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1,2-Dibromoethane in the Synthesis of 2-Bromoesters: Bromination *vs* Alkylation.

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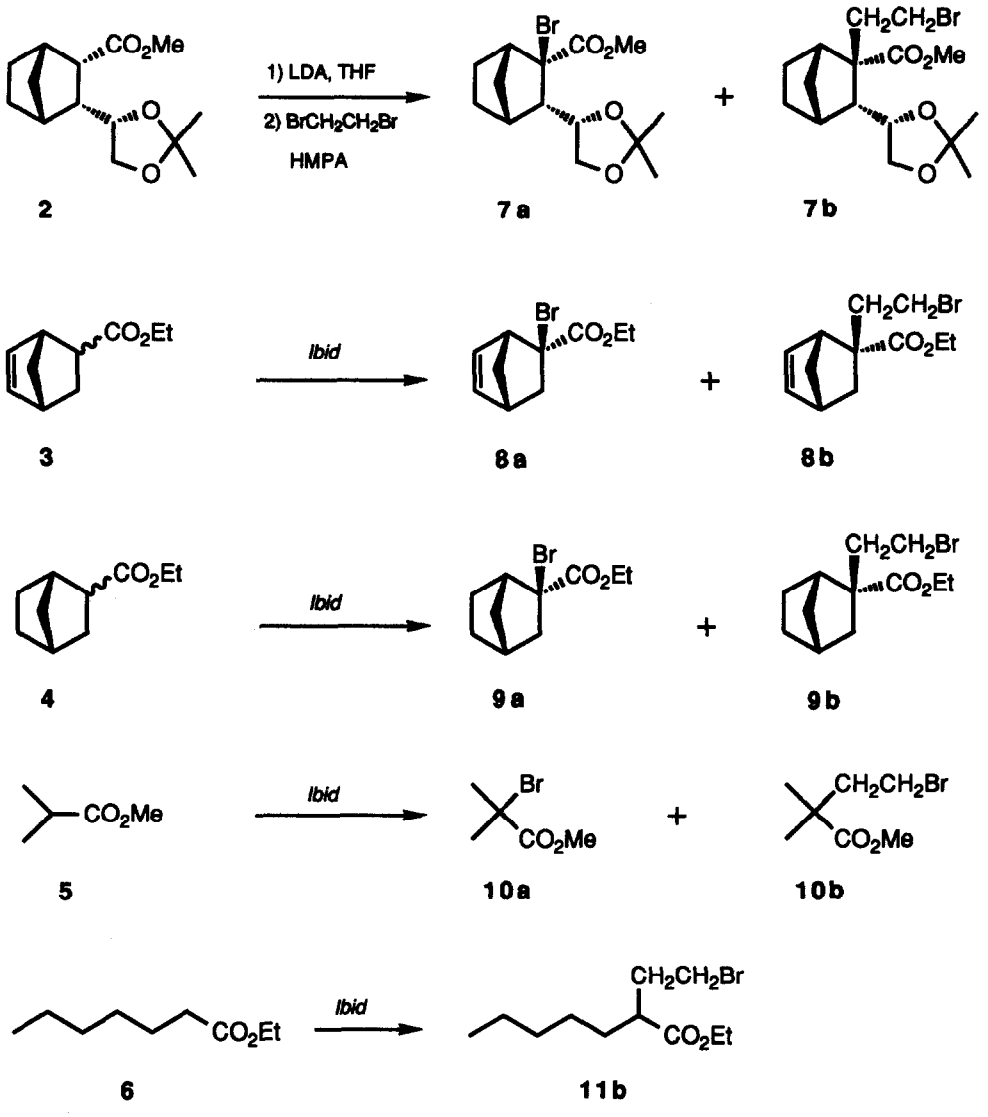
Abstract. *1,2-Dibromoethane has been employed as an efficient brominating agent of tertiary carbanions in sterically congested molecules, allowing the stereoselective synthesis of 2-bromoesters in mild conditions and being compatible with the presence of C-C double bonds. Alkylation is the predominating process when tertiary or secondary carbanions in flexible open chains were used. An interpretation of these facts is provided.*

INTRODUCTION

The most classical method to prepare 2-bromoesters is the Hell-Volhard-Zelinskii reaction of carboxylic acids[1] and subsequent esterification. Other methods involve the reaction of an ester enolate with bromine[2,3] or carbon tetrabromide.[3] 1,2-Dibromoethane, **1**, is a cheap and commercially available reagent which has been used for the formation of cyclopropanes,[4] in coupling reactions,[5] in *C*-,[6] *N*-,[7] and *O*-alkylation[8] reactions, as a protonating agent,[9] and as a brominating agent of 1-propenyllithium.[10] Another application lies in the finding that **1** appears to be superior to ethyl bromide as an entrainment reagent for the conversion of an unreactive halide into a Grignard reagent.[11] Nevertheless, as far as we know, only the works by Ourisson and coworkers on the bromination of lactones account for the ability of this reagent to brominate α-carbonyl positions.[12] These authors described the stereoselective introduction of bromine at the tertiary α-carbonyl position of bi-and tricyclic lactones, that is, in rigid systems, and in the presence of C-C double bonds which were not affected under the reaction conditions.

In connection with our research on the synthesis of carbocyclic nucleosides and related compounds through conjugated hemiesters as key intermediates,[13] we needed to introduce a good leaving group α to the ester in **2** (Scheme 1). Bearing the results of Ourisson in mind, we tried the introduction of bromine by using 1,2-dibromoethane, **1**, extending also the investigation to other esters.

In this paper we report a study on the preferential activity of **1** as a *C*-brominating or as *C*-alkylating agent in the reactions with the enolates of esters **2-6** (Scheme 1). Esters **2-4** have a tertiary α-carbon atom placed in a rigid bicyclic system. Ester **5** has also a tertiary position but in an open-chain structure, and ester **6** is a linear molecule containing, therefore, a secondary α-carbon.



Scheme 1

RESULTS AND DISCUSSION

The lithium enolates of esters **2-6** were reacted with 1,2-dibromoethane, **1**, in different conditions listed in Table 1. The obtained products, yield, and ratio of bromination *vs* alkylation is also shown.

Compound **2**[13] was made to react with LDA in THF at -78 °C to generate the corresponding enolate which was then reacted with **1** in the conditions shown in Table 1, entries 1-7, affording compounds **7a**[13] and **7b**.

Table 1. Reactions of enolates from esters **2-6** with 1,2-dibromoethane, **1**

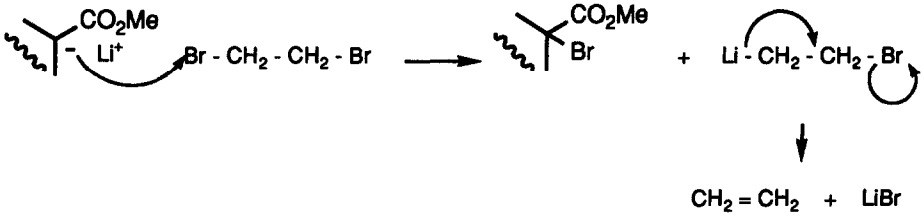
Entry	Ester	**1** nº eq	HMPA nº eq	Temperature (ºC)	Time (h)	Products	% Yield	% Recovery[a]	a:b Ratio[b]
1	**2**[c]	1.5	0	-78	3	----	0	100	-----
2	**2**[c]	6.0	0	-78	3	**7a , 7b**	13[a]	87	77 : 23
3	**2**[c]	1.5	0	0	3	**7a , 7b**	60[a]	40	60 : 40
4	**2**[c]	6.0	0	0	3	**7a , 7b**	60[a]	40	67 : 33
5	**2**[c]	1.5	7	-78	3	**7a**	60[a]	40	>99 : <1
6	**2**[c]	1.5	7	0	3	**7a , 7b**	78[d]	15	91 : 9
7	**2**[c]	20	7	0	5	**7a , 7b**	80[a]	20	91 : 9
8	**2**[e]	1.5	7	25	18	**7a , 7b**	51[a]	49	84 : 16
9	**3**[c]	1.5	7	0	4	**8a , 8b**	70[d]	13	88 : 12
10	**4**[c]	1.5	7	0	4	**9a , 9b**	16[a]	84	68 : 32
11	**4**[c]	1.5	7	25	4	**9a , 9b**	74[d]	10	72 : 28
12	**5**[c]	1.5	7	-78	3	**10a, 10b**	65[d]	---	17 : 83
13	**5**[c]	1.5	7	0	3	**10a, 10b**	69[d]	---	30 : 70
14	**6**[c]	1.5	7	0	3	**11b**	53[d]	30	<1 : >99

[a] Determined by GLC. [b] Determined by GLC for **7** and by ^{1}H NMR for **8-10**. [c] Lithium enolate. [d] Isolated yield. [e] Bromomagnesium enolate.

Several reaction conditions were tried in order to optimize the production of **7a**. While temperature and number of equivalents of **1** play a secondary role, the use of excess HMPA (7 eq) was crucial to accelerate the reaction and to favour the formation of the brominated derivative **7a** over **7b**. Thus, in the optimal conditions (1.5 eq of **1**, 0 ºC, 3 h. See Table 1, entry 6) a 10:1 mixture of **7a/7b** was obtained in 78% isolated yield along with 15% unreacted **2**. Longer reaction times did not improve the conversion yield. Product **7a**, obtained as a single stereoisomer, could be isolated by column chromatography and from their ^{1}H and ^{13}C NMR, and mass spectra.[13] The stereochemistry was assigned by assuming that the reaction takes place preferentially by the less hindered side of the norbornane moiety and by comparison with the result obtained in the alkylation of a related system by using **1**.[6d] The alkylated compound **7b** was identified in enriched chromatographic

fractions by means of their spectral data. For instance, the side-chain diastereotopic protons -C*H*$_2$Br gave very characteristic signals at 3.14 and 3.27 ppm as two sets of eight bands each, and MS also agrees with the structure proposed.

In these cases, bromination probably occurs via a metal-halogen exchange leading to the brominated product and 2-bromoethyllithium. This intermediate must evolve quickly towards the formation of lithium bromide and ethylene (Scheme 2). The thermodynamic stability of this last compound could provide the driving force that conducts the overall process.



Scheme 2

The influence exerted by the nature of metal accompanying the base used to generate the enolates was also investigated by employing bromomagnesium diisopropylamide.[14] In this case the reaction was much slower, probably due to the low solubility of the base in the reaction medium and the lower reactivity of the bromomagnesium enolate, but, in any case, the bromination product **7a** was predominant (Table 1, entry 8).

In a similar manner, reaction between ester **3**[15] and **1** at 0 °C for 4 h afforded a 8:1 mixture of **8a/8b** in 70 % isolated yield (Table 1, entry 9) and 13% recovered **3**. By-products arising from competitive processes involving the C-C double bond were not detected. Compound **8a** was obtained as a 93:7 mixture of epimers (only the major isomer is shown) as determined by capillary GLC-MS. In turn, ester **4**,[16] easily obtained from **3** by Pd/C catalyzed hydrogenation, was less reactive in those conditions, and only a 16% conversion was observed after 4 h at 0 °C. However, the yield was improved to 70% working at 25 °C, although in this case the ratio of alkylated product was higher than that obtained for the reaction of **2** in similar conditions. (Table 1, compare entries 8 and 11). Also in this case, the bromoderivative **9a** was produced as a mixture of epimers (91:9). Minor compounds **8b** and **9b** could not be isolated in pure form by chromatographic techniques and they were identified from respective enriched fractions in a similar manner as described above for **7b**.

The stereochemistry of the *exo*-bromo isomer in **8a** is sustained by the remarkable diastereotopicity observed in the ^{1}H NMR spectrum for the two methylene protons of the ethyl ester that can be explained by the close anisotropic double bond. These protons appear as an ABX$_3$ system giving a complex absorption. By the contrary, a quadruplet is observed for the signal of the related methylene protons for the major epimer in **9a**, in which the anisotropy owing to a double bond does not exist.

These results are in discrepancy with those reported by Ichihara *et al* on the alkylation of a related system by using **1**. Nevertheless, neither experimental details nor complete reaction conditions were given in this work.[6d]

Reaction with ethyl isobutyrate, **5**, was tried in order to verify the applicability of the bromination method to open-chain tertiary esters. In this case, however, the alkylation derivative **10b**[17] was obtained as a major

product, lower temperature favouring the alkylation over the bromination process leading to **10a**.[3,18] (Compare entries 11 and 12 in Table 1).

Finally, the reaction was performed on ethyl heptanoate, **6**, in which the α-carbonyl position is secondary. In this case, alkylated **11b** was formed as the only reaction product in 53% isolated yield, whereas the bromination product was not detected. Ester **6** is a new product but, unfortunately, could not be completely purified, remaining contaminated by traces of the starting material. Nevertheless, it was completely identified and characterized by their spectral data. (See Experimental Section).

CONCLUSIONS

1,2-Dibromoethane behaves towards ester enolates both as brominating or alkylating agent, in the presence of HMPA. The predominance of each process seems to depend on electronic and steric factors. Thus, tertiary carbon atoms are brominated better than secondary ones, and bromination prevails when the carbanion is located in a rigid system. Contrariwise, alkylation was the only observed process when a secondary carbanion in a linear chain was used. These findings account for the mechanistic pathway proposed for the bromination process to be favoured. On the other hand, tertiary carbanions in sterically congested molecules are less reactive according to the stereoelectronic requirements of a S_N2 process, which is probably involved in the alkylation reaction. This interpretation are also in accordance with the results described by Ourisson on the bromination of tertiary carbanions in rigid bi- and tricyclic lactone derivatives.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh). Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

General Procedure for reactions of esters 2-6 and 1,2-dibromoethane, 1. A typical experiment was run as follows. A 1.6 M solution of BuLi in hexane (2.0 ml, 3.6 mmol) was added dropwise to a solution of diisopropylamine (0.5 ml, 3.6 mmol) in anhydrous THF (15 ml) cooled at -78 °C, and the mixture was stirred for 30 min. Then a solution of ester **3** (300 mg, 1.8 mmol) in THF (10 ml) and HMPA (2.0 ml, 12.6 mmol) was subsequently added. After stirring for two hours to reach 0 °C, 1,2-dibromoethane (230 ml, 2.7 mmol) was added and the resultant solution was stirred at 0 °C for 4 hours, diluted with ethyl acetate and washed twice with diluted HCl and satured solution of NaCl, respectively. The organic solvents were removed and the residue was chromatographed (mixtures of hexane-ether) to afford 39 mg of recovered **3**, compound **8a** (234 mg, 62% yield) and compound **8b** (32 mg, 8% yield).

Ethyl (1*RS*,2*RS*,4*RS*)-2-bromobicyclo[2.2.1]hept-4-en-2-yl carboxylate, 8a. O.t. 75 °C (0.1 Torr); IR (film) 1736 cm^{-1}; MS, m/e 246-244 (M, 2), 181-179 (5), 91 (17), 66 (100), 65 (9); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.26 (t, J=7.3 Hz, CH_3), 1.75 (m, 1H), 2.07 (m, 1H), 2.34-2.38 (complex absorption, 2H), 2.91 (m, 1H), 3.36 (m, 1H), 4.15-4.16 (dq, J=12.7 Hz, J'=7.3 Hz, OCH_2), 5.94 (dd, J= 5.5 Hz, J'=2.9 Hz, 1H), 6.25 (dd, J= 5.5 Hz, J'= 2.9 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 13.8, 41.9, 42.6, 48.1, 53.8,

61.5, 62.6, 132.5, 140.5, 170.4 (CO_2CH_3). HRMS m/e Calcd. for $C_{10}H_{13}O_2Br$: 244.0098. Found: 244.0093.

Ethyl (1*RS*,2*RS*,4*RS*)-2-bromobicyclo[2.2.1]heptan-2-yl carboxylate, 9a. O.t. 85 °C (0.2 Torr); IR (film) 1736 cm-1; MS, m/e 203-201 (M-45, -OCH_2CH_3, 1), 169-167 (82),121 (16), 101 (32), 93 (66), 67 (100); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.09-1.23 (complex absorption, 2H), 1.29 (t, J=7.3 Hz, CH_3), 1.40-1.60 (complex absorption, 4H), 2.13 (m, 1H), 2.32 (m, 1H), 2.51 (dd, J=14.3 Hz, J'=2.6 Hz, 1H), 2.75 (m, 1H), 4.23 (q, J=7.3 Hz, OCH_2); 62.5-MHz ^{13}C NMR ($CDCl_3$) 13.9, 24.8, 27.6, 37.5, 38.2, 45.3, 48.9, 61.6, 66.0, 170.8 (CO_2CH_3). HRMS m/e Calcd. for $C_{10}H_{15}O_2Br$: 246.0255. Found: 246.0270.

Methyl 2-bromo isobutyrate, 10a.[3,18] Previously undescribed spectrum follows: 62.5-MHz ^{13}C NMR ($CDCl_3$) 25.0, 43.6, 53.1, 177.1 (CO_2CH_3).

Methyl 4-bromo-2,2-dimethyl butanoate, 10b.[17] Previously undescribed spectra follows: MS, m/e 179-177 (M-31, -OCH_3, 2), 151-149 (14), 102 (100), 69 (70), 43 (11), 41 (34); 250-MHz ^{1}H-NMR ($CDCl_3$) 1.18 (s, 6H, CH_3), 2.11 (m, 2H), 3.29 (m, 2H), 3.65 (s, 3H, OCH_3); 62.5-MHz ^{13}C NMR ($CDCl_3$) 25.0, 28.2, 30.8, 42.7, 51.9, 177.1 (CO_2CH_3).

Ethyl 2-(2'-bromoethyl)-heptanoate, 11b. B.p. 138-140 °C (25 Torr); IR (film) 1729 cm-1; MS, m/e 220-218 (M-45, -OCH_2CH_3, 6), 196-194 (35), 158 (57), 115 (27), 101 (100), 73 (39), 69 (36), 55 (48), 43 (22), 41 (51); 250-MHz ^{1}H-NMR ($CDCl_3$) 0.95 (t, J=6.9 Hz, CH_3), 1.10-1.58 (complex absorption, 11H), 1.92 (m, 1H), 2.20 (m, 1H), 2.54 (m, 1H), 3.26-3.44 (complex absorption, 2H), 4.13 (q, J=6.9 Hz, OCH_2); 62.5-MHz ^{13}C NMR ($CDCl_3$) 13.9, 14.2, 22.4, 26.6, 31.1, 31.5, 31.9, 34.9, 43.9, 60.4, 175.2 (CO_2CH_3).

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