Pergamon

Tetrahedron Letters, Vol. 36, No. 36, pp. 6457-6460, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01291-5

Drastic Effects of Dioxygen on the Selectivity of Reduction by $LiAlH_4$. Milder Conditions Made Possible by Strictly Anaerobic Conditions.

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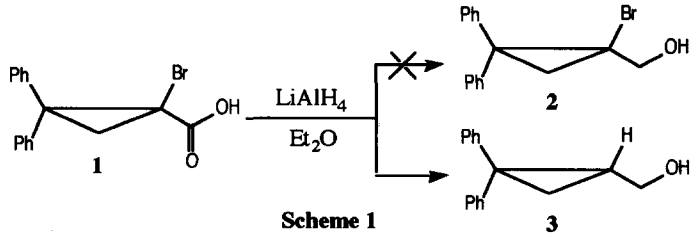
Abstract: Reduction of the gem-disubstituted cyclopropane **1** with $LiAlH_4$ yields different results under strictly anaerobic conditions and loosely anaerobic ones. Under strictly anaerobic conditions, (+)-1-bromo-2,2-diphenylcyclopropanecarbinol **2** is quantitatively reduced to **3** with complete racemization. These observations are explained by a radical chain mechanism. They open the way to reductions by $LiAlH_4$ under mild conditions.

We started recently a study aiming at specifying the mechanism of the Grignard reagent formation[1]. As a mechanistic probe, we decided to use the optically active 1-bromo-1-methyl-2,2-diphenylcyclopropan[2-5]. However, the reduction step of the carboxylic acid **1** by $LiAlH_4$ did not yield the alcohol **2** as reported by Walborsky[6], but rather the totally reduced alcohol **3**.(Scheme 1). The aim of this communication is to show which experimental conditions may lead to such changes in selectivity of $LiAlH_4$ and to propose reasons explaining the variety of roles possibly played by trace amounts of O_2 present in $LiAlH_4$ reductions.



Scheme 1

Lithium aluminum hydride and, more generally, metal hydrides often react as nucleophilic species[7-11]. The reduction of the carbonyl or carboxylic groups with lithium aluminum hydride ($LiAlH_4$), for example, is believed to involve a direct hydride transfer as the rate-determining step[12,13].

S_N1 and S_N2 processes are reported[14,15] to occur in the metal hydride reductions of alkyl and aryl halides. Vinyl, bridgehead, and cyclopropyl halides are generally considered to be inert toward an S_N2 process[16]. Depending on the reaction conditions, however, the reduction of these halides with alkali metal napthalene[17] and with $LiAlH_4$[18-28] has been reported. Ashby and his co-workers reported that $LiAlH_4$ reduction of secondary and tertiary alkyl halides could involve radical intermediates[29-36].

The results obtained in the $LiAlH_4$ reduction of the 1-bromo-2,2-diphenylcyclopropanecarboxylic acid **1** are given in Table 1. All manipulations were conducted by standard Schlenck techniques, under an atmosphere of purified argon. The prepurified grade argon (Linde) was further purified by passage over a column of molecular sieves (3Å), a BASF R3-11 catalyst column at 150° C and a phosphorus pentoxide column. All glassware and transfer needles were oven-dried at 150° C and cooled on a dual manifold vacuum / argon system just prior to use. All liquid substrates and solvents were degassed by freeze-pump-thaw cycles before being used in the reaction. We insist on these experimental conditions because the reduction reported in Scheme 1 was described[37] as being realized under N_2 and nevertheless yielded 75% of **2** in direct contrast with results gathered in Table 1. The difference does not originate from a difference in $LiAlH_4$ origin[33] because, if one operates under weakly aerobic conditions (entry 5, Table 1), one obtains **2** as reported by Walborsky.

Table 1. Results of Reactions of **1** with $LiAlH_4$ in Et_2O at 0° C

Run[a]	**1** / mmol	$LiAlH_4$ / mmol	Addition time (h)	Reaction time[b] (h)	Yields / % **2**	**3**
1	2	8	0.5	4.5	0	100
2	4	4	0.5	4.5	0	100
3	6.5	5	1.5	4.5	0	100
4	6.5	5	0.5	2.5	0	100
5[c]	100	80	1.5	6	75	0

a Runs 1,2,3,5 : Solution of **1**/Et_2O was added over the slurry of $LiAlH_4$/Et_2O
Run 4 : Filtered solution of $LiAlH_4$/Et_2O was added over the solution of **1**/Et_2O
b Reaction time = addition time + agitation time
c Leak of air purposedly left in the mixture

Examination of this Table 1 (Runs 1-4) shows that $LiAlH_4$ gives, in all cases, the reduced alcohol **3** and not the corresponding halide **2**.

Reductions of gem-dihalocyclopropanes with $LiAlH_4$ have been reported to proceed, at least in part, via radical intermediates[19,25]. The major or single product of these reductions was the monohalocyclopropane. However, the experimental conditions are not specified[18] or the reductions occur under N_2[24] but without the strict precautions described in the present paper. They could converge therefore with Walborsky's report[3,5,6] and contrast with the mild reduction of the bromine present in **2**. The reduction of monohalocyclopropanes by $LiAlH_4$ without a specific control of completely anaerobic conditions demands temperatures higher than 50° C and / or excess of hydride[24,38].

A possible explanation of these conflicting results could be searched in the direction of the Beckwith's report concerning the $LiAlH_4$ reduction of halogenoarenes[28]. This author suggested that, under conditions where oxygen is scrupulously excluded from the reaction medium, the active intermediate is an arylmetal ArM (M= Li or an Al-centred group). This intermediate, after hydrolysis, would yield the arene. Transposed to our case, this would mean that the active intermediate involved under our specific conditions could be RM (R= cyclopropyl).

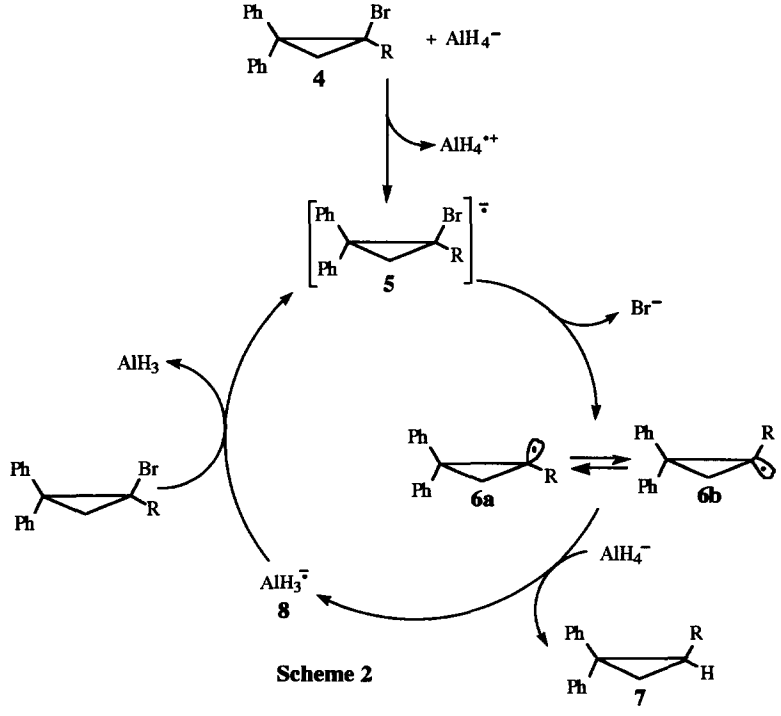
Two data disagree however with such an hypothesis. The first one is that, under strictly anaerobic conditions, the reduction of bromoarenes was far slower than their reduction when small amounts of air leaked

into the mixture[28]. For the bromocyclopropanes studied here, the effect of O_2 is just the opposite in terms of rates of reaction. The second data is provided by the reduction of the (+)-1-bromo-2,2-diphenylcyclopropane carbinol **2** (ee=97%) under strictly anaerobic conditions in Et_2O at 0° C. This reduction yields quantitatively the alcohol **3** totally racemic. Such a result strongly suggests the intermediacy of radicals for the reactions reported in table 1. Indeed, if the reduction were following the RM pathway, a retention of configuration would have been expected[39].

We conclude that the $LiAlH_4$ reduction of cyclopropyl bromide **1**, under strictly anaerobic conditions, proceeds via a radical chain reaction (scheme 2) and is very sensitive to trace amounts of dioxygen. The scheme 2 deserves some comments. The E° value of $LiAlH_4$ is about -0.3V (vs NHE)[40], that of most halocyclopropanes lies in the range of -0.8V (1-bromo-2,2-diphenylcyclopropanecarboxylique acid) at -1.9V (1-bromo-1-methyl-2,2-diphenylcyclopropane) (vs NHE)[41]. Therefore one cannot be totally confident in suggesting an initiation step involving electron transfer. Any paramagnetic impurity could as well initiate the chain by S_H2 step. The chain would then still be an electron transfer chain because of the step **8** -> **5** but the initiation would be of the inner sphere type (see ref [42], Table II). This point has been raised by other authors[43] and is still controversial[35]. From the very first studies about chain reactions, the nature of the initiation step has been a controversial one[44].

Traces of O_2 may be extremely efficient as scavenger because they could possibly interfere with steps **4** -> **5**, or **6** -> **7** or **8** -> **5**. Furthermore one must remember that O_2 has a rather high coefficient of diffusion[45]. This is important because the rate of reaction of radicals such as **6** with O_2 is diffusion controlled ($O_2 + R\cdot > 10^9\ M^{-1}\ s^{-1}$)[46].

A practical consequence of the present results is that reductions under mild conditions become feasible for "inert" Csp^3 centered halides provided that O_2 or other inhibitors are strictly removed from the reaction mixture.



Scheme 2

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(*Received in France* 15 *May* 1995; *accepted* 10 *July* 1995)