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Convenient Synthesis of 2-Substituted-6 or 7-Acylated-1,4-Benzodioxin or 2,3-Dihydro-1,4-Benzodioxin Derivatives

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Abstract: The Friedel-Crafts acylation of 2-substituted-1,4-benzodioxin derivatives provides regioselectively the 6-acyl compounds. The same reaction with the saturated analogs affords two regioisomers with the 7-acyl compounds as the main products.

Present in many natural and synthetic products, the 2,3-dihydro-1,4-benzodioxinic ring has generated much interest in chemistry on account of its excellent pharmacological activity. Some 2,3-dihydro-1,4-benzodioxinic derivatives are cardiovascular agents as adrenoreceptor antagonists[1], while other compounds with a high affinity for 5-HT receptor subtypes[2] have been shown to exhibit neuroleptic activity . The 1,4-benzodioxane structure constitutes an ideal precursor of 1,4-benzodioxins, a relatively little studied class of compounds with only a few synthetic preparation methods available[3].

In the course of our work on the synthesis of therapeutically valuable benzodioxinic compounds, we needed 2-substituted-1,4-benzodioxin and 2-substituted-2,3-dihydro-1,4-benzodioxin derivatives bearing various acyl groups on position 6 or 7. To date, procedures permitting regioselective functionalization on the aromatic ring of benzodioxins have apparently not been described and are thus of great interest (the electrophilic reactions of corresponding dithia and oxathia compounds have been observed to occur on the hetero-ring[4]).

The present paper describes unequivocal synthetic routes towards 6 and 7 acyl-2-substituted-1,4-benzodioxin and 2-substituted-2,3-dihydro-1,4-benzodioxin derivatives.

Under typical conditions of Friedel-Crafts reaction[5], using acetyl chloride in the presence of aluminium trichloride in carbon disulfide, the acylation of 1,4-benzodioxin-2-carboxylic acid ethyl ester **1** occured in excellent yield exclusively at C_6. On the other hand, the electrophilic substitution of 2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester **15** lead to an isomeric mixture of two monoacylated products with the acyl group located respectively at the 6 and 7 positions.

Using various aromatic and aliphatic acyl chlorides we generalized these regioselective Friedel-Crafts acylations of 2-substituted-1,4-benzodioxins **1-5** (Scheme 1, Table 1) and of the saturated analogs **15-17** (Scheme 2, Table 2). Friedel-Crafts reactions on compounds **1** and **2** resulted in the formation of the corresponding C_6 monoacylated products in good yields. Decomposition was observed with alkyloxy derivatives **3, 4, 5** where R_1 is respectively CH_2OH, $CH_2OCH_2C_6H_5$, CH_2OCH_3.

Scheme 1

1 R_1 = COOEt
2 R_1 = CN
3 R_1 = CH_2OH
4 R_1 = CH_2OCH_2Ph
5 R_1 = CH_2OCH_3

6-10 R_1 = COOEt
11-14 R_1 = CN

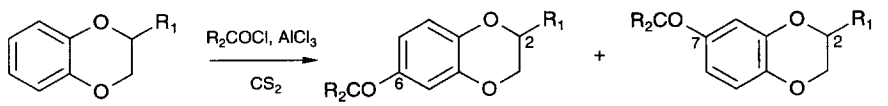
Table 1

R_2	Product	Yield %	Product	Yield %
CH_3[a]	**6**	95	**11**	89
$CH_3(CH_2)_2$[b]	**7**	82	**12**	92
$CH_3OCO(CH_2)_2$[b]	**8**	87	**13**	83
 [b]	**9**	72	**14**	75
C_6H_5[b]	**10**	69	-[c]	-

[a]: The reaction is performed at room temperature. [b]: The reaction is carried out at 40° C. At room temperature 80% of starting material are recovered [c]: The starting material is degradated in large quantities. Only trace amounts of the desired product are isolated.

In contrast, the same acylation reaction performed with 2-substituted-2,3-dihydro-1,4-benzodioxin analogs **15-17** afforded an isomeric mixture of two monoacylated derivatives, the acyl group being located on C_7 and C_6 (scheme 2). Whatever the nature of the group R_1, the C_7 acylated compound (**18b-23b**) was the main product (Table 2). The ratios of the components were found to be independent on the ratio of the reagents or on temperature.

Scheme 2



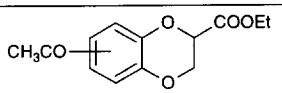
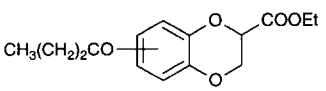
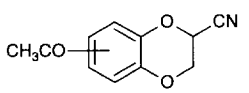
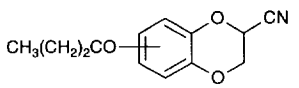
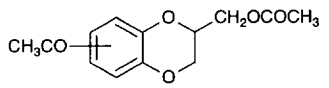
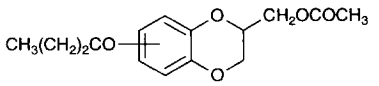
15 R_1 = COOEt
16 R_1 = CN
17 R_1 = CH_2OCOCH_3

6-acyl : product **a**
18-23

7-acyl : product **b**
18-23

The isomer ratios were calculated from the integration of well separated signals in the ^1H nmr spectra and confirmed by HPLC. After various fruitless attempts with HPLC using silica or reversed phase columns and capillary gas chromatography, we have successfully used porous graphitic carbon as LC packing[6].

Table 2

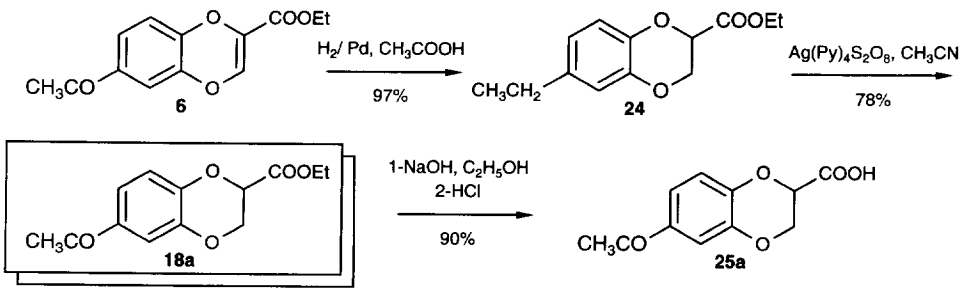
Product	isomeric ratio	global yield
	**18a / 18b** = 20 / 80	75%
	**19a / 19b** = 25 / 75	80%
	**20a / 20b** = 10 / 90	76%
	**21a / 21b** = 10 / 90	78%
	**22a / 22b** = 40 / 60	82%
	**23a / 23b** = 40 / 60	83%

The unsaturated (**6-14**) and saturated (**18a,b-23a,b**) acylated compounds are key synthetic intermediates for the synthesis of C_6 saturated and C_7 unsaturated functionalized analogs. We shall now describe unequivocal synthetic routes towards compound **18a** from **6** (scheme 3) and compound **27**, regioisomer of **6**, from the mixture **18a,b** (scheme 4). These compounds were needed for the synthesis of 6 and 7-acetyl-2,3-dihydro-1,4-benzodioxin derivatives and of 6 and 7-acetyl-1,4-benzodioxin derivatives.

Catalytic hydrogenation of derivative **6** in acetic acid with 10% palladium on charcoal (Pd-C) under hydrogen atmosphere lead to the saturated compound **24** in quantitative yields. Initial attempts employing Pd-C or PtO_2 in alcohol resulted in poor yields (< 35%) of saturated analog **18a**. Benzylic

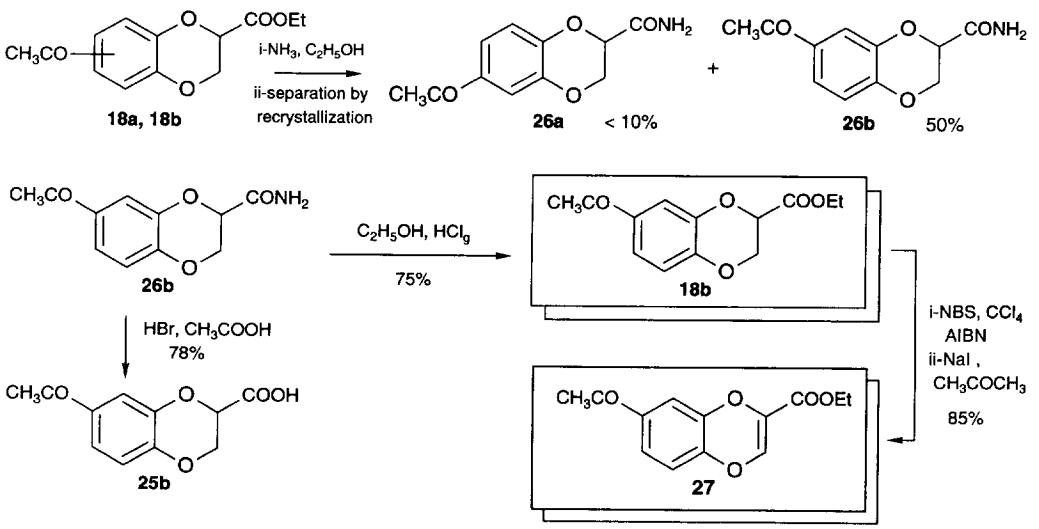
oxidation[7] of product **24** with tetrapyridinesilver (II) peroxydisulfate in refluxing acetonitrile afforded the C_6 acylated saturated analog **18a** in excellent yields (scheme 3).

Scheme 3



The derivative **18b** was readily obtained in pure form from the regioisomeric mixture **18a, 18b** after the following steps (scheme 4). Ammonolysis in alcoholic ammonia of the mixture of **18a** and **18b** gave the carboxamides **26a** and **26b** which were separated after several recrystallizations in ethanol[8] . Esterification of amide **26b** in boiling ethanol saturated in HCl gas[9] gave the C_7 acylated saturated derivative **18b**. A classical sequence of bromination-elimination[10] provided the C_7 acylated unsaturated analog **27**.

Scheme 4



Structural assignments of these acylated products were confirmed by converting compound **6** and its saturated analogues **18a** and **18b** to 6 or 7-acylated-2,3-dihydro-1,4-benzodioxin-2-carboxylic acids **25a** and

25b unambiguously prepared by Campbell *et al*[11](scheme 3 and scheme 4). Alkaline hydrolysis of **18a** at room temperature, followed by acid workup (scheme 3) provided the corresponding acid **25a**. The melting point and NMR spectra were identical with whose described for acids **25a** and **25b**. The conversion of the carboxamide **26b** into the carboxylic acid **25b** was accomplished by treatment with HBr[12] in refluxing acetic acid. The ^{1}H NMR spectrum of acid **25b** and the melting point, which is very different from that of **25a**, are rigorously identical with the published data[11] .

Conclusion

The Friedel-Crafts acylation of 2-substituted-1,4-benzodioxin derivatives resulted in the formation of C_6 monoacylated corresponding products. In contrast, in the saturated series two monoacylated compounds are obtained with the acyl group located in C_7 position for the major isomer and in C_6 for the minor isomer. *Via* this way, we have succeeded in developing, efficient synthetic routes towards **18b** and **27**. Molecular modeling studies showing cleary the correlation between electronic data and the regioselectivity of the substitution reactions will be published elsewhere.

Acknowledgments

We would like to thank Dr. Simon F. Campbell (Pfizer Central Research, Sandwich, Kent, U.K.) for providing the ^{1}H NMR spectra concerning the acids **25a** and **25b**. We are grateful to ADIR (Courbevoie, France) for financial support of this research.

EXPERIMENTAL

Melting points were determined on a Köfler apparatus and were uncorrected.The IR spectra were obtained on a Perkin-Elmer 196 infrared-spectrometer.The ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker AM 300WB spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as an internal standard (δ units). Mass spectra were measured on a Nermag R-10-10C spectrometer. Analytical thin layer chromatography (tlc) was performed on Merck 60F-254 silica gel plates. Preparative column chromatography was performed by using Merck silica gel (70-230 mesh). The unsaturated and saturated benzodioxinic precursors **1, 2, 3, 15, 16** were respectively obtained according to the literature procedures[10, 13, 14, 15, 16].

2-Benzyloxymethyl-1,4-benzodioxin (4)

To a stirred suspension of compound **3** (0.760 g, 3 mmol) and sodium hydride (60% dispersion in mineral oil, 0.125 g, 3.3 mmol) in 30 ml of DMF was added dropwise benzylchloride (0.415 g, 3.3 mmol). After 2 hr the solvent was removed with a vacuum rotatory evaporator. Column chromatography (eluent: petroleum ether / ethyl acetate : 8/2) gave the product as a colorless oil. Yield: 80%. IR : ν (cm^{-1}) : 1685 (C = C), 1240 (ether). ^{1}H-NMR ($CDCl_3$) : δ 3.87 (s, 2H, **CH_2**O**CH_2**Ar), 4.6 (s, 2H, O**CH_2**Ar), 5.95 (s, 1H, H_3), 6.6-6.89 (m, 4H, H_{arom}), 7.27-7.38 (m, 5H, $H_{arom.}$). MS *m/z* : 255 (M+1). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58 ; H, 5.55. Found : C, 75.61 ; H, 5.58.

2-Methoxymethyl-1,4-benzodioxin (5)

This compound was prepared from precursor **3** and methyliodide, as described above for **4**.

Yield: 87%. IR : ν (cm^{-1}) : 1685 (C=C). ^{1}H-NMR ($CDCl_3$) : δ 3.39 (s,3H, **CH_3**O), 3.79 (s, 2H, **CH_2**O), 5.97 (s, 1H, H_3), 6.59-6.86 (m, 4H, $H_{arom.}$). MS *m/z* : 179 (M+1). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40 ; H, 5.66. Found : C, 67.52 ; H, 5.78.

Acetic acid 2,3-dihydro-1,4-benzodioxin-2-ylmethyl ester (17)

Pyridine (2 ml) was added to a stirred solution of commercial 2,3-dihydro-1,4-benzodioxin-2-methanol (1.23 g, 6 mmol) in one volume of acetic anhydride (0.920 g, 9mmol) at 0°C. The solution was stirred at room temperature for another 2 hours, then neutralized with concentrated $NaHCO_3$ solution and ether was added. The combined organic extracts were dried over magnesium sulfate. Removal of solvent under reduced pressure gave the product as a colorless oil. Yield: 88%.IR : ν (cm^{-1}) : 1735 (C=O), 1260 (ether). ^{1}H-NMR ($CDCl_3$) : δ 2.11 (s, 3H, **CH_3**COO), 4.06 (dd, J_1 = 11.75Hz, J_2 = 6.60Hz, 1H, H_{3a}), 4.27-4.44 (m, 4H, H_2, H_{3b}, **CH_2**O), 6.83-6.91 (m, 4H, $H_{arom.}$). MS *m/z* : 209 (M+1). Anal. Calcd for $C_{11}H_{12}O_3$: C, 63.45 ; H, 5.81. Found : C, 63.57 ; H, 5.92.

6-Acyl-2-substituted-1,4-benzodioxinic compounds : General Procedure

The acyl chloride (12 mmol) then the anhydrous aluminium chloride (17.6 mmol) were added at 0°C under an argon atmosphere, to a solution of 2-substituted-1,4-benzodioxin derivatives (8 mmol) in 30 ml of carbon disulfide . The cooling bath was removed and the stirred mixture was heated at 40°C for 8 hours. Only with acetyl chloride was the mixture stirred for 3 hours at room temperature. After cooling the residue was hydrolyzed with water, cold HCl 2N and extracted with dichloromethane. The organic layers were washed with a saturated solution of $NaHCO_3$ then dried over magnesium sulfate and evaporated *in vacuo*. The benzodioxinic solid products **6-14** were washed with ethanol.

6-Acetyl-1,4-benzodioxin-2-carboxylic acid ethyl ester (6)

This compound was obtained as colorless needles. mp 124 -125 °C. IR : ν (cm^{-1}) : 1715 (C=O), 1675 (C = O), 1270 (ether).^{1}H-NMR ($CDCl_3$) : δ 1.34 (t, J = 7.1Hz, 3H, CH_2**CH_3**), 2.51 (s, 3H, **CH_3**CO), 4.29 (q, J = 7.1Hz, 2H, **CH_2**CH_3), 6.87 (d, $J_{8,7}$ = 8.7Hz, 1H, H_8), 6.97 (s, 1H, H_3), 7.31 (d, $J_{5,7}$ = 2.35Hz, 1H, H_5), 7.53 (dd, $J_{7,8}$ = 8.7Hz, $J_{7,5}$ = 2.35Hz, 1H, H_7). MS *m/z* : 249 (M+1). Anal. Calcd for $C_{13}H_{15}O_2$: C, 62.90 ; H, 4.87. Found : C, 63.02 ; H, 4.93.

6-Butyryl-1,4-benzodioxin-2-carboxylic acid ethyl ester (7)

This compound was obtained as colorless needles. mp 97-99 °C. IR : ν (cm^{-1}) : 1710 (C=O), 1670(C= O), 1290 (ether). ^{1}H-NMR ($CDCl_3$) : δ 0.98 (t, J = 7.35Hz, 3H, **CH_3**CH_2), 1.34 (t, J = 7.35Hz, 3H, OCH_2**CH_3**), 1.65-1.8 (m, 2H, CH_3**CH_2**CH_2), 2.82 (t, J = 7.35Hz, 2H, **CH_2**CO), 4.38 (q, J = 7.35Hz, 2H, O**CH_2**CH_3), 6.87 (d, $J_{8,7}$ = 8.45Hz, 1H, H_8), 6.97 (s, 1H, H_3), 7.31 (d, $J_{5,7}$ = 1.45Hz, 1H, H_5), 7.53 (dd, $J_{7,8}$ = 8.45 Hz, $J_{7,5}$ = 1.45Hz, 1H, H_7). MS *m/z* : 277 (M+1). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21 ; H, 5.84. Found : C, 65.38; H, 5.68.

6-(3-Methyloxycarbonyl-propionyl)-1,4-benzodioxin-2-carboxylic acid ethyl ester (8)

This compound was obtained as colorless needles. mp 122-123 °C. IR : ν (cm^{-1}) : 1730 (C=O), 1660 (C= O), 1290 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1.34 (t, J = 6.6Hz, 3H, CH_2**CH_3**), 2.75 (t, J = 6.6Hz, 2H, CO**CH_2**CH_2), 3.18 (t, J = 6.6Hz, 2H, **CH_2**COAr), 3.71 (s, 3H, O**CH_3**), 4.31 (q, J = 6.6Hz, **CH_2**CH_3), 6.89 (d, $J_{8,7}$ = 8.45Hz, 1H, H_8), 6.97 (s, 1H, H_3), 7.34 (d, $J_{5,7}$ = 2.2Hz, 1H, H_5), 7.56 (dd, $J_{7,8}$ = 8.45Hz, $J_{7,5}$ = 2.2Hz, 1H, H_7). MS *m/z* : 321 (M+1). Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00 ; H, 5.03. Found : C, 60.14 ; H, 5.15.

6-(2-Furoyl)-1,4-benzodioxin-2-carboxylic acid ethyl ester (9)
This compound was obtained as colorless needles. mp 120 °C. IR : ν (cm^{-1}) : 1720 (C=O), 1665 (C=O). ^{1}H-NMR ($CDCl_3$) : δ 1.34 (t, J = 7.1Hz, 3H, $CH_2\mathbf{CH_3}$), 4.29 (q, J = 7.1Hz, 2H, $\mathbf{CH_2}CH_3$), 6.59 (dd, J = 3.15Hz, J = 1.2Hz, 1H, $H_{fur.}$), 6.91 (d, $J_{8,7}$ = 8.5Hz, 1H, $H_{arom.}$), 6.98 (s, 1H, H_3), 7.4 (d, $J_{5,7}$ = 2Hz, 1H, H_5), 7.3 (d, J = 1.2Hz, 1H, $H_{fur.}$), 7.65-7.68 (m, 2H, H_7, $H_{fur.}$). MS *m/z* : 301 (M+1). Anal. Calcd for $C_{16}H_{12}O_6$: C, 65.93 ; H, 4.80. Found : C, 66.03 ; H, 4.92.

6-Benzoyl-1,4-benzodioxin-2-carboxylic acid ethyl ester (10)
This compound was obtained as colorless needles. mp 98 °C. IR : ν (cm^{-1}) : 1725 (C=O), 1680 (C=O), 1290 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1.34 (t, J = 7.1Hz, 3H, $CH_2\mathbf{CH_3}$), 4.31 (q, J = 7.1Hz, 2H, $\mathbf{CH_2}CH_3$), 6.88 (d, $J_{8,7}$ = 8.1Hz, 1H, H_8), 6.98 (s, 1H, H_3), 7.23 (d, $J_{5,7}$ = 1.6Hz, 1H, H_5), 7.38 (dd, $J_{7,8}$ = 8.1Hz, $J_{7,5}$ = 1.6Hz, 1H, H_7), 7.44-7.75 (m, 5H, $H_{arom.}$). MS *m/z* : 311 (M+1). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67 ; H, 4.55. Found : C, 69.72 ; H, 4.62.

6-Acetyl-1,4-benzodioxin-2-carbonitrile (11)
This compound was obtained as colorless needles. mp 163-164 °C. IR : ν (cm^{-1}) : 2205 (CN), 1665 (C=O), 1260 (ether). ^{1}H-NMR ($CDCl_3$) : δ 2.51 (s, 3H, $\mathbf{CH_3}CO$), 6.60 (s, 1H, H_3), 6.78 (d, $J_{8,7}$ = 8.3Hz, 1H, H_8), 7.33 (d, $J_{5,7}$ = 1.6Hz, 1H, H_5), 7.54 (dd, $J_{7,5}$ = 1.6Hz, $J_{7,8}$ = 8.3Hz, 1H, H_7). MS *m/z* : 202 (M+1). Anal. Calcd for $C_{11}H_7O_3N$: C, 65.67 ; H, 3.51 ; N, 6.96. Found : C, 65.73 ; H, 3.57 , N, 7.01.

6-Butyryl-1,4-benzodioxin-2-carbonitrile (12)
This compound was obtained as colorless needles. mp 110-112°C. IR : ν (cm^{-1}) : 2205 (CN), 1670 (C=O), 1290 (ether). ^{1}H-NMR ($CDCl_3$) : δ 0.99 (t, J = 7.9Hz, 3H, $\mathbf{CH_3}CH_2$), 1.74 (m., J = 7.9Hz, 2H, $CH_3\mathbf{CH_2}$), 2.84 (t, J = 7.9Hz, 2H, $\mathbf{CH_2}CO$), 6.59 (s, 1H, H_3), 6.79 (d, $J_{8,7}$ = 8.7Hz, 1H, H_8), 7.34 (d, $J_{5,7}$ = 1.6Hz, 1H, H_5), 7.56 (dd, $J_{7,8}$ = 8.7Hz, $J_{7,5}$ = 1.6Hz, 1H, H_7). MS *m/z* : 230 (M+1). Anal. Calcd for $C_{13}H_{11}O_3N$: C, 68.12 ; H, 4.83 ; N, 6.11. Found : C, 68.25 ; H, 4.85 ; N, 6.18.

4-(2-Cyano-1,4-benzodioxin-6-yl)-4-oxo-butyric acid methyl ester (13)
This compound was obtained as colorless needles. mp 128-129 °C. IR : ν (cm^{-1}) : 2205 (CN), 1730 (C=O), 1660 (C=O), 1290 (ether). ^{1}H-NMR ($CDCl_3$) : δ 2.75 (t, J = 6.35Hz, 2H, $\mathbf{CH_2}CH_2$), 3.18 (t, J = 6.35Hz, 2H, $CH_2\mathbf{CH_2}$), 3.7 (s, 3H, $\mathbf{CH_3}O$), 6.59 (s, 1H, H_3), 6.8 (d, $J_{8,7}$ = 7.9Hz, 1H, H_8), 7.36 (d, $J_{5,7}$ = 2.15Hz, 1H, H_5), 7.6 (dd, $J_{7,8}$ = 7.9Hz, $J_{7,5}$ = 2.15Hz, 1H, H_7). MS *m/z* : 274 (M+1). Anal. Calcd for $C_{14}H_{11}O_5N$: C, 61.54 ; H, 4.06 ; N, 5.13. Found : C, 61.64 ; H, 4.22 ; N, 5.20.

6-(2-Furoyl)-1,4-benzodioxin-2-carbonitrile (14)
This compound was obtained as colorless needles. mp 187-189 °C. IR : ν (cm^{-1}) : 2205 (CN), 1665 (C=O). ^{1}H-NMR ($CDCl_3$) : δ 6.6 (s, 1H, H_3), 6.83 (d, $J_{8,7}$ = 8.7Hz, 1H,H_8), 7.29 (d, J = 3.1Hz, 1H, $H_{fur.}$), 7.45 (d, $J_{5,7}$ = 1.95Hz, 1H, H_5), 7.67-7.73 (m, $J_{7,5}$ = 1.95Hz, $J_{7,8}$ = 8.7Hz, 3H, H_7, $2H_{fur.}$). MS *m/z* : 254 (M+1). Anal. Calcd for $C_{14}H_7O_4N$: C, 69.01 ; H, 3.57 ; N, 6.20. Found : C, 69.05 ; H, 3.58 ; N, 6.22.

7 and 6-Acyl-2-substituted-2,3-dihydro-1,4-benzodioxinic compounds : General Procedure
The acylated saturated compounds are prepared by the procedure described above with the unsaturated precursors.The saturated crude products **18-23a,b** were purified but not separated by silica gel column chromatography (eluent: petroleum ether / ethyl acetate: 8/2).

6 and 7-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (18a, 18b)
The spectroscopic data of these regioisomers, isolated in pure form in several steps are given below.

6 and 7-Butyryl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (19a, 19b)
These compounds were obtained as a colorless oil. IR : ν (cm^{-1}) : 1740 (C=O), 1270 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1 (t, J = 7.9Hz, 6H, 2 x **CH_3**CH_2), 1.29 (t, J = 7.9Hz, 6H, 2 x CH_3**CH_2**), 1.76 (m., J = 7.9Hz, 4H, 2 x CH_3**CH_2**), 2.88 (t, J = 7.9Hz, 4H, 2 x **CH_2**CO), 4.28 (q, J = 7.1Hz, 4H, 2 x **CH_2**CH_3), 4.38-4.54 (m, 4H, 2 x H_{3a}, H_{3b}), 5.18 (t, J = 3.55Hz, 2H, 2 x H_2), 6.92 (d, $J_{5,6}$ = 8.3Hz, 2H, H_5), 7.05 (d, $J_{8,7}$ = 8.3Hz, 1H, H_8), 7.58-7.64 (m, 4H, $H_{7(2.6)}$, $H_{5(2.6)}$, $H_{8(2.7)}$, $H_{6(2.7)}$). MS *m/z* : 279 (M+1).

6 and 7-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (20a, 20b)
These compounds were obtained as a colorless oil. IR : ν (cm^{-1}) : 2200 (CN), 1665 (C=O), 1260 (ether). ^{1}H-NMR ($CDCl_3$) : δ 2.51-2.52 (s, 6H, 2 x **CH_3**CO), 4.35-4.55 (m, 4H, 2 x H_{3a}, H_{3b}), 5.16-5.21 (m, 2H, 2 x H_2), 7.02 (d, $J_{5,6}$ = 8.75Hz, 2H, $H_{8(2.6)}$, $H5_{(2.7)}$, 7.54-7.64 (m, 4H, $H_{7(2.6)}$, $H_{5(2.6)}$, $H_{8(2.7)}$, $H_{6(2.7)}$). MS *m/z* : 204 (M+1).

6 and 7-Butyryl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (21a, 21b)
These compounds were obtained as a colorless oil. IR : ν (cm^{-1}) : 2200 (CN), 1675 (C=O), 1260 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1 (t, J = 7.9Hz, 6H, 2 x **CH_3**CH_2), 1.76 (m., J = 7.9Hz, 4H, 2 x CH_3**CH_2**), 2.88 (t, J = 7.9Hz, 4H, 2 x CH_2CO), 4.38-4.54 (m, 4H, 2 x H_{3a}, H_{3b}), 5.18 (t, J = 3.55Hz, 2H, 2 x H_2), 7.02 (d, $J_{5,6}$ = 8.9Hz, 2H, H_5, $H_{8(2.6)}$), 7.58-7.64 (m, 4H, $H_{7(2.6)}$, $H_{5(2.6)}$, $H_{8(2.7)}$, $H_{6(2.7)}$). MS *m/z* : 232 (M+1).

Acetic acid 6 and 7 acetyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl ester (22a, 22b)
These compounds were obtained as a colorless oil. IR : ν (cm^{-1}) : 1770 (C=O), 1645 (C=O), 1270 (ether). ^{1}H-NMR ($CDCl_3$) : δ 2.12 (s, 6H, 2 x **CH_3**COO), 2.53 (s, 6H, 2 x **CH_3**CO), 4.08-4.14 (m, 2H, 2 x H_{3a}), 4.3-4.5 (m, 8H, 2 x H_{3b}, H_2, **CH_2**O), 6.93 (d, $J_{5,6}$ = 8.8Hz, 1H, H_5), 6.95 (d, $J_{8,7}$ = 8.1Hz, 1H, H_8), 7.5-7.55 (m, 4H, $H_{6(2.6)}$, $H_{8(2.6)}$, $H_{5(2.7)}$, $H_{7(2.7)}$). MS *m/z* : 251 (M+1).

Acetic acid 6 and 7 butyryl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl ester (23a, 23b)
These compounds were obtained as a colorless oil. IR : ν (cm^{-1}) : 1740 (C=O), 1665 (C=O), 1260 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1 (t, J = 7.2Hz, 6H, 2 x **CH_3**CH_2), 1.74 (m., J = 7.2Hz, 4H, 2 x CH_3**CH_2**), 2.12 (s, 6H, 2 x **CH_3**CO), 2.87 (t, J = 7.21Hz, 4H, 2 x **CH_2**CO), 4.04-4.5 (m, 10H, 2 x H_2, H_{3a}, H_{3b}, **CH_2**O), 6.93 (d, $J_{5,6}$ = 8.7Hz, 1H, H_5), 6.97 (d, $J_{8,7}$ = 8.3Hz, 1H, H_8), 7.5-7.6 (m, 4H, $H_{6(2.7)}$, $H_{8(2.7)}$, $H_{5(2.6)}$, $H_{7(2.6)}$). MS *m/z* : 279 (M+1).

6-Ethyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (24)
The compound **6** (0.5 g, 2 mmol) and 5% palladium on charcoal (0.125g) were suspended in 10 ml of acetic acid and stirred in a Parr bottle under H_2 pressure (50 psi) for 2 hours. The mixture was filtered through Celite and evaporated. Pure material **24** was obtained as a colorless oil by purification on silica gel column chromatography (eluent: petroleum ether / ethyl acetate: 8/2). Yield: 97%. IR : ν (cm^{-1}) : 1745 (C=O), 1250 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1.2 (t, J = 7.5Hz, 3H, **CH_3**CH_2Ar), 1.3 (t, J = 7.1Hz, 3H, **CH_3**CH_2), 2.56 (q, J= 7.5Hz, 2H, CH_3**CH_2**Ar), 4.28 (q, J = 7.1Hz, 2H, CH_3**CH_2**), 4.36-4.38 (m, 2H, H_{3a}, H_{3b}), 4.79(t, J = 3.95Hz, 1H, H_2), 6.7-6.74 (m, 2H, H_7, H_5), 6.92 (d, $J_{8,7}$ = 8.7Hz, 1H, H_8). MS *m/z* : 237 (M+1). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09 ; H, 6.82. Found : C, 66.14 ; H, 6.87.

6-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (18a)
To a solution of compound **24** (0.5 g, 2.1 mmol) in 30 ml of acetonitrile was added tetrapyridinesilver (II) peroxydisulfate[7] (3.6 g, 6.33 mmol). The stirred mixture was refluxed for 3 hours then left at room temperature for 30 minutes and filtered. The solid material was washed with acetonitrile. The solvent was evaporated to dryness. The resulting material was purified on silica gel column chromatography (eluent:

petroleum ether / ethyl acetate: 8/2) and pure product **18a** was obtained as a colorless oil. Yield: 78%. IR : ν (cm^{-1}) : 1740 (C=O), 1665 (C=O), 1250 (ether).^{1}H-NMR ($CDCl_3$) : δ 2.53 (s, 3H, **CH_3**CO), 4.27 (q, J = 7.35Hz, 2H, CH_3**CH_2**), 4.41 (q, J = 3.55Hz, J = 11.85Hz, 2H, H_{3a}, H_{3b}), 4.88 (d, J = 3.55Hz, 1H, H_2),7.05 (d, $J_{8,7}$ = 8.05Hz, 1H, H_8), 7.52 (dd, $J_{7,8}$ = 8.05Hz, $J_{7,5}$ = 1.9Hz, 1H, H_7), 7.56 (d, $J_{5,7}$ = 1.9 Hz, 1H, H_5). MS *m/z* : 251 (M+1). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40 ; H, 5.64. Found : C, 62.38 ; H, 5.54.

7-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid amide (26b)

5 g of the mixture **18a, 18b** in 30 ml of ethanol was treated with 90 ml of concentrated ammonia. The stirred solution was allowed to stand at room temperature for 2 days. The C_7 isomer **26b** which is relatively insoluble in the ethanol precipitated. It was collected and recrystallisation from ethanol 70% provided colorless needles. Yield: 50%. mp 220- 222°C. IR : ν (cm^{-1}) : 3340-3160 (NH_2), 1680 (C=O), 1270 (ether). ^{1}H-NMR (DMSO) : δ 2.5 (s, 3H, **CH_3**CO), 4.36 (d, J = 3.95 Hz, 2H, H_{3a}, H_{3b}), 4.82 (t, J = 3.95Hz, 1H, H_2), 6.97 (d, $J_{5,6}$ = 8.3Hz, 1H, H_5), 7.47-7.55 (m, 2H, H_6, H_8), 7.61 (bs, 2H, CO**NH_2**). MS *m/z* : 222 (M+1), 239 (M+18). Anal. Calcd for $C_{11}H_{11}O_4$: C, 59.72 ; H, 5.01 ; N, 6.33. Found : C, 59.82 ; H, 5.08 ; N, 6.43.

Concentration of initial filtrate followed by washing in ethanol gave impure carboxamide **26a**. Yield: < 10%.

7-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (18b)

A solution of 3 g of carboxamide **26b** (13.5 mmol) in 150 ml of ethanol saturated with dry hydrogen chloride was refluxed for 20 hours. The cooled mixture was filtered and the solvent was removed by evaporation under reduced pressure. The crude material dissolved in water was neutralized with solid $NaHCO_3$ and extracted with ether. The residual oily solid obtained after removal of the solvent was purified by silica gel column chromatography (eluent: petroleum ether / ethyl acetate: 8/2). Yield: 75%. mp 57-58 °C. IR : ν (cm^{-1}) : 1740 (C=O), 1670 (C=O), 1260 (ether).^{1}H-NMR ($CDCl_3$) : δ 1.28 (t, J = 6.9Hz, 3H, CH_2**CH_3**), 2.53 (s, 3H, **CH_3**CO), 4.28 (q, J = 6.9Hz, 2H, **CH_2**CH_3), 4.4-4.5 (m, 2H, H_{3a},H_{3b}), 4.86 (t, J = 3.55Hz, 1H, H_2), 6.92 (d, $J_{5,6}$ = 8.7Hz, 1H, H_5), 7.52 (dd, $J_{6,8}$ = 1.95Hz, $J_{6,5}$ = 8.7Hz, 1H, H_6), 7.63 (d, $J_{8,6}$ = 1.95Hz, 1H, H_8). MS *m/z* : 251 (M+1). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40 ; H, 5.64. Found : C, 62.45 ; H, 5.59.

7-Acetyl-1,4-benzodioxin-2-carboxylic acid ethyl ester (27)

To a solution of compound **18b** (0.75g, 3 mmol) in dry carbon tetrachloride was added N-bromosuccinimide (11.35g, 66 mmol) and a catalytic quantity of AIBN. The resulting mixture was stirred and heated with a bulb lamp at reflux for 6 hours. The mixture was allowed to cool and the succinimid was filtered off. The filtrate was evaporated to yield a solid sufficiently pure to be used directly in the next step of the reaction. A solution of dibromo compound (1.22g, 3 mmol) in 60 ml of acetone was stirred at room temprerature for 2 hours with 1.57g (10.5 mmol) sodium iodide. The acetone was removed from the greenish slurry under reduced pressure then water, diethylether and 1N solution sodium hyposulfite were added to the resulting brown residue. After extraction the dried organic layers were removed. The crude compound was purified by silica gel column chromatography (eluent: petroleum ether / ethyl acetate: 8/2) to give white needles. Yield: 85%. mp 144 - 145°C; IR : ν (cm^{-1}) : 1715 (C=O), 1675 (C = O), 1270 (ether). ^{1}H-NMR ($CDCl_3$) : δ 1.33 (t, J = 7.1Hz, 3H, **CH_3**CH_2), 2.5 (s, 3H, **CH_3**CO), 4.3 (q, J = 7.1 Hz, 2H, **CH_2**CH_3), 6.76 (d, $J_{5,6}$ = 8.3Hz, 1H, H_5), 6.94 (s, 1H, H_3), 7.41 (d, $J_{8,6}$ = 2Hz, 1H, H_8), 7.5 (dd, $J_{6,8}$ = 2Hz, $J_{6,5}$ = 8.3Hz, 1H, H_6). MS *m/z* : 249 (M+1). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90 ; H, 4.87. Found : C, 62.93 ; H, 4.77.

6-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid (25a)

A stirred solution of product **18a** (0.500 g, 2 mmol) in 10 ml of ethanol was treated with 10% aqueous sodium hydroxyde (20 mmol). After 2 hours at room temperature and evaporation under reduced pressure of ethanol, the aqueous phase was acidified with HCl 2N. The combined extracts were dried over magnesium sulfate. Evaporation of the solvent yielded the crude acid **25a** as a white solid (90%). mp 174-175°C. IR :ν (cm^{-1}):

3500-2500 (COOH), 1760 (C=O), 1650 (C=O).^{1}H-NMR (DMSO + D_2O) : δ 2.51 (s, 3H, **CH_3**CO), 4.27-4.55 (m, 2H, H_{3a}, H_{3b}), 5.13 (t, J = 3.15Hz, 1H, H_2), 7.05 (d, $J_{8,7}$ = 8.85 Hz, 1H, H_8), 7.41 (d, $J_{5,7}$ = 2.5Hz, 1H, H_5), 7.5 (dd, $J_{7,5}$ = 2.5Hz, $J_{7,8}$ =8.85Hz, 1H, H_7). MS *m/z* : 223 (M+1), 240 (M+18)

7-Acetyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid (25b)

Compound (0.250 g) **26b** was refluxed for 2 hours in 2ml of HBr 48% and 8 ml of acetic acid. The solvent was removed under reduced pressure. The crude product was washed with dichloromethane. Recrystallization from ether gave pure acid **25b**. Yield: 78%. mp 167-168°C. IR : ν (cm^{-1}) : 3500-2500 (COOH), 1725 (C=O), 1680 (C=O), 1250 (ether).^{1}H-NMR (DMSO + D_2O) : δ 2.50 (s, 3H, **CH_3**CO), 4.29-4.53 (m, 2H, H_{3a}, H_{3b}), 5.11 (t, J = 3.5Hz, 1H, H_2), 6.94 (d, $J_{5,6}$ = 8.2Hz, 1H, H_5), 7.47-7.51 (m, 2H, H_6, H_8). MS *m/z* : 223 (M+1), 240 (M+18).

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