Applied Organometallic Chemistry

Received: 24 January 2008 Revised: 6 June 2008 Accepted: 6 June 2008 Published online in Wiley Interscience

(www.interscience.com) DOI 10.1002/aoc.1437

Application of the anionic homologous Fries-rearrangement to the synthesis of 3-alkylbenzofuran-2(3*H*)-ones

Ugo Azzena*, Luisa Pisano and Mario Pittalis

We have developed an effective organometallic-based procedure allowing the employment of 2-methylphenols as easily available starting materials in the synthesis of 3-alkylbenzofuran-2(3*H*)-ones. The first step of this protocol, an anionic homologous Fries-rearrangement, afforded 2-(2-*tert*-butyldimethylsilyloxyaryl)acetamides, which were selectively metalated and monoalkylated at the benzylic position. Acidic work-up of crude products afforded the desired heterocycles in satisfactory overall yields.

Keywords: alkylation; benzofuran-2(3*H*)-ones; Fries rearrangement; metalation; organolithiums; regioselectivity

Introduction

Benzofuran-2(3*H*)-ones are an important class of natural and synthetic heterocycles, endowed with interesting biological and pharmacological properties.[1] Furthermore, due to their antioxidative properties, they have found application in polymer technology.[2] Among several approaches aimed at their synthesis,[3] Snieckus and co-workers have developed a methodology involving, as a key step, an anionic homologous Fries rearrangement of 2-methylaryl esters of *N*,*N*-diethylcarbamic acid, easily prepared from the corresponding *ortho*-methylphenols.[4] Accordingly, 2-methylaryl esters of *N*,*N*-diethylcarbamic acid are regioselectively laterally metalated with LDA in THF at −78 °C and in the presence of TBDMSCl, thus affording the corresponding 2-OTBDMS phenyl acetamide which, in turn, were converted into the desired benzofuran-2(3*H*)-ones under acidic conditions (Scheme 1).

It is, however, worth noting that this procedure cannot be efficiently applied to the synthesis of 3-monoalkyl-substituted benzofuran-2(3*H*)-ones, a class of compounds investigated as potential antiinflammatory agents.[1h] Indeed, metalation of the 2-ethylphenyl ester of *N*,*N*-diethylcarbamic acid is no longer regioselective, leading to a 1 : 1 mixture of the desired phenylacetamide and an isomeric salicyl amide, the last one being the product of a competitive aromatic *ortho* metalation.[4,5] Such a limitation is made more severe by the difficulties encountered in the mono-alkylation of benzofuran-2(3*H*)-one at C(3). According to the literature, metalation of this substrate with LDA in HMPA, followed by reaction with methyl iodide, affords the corresponding 3,3-dialkylated derivative as the main reaction product.[6] We were unable to improve this result under different reaction conditions (LDA/THF, NaH/DME or THF, *t*-BuOK/THF, K_2CO_3/DMF).[7]

In this paper, we wish to present full experimental details concerning an investigation aiming to supersede this limitation, thus allowing the employment of easily available *ortho*-methylphenols as starting materials towards the synthesis of 3-alkylbenzofuran-2(3*H*)-ones.

Results and discussion

Our approach to the synthesis of 3-alkylbenzofuran-2(3*H*)-ones relies on the possibility of achieving selective metalation at the benzylic position of 2-(2-*tert*-butyldimethylsilyloxyaryl)acetamides, followed by trapping these intermediates with alkyl halides, and acidic cyclization of the resulting 2-substitued arylacetamides (Scheme 2 and Table 1).

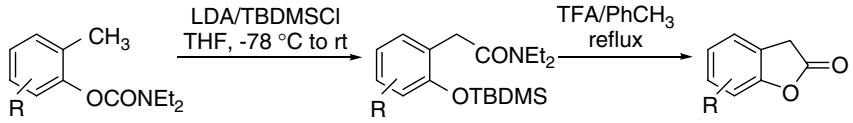
By applying the procedure developed by Snieckus *et al*.,[4] to the 2-methylaryl esters of *N*,*N*-diethylcarbamic acid **1a–c**, we synthesized the corresponding 2-(2-*tert*-butyldimethylsilyloxyaryl)acetamides, **2a–c**, in satisfactory yields.

Metalation of amide **2a**, taken as a model compound, was investigated in some detail. Reaction of **2a** with LDA in THF at −80 °C, followed by quenching with D_2O, showed that formation of the desired organometal was quantitative within 1 h (Table 1, entry 1). It is worth noting that this intermediate, generated as reported above, is stable for at least 2–3 h up to −60 °C (not reported in Table 1), undergoing slow protonation at higher temperatures. Indeed, 65% deuterium incorporation at the benzylic position was observed after a further 3 h at −40 °C (Table 1, entry 2). It is also interesting to observe that ^{1}H-NMR analyses of crude mixtures obtained from deuteration experiments showed that the TBDMS protection was stable under the above reported reaction conditions.[8] Although similar results were obtained employing *n*-BuLi as a base, LDA was preferred as a metalation reagent in order to avoid halogen–lithium exchange reactions, which could lead to the formation of mixtures of alkylated products.

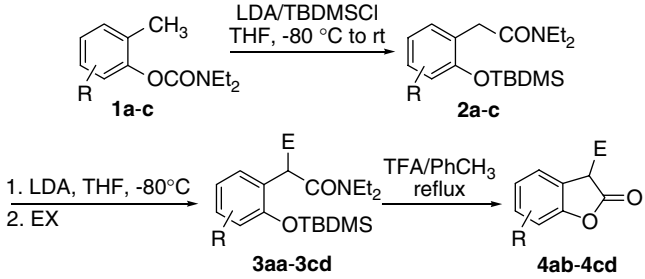
According to the above results, metalation reactions were run with LDA at −80 °C, and the intermediate organometal was reacted with an excess (1.2 equiv.) of an alkyl halide at

* *Correspondence to: Ugo Azzena, Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy. E-mail: ugo@uniss.it*

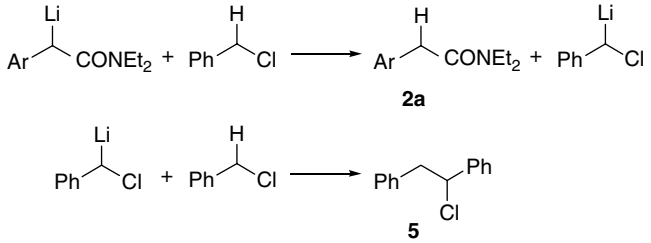
Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy



Scheme 1. Metalation of 2-methylphenyl esters of *N*,*N*-diethylcarbamic acid, and synthesis of benzofuran-2(3*H*)-ones, according to Kalinin *et al*.[4].



Scheme 2. Synthesis of 3-alkylbenzofuran-2(3*H*)-ones. **1a–4a**, R = H; **1b**, R = 4-Cl; **1c**, R = 5-$(CH_3)_2CH$; **2b–4b**, R = 5-Cl; **2c, 3c**, R = 4-$(CH_3)_2CH$; **4c**, R = 6-$(CH_3)_2CH$; EX = D_2O or AlkylX (see text).



Scheme 3. Synthesis 1,2-diphenylchloroethane, **5**. Ar = 2-(TBDMSO)C_6H_4.

Table 1. Metalation of amides **2a–c** and reaction with electrophiles[a]

Entry	Substrate, R =	Electrophile, EX	Product No.	Product E	Yield (%)[b]
1	**2a**, H	D_2O	**3aa**	D	>90[c]
2	**2a**, H	D_2O[d]	**3aa**	D	65[c]
3	**2a**, H	CH_3I	**4ab**	CH_3	70
4	**2a**, H	*n*-C_4H_9Br	**4ac**	*n*-C_4H_9	62
5	**2a**, H	*i*-C_3H_7Br	**4ad**	*i*-C_3H_7	65
6	**2a**, H	$PhCH_2Br$	**4ae**	$PhCH_2$	53
7	**2a**, H	$ArCH_2Br$[e]	**4af**	$ArCH_2$	70
8	**2a**, H	$Cl(CH_2)_3Br$	**4ag**	$(CH_2)_3Cl$	85
9	**2a**, H	Ar^1CH_2Br[f]	**4ah**	Ar^1CH_2	43
10	**2b**, 5-Cl	CH_3I	**4ba**	CH_3	69
11	**2b**, 5-Cl	*i*-C_3H_7Br	**4bb**	*i*-C_3H_7	62
12	**2c**, 4-$(CH_3)_2CH$	CH_3I	**4ca**	CH_3	71
13	**2c**, 4-$(CH_3)_2CH$	*n*-C_4H_9Br	**4cb**	*n*-C_4H_9	65
14	**2c**, 4-$(CH_3)_2CH$	*i*-C_3H_7Br	**4cc**	*i*-C_3H_7	62
15	**2c**, 4-$(CH_3)_2CH$	$PhCH_2Br$	**4cd**	$PhCH_2$	45

[a] All reactions were run at −80 °C for 1 h, then quenched with 1.2 equiv. of the electrophile, unless otherwise indicated.
[b] Isolated yields, unless otherwise indicated.
[c] As determined by ^{1}HNMR analysis of crude reaction mixtures.
[d] After 1 h at −80 °C, the reaction mixture was allowed to stir at −40 °C for 3 h before quenching it with the electrophile.
[e] Ar = 4-$(CH_3O)C_6H_4$.
[f] Ar^1 = 4-BrC_6H_4.

the same temperature. Good results were obtained employing CH_3I, *n*-BuBr, and *i*-PrBr as electrophilic reagents, and the corresponding alkylated derivatives were directly cyclized to the corresponding benzofuran-2(3*H*)-ones **4ab–4ad** (Table 1, entries 3–5). Interestingly, ^{1}H-NMR analysis of the crude reaction mixture containing compound **4ab** ruled out formation of the corresponding product of a double alkylation at C(3), independently synthesized according to a literature procedure.[9]

At variance with these results, quenching the lithium intermediate with $PhCH_2Cl$ led to the quantitative recovery of amide **2a**, as well as to the formation of 1,2-diphenylchloroethane, **5** (not reported in Table 1). Formation of this halide can be rationalized by assuming that $PhCH_2Cl$ undergoes preferential deprotonation at the benzylic position, leading to the formation of α-chlorobenzyllithium which, in turn, acts as a nucleophile in front of the unreacted benzyl halide (Scheme 3).[10]

Support to this hypothesis was given by reacting the metalated amide with the less acidic $PhCH_2Br$, a reaction leading, after cyclization, to the recovery of the corresponding benzylated benzofuran-2(3*H*)-one **4ae** in satisfactory yield (Table 1, entry 6). A comparable result was obtained employing 4-$(CH_3O)C_6H_4CH_2Br$ as an electrophile (Table 1, entry 7).

Furthermore, we extended this procedure to the employment of electrophilic reagents suitable for an additional manipulation of the reaction products. Accordingly, quenching the metalated amide with $Br(CH_2)_3Cl$ and 4-$BrC_6H_4CH_2Br$, followed by acidic cyclization of the crude reaction mixtures, led to the recovery of benzofuranones **4ag** and **4ah**, respectively (Table 1, entries 8 and 9).[11]

The procedure was successfully extended to amides **2b** and **2c**, thus allowing the synthesis of the alkylated amides **3ba–bb** and **3ca–cd**, respectively. Acidic cyclization of these crude compounds afforded the corresponding benzofuran-2(3*H*)-ones, **4ba–bb** and **4ca–cd**, in satisfactory overall yields (Scheme 2, Table 1, entries 10–15).

In summary, we have established the feasibility of an organometallic-based procedure allowing the employment of 2-methylphenols as easily available starting materials in the synthesis of 3-alkylbenzofuran-2(3*H*)-ones. The first step of this protocol, an anionic homologous Fries-rearrangement, is followed by a second, highly regioselective, metalation step, thus providing a practical and useful extension of the methodology originally developed by Snieckus *et al*.[4]

Experimental

General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior

to use. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard on a Varian VXR 300 spectrometer. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of crude reaction mixtures. IR spectra were recorded on a FT-IR Jacso 480 P. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

Synthesis of 2-methylaryl esters of *N,N*-diethylcarbamic acid (1a–c)

NaH (4.80 g of a 60% dispersion in mineral oil, 0.12 mol) was placed under dry nitrogen in a 250 ml two-necked flask equipped with reflux condenser and magnetic stirrer, washed with dry THF (3 × 15 ml), and suspended in dry THF (100 ml). The mixture was chilled to 0 °C and a solution of the appropriate 2-methylphenol (0.10 mol) dissolved in THF (15 ml) was added dropwise. The resulting mixture was stirred for 4 h at room temperature. To this reaction mixture, chilled to 0 °C, a solution of *N,N*-diethylcarbamoyl chloride (14.9 g, 0.11 mol), dissolved in 50 ml of THF, was slowly added. After stirring for 4 h at room temperature, the mixture was quenched by slow dropwise addition of H_2O (20 ml), and the resulting mixture was extracted with Et_2O (3 × 30 ml). The organic phase was washed brine (30 ml), H_2O (30 ml), dried ($CaCl_2$) and evaporated. Crude products were purified by distillation, and were characterized as follows.

2-Methylphenyl ester of N,N-diethylcarbamic acid (**1a***)*

17.4 g, 84 mmol, 84% yield; light yellow oil; b.p. 85 °C/1 mmHg (lit.[12] 178–179 °C/15 mmHg). IR (neat) 1719 cm^{-1}. ^{1}H NMR: δ 1.17–1.32 (6H, m, 2 × $\underline{CH_3}CH_2$), 2.22 (3H, s, CH_3Ar), 3.32–3.52 (4H, m, 2 × CH_2), 7.03–7.13 (2H, m, H4 and H6), 7.16–7.22 (2H, m, H2 and H5). ^{13}C NMR: δ 13.4 (CH_3), 14.3 (CH_3), 16.3 (CH_3Ar), 41.9 (CH_2), 42.2 (CH_2), 122.2 (C6), 125.3 (C4), 126.7 (C5), 130.4 (C2), 130.9 (C3), 150.0 (C1), 153.9 (CO).

4-Chloro-2-methylphenyl ester of N,N-diethylcarbamic acid (**1b***)*

20.5 g, 85 mmol, 85% yield; light yellow oil; b.p. 98–100 °C/1 mmHg. IR (neat) 1720 cm^{-1}. Anal. found: C, 59.32; N, 5.41; H, 6.95; $C_{12}H_{16}ClNO_2$ requires: C, 59.63; N, 5,79; H, 6.67%. ^{1}H NMR: δ 1.20 (3H, t, J = 5.4 Hz, $\underline{CH_3}CH_2$), 1.26 (3H, t, J = 5.4 Hz, $\underline{CH_3}CH_2$), 2.19 (3H, s, CH_3Ar), 3.38 (2H, q, J = 5.4 Hz, CH_2), 3.45 (2H, q, J = 5.4 Hz, CH_2), 6.99 (1H, d, J = 6.6 Hz, H6), 7.14 (1H, dd, J = 6.6, 1.8 Hz, H5), 7.18 (1H, d, J = 1.8 Hz, H3). ^{13}C NMR: δ 13.3 (CH_3), 14.2 (CH_3), 16.2 (CH_3Ar), 41.8 (CH_2), 42.2 (CH_2), 123.5 (C6), 126.6 (C5), 130.3 (C2), 130.6 (C3), 132.3 (C4), 148.5 (C1), 153.6 (CO).

5-Isopropyl-2-methylphenyl ester of N,N-diethylcarbamic acid (**1c***)*

20.2 g, 81 mmol, 81% yield; light yellow oil; b.p. 135–140 °C/1 mmHg. IR (neat) 1719 cm^{-1}. Anal. found: C, 71.87; N, 5.33; H, 9.76; $C_{15}H_{23}NO_2$ requires: C, 72.25; N, 5.62; H, 9.30%. ^{1}H NMR: δ 1.16–1.32 (6H, m, 2 × $\underline{CH_3}CH_2$), 1.23 (6H, d, J = 7.2 Hz, 2 × $\underline{CH_3}CH$), 2.18 (3H, s, CH_3Ar), 2.87 (1H, hept, J = 7.2 Hz, CH), 3.34–3.52 (4H, m, 2 × CH_2), 6.93 (1H, d, J = 1.5 Hz, H6), 6.97 (1H, dd, J = 7.8, 1.5 Hz, H4), 7.12 (1H, d, J = 7.8 Hz, H3). ^{13}C NMR: δ 13.4 (CH_3), 14.2 (CH_3), 15.9 (CH_3Ar), 23.9 (2 × $\underline{CH_3}$CH), 33.6 (CH), 41.8 (CH_2), 42.1 (CH_2), 120.2 (C6), 123.3 (C4), 127.5 (C2), 130.7 (C3), 147.8 (C5), 149.8 (C1), 154.2 (CO).

Synthesis of *N,N*-diethyl 2-(2-*tert*-butyldimethylsilyloxyaryl)acetamides 2a–c. General procedure

A 14.0 ml aliquot of diisopropylamine (10.1 g, 0.10 mol) was placed under argon in a 250 ml two-necked flask equipped with reflux condenser and magnetic stirrer, and dissolved in 60 ml of THF. To this solution, chilled at 0 °C, 40.0 ml of a 2.5 M solution of *n*-BuLi (0.10 mol) in hexane was slowly added. The mixture was stirred at 0 °C for 10 min, then chilled to −80 °C, and a solution of the appropriate ester (30 mmol) and 5.43 g of *tert*-butyldimethylsilylchloride (36 mmol) dissolved in 50 ml of THF was added dropwise. The reaction mixture was stirred for 90 min at the same temperature, then warmed to −20 °C within 4 h, and quenched by adding 50 ml of a saturated solution of NH_4Cl. After stirring at −20 °C for 30 min, the cold bath was removed, and 45 ml of H_2O were added to dissolve formed solid materials. The resulting mixture was extracted with Et_2O (3 × 40 ml), and the organic phase dried ($CaCl_2$) and evaporated. Crude products were purified and characterized as follows.

N,N-Diethyl 2-(2-tert-butyldimethylsilyloxyphenyl)acetamide (**2a***)*

Purified by flash chromatography (petroleum ether:AcOEt:Et_3N = 8:2:0.1), light yellow oil; R_f = 0.61 (petroleum ether:AcOEt:Et_3N = 8:2:0.1). IR (neat) 1645 cm^{-1}. Anal. found: C, 66.91; N, 4.68; H, 9.95; $C_{15}H_{23}NO_2$ requires: C, 67.24; N, 4.36; H, 9.72%. ^{1}H NMR: δ 0.23 (6H, s, 2 × CH_3Si), 1.00 (9H, s, 3 × CH_3C), 1.04 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 1.12 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 3.23 (2H, q, J = 7.2 Hz, CH_2N), 3.38 (2H, q, J = 7.2 Hz, CH_2N), 3.67 (2H, s, CH_2CO), 6.81 (1H, dd, J = 7.8, 1.2 Hz, H3), 6.91 (1H, td, J = 7.8, 1.2 Hz, H5), 7.11 (1H, td, J = 7.8, 1.2 Hz, H4), 7.21 (1H, dd, J = 7.8, 1.2 Hz, H6). ^{13}C NMR: δ −4.2 (CH_3Si), 12.9 ($\underline{CH_3}CH_2$), 14.0 ($\underline{CH_3}CH_2$), 18.2 ((CH_3)$_3\underline{C}$), 25.8 (($\underline{CH_3}$)$_3$C), 35.1 (CH_2Ar), 39.8 (CH_2N), 42.1 (CH_2N), 118.4 (C3), 121.3 (C5), 126.2 (C1), 127.6 (C4), 129.5 (C6), 152.9 (C2), 170.6 (CO).

N,N-Diethyl 2-(5-chloro-2-tert-butyldimethylsilyloxyphenyl) acetamide (**2b***)*

Purified by flash chromatography (petroleum ether:AcOEt:Et_3N = 7:3:0.1), yellow oil; R_f = 0.67 (petroleum ether:AcOEt:Et_3N = 7:3:0.1). IR (neat) 1646 cm^{-1}. Anal. found: C, 60.34; N, 4.09; H, 8.16; $C_{15}H_{23}NO_2$ requires: C, 60.73; N, 3.93; H, 8.49%. ^{1}H NMR: δ 0.22 (6H, s, 2 × CH_3Si), 0.99 (9H, s, 3 × CH_3C), 1.10 (3H, t, J = 6.9 Hz, $\underline{CH_3}CH_2$), 1.13 (3H, t, J = 6.9 Hz, $\underline{CH_3}CH_2$), 3.25 (2H, q, J = 6.9 Hz, CH_2), 3.39 (2H, q, J = 6.9 Hz, CH_2), 3.62 (3H, s, CH_2CO), 6.72 (1H, d, J = 8.4 Hz, H3), 7.07 (1H, dd, J = 8.4, 2.7 Hz, H4), 7.20 (1H, d, J = 2.7 Hz, H6). ^{13}C NMR: δ −4.3 (CH_3Si), 12.9 ($\underline{CH_3}CH_2$), 14.1 ($\underline{CH_3}CH_2$), 18.2 ((CH_3)$_3\underline{C}$), 25.7 (($\underline{CH_3}$)$_3$C), 34.8 (CH_2Ar), 40.0 (CH_2N), 42.1 (CH_2N), 119.4 (C3), 126.1 (C5), 127.5 (C4), 128.1 (C1), 129.7 (C6), 151.7 (C2), 169.7 (CO).

N,N-Diethyl 2-(4-isopropyl-2-tert-butyldimethyl-silyloxyphenyl)acetamide (**2c***)*

Purified by flash chromatography (petroleum ether:AcOEt:Et_3N = 7:3:0.1), light yellow oil; R_f = 0.58 (petroleum ether:AcOEt:Et_3N = 7:3:0.1). IR (neat) 1645 cm^{-1}. Anal. found: C, 69.43; N, 4.17; H, 10.57; $C_{15}H_{23}NO_2$ requires: C, 69.37; N, 3.85; H,

10.26%. ^{1}H NMR 0.23 (6H, s, 2 × CH_3Si), 1.00 (9H, s, 3 × CH_3C), 1.04 (3H, t, J = 6.9 Hz, $\underline{CH_3}CH_2$), 1.12 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 1.21 (6H, d, J = 6.9 Hz, 2 × CH_3), 2.82 (1H, hept, J = 6.9 Hz, CH), 3.23 (2H, q, J = 7.2 Hz, CH_2N), 3.38 (2H, q, J = 7.2 Hz, CH_2N), 3.62 (2H, s, CH_2CO), 6.63 (1H, d, J = 1.8 Hz, H3), 6.77 (1H, dd, J = 7.8, 1.8 Hz, H5), 7.12 (1H, d, J = 7.8 Hz, H6). ^{13}C NMR −4.2 (CH_3Si), 12.9 ($\underline{CH_3}CH_2$), 14.0 ($\underline{CH_3}CH_2$), 18.2 ((CH_3)$_3$C)) 23.9 ($\underline{CH_3}$CH), 25.8 (($\underline{CH_3}$)$_3$C), 33.6 (CH_2Ar), 34.8 (CH), 39.9 (CH_2N), 42.1 (CH_2N), 116.6 (C3), 119.5 (C5), 123.3 (C1), 129.2 (C6), 148.6 (C4), 152.7 (C2), 170.8 (CO).

Metalation of *N,N*-diethyl 2-(2-*tert*-butyldimethylsilyloxyaryl) acetamides, and reaction with electrophiles. General procedure

A 0.35 ml aliquot of diisopropylamine (0.25 g, 2.5 mmol) was placed under argon in a 50 ml two-necked flask equipped with reflux condenser and magnetic stirrer, and dissolved in 5 ml of THF. To this solution, chilled at 0 °C, 1.0 ml of a 2.5 M solution of *n*-BuLi (2.5 mmol) in hexane was slowly added. The mixture was stirred at 0 °C for 10 min, then chilled to −80 °C, and a solution of the appropriate amide (2.1 mmol) dissolved in 5 ml of THF was added dropwise. After 1 h stirring at the same temperature, a solution of 2.5 mmol of the appropriate alkyl halide, dissolved in 5 ml of THF, was slowly added. The mixture was allowed to reach room temperature during 12 h, quenched with H_2O (10 ml), extracted with Et_2O (3 × 10 ml), dried ($CaCl_2$) and evaporated. D_2O quenching was performed by adding 0.75 ml of the electrophile dissolved in 2 ml of THF, followed by aqueous work-up as described above.

Compounds **3ab**–**3cd** (see Scheme 2) were not characterized, but directly cyclized to the corresponding 3-alkylbenzofuran-2(3*H*)-ones **4ab**–**4cd**, as described below. Compounds **3aa** and **5** were characterized as follows.

*N,N-Diethyl 2-deutero-2-(2-tert-butyldimethyl-silyloxyphenyl)acetamide (**3aa**)*

Crude product, light yellow oil. R_f = 0.61 (petroleum ether:AcOEt:Et_3N = 8:2:0.1). IR (neat) 1645 cm^{-1}. ^{1}H NMR: δ 0.23 (6H, s, 2 × $SiCH_3$), 1.00 (9H, s, 3 × CH_3C), 1.04 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 1.12 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 3.23 (2H, q, J = 7.2 Hz, NCH_2), 3.38 (2H, q, J = 7.2 Hz, NCH_2), 3.65 (1H, bs, CHD), 6.81 (1H, dd, J = 7.8, 1.2 Hz, H3), 6.91 (1H, td, J = 7.8, 1.2 Hz, H5), 7.11 (1H, td, J = 7.8, 1.2 Hz, H4), 7.21 (1H, dd, J = 7.8, 1.2 Hz, H6). ^{13}C NMR: δ −4.2 (CH_3Si), 12.9 ($\underline{CH_3}CH_2$), 14.0 ($\underline{CH_3}CH_2$), 18.2 ((CH_3)$_3$C), 25.8 (($\underline{CH_3}$)$_3$C), 34.7 (t, J = 21 Hz, CD), 39.8 (CH_2N), 42.1 (CH_2N), 118.4 (C3), 121.3 (C5), 126.2 (C1), 127.6 (C4), 129.5 (C6), 152.9 (C2), 170.6 (CO).

*1,2-Diphenylchloroethane (**5**)*

Purified by flash-chromatography (petroleum ether:AcOEt:NEt_3 = 9:1:0.1), light yellow solid. R_f = 0.35 (petroleum ether:AcOEt:NEt_3 = 9:1:0.1). ^{1}H NMR: δ 3.32 (1H, dd, J = 13.8, 6.6 Hz, CHPh), 3.39 (1H, dd, J = 13.8, 7.8 Hz, CHPh), 5.04 (1H, t, J = 7.2 Hz, CHCl), 7.08–7.13 (2H, m, 2 × ArH), 7.17–7.40 (7H, m, 7 × ArH), 7.49–7.54 (1H, m, ArH). ^{13}C NMR: δ 46.5 (CH_2), 64.1 (CHCl), 126.5 (C4′), 127.1 (C4), 128.3 (C2′), 128.5 (C2 or C3′), 128.7 (C2 or C3′), 129.4 (C3), 137.4 (C1), 141.1 (C1′). (^{1}H NMR spectrum in agreement with literature data.[13])

Acidic cyclization of *N,N*-diethyl 2-alkyl-2-(2-*tert*-butyldimethylsilyloxyaryl)acetamides 3ab-3cc. General procedure

An aliquot of 1.1–1.5 mmol of the appropriate arylamide was placed under argon in a 50 ml reaction flask and dissolved in a mixture of 10 ml of toluene and 0.3 ml of CF_3COOH. The mixture was stirred at reflux temperature and periodically checked by TLC until the starting material was consumed (3–5 h), then chilled to room temperature, and 10 ml of H_2O were added. The mixture was extracted with Et_2O (3 × 10 ml), washed with sat. $NaHCO_3$ (10 ml), brine (10 ml), H_2O (10 ml), dried ($CaCl_2$) and evaporated. Crude products were purified and characterized as follows.

*3-Methylbenzofuran-2(3H)-one (**4ab**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8:2), light yellow oil. R_f = 0.69 (petroleum ether:AcOEt = 8:2). IR (neat) 1804 cm^{-1}. ^{1}H NMR: δ 1.58 (3H, d, J = 7.5 Hz, CH_3) 3.73 (1H, q, J = 7.5 Hz, H3), 7.07–7.14 (1H, m, H7), 7.17 (1H, dd, J = 7.5, 0.9 Hz, H4), 7.24–7.34 (2H, m, H5 and H6). (^{1}H NMR spectrum in agreement with literature data.[14])

*3-Butylbenzofuran-2(3H)-one (**4ac**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8:2), oil. R_f = 0.77 (petroleum ether:AcOEt = 8:2). IR (neat) 1809 cm^{-1}. Anal. found: C, 75.48; H, 7.69; $C_{12}H_{14}O_2$ requires: C, 75.76; H, 7.42%. ^{1}H NMR: δ 0.89–0.94 (3H, m, CH_3), 1.32–1.44 (4H, m, 2 × CH_2), 1.92–2.08 (2H, m, $\underline{CH_2}$CH), 3.72 (1H, t, J = 6.3 Hz, H3), 7.08–7.13 (1H, m, H7), 7.16 (1H, dd, J = 7.5, 0.9 Hz, H4), 7.25–7.34 (2H, H5 and H6). ^{13}C NMR: δ 13.8 (CH_3), 22.4 (CH_2), 28.0 (CH_2), 30.8 ($\underline{CH_2}$CH), 43.4 (C3), 110.7 (C7), 124.0 (C5), 124.2 (C6), 127.6 (C4), 128.7 (C3a), 153.8 (C7a), 177.4 (C2).

*3-Isopropylbenzofuran-2(3H)-one (**4ad**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 7:3), oil. R_f = 0.65 (petroleum ether:AcOEt = 7:3). IR (neat) 1807 cm^{-1}. Anal. found: C, 74.63; H, 7.02; $C_{11}H_{12}O_2$ requires: C, 74.98; H, 6.86%. ^{1}H NMR: δ 0.98 (3H, d, J = 6.9 Hz, CH_3), 1.09 (3H, d, J = 6.9 Hz, CH_3), 2.49 (1H, heptd, J = 6.9, 3.6 Hz, CH), 3.65 (1H, d, J = 3.6 Hz, H3), 7.08–7.12 (1H, m, H7), 7.15 (1H, dd, J = 7.5, 1.2 Hz, H4), 7.26–7.35 (2H, m, H5 and H6). ^{13}C NMR: δ 18.4 (CH_3), 19.3 (CH_3), 31.3 (CH), 49.7 (C3), 110.6 (C7), 123.9 (C5), 124.6 (C6), 126.1 (C4), 128.7 (C3a), 154.1 (C7a), 176.5 (C2).

*3-Benzylbenzofuran-2(3H)-one (**4ae**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 9:1), viscous oil, which solidifies upon standing. R_f = 0.44 (petroleum ether:AcOEt = 9:1). IR (neat) 1804 cm^{-1}. ^{1}H NMR: δ 3.03 (1H, dd, J = 13.8, 9.0 Hz, CH), 3.50 (1H, dd, J = 13.8, 5.1 Hz, CH), 4.00 (1H, dd, J = 9.0, 5.1 Hz, H3), 6.74–6.81 (1H, m, H7), 6.98–7.06 (2H, m, 2 × H2′), 7.12–7.18 (2H, m, H5 and H6), 7.20–7.33 (4H, m, 2 × H3′, H4 and H4′). ^{13}C NMR: δ 37.1 (CH_2), 45.0 (C3), 110.6 (C7), 123.8 (C4′), 124.8 (C5), 126.6 (C3a), 127.1 (C6), 128.6 (C2′), 128.9 (C4), 129.3 (C3′), 136.6 (C1′), 153.7 (C7a), 176.4 (C2). (^{1}H NMR spectrum in agreement with literature data.[15])

*3-(4-Methoxybenzyl)benzofuran-2(3H)-one (**4af**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 7:3), yellow oil. R_f = 0.65 (petroleum ether:AcOEt = 7:3). IR (neat) 1799 cm^{-1}. ^1H NMR: δ 2.97 (1H, dd, J = 14.1, 8.7 Hz, CHPh), 3.39 (1H, dd, J = 14.1, 4.8, CHPh), 3.74 (3H, s, OCH_3), 3.92 (1H, dd, J = 8.7, 4.8 Hz, H3), 6.74–6.80 (2H, m, 2 × H3′), 6.83 (1H, d, J = 7.2 Hz, H7), 6.95–7.07 (4H, m, 2 × H2′, H5 and H6), 7.18–7.26 (1H, m, H4). ^{13}C NMR: δ 36.1 (CH_2), 45.0 (C3), 55.0 (CH_3), 110.5 (C7), 113.7 (C3′), 123.7 (C5), 124.7 (C6), 126.6 (C3a), 128.3 (C1′), 128.7 (C4), 130.2 (C2′), 153.5 (C7a), 158.5 (C4′), 176.4 (C2). (^1H NMR spectrum in agreement with literature data.[15])

*3-(3-Chloropropyl)benzofuran-2(3H)-one (**4ag**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8:2), yellow oil. R_f = 0.46 (petroleum ether:AcOEt = 8:2). IR (neat) 1807 cm^{-1}. Anal. found: C, 62.58; H, 5.45; $C_{11}H_{11}ClO_2$ requires: C, 62.72; H, 5.26%. ^1H NMR: δ 1.83–1.96 (2H, m, CH_2), 2.06–2.24 (2H, m, CH_2), 3.56 (2H, t, J = 6.0 Hz, CH_2Cl), 3.78 (1H, t, J = 6.3 Hz, H3), 7.16 (1H, d, J = 8.1 Hz, H7), 7.17 (1H, td, J = 7.8, 0.9 Hz, H5), 7.26–7.37 (2H, m, H4 and H6). ^{13}C NMR: δ 28.3 (CH_2), 28.6 (CH_2), 42.6 (CH_2Cl), 44.2 (C3), 110.7 (C7), 124.1 (C5), 124.2 (C6), 126.8 (C3a), 129.0 (C4), 153.7 (C7a), 176.7 (C2).

*3-(4-Bromobenzyl)benzofuran-2(3H)-one (**4ah**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 9:1), viscous oil, which solidifies upon standing. R_f = 0.31 (petroleum ether:AcOEt = 9:1). IR (nujol) 1796 cm^{-1}. Anal. found: C, 59.16; H, 3.98; $C_{15}H_{11}BrO_2$ requires: C, 59.43; H, 3.66%. ^1H NMR: δ 3.05 (1H, dd, J = 13.8, 8.4 Hz, CHPh), 3.40 (1H, dd, J = 13.8, 5.1, CHPh), 3.98 (1H, dd, J = 8.4, 5.1 Hz, H3), 6.89 (1H, d, J = 7.5 Hz, H4), 6.98–7.03 (2H, m, 2 × H2′), 7.03–7.10 (2H, m, H5 + H6), 7.23–7.30 (1H, m, H7), 7.36–7.41 (2H, m, 2 × H3′). ^{13}C NMR: δ 36.4 (CH_2), 44.7 (C3), 110.8 (C7), 121.1 (C4′), 123.9 (C5), 124.6 (C6), 126.2 (C3a), 129.1(C4), 131.0 (C2′), 131.6 (C3′), 135.4 (C1′), 153.7 (C7a), 176.1 (C2).

*5-Chloro-3-methylbenzofuran-2(3H)-one (**4ba**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 7.5:2.5), viscous oil, which solidifies upon standing. R_f = 0.56 petroleum ether:AcOEt = 7.5:2.5). IR (neat) 1809 cm^{-1}. Anal. found: C, 59.03; H, 4.06; $C_9H_7ClO_2$ requires: C, 59.20; H, 3.86%. ^1H NMR: δ 1.58 (3H, d, J = 7.5 Hz, CH_3), 3.74 (2H, q, J = 7.5 Hz, H3), 7.01–7.08 (1H, dd, J = 8.4, 0.6 Hz, H7), 7.22–7.35 (2H, m, H4 and H6). ^{13}C NMR: δ 15.7 (CH_3), 38.5 (C3), 111.8 (C7), 124.2 (C6), 128.8 C(4), 129.3 (C5), 130.3 (C3a), 151.8 (C7a), 177.1 (C2).

*5-Chloro-3-isopropylbenzofuran-2(3H)-one (**4bb**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8:2), viscous oil, which solidifies upon standing. R_f = 0.42 (petroleum ether:AcOEt = 8:2). IR (neat) 1812 cm^{-1}. Anal. found: C, 62.47; H, 5.53; $C_{11}H_{11}ClO_2$ requires: C, 62.72; H, 5.26%. ^1H NMR: δ 1.00 (3H, d, J = 6.9 Hz, CH_3), 1.08 (3H, d, J = 6.9 Hz, CH_3), 2.48 (1H, heptd, J = 6.9, 3.6 Hz, CH), 3.66 (1H, d, J = 3.6 Hz, H3), 7.01–7.06 (1H, d, J = 8.7 Hz, H7), 7.25–7.31 (2H, m, H4 and H6). ^{13}C NMR: δ 18.3 (CH_3), 19.1 (CH_3), 31.2 (CH), 49.7 (C3), 111.6 (C7), 124.7 (C6), 127.8 (C5), 128.7 (C4), 129.1 (C3a), 152.4 (C7a), 175.6 (C2).

*6-Isopropyl-3-methylbenzofuran-2(3H)-one (**4ca**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8:2), light yellow oil. R_f = 0.69 (petroleum ether:AcOEt = 8:2). IR (neat) 1806 cm^{-1}. Anal. found: C, 75.61; H, 7.78; $C_{12}H_{14}O_2$ requires: C, 75.76; H, 7.42%. ^1H NMR: δ 1.26 (6H, d, J = 6.9 Hz, 2 × CH_3), 1.56 (3H, d, J = 7.5 Hz, CH_3), 2.93 (1H, hept, J = 6.9 Hz, CH), 3.69 (1H, q, J = 7.5 Hz, H3), 6.99 (1H, s, H7), 7.02 (1H, dd, J = 7.8, 1.5 Hz, H5), 7.16 (1H, d, J = 7.8 Hz, H4). ^{13}C NMR: δ 15.9 ($\underline{CH_3}$C3), 23.9 ($\underline{CH_3}$CH), 34.3 (CH), 38.3 (C3), 108.7 (C7), 122.2 (C5), 123.5 (C4), 126.0 (C3a), 150.5 (C6), 153.6 (C7a), 178.4 (C2).

*3-Butyl-6-isopropylbenzofuran-2(3H)-one (**4cb**)*

Purified by flash-chromatography (petroleum ether:AcOEt:Et_3N = 9:1:0.1), light yellow oil. R_f = 0.65 (petroleum ether:AcOEt:Et_3N = 9:1:0.1). IR (neat) 1809 cm^{-1}. Anal. found: C, 77.23; H, 8.91; $C_{15}H_{20}O_2$ requires: C, 77.55; H, 8.68%. ^1H NMR: δ 0.90 (3H, t, J = 7.2 Hz, $\underline{CH_3}CH_2$), 1.26 (6H, d, J = 6.9 Hz, 2 × CH_3), 1.30–1.44 (4H, m, 2 × CH_2), 1.86–2.07 (2H, m, CH_2), 2.93 (1H, hept, J = 6.9 Hz, CH), 3.67 (1H, t, J = 6.3 Hz, H3), 6.99 (1H, s, H7), 7.03, (1H, dd, J = 7.8, 1.5 Hz, H5), 7.16 (1H, d, J = 7.8 Hz, H4). ^{13}C NMR: δ 13.8 ($\underline{CH_3}CH_2$), 22.5 ($\underline{CH_3}CH$), 23.9 ($\underline{CH_3}CH$), 28.0 ($\underline{CH_2}CH_3$), 30.9 (CH_2), 34.3 ($\underline{CH_2}CH$), 43.3 (C3), 108.7 (C7), 122.1 (C5), 123.9 (C4), 124.8 (C3a), 150.4 (C6), 154.0 (C7a), 177.9 (C2).

*3,6-Diisopropylbenzofuran-2(3H)-one (**4cc**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 7:3), viscous oil, which solidifies upon standing. R_f = 0.64 (petroleum ether:AcOEt = 7:3). IR (neat) 1803 cm^{-1}. Anal. found: C, 76.81; H, 8.71; $C_{14}H_{18}O_2$ requires: C, 77.03; H, 8.31%. ^1H NMR: δ 0.96 (3H, d, J = 6.8 Hz, CH_3), 1.09 (3H, d, J = 6.8 Hz, CH_3), 1.26 (6H, d, J = 7.2 Hz, 2 × CH_3), 2.46 (1H, heptd, J = 6.8, 4.0 Hz, CH), 2.93 (1H, hept, J = 7.2 Hz, CH), 3.60 (1H, d, J = 4.0 Hz, H3), 6.97 (1H, s, H7), 7.01 (1H, dd, J = 7.6, 2.2 Hz, H5), 7.18 (1H, d, J = 7.6 Hz, H4). ^{13}C NMR: δ 18.4 (CH_3), 19.4 (CH_3), 23.9 (2 × CH_3), 31.3 (CH), 34.3 (CH), 49.7 (C3), 108.6 (C7), 122.0 (C5), 123.3 (C3a), 124.3 (C4), 150.4 (C6), 154.3 (C7a), 177.0 (C2).

*3-Benzyl-6-isopropylbenzofuran-2(3H)-one (**4cd**)*

Purified by flash-chromatography (petroleum ether:AcOEt = 8.5:1.5), light yellow oil. R_f = 0.70 (petroleum ether:AcOEt = 8.5:1.5). IR (neat) 1807 cm^{-1}. Anal. found: C, 80.93; H, 7.03; $C_{18}H_{18}O_2$ requires: C, 81.17; H, 6.81%. ^1H NMR: δ 1.21 (6H, d, J = 6.9 Hz, 2 × CH_3), 2.88 (1H, hept, J = 6.9 Hz), 2.96 (1H, dd, J = 13.5, 9.6 Hz, CH_2), 3.50 (1H, dd, J = 13.5, 4.5 Hz, CH), 3.96 (1H, dd, J = 9.6, 4.5 Hz, H3), 6.65 (1H, d, J = 7.5 Hz, H4), 6.87 (1H, dd, J = 7.5, 1.5 Hz, H5), 6.92 (1H, d, J = 1.5 Hz, H7), 7.16–7.20 (2H, m. 2 × H2′), 7.24–7.33 (3H, m, 2 × H3′ and H4′). ^{13}C NMR: δ 23.9 (CH_3), 34.2 (CH), 37.2 (CH_2), 44.8 (C3), 108.6 (C7), 121.9 (C5), 123.9 (C3a), 124.5 (C4), 127.0 (C4′), 128.5 (C2′), 129.3 (C3′), 136.9 (C1′), 150.5 (C6), 153.8 (C7a), 176.9 (C2).

References

[1] Q. Gu, R.-R. Wang, X.-M. Zhang, Y.-H. Wang, Y.-T. Zheng, J. Zhou, J.-J. Chen, *Planta Med.* **2007**, *73*, 279. DOI: 10.1055/s-2007-967113; b) L. Morales-Escobar, A. Braca, C. Pizza, N. De Tommasi, *ARKIVOC* **2007**, *vii*, 349; c) E. Rizzi, S. Dallavalle, L. Merlini, G. L. Beretta, G. Pratesi, F. Zunino, *Bioorg. Med. Chem. Lett.* **2005**,

15, 4313. DOI: 10.1016/j.bmcl.2005.06.045; d) K. Suzuki, T. Okawara, T. Higashijima, K. Yokomizo, T. Mizushima, M. Otsuka, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2065. DOI: 10.1016/j.bmcl.2005.02.052; e) A. Buettner, P. Schieberle, *J. Agric. Food Chem.* **2001**, *49*, 2387. DOI: 10.1021/jf001363l; f) W. R. Phillips, N. J. Baj, A. A. L. Gunatilaka, D. G. I. Kimgston, *J. Nat. Prod.* **1996**, *59*, 495. DOI: 10.1021/np960240l; g) J. K. Chakrabarti, R. J. Eggleton, P. T. Gallagher, J. Harvey, T. A. Hicks, E. A. Kitchen, C. W. Smith, *J. Med. Chem.* **1987**, *30*, 1663. DOI: 10.1021/jm00392a024; h) A. Closse, W. Haeflinger, D. Hauser, H. U. Gubler, B. Dewald, M. Baggiolini, *J. Med. Chem.* **1981**, *24*, 1465. DOI: 10.1021/jm00144a019.

[2] X. Meng, Z. Xin, Y. Li, Z. Cai, *Polymer Degradation and Stability* **2007**, *92*, 184, and references therein. DOI: 10.1016/j.polymdegradstab.2006.07.024; b) C. V. Lundgren, A. L. Koner, M. Tinkl, U. Pischel, W. M. Nau, *J. Org. Chem.* **2006**, *71*, 1977. DOI: 10.1021/jo052440k.

[3] See, for example: W. Luo, Q.-S. Yu, H. W. Holloway, D. Parrish, N. H. Greig, A. Brossi, *J. Org. Chem.* **2005**, *70*, 6171. DOI: 10.1021/jo0503052; b) E. Vedejs, J. Wang, *Org. Lett* **2000**, *2*, 1031. DOI: 10.1021/ol005547x; c) F. Lach, C. J. Moody, *Tetrahedron Lett.* **2000**, *41*, 6893. DOI: 10.1016/S0040-4039(00)01118-7; d) T. Satoh, T. Tsuda, Y. Terao, M. Miura, M. Nomura, *J. Mol. Catal. A, Chemical* **1999**, *143*, 203. DOI: 10.1016/S1381-1169(98)00388-4; e) P. Wipf, F. Yokokawa, *Tetrahedron Lett.* **1998**, *39*, 2223. DOI: 10.1016/S0040-4039(98)00231-7; f) J.i. Setsune, T. Ueda, K. Shikata, K. Matsukawa, T. Iida, T. Kitao, *Tetrahedron* **1986**, *42*, 2647. DOI: 10.1016/S0040-4020(01)90550-2.

[4] A. V. Kalinin, M. A. J. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. L. Coelho, M. Kerr, V. Snieckus, *Synlett* **1997**, 839. DOI: 10.1055/s-1997-5743.

[5] V. Snieckus, *Chem Rev.* **1990**, *90*, 879. DOI: 10.1021/cr00104a001.

[6] R. Bloch, P. Orvane, *Tetrahedron Lett.* **1981**, *22*, 3597, and references cited therein. DOI: 10.1016/S0040-4039(01)81969-9.

[7] 3-Monoalkyl-substituted benzofuran-2(3*H*)-ones are usually synthesized by the metalation of *ortho*-alkoxy-substituted phenylacetic acids (mainly nitriles or esters), followed by acidic work-up of the resulting reaction products. See, for example: S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925. DOI: 10.1021/ja056150x; b) D. C. Harrowven, M. C. Lucas, P. D. Howes, *Tetrahedron Lett.* **1999**, *40*, 4443. DOI: 10.1016/S0040-4039(99)00768-6; see also ref. 6.

[8] Migration, cleavage or metalation (at a methyl group) of different TBDMS-protected alcohols and phenols in the presence of organolithium reagents have been reported; see: T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn. Wiley: Chichester, **1999**, pp. 113–115 and 127–131, and references cited therein; b) T. A. Hase, L. Lahtinen, *Synth. Commun*. **1978**, *8*, 573. DOI: 10.1080/00397917808063589.

[9] B. A. M. Oude-Alink, A. W. K. Chan, C. D. Gutsche, *J. Org. Chem.* **1973**, *38*, 1993. DOI: 10.1021/jo00951a006.

[10] G. P. Gisby, P. G. Sammes, R. A. Watt, *J. Chem. Soc., Perkin Trans. 1* **1982**, 249. DOI: 10.1039/P19820000249.

[11] The reactivity of the intermediate organometal towards aldehydes was briefly investigated. Quenching the reaction mixture with PhCHO (1.2 equiv., −80 °C), followed by acidic cyclization of the crude reaction mixture, led to the recovery of 3-benzylidenebenzofuran-2(3*H*)-one, as an 85 : 15 mixture of (*E*)/(*Z*) diastereoisomers, characterized by comparison with literature data. Owing to the possibility to synthesize similar compounds by employing benzofuran-2(3*H*)-one as a starting material, we do not investigate further on this reactivity. M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, B. Laude, *Synthesis* **1997**, 1495. DOI: 10.1055/s-1997-1369.

[12] B. de la Roche, *Bull. Soc. Chim. Fr.* **1904**, *31*, 20.

[13] T. Satoh, K. Takano, *Tetrahedron* **1996**, *52*, 2349. DOI:10.1016/0040-4020(95)01078-5.

[14] G. W. Rewcastle, G. J. Atweel, B. C. Baguley, M. Boyd, L. L. Thomsen, L. Zhuang, W. A. Denny, *J. Med. Chem.* **1991**, *34*, 2864. DOI: 10.1021/jm00113a027.

[15] E. Yoneda, T. Sugioka, K. Hirao, S.-W. Zhang, S. Takahashi, *J. Chem. Soc., Perkin Trans. 1* **1998**, 477. DOI: 10.1039/a706622h.

