Regiospecific Synthesis of α-Haloketones using α-Haloalkyllithium Reagents

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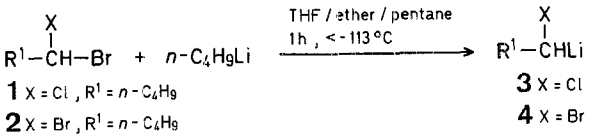
Although α-haloketones can be prepared by direct halogenation of the parent ketones[1], this method suffers from a lack of regiospecificity in cases where one of the alpha positions is not sterically hindered. Alternative methods of preparation are: (1) condensation of lithium dihalocarbenoids with carbonyl compounds followed by cyclisation of the resultant *O*-lithiated halohydrins to halooxiranes and isomerisation of the latter to α-haloketones[2,3] or (2) coupling of dichloromethyllithium with carbonyl compounds, treatment of the resulting halohydrins with a base, and hydrolysis[4].

We considered that the direct coupling of α-monohalocarbenoids with carboxylic acid derivatives should also lead to α-haloketones. Although α-halocyclopropylcarbenoids are well known and used in synthesis[5], the non-cyclic monohalocarbenoids have received less attention[6,7]. We have now optimised the conditions of our method to give a reproducible high-yield synthesis of the reagents **3** and **4** which are unstable above −100 °C.



Compounds **1** and **2** are easily prepared by alkylation of bromochloromethyllithium[8] and dibromomethyllithium[3], respectively. Bromine/lithium exchange[6,7] in **1** or **2** using *n*-butyllithium in tetrahydrofuran/ether/pentane at −115 to −113 °C gives the products **3** or **4** in 90% yield together with about 7% of the alkene R^1—CH=CH—R^1 resulting from C—C coupling during formation of the organometallic derivatives.

We have previously described the condensation of dichloro- and dibromomethyllithium[9] with esters to give good yields of α,α-dichloromethyl ketones. The same reaction with acid chlorides gave tertiary alcohols and their derivatives[10]. We have now extended these studies to the reactions of **3** and **4** with esters **5** and obtained the α-haloketones **8** regiospecifically in good yields (Table 1). The absence of tertiary alcohol products suggests (as in the case of the reactions of dihalocarbenoids) that the intermediate **6** is stable at low temperature and is converted to the ketone **8** by hydrolysis.

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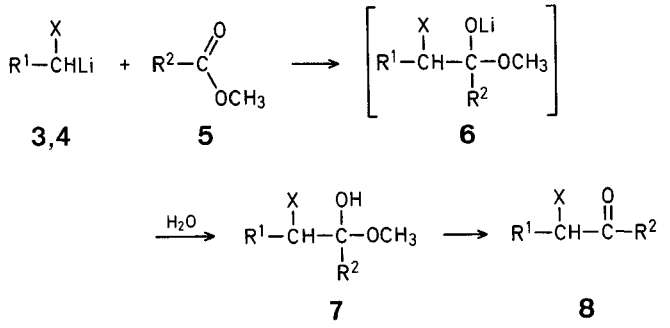


3,4 5 6

7 8

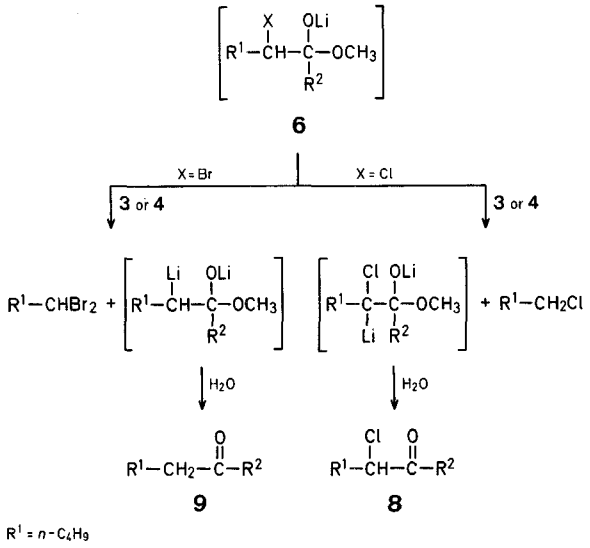
This reaction is directly analogous to that of the reagents **3** and **4** with methyl formate to give α-haloaldehydes[7], in which case the hemiacetal corresponding to **7** is also stable.

The presence of a bulky R^2 group (e.g. cyclohexyl) moderates the rate of the coupling reaction and side reactions, e.g., exchange when X = Br or metallation when X = Cl, of the CHX moiety of the intermediate **6** by the reagent **3** or **4**, become predominant. When X = Br, a major by-product is the non-halogenated ketone **9**. When X = Cl, use of an increased amount of **3** should improve the yield of the α-chloroketone **8**.

All products obtained were characterised by ^{1}H- and ^{13}C-N.M.R. spectrometry. G.L.C. analysis were performed with a Carlo Erba Fractovap 2150 chromatograph using a 2 m × 6 mm glass column packed with 10% SE 30 on chromosorb W-HMDS, 80–100 mesh. All reactions were carried out under a slight positive pressure of dry nitrogen.

3-Bromo-2-heptanone (8a; $R^1 = n$-C_4H_9, $R^2 = CH_3$, X = Br); Typical Procedure:

1,1-Dibromopentane (**2**; $R^1 = C_4H_9$, X = Br; 5.75 g, 0.025 mol), tetrahydrofuran (60 ml), diethyl ether (40 ml), and pentane (30 ml) are placed in a four-necked flask equipped with a mechanical stirrer, addition funnel, low temperature thermometer, and nitrogen inlet tube. 1.23 Molar *n*-butyllithium solution (21.1 ml) in hexane is added dropwise at −115 °C under stirring during 20 min. The solution becomes pale yellow in colour. Methyl acetate (**5**; $R^2 = CH_3$; 2.22 g, 0.022 mol) diluted with tetrahydrofuran (10 ml) is then added at −115 to −120 °C during 10 min and the temperature is then allowed to reach −100 °C during 30 min. Hydrolysis is performed rapidly by addition of 2 normal sulfuric acid (50 ml). The organic layer is extracted with hexane (3 × 50 ml) and the extract washed with saturated aqueous sodium chloride solution (2 × 50 ml). The organic layer is dried with magnesium sulfate. The solvents are removed and the residue is distilled at reduced pressure: yield: 3.1 g (64%); b.p. 87–90 °C/23 torr.



1-Bromo-1-chloropentane (1; $R^1 = n$-C_4H_9, X = Cl):

To a mixture of diisopropylamine (62 g, 0.6 mol), tetrahydrofuran (600 ml), pentane (300 ml), and diethyl ether (150 ml) is added 1.49 normal

Table. α-Haloketones **8** ($R^1 = n$-C_4H_9) prepared

Product No.	R^2	X	Yield [%]	b.p. [°C]/torr (n_D^{20})	Molecular formula[a] or Lit. b.p. [°C]/torr	^{1}H-N.M.R. (CCl_4/TMS) $\delta_{CHX\ CO}$ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS) $\delta_{C=O}$	$\delta_{CHX\ CO}$ [ppm]
8a	CH_3	Br	64	87–90°/23 (1.4590)	80°/9[12] (n_D^{20}: 1.4613)	4.10	201.2	54.4
8b	C_2H_5	Br	60	97°/18 (1.4559)	$C_8H_{15}BrO$ (207.1)	4.15	204.6	53.3
8c	*i*-C_3H_7	Br	32[b]	103°/20 (1.4580)	99–101°/19[11]	4.25	199.5	51.6
8d	—$(CH_2)_3$—Cl	Br	70	96°/0.7 (1.4807)	$C_9H_{16}BrClO$ (255.6)	4.15	201.9	52.3
8e	C_6H_5	Br	80	98°/0.3 (1.5380)	$C_{12}H_{15}BrO$ (255.2)	5.0	192.5	47.3
8f	2-furanyl	Br	78	90°/0.2 (1.5301)	$C_{10}H_{13}BrO_2$ (245.1)	4.85	193.9	47.8
8g	CH_3	Cl	62	69°/18 (1.4368)	$C_7H_{13}ClO$ (148.6)	4.03	202.9	64.3
8h	C_2H_5	Cl	67	78°/13 (1.4404)	$C_8H_{15}ClO$ (162.7)	4.1	205.8	63.6
8i	*i*-C_3H_7	Cl	44	89°/14 (1.4396)	$C_9H_{17}ClO$ (176.7)	4.15	199.5	61.7
8j	*t*-C_4H_9[c]	Cl	trace	105°/15	—	—	—	—
8k	—$(CH_2)_3$—Cl	Cl	66	77°/0.3 (1.4653)	$C_9H_{16}Cl_2O$ (211.1)	4.2	203.9	63.7
8l	C_6H_5	Cl	75	104°/0.5 (1.5224)	$C_{12}H_{15}ClO$ (210.7)	4.9	193.5	57.8
8m	2-furanyl	Cl	82	89–90°/0.3 (1.5062)	$C_{10}H_{13}ClO_2$ (200.7)	4.85	192.5	58.4

[a] Satisfactory microanalyses obtained: C ±0.42, H +0.30, Br ±0.31, Cl ±0.38.
[b] Formation of *n*-C_4H_9—$CHBr_2$ detected by G.L.C.
[c] The corresponding α-bromoketone is not formed.

solution of *n*-butyllithium in ether (370 ml, 0.55 mol) at −30 °C. The mixture is cooled to −90 °C, bromochloromethane (104 g, 0.8 mol) is added dropwise during 10 min, and stirring is continued for 1.5 h at < −88 °C. 1-Iodobutane (73.6 g, 0.40 mol) in diethyl ether (40 ml) is then added at −100 °C, followed by addition of a mixture of hexamethylphosphoric triamide (80 ml, 0.5 mol) and tetrahydrofuran (80 ml) with subsequent stirring at −100 °C for 2 h. The temperature of the mixture is then allowed to increase to −60 °C during 2 h. The mixture is hydrolysed by addition of 2 normal sulfuric acid (500 ml) and then extracted with technical grade hexane (3 × 150 ml). The extracts are washed with saturated sodium chloride solution (100 ml), saturated sodium thiosulfate solution (100 ml), and saturated sodium chloride solution (2 × 100 ml). The organic layer is dried with magnesium sulfate, solvents are removed under reduced pressure and the residual oil is distilled; yield: 65 g (87%); b.p. 88 °C/70 torr; n_D^{20}: 1.4696.

2-Chloro-1-phenyl-1-hexanone (8 l; $R^1 = n\text{-}C_4H_9$; $R^2 = C_6H_5$, X = Cl): 1-Bromo-1-chloropentane (**1**; 4.6 g, 0.025 mol) is diluted with tetrahydrofuran (60 ml), diethyl ether (40 ml), and pentane (30 ml). To this solution, cooled at −120 °C, is added dropwise a hexane solution of *n*-butyllithium (0.025 mol) *below* −113 °C. After the addition, agitation of the mixture is continued for 15 min at −115 °C and then methyl benzoate (**5**, $R^2 = C_6H_5$; 3.0 g, 0.022 mol) in diethyl ether (20 ml) is added at −120 °C. After 15 min, the temperature of the mixture is allowed to reach −100 °C during 1 h. Hydrolysis is achieved by addition of 2 normal sulfuric acid (50 ml). Extraction with technical grade hexane (3 × 50 ml), washing of the extract with saturated sodium chloride solution (2 × 50 ml), and drying with magnesium sulfate are followed by evaporation of the solvents at reduced pressure. Distillation of the oily residue gives the product **8l**; yield 2.88 g (75%); 104 °C/0.5 torr; n_D^{20}: 1.5224.

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