Journal of Fluorine Chemistry, 18 (1981) 447–457

Received: April 24, 1981

PERFLUOROALKYLATED EIGHT- AND NINE-MEMBERED BENZOHETEROCYCLES FROM F-2-METHYL-2-PENTENE

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SUMMARY

The reactions of F-2-methyl-2-pentene (1) with several ortho-difunctional benzenes afforded eight- and nine-membered benzoheterocyclic compounds carrying perfluoroalkyl groups. Salicylic acid, salicylaldehyde, and their methyl or chloro derivatives reacted in triethylamine-acetonitrile system giving perfluoroalkylated 2H,6H-1,5-benzodioxocin-2,6-dione (8) and 4H,6H-1,5-benzodioxocin (9) compounds respectively, while phthalyl alcohol and o-hydroxyphenethyl alcohol in triethylamine-diethyl ether system gave perfluoroalkylated 1H,3H,7H-2,6- and 4H,6H,7H-1,5-benzodioxonin compounds, (10) and (11). o-Aminobenzyl alcohol and (1) in diethyl ether afforded a perfluoroalkylated benzoxazocinobenzoxazocinone compound (15).

INTRODUCTION

In the course of our works on the nucleophilic reactions of perfluoro-olefins, we have reported the preparation of five- to seven-membered benzoheterocycles utilizing the reactivities of F-propene [1-3], its oxide [4] and F-2-methylpropene [5]. Especially, in our previous paper [6], we revealed the formation of fluorinated seven-membered benzoheterocycles, such as 1,5-benzoxazepine and benzoxazepino[4,3-b]1,6-benzoxazepine, by the reaction of F-2-methyl-2-pentene (1) or F-2,4-dimethyl-3-heptene with ortho-difunctional benzenes.

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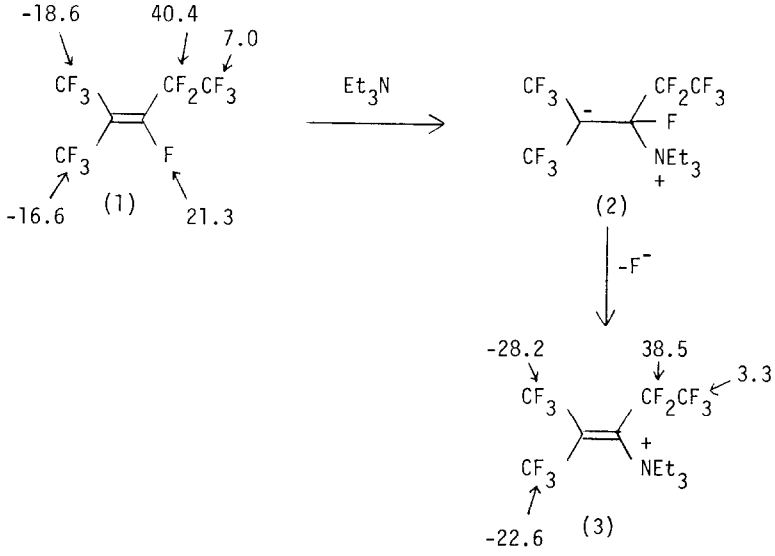
In our continuing search for new types of heterocyclic compounds, we found a facile route to eight- and nine-membered benzoheterocycles, by having (1) react with salicylic acid, salicylaldehyde, phthalyl alcohol, o-hydroxyphenethyl alcohol and o-aminobenzyl alcohol, respectively.

RESULTS AND DISCUSSION

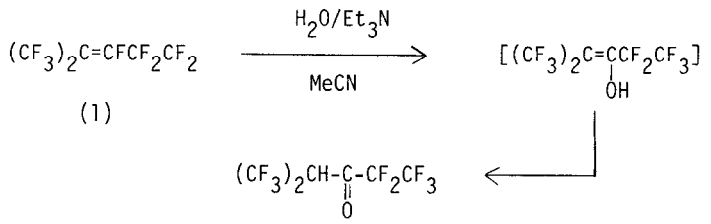
F-2-Methyl-2-pentene (1) in triethylamine-acetonitrile system

The perfluoro inner alkene (1), one of the dimers of F-propene, is known to be susceptible to the attack of nucleophiles in the presence of a base [7]. This compound, a colorless liquid, is immiscible with acetonitrile, however, when one mole of triethylamine is added they instantly make a pale yellow solution. This phenomenon seemed to be caused by the formation of a (1)-triethylamine complex, and it was proved by the ^{19}F nmr analysis. The chemical shifts for fluorine atoms of (1) in triethylamine-acetonitrile system were considerably different from those of neat (1), as shown below.



Thus the solution of (1) in triethylamine-acetonitrile system revealed none of the signal due to the fluorine atom attached to the double bond, and the signals due to the two trifluoromethyl groups attached to the double

bond appeared unequivalently. The nmr pattern like this means that the fluorine atom attached to the double bond has been replaced by triethylamine giving a highly reactive perfluoroalkenyl ammonium ion (3) and the intermediate adduct (2) is not present in the solution. This is consistent with the reported fact that (1) in triethylamine-acetonitrile system reacts even with water to give a ketone (4) [8].



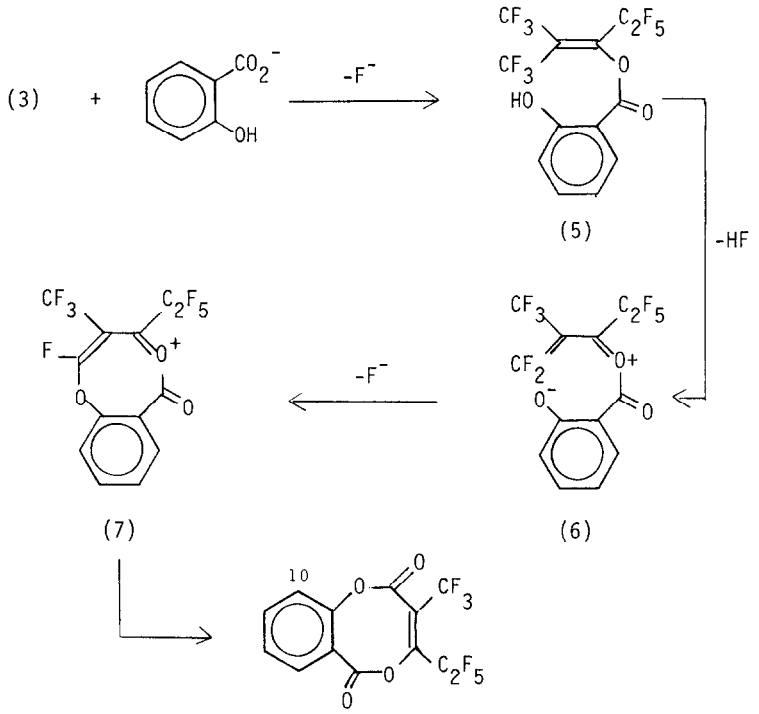
(1) (4)

Utilizing such an enhanced reactivity of (3) for nucleophiles, we allowed (1) to react with ortho-difunctional benzene derivatives in acetonitrile or diethyl ether in the presence of triethylamine and obtained various kinds of perfluoroalkylated benzoheterocyclic compounds.

Reaction of (1) with salicylic acid

The chemical behaviors of (1) toward phenols [9, 10] and carboxylic acids [11] are evident in recent reports. Then we carried out the reaction of (1) with salicylic acid first in the triethylamine-acetonitrile system which was the most effective among the various aprotic solvents examined. Two moles of triethylamine were used so that one mole was consumed for the formation of salicylate anion. The reaction proceeded smoothly at room temperature and a 2H,6H-1,5-benzodioxocindione compound (8) was obtained as the major product.

The nucleophilic attack of the salicylate anion towards the perfluoroalkenyl triethylammonium ion (3) leading to a vinyl ester (5) must be the initial step. A fluorine atom of the trifluoromethyl group attached to the double bond of (5) should be easily removed owing to the conjugative electron-donative effect of the ester oxygen atom and owing to the H-F bond formation with the phenolic hydroxyl group. Thus the formation of a terminal difluoromethylene compound (6) might be reasonable, and it would be followed by the ring-closure leading to (7), which was hydrolyzed to the 1,5-benzodioxocindione (8).



The structure of (8) was supported by various spectral data. The ir spectrum showed an absorption band at 1620 cm^{-1} due to C=O. The ^{19}F nmr spectrum* showed signals at δ -19.0, 4.5 and 34.5 ppm in the ratio 3 : 3 : 2. The signal at δ -19.0 due to CF_3 was an overlapping quartets of triplets split by all other nuclei in the molecule ($J_{CF_3\text{-}CF_2CF_3}$ = 18.8 Hz, $J_{CF_3\text{-}CF_2CF_3}$ = 3.8 Hz). The signals at δ 4.5 and 34.5 were assigned to the fluorine nuclei of the CF_2CF_3 group. In the mass spectrum, the molecular ion, M^+ 376, and other fragment peaks appeared appropriately.

3-Substituted salicylic acids, such as 3-chloro-2-hydroxy- and 2-hydroxy-3-methylbenzoic acids, reacted similarly with (1), affording chloro- and methylbenzodioxocindione compounds (10-Cl- and 10-Me-(8)).

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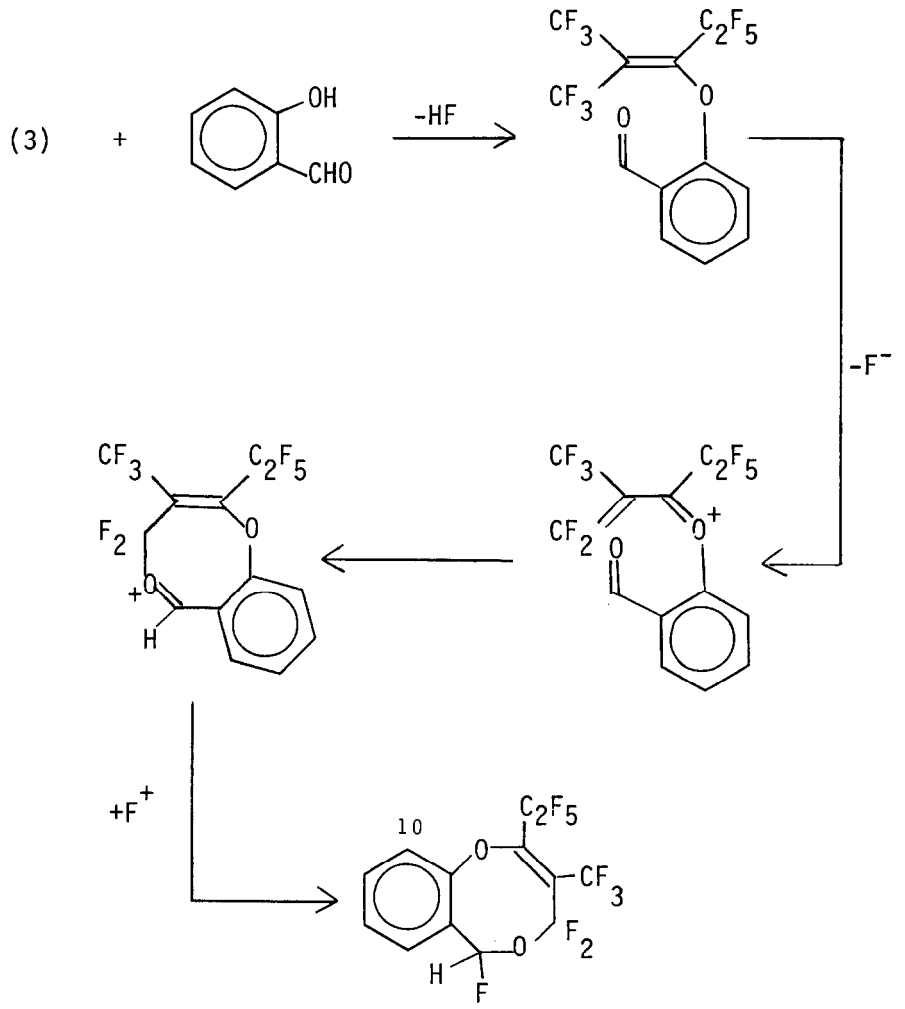
* All the ^{19}F nmr chemical shifts throughout this article are given in δ ppm from external CF_3CO_2H, using $CDCl_3$ as a solvent.

Reaction of (1) with salicylaldehyde

Even salicylaldehyde reacted smoothly with (1) under the similar conditions. In this case, however, the hydroxy group naturally attacked (1) first, followed by the internal nucleophilic cyclization affording a 4H,6H-1,5-benzodioxocin compound (9).



(9)

The structure of (9) was elucidated by the study of various spectral data. The ir spectrum showed a characteristic absorption band due to the C=C bond at 1660 cm^{-1}, and the ^1H nmr spectrum showed two signals due to CHF and aromatic protons at δ 6.70 (J_{H-F} = 56 Hz) and 7.00 - 7.67, respectively. In the ^{19}F nmr spectrum, six resonances at δ -25.0, 1.5, 25.3, 26.6, 46.3 and 47.0 ppm appeared in the ratio 3 : 3 : 1 : 2 : 1 : 1. The resonance at δ -25.0 due to the CF_3 group was overlapping triplets of quartets split by CF_2CF_3 nuclei ($J_{CF_3-CF_2CF_3}$ = 22.6 Hz, $J_{CF_3-CF_2CF_3}$ = 7.1 Hz)

The resonance at 25.3 was assigned to CHF and that at δ 26.6 due to CF_2CF_3 was multiplets. The resonances at 46.3 ($J_{F_A-F_B}$ = 7.1 Hz, J_{F_A-CHF} = 2.3 Hz) and at δ 47.0 ($J_{F_B-CF_2CF_3}$ = 2.8 Hz) were assigned to the magnetically unequivalent fluorine nuclei CHF-O-CF_2-C=C(CF_3). The molecular ion, M^+ 402, and fragment peaks appeared at appropriate positions in the mass spectrum.

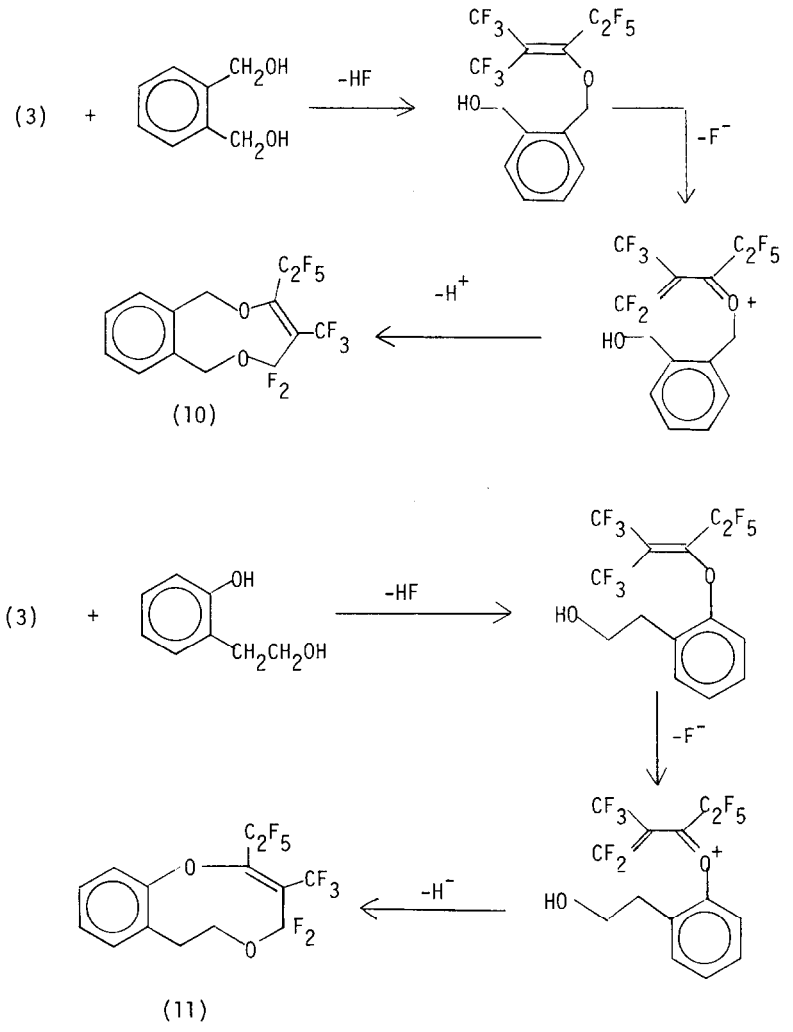
3-Chloro-2-hydroxybenzaldehyde also gave a similar compound, chlorobenzodioxocin (10-Cl-(9)).

Reaction of (1) with phthalyl alcohol and with o-hydroxyphenethyl alcohol

For the purpose of obtaining nine-membered benzoheterocycles, the reactions of (1) with phthalyl alcohol and with o-hydroxyphenethyl alcohol were carried out in triethylamine-diethyl ether system. The reactions proceeded exothermally and the products obtained were 1H,3H,7H-2,6- and 4H,6H,7H-1,5-benzodioxonins, (10) and (11), which were isolated in 63 and 74% yields, respectively.

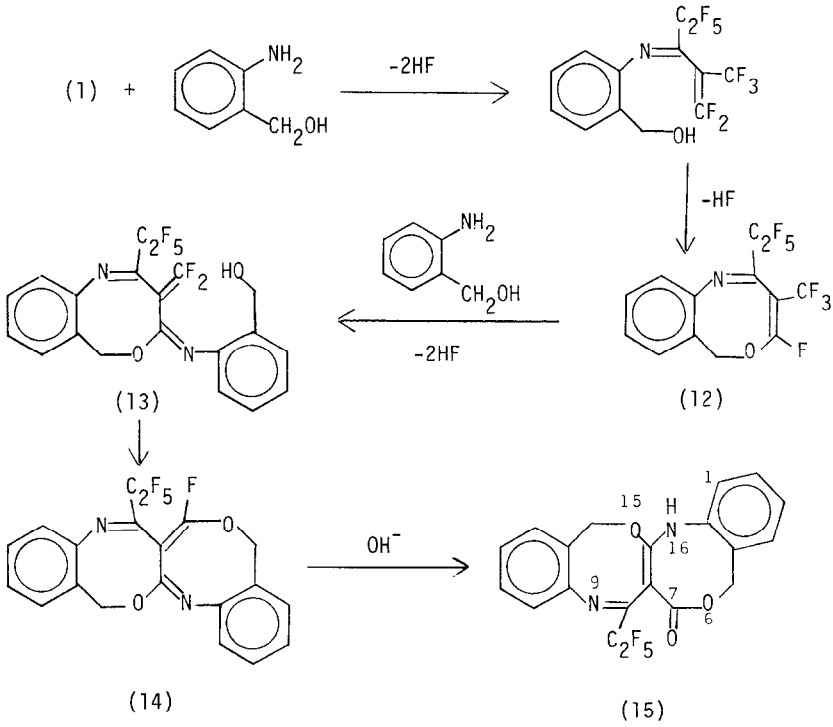
The ^{19}F nmr spectrum for (10) showed signals at δ -28.7 (OCF_2, $J_{OCF_2-CF_3}$ = 2.6 Hz), -23.0 (CF_3, $J_{CF_3-CF_2CF_3}$ = 4.2 Hz, $J_{CF_3-CF_2CF_3}$ = 19.1 Hz), 3.0 (CF_2CF_3) and 38.0 (CF_2CF_3). In the ^1H nmr spectrum, two signals appeared at δ 3.06 (CH_2) and 6.90 - 7.50 (Ar-H). The molecular ion, M^+ 398, and other fragment peaks were obtained from the mass spectrum.

The structure of (11) was similarly established on the basis of spectral data.



Reaction of (1) with o-aminobenzyl alcohol

The behavior of o-aminobenzyl alcohol with (1) was of considerable interest compared with those of other oxygen-functional benzenes described above. The reaction proceeded smoothly in acetonitrile without any base and a benzoxazocinobenzoxazocinone compound (15) was obtained in a yield of 84%.



The ^{19}F nmr spectrum for this compound showed signals at δ 4.2 ($CF_2\underline{C}F_3$) and 41.4 ppm ($\underline{C}F_2CF_3$) in the ratio 3 : 2. The ^{1}H nmr spectrum showed signals at δ 4.61 (CH_2), 7.10 - 7.35 (Ar-H) and 7.50 (NH). In the mass spectrum, the molecular ion, M^+ 424, and other appropriate fragment peaks appeared.

The reaction pathway was postulated as was shown above. The first step should be nucleophilic attack by the amino group leading to an eight-membered benzoheterocycle (12), which must react with another molecule of o-aminobenzyl alcohol, and resulting (13) would cyclize to (14), followed by the hydrolysis giving (15) finally.

Reviewing these results, the facile routes to new types of benzoheterocycles suggest that a wide variation of fluoroalkylated benzoheterocycles may be prepared from F-2-methyl-2-pentene derived from F-propene.

TABLE 1

Physical properties of the products

Compound	bp (^{o}C/mmHg) [mp (^{o}C)]	Yield (%)	^{19}F NMR (δ ppm)	Anal (%) Found (Calcd) C	H	N
(8) (nc)	105-107/1	45	-19.0(CF_3), 4.5($CF_2\underline{CF}_3$), 34.5($\underline{CF}_2CF_3$)	42.00 (41.51)	1.29 (1.07)	—
10-CH_3-(8) (nc)	[72-74]	55	-19.1(CF_3), 4.6($CF_2\underline{CF}_3$), 34.9($\underline{CF}_2CF_3$)	43.26 (43.10)	1.52 (1.55)	—
10-Cl-(8) (nc)	[84-85]	41	-15.8(CF_3), 3.6($CF_2\underline{CF}_3$), 44.2($\underline{CF}_2CF_3$)	39.26 (39.57)	0.82 (0.77)	—
(9) (nc)	78-80/1	50	-25.0(CF_3), 1.5($CF_2\underline{CF}_3$), 25.3(CHF), 26.6($\underline{CF}_2CF_3$), 46.3, 47.0(OCF_2)	38.47 (38.81)	1.42 (1.24)	—
10-Cl-(9) (nc)	86-88/1	53	-25.2(CF_3), 1.5($CF_2\underline{CF}_3$), 24.9(CHF) 26.3($\underline{CF}_2CF_3$), 46.5(OCF_2)	35.87 (35.76)	0.86 (0.92)	—
(10) (nc)	131-133/1	63	-28.7(OCF_2), -23.0(CF_3), 3.0($CF_2\underline{CF}_3$), 38.0($\underline{CF}_2CF_3$)	42.99 (42.23)	2.15 (2.03)	—
(11) (nc)	134-136/1	74	-28.7(OCF_2), -23.1(CF_3), 3.5($CF_2\underline{CF}_3$), 38.6($\underline{CF}_2CF_3$)	42.86 (42.23)	1.86 (2.03)	—
(15) (nc)	[91]	84	4.2(CF_3), 41.4(CF_2)	56.03 (56.61)	3.24 (3.09)	6.86 (6.60)

EXPERIMENTAL

General procedures will be described.

4-(F-Ethyl)-3-(F-methyl)-2H,6H-1,5-benzodioxocin-2,6-dione (8) (nc)

A mixture of salicylic acid (1.38 g, 10 mmol), F-2-methyl-2-pentene (1) (3.60 g, 12 mmol), triethylamine (2.02 g, 20 mmol) and acetonitrile (20 ml) was stirred at room temperature for 5 h. The reaction mixture was poured into water and an oily material was extracted with diethyl ether. After drying over magnesium sulfate, the solvent was removed. The residual oily material was subjected to distillation affording (8), bp 105 - 107 ^{o}C/1 mmHg, in 45% yield.

3-Methyl- and 3-chlorosalicylic acid were used in the reaction, and the products, 10-methyl and 10-chloro-(8), were isolated similarly.

2-(F-Ethyl)-4,4,6-trifluoro-3-(F-methyl)-4H,6H-1,5-benzodioxocin (9) (nc)

Salicylaldehyde (1.22 g, 10 mmol) was allowed to react with (1) (3.60 g, 12 mmol) in acetonitrile (20 ml) and triethylamine (2.02 g, 20 mmol) at room temperature for 5 h. The reaction mixture was worked up as described above. Distillation of an oily product in vacuo gave (9), bp 78 - 80 ^{o}C/1 mmHg, in 50% yield.

When 3-chlorosalicylaldehyde was used in the above reaction, a corresponding product, 10-chloro-(9), was obtained.

5-(F-Ethyl)-3,3-difluoro-4-(F-methyl)-1H,3H,7H-2,6-benzodioxonin (10) (nc)

Into a mixture of phthalyl alcohol (1.38 g, 10 mmol), (1) (3.90 g, 13 mmol) and diethyl ether (20 ml), triethylamine (2.02 g, 20 mmol) was added dropwise, keeping the temperature at -10 $\sim$ -5 ^{o}C. After stirring for 2 h at that temperature, the reaction mixture was poured into water and an ethereal layer was separated, washed with water, and dried over magnesium sulfate. After removing the solvent, the residual oily material was dissolved in n-hexane. The solution was subjected to column chromatography on silica gel, affording (10), as an oil (63%). This compound was distilled, giving the pure product, bp 131 - 133 ^{o}C/ 1 mmHg.

2-(F-Ethyl)-4,4-difluoro-3-(F-methyl)-4H,6H,7H-1,5-benzodioxonin (11) (nc)

A mixture of o-hydroxyphenethyl alcohol (2.07 g, 15 mmol), (1) (6.00 g, 20 mmol), triethylamine (3.03 g, 30 mmol) and diethyl ether (30 ml) was stirred for 2 h at -10 ~ -5 °C. The reaction mixture was poured into water, and the ethereal layer was separated. After drying over magnesium sulfate, the solvent was removed. The residual oily material was dissolved in chloroform and the solution was subjected to column chromatography on silica gel, yielding pure (11) as an oil (bp 134 - 136 °C/1 mmHg, 74%).

8-(F-Ethyl)-7H-15,9-benzoxazocino[4,3-b]6,16-benzoxazocin-7-one (15) (nc)

A mixture of o-aminobenzyl alcohol (2.46 g, 20 mmol), (1) (3.00 g, 10 mmol) and acetonitrile (20 ml) was stirred at -10 ~ -5 °C for 2 h. The reaction mixture was poured into water, and products were extracted with diethyl ether. After removal of the solvent, the residue was dissolved in methanol and the solution was subjected column chromatography on silica gel. The separated solid material was recrystallized from cyclohexane giving pure (15) (mp 91 °C, 84%).

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