Short Communication

(Trimethylsilyl)methyl Ketones in the Synthesis of Bromomethyl and Chloromethyl Ketones

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Selective formation of halomethyl ketones by direct halogenation of a methyl ketone may be difficult to effect when the other α carbon also carries a hydrogen atom, because the course of the reaction is decided by the formation of a reactive enol intermediate which may be generated from either α carbon. A few indirect methods to get around this problem have been reported.[1–4] We describe here a method for the synthesis of bromomethyl and chloromethyl ketones from (trimethylsilyl)methyl ketones. The latter belongs to the class of β-keto silanes which are important synthons and readily available.[13]

$$\underset{1}{RCOCH_2SiMe_3} \xrightarrow[\text{or } SO_2Cl_2/CH_2Cl_2]{Br_2/CCl_4} \underset{2}{RCOCH_2X}$$

1a R = Ph, *1b* R = i-Pr, *1c* R = Pent, *1d* R = cycloHex, *1e* = CH_2Ph, *1f* = $CH_2CH_2CO_2Me$, *1g* = 2-Furyl; *2* X = Br,Cl.

When the (trimethylsilyl)methyl ketone is treated with bromine or sulfuryl chloride, cleavage of the carbon-silicon bond results in the formation of the corresponding halomethyl ketone. Our approach was, in particular, based on an old report that the C-Si bond in ethyl (trimethylsilyl)acetate was readily cleaved by bromine,[14] that the oxidation of 5-trimethylsilyl-4-octanol with chlorine in dimethylsulfoxide gave 5-chloro-4-octanone as the major product,[15] and that, generally, the C-Si bond in allyl and arylsilanes is readily cleaved by bromine or iodine.[5,6]

Good yields of the halomethyl ketone *2* in the halodesilylation were obtained (Table). The corresponding methyl ketone was sometimes a by-product (usually in the range 1–10 % by GLC and ^{1}H NMR estimations). No systematic study was undertaken to avoid its formation. Addition of 0.1–0.2 molar equivalent of triethylamine or 2,6-lutidine had little effect on the methyl ketone formation but was advantageous for the formation of the halomethyl ketone; whereas, the presence of equimolar amounts of the amine reduced the yield. Polyhalogenation was not an important side reaction, but products from such reactions could be detected by GLC-MS and sometimes by ^{1}H NMR. Thus, the ^{1}H NMR spectrum of the crude material from the reaction between *1a* and sulfuryl chloride showed a singlet at 6.58 ppm besides the expected signals from α-chloroacetophenone, which indicated the presence of some α,α-dichloroacetophenone.[16]

The halotrimethylsilane, which was one of the products from the reaction, can catalyze the isomerization of the halomethyl ketone. This was avoided by removal of the silane together with the solvent at low pressure and temperature when the reaction was complete. In the reaction between *1c* and bromine an attempt to remove bromotrimethylsilane and the solvent by distillation at atmospheric pressure resulted in substantial isomerization of 1-bromo-2-heptanone to the thermodynamically more stable 3-bromo-2-heptanone[1d] (^{1}H NMR, MS-GLC).

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Table. Formation of halomethyl ketones from (trimethylsilyl)methyl ketones.

Substrate	Product	Reagent solv.[a]	Base/M equiv.	Isolated yield/%	Purity[b]/ %	^{1}H NMR (CCl_4) $-CH_2X$/ppm	M.p./°C or B.p./mmHg/°C
1a[17]	$PhCOCH_2Cl$[25]	A	–	64	99	4.53	56*
	$PhCOCH_2Br$[26]	B	–	81	99	4.30	50*
1b[19]	i-$PrCOCH_2Cl$[27]	A	0.2 NEt_3	64	97(2)[c]	4.20[d]	86/80
	i-$PrCOCH_2Br$[28]	B	–	70	96(3)[c]	3.97[d]	86–90/40
1c[8]	$PentCOCH_2Cl$[20]	A	0.2 NEt_3	76	93(2)[c]	3.95	76–78/12–15
	$PentCOCH_2Br$[29]	B	–	55	99	3.85	87–89/15
1d[21]	$CyclohexCOCH_2Cl$[1]	A	0.2 NEt_3	78	89(10)[c]	4.17[d]	90/0.1[e]
1e[22]	$PhCH_2COCH_2Cl$[30]	A	–	89	75(25)[c]	4.10	100/0.2[e]
	$PhCH_2COCH_2Br$[12]	B	–	91	95(5)[c]	3.90	100/0.1[e]
1f	$MeO_2CCH_2CH_2COCH_2Cl$[22]	A	–	88	87(13)[c]	4.20	100/0.2[e]
	$MeO_2CCH_2CH_2COCH_2Br$[22]	B	–	90	99	4.00	100/0.1[e]
1g	2-Furyl $COCH_2Br$[24]	B	–	64	99	4.35	60–63/0.3

[a] A = SO_2Cl_2/CH_2Cl_2, B = Br_2/CCl_4. [b] GLC, area %. [c] % protiodesilylated methyl ketone. [d] Solvent $CDCl_3$. [e] Kugelrohr distillation.

Experimental

The methyl ketone derivatives were analyzed by GLC on a 3% SP-2100 column and were identified by comparison with authentic samples. The ^{1}H NMR spectra were recorded at 60 MHz or 300 MHz and the mass spectra at 70 eV ionizing voltage and are presented as *m/z* (% res. int.).

Preparation of (trimethylsilyl)methyl ketones, 1. The compounds *1* were prepared from trimethylsilyl)methylmagnesium chloride by reaction with the respective acid anhydride.[17]

Benzyl (trimethylsilyl)methyl ketone, 1e.[18] The yield of *1e* was 44%. ^{1}H NMR (CCl_4): δ 0.17 (Me_3Si), 2.18 (CH_2Si), 3.55 (CH_2Ph), 7.22 (Ph). MS: 206 (9, M), 191 (14), 117 (18), 115 (65), 91 (12), 73 (100).

2-Methoxycarbonylethyl (trimethylsilyl)methyl ketone, 1f. The yield of *1f* was 70%. Anal. $C_9H_{18}O_3Si$: C,H. ^{1}H NMR (CCl_4): δ 0.17 (Me_3Si), 2.10 (CH_2Si), 2.5 (CH_2CH_2, m), 3.55 (OMe). MS: 202 (99, M), 187 (31), 171 (98), 115 (61), 99 (100).

2-Furyl (trimethylsilyl)methyl ketone, 1 g. The yield of *1g* was 60%. Anal. $C_9H_{14}O_2Si$: C,H. ^{1}H NMR (CCl_4): δ 0.17 (Me_3Si), 2.47 (CH_2Si), 6.42 (H-4′), 6.98 (H-3′), 7.42 (H-5′). MS: 182 (38, M), 181 (23), 167 (43), 139 (16), 125 (55), 75 (100).

General procedures for the preparation of halomethyl ketones, 2. *Method I. No base added:* The (trimethylsilyl)methyl ketone (10 mmol) was dissolved in dry tetrachloromethane (20 ml) at −20°C or dry dichloromethane (20 ml) at 0°C. The halogenating agent (10 mmol) in dry tetrachloromethane (10 ml) or dry dichloromethane (10 ml) was added dropwise with stirring (N_2). The stirring was continued at ambient temperature for 30–60 min and the solvent and the trimethylhalosilane removed at reduced pressure without heating. The crude product was purified by distillation or crystallization.

Method II. Presence of triethylamine: The (trimethylsilyl)methyl ketone (10 mmol) and triethylamine (2 mmol) were dissolved in dry tetrachloromethane (20 ml) at −20°C or dry dichloromethane (20 ml) at 0°C. The halogenating agent

(10 mmol) in dry tetrachloromethane (10 ml) or dry dichloromethane (10 ml) was added dropwise with stirring (N_2). The mixture was stirred at ambient temperature for 30–60 min, shaken with aqueous $NaHCO_3$ (2x) and water before the dried ($MgSO_4$) solution was evaporated at reduced pressure. The crude product was purified by distillation.

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