III (1.14 g) was hydrogenated at 420 kPa and room temperature with 10 % palladium on charcoal in ethanol (70 ml) containing triethylamine (0.6 ml) overnight.

Filtration and concentration gave a syrup which was dissolved in chloroform. The chloroform solution was washed with aqueous sodium hydrogen carbonate, water, dried over sodium sulfate, filtered and concentrated. The product was purified by column chromatography (toluene-ethyl acetate 1:1) to yield pure IV (0.52 g). $[\alpha]_D$ −105° (*c*, 0.8, chloroform). (Found: C 63.2; H 6.74. $C_{14}H_{18}O_5$ requires: C 63.1; H 6.81). NMR ($CDCl_3$): δ 1.27 (3 H, d, $J_{5,6}$ 6.5 Hz, H-6), 1.7–2.1 and 2.2–2.4 (2 H, m, H-3 and H-3'), 2.65 (1 H, broad s, OH), 3.60 (3 H, s, OCH_3), 3.67–4.05 (2 H, m, H-2 and H-5), 4.23 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1), 5.13–5.33 (1 H, m, H-4), 7.40–7.67 (3 H, C_6H_5), 8.03–8.25 (2 H, C_6H_5).

*Methyl 3,6-dideoxy-β-*D*-xylo-hexopyranoside (V).* The 4-benzoate IV (75 mg) in methanol (10 ml) was treated with barium oxide (excess) at reflux temperature for 30 min. TLC (toluene-ethyl acetate 1:1) showed complete debenzoylation. The reaction mixture was neutralized with solid carbon dioxide, filtered and concentrated to a syrup (38 mg). The syrup was found to be chromatographically pure by TLC (ethyl acetate-methanol-water 85:10:5), having $[\alpha]_D$ −74° (*c*, 0.9, chloroform), $[\alpha]_D$ −66° (*c*, 0.5, methanol) and $[\alpha]_{546}$ −79° (*c*, 0.5, methanol) in agreement with previously recorded values.[10] An NMR spectrum ($CDCl_3$) was identical to that previously recorded for this substance.[10]

A small sample was hydrolyzed with 0.25 M aqueous sulfuric acid for 30 min at 100 °C, reduced with sodium borohydride and then acetylated.[11] The abequitol acetate thus obtained was indistinguishable from an authentic sample by GLC-MS.

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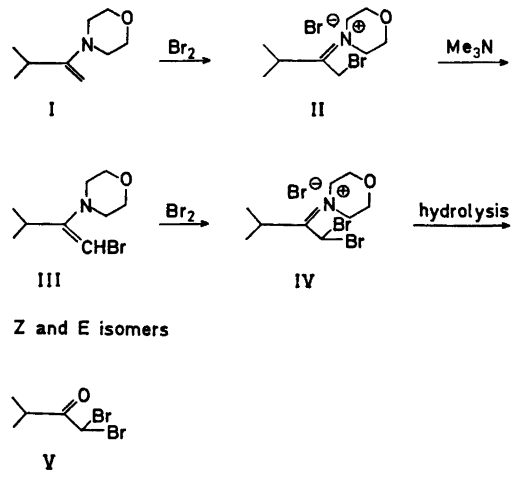
Bromination of Enamines from Methyl Isopropyl Ketone. II. A Convenient Preparation of Dibromomethyl Isopropyl Ketone

ROLF CARLSON and CHRISTOFFER RAPPE

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

Dibromomethyl ketones, $CHBr_2COCHR_1R_2$, are rather difficult to prepare; generally they are obtained from the corresponding diazoketone with bromine.[1–3] However, this method is not very attractive for synthesis on a larger scale since it involves the use of excessive amounts of the noxious agent diazomethane. The preparation of bromomethyl isopropyl ketone from the morpholine enamine has recently been reported by us.[4] In our investigation of the scope of this reaction we have developed a convenient synthesis of dibromomethyl isopropyl ketone V; the reaction steps involved are summarized in



Scheme 1.

Scheme 1. The enamine I is easily prepared from methyl isopropyl ketone [5,6] with an average yield of *ca.* 70 %. The overall yield of V is *ca.* 40 % calculated from the starting ketone.

The bromo immonium salt II is formed by reaction of I with one equivalent of bromine in methylene chloride at −78 °C. II is rapidly deprotonated *in situ* when treated with trimethyl amine or triethyl amine giving the bromo enamine III. The deprotonation of II is complete after 5 min at −20 °C. III is converted to the dibromo immonium salt IV when reacted with a slight excess of bromine at −20 °C. Dibromomethyl isopropyl ketone V is obtained from IV by hydrolysis and the usual work up procedure. The yield of V from I was 60 % calculated from the ^{1}H NMR spectrum of the distilled crude product. The purity was 80 % (NMR). The main impurities was bromomethyl isopropyl ketone (15 %) and methyl α-bromoisopropyl ketone (4 %); other impurities were *ca.* 1 %. However, V is rather unstable and further purification by fractionation has not been successful due to a rapid rearrangement to the more stable 1,3-dibromoketone. The rearrangement is catalyzed by hydrogen bromide; this seems to be a general feature of α,α-dibromo ketones.[2,3]

The intermediates II and III have been investigated by studying their ^{1}H NMR spectra. The spectra were determined from a model experiment using deuteriochloroform as solvent instead of methylene chloride, since the resonance signal from the latter solvent obscured the desired spectra and deuterated methylene chloride was not available. However, conclusions drawn from these experiments are probably valid for explaining reactions in methylene chloride since this solvent and chloroform have very similar dissolving properties towards ion pairs.[7] The ^{1}H NMR spectra were recorded at different temperatures. At −60 °C the absorption signals from II give rise to very broad lines at δ 1.2, 3.9, and 4.4. We explain the line broadening as a result of a massive association of ion pairs to large clusters of ions. This is supported by the fact that II precipitates from the solution if the temperature is only slightly lowered. At 0 °C the lines are sharpened and give the following spectral data: A doublet *J ca.* 7 Hz at δ 1.54 from the geminal methyl groups, a septet from the isopropyl methine proton (overlapping with the morpholine signals) *J ca.* 7 Hz, δ 3.96, and a singlet from the bromomethyl group at δ 4.77. The signals from the morpholine protons appeared as a broad multiplet at δ 4.0−4.7 and not as two distinct bands as in free morpholine or in morpholinium salts. This agrees with results obtained from studies on protonation of the enamine I.[8] The ^{1}H NMR spectrum of III indicates that both the *Z*- and *E*-isomers are formed when II is treated with base (Fig. 1). In the spectrum there are two signals in the region where enaminic vinyl protons are expected to give resonance signals, and we assign the signal at low field to the vinyl proton of the *Z*-isomer. A calculation of the expected chemical shift for the vinyl protons of III (*Z*) and III (*E*) using shielding increments for substituents on ethylene [9] shows that the *Z*-isomer is expected to give resonance at a lower field than the *E*-isomer. Integration over the vinylic signals at −60 °C shows a ratio *Z*:*E* = 4:6. No change in this ratio was found by varying the temperature. This isomeric distribution is probably kinetically determined, but we have not yet studied the equilibrium conditions. No changes in chemical shift were noted in the spectra recorded at different temperatures, −60, 0 and 31 °C. The following data for III (*Z*) and III (*E*) were found: III (*Z*) shows a doublet, *J ca.* 7 Hz, δ 1.11 and a somewhat broadened signal from the vinyl proton at δ 5.52. III (*E*) shows a doublet, *J ca.* 7 Hz, δ 1.19, and a sharp singlet at δ 5.33. The expected septets from the methine protons were not distinguished due to overlap with the morpholine signals. The bromoenamine is not stable at room temperature and it decomposes within an hour at this temperature. Attempts to record ^{1}H NMR spectra from IV has not been successful. IV is not very soluble in deuteriochloroform at low temperature and decomposes rapidly at room temperature.

The ^{1}H NMR samples were hydrolyzed and the organic layer analyzed by means of GLC. The bromoketones found agreed with the results from the ^{1}H NMR analysis of II and III. GLC-analysis of attempted small scale preparations of IV and subsequent hydrolysis did not agree with large scale experiments and are therefore of questionable reliability.

We have examined the optimum conditions for synthesis of V and these are presented in the experimental section. In this context some experimental findings are of importance: The conversion of I to II is best performed by adding the enamine to an equivalent amount of bromine in methylene chloride at −78 °C. The proton abstraction from II is rather fast at −78 °C but the reaction goes still faster if the reaction mixture is warmed to −20 to −10° after the base has been added. Under these conditions proton abstraction is complete within 5 min. Use of excess base did not improve the yield of V. The reaction mixture should be kept below 0 °C during the reactions involving brominations. Brominations performed at room temperature yielded

III (E) III (Z)

Fig. 1.

mostly the 1,3-dibromoketone. Attempts to use the stronger base potassium *tert*-butoxide instead of trimethyl- or triethylamine were unsuccessful, since only traces of V were formed. The main product from these experiments was the bromomethyl isopropyl ketone in *ca.* 80 % yield (GLC). A probable explanation is the low solubility of potassium *tert*-butoxide in methylene chloride and that the proton abstraction from II with base in a two phase system is a very slow reaction. Immediate work up of V is necessary since even traces of acid catalyse the rearrangement to the isomeric 1,3-dibromoketone.

Experimental. ^{1}H NMR spectra were recorded on a Varian A-60 A instrument fitted with a Varian V 60–40 Temperature Programming Unit using liquid nitrogen as cooling agent. Probe temperature was measured with a thermometer inserted in the sample area. The thermometer readings corresponded to the calibrated methanol spectra. The purity of V was checked on a JEOL C-60 HL NMR-spectrometer. TMS was used in all experiments as an internal reference. GLC analysis was performed on a PYE M 64 Gas Chromatograph with flame ionization detector. A 270 cm × 6 mm 12 % QF-1 column at 120 °C was used. Mass spectrum of V was obtained with a LKB 9000 Mass spectrometer *via* the GLC-MS inlet system.

Compound I was prepared by the method of White and Weingarten [5] and the work up procedure was essentially that described by Pocar *et al.*[6] The purity of I prepared by this method was high, > 95 % (^{1}H NMR).

Small scale experiment for obtaining ^{1}H NMR-spectra of II and III. 0.78 g of I (5.0 mmol) was added in one portion to an equivalent amount of bromine in 10 ml of deuteriochloroform at − 50 °C. The resulting mixture was stirred for 1 min and a 2.5 ml aliquot was withdrawn, 0.5 ml of which was taken to ^{1}H NMR analysis the rest being hydrolyzed by shaking with 2 ml of distilled water in a ground glass stoppered test tube. The organic layer was dried ($MgSO_4$) and analysed by GLC. To the reaction mixture containing II 0.6 ml of trimethyl amine (excess) was added and the resulting mixture was warmed to − 20 °C and stirred for 5 min. A 2.5 ml aliquot was taken, filtered and treated as above with the exception that 0.3 ml of concentrated hydrochloric acid was added prior to hydrolysis, to avoid base induced rearrangement of the bromo ketone formed. The ^{1}H NMR samples were kept at − 78 °C between recordings. Details of the attempted preparation of IV have been omitted since we did not succeed in obtaining a ^{1}H NMR spectrum of this compound.

Preparation of dibromomethyl isopropyl ketone V. To a stirred solution of 5.2 ml of bromine in 150 ml of methylene chloride at − 78 °C 15.5 g (0.10 mol) of I dissolved in 50 ml of methylene chloride was rapidly added. The mixture was stirred for 2 min whereafter 11.0 g (0.109 mol) of triethyl amine diluted with 25 ml of methylene chloride was added with vigorous stirring and the resulting mixture was kept at − 78 °C for 2 min. It was then warmed to − 20 °C (crushed ice-acetone) and stirring was continued at this temperature for an additional 5 min. 6 ml of bromine in 25 ml of methylene chloride was then added rapidly with vigorous stirring. After 5 min 100 ml of distilled water were introduced and the cooling bath was replaced by a water bath at room temperature. Stirring with water was continued for 15 min. (It is not advisable to exceed this period since V rearranges rapidly to the 1,3-dibromo ketone in acidic media.) The layers were separated and the aqueous layer was extracted with 2 × 50 ml of methylene chloride. The combined organic layers were shaken with dilute $NaHSO_3$-solution to destroy excess of bromine and washed with 4 × 100 ml of distilled water. The organic layer was dried by shaking with anh. sodium sulfate for 5 min. Filtration and rapid evaporation of the solvent *in vacuo* afforded the crude bromo ketone which was freed from low boiling impurities by an immediate "bulb to bulb" distillation yielding 17.1 g of distilled product, b.p. 63 – 67 °C/0.8 mmHg. ^{1}H NMR analysis showed that it contained 80 % of V, the main impurities being the monobromo ketones $CH_2BrCOCH(CH_3)_2$ (15 %) and $CH_3COCBr(CH_3)_2$ (4 %). The product contained only 1 % of the 1,3-dibromo ketone $CH_2BrCOCBr(CH_3)_2$. The actual yield of V from I was thus 14.7 g (60 %). ^{1}H NMR-spectrum of V (*ca.* 10 % in CCl_4) shows a doublet (6 H) J *ca.* 7 Hz, δ 1.23, a septet (1 H) J *ca.* 7 Hz, δ 3.30, and a singlet (1 H) δ 5.87. Mass spectrum of V shows a typical Br_2-isotopic cluster at $m/e = 242$, 244, and 246 (molecule ion), and a similar cluster at $m/e = 171$, 173, and 175 characteristic for the $CHBr_2$-ion. The base peak appeared at $m/e = 71$ indicating a loss of $CHBr_2$ from the molecule ion.

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