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CYCLOPROPANES

XL *. A CHIRAL CYCLOPROPYLCOPPER REAGENT

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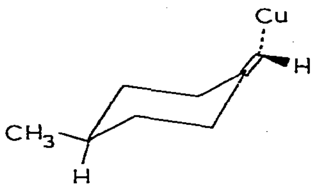
Summary

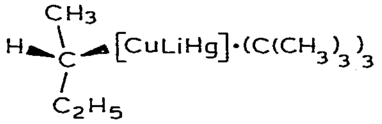
Chiral (*R*)-1-cuprous-1-isocyano-2,2-diphenylcyclopropane was prepared from the corresponding (*S*)-1-lithio-1-isocyano-2,2-diphenylcyclopropane by reaction with cuprous iodide. In contrast to the lithium reagent the chiral copper(I) reagent was configurationally stable at room temperature. The effect of complexing reagents such as tri-n-butylphosphine, tetramethylethylenediamine and crown ethers (oxygen and sulfur) on the configurational stability and reactivity of the copper reagent discussed.

Introduction

Although organocopper(I) reagents have been extensively explored, there are very few samples of chiral copper reagents in which the copper is attached to the chiral center [1]. Recently, we reported the preparation of the first optically active vinylcopper(I) derivative, (*S*)-4-methylcyclohexylidenemethylcopper(I), which was shown to be configurationally stable at —35°C [2]. Bergbreiter and Whitesides [3] also reported that a ternary ate complex containing copper(I), mercury(II), lithium, t-butyl and (*S*)-2-butyl(II) was optically stable at —78°C. Saegusa [4] proposed an organocopper intermediate, which race-



((S)-I)



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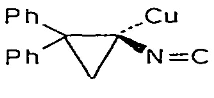

((*R*)-III)

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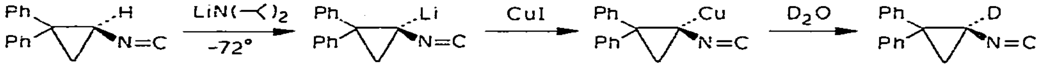
* For Part XXXIX see ref. 11.

mized in the reaction of cuprous oxide with optically active α-phenethyl isocyanide. The synthesis, configurational stability and attempted reactions of optically active 1-copper(I)-1-isocyano-2,2-diphenylcyclopropane (III) is the subject of this report [5].

Results

Synthesis of chiral III

Chiral 1-copper-1-isocyano-2,2-diphenylcyclopropane (III) was generated from chiral (*S*)-(+)-1-isocyano-2,2-diphenylcyclopropane in two different ways. The first method was based on the observation [6] that 1-lithio-1-isocyano-2,2-diphenylcyclopropane, generated by the reaction of (*S*)-(+)-1-isocyano-2,2-diphenylcyclopropane with lithium diisopropylamide, was capable of maintaining its configuration at temperatures between —50 to —70° C. Treatment of the lithium reagent, formed at —72° C with an equivalent of cuprous iodide and allowing the reaction mixture to come to room temperature (ca. 23° C) produced * III. Quenching the reaction mixture with deuterium oxide produced 1-deuterio-1-isocyano-2,2-diphenylcyclopropane in 70% yield with retention of configuration (91% optical purity) and 89% deuterium incorporation.



((S)-(+)) (III) ((S)-(+))

The second method of forming III was by the direct reaction of 1-isocyano-2,2-diphenylcyclopropane with copper diisopropylamide at ambient temperature. However, under these conditions the reaction was not complete as evident, after quenching with deuterium oxide, of only 25% deuterium incorporation although the optical purity was 91%. The former method was therefore the method of choice for our studies.

Reactions of chiral III

Table 1 gives the results of the deuterolysis of III at different temperatures and reaction times. The high deuterium content and high optical purity shows that III is configurationally stable and that the stability is unaffected by change in temperature (10—23° C) and length of reaction time (0.5—2 h). The low yields obtained in runs 1—3 are due to copper-isocyanide complex which was formed as the major product. The yield of III was increased dramatically (run 4) when the workup procedure was modified to include a wash with aqueous potassium cyanide to destroy the copper-isonitrile complex.

The influence of cation complex reagents on the configurational stability of III was investigated. The complexing reagents selected were tetramethylethylenediamine (TMEDA), tri-n-butylphosphine, 15-crown-5 and the macrocyclic polythioethers 15-ethano-S_5 and 18-ethano-S_6. As in the case of 1-lithio-1-isocyano-2,2-diphenylcyclopropane, the copper derivative III was configuration-

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* These was no apparent reaction with cuprous iodide at —72° C, it is assumed that the reaction occurred at about —50° C as evident by a color change yellow to green.

TABLE 1

DEUTEROLYSIS OF CHIRAL 1-COPPER-1-ISOCYANO-2,2-DIPHENYLCYCLOPROPANE (III)

Run	Temp. (°C)	Time (h)	Yield (%)	D (%)	Optical purity (%)
1	10	0.5	20	—	95
2	10	0.5	16	90	98
3	23	2.0	20	89	91
4	23	0.5	70	91	98

ally stable at 23°C upon the addition of TMEDA or tri-n-butylphosphine (Table 2) as judged by the high optical purity and high deuterium content of the deuterolysis product. When the reaction was carried out using one equivalent of 15-crown-5, the optical purity was still quite high but the deuterium content of the product decreased to 70%. Repeating this reaction but increasing the time from 0.5 h to 12 h decreased not only the optical purity but the deuterium content as well. In the case of 15-ethano-S_5 the optical purity was estimated to be 74% and the deuterium content 56%. However, using 18-ethano-S_6 as the complexing reagent the optical purity of the product was high (91%) but the deuterium content was decreased to 22%.

All attempts to methylate III with an excess of methyl iodide to produce 1-methyl-2,2-diphenylcyclopropyl isocyanide failed. Addition of one equivalent of TMEDA, three equivalents of tri-n-butylphosphine or four equivalents of HMPA to III, before introducing methyl iodide, did not result in methylation. Similarly, the addition of three equivalents of triethyl phosphite, a procedure developed by Normant [7] for alkylating vinylcopper reagents, also failed.

Finally, attempts to oxidatively dimerize III by bubbling a stream of oxygen into a tetrahydrofuran solution of III were abortive. No dimeric product could be isolated.

Discussion

In general, organocopper reagents are chemically reactive and thermally unstable at ambient temperature. In addition, chiral copper reagents have been shown to retain their optical activity only at low temperatures. In contrast, our

TABLE 2

THE EFFECT OF CATION COMPLEXING REAGENTS ON THE CONFIGURATIONAL STABILITY OF III AT 23°C FOR 0.5 H

Run	Reagent (equiv.)	Yield (%)	D (%)	Optical purity (%)
1	TMEDA (1)	84	95	94
2	n-Bu_3P (3)	75	82	99
3	15-crown-5 (1)	40	70	88
4	15-crown-5 (1)	20 [a]	19	68
5	15-ethano-S_5 (1)	40	56	74
6	18-ethano-S_6 (1)	60	22	91

[a] 12 h/reaction time.

results show that III is chemically, thermally and configurationally stable under ambient reaction conditions. This unusual behavior indicates that the factors responsible for the thermal and chemical stability are related to the observed stereochemical stability.

It has been demonstrated that organocopper reagents exist in aggregated form in solution [8]. Moreover, it has been shown that the thermal and chemical stability of an organocopper reagent may be enhanced by either intra- or intermolecular coordination with a variety of ligands such as isocyanides and amines [1,9]. These observations suggest that III might also exist in an aggregated form in which the intermolecular complex involves either the isocyano group or the diisopropylamine formed in the reaction, coordinating with the Cu (I). According to Saegusa [10], the increased thermal stability of cyanomethylcopper over methylcopper is due to the inductive effect of the cyano group. Since the isocyano group has also been shown to be electron-withdrawing [11] this, combined with the cyclopropyl moiety, may also be a stabilizing factor. All of these effects may be contributing to the observed chemical, thermal and configurational stability of III.

The effect of complexing reagents, as shown in Table 2, is not entirely clear. It could be reasoned that the addition of cation complexing reagents would destabilize the copper-carbon bond in III by disturbing the intermolecular complex and by breaking up the aggregates. Since TMEDA and tri-n-butylphosphine are known to stabilize organocopper reagents, the addition of these reagents should not affect the configurational stability of III as is observed. The addition of crown ethers and crown thioethers may be entirely different. It is possible that the addition of these reagents could result in loosening the bond by strongly complexing the copper-carbon bond after breaking up the aggregated forms of III. This may particularly be the case with the cyclic polythioethers since they are reported to complex copper [12] well. This new species of III might well possess a lower stereochemical stability and an increased reactivity [11]. This would account for the results reported in Table 2 which shows a marked decrease in deuterium incorporation upon deuterolysis and a somewhat lower optical purity. This would mean that III is reacting rapidly either with the solvent or crown ethers [11].

Experimental

Melting points were measured with a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained using a Perkin—Elmer Model 257 spectrometer. Nuclear magnetic resonance spectra were recorded on a Brucker 90 or 270 MHz spectrophotometer; chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants are in Hertz. Optical rotations were recorded at 546 Å with a Bendix-Ericson Model 987 ETL/NPL Polarimeter.

Solvents

Reagent grade tetrahydrofuran and diethyl ether were distilled from lithium aluminium hydride under nitrogen and stored over 3A Molecular Sieves. Bulk solvents were distilled before use.

Reagents

Chiral 2,2-diphenylcyclopropyl isocyanide was synthesized using an established procedure [13]. Organolithium reagents purchased from Alfa Products were titrated before use [14]. TMEDA, HMPA, tri-n-butylphosphine and triethylphosphite were distilled prior to use.

Deuterium content determination

The determination of the ratio 2,2-diphenylcyclopropyl isocyanide to 1-deuterio-2,2-diphenylcyclopropyl isocyanide from the deuterolysis of III was carried out as follows. A comparison of IR and m.p. of the isolated reaction product with that of the authentic sample was made in each case to determine the purity of the product. The NMR spectrum of the sample was recorded, with integration, on a Bruker-90 or 270 MHz NMR spectrometer. The amount of 2,2-diphenylcyclopropyl isocyanide was determined by comparing the integration of the 1-proton (3.30—3.50 ppm) with that of the cyclopropyl methylene protons (1.50—1.95 ppm). This determination was checked by also comparing the integration of the 1-proton with that of the phenyl protons. The estimated error is ±5%.

Deuterolysis of 1-copper-1-isocyano-2,2-diphenylcyclopropane (III)

To a stirred solution of lithium diisopropylamide (4 mmol) in THF at —72°C under a nitrogen atmosphere was added a 5 cm^3 solution of 200 mg of (*S*)-(+)-2,2-diphenylcyclopropyl isocyanide over a period of 2 min. The reaction mixture was stirred for 15 min and 0.95 g (5 mmol) of anhydrous cuprous iodide was added. The reaction mixture was allowed to warm to ambient temperature over a period of 30 min, deuterium oxide added and stirring continued for an additional 15 min. The reaction mixture was poured into an aqueous KOH-KCN solution and extracted with ether. The crude product was purified by column chromatography (neutral alumina) to yield 140 mg. (70%) of product, m.p. 122—124°C, optical purity * 91.5%, whose IR and NMR spectra were identical with those of an authentic sample.

Effect of TMEDA on the configurational stability of III

To a stirred solution of lithium diisopropylamide (5 mmol) in THF at —71°C, under a nitrogen atmosphere, was added a 5 cm^3 solution of 220 mg (1 mmol) of (*S*)-(+)-2,2-diphenylcyclopropyl isocyanide over a 2 min period. The reaction mixture was stirred for 15 min and 0.95 g (5 mmol) of dry cuprous iodide was added. The reaction mixture was allowed to warm to 23°C over a period of 30 min and 0.76 g (6.5 mmol) of TMEDA was added. Stirring was continued for 0.5 h and the solution was treated with an excess of deuterium oxide. The isolated crude mixture was purified by column chromatography to yield 183 mg (83%) of product, m.p. 122—124°C, optical purity 94%, deuterium content 95%. IR and NMR spectra were identical with there of an authentic sample.

Effect of tri-n-butylphosphine on the configurational stability of III

In a similar manner, III was treated with 3 equivalents of tri-n-butylphos-

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* The optical purity of the products reported includes the correction for the optical purity of the starting material.

phine for thirty minutes at 23°C and quenched with an excess of methanol-d_4. The crude product, obtained from KCN/KOH workup, was purified by chromatography through a neutral alumina column to give 165 mg (75%) of material, m.p. 115—122°C, deuterium content 82%, optical purity 99% and whose IR and NMR spectra were identical with those of an authentic sample.

Effect of addition of 15-crown-5 on the configuration stability of III

In a like manner, III was stirred with one equivalent of 15-crown-5 for 30 min at 23°C and then treated with an excess of deuterium oxide. The isolated crude product was purified by column chromatography to yield 90 mg (40%) of isonitrile, m.p. 112—122°C, deuterium content 70% and an optical purity of 88%. The IR and NMR spectra were identical with those of an authentic sample.

Effect of addition of 15-ethano-S_5 on the configurational stability of III

In a like manner, III was stirred with one equivalent of 15-ethano-S_5 for 0.5 h and then treated with an excess of methanol-d_4. The crude product obtained from KCN/KOH workup was purified by column chromatography to give 45 mg (40%) of isonitrile, m.p. 110—116°C, optical purity 74% and a deuterium content of 56%. The IR and NMR spectra were identical with those of an authentic sample.

Effect of addition of 18-ethano-S_6 on the configurational stability of III

In a like manner, III was stirred with one equivalent of 18-ethano-S_6 for 0.5 h at 23°C and then treated with an excess of methanol-d_4. Standard workup yielded 63 mg (60%) of product, m.p. 117—122°C, deuterium content 22% and an optical purity of 91%.

Reaction of (S)-(+)-2,2-diphenylcyclopropyl isocyanide with copper diisopropylamide

To a stirred solution of lithium diisopropylamide (5 mmol) in THF at 23°C, under a nitrogen atmosphere, was added 0.95 g (5 mmol) of anhydrous cuprous iodide. To this solution (black) was added 200 mg of (*S*)-(+)-2,2-diphenylcyclopropyl isocyanide dissolved in 2 cm³ of THF and the mixture was treated with an excess of deuterium oxide and poured onto an aqueous solution of KCN-KOH. Ether extraction yielded 160 mg (80%) of product m.p. 111—121°C, deuterium content 25% and an optical purity of 90%. The IR and NMR spectra were identical with those of an authentic sample.

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