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REDUCTIVE DEHALOGENATION OF α-HALOKETONES PROMOTED BY HYDROIODIC ACID AND WITHOUT SOLVENT

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Abstract - Several α-haloketones have been transformed into the corresponding ketones by reaction with aqueous 57% HI, without solvent. The products are obtained in nearly quantitative yields and with high purity (>99%) even in the case of sterically hindered starting materials.

The reductive dehalogenation of α–haloketones **1** to the parent ketones **2-8**,[1] promoted by hydroiodic acid or its equivalent salts (scheme 1), was studied in 1921 by Backes *et al.*.[2]

New and, in some cases, complex methods to realize this interesting transformation have emerged recently.[3-9] The system proposed by Mandal and

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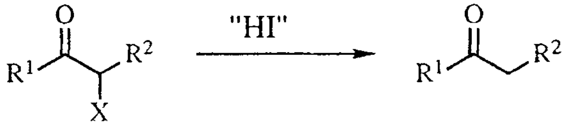


1

2-8

X = Cl, Br, I

Scheme 1

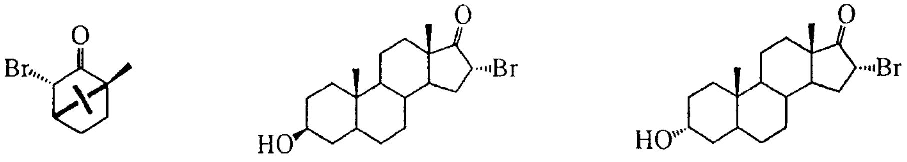
Nijasure,[3] employing a catalytic amount of NaI or 57% HI and phosphorous acid in CH_3CN, and that by Gemal and Luche,[7] employing NaI and concentrated H_2SO_4 in THF or dioxane, seem very attractive.

In fact both are simple, from the experimental point of view, and economically convenient, using cheap and readily available materials. However, even these interesting reactions suffer some drawbacks, like long reaction times, high temperature, and applicability to very reactive substrates only. For example the reduction of aliphatic substrates by NaI/H_2SO_4 requires a refluxing dioxane-water mixture as solvent and takes 2-6 h; hindered α-haloketones, such as *endo*-2-bromocamphor (**1g**) and 16α-bromo-3β-hydroxyandrostan-17-one (**1h**) or the corresponding 3α-hydroxy epimer (**1i**), do not react at all (figure 1).[7]

We found, and here report, that the use of aqueous 57% HI, without solvent, represents an effective and mild method for such a dehalogenation.

The reactions were carried out by stirring a heterogeneous mixture of the α–haloketone **1** (1 mol) and aqueous 57% HI (2-4 mol) at 25°C.

Linear aliphatic α-haloketones (see table), α-haloalkylaryl ketones, α-halocycloalkyl ketones and α-haloketosteroids are reactive under the above



1g **1h** **1i**

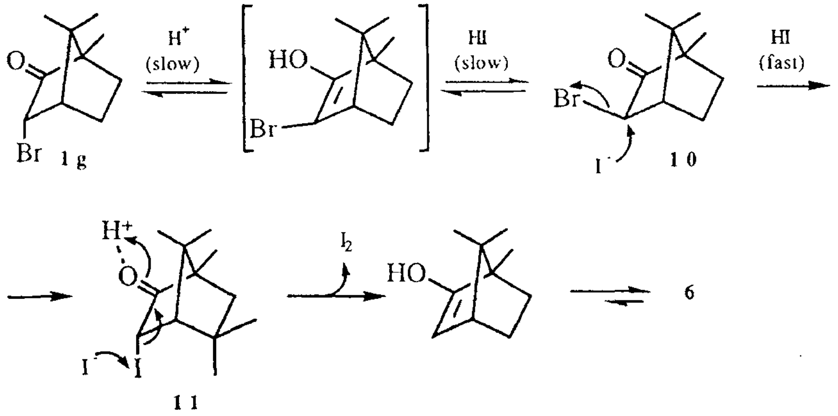
FIGURE 1

conditions and nearly quantitative yields of the corresponding ketones were obtained (see table).

In order to determine the reaction mechanism, we conducted the debromination of the highly hindered *endo*-2-bromocamphor (**1g**) in the presence of 4 molar equivalents of HI at 110°C for 120 min. It is well known[10] that in the reduction of this kind of substrates the rate-determining step is the epimerization *endo* to *exo* of the carbon-halogen bond. In fact, also in our reaction conditions, we were able to evidence by ^{1}H NMR analysis the formation of the *exo* epimer **10** at an early stage of the process. For these reasons we can exclude a direct BrI elimination from the less hindered *endo* side of **1g**. Probably the slow epimerization to produce **10** is followed by a nucleophilic bimolecular substitution at the less hindered *endo* side of **10** to produce **11**. A fast iodine elimination from the *endo* position of **11** gives camphor (**6**) (scheme 2).

According to this hypothesis, 2-bromocycloheptanone (**1f**) in the presence of 2 molar equivalents of HI, gave at 25°C, after 5 min, 94% of cycloheptanone (**5**), whereas by employing 1 molar equivalent of hydroiodic acid a maximum conversion of 50% of **5** was detected by GLC analysis after 5 min.

The presence of catalytic amounts of a typical phase-transfer agent, i.e. quaternary onium salts or crown ethers, did not afford any reaction improvements.



Scheme 2

^{1}H NMR spectra are recorded in $CDCl_3$ at 80 and 300 MHz, using TMS as external standard. GLC analyses are obtained with Alltech RSL-150 (10 m x 0.35 mm, polydimethylsiloxane, 0.25 µm thickness) and OV 101 columns (0.5 m, O.D. 1/8", I.D. 0.85", material SS, mesh 100/120, support Chrom-WHP). TLC analyses are obtained with silica gel 60 F_{254} and with RP-8 F_{254} S (Merck) pre-coated plates.

Starting α-haloketones **1c**, **1d**, **1g** are commercially available and are recrystallized before use. **1a**[14], **1b**[14], **1e**[15], **1f**[16], **1h**[17], and **1i**[17] are known compounds and have been prepared by literature methods.

General Procedure for the reduction of a-haloketones 1a-i

In a screw-capped vial a mixture of haloketone **1a-i** (2 mmol) and 57% HI (4mmol) is stirred at room temperature until starting material is no longer

TABLE. REDUCTION OF α–HALOKETONES **1a-i** WITH HI.[a]

Starting Material	Time, m	Reaction Product	Yield, %[b]	Mp, °C or n_D^{20}	Literature Data
1a MeCOCHBr(CH$_2$)$_4$Me	15	**2**	98	1.4148	1.4151[11]
1b Me(CH$_2$)$_5$COCH$_2$Br	15	**2**	97	1.4154	
1c PhCOCH$_2$Br	1	**3**	98	1.5323	1.5325[12]
1d PhCOCH$_2$Cl	120	**3**	100[c]	1.5327	
1d	210	**3**	97	1.5320	
1e 2-bromocyclohexanone	1	**4**	96	1.4509	1.4512[13]
1f 2-bromocycloheptanone	5	**5**	93	1.4613	1.4608[11]
1f	5	**5**	(50)[d]		
1g *endo*-2-bromocanfora	120	**6**	98[c,e]	177-180	179[11]
1h 16α-bromo-3β–*hydroxy*-androstan-17-one	180	**7**	95[c]	179-183	185-186[11]
1i 16α-bromo-3α-*hydroxy*-androstan-17-one	480	**8**	93[c]	171-174	175-176[11]

[a] α-Haloketone **1** (1 mol), 57% HI (2 mol) at 25°C.[b] Isolated yields of the parent ketones **2-8**.[c] Using 4 molar equivalents of 57% HI.[d] Highest conversion reached (by GLC analysis) using 1 molar equivalent of 57% HI.[e] At 110°C.

detectable (GLC analysis for **1a-f**; TLC analysis on silica gel 60, using the mixture AcOEt and petroleum ether (1:1.5) as eluent, for **1h**; TLC analysis on RP-8, using the mixture CH_3CN and H_2O (1:1) as eluent, for **1i**). The crude of the reaction is diluted with Et_2O (10 ml) and washed with water (15 ml) and three times with 5% $NaHSO_3$ (2 ml) and 5% $NaHCO_3$ (2 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The products obtained are pure compounds (>99% by GLC and ^1H NMR analyses) and their physical and spectroscopic (^1H NMR and IR) characteristics match those reported in literature. Starting materials, reaction times, yields and physical data of the reaction products are reported in the Table.

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