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Halogenation of Enamines. I. Synthesis of Haloketones from Enamines. α-Halogenated Pinacolones

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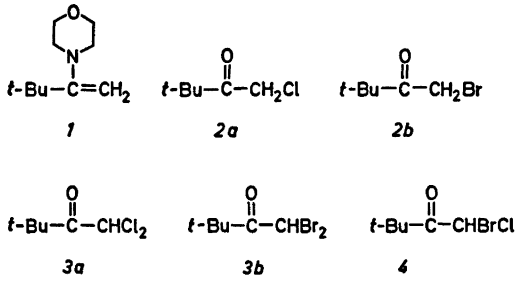
The reactions of 2-(4-morpholinyl)-3,3-dimethyl-1-butene, *1*, with chlorine and bromine were studied under varying conditions for possible transformations to mono- and dihaloketones. A convenient synthesis of 1-chloro-3,3-dimethyl-2-butanes is described. The usefulness and limitations of the reaction of *1* with halogen for obtaining haloketones are briefly discussed.

The preparation of 1-monohalo- and 1,1-dihalo-3,3-dimethyl-2-butanone, *2a*, *2b*, *3a*, *3b* (Fig. 1) has been reported by several authors.[1–9] These methods include both the direct halogenation of the parent ketone [1–6] and indirect routes.[7–9] *2a* cannot, however, be prepared in good yields from pinacolone using simple procedures. Photochlorination in the liquid phase yielded 23 % of *2a*.[1] Vapour phase chlorination of pinacolone under various conditions has been reported as giving acceptable yields of *2a* (85–88 %).[2,3] However, these methods call for special equipment which is not ordinarily available. *2a* has been obtained indirectly by the action of butyllithium or *N*-piperidyllithium on the lithium 1,1-dichloro-3,3-dimethyl-2-butanolate in yields of 51 and 88 %, respectively.[7] The reaction of diazoketone with hydrogen halide is often used for the synthesis of halomethyl ketones [10] and a yield of 64 % of *2a* was obtained by this method, (see experimental part). The diazoketone method is not an attractive one since it involves the use of excessive amounts of diazomethane.

1-Bromo-1-chloro-3,3-dimethyl-2-butanone, *4*, does not seem to have been reported previously. It can be prepared from *2b* and sulfuryl chloride, (see experimental part).

Enamines can be used for the synthesis of α-haloketones [11–15] and the purpose of the present investigation was to study whether the enamine *1* can be a useful substrate for the preparation of the haloketones shown in Fig. 1. The aim was to determine suitable conditions for simple procedures using cheap and readily available chemicals and glassware. A method for obtaining *2a* was particularly sought since this ketone is rather difficult to obtain, (see above). The synthetic routes studied are shown in Scheme 1.



1 2a 2b

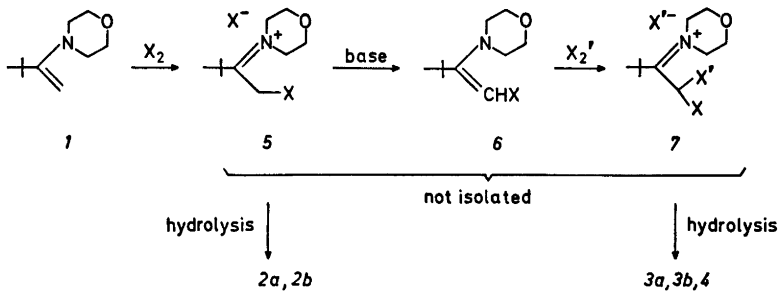
3a 3b 4

Fig. 1.

METHODS

The enamine *1* was obtained from pinacolone, morpholine and titanium(IV) chloride,[16] with modifications given in the experimental part.

The conversion of *1* to the haloenamines *6a* and *6b*, in 50 and 48 % yields, respectively, have been described by Duhamel *et al.*[17] They used the technique of bubbling chlorine diluted with nitrogen, *viz.* adding a solution of bromine to an ethereal solution of *1* at low temperature,



1 5 6 7

2a, 2b 3a, 3b, 4

Scheme 1. Order of halogenation: *a*, X = X′ = Cl; *b*, X = X′ = Br; *c*, X = Cl and X′ = Br; *d*, X = Br and X′ = Cl.

followed by addition of triethylamine. According to our experience, an inverse addition procedure gives better yields, *i.e.* a *rapid* addition of the enamine to a solution of the halogen. The reaction of enamines with halogen is very fast and a thorough and rapid mixing of the reactants is necessary in order to minimize competing side reactions, such as proton abstraction by *1* from the haloimmonium ions *5a* and *5b*.

The syntheses of bromomethyl isopropyl ketone and dibromomethyl isopropyl ketone were recently reported.[14,15] In these preparations (2-(4-morpholinyl)-3-methyl-1-butene was reacted with bromine in methylene chloride at low temperature followed by hydrolysis to afford the bromomethyl ketone, *viz.* reacted consecutively in methylene chloride with bromine, triethylamine and a second portion of bromine followed by hydrolysis to afford the dibromomethyl ketone. In order to investigate whether this technique could be used for the synthesis of the haloketones in Fig. 1 and to determine suitable conditions, the reactions in Scheme 1 were subjected to variations. Some of the experiments are reported in Tables 1 and 2 and some experimental findings are given in the text. Since we were interested in the direct conversion of *1* and, if possible, a one-pot procedure for obtaining *2a*, *2b*, *3a*, *3b* and *4*

Table 1. Synthesis of dihalopinacolones using triethylamine as base. Base treatment 1h, and second halogenation 1 h.

Order of halogenation [a]	Base treatment Temp./°C	Second halogenation Temp./°C	Yield of haloketones % 2a	2b	3a	3b	4	Others
a	−20 [b]	−20 [c]	42		48			−
a	0	0	5		65			2 [d]
a	RT	0	5		54			3 [e]
a	RT	RT	3		41			14 [e]
b	0 [b]	0		17		40		
b	0	0		11		47		
b	0	RT		18		48		
b	RT	0		15		63		
b	RT	RT		21		69		
c	RT	RT					18	57 [f]
c	RT	0					52	27 [f]
c [g]	RT	0					46	38 [f]
c [g]	RT	RT					29	46 [f]
c [h]	0	0					22	59 [f]
d [h]	0	0					10	33 [f]

[a] See Scheme 1. [b] 15 min. [c] 30 min. [d] Pinacolone. [e] 1,1,1-Trichloro-3,3-dimethyl-2-butanone. [f] The distribution of the different haloketones is not shown. [g] Propene was bubbled prior to the second halogenation. [h] Triethyl ammonium bromide was precipitated by trituration with carbon tetrachloride and removed by filtration prior to the second halogenation step.

Table 2. Synthesis of dihalopinacolones using ion-exchange resin Amberlyst A 21 as base.

Order of halogenation [a]	Base treatment Amount of resin g/mmol of *1* [b]	Time h	Yield of haloketones % *3a*	*4*	Others [c]
a	0.2 B	0.5	55		16
a	0.4 B	0.25	63		15
a	0.4 B	1	53		16
a	0.6 B	1	49		19
a	0.6 C	–	49		14
c	0.4 B	0.2		53	26
c	0.6 C	–		50	43
d	0.4 B	0.2		53	46
d	0.6 C	–		16	66

[a] See Scheme 1. [b] B, batch; C, column. [c] The distribution of the individual different haloketones is not shown.

without isolation of the intermediates, methods involving the isolation of these intermediates were not further studied.

Different techniques were tested for effecting the deprotonation of *5* to the corresponding haloenamine *6*. Triethylamine was tested for possible one-pot procedures. The weakly basic ion-exchange resin Amberlyst A 21, with tertiary amino groups as active groups was studied in batch and column operations.

The choice of solvent requires a comment. Chloroform and methylene chloride are useful solvents for the reactions in Scheme 1, since the immonium salts are soluble in these solvents. Methylene chloride was used for bromination reactions and chloroform for chlorinations. The first halogenation step must be performed at low temperature. The freezing point of chloroform imposes a lower limit for chlorinations. Methylene chloride cannot be used for chlorinations since preparing solutions of chlorine in this solvent sometimes leads to a vigorous chlorination of the solvent. This does not occur with chloroform if care is taken to keep the concentration of chlorine low (≤ 0.5 M).

The yields of the haloketones reported in Tables 1 and 2 were determined by gas chromatography using internal standard technique.

RESULTS

Monohaloketones. The preparation of the monohaloketones was best performed by adding *1* to a well-stirred solution of an equivalent amount of the halogen at low temperature, followed by hydrolysis at room temperature. In small scale runs at -65 °C, *2a* was obtained in 75–77 % yield (GC). The amount of *3a* was less than 1 %. Use of higher temperature gave mixtures of *2a* and *3a*. Synthetic scale (0.1 mol) preparation of *2a* gave 72 and 68 % as isolated yields in a duplicate run. The bromoketone *2b* was obtained in 78 % yield by bromination in methylene chloride at -78 °C.

Dihaloketones, triethylamine as base. Some experimental findings not shown in Table 1 ought to be mentioned. The first halogenation was performed at low temperature. In the second halogenation step, greater yields of *3a* were obtained if a solution of chlorine in carbon tetrachloride was added to the chloroenamine *6a*, because a more concentrated solution of chlorine can be prepared in this solvent. A rapid mixing of the reactants is obviously necessary for achieving a good conversion to *3a*. Use of more dilute chlorine in chloroform gave poorer yields. The results given in Table 1 were obtained where carbon tetrachloride was used in the second chlorination step. In the second bromination step a *ca.* 1 M solution of bromine in methylene chloride was used. A dilute solution gave poorer yields and neat bromine occasionally gave tarry products.

A slight excess of triethylamine was used. The amount of base was not varied, since it was found in the analogous preparation of dibromomethyl isopropyl ketone that the use of large excess of base did not improve the yield.[15]

One result shown in Table 1 requires a brief comment. While chlorination at ambient temperature gives some 1,1,1-trichloro-3,3-dimethyl-2-butanone, *8*, (identified by GC-MS, see experimental part) neither the corresponding tribromoketone nor pivalic acid (haloform cleavage hydrolysis) could be detected (GC) from bromination under similar conditions. All attempts at preparing *8* by independent routes failed and it was thus not possible to unambiguously establish the structure of the compound supposed to be *8* by chromatography using pure *8* as reference and for spiking experiments.

Attempts at preparing *4* by sequential introduction of different halogens into *1* have not been successful. The best yield recorded was 52 % and the amount of other haloketones present in the hydrolysate was 27 %. The possibility that the first halogenation had not gone to completion and that remaining halogen might have given unwanted side reactions in subsequent steps was studied by quenching the reaction mixture with propene prior to the addition of base. However, no increase in the yield was found by this technique. A modified technique was tried for reversing the order of halogenation, *viz.* bromination followed by chlorination, which made it necessary to remove bromide ions from the reaction mixture. The removal was performed by precipitation of the triethyl ammonium bromide formed by trituration with carbon tetrachloride. The filtrate was then added to a solution of chlorine. The yield of *4* by this procedure was only 10 % and of other haloketones 33 %. Use of the same technique, but with chlorination followed by bromination, yielded 22 % of *4* and the major part of 59 % was a mixture of other haloketones.

Dihaloketones, ion-exchange resin as base. Since the syntheses of dihalopinacolones were not promising when triethylamine was used, polymer-bound bases were tried. The weakly basic ion-exchange resin Amberlyst A 21 seemed to be a promising alternative to triethylamine in these syntheses. The high content of water, *ca.* 50 % in the commercial product must, however, be reduced (see experimental part.). As Table 2 shows, the use of ion-exchange resin as a heterogeneous base did not give better yields than the use of triethylamine. One exception is noted: When reactions were carried out with bromination prior to chlorination a better yield of *4* was obtained with ion-exchange resin than with triethylamine.

CONCLUSION

The monochloroketone *2a* is conveniently prepared from *1* and since it is not easily and safely prepared by routine procedures this method may be synthetically useful. The haloketones *2b*, *3a* and *3b* are more easily prepared by direct halogenation of pinacolone. *4* is obtained in good yield by chlorination of *2b*. The route to these ketones *via* enamine halogenation do not seem to offer any advantages.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian A-60A instrument. Mass spectra were obtained on an LKB 9000 Mass Spectrometer. GC-analyses were performed on a PYE M 64 Gas Chromatograph with flame ionization detector. The identities of the various ketones present in the reaction mixtures were established by analyses on two different GC-columns: 10 % APM (270 cm, 6 mm o.d.) and 12 % QF-1 (270 cm, 6 mm o.d.) on Chromosorb W AW-DMCS 110–120 mesh. 2,5-Dimethyl-3-hexanone was used as internal standard. Integrated peak areas were used for quantifications. A Houston Instrument integrating recorder was used. Pure samples of authentic ketones were prepared by independent routes and used as references and for calibration of FID-responses.

2-(4-Morpholinyl)-3,3-dimethyl-1-butene *1* was prepared according to White and Weingarten.[16] However, when prepared according to the original directions (room temperature) moderate yields were obtained, despite the extended reaction time of 150–200 h. Greater yields were obtained by refluxing the reaction mixture after the titanium(IV) chloride had been added. A yield of 55 % of *1* was obtained using pentane as solvent and allowing a reaction time of 24 h. When benzene was used as solvent yields of 65–70 % were obtained after 24 h, but the crude reaction product caused severe foaming on distillation. This was not encountered when pentane was used. B.p. 99–101 °C/35 mmHg.

1-Bromo-3,3-dimethyl-2-butanone, *2b*,[4] *1,1-dichloro-3,3-dimethyl-2-butanone*, *3a* [4] and *1,1-dibromo-3,3-dimethyl-2-butanone*, *3b* [6] were prepared by published methods for use as GC-references.

1-Bromo-1-chloro-3,3-dimethyl-2-butanone, *4*. 1.79 g (10 mmol) of *2b* and 0.81 ml of sulfuryl chloride were mixed and stirred at room temperature for 6 h. The temperature was then raised to 55–60 °C and the mixture stirred for

another 3 h. 5 ml of water was added to destroy remaining SO_2Cl_2 and the mixture was stirred at this temperature for 1 h and then allowed to cool to room temperature. 5 ml of methylene chloride was added to dissolve the precipitated ketone. The organic layer was washed three times with distilled water and then dried ($MgSO_4$). Evaporation of the solvent and recrystallisation of the crude product from hexane yielded 1.85 g (85 %) of *4*.

M.p. 60–61 °C. ^{1}H NMR (CCl_4) δ 1.32 (9 H, s) and 6.50 (1 H, s). MS (20 eV) Typical ClBr isotope cluster at *m/e* 212, 214, 216 (0.1 %) (molecule ion), 155, 157, 159 (1.0 %) (M–*t*-Bu) and 127, 129, 131 (0.2 %) (CHClBr). Base peak (100 %) at 57 and 85 (22.4 %) shows the presence of the pivaloyl group.

MS determination of 1,1,1-trichloro-3,3-dimethyl-2-butanone, 8. The presence of *8* in the reaction product was found by GC-MS analysis. No molecule ion was detected even at low ionization potential (14 eV). The base peak (100 %) appearing at *m/e* 57 and a peak at 85 suggest the presence of the pivaloyl group. A typical Cl_3 isotope cluster of low abundance (0.1 %) at 117, 119, 121, 123 is from the CCl_3 fragment and a similar cluster at 187, 189, 191, 193 is from the ($M-CH_3$) ion.

General procedure for halogenation of 1. Monohalogenation. To a cooled (–65 °C, $CHCl_3$ or –78 °C, CH_2Cl_2) solution of the halogen (0.5 M) was rapidly added, with vigorous stirring 1.69 g (10 mmol) of *1* in 20 ml of solvent. Stirring was continued for 5 min, then the cooling bath was replaced by a room temperature water bath, and 20 ml of water and 5 ml of 2 % $NaHSO_3$ were introduced. The mixture was stirred for 1 h to complete hydrolysis. The layers were separated and the aqueous layer extracted with 5 ml of CH_2Cl_2. The combined organic layers were transferred to a volumetric flask and the volume adjusted to 50 ml. To an aliquot was added a known amount of 2,5-dimethyl-3-hexanone and the sample analyzed by GC. The yields given are the averages of two analyses by GC.

Dihalogenation, triethylamine as base. The first halogenation was performed as for monohalogenation. After 5 min the cooling bath was replaced by an ice bath and 1.40 g of triethylamine in 5 ml of solvent was added in one portion with vigorous stirring. After the time given in Table 1 15 ml of 1 M solution of the halogen was added in one portion with vigorous stirring. After 1 h 20 ml of distilled water was introduced, followed by a careful addition of just enough 5 % $NaHSO_3$ solution to cause complete decolourisation of the halogen. The mixture was stirred for 1 h. The aqueous layer was extracted with 10 ml of CH_2Cl_2 and the combined organic layers were adjusted to 100 ml and analyzed as above.

Dihalogenation, Amberlyst A 21 ion-exchange resin as base. First halogenation as above, but 5 mmol of *1* was used.

A, Batch procedure. The resulting reaction mixture after the first halogenation was warmed to 0 °C and the amount of dried (see below) ion-exchange resin given in Table 2 was added. The mixture was stirred magnetically for the time given in Table 2. The resin was removed by filtration and washed three times with 3 ml of solvent. The filtrate was added in one amount to a well-stirred solution of the halogen (50 % excess) at –50 °C. The reaction mixture was stirred with no external cooling for 30 min and at room temperature (water bath) for 30 min. Hydrolysis and GC-analysis as above.

B, Column procedure. The reaction mixture from the first halogenation was slowly passed through a column (10 mm id) filled with 3.0 g of ion-exchange resin in the solvent used. This gave *ca.* 15 cm of bed height. The column was eluted with 20 ml of solvent. The second halogenation, hydrolysis and analysis were performed as for batch procedure.

Drying of Amberlyst A 21. Mere drying *in vacuo* over phosphorus(V) oxide was unsatisfactory, a more laborious drying procedure was necessary: The moist resin was extracted in a Soxhlet extractor for 24 h with ethanol refluxing from calcium oxide heated to 900 °C for 12 h in an oven prior to use. Extraction with ethanol was repeated once. The final drying was performed by extracting with ethanol boiling from a solution of sodium ethoxide in diethyl phthalate.[18] During this process good stirring was necessary to prevent bumping. The resin was free from ethanol by evaporation at 100 °C/10 mmHg for 6 h and at 1 mmHg for 10 h. The weight loss of the resin by this procedure was 45–48 %. The dried resin was stored in vacuum over phosphorus(V) oxide.

Synthesis of 1-chloro-3,3-dimethyl-2-butanone, 2a. From diazoketone. The reaction was performed in a magnetically stirred 3 l Erlenmeyer flask. Diazomethane (0.60 mol) was prepared in ethereal solution according to *Organic Syntheses* [19] and dried over solid KOH overnight. The dried diazomethane solution was used without purification. Pivaloyl chloride (Fluka, pract.) 24.1 g (0.20 mol) in 100 ml of dry ether, was added dropwise with stirring to the diazomethane solution at 0 °C over a period of 1.5 h followed by stirring at room temperature for 2 h. Dry hydrogen chloride was then bubbled through the solution. The yellow colour from the diazoketone disappeared in a few minutes. 200 ml of water was added to destroy unreacted pivaloyl chloride. The ethereal layer was washed three times with 100 ml of 5 % $NaHCO_3$ and finally with sat. NaCl. Drying ($MgSO_4$) and evaporation of ether yielded 17.2 g of *2a* (64 %). The purity of the crude product was 95 % (GC, ^{1}HNMR). Distillation yielded 14.1 g (52 %) of pure (> 99 %) *2a*.

B.p. 83.5–85 °C/35 mmHg. 2,4-Dinitrophenyl hydrazone m.p. 142.5–143 °C (lit.[3] 143–144 °C). ^{1}HNMR (CCl_4) δ 1.33 (9 H, s) and 4.40 (2 H, s).

From the enamine. To a well-stirred solution of 7.1 g of chlorine in 200 ml of chloroform at −65 °C was added in one portion 16.9 g of *1* (0.10 mol) in 40 ml of chloroform. After 5 min the cooling bath was replaced by a room temperature water bath, and 200 ml of water and 10 ml of 2 % $NaHSO_3$ was added. Stirring of the mixture was continued for 1 h. The aqueous layer was extracted with 50 ml of chloroform. The combined organic layers were washed twice with 50 ml of water and finally with sat. NaCl. The chloroform was removed by distillation with a short column. By this procedure residual water is removed by azeotropic distillation. The residue from this distillation was distilled under reduced pressure and yielded 9.46 g (72 %) of *2a*. A high boiling residue remained in the distillation flask. TLC-analysis showed a complex mixture of at least 11 products. The nature of these were not elucidated.

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