Tetrahedron Letters,Vol.24,No.51,pp 5767-5770,1983 0040-4039/83 $3.00 + .00
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SPIROANNELATION *VIA GEM*-DIHALOCYCLOPROPANE SUBSTRATES AND A CYCLOCUPRATE SPECIES

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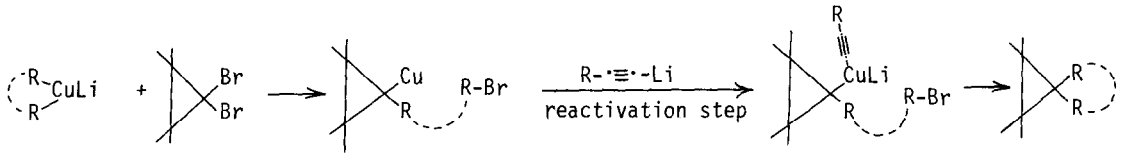
Abstract: The dialkylation of *gem*-dibromocyclopropanes with a new 'cyclocuprate' species to yield spiro compounds is possible if the reaction is performed in the presence of a lithium acetylide.

The reactions of lithium diorganocuprate reagents with *gem*-dihalocyclopropanes have been studies extensively [1]. These reports illustrate that lithium divinyl and dimethylcuprate reagents produce mono-substituted bromocyclopropanes or disubstituted cyclopropanes. However, other cuprates, for example lithium dibutylcuprate, yield products originating from simultaneous reduction and substitution of the *gem*-dihalide functionality.

In view of the mechanisms proposed [1d] for the reaction of *gem*-dihalocyclopropanes with lithium dibutylcuprate we considered the possibility of producing *gem*-dialkylated and spiro products by coupling the alkyl bromide produced *in situ* with a reactivated copper species (2) [2], Scheme 1.



(1) (2)

Scheme 1

A previous report [3] stated that cuprate reagents prepared from the corresponding Grignard reagents (solvent not specified) did not produce the alkylated copper intermediate (1). We have found that when employing THF as solvent 7,7-dibromonorcarane with two equivalents of $Bu_2CuMgCl$ at -80° give, after hydrolysis, 7-butylnorcarane (one isomer) and octane each in 95% yield.

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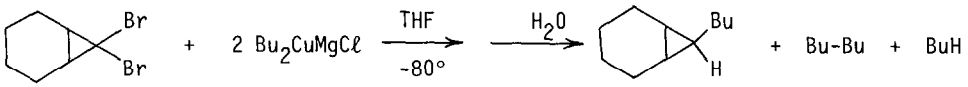
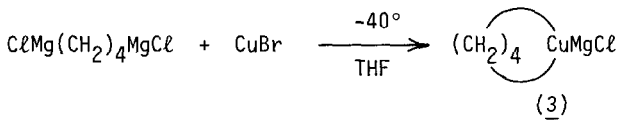


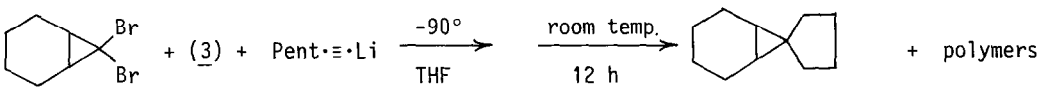
The cyclocuprate reagent (3)[4] required for the synthesis of spiro compounds was prepared from the readily available 1,4-bis(chloromagnesio)butane[5] by addition of one equivalent of a 0,4 M THF solution of the bis-Grignard reagent to one equivalent of CuBr or CuBr.SMe_2 in THF at -40°. Stirring the reaction mixture for 30 minutes at -40° produced a negative Gilman test.[6]



(3)

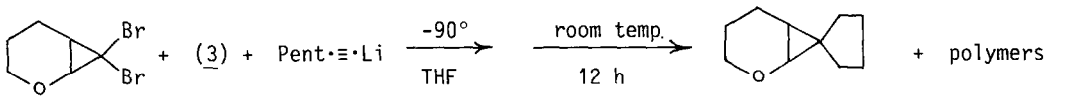
Reaction of the cyclocuprate (3) with 7,7-dibromonorcarane in THF from -80° to -50°, over a period of one hour, followed by addition of one equivalent of 1-lithio heptyne according to scheme 1, produced, after work-up of the reaction mixture, an 80% yield of *trans*-7-bromonorcarane[7]. The reduction proceded stereospecifically since only *trans*-7-bromonorcarane was detedted. In contrast, the reported reaction between CH_3MgBr and 7,7-dibromonorcarane in THF solution produces both *cis*- and *trans*-isomers of 7-bromonorcarane before hydrolysis[8].

It was subsequently established that 1) at -80° the cyclo cuprate(3) does not react with 7,7-dibromonorcarane as the starting *gem*-dihalide is recovered in quantitative yield on work-up of the reaction mixture after two hours and 2) the reduction of 7,7-dibromonorcarane by the cyclocuprate (3)takes place at -50° before introduction of the lithium acetylide. However, when 1-lithioheptyne was added to a mixture of the cyclocuprate (3) and 7,7-dibromonorcarane at -90° and the stirred reaction mixture was allowed to reach room temperature overnight, the tricyclic spiroalkane (4) [9] was isolated in 40% yield.



(4) 40%

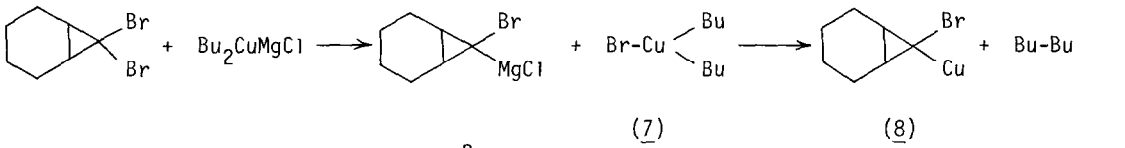
The *gem*-dibromocyclopropane ether (5) under similar reaction conditions produced the tricyclic spiro-ether (6) in 19% isolated yield.



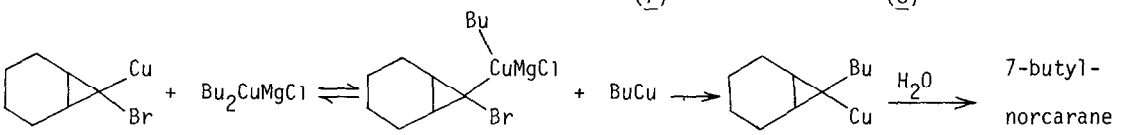
(5) (6) 19%

Spectroscopic and analytic data of compounds (4) and (6) are in accord with the assigned structures [10].

In the case of $Bu_2CuMgC\ell$ the formation of one equivalent of octane from two equivalents of cuprate may be explained by a mechanism where the initial step of metal-halogen exchange produces an unstable copper(III) intermediate (7). Decomposition of (7) will produce octane [11] and the carbenoid (8) which then reacts with additional cuprate to give 7-butyl norcarane after hydrolysis.



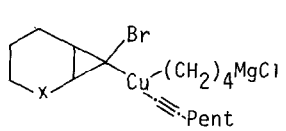
(7) (8)



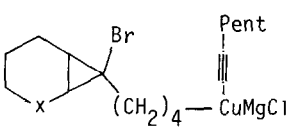
(8)

The fact that the cyclocuprate (3) does not react with 7,7-dibromonorcarane at -80° indicates that it is less reactive than $Bu_2CuMgC\ell$. The *in situ* formation (at -50°) of *trans*-7-bromonorcarane when the cyclocuprate (3) is employed may be explained by hydrogen abstraction from the solvent by transient radical intermediates generated during metal-halogen exchange [8]. The highly reactive carbenoid (8), on the other hand, may be attacked less efficiently by the less reactive cyclocuprate (3) and preferentially be reduced by the solvent.

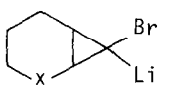
The role of the lithium acetylide, which suppresses this reduction process, is probably to convert (3) to a more reactive species of the type R_3CuM_2, which could also promote metal-halogen exchange and lead to an unsymmetrical copper (III) intermediate (9). *Syn* elimination from (9), followed by formation of a new cuprate (10) and intramolecular substitution yields the spiro products (4) or (6). Alternatively, the carbenoid (11), produced by metal-halogen exchange, could insert [12] into (3) to produce a new cuprate (12) which on thermal decomposition yields (4) and (6). (X = CH_2 or O)



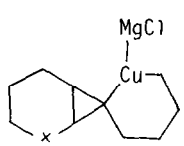
(9)



(10)



(11)



(12)

Evidence for this mechanism was found when (11, X = CH_2), prepared independently at -95°, [13] was treated with a solution of prepared cyclocuprate (3). Allowing the reaction mixture to reach room temperature produced the spiroalkane (4) in 20% yield together with unidentified products.

Although the exact mechanism for the above reactions is not known, the results illustrate the important role of metal-halogen exchange. The different carbenoids generated give rise to *trans*-7-bromonorcarane, 7-butylnorcarane, (4) and (6).

Experiments using complex cyclo-organocopper species are in progress to establish their synthetic application in the synthesis of spiro compounds.

Acknowledgements: BGM and FS thank the South African Council for Scientific and Industrial Research and the University of Fort Hare for financial assistance.

References and notes

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(b) ibid, 1968, 90, 5615.
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4. The structure (3) merely indicates stoichiometry. Whether the cuprate exists as a monomer, dimer or polymer, is not known.

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7. ^{1}H-nmr ($CC\ell_4$), 2.53 ppm triplet CBrH J = 3.7 Hz: ^{13}C-nmr ($CDC\ell_3$), 25.44 ppm: CBrH.

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10. (4) ^{1}H-nmr ($CC\ell_4$), 0.6-1.8 ppm complex multiplets: ^{13}C-nmr ($CDC\ell_3$) 28.50 ppm C_{spiro}:$C_{11}H_{18}$ requires 150.14042, found 150.14083, base peak 67.

(6) ^{1}H-nmr ($CDC\ell_3$), 0.77 ppm multiplet 1H, C<u>H</u>; 3.13 ppm doublet J = 7.5 Hz O-C-<u>H</u>; 3.35 ppm multiplet CH_2 -O: ^{13}C-nmr ($CDC\ell_3$) 29.55 ppm C_{spiro}, 64.42 and 58.75 ppm O-<u>C</u>-H and -<u>C</u>H_2-O : $C_{10}H_{16}O$ requires 152.120290, found 152.120098, base peak 41.
(Compound (6) is unstable in solution. Its decomposition is accelerated in the presence of halogenated solvents).

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(Received in UK 10 August 1983)