C/O-Alkylation Ratios in the Ring-Closures of 7-Halo-3-oxo Esters

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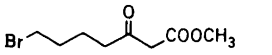
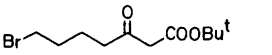
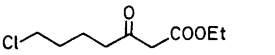
Four acyclic 7-halo-3-oxo esters have been treated with bases under various conditions to obtain six-membered ring compounds. These halo keto esters give more *O*-alkylation (*C/O* = 0.18–3.2) than do the analogous halo ketones.

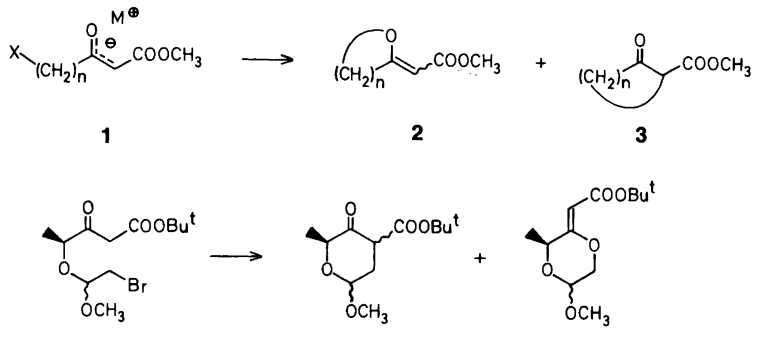
Intramolecular alkylation of an ω-halo-β-keto ester anion (**1**) gives a cyclic ether (**2**) or a cyclic ketone (**3**) of equal ring size depending on which atom in the anion is acting as the nucleophile (Fig. 1). When the cyclisation leads to five-membered rings (n = 3), *O*-alkylation is strongly predominant.[1-3] There seems to be only one example of the formation of a six-membered ring. Huckin and Weiler[4] treated methyl acetoacetate in tetrahydrofuran (THF) sequentially with equimolar amounts of sodium hydride in mineral oil, butyllithium in hexane, and 1,3-dibromopropane. The intermediate **1** (n = 4; X = Br; M = Li, Na) underwent substitution of the bromo group, either intramolecularly (to ca. 50 % extent) or intermolecularly (ca. 50 %) with dimetallated methyl acetoacetate. Only the ketone **3** (isolated yield, 33 %), i.e. no cyclic ether **2**, was reported as a product from the intramolecular reaction.[4]

Working on a synthesis of 6-deoxy-L-sugars, we studied the ring-closure **4**→**5**. It turned out that substantial amounts of *O*-alkylation products (**6**) were formed along with **5** under all conditions tried (Table 1). This result prompted us to investigate the behaviour of other 7-halo-3-oxo esters. Repetition of the experiment of Huckin and Weiler[4] described above gave, as reported, two major products. One of these was dimethyl 3,9-dioxoundecanedioate; the other one was not **3** (n = 4), however, but the bromo keto ester **7**. Evidently, the reaction conditions given in the literature were, in our hands, too mild to bring about ring-closure of **1** (n = 4; X = Br; M = Li, Na). The formation of **7** was later recognized by Sum and Weiler but no experimental details were reported.[5] We found that when the reaction mixture was heated before work-up

Table 1. *C/O*-Alkylation ratios found in the ring-closures of the halo keto esters **4** and **7–9**.

Starting material	Base, solvent	*C/O* Ratio
4	$Mg(OEt)_2$, DMF	2.1[a]
	NaOMe, HOMe	3.2[a]
	$LiOBu^t$, THF	1.4[a]
	$KOBu^t$, THF	1.3[a]
 **7**	MH,[b] THF	0.42–0.66[c,d]
	NaH, LiBr, THF, hexane	0.47[c]
 **8**	$KOBu^t$, THF	0.8[a]
	LiOMe, HOMe	2.1[a]
 **9**	$KOBu^t$, THF	0.17[c]
	MgO, DMSO	1.0[c]
	NaOEt, HOEt	0.75[c]

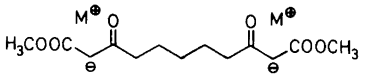
[a]After separation on silica gel. [b]NaH and LiH gave practically the same result. [c]As found by GLC. [d]The higher value at higher concentration.



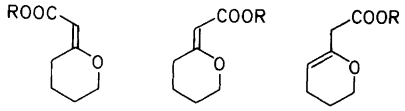
1 **2** **3**

4 **5** **6**

Fig. 1.



10



11 **12** **13**

(67 °C, 0.5 h) the product mixture then contained **2** and **3** (n = 4) instead of **7**. GLC showed a *C/O*-alkylation ratio of 6.8. However, treatment of isolated **7** or the analogous halo keto esters **8** and **9** under various basic conditions (Table 1) gave much lower *C/O* ratios. We conclude that it is the particular conditions prevailing in the Huckin–Weiler synthesis that strongly favour *C*-alkylation. In this synthesis **1** (n = 4; X = Br) undergoes ring-closure in THF–hexane (5:1) in the presence of ca. 3 mol equiv. of lithium or sodium bromide and 1 mol equiv. of the dienolate **10** (M = Li, Na).

The ring-closures of **7–9** gave, in each case, three *O*-alkylation products (**11–13**) in varying proportions, along with the *C*-alkylation product. As found by GLC, **12** generally predominated when the ring-closure was carried out at or below room temperature and the rearranged product **13** predominated when higher temperatures were used; differences in pH during work-up may also have affected the ratios of **11–13**. Ring-closure of **4** (two isomers) and separation on silica gel afforded, as the main products, two isomers **5** (α + β) and two isomers **6** (α + β), both probably with the shown *Z* configuration.

Since the formation of substituted cyclohexanones from precursors such as **7** is a reaction of considerable synthetic potential, we tried to increase the low *C/O*-alkylation ratio (0.42) obtained in the reaction of **7** with sodium hydride. Thus, the reaction conditions in the Huckin–Weiler synthesis were mimicked by having additives present during the ring-closure of **7**; the solvent was THF–hexane (5:1). A slight increase in the *C/O* ratio up to 0.47 was obtained with 3 mol equiv. of lithium bromide; a stronger effect (*C/O* = 1.5) was seen after attempted *in situ* formation of the dienolate **10** from dimethyl 3,9-dioxoundecanedioate plus sodium hydride. The presence of lithium bromide in the latter reaction did not improve the result. However, it is questionable as to whether **10** was formed in more than a modest yield in these experiments and **10** is therefore still regarded as the main reason why the *C/O*-alkylation ratio in the Huckin–Weiler reaction is higher than in the reaction of **7** with sodium hydride or lithium hydride. Finally, it appeared that monoenolates can replace the dienolate **10** and boost the *C/O* ratio. When the concentration of **7** was increased from ca. 0.2 to 1.0 M in its reaction with sodium hydride, the *C/O* ratio increased from 0.42 to 0.66. A much stronger effect was obtained from the monosodium enolate made from methyl acetoacetate. Thus, treatment of a 6.7:1 mixture of methyl acetoacetate (0.8 M) and **7** with sodium hydride (8.1 equiv.) in THF led to the ring-closure of **7** in which *C*-alkylation was strongly favoured (*C/O* = 17). Since the intermolecular reaction was negligible, this technique seems to be preparatively useful. A detailed evaluation will be published in due course.

Some analogous ring-closures have been described in the literature and the *C/O* ratios seem to be strongly dependent on the structures of the starting materials. 6-Bromo-3,3-dimethyl-2-hexanone gives > 95 % *C*-alkylation[6] and from 6-bromo-4,4-dimethyl-2-hexanone, reacting via the Δ^1-enolate under non-equilibrating conditions, only the *C*-alkylation product was reported.[7] The same applies to a bromo ketone in which two of the carbons between the reacting ends are part of a cyclohexane ring;[7] however, a similar case involving a cyclopentane ring gave a *C/O* alkylation ratio of ca. 1.[8] β-Keto sulphones analogous to our β-keto esters **7** and **8** have been cyclized under various basic conditions and the *C/O*-alkylation ratio was found to vary between 1.5 (KH, toluene) and 0.33 (triethylbenzylammonium hydroxide, H_2O–CH_2Cl_2).[9] The cyclization of a phenyl-substituted analogue, 6-bromo-3-phenyl-1-phenylsulfonyl-2-hexanone, was much more dependent on the reaction consitions.[10] In conclusion, simple bromo ketones follow Baldwin's rules for ring-closure[6] to six-membered rings and give cyclohexanones with high selectivity, but the *C*-alkylation becomes less favoured when an ester or sulfone group also is bonded to the anionic α-carbon.

Experimental

General conditions have been presented elsewhere.[11] ^{1}H and ^{13}C NMR spectra were run in $CDCl_3$. Kieselgel 60 (70–230 mesh, Merck) was used in the separations and purifications.

Preparation of halo keto esters.

Ethyl (2S)-2-[(2-bromo-1-methoxy)ethoxy]propanoate. A mixture of 2-bromo-1,1-dimethoxyethane (10.0 g, 59 mmol) and acetyl bromide (6.6 g, 54 mmol) was heated at 45 °C (2 h) and then cooled in an ice-bath. To the resulting crude α-bromo ether was added dropwise a stirred and cooled (0 °C) solution of ethyl (*S*)-lactate (6.0 g, 51 mmol) and *N*-ethyldiisopropylamine (7.5 g, 58 mmol) in dichloromethane (50 ml) such that the temperature did not exceed 10 °C. After further reaction at 22 °C for 2.5 h, most of the solvent was evaporated off and diethyl ether was added (140 ml). The precipitate was filtered off and the organic phase was washed with water (2×15 ml) and with saturated aqueous sodium hydrogen carbonate (15 ml). Drying (Na_2SO_4), evaporation of the solvent and distillation of the residue (64–68 °C, 4×10^{-3} Pa) afforded a 62 % yield of the title compound as a 46:54 mixture of diastereomers (GLC, ^{13}C NMR); GLC purity, 95 %. ^{1}H NMR: δ 4.67 (m, 1 H), 4.0–4.4 (m, 3 H, including a t at 4.15) 3.2–3.5 (m, 5 H,

including CH_3O singlets at 3.37 and 3.40), 1.41 (d), 1.39 (d), 1.27 (t) (in all 6 H). ^{13}C NMR: δ 172.5, 172.4, 102.3, 101.6, 71.9, 71.3, 60.9, 53.8, 53.2, 30.9, 30.7, 18.5, 14.1 ($CDCl_3$ signal at δ 77.17 as reference).

tert-*Butyl (4S)-4-(2-bromo-1-methoxyethoxy)-3-oxopentanoate* (**4**) was prepared from the ethyl ester described above (10.2 g) according to method A of Ohta *et al.*;[12] distillation at 55–60 °C/1×10^{-3} Pa gave 12.2 g (94 %) which was 90–95 % pure (^{13}C NMR). ^1H NMR: δ 4.72 (t, 0.5 H), 4.66 (t, 0.5 H), 4.30 (q, 0.5 H), 4.12 (q, 0.5 H), 3.60–3.30 (m, 7 H, including α-CH_2 and CH_3O singlets at 3.59 and 3.41, respectively), 1.6–1.3 [m, 14 H (theoretically, 12 H)]. ^{13}C NMR: δ 204.5, 204.2, 166.6, 166.4, 102.7, 102.4, 81.6, 78.7, 78.5, 55.3, 53.4, 46.3, 45.9, 31.2, 30.8, 28.0, 17.7, 17.0.

Methyl 7-bromo-3-oxoheptanoate (**7**). The reaction between methyl acetoacetate (2.56 g, 22 mmol), sodium hydride and butyllithium was performed as described.[4] 1,3-Dibromopropane (4.44 g, 22 mmol), dissolved in THF (5 ml) was added (5 s). After reaction at 0 °C (20 min), the reaction mixture was poured onto a stirred mixture of ice, 1 M hydrochloric acid (33 ml), and brine (25 ml). Diethyl ether was added, the mixture was shaken and the phases were separated. After two additional extractions with diethyl ether, the organic phases were combined and dried (Na_2SO_4). The solvents were evaporated and volatile components were distilled off (< 40 °C, $p > 2$ Pa) to give a residue (2.4 g) which (^1H NMR) contained **7** and the keto ester derived from **10** as the main products in the approximate molar ratio 1:1. Separation of this on silica gel (3×22 cm) using chloroform as the eluant gave ca. 1.1 g of **7** (21 %). The best fraction showed a GLC purity of 96 %. ^1H NMR: δ 3.74 (s, 3 H), 3.46 (s, 2 H), 3.41 (t, 2 H), 2.60 (t, 2 H), 1.87 (m, 2 H), 1.77 (m, 2 H); evidence for an enol form (ca. 10 %): δ 4.99 (s), 3.73 (s), 2.17 (t). ^{13}C NMR: δ 202.0 (s), 167.5 (s), 52.3 (q), 48.8 (t), 41.7 (t), 33.2 (t), 31.7 (t), 21.8 (t); evidence for an enol form: δ 177.8 (s), 89.0 (d), 51.0, 33.2, 24.7 ($CDCl_3$ signal at δ 77.17 as reference).

tert-*Butyl 7-bromo-3-oxoheptanoate* (**8**) was prepared essentially following Ohta's method A;[12] distillation at 90 °C (5×10^{-3} Pa) gave 1.36 g (16 %) of **8** which was ca. 95 % pure (^1H NMR, ^{13}C NMR). The low yield was due to the use of partly deteriorated butyllithium. ^1H NMR: δ 3.40 (t, 2 H), 3.34 (s, 2 H), 2.57 (t, 2 H), 2.0–1.6 (m, 4 H), 1.46 (s, 9 H). ^{13}C NMR: δ 202.5, 166.3, 81.8, 50.5, 41.6, 33.1, 31.8, 27.9 (CMe_3), 21.9; evidence for an enol form (8 %): δ 90.7, 28.3 (CMe_3) ($CDCl_3$ signal at δ 77.17 as reference).

Ethyl 7-chloro-3-oxoheptanoate (**9**) was prepared (72 %) from 5-chloropentanenitrile, zinc and ethyl bromoacetate according to the technique of Hannick and Kishi.[13] The ^1H and ^{13}C NMR data were indistinguishable from those given by Lambert *et al.*[14]

Ring-closures. Experiments were generally performed on a 0.2–0.3 g scale. Reaction conditions are given below. In the general work-up procedure, the reaction mixture was cooled in ice–water and then poured into a stirred mixture of large volumes of water (containing acid when a large excess of base was used in the ring-closure) and dichloromethane (sometimes diethyl ether). If the aqueous phase was strongly alkaline, dilute hydrochloric acid (0.1 M) was added until the preferred pH was reached (pH 8–9). The aqueous phase was extracted three times with the organic solvent and the organic phases were combined and dried (Na_2SO_4).

Commercial potassium *tert*-butoxide was added to solutions of **4** (0.6 M), **8** (0.25 M) or **9** (0.3 M) in dry THF (1.3, 1.5 and 1.5 mol equiv. of base, respectively). Reactions were performed at 45 °C (2 h), 22 °C (1.5 h) and 66 °C (1.3 h), respectively.

Lithium *tert*-butoxide was prepared in THF from *tert*-butyl alcohol (1.7 mol equiv.) and 1.6 M butyllithium in hexane (1.1 mol equiv.). The reaction of **4** (0.45 M) was run at 66 °C (4 h).

Sodium methoxide (1.3 mol equiv.) and sodium ethoxide (1.5 mol equiv.) were prepared from sodium and the appropriate alcohol and were used at 65 °C (2.5 h) and 78 °C (0.5 h), respectively. Lithium methoxide (1.8 mol equiv.) was made from lithium hydride and methanol and was used at 22 °C (17 h).

Commercial magnesium ethoxide (5.0 mol equiv.) was used in *N,N*-dimethylformamide at 85–90 °C for 2 h.

Sodium hydride (1.2 mol equiv., 55 % in mineral oil) and lithium hydride (1.3 mol equiv.) were used in refluxing THF (0.5 h). The latter reaction gave only ca. 70 % conversion (GLC).

Magnesium oxide (5.0 mol equiv.) was added to dimethyl sulfoxide (DMSO) (ca. 2 ml) of which about 1 ml was then distilled off. Compound **9** (0.21 g) was added and was allowed to react at 165 °C for 0.5 h. About 100 ml of water and 2×20 ml of diethyl ether were used in the work-up.

Identification of products and determination of C/O *ratios.* The products obtained from **4** (2.0 g, 6.2 mmol, NaOMe as base) were separated on silica gel. A 9:1 (v:v) mixture of 2,2,4-trimethylpentane and ethyl acetate first eluted **5** (0.80 g, 53 %) as a ca. 1:1 mixture of α and β anomers. A 3:1 mixture of these solvents then sequentially eluted the two anomers of **6** (in all 0.25 g, 17 %, ca. 1:1 ratio, R_F 0.28 and 0.17 on TLC in the same system).

tert-*Butyl (2S)-6-methoxy-2-methyl-3-oxotetrahydropyran-4-carboxylate* (**5**). ^1H NMR: δ 12.2 (s, 0.7 H), 4.83 (dd, 0.4 H, *J* 4.4, 1.5 Hz), 4.57 (dd, 0.4 H, *J* 7.6, 3.2 Hz), 4.30 (m, 0.8 H), 3.50 (s, 1.5 H), 3.43 (s, 1.5 H), 2.8–1.9 (m, 2 H), 1.49 (s, 9 H), 1.42 (d, 3 H, *J* 6.8 Hz).

tert-*Butyl* (Z)-*(3S)-5-methoxy-3-methyl-1,4-dioxan-2-ylideneacetate* (**6**). ^{1}H NMR of first eluted isomer: δ 4.93 (partially obscured dd, 1 H, $J_1 + J_2$ = 13.2 Hz), 4.90 (d, 1 H, *J* 1.0 Hz), 4.51 (br q, *J* ca. 6.3 Hz), 4.39 (δ_A) and 3.85 (δ_B) (2 H, AB part of ABX spectrum, J_{AB} 12.2, J_{AX} 5.9, J_{BX} 7.5 Hz), 3.44 (s, 3 H), 1.47 (s, 9 H), 1.37 (d, 3 H, *J* 6.3 Hz). ^{1}H NMR of **6** (slower anomer): δ 4.90 (d, 1 H, *J* 1.0 Hz), 4.87 (partially obscured dd, 1 H, J_1 3.4 Hz), 4.40 (dq, 1 H, *J* 1.0, 5.9 Hz), 4.31 (δ_A) and 4.05 (δ_B) (2 H, AB part of ABX spectrum, J_{AB} 11.7, J_{AX} 3.4, J_{BX} 5.4 Hz), 3.46 (s, 3 H), 1.47 (s, 9 H), 1.43 (partially obscured d, 3 H).

The product mixtures obtained from **7–9** were analysed by capillary column GLC assuming equal response factors for all isomers. References: ethyl 2-oxocyclohexanecarboxylate (the corresponding methyl ester was made by transesterification) and a mixture of **11–13** (R = CH_3) obtained from δ-valerolactone and methyl lithio(trimethylsilyl)acetate.[15] Isomers **11** and **12** were described as products in the literature,[15] but we obtained also **13**, probably due to a more acidic work-up. GLC retention times in the methyl ester series (SE-52, 25 m, 130 °C): **12**, 4.73; **3** (*n* = 4), 5.31; **11**, 6.47; **13**, 9.01; **7**, 14.53 min. The GLC elution order of **11–13** (R = *tert*-butyl) was determined by GLC and the ^{1}H NMR spectra[15] of partially purified (silica gel) cyclised products.

tert-*Butyl 3,4-dihydro-2H-pyran-6-acetate* (**13**, R = *tert*-butyl) (a new product) showed ^{1}H NMR: δ 4.62 (t, 1 H, *J* 3.4 Hz), 4.06 (t, 2 H, 5.1 Hz), 2.92 (s, 2 H), 2.2–1.7 (m, 4 H, including a q at δ 1.83, *J* 5.1 Hz), 1.46 (s, 9 H). ^{13}C NMR: δ 169.8, 148.6, 98.8, 80.5, 66.4, 41.6, 28.1, 22.2, 20.3.

The GLC elution order of **11–13** (R = ethyl) was identical with that of the *tert*-butyl ester series and was evident from ^{1}H NMR spectra[15] of crude cyclisation mixtures obtained from **9** and t-BuOK on the one hand [major olefinic hydrogen at δ 4.80 (t, *J* 1.0 Hz)] and **9** and NaOEt on the other hand [major olefinic hydrogen at δ 4.66 (t, *J* 3.7 Hz)]. Except for the expected differences in retention time, the gas chromatograms of reaction mixtures containing **11–13** (R = CH_3) were similar to those in the ethyl ester series and were assumed to show the same elution order.

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