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A Simple and Efficient Hydrodehalogenation of 1,1-Dihalocyclopropanes

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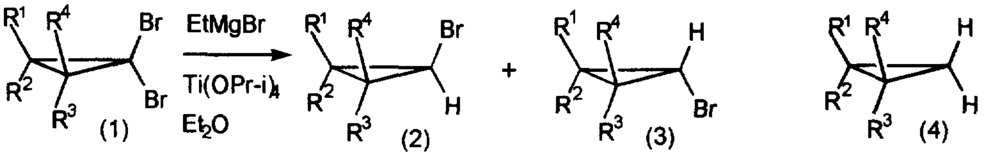
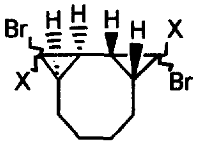
Abstract 1,1-Dibromo- and 1,1-dichlorocyclopropanes are converted into the corresponding monohalocyclopropanes (as mixtures of stereoisomers where appropriate) by reaction with 1.2-1.3 mol. equiv. of ethyl magnesium bromide and a small amount of titanium isopropoxide in ether. In the presence of an excess of ethylmagnesium bromide the product from the dibromide is the non- halogenated cyclopropane.

The cyclopropanation of esters by reaction with titanium isopropoxide and ethylmagnesium bromide discovered by Kulinkovich has proved to be very valuable;[1] we now report that the same combination of reagents is also extremely effective in bringing about the simple, clean and efficient conversion of 1,1-dibromo- and 1,1-dichlorocyclopropanes into the corresponding monohalides.* Reaction of dibromide (**1a**) with 1.3 mol.equiv. of ethylmagnesium bromide and 2 % titanium isopropoxide in ether for 20 m at 20°C followed by quenching with water led to a 92% distilled yield of a 2:1 mixture of monobromides (**2a**) and (**3a**) respectively:



	(a)	(b)	(c)	(d)	(e)	(f)	(g)
R^1	Me	H	Me	H	Oct	But	Br
R^2	Ph	Ph	Me	$-(CH_2)_2-$	Br	Br	Br
R^3	H	H	H	$-(CH_2)_2-$	H	H	Me
R^4	H	H	H	H	H	H	Me



(5a) X = Br
(5b) X = H

Under these conditions, glc showed 1% unreacted dibromide (**1a**), and <<1% of the completely reduced cyclopropane (**4a**). However, 0.5 mol.% of catalyst led to only 18% reduction of the dibromide under the same conditions. Moreover with 10 mol.% of catalyst and 3 mol.equiv. of EtMgBr, complete debromination occurred in 90 m at 20 °C and (**4a**) was isolated (93%). The results of these and other experiments are given in Table 1. Although the exo/endo selectivity of this reaction is relatively low, the method is of particular value in those cases where the desired monobromides are to be dehydrobrominated to provide cyclopropenes and hence the stereochemistry is not important.[2] The mechanism of these reactions is the subject of further work but it is clear that quenching the reaction converting (**1a**) in (**2a**) and (**3a**) with D_2O rather than water does not lead to the incorporation of any deuterium. The method is also successful using 10 mol.% of titanium trichloride in dichloromethane as the catalyst, as seen in the reduction of (**1b**).

The reduction of the tetrabromide (**5a**) with 2.3 mol.equiv. of EtMgBr and 10 % $Ti(OPr^i)_4$ in ether for 30 m at 20°C is also successful, leading to a mixture of three isomeric dibromides (**5b**) [84% isolated yield, 28 (endo,endo) : 8 (endo,exo) : 1 (exo,exo)] with only 2% of two tribromides, while particularly clean reactions occur with the tribromides (**1e**) or (**1f**), leading to mixtures of isomeric 1,2-dibromides (95 %) with less than 1 % of either tribromide or further reduced material in the crude product. Indeed, the tetrabromide (**1g**) is also cleanly converted into the tribromide (**2g**).

Table 1. Reduction of 1,1-dibromocyclopropanes

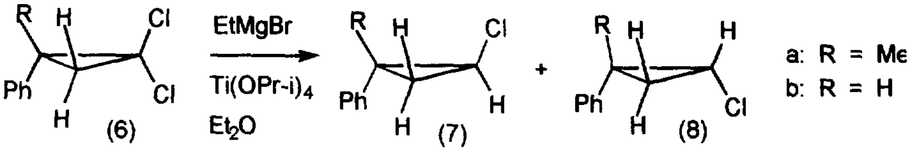
starting material	quant, mmol	reagent, solvent	reagent, mol. eq.	cat, mol. %	time of addition, min	time of stirring, min	isolated yield,^{g} %	GLC control			ratio (2):(3)
								(1)	(2)+(3)	(4)	
(1a)	10.0	EtMgBr, Et$_2$O	1.3	22	10	10	92	0	99	1	2.0:1
	10.0	EtMgBr, Et$_2$O	1.3	2	10	10	94	2	88	0	2.0:1
	10.0	EtMgBr, Et$_2$O	1.3	2	10	10	92^{a}	1	98	<<1	2.0:1
	10.0	EtMgBr, Et$_2$O	1.3	0.5	10	10	-	78	18	0	2.0:1
	2.0	MeMgBr,^{f} THF, MePh	1.2	-	3	15^{b}	-	2	92	4	1.5:1
	10.0	EtMgBr, Et$_2$O	3.0	10	60	30	93	0	0	97	-
(1b)	2.0	EtMgBr, Et$_2$O	1.7	TiCl$_3$,^{e}10	22	30	-	<1	93	0	1:1.1
	10.0	EtMgBr, Et$_2$O	1.25	2	12	20	90	3	93	0	1:1.1
(1c)	50.0	EtMgBr, Et$_2$O	1.3	5	30	20	85	0	99	d	-
(1d)	10.0	EtMgBr, Et$_2$O	1.4	10	25	20	90	0	99	<1	1:3.8
	2.0	MeMgBr,^{f} Et$_2$O, THF,MePh	2.0	10	20	18h	-	22	77	d	1:3.0
	2.0	MeMgBr,^{f} THF, MePh	2.0	-	4	20^{b}	-	<1	99	d	1:3.1
(1e)	5.0	EtMgBr, Et$_2$O	1.0	10	10	10	96	1	89	0	3.5:1
(1f)	5.0	EtMgBr, Et$_2$O	1.0	2	10	10	95	0	97	0	3.5:1
(1g)	1.0	EtMgBr, Et$_2$O	1.05	10	10	10	95	3	92	4^{c}	-

a Distilled yield without column chromatography, b Reaction carried out at reflux, c Mixture of isomeric 1,2-dibromocyclopropanes,
d The % of (**4d**) could not be determined by glc in this solvent, e In CH$_2$Cl$_2$, f Aldrich 28,223-5, g after short column chromatography

Many methods are already available which allow the selective reduction of 1,1-dibromocyclopropanes to either exo- or endo-monobromides.[3] One of the most frequently used is the radical reduction using tri-n-butyl tin hydride at about 40 °C;[4] where it is possible, the endo-isomer of monobromide normally predominates. Other reagents such as zinc-ethanol-potassium hydroxide,[5] zinc-copper couple,[6] zinc-acetic acid,[7] O,O-diethyl-α-lithiomethyl phosphonate,[8] photo-chemical[9] and electrochemical,[10] complex hydrides,[11] and butyl lithium followed by methanol,[12] have also been reported. Reduction with sodium dimethylsulphoxide in DMSO leads predominantly to exo-isomers.[13] Although these methods are all effective, they do suffer from disadvantages; thus reduction with Zn-EtOH requires a rather tedious work-up, butyltin hydride requires the removal of toxic organotin residues, and dimsyl sodium uses a reagent which is tedious to make and reaction conditions which require careful control. A more recent method using low valent vanadium and diethylphosphonate or triethyl-phosphite can lead to very high selectivities between stereoisomeric monobromides.[14] However, isolated yields are rather variable and reaction times are quite long. Reduction also occurs with a trialkylmanganesemagnesium bromide at -78 °C followed by quenching with water at that temperature, although careful temperature control is required and the yield from 1,1-dibromo-2-hexylcyclopropane is moderate.[15] It is also important to note that the reaction of methylmagnesium bromide with dibromocyclopropanes in refluxing tetrahydrofuran does lead to monobromides.[16] However, the reported yields are lower than those for the present method and, in the cases we have examined, the selectivities for monoreduction are generally, though not always, lower. The addition of 10 mol.% of

Ti(OPr-i)$_4$ to the reaction of (**1d**) with MeMgBr in ether-thf-toluene did not lead to a rapid reaction at 20 °C and a considerable amount of dibromide remained even after 18 h. It is also reported that reaction of two dibromocyclopropanes with LAH-Ti(OBu)$_4$ or DIBAL-Ti(OBu)$_4$ in refluxing dioxan or these reagents in combination with a range of other related catalysts and solvents leads to monobromides and fully reduced hydrocarbons.[17]

As Table 2 indicates, the reaction may also be applied to dichlorides:



Monochlorocyclopropanes have previously been available by the reduction of the corresponding 1,1-dichorides by reaction with DIBAL and a catalyst such as Ti(OBu)$_4$ for 6h at 75°C in dioxan; though this works well for 2-alkyl-1,1-dichlorocyclopropanes over reduction is a problem in other cases and it is not clear in all cases how good isolated yields are.[17] They have also been obtained by the reduction of dichlorocyclopropanes with tri-n-butyltin hydride at ca 140 °C,[18] or by reaction with Ph$_2$PK in DMSO at ambient temperature. Although the yield of this latter reaction is sometimes good (up to 80 %), and exo/endo selectivities can be excellent (83:5 for the exo/endo monochlorides derived from 7,7-dichlorobicyclo[4.1.0]heptane), in other cases the products are complex; the use of liquid ammonia as solvent can then lead to simplification.[19] Reduction using hydrazine - Raney nickel - sodium hydroxide has also been reported.[20] The present method provides a very efficient alternative. An example of its potential application is seen in the efficient dehydrochlori-nation of the mixture of monochlorides (**7c**) and (**8c**) to the cyclopropene (**9**):**

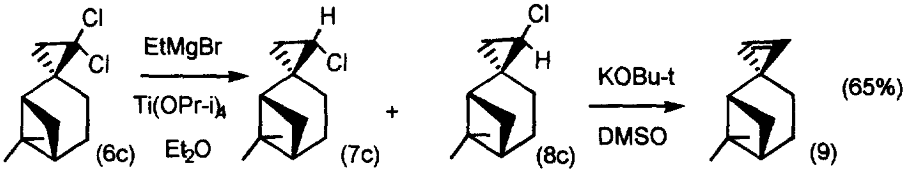


Table 2. Reduction of 1,1-dichlorocyclopropanes

starting material	quant, mmol	reagent, solvent	reagent, mol. equiv.	catalyst, mol.%	time of addition, min	time of stirring, min	isolated yield,[g] %	GLC control			ratio (7) : (8)
								(6)	(7) + (8)	h	
(**6a**)	10.0	EtMgBr, Et$_2$O	2.0	10	20	40		19	79	0	
						40h	-	0	88	11	2.0:1
	10.0	EtMgBr, Et$_2$O	2.0	10	20[b]	30[b] + 90	94	1	96	1	2.0:1
	2.0	MeMgBr, THF, MePh	1.5	-	3	4 h[b]	-	90	6	0	1.8:1
(**6b**)	10.0	EtMgBr, Et$_2$O	2.0	10	30[b]	30[b]	93	3	94	<1	1:1.2
(**6c**)	62.5	EtMgBr, Et$_2$O	1.6	10	30	3.5h	87[a]	5	94	0	1:2.6
	10.0	EtMgBr, Et$_2$O	2.4	10	70	60	95	0	98	0	1:2.6

a Distilled yield, b Reaction carried out at reflux, g after short column chromatography , h Fully dechlorinated

Typical procedure: A 1.0 M solution of ethyl magnesiumbromide in ether (12.5 - 14 ml, 1.25 - 1.4 mol.equiv.) was added over 10 - 30 m to a stirred solution of the gem-dibromocyclopropane (10 mmol) and titanium isopropoxide (0.2 - 2 mmol) in dry ether (20 - 25 ml) under nitrogen. Stirring was continued for 10 - 30 m at 20 °C when water (5 ml) was added carefully, followed by 10 % sulphuric acid (50 ml). The aqueous layer was extracted with ether (50 ml) and the combined organic layers were washed with water (25 ml), dried ($MgSO_4$) and evaporated at either 760 or 14 mmHg. The crude product was treated with petroleum (5 ml, bp. 40 - 60 °C), filtered through Matrix Silica 60 (5 g), washing the silica with further petroleum (20 - 50 ml), and evaporated to give the monohalocyclopropane(s). The product was generally pure enough to use directly; if necessary it was further purifed by distillation or column chromatography.

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* This work was carried out with the support of the INTAS programme.

** Compound (**9**) showed δ_H 7.41 (1 H, d, J 0.9 Hz), 7.36 (1 H, d, J 0.9 Hz), 2.2 - 2.3 (2 H, m), 1.7 - 2.0 (4 H, m), 1.55 (1 H, d, J 9.7 Hz), 1.03 (3 H, s), 1.22 (3 H, s), 1.1 - 1.3 (1 H, m); δ_C 21.61, 24.24, 24.34, 26.46, 27.27, 30.80, 40.70, 40.84, 54.31, 120.88, 123.37; υ_{max} 1627 cm^{-1}.

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