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Efficient synthesis of functionalized furans and benzofurans based on a '[3+2] cyclization/oxidation' strategy

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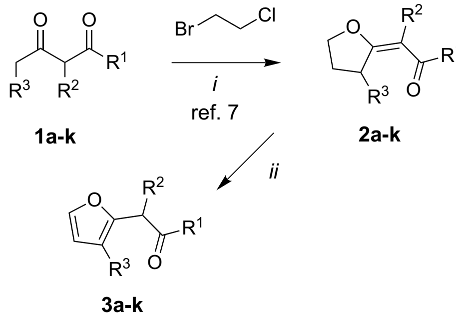
Abstract—Functionalized furans and benzofurans were prepared by DDQ oxidation of 2-alkylidenetetrahydrofurans, which are readily available by one-pot cyclizations of 1,3-dicarbonyl dianions or 1,3-bis-silyl enol ethers.

Functionalized furans and benzofurans represent important synthetic building blocks and are present in a variety of biologically relevant natural products, such as the calicogorgins, furan fatty acids, cyctotoxic furanocembranes, gersolanes, pseudopteranes, rosefuran, agassizin, furodysin, mikanifuran or α-clausenan.[1,2] Although a variety of furan syntheses are known,[3] the development of new and convenient strategies is of considerable interest. In the recent years, we reported a number of one-pot syntheses of 2-alkylidenetetrahydrofurans by [3+2] cyclization of free and masked 1,3-dicarbonyl dianions with 1,2-dielectrophiles.[4] Herein, we wish to report a new and convenient approach to functionalized furans and benzofurans based on a '[3+2] cyclization/oxidation' strategy.[5,6]

Treatment of 2-alkylidenetetrahydrofuran **2a**, prepared by cyclization of the dianion **1a** of methyl acetoacetate with 1-bromo-2-chloroethane,[7a] with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) afforded the known[8] furan **3a** (Scheme 1). Optimal results were obtained when an excess of DDQ was employed (2 equiv) and when the reaction was carried out in 1,4-dioxane under reflux for 48 h.[9] The use of other solvents, oxidizing agents (MnO_2) and conditions proved less effective in terms of yield (Table 1). The formation of **3a** can be explained by oxidation and subsequent aromatization by migration of the exocyclic double bond.



Scheme 1. Synthesis of furans **3a**–**k**. Reagents and conditions: (i): (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) −78 °C → 20 °C, 14 h, (3) reflux, 12 h; (ii): DDQ (2 equiv), 1,4-dioxane, reflux, 48 h.

Table 1. Optimization of the synthesis of **3b**

Solvent	*t* [h]	Conditions	%[a]
CH_3CN	24	Reflux	0
THF	24	Reflux	17
Dioxane	24	20 °C	0
Dioxane	24	Reflux	34
Dioxane	48	Reflux	75
Toluene	24	Reflux	12
CH_2Cl_2	24	Reflux	5

[a] Conversion (by ^1H NMR of the crude product).

The preparative scope of our methodology was studied (Table 2). The synthesis of 2-alkylidenetetrahydrofurans **2a**,**b** and **2d**–**j** has been previously reported.[7] The furans **3b**–**d** were prepared from **2b**–**d**, containing ethyl, *iso*-propyl and *tert*-butyl ester groups, respectively. The

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Table 2. Products and yields

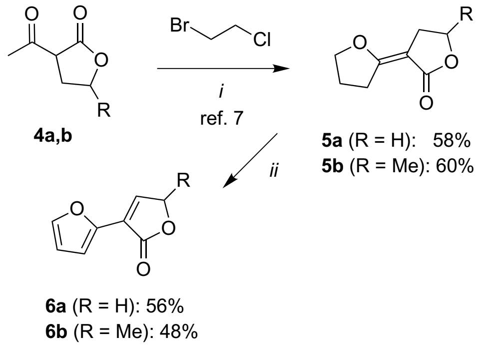
2,3	R^1	R^2	R^3	% (**2**)[a,b]	% (**3**)[a]
a	OMe	H	H	65	57
b	OEt	H	H	75	59
c	O*i*Pr	H	H	70	52
d	O*t*Bu	H	H	74	55
e	OMe	H	Me	68	41
f	OEt	H	Et	80	53
g	O*t*Bu	H	$(CH_2)_2CH(CH_3)_2$	48	54
h	O*t*Bu	H	$(CH_2)_6Cl$	91	67
i	OEt	Me	H	64	51
j	OEt	Et	H	61	55
k	OEt	$–(CH_2)_9–$		57	80

[a] Isolated yields.

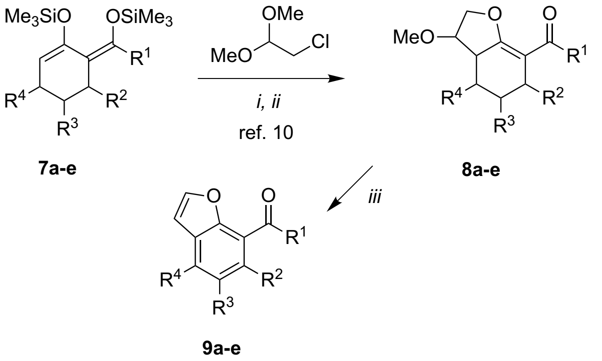
[b] See Ref. 7.

oxidation of 2-alkylidenetetrahydrofurans **2e**–**g**, prepared by cyclization of the corresponding 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane, afforded the furans **3e**–**g**. The oxidation of chloro-substituted 2-alkylidenetetrahydrofuran **2h**, prepared from dilithiated *tert*-butyl 10-chloro-3-oxodecanoate (**1h**), afforded the corresponding furan **3h**. The oxidation of 2-alkylidenetetrahydrofurans **2i**,**j**, prepared from ethyl 2-methylacetoacetate and ethyl 2-ethylacetoacetate, gave the methyl and ethyl substituted furans **3i**,**j**. The cyclization of the dianion of ethyl 2-oxo-cyclododecanecarboxylate with 1-bromo-2-chloroethane afforded the novel 5,12-bicyclic 2-alkylidenetetrahydrofuran **2k**. Treatment of the latter with DDQ gave the furan **3k**.

The 2,3′-bifuranylidenes **5a**,**b** were prepared, according to our recently reported methodology,[7] by cyclization of dilithiated α-acetyl-γ-butyrolactones **4a**,**b** with 1-bromo-2-chloroethane (Scheme 2). The synthesis of **5a** has been previously reported.[7] Treatment of **5a**,**b** with DDQ afforded the furans **6a**,**b**. The formation of **6a**,**b** can be explained by oxidation of both the tetrahydrofuran and the lactone moiety. The employment of only one (rather than two) equivalents of DDQ resulted in the formation of a complex mixture.



Scheme 2. Synthesis of furans **6a**,**b**. Reagents and conditions: (i): (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) −78 °C → 20 °C, 14 h, (3) reflux, 12 h; (ii): DDQ (2 equiv), 1,4-dioxane, reflux, 48 h.



Scheme 3. Synthesis of benzofurans **9a**–**e**. Reagents and conditions: (i): Me_3SiOTf (0.5 equiv), CH_2Cl_2, −78 °C → 20 °C; (ii): 2.0 equiv DBU, THF, 20 °C; (iii): DDQ (2 equiv), 1,4-dioxane, reflux, 24 h.

Table 3. Products and yields

8,9	R^1	R^2	R^3	R^4	% (**8**)[a,b]	% (**9**)[a]
a	OEt	H	H	H	38	53
b	OEt	Me	H	H	71	75[c]
c	OMe	H	Me	H	90	53
d	OEt	H	Ph	H	85	66[c]
e	OEt	H	H	Me	60	62

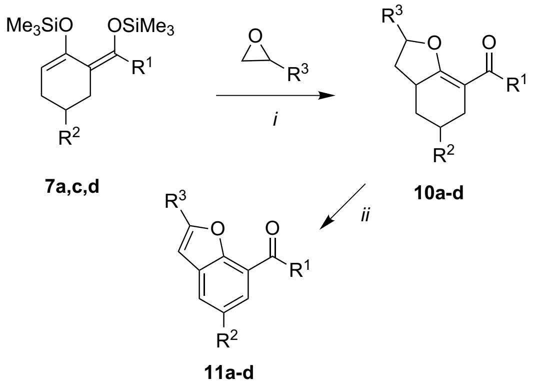
[a] Isolated yields.

[b] Yields over two steps (see Ref. 10).

[c] Prepared in two steps: (1) dioxane, reflux, (2) DDQ, dioxane, reflux.

The cyclization of cyclic 1,3-bis-silyl enol ethers **7a**–**e** with 1-chloro-2,2-dimethoxyethane afforded, following our recently reported methodology,[10] the 5,6-bicyclic 2-alkylidenetetrahydrofurans **8a**–**e**. The synthesis of **8a**,**d**,**e** has been previously reported.[10] Treatment of the latter with DDQ resulted in formation of the 2,3-unsubstituted benzofurans **9a**–**e** by thermal elimination of methanol and oxidation of the cyclohexene moiety (Scheme 3, Table 3).

A second approach was developed, which allows an efficient synthesis of 2-substituted benzofurans: The cyclization of 1,3-bis-silyl enol ethers **7a**,**c**,**d** with propenoxide and epibromohydrin afforded the 5,6-bicyclic 2-alkylidenetetrahydrofurans **10a**–**d** as a mixture of diastereomers. These transformations represent the first examples of cyclizations of cycloalkanone-derived 1,3-bis-silyl enol ethers with epoxides.[11] The oxidation of **10a**–**d** with DDQ afforded the benzofurans **11a**–**d** (Scheme 4, Table 4).



Scheme 4. Synthesis of benzofurans **11a**–**d**. (i): $TiCl_4$ (2 equiv), 4 Å MS, CH_2Cl_2, −78 °C → 20 °C, 14 h, 20 °C, 2 h; (ii): DDQ (2 equiv), 1,4-dioxane, reflux, 24–48 h.

Table 4. Products and yields

10,11	R^1	R^2	R^3	% (**10**)[a]	% (**11**)[a]
a	OEt	H	Me	28	60
b	OMe	Me	Me	30	65
c	OMe	Ph	Me	32	63
d	OMe	Ph	CH_2Br	37	31[b]

[a] Isolated yields.

[b] Besides, the corresponding 2,3-dihydrobenzofuran was isolated in 40% yield.

In summary, we have reported a new and efficient approach to a variety of furans and benzofurans based on a [3+2] cyclization/oxidation strategy.

Acknowledgements

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9. Representative experimental procedure: To a 1,4-dioxane solution (10 mL) of **2d** (0.100 g, 0.54 mmol) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (0.246 g, 1.09 mmol) under Argon atmosphere at 20 °C. The mixture was heated for 48 h at reflux and, after cooling, the solvent was removed in vacuo. To the residue was added diethylether to give a precipitate which was filtered off. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 100:1 → 50:1) to give **3d** as a slight yellow oil (0.054 g, 55%); $R_f = 0.77$ (*n*-hexane/EtOAc = 5:1). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.46$ (s, 9H, O*t*Bu), 3.59 (s, 2H, CH_2), 6.20 (dt, $J = 3.3$, 0.9 Hz, 1H, CH), 6.33 (dd, $J = 3.3$, 1.8 Hz, 1H, CH), 7.36 (dd, $J = 1.8$, 0.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta_C = 28.21$ (CH_3), 35.49 (CH_2), 81.54 (C), 107.86, 110.63, 142.06 (CH), 148.64 (C), 168.90 (O=C–O). IR (neat, cm^{-1}): $\tilde{\nu} = 2980$ (w, C–H), 1739 (s, O=C–O), 1394 (w), 1370 (m), 1340 (w), 1279 (w), 1255 (w), 1234 (m), 1152 (s), 1096 (w), 1013 (w), 734 (w). MS (EI, 70 eV): *m*/*z* (%) = 183 (M^+, 13), 123 (20), 116 (100), 108 (8), 101 (48), 81 (65). The exact molecular mass *m*/*z* = 182.0943 ± 2 ppm [M^+] for $C_{10}H_{14}O_3$ was confirmed by HRMS (EI, 70 eV). All products gave satisfactory spectroscopic data and correct elemental analyses and/or high resolution mass data.
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