Journal of Organometallic Chemistry, 55 (1973) C53–C57
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Preliminary communication

Stereospecific routes to the isomeric 7-bromo-7-lithionorcaranes

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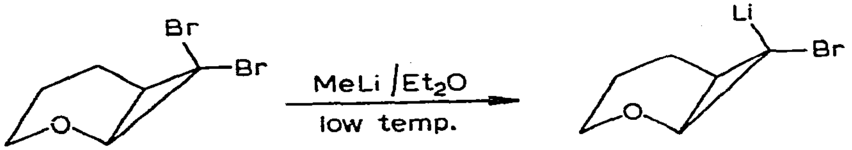
(Received May 8th, 1973)

SUMMARY

anti-7-Bromo-*syn*-7-lithionorcarane can be prepared stereospecifically by the reaction of n-butyllithium with 7,7-dibromonorcarane in THF, provided that a slight excess of the dibromo compound is present and the temperature is allowed to rise briefly from −107° to about −93°. *syn*-7-Bromo-*anti*-7-lithionorcarane results when n-butyllithium is allowed to react with *syn*-7-bromo-*anti*-7-trimethyltinnorcarane in THF at low temperature. Stereospecific reactions of these reagents with Me_3SiCl, Me_3SnCl, CO_2 and C_2Cl_6 are reported.

A stereospecific conversion of a *gem*-dibromocyclopropane to a *gem*-bromolithiocyclopropane (I) has been reported by Taylor *et al.*[1] (Eq. 1). This result was rationalized in terms of intramolecular coordination of the lithium to the oxygen atom. We report here another example of the preferential formation of a single isomer during the preparation of a *gem*-bromolithiocyclopropane but in which there is no such possibility of intramolecular coordination as a directive factor.



(1)

(I)

During studies devoted to the preparation of 7-bromo-7-lithionorcarane by the reaction shown in Eqn. 2*, we encountered a reaction in which only one isomer, *anti*-7-

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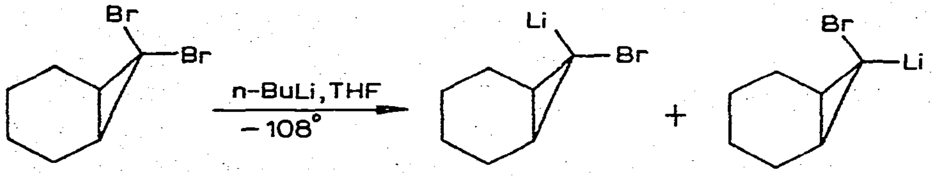
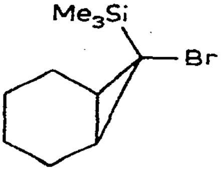
*The temperatures given in this paper are corrected values, obtained by calibration of the pentane thermometer used with a low temperature thermocouple. The actual thermometer readings (bulb immersion) were about 8°C higher.



(II) (III)

(2)

bromo-*syn*-7-lithionorcarane (II) was formed. This was indicated by an acid hydrolysis of the reagent solution, which gave only *anti*-7-bromonorcarane. Closer investigation revealed that about 2% of the 7,7-dibromonorcarane had not been converted to the lithium reagent. With the possibilities in mind that the presence of an excess or a deficiency of n-butyllithium and the reaction temperature might be critical factors, we carried out further experiments in which the effects of these variables were examined. Ultimately, it was found that two conditions appear to be necessary for the preparation of a reagent solution containing only II: a slight excess of 7,7-dibromonorcarane was required and a brief (~ 10 min) exposure of the reagent solution to a slightly higher temperature (about −93°). Thus, a reaction of 50 mmol of 7,7-dibromonorcarane with a slight deficiency of n-butyllithium in a THF/Et$_2$O solvent mixture was carried out at −103° during the addition and at −93° for 30 min subsequent to completion of the addition. Treatment with trimethylchlorosilane at −95° gave a product mixture



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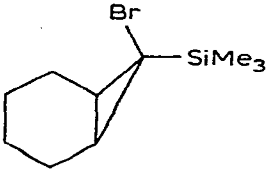
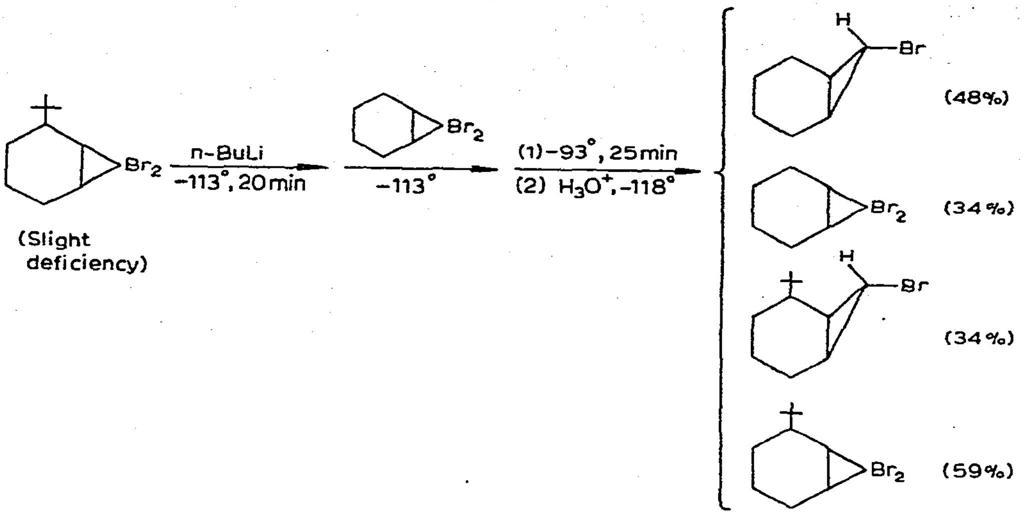


(V)

containing IV in 76% yield (and none of V), together with a small amount (5%) of 7-bromonorcarane. A similar reaction with identical thermal history, but in which a slight excess of n-butyllithium was present, gave a mixture of IV (61% yield) and V (16% yield), while a reaction mixture in which a slight excess of 7,7-dibromonorcarane had been used, but in which the reaction temperature was kept at −124°, also produced a mixture of isomers on treatment with Me$_3$SiCl (IV in 55%, V in 17% yield). Further work demonstrated that the most likely route for isomerization was a chain of successive bromine/lithium exchanges involving the excess dibromonorcarane, until II was the only lithium reagent present. Experiments of the type indicated in Eqns. 3 and 4 clearly demonstrated that such li/Br exchange occurs. These data confirm that extensive exchange has occurred. Also, it seems clear that an equilibrium situation obtains it may be that the preference for a *syn* lithium reagent is due to the greater steric requirement of the bromine atom. However, further discussion of this point is not warranted in view of our lack of knowledge of the constitution of reagents II and III in THF medium.



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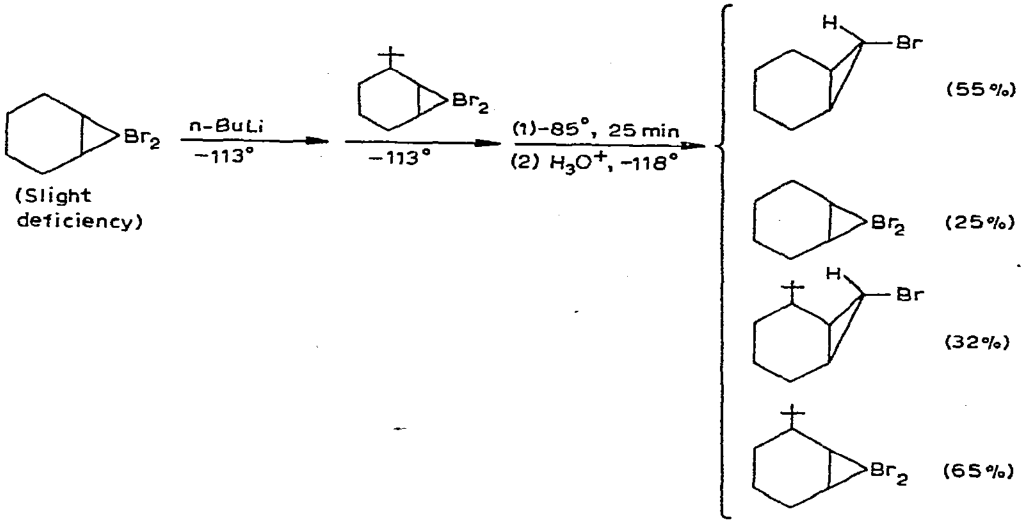
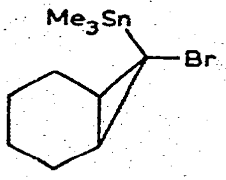


(4

This procedure, in which a slight excess of the *gem*-dibromocyclopropane is used provides a simple route to preparatively useful quantities of II. Application of this procedure in synthesis is nicely shown by some reactions of solutions of II: with trimethyltin chloride to give VI in 63% yield; with CO_2, followed by acidification, to give VII in 76% yield, which was converted to its methyl ester in 80% yield; with hexachloroethane to give VIII in 63% yield.



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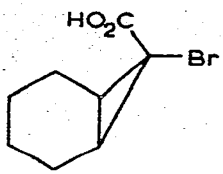

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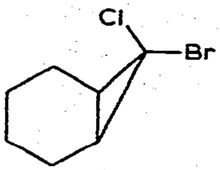
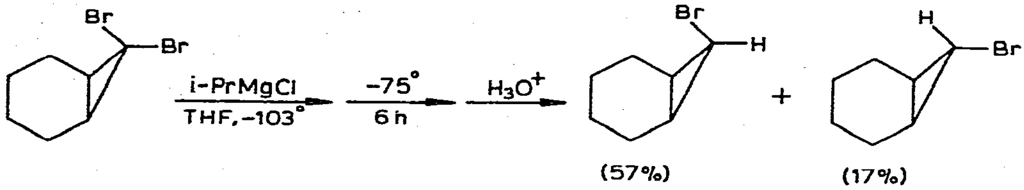


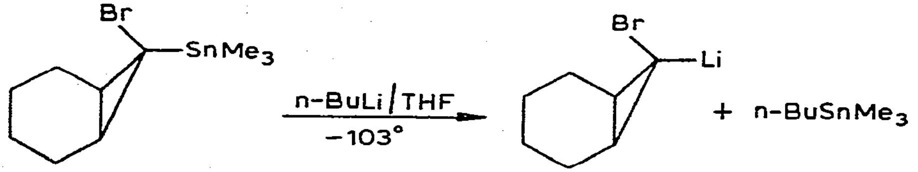
(VIII)

A similar exchange reaction of 7,7-dibromonorcarane with isopropylmagnesium chloride in THF gave a mixture of isomeric Grignard reagents in which the *anti*-MgCl isomer predominated by at least 3/1 (Eqn. 5). However, treatment of such a mixture of



(5)

Grignard reagents with trimethyltin chloride under these conditions resulted in the isolation of only *syn*-7-bromo-*anti*-7-trimethyltinnorcarane (IX). The ready availability of isomerically pure IX permitted the preparation of the other 7-bromo-7-lithionorcarane isomer, III, in high yield via the stereospecific transmetalation reaction with n-butyllithium, Eqn. 6. Reactions of solutions of III with trimethylchlorosilane, carbon dioxide (followed by acidification) and with hexachloroethane proceeded stereospecifically to give X, XI and XII, respectively.



(IX)

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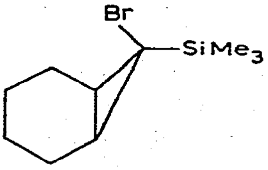
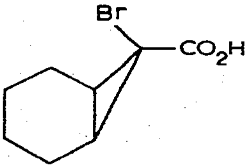
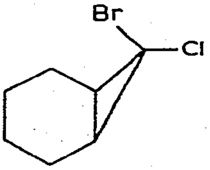


(X)



(XI)



(XII)

This availability of II, free of III, and of III, free of II, represents a very useful advance in halocyclopropane chemistry that should allow the preparation of both isomers in high purity of many more norcarane derivatives than those reported here. The general concepts demonstrated here should be capable of limited generalization to other cyclopropane systems where steric factors are of sufficient importance. We note also that this study has provided further examples of the previously demonstrated[2] configurational stability of cyclopropyllithium reagents.

All new compounds were characterized by elemental analysis and IR and NMR spectroscopy. Full details of this and related work will be reported in the near future.

ACKNOWLEDGEMENTS

The authors are grateful to the U.S. Air Force Office of Scientific Research (NC)-AFSC (Grant AF-AFOSR-72-2204) and to the National Science Foundation (Grant GP-31429X) for generous support of this work and to the Union Carbide Corporation and M&T Chemicals, Inc. for gifts of chemicals. R.L.L. acknowledges the award of an Air Pollution Special Fellowship (5 FO3 AP36,021). We also thank Miss Carol K. Haas for a useful suggestion relating to this work.

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