Tetrahedron Letters No. 49, pp 4933 - 4936, 1973. Pergamon Press. Printed in Great Britain.

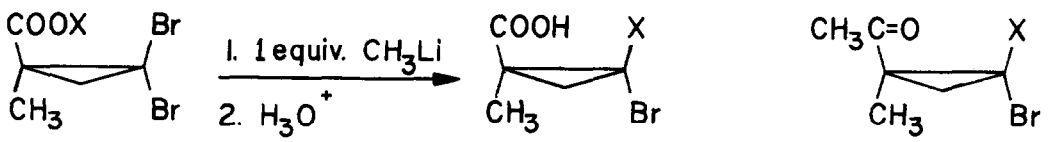
METHYLLITHIUM UNDERGOES HALOGEN EXCHANGE FASTER THAN IT ABSTRACTS A CARBOXYLIC PROTON: STEREOSELECTIVE REDUCTION OF 1-METHYL-2,2-DIBROMOCYCLOPROPANECARBOXYLIC ACID

Cy A. Stein and Thomas Hellman Morton*

Metcalf Research Laboratories, Brown University, Providence, Rhode Island, USA 02912

(Received in USA 9 October 1973; received in UK for publication 29 October 1973)

Among the reactions of alkyllithium compounds, two of the best known are the abstraction of a proton from a carboxylic acid to form a lithium salt[1] and the exchange of lithium with one bromine from a gem-dibromoalkane to form an α-bromoalkyllithium intermediate[2]. This paper reports the results of an intramolecular competition experiment, which suggest that the latter reaction proceeds faster than the former, and the utilization of this phenomenon to effect the stereoselective reduction of compound 1 to compound 2 shown below.



1 a: X = H
b: X = D

2 a: X = H
b: X = D

3 a: X = H
b: X = D

The methyl ester of 1 was prepared in 25% yield by addition of dibromocarbene to methyl methacrylate by the Doering-Hoffmann procedure[3]. A sample of this ester has also been prepared by reaction of methyl methacrylate with phenyl(tribromomethyl)mercury in refluxing benzene by the method of Seyferth, et al[4]: bp. 106-109° (25 mm.); n_D^{25} 1.5173; ir (CCl_4) $\nu_{C=O}$ 1740 cm^{-1}; pmr (CCl_4) δ 3.77 (s, 3, OCH_3), 2.40 (d, 1, J = 7.5 Hz, HCH), 1.59 (s, 3, $C\text{-}CH_3$) 1.53 (d, 1, J = 7.5 Hz, HCH); mass spectrum (50 V) m/e (relative intensity) 274 (0.15), 272 (0.30), 270 (0.15), 193 (47), 191 (51), 165 (100), 163 (100). Carboxylic acid 1a is prepared by saponification of the ester: mp. 110-112.5°; ir (CCl_4) $\nu_{C=O}$ 1710 cm^{-1}; pmr ($CDCl_3$) δ 11.58 (s, 1, COOH), 2.44 (d, 1, J = 8 Hz, HCH), 1.63 (s, 3, CH_3), 1.62 (d, 1, J = 8 Hz, HCH). The large chemical shift difference between the two geminal cyclopropyl protons is consistent with nmr spectra reported for other 1-methylcyclopropyl carboxyl compounds, and the upfield doublet is assigned to the proton cis to the methyl group[5].

When 10 mMole methyllithium (Alfa) in 15 ml ether is added dropwise to a stirred solution of 2.6 g (10 mMole) of 1a in 15 ml ether at 0°, a pmr spectrum of an aliquot of the reaction mixture indicates the formation of methyl bromide. After stirring for 90 minutes at 0°, the clear reaction mixture is quenched with dilute hydrochloric acid, the ethereal layer separated, and the aqueous layer extracted with two 50 ml portions of ether. Removal of solvent from the combined ethereal solutions under reduced pressure affords 1.6 g of a residual oil. The pmr spectrum of this residue shows that it consists of a 2:5 ratio of starting material (22% recovery) to product 2a (58% yield): bp 161-163° (45 mm); n_D^{25} 1.5028; ir (CCl_4) $\nu_{C=O}$ 1690 cm^{-1}; pmr (CCl_4) δ 12.19 (s, 1, COOH), 3.54 (dd, 1, J = 6 Hz, 8 Hz, CBrH), 1.91 (dd, 1, J = 6 Hz, 8 Hz, HCH), 1.47 (s, 3, CH_3), 1.04 (t, 1, J = 6 Hz, HCH); mass spectrum (50 V) m/e (relative intensity) 180 (4), 178 (4), 99 (100).

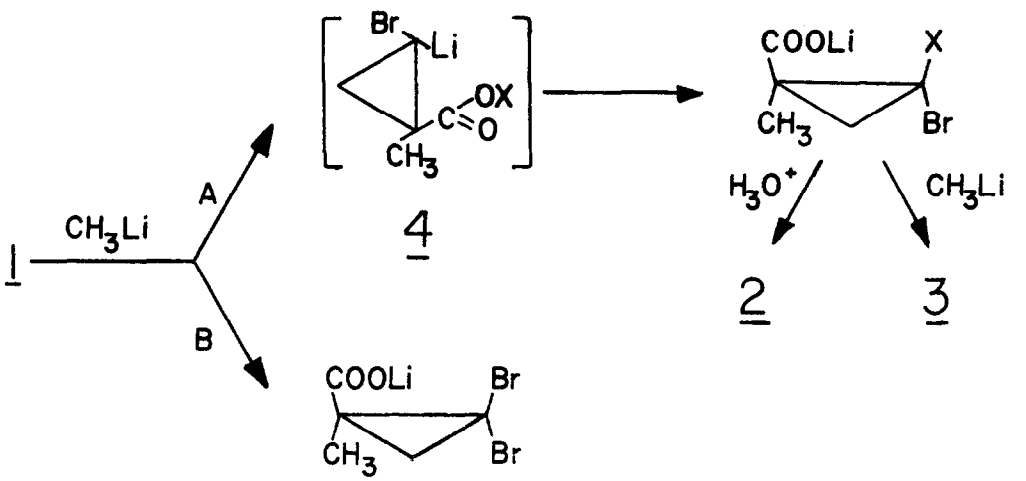
If a second equivalent of methyllithium is added to the reaction mixture before quenching, ketone 3a is recovered: ir (CCl_4) $\nu_{C=O}$ 1700 cm^{-1}; pmr (CCl_4) δ 3.31 (dd, 1, J = 5 Hz, 8 Hz, CHBr), 2.19 (s, 3, $COCH_3$), 1.84 (dd, 1, J = 5Hz, 8Hz, HCH), 1.57 (s, 3, CCH_3), 0.88 (t, 1, J = 5 Hz HCH); mass spectrum (50 V) m/e (relative intensity) 163 (1), 161 (1), 97 (100).

The stereochemistry of 2 and 3 is assigned with the aid of isotopic substitution: when 1 equivalent of methyllithium is added to the deuterium substituted carboxylic acid 1b, the pmr spectrum of the product shows the same singlets as 1a, but there is no resonance in the region 3.0 δ to 4.0 δ, and the resonances at 1.91 δ and 1.04 δ are both collapsed to doublets (J = 6 Hz). It is inferred that the methine position, geminal to bromine, is deuterated, > 95 atom % D, and that the geminal splitting constant of the methylene protons is 6 Hz. Hence, in 2a, the vicinal coupling between the downfield methylene proton and the methine proton is 8 Hz, while the vicinal coupling between the upfield methylene proton and the methine is 6 Hz. These coupling constants are comparable to those reported for other substituted cyclopropanes, and it is known that the vicinal coupling constant for cis protons is greater than for trans protons in substituted cyclopropanes[6]. As the downfield methylene proton in 2 must be cis to the carboxyl function, and as it also has a greater coupling to the methine, the methine proton in 2a must be cis to the carboxyl group. The pmr spectrum of 3b, from reduction of 1b with 2 equivalents of methyllithium, is consistent with this conclusion: both methylene resonances are collapsed to doublets, J = 5 Hz.

The following observations are made regarding the conversion of 1 to 2. First, the lithium salt of 1, prepared from reaction of 1a with lithium hydride, is stable under the reaction conditions. Second, quenching of the reduction of 1a with DCl, 4M in D_2O, affords no 2b; similarly, quenching the reduction of 1b with HCl affords no 2a. The sequence illustrated in Scheme I is proposed to explain these results. From the amount of starting material recovered in the conversion of 1 to 2, it is estimated that reaction via path A occurs at least 2.5 times as fast as reaction via path B.

No speculation is made regarding the mechanism of path A; whether intermediate 4 is formed stereoselectively or if, indeed, it is configurationally stable. However, as the lifetime of α-bromocyclopropyllithium compounds is brief, owing to the rapid elimination of lithium bromide to yield cyclopropylidenes[7], intramolecular quenching of 4 is postulated to account for the stereoselectivity of the reduction.

SCHEME 1



It is significant to note, by contrast, the reaction of 1 with a Grignard reagent, for methylmagnesium bromide is reported to reduce gem-dibromocyclopropanes, possibly via a radical process[8]. When methylmagnesium bromide in tetrahydrofuran (along with excess methyl bromide) is added dropwise to a stirred solution of 1a at 0°, immediate gas evolution is observed and the solution becomes slightly turbid. Apparently a magnesium salt is formed, for, on acid workup, a quantitative yield of starting material is recovered. This salt is inert to further reaction with the Grignard reagent, and starting material is recovered quantitatively even after 17 hours reflux with a second equivalent of methylmagnesium bromide.

ACKNOWLEDGMENTS: The support of the Research Corporation, through a Cottrell Grant to THM, and of E.I. DuPont de Nemours and Company, through a Science and Engineering Grant to Brown University, is gratefully acknowledged.

REFERENCES

1. R.G. Jones and H. Gilman, Organic Reactions, 6, 339 (1951).
2. W. R. Moore and H. R. Ward, J. Org. Chem., 27, 4179 (1962).
3. W. von E. Doering and A. K. Hoffmann, J. Amer. Chem. Soc., 76, 6162 (1954).
4. D. Seyferth, J. M. Burlitch, and J. K. Heeren, J. Org. Chem., 27, 1491 (1962).
5. A. A. Pavia, J. Wylde, R. Wylde, and E. Arnal, Bull. Soc. Chim. France, 2109 (1965).
6. K. B. Wiberg and B. J. Nist, J. Amer. Chem. Soc., 85, 2788 (1963).
7. L. Skattebøl, Chem. Ind. (London), 2146 (1962).
8. D. Seyferth and B. Prokai, J. Org. Chem., 31, 1702 (1966).