

Reduction of cyclopropanecarboxylic acids by borane, a chemoselective reduction sensitive to steric interactions and reaction conditions

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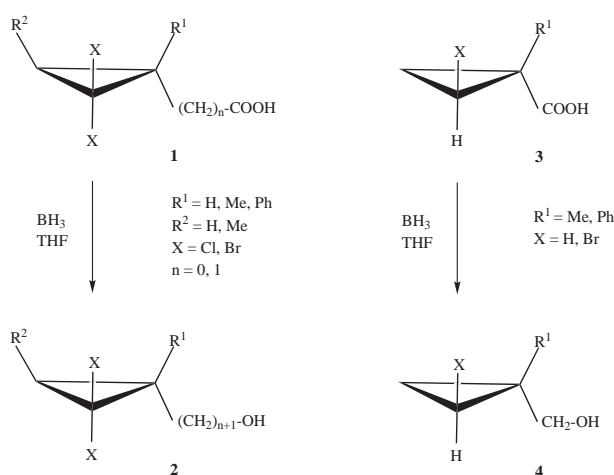
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A number of cyclopropanecarboxylic acids have been reduced by BH_3 reagents in THF to the corresponding cyclopropyl alcohols; the yield is sensitive to the steric influence of the substituents attached to the ring, the reaction temperature, and the nature of the borane reagent.

Keywords: cyclopropane carboxylic acids, borane

When selected carboxylic acids, some 2,2-dihalocyclopropanecarboxylic acids (**1a–1h**) and 2,2-dihalo-1-methylcyclopropylacetic acids (**1i–1j**), and a few non-halogenated cyclopropanecarboxylic acids and *trans*-2-bromocyclopropanecarboxylic acids (**3**), were reacted with borane in THF the corresponding primary alcohols, **2** and **4**, respectively, were the only products obtained (Scheme 1). The yields varied significantly and appeared, in general, to depend on the reaction temperature, the substrate structure, and whether the borane reagent was pre-made or generated *in situ*.

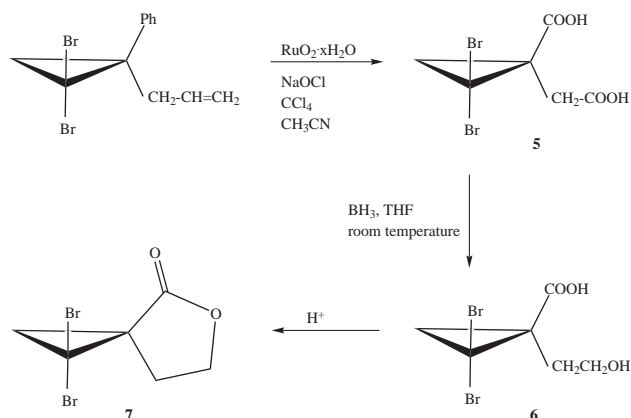


Scheme 1

With *pre-made borane* the success was very sensitive to the temperature. Whereas all the 2,2-dihalocyclopropanecarboxylic acids were reduced with difficulty at room temperature, **2** was obtained in excellent yields at 50 °C (Table 1) irrespective of the steric bulk of the substituents α to the carboxyl group. This observation is in accordance with findings reported by Brown and co-workers⁹. At ambient temperature (*ca* 20 °C), however, the yields were significantly lower for all substrates, as much as 80% lower for some of the acids with substituents α to the carboxyl group; consequently, steric interactions become important when the temperature is lowered.

Brown and co-workers⁹ have reported that introduction of electron-withdrawing substituents next to a carboxyl group *decreases* the rate of borane reduction of that group. Since there is (partial) conjugation between the cyclopropyl group and the carboxyl group in cyclopropanecarboxylic acids^{15,18} it

was envisaged that if the carboxyl group was separated from the cyclopropane ring with a methylene group, the reduction ought to occur more easily. This was indeed observed; borane reduction of 2,2-dihalo-1-methylcyclopropylacetic acids **1i** and **1j** at room temperature afforded the corresponding methanol derivatives (**2i** and **2j**) in essentially quantitative yields (Table 1). On this basis it was encouraging to observe that when 2,2-dibromo-1-carboxymethylcyclopropanecarboxylic acid **5** was treated with pre-made borane at room temperature, a highly regioselective attack on the acetic-acid carboxyl group took place, giving 2,2-dibromo-1-(2-hydroxyethyl)cyclopropanecarboxylic acid **6**, which was converted into the corresponding lactone **7** under acidic work-up. A valuable conclusion can therefore be drawn: the lower reactivity of pre-made borane at room temperature as compared to at 50 °C can be utilised to perform selective conversions of carboxylic acids into primary alcohols.



Scheme 2

The importance of the steric effects was substantiated by several experiments. For instance, when a mixture of a 2,2-dihalocyclopropanecarboxylic acid and the corresponding *trans*-2-halocyclopropanecarboxylic acid was treated with pre-made borane, the monohalogenated acid was almost exclusively reduced due to the steric congestion caused by the halogen atom *cis* to the carboxyl group.

The acids were also reacted in THF with borane generated *in situ* from sodium borohydride and boron trifluoride etherate. At ambient temperature the resulting alcohols **2** and **4** were obtained in yields comparable to those obtained with pre-made borane at 50 °C. Thus, *in situ*-generated borane is a

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Table 1 2,2-Dihalocyclopropyl alcohols (**2**) obtained by reacting acids **1** with pre-made borane

1	R ¹	R ²	X	n	R.t. ^a /°C	Product ^b	Yield (%) ^c
a	H	H	Cl	0	20	2a ¹¹	41
					50	2a	97
c	Me	H	Cl	0	20	2c ¹²	9
					50	2c	89
e	Ph	H	Cl	0	20	2e ¹³	9
					50	2e	88
f	Ph	H	Br	0	20	2f ⁷	11
					50	2f	76
i	Me	H	Cl	1	20	2i ^{14, 15}	99
j	Me	H	Br	1	20	2j ⁵	98

^aR.t. = reaction temperature. ^bAll compounds are known from the literature. For each known compound a literature reference is given as superscript to the compound number. ^cIsolated yields.

significantly more efficient reducing agent than pre-made borane at 20 °C; this conceivably might suggest that different intermediates are involved under the two sets of conditions.^{9,19}

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Techniques used: ¹H and ¹³C NMR, IR, MS and elemental analysis

References: 28 Tables: 3 Schemes: 2

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