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Halogenation of Enamines. II.* Regiospecific Synthesis of Halomethyl Ketones

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A simple procedure for regiospecific synthesis of bromomethyl and chloromethyl ketones by halogenation of morpholine enamines from unsymmetric methyl ketones is described. By regioselective deprotonation of immonium salts, mixtures of tautomeric enamines were transformed to the enamine isomer with a terminal double bond. This isomer was allowed to react with elementary halogen at low temperature, followed by hydrolysis at room temperature to yield the halomethyl ketone. Yields of bromomethyl ketones were 74–90 % and of chloromethyl ketones 45–79 %. Attempts at extending the method for synthesis of α-haloalkyl methyl ketones or dihalomethyl ketones were not successful.

Halomethyl ketones are difficult to prepare by direct halogenation of the parent ketone. Under acidic conditions substitution usually takes place at the most substituted site and not at the methyl group. Under basic conditions polyhalogenation of the methyl group occurs [2] with haloform cleavage. For some ketones, acid catalysed bromination in the presence of methanol has been reported to give enhanced yields of bromomethyl ketones.[3] Usually, however, indirect routes have been employed for halomethyl ketone synthesis, *e.g.*, reaction of diazomethyl ketones with hydrogen halide,[2b, 4] halogenation of imines,[5] photobromination of epoxides,[6] reaction of aldehydes with dihalomethyl lithium [7] and bromination of trimethylsilyl enol ethers.[8] Previous papers from this laboratory describe the syntheses of some halomethyl ketones from methyl ketone enamines.[1,9] The present paper presents an extension of the method to enamines derived from six different methyl ketones.

* Part I, *cf.* Ref. 1.

METHODS

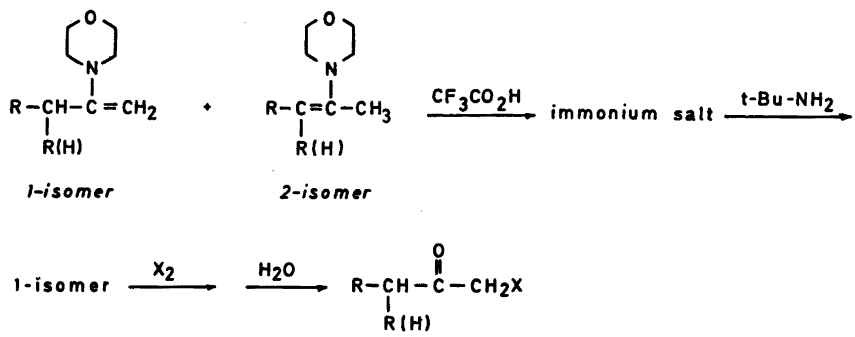
Scheme 1 summarizes the reactions used for regiospecific synthesis of halomethyl ketones. Mixtures of tautomeric enamines obtained from methyl ketones and morpholine were transformed to the enamine isomer with a terminal double bond (1-isomer) using a method for regioselective deprotonation of immonium salts.[10] Protonation of the tautomeric mixture with trifluoroacetic acid to give the immonium salt and deprotonation of the immonium salt with *tert*-butylamine to give the 1-isomer were conducted in pentane. In the subsequent halogenation two different procedures were used:

(1) Either the crude pentane solution of the enamine, after removal of the precipitated *tert*-butyl ammonium salt, was added to a solution of the halogen (bromine in dichloromethane or chlorine in chloroform) (*Method A*) or

(2) the enamine was freed from pentane and redissolved in either dichloromethane or chloroform prior to the addition to the halogen (*Method B*). (For a discussion on the choice of solvent see Refs. 1,9).

Method B was employed with chlorine to avoid uncontrolled radical chlorination of pentane. Isobutyl methyl ketone enamine, which isomerises rapidly in chloroform,[10] was halogenated by *Method A* both with bromine and chlorine. During chlorination of this enamine the reaction flask was protected from light.

The haloketones obtained by these procedures were identified by gas chromatography on two different columns (see Experimental) using authentic samples of the ketones prepared by independent routes as references. The



Scheme 1.

product distributions determined by GC were in agreement with ^{1}H NMR spectra obtained from small-scale pilot experiments of the enamine halogenation procedure.

Attempts at using a direct one-flask procedure, *i.e.*, treating the tautomeric enamines consecutively with trifluoroacetic acid, *tert*-butylamine and halogen afforded only poor yields of halomethyl ketones.

RESULTS

Table 1 gives the yields of halomethyl ketones obtained by the procedure in Scheme 1. Unless otherwise stated, the yields were determined by gas chromatography using the internal standard technique. The somewhat lower yields obtained by *Method A* are explained by the incomplete recovery of enamine after the protonation–

Table 1. Halogenation of enamines from alkyl methyl ketones, $RCOCH_3$.

Parent ketone R	Halogen	Method [a]	Yields [e] Halomethyl ketone	Parent ketone	3-Monohalo-ketone	Dihalo-ketone [f]
Isobutyl	Br	A	73	3	3	5
	Br	A [b]	79	0	3	1
	Cl	A	58	7	5	5
Neopentyl [c]	Br	B [d]	90	5	2	0
	Cl	B [d]	79	9	0	8
Isopropyl	Br	A	74	4	3	6
	Br	B	83	5	2	4
	Cl	B	72	0	0	4
Cyclopropyl [c]	Br	B	82	0	0	5
	Cl	B	69	11	0	3
Cyclopentyl	Br	A	83	2	0	5
	Cl	B	45	13	8	11
Cyclohexyl	Br	A	78	4	0	6
	Br	B	93	5	2	0
	Cl	B	74	7	1	0
	Cl	B [b]	69	9	<1	0

[a] A: 1-isomer in pentane solution was added to the halogen, B: isolated 1-isomer dissolved in CH_2Cl_2 or $CHCl_3$ was added to the halogen; [b] isolated yield in preparative scale run; [c] the enamine gives only the 1-isomer (*cf.* Ref. 10); [d] rate of hydrolysis is slow and a reaction time of 1–1.5 h was necessary to complete hydrolysis; [e] yields (%) determined by GC unless otherwise stated; [f] the individual distributions of 1,1-dihaloketones and 1,3-dihaloketone are not shown. The 1,1-dihaloketone was the most abundant in all cases.

deprotonation step. The yields given with *Method A* are calculated from the amount of starting enamine mixture but the yields with *Method B* refer to the amount of isolated 1-isomer. Neither method showed any difference in yield using isolated 1-isomer.

Attempts at extending the scope of enamine halogenation to include the regiospecific synthesis of dibromomethyl ketones, analogously to what has been described for isopropyl methyl ketone enamine,[11] have not been successful. Screening experiments with cyclopropyl methyl ketone enamine to determine the influence on yield of different experimental factors using a factorial design [12] followed by a Simplex optimisation strategy [13] with the most important factors, increased the yield of dibromomethyl cyclopropyl ketone from 16 to 47 %. However, the improvement was not considered significant enough for extension of the study to the other enamines in Table 1 and the method was not further explored.

The 2-isomer of some secondary alkyl methyl ketone enamines can easily be separated from an isomer mixture by selective protonation of the 1-isomer.[14] To investigate whether this technique could be used to achieve regiospecific synthesis of 3-halo-substituted methyl ketones, the halogenation of the 2-isomer of isopropyl, cyclopentyl and cyclohexyl methyl ketone enamines were studied using *Method B*. Chlorination of the 2-isomers afforded complex mixtures of mono-, di- and trichloro ketones together with considerable amounts of the parent ketone. Bromination afforded 93 % of α-bromoisopropyl methyl ketone (isolated yield), 61 % of α-bromocyclopentyl methyl ketone and 65 % of α-bromocyclohexyl methyl ketone. With cyclopentyl and cyclohexyl methyl ketone enamines *ca.* 5 % of the bromomethyl ketone and *ca.* 10 % of the 1,3-dibromo ketone were formed.

CONCLUSION

The only method of general scope, hitherto described, for regiospecific synthesis of halomethyl ketones is the reaction of diazomethyl ketones with hydrogen halide.[4] Yields obtained by the diazoketone route are very similar to what has been obtained in the present enamine procedure. Direct bromination of cyclohexyl methyl ketone,[3] cyclopropyl methyl ketone (see Experimental) and isopropyl methyl ketone [3] in anhydrous methanol is for these ketones probably more convenient than the enamine procedure. Other methods of more limited scope utilize less readily available chemicals (*e.g.* 1,2-epoxides,[6] dihalomethyl lithium,[7] silyl enol ethers [8]). In this perspective the monohalogenation of the regioselectively generated 1-isomer of methyl ketone enamines may be considered a preparatively useful method for the regiocontrolled synthesis of halomethyl ketones. The method may, for simple ketones, replace the diazoketone procedure and thereby eliminate the hazards involved in handling excessive amounts of diazomethane.

Monohalogenation of the 2-isomer is not useful for preparative purposes. The monobromoketones thus obtained are more easily prepared by direct halogenation of the parent ketone with *N*-bromo succinimide [15] or by acid catalyzed bromination.[16]

EXPERIMENTAL

The enamines were prepared by the titanium tetrachloride method [17] with the modifications previously reported.[18] Yields of isolated enamine were 75 – 90 %. Solvents were either *puriss.* or *p.a.* qualities and reagents were *purum* or *pro synth.* qualities. Solvents and reagents were used as delivered without further purification. Gas chromatographic analyses were performed on a PYE M 64 gas chromatograph, 10 % APM on Chromosorb W-AW 100 – 120 mesh (270 cm, 4 mm i.d.) and 10 % QF-1 on Chromosorb W-AW 100 – 120 mesh (210 cm, 2 mm i.d.) columns being used. Chromatograms were recorded on a Houston Instrument integrating recorder. Integrated peak areas were used in quantifications. Accuracies in yield determination can be estimated to ± 3 %.

Reference samples for GC identification and for calibration of FID responses of the ketones given in Table 1 were prepared by established procedures with the exception of chloromethyl cyclohexyl ketone and chloromethyl cyclopentyl ketone which were identified by their ^{1}H NMR spectra [19] obtained from small scale enamine halogenation. Calibration of FID responses for these ketones was performed using the isomeric α-chlorocycloalkyl methyl ketone.[20] *Bromomethyl cyclopropyl ketone* is not previously described. It was prepared by bromination of cyclopropyl methyl ketone in dry methanol analogously to the procedure in Ref. 7 b. Yield 70 %, b.p. 70 – 72 °C/18 mmHg, ^{1}H NMR (60 MHz,

CCl_4): δ 3.92 (s, 2H), 2.20 (m, 1H) and 0.83 – 1.07 (m, 4H), IR (neat film) (cm^{-1}) 3095 (w), 3010 (m), 1700 (s), 1021 (m) and 811 (w).[21] MS (70 eV) *m/e* (relative abundance, %) 164 (4.6), 162 (4.6) [M^+], 123 (3.5), 121 (3.5) [$M-C_3H_5^+$], 95 (5.7), 93 (5.5) [CH_2Br^+], 69 (100) [$M-CH_2Br$], 41 (48.7) and 39 (25.1).

Synthesis of halomethyl ketones from enamines. Typical procedures were:

Method A. Bromomethyl isobutyl ketone. To a stirred (Hershberg stirrer) solution of 16.9 g (0.10 mol) of a mixture of isobutyl methyl ketone enamine isomers in 80 ml of pentane at 0 °C was added dropwise over 15 min 11.4 g of trifluoroacetic acid in 20 ml of pentane. Stirring was continued for 20 min, then 7.3 g of *tert*-butylamine was introduced in one amount with vigorous stirring. After 10 min the mixture was filtered and the flask rinsed twice with 20 ml of cooled (0 °C) pentane. The pentane solution of the enamine was then rapidly added to a vigorously stirred (Hershberg stirrer) solution of 5.0 ml of bromine in 300 ml of dichloromethane at – 78 °C. A bright yellow precipitate was formed after *ca.* 30 s. The cooling bath was removed after 2 min and replaced by a room temperature water bath and the reaction mixture stirred for another 2 min. 200 ml of water was introduced and just enough of a 2 % $NaHSO_3$ solution to cause complete decolourisation of the bromine was added. Stirring with water was continued for 30 min. The layers were separated and the aqueous layer was extracted once with 100 ml of dichloromethane. The combined organic layers were washed consecutively with distilled water, 2 % $NaHCO_3$ solution and saturated NaCl solution. Drying ($CaCl_2$) and evaporation of the solvent afforded the crude bromoketone which was distilled bulb-to-bulb under reduced pressure (b.p. 69 – 71 °C/11 mmHg) (lit.[4a] b.p. 101 – 102 °C/50 mmHg) to yield 14.7 g of 96 % pure bromomethyl isobutyl ketone (79 % yield).

Method B. Chloromethyl cyclohexyl ketone. The transformation to the 1-isomer was performed as described above using 19.5 (0.10 mol) of a mixture of cyclohexyl methyl ketone enamine isomers. The pentane was evaporated under reduced pressure from a room temperature water bath. The pentane free enamine was dissolved in 50 ml of chloroform and added in one amount to a vigorously stirred solution of 7.1 g of chlorine in 250 ml of chloroform at – 66 °C (dry ice – chloroform). After 2 min the cooling bath was replaced by a room temperature water bath and the mixture was stirred for another 2 min. Hydrolysis and work-up were performed as above. Distillation bulb-to-bulb afforded 12.5 g of crude haloketone (contained 9 % of the parent ketone), b.p. 98 – 100 °C/10 mmHg, ^1H NMR (60 MHz, CCl_4) δ 4.05 (s, 2H) and 1.0 – 2.7 (m, 11 H) (Lit.[19] b.p. 75 – 85 °C/3.1 mmHg, ^1H NMR (CCl_4): δ 4.03 (s, 2H) and 1.0 – 2.9 (m, 11 H)).

The other haloketones listed in Table 1 were prepared analogously as given above, but 10 mmol of enamine was used. In these reactions the protonation-deprotonation steps were conducted in 50 ml centrifuge tubes and the precipitated *tert*-butyl ammonium trifluoroacetate was removed by centrifugation. Yields in these experiments were determined by GC after the addition of internal standard to reaction mixture after the hydrolysis.

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