H, 2.02; N, 7.75.

2,2,2-Trifluoro-1-(2-hydroxy-7-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5f) or 2,2,2-trifluoro-1-(2-hydroxy-8-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)ethanone (5f'): mp 102-103 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.52-8.53 (br, 1H, NH), 8.53-7.90 (br, 1H, OH), 7.63 (br s, 1H, H-4'), 6.90-6.58 (m, 3H, H_{arom}), 4.97 (br s, 1H, NH), 2.25 (s, 3H, CH_3); IR (KBr): 1559 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; N, 8.23. Found: C, 45.98; H, 3.07; N, 8.03.

2,2,2-Trifluoro-1-(2-hydroxy-7-nitro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-ethanone (5g) or 2,2,2-trifluoro-1-(2-hydroxy-8-nitro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)ethanone (5g'): mp 139-140 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 8.60-7.82 (m, 5H, NH, OH, H-4', H_{arom}), 7.25 (d, *J* = 10.0 Hz, 1H, H_{arom}), 5.98 (br s, 1H, NH); IR (KBr): 1623 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_7F_6N_3O_4$: C, 38.83; H, 1.90; N, 11.32. Found: C, 38.89; H, 2.10; N, 11.06.

1-(7-Benzoyl-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5h) or 1-(8-benzoyl-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)-2,2,2-trifluoroethanone (5h'): mp 166-167 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ = 8.75-8.20 (br, 1H, NH), 8.00-7.50 (m, 9H, OH, H-4', C_6H_5CO), 7.22 (d, *J* = 9.0 Hz, 1H, H_{arom}), 5.80 (br s, 1H, NH); IR (KBr): 1568 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{12}F_6N_2O_3$: C, 53.03; H, 2.81; N, 6.51. Found: C, 52.91; H, 2.91; N, 6.53.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic

acid (5i) or 2-hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid (5i'): mp 177-178 °C (*n*-hexane- EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 11.43-10.73 (br, 1H, NH), 8.61 (s, 1H, H-4'), 8.08-7.75 (m, 3H, H_{arom}, OH), 7.33 (d, *J* = 8.0 Hz, 1H, H_{arom}), 6.45 (br s, 1H, NH); IR (KBr): 1686 (C=O), 1611 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_8F_6N_2O_4$: C, 42.18; H, 2.18; N, 7.57. Found: C, 42.55; H, 2.26; N, 7.18.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic acid methyl ester (5j) or 2-hydroxy-3-trifluoroactyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid methyl ester (5j'): mp 160-161 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.67-9.15 (br, 1H, NH), 8.45 (s, 1H, OH), 8.09-7.79 (m, 3H, 4-H', H_{arom}), 7.22 (d, *J* = 8.8 Hz, 1H, H_{arom}), 5.70 (br s, 1H, NH), 3.93 (s, 3H, CH_3); IR (KBr): 1698 (C=O), 1627 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{10}F_6N_2O_4$: C, 43.76; H, 2.62; N, 7.29. Found: C, 44.08; H, 2.74; N, 6.85.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic acid butyl ester (5k) or 2-hydroxy-3-trifluoroactyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid butyl ester (5k'): mp 158-159 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.93-9.13 (br, 1H, NH), 8.47 (s, 1H, OH), 8.13-7.81 (m, 3H, H-4', H_{arom}), 7.24 (d, *J* = 10.0 Hz, 1H, H_{arom}), 5.70 (br s, 1H, NH), 4.37 (t, 2H, $C\mathbf{H}_2(CH_2)_2CH_3$), 1.83-0.80 (m, 7H, $CH_2(C\mathbf{H}_2)_2C\mathbf{H}_3$)); IR (KBr): 1687(C=O), 1630 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{16}F_6N_2O_4$: C, 47.90; H, 3.78; N, 6.57. Found: C, 47.92; H, 3.71; N, 6.66.

General procedure for the synthesis of bisperhaloalkanoylated 2-methyl-1-(vinyloxy)propane (6).

Method A (for 6a, b).

To an ice-cooled mixture of 2-methyl-1-(vinyloxy)propane (1.00 g, 10 mmol) and pyridine (2.37 g, 30 mmol) was added dropwise a solution of perhaloalkanoic anhydride (30 mmol) in dry $CHCl_3$ (1 mL) with continuous stirring. After stirring for 18 h at 50 °C, the crude mixture being poured into ice-cooled *n*-hexane (50 mL) resulted in the rapid precipitation of pyridinium salts. After filtration, the solution is dried over Na_2SO_4 and concentrated in vacuo to give **6a** (2.31 g, 71 %) or **6b** (3.18 g, 80 %).

1,5-Dichloro-1,1,5,5-tetrafluoro-3-(isobutoxymethylene)pentane-2,4-dione (6a): bp 110 °C / 3 mmHg; ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1H, CH=C), 4.20 (d, *J* = 7.0 Hz, 2H, CH_2), 2.47-1.78 (m, 1H, CH), 1.01 (d, *J* = 7.0 Hz, 6H, CH_3). Anal. Calcd for $C_{10}H_{10}Cl_2F_4O_3$: C, 36.95; H, 3.10. Found: C, 37.19; H, 2.79.

1,1,1,2,2,6,6,7,7,7-Decafluoro-4-(isobutoxymethylene)heptane-3,5-dione (6b): bp 150 °C / 5 mmHg; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H, CH=C), 4.19 (d, *J* = 6.4 Hz, 2H, CH_2), 2.43-1.76 (m, 1H, CH), 1.02 (d, *J* = 7.6 Hz, 6H, CH_3); IR (film): 1751 (C=O), 1682 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{10}F_{10}O_3$: C, 36.75; H, 2.57. Found: C, 36.36; H, 2.41.

Method B (for 6c-d')

To an ice-cooled mixture of (*E*)-1,1,1-trihalo-4-isobutoxybut-3-en-2-one (2 mmol) and pyridine (474 mg, 6 mmol) was added dropwise a solution of perhaloalkanoic anhydride (6 mmol) in dry $CHCl_3$ (0.5 mL) with continuous stirring. After stirring for 18 h at 50 °C, the mixture was dissolved in CH_2Cl_2 (10 mL). The whole mixture was washed with water (10 mL) and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a mixture of **6c** and **6c'** (512 mg, 71 %), or that of **6d** and **6d'** (458 mg, 67 %).

A mixture of (*E*)- and (*Z*)-1,1,1,5,5,6,6,6-octafluoro-3-(isobutoxymethylene)hexane-2,4-dione (6c, c'): ^1H NMR ($CDCl_3$) δ 8.04, 8.00 (s, 1H, CH=C), 4.18 (d, *J* = 6.4 Hz, 2H, CH_2), 2.43-1.75 (m, 1H, CH), 0.98 (d, *J* = 7.2 Hz, 6H, CH_3); IR (film): 1750 (C=O), 1697 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_8O_3$: C, 38.61; H, 2.95. Found: C, 38.42; H, 2.91.

A mixture of (*E*)- and (*Z*)-1,1,1-trichloro-5,5,5-trifluoro-3-(isobutoxymethylene)pentane-2,4-dione (6d, d'): ^1H NMR ($CDCl_3$) δ 8.09, 7.97 (s, 1H, CH=C), 4.25 (d, *J* = 6.4 Hz, 2H, CH_2), 2.45-1.78 (m, 1H, CH), 1.02 (d, *J* = 7.6 Hz, 6H, CH_3); IR (film): 1753 (C=O), 1692 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{10}Cl_3F_3O_3$: C, 35.17; H, 2.95. Found: C, 34.99; H, 2.91.

General procedure for the synthesis of 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepines (7a-d') from perhalo-(isobutoxymethylene)alkanediones (6).

To a solution of **6** (1.0 mmol) dissolved in MeCN (4 mL) was added 4,5-dimethylbenzene-1,2-diamine (143 mg, 1.1 mmol) and the mixture was stirred for 1 h at ambient temperature. After evaporation of the solvent, purification of a residue by silica gel column chromatography using *n*-hexane-EtOAc (10:1) afforded **7a-d'**. In the case of **7b**, pure **7b** could not be obtained by silica gel chromatography because of a contamination of small amounts of **8**. In the case of a mixture of **7d**, and **7d'**, small amount of single isomer **7d** could be isolated, while the other isomer **7d'** could not be separated from the mixture of two isomers by silica gel column chromatography.

2-Chloro-1-[2-(chlorodifluoromethyl)-2-hydroxy-7,8-dimethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]-2,2-difluoroethanone (7a): mp 123-124 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$-CD_3CN) δ 9.38-8.88 (br, 1H, NH), 8.78 (br s, 1H, OH), 7.98 (d, *J* = 10.0 Hz, 1H, H-4'), 6.82 (s, 2H, H_{arom}), 4.95 (br s, 1H, NH), 2.18 (s, 6H, CH_3); IR (KBr): 1563 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}Cl_2F_4N_2O_2$: C, 43.43; H, 3.12; N, 7.24. Found: C, 43.59; H, 2.76; N, 7.44.

2,2,3,3,3-Pentafluoro-1-(2-hydroxy-7,8-dimethyl-2-pentafluoroethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)propanone (7b): ^1H NMR (CD_3CN) δ 9.45-8.98 (br, 1H, NH), 8.83 (s, 1H, OH), 7.93 (d, 1H, *J* = 10.0 Hz, H-4'), 6.82 (s, 2H, H_{arom}), 5.09 (br s, 1H, NH), 2.23 (s, 6H, CH_3).

2,2,3,3,3-Pentafluoro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)propanone (7c): mp 134-135 °C (*n*-hexane-EtOAc); ^{13}C NMR (CD_3CN) δ 18.8, 19.4 (CH_3), 86.7 ($^2J_{CF}$ = 29.8 Hz, C-2'), 104.3 (C-3'), 110.6-130.0 (m, $\mathbf{C}F_2\mathbf{C}F_3$), 125.7 ($^1J_{CF}$ = 293.7 Hz, 2'-CF_3), 122.7, 123.1, 126.8, 132.0, 132.4, 137.4 (C_{arom}), 149.0 (C-4'), 180.7 ($^2J_{CF}$ = 23.8 Hz, $\mathbf{C}OCF_2CF_3$); ^1H NMR ($CDCl_3$-CD_3CN) δ 9.49-9.03 (br, 1H, NH), 8.46 (s, 1H, OH), 7.91 (d, *J* = 10.0 Hz, 1H, H-4'), 6.89 (s, 2H, H_{arom}), 5.00 (br s, 1H, NH), 2.20 (s, 6H, CH_3); IR (KBr): 1568 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{12}F_8N_2O_2$: C, 44.57; H, 2.99; N, 6.93. Found: C, 44.55; H, 3.03; N, 6.92.

2,2,2-Trichloro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (7d): mp 146-147 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.60-9.10 (br, 1H, NH), 8.57 (d, J = 10.0 Hz, 1H, H-4'), 8.34 (br s, 1H, OH), 7.87 (s, 2H, H_{arom}), 5.01 (br s, 1H, NH), 2.20 (s, 6H, CH_3); IR (KBr): 1567 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}Cl_3F_3N_2O_2$: C, 41.66; H, 3.00; N, 6.94. Found: C, 41.66; H, 3.27; N, 6.66.

4-[(2-Amino-4,5-dimethylphenylamino)methylene]-1,1,1,2,2,6,6,7,7,7-decafluoroheptane-3,5-dione (8): mp 178-179 °C (aqueous MeCN); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 11.67-10.90 (br, 1H, NH), 8.39 (br s, 1H, CH=C), 6.99 (s, 1H, H_{arom}), 6.74 (s, 1H, H_{arom}), 4.92-4.49 (br, 2H, NH_2), 2.20 (s, 6H, CH_3); IR (KBr): 1648 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_{10}N_2O_2$: C, 42.30; H, 2.66; N, 6.17. Found: C, 42.30; H, 2.78; N, 5.69.

General procedure for the synthesis of *N*-sulfinylanilines 9 from diazepinols 5.

To a solution of **5** (1 mmol) was added dropwise a solution of thionyl chloride (119 mg, 1 mmol) in CH_3CN (4 mL) with continuous stirring (in the case of a mixture of **5h** and **5h'**, 2 mmol of thionyl chloride was used). After stirring for 5 – 30 min at ambient temperature, removal of the solvent under vacuum afforded **9a-c**, **9g**, **g'** and **9h**, **h'**.

1,1,1,5,5,5-Hexafluoro-3-[[2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9a): mp 107-108 °C (*n*-hexane-CH_2Cl_2); ^{1}H NMR (CD_3COCD_3) δ 12.77 (br s, 1H, NH), 7.75-7.42 (m, 4H, H_{arom}, CH=C), 7.04-7.03 (m, 1H, H-6); IR (KBr): 1663 (C=O), 1608 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_6F_6N_2O_3S$: C, 38.74; H, 1.62; N, 7.53. Found: C, 38.66; H, 1.58; N, 7.72.

1,1,1,5,5,5-Hexafluoro-3-[[4,5-dimethyl-2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9b): mp 133-134 °C (*n*-hexane-CH_2Cl_2); ^{13}C NMR (CD_3COCD_3) δ 19.7, 20.4 (CH_3), 103.8 (**C**($COCF_3$)$_2$), 117.2 ($^1J_{CF}$ = 287.6 Hz, CF_3), 117.6 ($^1J_{CF}$ = 292.2 Hz, CF_3), 118.2, 129.6, 130.6, 132.6, 138.0, 143.4 (C_{arom}), 177.0 ($^2J_{CF}$ = 34.3 Hz, **C**OCF_3), 180.8 ($^2J_{CF}$ = 38.1 Hz, **C**OCF_3); ^{1}H NMR (CD_3COCD_3) δ 13.33-12.50 (br, 1H, NH), 8.80 (d, 1H, J = 14.0 Hz, CH=C), 8.44 (s, 1H, H_{arom}), 7.73 (s, 1H, H_{arom}), 2.41, 2.33 (s, 6H, CH_3); IR (KBr): 1648 (C=O), 1619 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{10}F_6N_2O_3S$: C, 42.01; H, 2.52; N, 7.00. Found: C, 42.02; H, 2.67; N, 6.80.

1,1,1,5,5,5-Hexafluoro-3-[[4,5-dichloro-2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9c): mp 116-118 °C (*n*-hexane-CH_2Cl_2); ^{1}H NMR (CD_3COCD_3) δ 12.60 (br s, 1H, NH), 8.53 (d, 1H, J = 14.0 Hz, CH=C), 8.43 (s, 1H, H_{arom}), 7.80 (s, 1H, H_{arom}); IR (KBr): 1658 (C=O), 1611 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_4Cl_2F_6N_2O_3S$: C, 32.67; H, 0.91; N, 6.35. Found: C, 32.52; H, 1.21; N, 6.20.

A mixture of 1,1,1,5,5,5-hexafluoro-3-[[4-nitro-2-(*N*-sulfinylamino)phenylamino]methylene]-pentane-2,4-dione (9g) and 1,1,1,5,5,5-hexafluoro-3-[[5-nitro-2-(*N*-sulfinylamino)phenylamino]-

methylene]pentane-2,4-dione (9g'): ^{1}H NMR (CD_3COCD_3) δ 12.72-12.13 (br, 1H, NH), 8.66-7.47 (m, 4H, H_{arom}, CH=C); IR (KBr): 1706 (C=O), 1657 (C=O), 1603 (C=O), 1585 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_5F_6N_3O_5S$: C, 34.54; H, 1.21; N, 10.07. Found: C, 34.32; H, 1.40; N, 10.08.

A mixture of 1,1,1,5,5,5-hexafluoro-3-[[4-benzoyl-2-(*N*-sulfinylamino)phenylamino]methylene]-pentane-2,4-dione (9h) and 1,1,1,5,5,5-hexafluoro-3-[[5-benzoyl-2-(*N*-sulfinylamino)phenylamino]-methylene]pentane-2,4-dione (9h'): ^{1}H NMR (CD_3COCD_3) δ 13.28-12.11 (br, 1H, NH), 8.92-8.47 (m, 1H, H_{arom}), 8.47-8.25 (m, 1H, H_{arom}), 7.71-7.23 (m, 7H, H_{arom}, CH=C); IR (KBr): 1711 (C=O), 1655 (C=O), 1608 (C=O), 1589 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{10}F_6N_2O_4S$: C, 47.91; H, 2.12; N, 5.88. Found: C, 48.16; H, 2.18; N, 5.57.

REFERENCES

1. A. Tajana, R. Pennini, and D. Nardi, *Farmaco Ed. Sci.*, 1980, **35**, 181.
2. K. C. Joshi, V. N. Pathak, P. Arya, and P. Chand, *Pharmazie*, 1979, **34**, 718.
3. G. Roma, E. Vigevani, A. Balbi, and A. Ermili, *Farmaco Ed. Sci.*, 1979, **34**, 62.
4. D. Nardi, E. Massarani, A. Tajana, R. Cappelletti, and M. Veronese, *Farmaco Ed. Sci.*, 1975, **30**, 727.
5. F. Giodano, C. Grieco, C. Silipo, and A. Vittoria, *Boll. Soc. Ital. Biol. Sper.*, 1975, **51**, 1069.
6. C. Grieco, C. Silipo, and A. Vittoria, *Farmaco Ed. Sci.*, 1977, **32**, 909.
7. A. I. Kravchenko, *Farmakol. Toksikol.*, 1974, **37**, 474.
8. D. P. Clifford, D. Jackson, R. V. Edwards, and P. Jeffrey, *Pestic. Sci.*, 1976, **7**, 453.
9. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
10. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
11. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
12. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
13. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi, and T. Nishigaki, *Synthesis*, 1986, 340.
14. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Moriomoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
15. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Moriomoto, and K. Okada, *Synthesis*, 1990, 195.
16. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095.
17. E. Okada, R. Masuda, M. Hojo, and R. Inoue, *Synthesis*, 1992, 533.
18. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.

19. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
20. E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, 1992, **34**, 791.
21. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett.*, 1996, **37**, 2845.
22. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
23. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-273,844, 2006.