Reaction of 2-Alkylidenetetrahydrofurans with Boron Tribromide: Chemo- and Regioselective Synthesis of 6-Bromo-3-oxoalkanoates by Application of a 'Cyclization-Ring-Opening' Strategy

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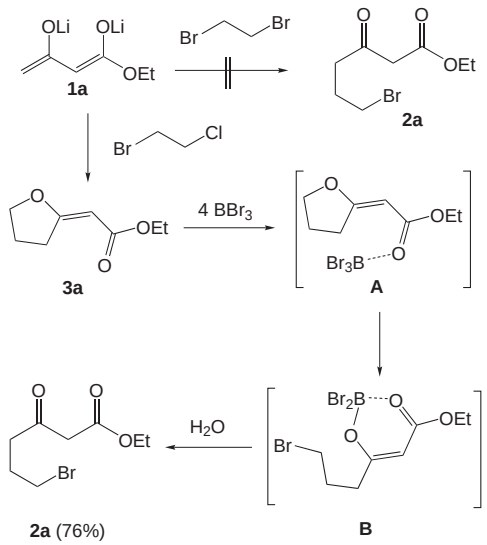
Abstract: 6-Bromo-3-oxoalkanoates, benzofurans and 1,7-dibromoheptan-4-ones were chemo- and regioselectively prepared by reaction of 2-alkylidenetetrahydrofurans with boron tribromide.

Key words: boron tribromide, domino reactions, nucleophilic substitution, halogenation, tetrahydrofurans

Boron tribromide (BBr_3) has been widely used for the demethylation of methylaryl ethers.[1] The reaction of cyclic ethers with BBr_3–MeOH has been reported to result in ring opening and formation ω-bromoalkanols.[2] ω-Halocarboxylic acids have been prepared by reaction of lactones with BBr_3.[3] Herein, we wish to report what are, to the best of our knowledge, the first reactions of BBr_3 with cyclic enol ethers, e.g. 2-alkylidenetetrahydrofurans. This transformation allows a chemo- and regioselective approach to 6-bromo-3-oxoalkanoates, benzofurans and 1,7-dibromoheptan-4-ones which all represent useful synthetic building blocks. Our methodology relies on a 'cyclization-ring-opening' strategy: the starting materials, 2-alkylidenetetrahydrofurans, are readily available by one-pot cyclizations. In contrast, the ring-opening products are in most cases not readily available by other methods.[4]

The reaction of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane has been reported to give 6-chloro-3-oxoalkanoates.[5] These products readily undergo 5-*exo*-tet cyclizations under the basic conditions employed. In fact, 2-alkylidenetetrahydrofurans **3** can be prepared in good yields by one-pot cyclizations.[6] Despite their synthetic usefulness, 6-bromo-3-oxoalkanoates **2** are not directly available by reaction of dianions with 1,2-dibromoethane, due to reduction of the dielectrophile.[7] We have found that this problem could be successfully solved by sequential treatment of 2-alkylidenetetrahydrofuran (**3a**) with BBr_3 and water. During the optimization, the use of an excess of BBr_3 (4 equiv) proved to be important.[8] A possible mechanism could involve the activation of **3a** (intermediate **A**), ring-opening (intermediate **B**) and subsequent protonation of the enolate. So far, we have no evidence for the mechanism and for the configuration of **B** (Scheme 1).



Scheme 1

The reaction of BBr_3 with 2-alkylidenetetrahydrofurans **3b**–**h**, containing a substituent located at the exocyclic double bond, afforded the 2-alkyl- and 2-aryl-6-bromo-3-oxoalkanoates **2b**–**h** (Scheme 2, Table 1). During the formation of **2h**, the methylaryl ether of the starting material was cleaved. The 4-alkyl-6-bromo-3-oxoalkanoates **2i**–**j** were prepared from 2-alkylidenetetrahydrofurans **3i**–**j** containing a substituent at carbon C-3. The reaction of 5,12-bicyclic 2-alkylidenetetrahydrofuran (**3k**), prepared from ethyl cyclododecan-1-one-2-carboxylate, afforded **2k**. The ring-opening of 5-alkyl-2-alkylidenetetrahydrofurans, readily available by cyclization of 1,3-bis-silyl enol ethers with epoxides,[9] was studied next. Treatment of **3l**–**n** with BBr_3 afforded the 6-methyl-, 6-ethyl- and 6-butyl-6-bromo-3-oxoalkanoates **2l**–**n**. The 6-bromo-7-chloro-3-oxoalkanoate (**2o**) was prepared in 80% yield from **3o**. Starting with 4-phenyl-2-alkylidenetetrahydrofuran (**3p**), 5-phenyl-6-bromo-3-oxoalkanoate (**2p**) was prepared. Treatment of tetrahydrofuran **3q** with BBr_3 afforded the 1,3-diketone **2q**. The reaction of 5-vinyl-2-alkylidenetetrahydrofuran, readily available by cyclization of dilithiated methyl acetoacetate with 1,4-dibromo-2-butene,[10] afforded ethyl 8-bromo-3-oxooct-6-enoate. In this reaction, the cleavage of the tetrahydrofuran moiety proceeded by a S_N' mechanism with migration of the double bond. All reactions proceeded in good yield and with

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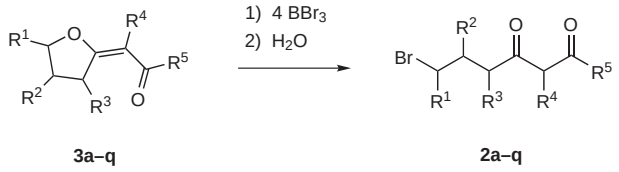


Scheme 2

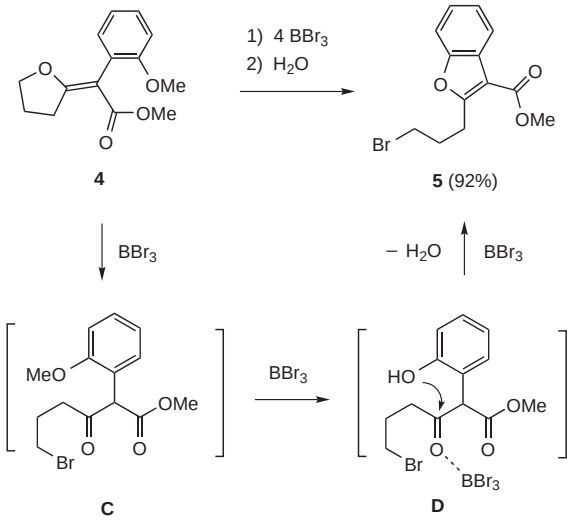
Table 1 Products and Yields

2	R^1	R^2	R^3	R^4	R^5	(%)
a	H	H	H	H	OEt	76
b	H	H	H	Oct	OEt	95
c	H	H	H	Bn	OMe	96
d	H	H	H	$(CH_2)_3Cl$	OMe	84
e	H	H	H	Ph	OMe	84
f	H	H	H	4-MeC_6H_4	OMe	89
g	H	H	H	4-ClC_6H_4	OMe	77
h	H	H	H	4-HOC_6H_4	OMe	72
i	H	H	Pr	H	OEt	96
j	H	H	$(CH_2)_3Cl$	H	OMe	86
k	H	H	-$(CH_2)_9$-		OEt	87
l	Me	H	H	H	OMe	80
m	Et	H	H	H	OMe	91
n	Bu	H	H	H	OMe	75
o	CH_2Cl	H	H	H	OMe	80
p	H	Ph	H	H	OEt	83
q	H	H	H	H	Ph	98

[a] Yields of isolated products.

very good chemo- and regioselectivity. As expected from the chemistry of boron tribromide, alkyl esters remained intact.[1]

Treatment of 2-alkylidenetetrahydrofuran **4** with BBr_3 afforded the functionalized benzofuran **5** (Scheme 3).[11] The formation of **5** can be explained by ring-opening of **4** to give intermediate **C**, deprotection of the arylmethyl ether (intermediate **D**) and subsequent BBr_3 mediated cyclization by attack of the hydroxy onto the carbonyl group. Functionalized benzofurans are of great pharmacological relevance and are used in the clinic.[12] For example, amiodarone represents a potent antiarrythmic drug (Figure 1).[12a,b] Brominated benzofurans related to **5** represent useful synthetic building blocks. In addition, they are interesting in their own right as metabolites of amiodarone.[12a]



Scheme 3

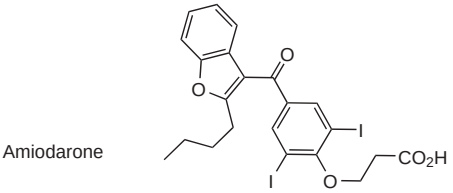
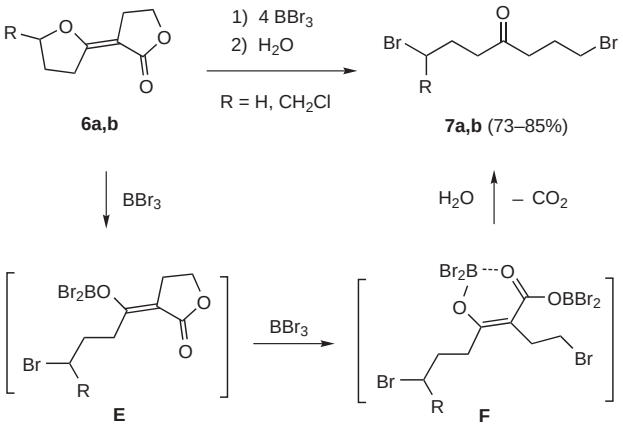


Figure 1



Scheme 4

The reaction of BBr_3 with dinuclear 2-alkylidenetetrahydrofuran (**6a**), available in one step from 2-acetyl-γ-butyrolactone, afforded 1,7-dibromoheptan-4-one (**7a**) in 73% yield (Scheme 4). The formation of **7a** can be explained by BBr_3 mediated ring-opening of the cyclic enol, cleavage of the lactone, decarboxylation and protonation.[13] The unsymmetrical 1,7-dibromoheptan-4-one (**7b**) was prepared in 85% yield from 2-alkylidenetetrahydrofuran (**6b**) which is available in one step from epichlorohydrin.[9] 1,7-Dibromoheptan-4-ones represent versatile synthetic building blocks.[14] For example, **7a** has been used for the synthesis of medium-sized carba- and heterocycles.[14a,b] Unsymmetrical 1,7-dibromoheptan-4-ones are not readily available by other methods.[14f]

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(8) **Typical Experimental Procedure for 2h:** To a CH_2Cl_2 solution (5 mL) of **3h** (0.130 g, 0.5 mmol) was added BBr_3 (0.525 g, 2.1 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C during 12 h. Water (2 mL) was added and the solution was stirred for 3 h at 20 °C. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 30:1 to 1:1) to give **2h** as a brownish solid (0.118 g, 72%). The product mainly resides in the keto tautomeric form (keto–enol = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (quint, *J* = 6.6 Hz, 2 H, CH_2), 2.68 (t, *J* = 6.9 Hz, 2 H, CH_2), 3.35 (t, *J* = 6.9 Hz, 2 H, CH_2-Br), 3.76 (s, 3 H, OCH_3), 4.70 (s, 1 H, CH), 5.65 (br, 1 H, OH), 6.83 (d, *J* = 8.7 Hz, 2 H, Ar), 7.20 (d, *J* = 8.7 Hz, 2 H, Ar), 13.03 (br, 1 H, enol from, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.33, 32.69 (CH_2), 39.44 (CH_2-Br), 52.76 (OCH_3), 63.92 (CH), 103.92 (*C*=C-O, enol), 115.96 (CH), 123.71 (C), 130.55 (CH), 156.08 (C), 169.64 (O=C-O), 175.04 (O-*C*=C, enol), 203.55 (C=O). IR (KBr): 3396 (m, OH), 3184 (w), 2957 (w, C-H), 1735 (s, O=C-O), 1703 (s, C=O), 1614 (w), 1594 (w), 1516 (s), 1439 (m), 1359 (m), 1335 (w), 1302 (w), 1274 (m), 1249 (m), 1213 (s), 1161 (m), 1095 (w), 991 (w), 832 (w), 557 (w), 528 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 315 (1) [M$^+$], 284 (14), 234 (5), 203 (1), 175 (5), 165 (85), 150 (29), 118 (3), 109 (100), 106 (55). Anal. Calcd for $C_{13}H_{15}O_4Br$ (315.163): C, 49.54; H, 4.80. Found: C, 49.63; H, 5.03. All products gave satisfactory spectroscopic and analytical and/or high-resolution mass data.

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(11) **Typical Experimental Procedure for 5:** To a CH_2Cl_2 solution (10 mL) of **4** (0.150 g, 0.6 mmol) was added BBr_3 (0.605 g, 2.4 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C and was stirred for 24 h. Water (15 mL) was slowly added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc, 100:1 to 1:1) to give **5** (0.163 g, 92%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (quint, *J* = 7.2 Hz, 2 H, CH_2), 3.35 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.47 (t, *J* = 6.9 Hz, 2 H, CH_2-Br), 3.95 (s, 3 H, OCH_3), 7.28–7.33 (m, 2 H, 2 × CH), 7.42–7.45 (m, 1 H, CH), 7.95–7.98 (m, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.83, 30.80 (CH_2), 32.41 (CH_2-Br), 51.44 (OCH_3), 109.17 (*C*=C-O), 110.88, 121.87, 123.86, 124.58 (CH), 125.82, 153.62 (C), 164.52 (O=C-O), 165.17 (O-*C*=C). IR (neat): 2952 (m, C-H), 1714 (s, O=C-O), 1593 (s), 1478 (m), 1451 (s), 1437 (s), 1386 (m), 1342 (w), 1284 (m), 1235 (s), 1174 (s), 1127 (w), 1106 (m), 1073 (s), 1010 (w), 959 (w), 935 (w), 861 (w), 790 (m), 752 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 297 (38) [M$^+$], 266 (7), 217 (16), 203 (10), 188 (100), 174 (5), 170 (29), 158 (47), 144 (4). Anal. Calcd for $C_{13}H_{13}O_3Br$ (297.148): C, 52.55; H, 4.41. Found: C, 52.84; H, 4.74.

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