Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5935–5940

TETRAHEDRON

Direct iodination of indanone and tetralone derivatives by elemental iodine activated by Selectfluor™ F-TEDA-BF_4

Marjan Jereb,[b] Stojan Stavber[a,*] and Marko Zupan[a,b]

[a]*Laboratory for Organic and Bioorganic Chemistry, 'Jožef Stefan' Institute, Jamova 39, 1000 Ljubljana, Slovenia*
[b]*Department of Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*

Received 3 March 2003; revised 5 June 2003; accepted 5 June 2003

Abstract—Derivatives of indan-1-one and 3,4-dihydronaphthalen-1(2*H*)-one bearing hydroxy or methoxy substituent on the aromatic ring were efficiently iodinated regioselectively at the α carbonyl position using elemental iodine activated by 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4) in methanol.

1. Introduction

The chemistry dealing with selective introduction of an iodine atom into organic molecules has attracted considerable interest in the wider scientific community[1] since iodinated organic molecules, though seldom used in medicine as drugs or diagnostics,[2] have been recognised as versatile synthetic tools, above all in carbon–carbon bond formation.[3] Iodine bonded at the position α to the carbonyl group makes the molecule a very convenient synthon for further functionalisation. For the preparation of α-iodinated ketones various indirect methods of halogen interchange reactions or electrophilic iodination of silyl enol ethers and enol acetates are used, while methods for direct iodofunctionalisation are still scarce and often include elemental iodine as an iodine atom transfer reagent and an oxidant as an activator of the iodonium donating system.[4] Several derivatives of 1-indanone or 1-tetralone, especially those with a hydroxy or methoxy functionalised aromatic ring, are building blocks that have been employed in the synthesis of biomedicinally active compounds such as some antidepressants,[5] acetylcholinesterase (AchE) inhibitors effective in the treatment of Alzheimer disease,[6] alkaloids bearing antitumour activity,[7] and antibiotics.[8] α-Iodo substituted analogues of these synthons could improve many of these synthetic protocols. In addition, 2-iodoindanone and 2-iodotetralone derivatives are also desirable compounds in view of the possible generation of α-carbonyl radicals from α-iodo ketones[9] and involvement of these reactive species in intermolecular radical cyclisation reactions.[10]

Organic compounds incorporating a reactive N–F bond has been proven to be versatile fluorinating reagents which revolutionized the perception of synthesis of organofluorine molecules in the last decade.[11] Among N–F reagents, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), known under the commercial name of Selectfluor™ F-TEDA-BF_4 (**1**), is one of the most popular and is also recognised as a convenient mediator of several 'fluorine-free' functionalisations of organic compounds.[12] These kinds of reactions are based on the fact that F-TEDA-BF_4 has considerable oxidative power, one of the strongest in the family of N–F reagents.[13] Taking advantage of this property we promoted F-TEDA-BF_4 recently as a mediator of direct iodination of arenes[14] and ketones.[15] In line with our continued interest in N–F reagents and further investigations of the iodine/F-TEDA-BF_4 system, we now report its use for selective iodination of 1-indanone and 1-tetralone derivatives.

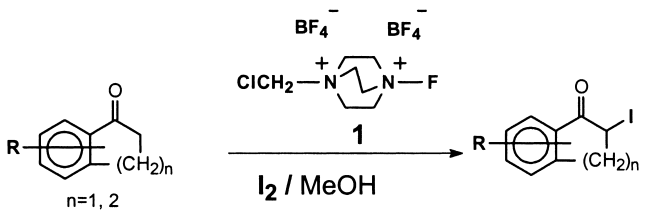
2. Results and discussion

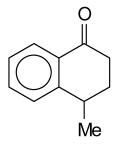
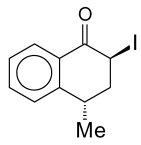
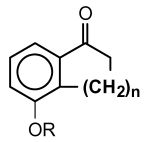
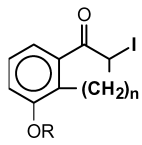
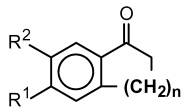
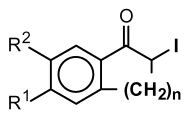
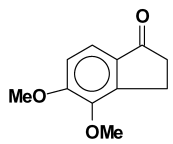
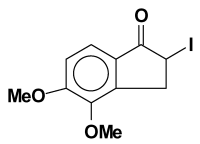
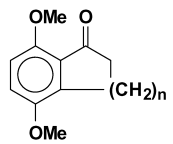
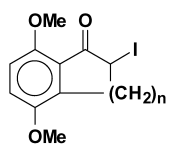
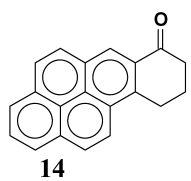
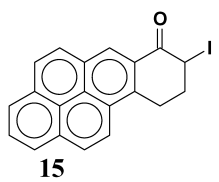
In our preliminary report we recognised F-TEDA-BF_4 as a very effective mediator for iodination of aryl alkyl ketones using elemental iodine as an iodine atom transfer reagent. In acetonitrile, the aromatic ring was exclusively iodinated, while in methanol, regioselective iodofunctionalisation of the α-carbonyl position was observed.[15a] Among other preliminary target molecules, 4-methoxyindan-1-one and 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one were also very effectively α-iodinated using the I_2/F-TEDA-BF_4/MeOH reaction system. In order to generalize these results further, we selected a wide range of substituted 1-indanone and 1-tetralone derivatives, bearing an aromatic ring activated by hydroxy or methoxy substituents or cycloalkyl

Keywords: iodination; Selectfluor™ F-TEDA-BF_4; 1-indanone; 1-tetralone.
* Corresponding author. Tel.: +386-1-477-36-60; fax: +386-1-477-38-11; e-mail: stojan.stavber@ijs.si

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00904-9

Table 1. Direct iodination of substituted 1-indanones and 1-tetralones by elemental iodine activated with 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4 **1**) in methanol

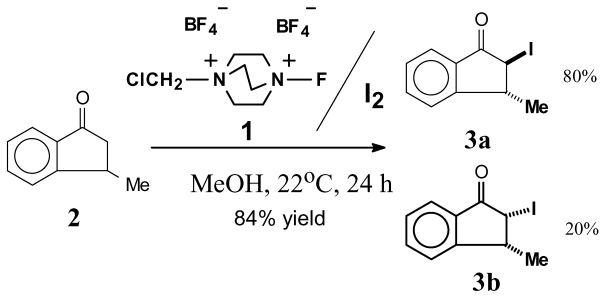


Entry	Ketone		Time (h)	Product	Yield[a] (%)
1	 **4**		24	 **5**	86
2	 **6**	**a**: n=1; R = H	20	 **7**	64
3		**b**: n=2; R = H	20		69
4		**c**: n=2; R = Me	20		87
5	 **8**	**a**: n=2; R^1 = OH; R^2 = H	20	 **9**	73
6		**b**: n=1; R^1 = OMe; R^2 = H	20		86
7		**c**: n=1; R^1 = H; R_2 = OMe	5		85
8		**d**: n=2; R^1 = H; R^2 = OMe	6		86
9		**e**: n=1; R^1 = R^2 = OMe	6		84
10		**f**: n=2; R^1 = R^2 = OMe	6		85
11	 **10**		6	 **11**	86
12	 **12**	**a**: n = 1	5	 **13**	85
13		**b**: n = 2	6		87
14	 **14**		24	 **15**	63

Reaction conditions: ketone (2 mmol), F-TEDA-BF_4 (1.1 mmol), I_2 (1 mmol), methanol (20 mL), 20°C, reaction time 5–24 h.
[a] Refers to the isolated pure products.

part of the molecule substituted by a methyl group, and checked the selectivity as well as the effectiveness of the reaction. The results are collected in Table 1.

A methyl group bonded α to the carbonyl group of the target molecules seemed to be unfavourable for iodination since after reaction of 2-methylindan-1-one as well as 2-methyl-3,4-dihydronaphthalen-1(2*H*)-one with I_2/F-TEDA-BF_4 in MeOH under the usual reaction conditions only the starting material was recovered. On the other hand, 3-methylindan-1-one (**2**, Scheme 1) and 4-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**4**, Table 1) were readily transformed to their 2-iodo analogues **3** and **5** almost quantitatively. Careful analysis of the NMR spectra of the crude product 2-iodo-3-



Scheme 1.

methylindan-1-one **3** and the corresponding sample purified by flash chromatography revealed that a diastereoisomeric pair of **3** was formed. On the basis of differences in chemical shifts and coupling constants corresponding to H-2 and H-3, we established that the main product is the *trans* isomer **3a** while four time less of the *cis* isomer **3b** was formed. On the other hand, stereospecific iodination of **4** was observed and according to interactions on its NOESY spectrum and the analysis of its ^{1}H NMR spectrum by homonuclear decoupling the stereochemistry of the product **5** was assigned as *trans* and the formation of (±)-2-iodo-t-4-methyl-3,4-dihydronaphthalene-1(2*H*)-one established.

An aromatic ring activated with a hydroxy group did not interfere with the regioselectivity of the iodination and 4-hydroxy-2-iodoindan-1-one **7a** as well as 5-hydroxy-2-iodo- **7b** and 6-hydroxy-2-iodo-3,4-dihydronaphthalen-1(2*H*)-one **9a** were formed regioselectively and in high yield from target hydroxy substituted substrates **6a**, **6b** and **8a**. Despite activation of the aromatic ring with methoxy substituents, even better α-iodination was achieved. In this series, 5-methoxyindan-1-one **8b** and 6-methoxyindane-1-one **8c** were selectively transformed to their 2-iodo-substituted final products **9b** or **9c**, as well their tetralone analogues 5-methoxy- **6c** and 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **8d** were iodinated to 2-iodo substituted products **7c** and **9d** in almost quantitative yield. Additional activation of the aromatic ring with a second methoxy substituent did not change the regioselective course of the reaction. 5,6-Dimethoxyindan-1-one **8e** or its 4,5-dimethoxy- (**10**) and 4,7-dimethoxy (**12a**) analogues were readily transformed to their 2-iodo-substituted products **9e**, **11**, and **13a**, while the transformation of the corresponding dimethoxy tetralone target molecules **8f** and **12b** also resulted in the formation of α-iodo-substituted derivatives **9f** and **13b**. We finally applied the I_2/F-TEDA-BF_4/MeOH reaction system for the iodination of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one **14**, a molecule which has a certain importance in investigations in the field of carginogenesis,[16] and recognised that also in this case the α-iodo carbonyl derivative (±)-9-iodo-9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one **15** could be obtained in high yield.

In present time the mechanism of this synthetically very useful reaction is not completely clear but some facts important for its elucidation should be pointed out. For the interaction of ketone and F-TEDA-BF_4 the solvent and reaction temperature are crucial in order to direct the reaction to the desired way. At higher reaction temperatures F-TEDA-BF_4 behaves as a fluorine atom transfer reagent, transforming ketones to their fluorinated products,[17] while at lower temperatures the oxidative properties of F-TEDA-BF_4 prevail and activation of iodine, thus forming the iodonium cation reactive species, is the starting point of the reaction. Reaction could additionally be directed by the solvent. If the ketone target molecule bears an activated aromatic structural block, reactions in acetonitrile solutions resulted selectively in aromatic ring functionalisation, while in methanol suspensions the α-carbon atom is exclusively the reactive part of the substrate.[15,18]

3. Conclusions

In summary I_2/F-TEDA-BF_4/MeOH is an efficient reaction system for selective iodination of indanone and tetralone derivatives at the position α to the carbonyl functional group. The reaction protocol is easy to perform, both iodine atoms in elemental iodine are involved in the iodination process and half an equivalent of F-TEDA-BF_4 is sufficient for consumption of each equivalent of starting material. Further investigations towards the elucidation of reaction mechanism are currently underway.

4. Experimental

4.1. General

1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4; **4**) was purchased from Apollo and used as received. Starting materials in Table 1 were Sigma-Aldrich samples and were used as received. Solvents (ACS grade) were dried prior to use. Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Inova 300 spectrometer at 300 MHz and ^{13}C NMR on the same instrument at 75 MHz. Chemical shifts are reported in ppm from TMS as the internal standard. Data for ^{1}H NMR are reported as follows: chemical shift, number of protons, multiplicity, coupling constant, and assignment, while for ^{13}C NMR as follows: chemical shift, assignment. IR spectra were recorded on a Perkin–Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN analyser.

4.2. General procedure for the direct iodination of indanone and tetralone derivatives by elemental iodine activated with Selectfluor™ F-TEDA-BF_4

To a solution of 2 mmol of the starting material listed in Table 1 in MeOH (20 mL) iodine (254 mg, 1 mmol) and F-TEDA-BF_4 (390 mg, 1.1 mmol) were added and the reaction suspension stirred at 22°C for 5–24 h (see Table 1). The solvent was removed under reduced pressure and the crude reaction mixture dissolved in CH_2Cl_2 (50 mL). Insoluble material was filtered off, the solution was washed

with aqueous sodium thiosulfate pentahydrate (10%, 50 mL) and water (50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude reaction mixtures analysed by ^1H NMR, MS and TLC. The crude products were purified by flash chromatography over SiO_2 (elution with CH_2Cl_2), followed by crystallisation in the case of solid products or distillation under reduced pressure in the case of liquid compounds. Pure α-iodo ketones were stable in cold and dark while their physico-chemical and spectroscopic characteristics were validated as stated below.

4.2.1. (±)-2-Iodo-*t*-3-methylindan-1-one (3a) and (±)-2-iodo-*c*-3-methylindan-1-one (3b). Yield 84% of an oily mixture of both isomers in 4:1 relative yield. The relative ratio of isomers, established by ^1H NMR, remained constant along the temperature range from −50°C to +90°C.

Compound **3a**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (3H, d, J=7.2 Hz, CH_3), 3.66 (1H, dq, J=3.6, 7.2 Hz, H-3), 4.52 (1H, d, J=3.6 Hz, H-2), 7.38–7.82 (4H, m, H4-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 (CH_3), 29.4 (C-2), 46.6 (C-3), 124.6, 124.7, 128.1, and 135.7 (Ar–CH), 156.3 (Ar–C), 200.3 (CO).

Compound **3b**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (3H, d, J=7.0 Hz, CH_3), 3.28 (1H, dq, J_1=J_2=7.0 Hz, H-3), 5.23 (1H, d, J=7.0 Hz, H-2), 7.38–7.82 (4H, m, H4-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (CH_3), 36.3 and 36.5 (C-2 and C-3), 124.9, 120.0, 132.4, and 135.3 (Ar–CH), 155.2 (Ar–C), 200.6 (CO). IR (neat) for a 4/1 mixture of **3a** an **3b**: ν 2940, 2895, 2828, 1700, 1591, 1452, 1325, 1257, 1102, 780, 642 cm^{-1}. Anal. for a 4/1 mixture of **3a** an **3b**: calcd for C_9H_9IO: C 44.14, H 3.33. Found: C 44.12, H 3.62.

4.2.2. (±)-2-Iodo-*t*-4-methyl-3,4-dihydronaphthalene-1(2*H*)-one (5, entry 1 in Table 1). Yield 86%; white crystals (from *n*-pentane/acetone) with mp 67.5–68.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (3H, d, J=6.9 Hz, 4-CH_3e), 1.88 (1H,ddd, J=14.9, 10.0, 3.8 Hz, H-3a), 2.30 (1H, ddd, J=14.8, 4.0, 3.9 Hz, H-3e), 3.20 (1H, qdd, J=10.0, 6.9, 4.0 Hz, H-4a), 5.04 (1H, dd, J=3.9, 3.9 Hz, H-2e), 7.33 (1H, dd, J=7.7, 7.9 Hz, H-7), 7.42 (1H, d, J=7.8 Hz, H-5), 7.58 (1H, ddd, J=7.7, 7.8, 1.3 Hz, H-6), 8.10 (1H, dd, J=7.9, 1.3 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (CH_3), 29.6 (C-4), 31.2 (C-3), 41.0 (C-2), 126.7, 126.8, 128.7, 134.2 (Ar–CH), 146.9, 147.0 (Ar–C), 192.0 (CO); IR (KBr) ν 2960, 2940, 1722, 1595, 1290, 1240, 1188, 1002, 911, 750 cm^{-1}; MS (EI, 70 eV) m/z 286 (M^+, 45%), 159 (61), 158 (100), 132 (34), 131 (67), 115 (44), 104 (25), 91 (33), 77 (16). Anal. calcd for $C_{11}H_{11}IO$: C 46.18, H 3.88. Found: C 46.33, H 3.88.

4.2.3. (±)-4-Hydroxy-2-iodoindan-1-one (7a, entry 2 in Table 1). Yield 64% of brown crystals (from CH_2Cl_2/acetone) starting decomposing at 124°C; ^1H NMR (300 MHz, $CDCl_3$/$DMSO_{d6}$) δ 3.23 (1H, dd, J=18.1, 2.1 Hz, H-3), 3.75 (1H, dd, J=18.1, 7.2 Hz, H-3′), 5.18 (1H, dd, J=7.2, 2.1 Hz, H-2); 7.18 (1H, dd, J=8.1, 1.4 Hz, H-7), 7.22 (1H, t, J=8.1 Hz, H-6), 7.28 (1H, dd, J=8.1, 1.4 Hz, H-5), 10.16 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$/$DMSO_{d6}$) δ 20.7 (C-2), 36.1 (C-3), 114.4, 120.8, and 129.4 (Ar–CH), 133.9 and 137.9 (Ar–C), 154.8 (C-5), 201.8 (CO); IR (KBr) ν 3220, 2902, 2828, 1675, 1582, 1266, 1042, 800, 743 cm^{-1}; MS (EI, 70 eV) m/z 274 (M^+, 100%), 147 (69), 119 (24), 91 (67), 65 (27); HRMS calcd for $C_9H_7IO_2$: 273.9491. Found: 273.9500.

4.2.4. (±)-5-Hydroxy-2-iodo-3,4-dihydronaphthalen-1(2*H*)-one (7b, entry 3 in Table 1). Yield 69%, brown crystals (from CH_2Cl_2/acetone) starting decomposing at 160°C; ^1H NMR (300 MHz, $CDCl_3$/$DMSO_{d6}$) δ 2.08 (1H, m, H-3), 2.28 (1H, m, H-3′), 2.74 (1H, ddd, J=17.9, 10.6, 4.6 Hz, H-4), 3.04 (1H, td, J=17.9, 3.9 Hz, H-4′), 4.97 (1H, t, J=3.5 Hz, H-2), 7.09 (1H, dd, J=8.1, 1.5 Hz, H-8), 7.81 (1H, dd, J=8.0, 7.8 Hz, H-7), 7.56 (1H, dd, J=7.8, 1.5 Hz, H-6); ^{13}C NMR(75M Hz, $CDCl_3$/$DMSO_{d6}$) δ 21.5 (C-4), 31.0 (C-2), 31.8 (C-3), 119.1, 120.0, 126.9 (ArCH), 130.0, 130.1 (Ar–C), 154.7 (C-5), 192.3 (CO); IR (KBr) ν 3240, 2941, 1650, 1600, 1595, 1466, 1288, 1188, 1146, 945, 908, 719 cm^{-1}; MS (EI, 70 eV) m/z 288 (M^+, 79%), 162 (43), 161 (100), 160 (45), 134 (55), 133 (68), 106 (55), 105 (57), 77 (49). Anal. calcd for $C_{10}H_9IO_2$: C 41.69, H 3.15. Found: C 42.06, H 2.91.

4.2.5. (±)-2-Iodo-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (7c, entry 4 in Table 1). Yield 87%, white crystals (from n-pentane/acetone) with mp 121–122.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (1H, m, H-3), 2.28 (1H, m, H-3′), 2.74 (1H, ddd, J=17.9, 10.6, 4.6 Hz, H-4), 3.04 (1H, td, J=17.9, 3.9 Hz, H-4′), 3.90 (3H, s, OCH_3) 5.00 (1H, t, J=3.5 Hz, H-2), 7.04 (1H, d, J=7.8 Hz, H-8), 7.30 (1H, 7, J=7.8 Hz, H-7), 7.69 (1H, d, J=7.8 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (C-3), 30.4 (C-2), 31.8 (C-4), 55.7 (OCH_3), 114.7, 120.1, 127.3 (ArCH), 130.2, 131.8 (ArC), 156.6 (C-5), 192.1 (CO); IR (KBr) ν 2940, 2923, 1665, 1580, 1260, 1052, 755 cm^{-1}; MS (EI, 70 eV) m/z 302 (M^+, 100%), 175 (80), 160 (22), 147 (57), 115 (44), 103 (33), 91 (44), 77 (39). Anal. calcd for $C_{11}H_{11}IO_2$: C 43.73, H 3.67. Found: C 43.60, H 3.60.

4.2.6. (±)-6-Hydroxy-2-iodo-3,4-dihydronaphthalen-1(2*H*)-one (9a, entry 5 in Table 1). Yield 73% of white crystals (from CH_2Cl_2/acetone) with mp 160.5–161.5 (decomp.); ^1H NMR (300 MHz, $CDCl_3$/$DMSO_{d6}$) δ 2.12 (1H, m, H-3), 2.22 (1H, m, H-3′), 2.80 (1H, td, J=16.5, 3.7 Hz, H-4), 3.00 (1H, ddd, J=16.5, 10.9, 4.5 Hz), 4.96 (1H, t, J=3.7 Hz, H-2), 6.68 (1H, d, J=2.0 Hz, H-5), 6.78 (1H, dd, J=8.7, 2.0 Hz, H-7), 7.85 (1H, d, J=8.7 Hz, H-8), 10.2 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$/$DMSO_{d6}$) δ 27.9 (C-4), 31.8 (C-2), 32.7 (C-3), 114.3, 115.1, 130.8 (Ar–CH), 121.1, 145.5 (Ar–C), 162.9 (C-6), 190.3 (CO); IR (KBr) ν 3150, 2900, 1620, 1580, 1545, 1252, 1175, 816 cm^{-1}; MS (EI, 70 eV) m/z 288 (M^+, 100%), 161 (69), 134 (47), 133 (68), 105 (28), 77 (25). Anal. calcd for $C_{10}H_9IO_2$: C 41.69, H 3.15. Found: C 41.73, H 3.21.

4.2.7. (±)-2-Iodo-5-methoxyindan-1-one (9b, entry 6 in Table 1). Yield 86% of white crystals (from *n*-pentane/acetone) with mp 125.0–127.0°C (decomp.); ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (1H, dd, J=18.4, 2.3 Hz, H-3), 3.84 (1H, dd, J=18.4, 7.4 Hz, H-3′), 3.90 (3H, s, OCH_3), 4.93 (1H, dd, J=7.4, 2.3 Hz, H-2), 6.85 (1H, d, J=2.2 Hz, H-4), 6.95 (1H, dd, J=8.5, 2.2 Hz, H-6), 7.79 (1H, d, J=8.5 Hz, H-7); ^{13}C NMR(75M Hz, $CDCl_3$) δ 20.1 (C-2), 39.6 (C-3), 55.8 (OCH_3), 109.6, 116.2, 126.7 (Ar–CH), 154.3, 158.2 (Ar–C), 165.8 (C-5), 199.3 (CO); IR (KBr) ν

2958, 1686, 1585, 1290, 1245, 1082, 839 cm^{-1}; MS (EI, 70 eV) *m/z* 288 (M^+, 100%), 162 (18), 161 (87), 133 (45), 118 (28), 89 (25), 77 (23). Anal. calcd for $C_{10}H_9IO_2$: C 41.69, H 3.15. Found: C 42.01, H 2.92.

4.2.8. (±)-2-Iodo-6-methoxyindan-1-one (9c, entry 7 in Table 1). Yield 85% of white crystals (from *n*-pentane/acetone) with mp 88.0–90.0°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (1H, dd, *J*=18.1, 2.2 Hz, H-3), 3.80 (1H, dd, *J*=18.1, 7.2 Hz, H-3′), 3.85 (3H, s, OCH_3), 4.96 (1H, dd, *J*=7.2, 2.2 Hz, H-2), 7.2–7.4 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 (C-2), 39.0 (C-3), 55.7 (OCH_3), 106.0, 1251.2, 127.2 (Ar–CH), 134.0, 144.0 (Ar–C), 159.9 (C-5), 195.3 (CO); IR(KBr) ν 3002, 2958, 2915, 1695, 1605, 1486, 1281, 1262, 1151, 1040, 845; MS (EI, 70 eV) *m/z* 288 (M^+, 100%), 162 (16), 161 (74), 133 (45), 118 (28), 89 (22), 77 (13). Anal. calcd for $C_{10}H_9IO_2$: C 41.69, H 3.15. Found: C 41.73, H 2.95.

4.2.9. (±)-2-Iodo-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one[4e] (9d, entry 8 in Table 1). Yield 86%, white crystals (from *n*-pentane/acetone) with mp 95–96°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (1H, m, H-3), 2.25 (1H, m, H-3′), 2.80 (1H, td, *J*=16.3, 3.7 Hz, H-4), 3.04 (1H, ddd, *J*=16.3, 11.0, 4.4 Hz, H-4′), 3.84 (3H, s, OCH_3), 5.02 (1H, t, *J*=3.5 Hz, H-2), 7.10 (1H, dd, *J*=8.4, 2.8 Hz, H-6), 7.20 (1H, d, *J*=8.4 Hz, H-5), 7.56 (1H, d, *J*=2.8 Hz, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1 (C-3), 30.7 (C-2), 32.8 (C-4), 55.5 (OCH_3), 110.2, 122.6, 130.0 (ArCH), 130.2, 135.3 (ArC), 158.6 (C-5), 191.9 (CO); IR (KBr) ν 2902, 2802, 1655, 1600, 1260, 1045, 835, 755 cm^{-1}; MS (EI, 70 eV) *m/z* 302 (M^+, 100%), 175 (80), 174 (52), 160 (12), 147 (73), 115 (41), 103 (43), 91 (45), 77 (42). Anal. calcd for $C_{11}H_{11}IO_2$: C 43.73, H 3.67. Found: C 43.93, H 3.49.

4.2.10. (±)-2-Iodo-5,6-dimethoxyindan-1-one (9e, entry 9 in Table 1). Yield 84% of white crystals (from *n*-pentane/acetone) with mp 163–164.50°C (decomp.); ^1H NMR (300 M Hz, $CDCl_3$) δ 3.40 (1H, dd, *J*=18.2, 2.2 Hz, H-3), 3.83 (1H, dd, *J*=18.2, 7.2 Hz, H-3′), 3.92 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.95 (1H, dd, *J*=7.2, 2.2 Hz, H-2), 6.85 (1H, s, H-4), 7.23 (1H, s, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (C-2), 39.4 (C-3), 56.2 and 56.4 (OCH_3), 105.1 and 107.3 (Ar–CH), 125.6 and 146.7 (Ar–C), 150.0 and 156.3 (C-5 and C-6), 200.0 (CO); IR(KBr) ν 2965, 1680, 1580, 1445, 1305, 1260, 1048, 715 cm^{-1}; MS (EI, 70 eV) *m/z* 318 (M^+, 100%), 191 (83), 163 (48), 81 (31), 69 (59). Anal. calcd for $C_{11}H_{11}IO_3$: C 41.53, H 3.48. Found: C 41.67, H 3.16.

4.2.11. (±)-2-Iodo-6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (9f, entry 10 in Table 1). Yield 85%, white crystals (from *n*-pentane/acetone) with mp 116–117°C (decomp.); ^1H NMR(300 M Hz, $CDCl_3$) δ 2.10 (1H, m, H-3), 2.25 (1H, m, H-3′), 2.75 (1H, td, *J*=16.9, 3.2 Hz, H-4), 3.04 (1H, ddd, *J*=16.9, 11.1, 4.3 Hz, H-4′), 3.90 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.00 (1H, t, *J*=3.4 Hz, H-2), 6.75 (1H, s, H-5), 7.6 (1H, s, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 (C-3), 30.6 (C-2), 33.1 (C-4), 56.1 (OCH_3), 109.5 and 110.1 (C-5 and C-8), 122.4 and 137.8 (Ar–C), 148.3 and 154.1 (C-6 and C-7), 191.0 (CO); IR (KBr) ν 2940, 2810, 1680, 1590, 1505, 1265, 1038, 792 cm^{-1}; MS (EI, 70 eV) *m/z* 332 (M^+, 66%), 205 (43), 177 (100), 161 (14), 146 (49), 131 (26), 91 (25). Anal. calcd for $C_{12}H_{13}IO_3$: C 43.40, H 3.94. Found: C 43.61, H 3.93.

4.2.12. (±)-2-Iodo-4,5-dimethoxyindan-1-one (11, entry 11 in Table 1). Yield 86% of white crystals (from *n*-pentane/acetone/CH_2Cl_2) with mp 104.7–105.2°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (1H, dd, *J*=18.6, 2.4 Hz, H-3), 3.70 (1H, dd, *J*=18.6, 7.3 Hz, H-3′), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.88 (1H, dd, *J*=7.3, 2.4 Hz, H-2), 6.75 (1H, d, *J*=8.8 Hz, H-7), 7.05 (1H, d, *J*=8.8 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (C-2), 35.9 (C-3), 55.8 and 56.0 (OCH_3), 110.2 and 117.6 (Ar–CH), 121.8 and 141.3 (Ar–C), 149.9 and 152.3 (C-5 and C-6), 199.0 (CO); IR(KBr) ν 2905, 2803, 1702, 1562, 1475, 1352, 1046, 795 cm^{-1}; MS (EI, 70 eV) *m/z* 318 (M^+, 100%), 191 (98), 176 (24), 163 (18), 161 (32), 133 (34), 118 (26), 105 (27), 89 (21), 77 (29). Anal. calcd for $C_{11}H_{11}IO_3$: C 41.53, H 3.48. Found: C 41.20, H 3.12.

4.2.13. (±)-2-Iodo-4,7-dimethoxyindan-1-one (13a, entry 12 in Table 1). Yield 85% of white crystals (from *n*-pentane/acetone) with mp 132–134°C (decomp.); ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (1H, dd, *J*=18.6, 2.7 Hz, H-3), 3.80 (1H, dd, *J*=18.6, 7.6 Hz, H-3′), 3.94 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.86 (1H, dd, *J*=7.6, 2.7 Hz, H-2), 6.89 (1H, d, *J*=8.4 Hz, H-6), 7.55 (1H, d, *J*=8.4 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6 (C-2), 36.4 (C-3), 56.2 (OCH_3), 113.0 and 121.4 (Ar–CH), 126.7, 143.8, 145.2 and 158.1 (Ar–C), 198.8 (CO); IR (KBr) ν 2920, 2805, 1701, 1578, 1270, 1073, 810, 735 cm^{-1}; MS (EI, 70 eV) *m/z* 318 (M^+, 100%), 191 (79), 176 (21), 163 (28), 163 (27), 161 (12), 148 (31), 133 (23), 131 (34) 118 (20), 105 (27), 103 (28), 91 (24), 89 (21), 77 (28). Anal. calcd for $C_{11}H_{11}IO_3$: C 41.53, H 3.48. Found: C 41.15, H 3.60.

4.2.14. (±)-2-Iodo-5,8-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (13b, entry 13 in Table 1). Yield 87%, white crystals (from *n*-pentane/acetone/CH_2Cl_2) with mp 109.3–110.3°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (1H, m, H-3), 2.22 (1H, m, H-3′), 2.79 (1H, ddd, *J*=18.7, 10.9, 5.0 Hz, H-4′), 3.05 (1H, td, *J*=18.7, 3.9 Hz, H-4), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.84 (1H, t, *J*=3.5 Hz, H-2), 6.80 (1H, d, *J*=9.0 Hz, H-6), 7.98 (1H, d, *J*=9.0 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2 (C-3), 31.3 (C-2), 32.4 (C-4), 55.8 and 56.3 (OCH_3), 110.2 and 115.8 (C-6 and C-7), 119.4, 133.1 149.8, and 155.3 (Ar–C), 190.6 (CO); IR (KBr) ν 2905, 2801, 1685, 1575, 1510, 1265, 1062, 792 cm^{-1}; MS(EI, 70 eV) *m/z* 332 (M^+, 18%), 205 (45), 177 (36), 161 (20), 146 (21), 131 (46), 91 (100). Anal. calcd for $C_{12}H_{13}IO_3$: C 43.40, H 3.94. Found: C 42.89, H 4.17.

4.2.15. (±)-9-Iodo-9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one (15, entry 14 in Table 1). Yield 63% of white crystals (from *n*-pentane/acetone/CH_2Cl_2) with mp 176.0–177.5°C; ^1H NMR (300 MHz, $CDCl_3$/$DMSO_{d6}$) 2.45 (1H, m, H-10), 2.56 (1H, m, H-10′), 3.48 (1H, ddd, *J*=17.5, 10.9, 4.9 Hz, H-11), 3.76 (1H, td, *J*=17.5, 4.0 Hz, H-11′), 5.27 (1H, t, *J*=3.7 Hz, H-9), 8.02–8.12 (3H, m), 8.16–8.25 (3H, m), 8.35 (1H, d, *J*=9.3 Hz), 8.80 (1H, s, H-8); ^{13}C NMR (75 MHz, $CDCl_3$/ $DMSO_{d6}$) δ 24.6 (C-10), 30.7 (C-9), 31.8 (C-11); 123.1, 123.8, 125.5, 125.6, 127.4, 127.6, 127.9, and 128.3 (Ar–CH); 126.3, 126.6, 126.8, 129.4, 131.3, 131.7, and 135.9 (Ar–C), 192.3 (CO); IR(KBr) ν 3020, 2925, 1625, 1582, 1308, 1172, 840, 826 cm^{-1}; MS (EI, 70 eV) *m/z* 396 (M^+, 63%), 269 (100), 268 (56), 239 (80), 214 (57), 213

(43), 117 (33), 106 (26). Anal. calcd for $C_{20}H_{13}IO$: C 60.62, H 3.31. Found: C 60.21, H 3.13.

Acknowledgements

The authors are grateful to T. Stipanovic and Professor B. Stanovnik for elemental combustion analysis, and to the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support.

References

1. (a) Merkushev, E. B. *Synthesis* **1988**, 923. (b) Sasson, Y. Formation of Carbon–Halogen Bonds (Cl, Br, I). In *The Chemistry of Functional Groups, Supplement D2: The Chemistry of Halides, Pseudo Halides and Azides, Part 2*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1995; pp 535–620. (c) Steel, P. G. Halobenzenes. 2nd ed. *Rodd's Chem. Carbon Compd*, Sainsburry; M., Ed.; Elsevier: Amsterdam, 1996; Vol. 3(1), pp 178–224. (d) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 431–436.
2. (a) Sovak, M. *Radiocontrast Agents*. *Handbook of Experimental Pharmacology*; Springer: Berlin, 1993; Vol. 73. (b) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575–590.
3. (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–523. (b) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–394.
4. (a) Barluenga, J.; Martinez-Gallo, J. M.; Najera, C.; Yus, M. *Synthesis* **1986**, 678–680. (b) Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn* **1992**, *65*, 1731–1733. (c) Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn* **1997**, *70*, 421–426. (d) Whang, J. P.; Yang, S. G.; Kim, Y. H. *Chem. Commun.* **1997**, 1355–1356. (e) Bakaert, A.; Barberan, O.; Gervais, M.; Brion, J.-D. *Tetrahedron Lett.* **2000**, *41*, 2903–2905.
5. Perrone, R.; Berardi, F.; Leopoldo, M.; Tortorella, V. *J. Med. Chem.* **1996**, *39*, 3195–3202.
6. Sugimoto, H.; Limura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821–4829.
7. Geen, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *Tetrahedron* **1998**, *54*, 9875–9894.
8. Suh, Y.-G.; Shin, D.-Y.; Min, K.-K.; Hyun, S.-S.; Jung, J.-K.; Seo, S.-Y. *Chem. Commun.* **2000**, 1203–1204.
9. (a) Curran, D. P.; Chang, C. T. *Tetrahedron Lett.* **1987**, *28*, 2477–2480. (b) Ravinder, S. J.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536–7538.
10. (a) Curran, D. P. *Synthesis* **1988**, 417–439, and references therein. (b) Sha, C. K.; Jean, T. S.; Wang, D. C. *Tetrahedron Lett.* **1990**, *31*, 3745–3748, and references therein.
11. (a) *Organofluorine Compounds in Methods of Organic Chemistry (Houben-Weyl)*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds.; Thieme: New York, 1999; Vols. E 10a and 10b. (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477. (c) Furin, G. G.; Fainzilberg, A. A. *Russ. Chem. Rev.* **1999**, *68*, 653–654.
12. (a) Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett* **1994**, 831–832. (b) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2001**, 1152–1154. (c) Stavber, S.; Kralj, P.; Zupan, M. *Acta Chim. Slov.* **2002**, *49*, 553–560. (d) Liu, J.; Wong, C.-H. *Tetrahedron Lett.* **2002**, *43*, 3915–3917. (e) Liu, J.; Wong, C.-H. *Tetrahedron Lett.* **2002**, *43*, 4037–4039.
13. (a) Gilicinski, A. G.; Pez, G. P.; Syvret, R. G.; Lal, G. S. *J. Fluorine Chem.* **1992**, *59*, 157–162. (b) Differding, E.; Bersier, P. M. *Tetrahedron* **1992**, *48*, 1595–1604. (c) Girina, G. P.; Faizil'berg, A. A.; Feoktistov, L. G. *Russ. J. Electrochem.* **2000**, *36*, 162–163.
14. (a) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305–6306. (b) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2002**, 598–600. (c) Stavber, S.; Kralj, P.; Zupan, M. *Synthesis* **2002**, 1513–1518.
15. (a) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488–489. (b) Jereb, M.; Stavber, S.; Zupan, M. *Synthesis* **2003**, 853–858.
16. Dong, S.; Hwang, H.-M.; Harrison, C.; Holloway, L.; Shi, X.; Yu, H. *Bull. Environ. Contam. Toxicol.* **2000**, *64*, 467–474.
17. Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609–2615.
18. Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2000**, 1323–1324.