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Reactions of the Dianion Obtained by Reductive Metallation of 3,4-Diphenylcinnoline

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Summary. The reductive metallation of 3,4-diphenylcinnoline (**1**) by sodium metal in tetrahydrofuran under an inert atmosphere to the monomeric dianion **2** has been explored, and the nucleophilicity of the disodium adduct towards various protonation, alkylation, and acylation reagents has been investigated. Generally, **2** reacts *via* its 1,4-positions forming 1,4-dihydro derivatives of **1**.

Keywords. Alkylation; Acylation; Dianion; 3,4-Diphenylcinnoline; Reductive metallation.

Reaktionen des durch reduktive Metallierung aus 3,4-Diphenylcinnolin gebildeten Dianions

Zusammenfassung. Die Herstellung des monomeren Dianions von 3,4-Diphenylcinnolin durch reduzierende Metallierung mit metallischem Natrium in Tetrahydrofuran unter einer inerten Atmosphäre sowie die Nucleophilie dieses Dinatriumaddukts gegenüber verschiedener Protonierungs-, Alkylierungs- und Acylierungsreagenzien wurden untersucht. Das Dianion reagiert durchwegs über die Positionen 1 und 4 zu 1,4-Dihydroderivaten von 3,4-Diphenylcinnolin.

Introduction

Dianions obtained by reduction of $(4n+2)\pi$ electron compounds have a $4n\pi$ array of electrons and can therefore serve as model compounds for antiaromatic species. The effect of heteroatoms on the main characteristics of these charged systems such as their paratropicity, charge delocalization, and ion-pairing, seems interesting. The introduction of a heteroatom into a delocalized system may increase the regioselectivity of its reactions (such as alkylation) and even change its chemistry. The study of π-conjugated charged systems, especially the reductive metallation of heterocycles, can provide synthetically useful dihydro dianionic derivatives. Although many carbocyclic systems have been reduced by alkali metals to their respective dianions most of which are stable enough to be characterized by NMR spectroscopy, only few dianions of fused benzenoid heterocyclic systems, *e.g.* benzo[*c*]cinnoline, dibenzo[*a*,*c*]phenazine, and quinoxaline derivatives, are known [1–3]. Continuing interest in interactions of alkali

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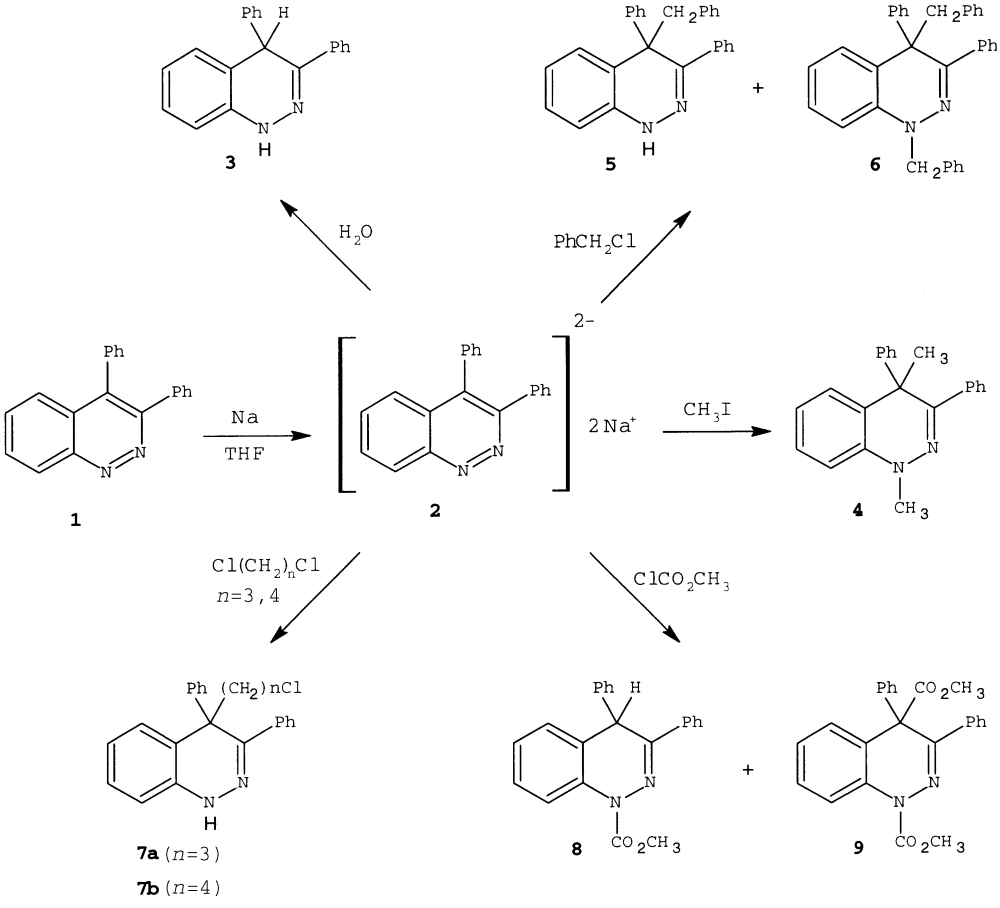
metals with nitrogen containing heterocycles has prompted us to investigate the reductive metallation of aryl substituted phthalazine and pyrazine systems, and we have reported on various derivatives of these compounds obtained *via* reaction of the resulting organometallic product with different reagents [4, 5]. In this report, the reductive metallation of 3,4-diphenylcinnoline (**1**) is described.

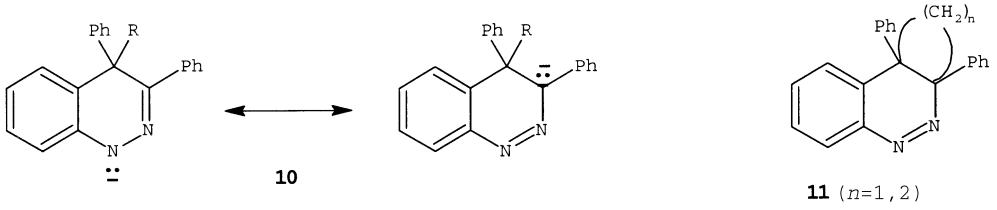
Results and Discussion

3,4-Diphenylcinnoline (**1**), a system containing conjugated alkene and azo functionalities as well as electron donating phenyl groups, was metalleted by reduction with an excess of sodium in tetrahydrofuran under an argon atmosphere to form a deep colored solution of the dianion **2**. The reactivity of this dianion was examined with several reagents. Protonation of **2** with water occurred at the 1,4-positions of the cinnoline ring, and 1,4-dihydro-3,4-diphenylcinnoline (**3**) was isolated. **3** has also been obtained by reduction of **1** in absolute alcohol at 70° using *Adams* catalyst [6].

Alkylation of **2** with either methyl iodide or benzyl chloride produced the 1,4-dialkyl-1,4-dihydro-3,4-diphenylcinnolines **4** and **6**, respectively. Since the anionic



Scheme 1



Scheme 2

centers of **2** are highly delocalized, attempts were made to direct reactions to the 1,2-positions using 1,3-dichloropropane and 1,4-dichlorobutane as alkylating agents. However, only monoalkylation products **7a** and **7b** were isolated. Obviously, the mono alkylated monoanion **10** is a relatively weak nucleophile; subsequent alkylation to **11** was not observed. Indeed, even with benzyl chloride significant amounts of monoalkylated derivative **5** were obtained. Attempts to obtain alkylated product with 1,2-dichloroethane were unsuccessful because of the instability of the expected compound; only the 1,4-dihydro derivative was isolated.

Acylation of 2 with methyl chloroformate produced a mixture of 1-carbomethoxy-1,4-dihydro-3,4-diphenylcinnoline (**8**) and 1,4-dicarbomethoxy-1,4-dihydro-3,4-diphenylcinnoline (**9**). In every experiment, some 3,4-diphenylcinnoline (**1**) was recovered, probably because of incomplete reduction of **1** to **2** or because of conversion of **2** to **1** by traces of oxygen introduced into the system during the handling of the reagents.

Experimental

Melting points are uncorrected and were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. Infrared spectra were recorded on a Philips PU 9714 spectrometer in KBr pellets unless otherwise indicated. NMR spectra were determined on a Varian 200 MHz Gemini spectrometer in $CDCl_3$ with *TMS* as internal standard. Mass spectra were obtained with a Shimadzu GS/MS QP 2000 A spectrometer with 70 eV electron impact ionization. Column chromatography was performed with silica gel 60 (70–230 mesh) purchased from E. Merck AG. Thin layer chromatography (TLC) was effected with Eastman Kodak Chromatogram 13181 silica gel sheets with fluorescent indicator.

3,4-Diphenylcinnoline was prepared from benzyl monophenylhydrazone according to a published procedure [6]. Tetrahydrofuran (*THF*) [7] was purified by refluxing for at least 8 h over lithium aluminum hydride (*LAH*) under nitrogen and stored over LAH. Required amounts were redistilled immediately before use after refluxing for 2 h. All reactions involving alkali metal compounds were conducted under an atmosphere of purified and dried argon.

Reductive metallation of 3,4-diphenylcinnoline on a preparative scale was performed in an argon-filled modified *Schlenk* tube as described in the literature [8]. Removal of weighed aliquots of the solution during the reaction between **1** and sodium in *THF*, quenching the aliquots in 1:1 water/methanol, and titrating with standardized hydrochloric acid indicated that formation of the deep violet solution of the dianion **2** was complete after 20 h.

A detailed description of one experiment is given below to illustrate the procedures. All crude reaction products were examined by TLC using toluene as eluent and compared with starting material **1** and the reagent in order to follow the progress of the reaction. The purification procedures

as well as additional comments together with the IR, NMR, and MS data are given for each compound. The analytical data agreed with the calculated values within experimental error.

1,4-Dihydro-3,4-diphenylcinnoline (**3**; $C_{20}H_{16}N_2$); *general procedure*

Dianion **2** was obtained from the reaction of 0.282 g (1 mmol) of **1** in 100 cm^3 of *THF* with freshly cut sodium metal (*ca.* 1 g) in a specially designed flask [9]. The mixture was shaken under an argon atmosphere for about 20 h and then the excess sodium was removed from the solution of **2**. After the solution was cooled to −78°C, 0.144 g (4.0 mmol) of water were injected, and stirring was continued for 3 h at −78°C. During subsequent warming of the reaction mixture to room temperature the color changed from violet to yellow. After addition of 1 cm^3 methanol by injection, the flask was opened, the reaction mixture was diluted with water, extracted with diethyl ether (3×100 cm^3), and the etheral solution was dried over sodium sulfate and evaporated. The crude reaction product was chromatographed on silica gel. Elution of the column with toluene gave colorless needles of m.p. 130°C (0.270 g, 95%) when recrystallized from a mixture of 40–60°C petroleum ether-diethyl ether (1:1).

IR (KBr): $\nu = 3370$, 3020, 1570, 1460, 1300, 740, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 5.34 (1H, s, CH), 6.79–7.80 (15H, m, aromatic and NH (exchangeable with D_2O)) ppm; MS: $m/z = 284$ (M^+, 100), 207 (M^+-Ph, 29), 181 (M^+-PhC=N, 18), 130 (M^+-2Ph, 17).

1,4-Dimethyl-1,4-dihydro-3,4-diphenylcinnoline (**4**; $C_{22}H_{20}N_2$)

0.284 g (2.0 mmol) of methyl iodide was added to a solution of **2** at −78°C, and the resulting solution was stirred for 2 h. The crude reaction product was isolated as described above and chromatographed on silica gel. Elution with toluene gave a yellow oil. Recyristallization from a mixture of 40–60°C petroleum ether-diethyl ether (1:1) yielded yellowish plates (0.198 g, 64%), m.p.: 154°C.

IR (KBr): $\nu = 3020$, 2950, 2870, 1580, 1435, 1300, 740, 685, 530 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 1.84 (3H, s, C-CH_3), 3.62 (3H, s, N-CH_3), 6.76–7.37 (14H, m, aromatic) ppm; MS: $m/z = 312$ (M^+, 80), 297 (M^+-CH_3, 60), 282 (M^+-2CH_3, 8), 235 (M^+-Ph, 100), 209 (M^+-PhC=N, 4), 158 (M^+-2Ph, 6).

4-Benzyl-1,4-dihydor-3,4-diphenylcinnoline (**5**; $C_{27}H_{22}N_2$)

The deep violet solution of **2** prepared from **1** (0.282 g, 1 mmol) was treated with benzyl chloride (0.253 g, 2 mmol) at −78 °C under argon. Stirring was continued for 2 h at this temperature. After warming to room temperature, the color of the solution changed from green to orange. H_2O (*ca.* 1 cm^3) was injected through the septum, and a mixture of two products was isolated as an oil by diethyl ether (3×100 cm^3) extraction. After purification by column chromatography (silica, toluene), evaporation of the elute first gave **5** (0.167 g, 42%) as yellowish plates (m.p.: 105°C).

IR (KBr): $\nu = 3300$, 3020, 2940, 1580, 1465, 1310, 750, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 3.52–3.84 (2H, q, CH_2Ph), 6.39–7.58 (20H, m, aromatic and NH (exchangeable with D_2O)) ppm; MS: $m/z = 374$ (M^+, 100), 297 (M^+-Ph, 59), 283 (M^+-CH_2Ph, 77).

1,4-Dibenzyl-1,4-dihydro-3,4-diphenylcinnoline (**6**; $C_{34}H_{28}N_2$)

6 (0.253 g, 51%) was obtained as the second fraction of the above chromatographic separation as bright colorless plates (m.p.: 168°C).

IR (KBr): $\nu = 3010$, 2940, 2900, 1590, 1480, 1440, 745, 690, 510 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 3.53–3.88 (2H, q, C-CH_2Ph), 4.81–4.84 (2H, d, N-CH_2Ph), 6.30–7.79 (24H, m, aromatic) ppm; MS: $m/z = 464$ (M^+, 13), 373 (M^+-CH_2Ph, 28), 282 (M^+-2CH_2Ph, 52).

4-(3-Chloropropyl)-1,4-dihydro-3,4-diphenylcinnoline (**7a**; $C_{23}H_{21}ClN_2$)

The preceding reaction was repeated with 0.282 g (1 mmol) of **2** in *THF* and 1,3-dichloropropane (0.225 g, 2 mmol) at −78°C. Chromatography (silica, toluene) of the crude product provided one major fraction of **7a** (0.206 g, 62%) as a viscous oil which was crystallized from 40–60°C petroleum ether to afford bright colorless crystals (m.p.: 76°C).

IR (KBr): $\nu = 3280$, 3040, 2940, 1580, 1460, 1300, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 1.70–1.78 (2H, p), 2.41–2.53 (2H, t), 3.33–3.41 (2H, t), 6.63–7.70 (15H, m, aromatic and NH (exchangeable with D_2O)) ppm; MS: $m/z = 360$ (M^+, 74), 283 (M^+-$CH_2CH_2CH_2Cl$, 46), 206 (M^+-2Ph, 16).

4-(4-Chlorobutyl)-1,4-dihydro-3,4-diphenylcinnoline (**7b**; $C_{24}H_{23}ClN_2$)

The above experiment was repeated using 1,4-dichlorobutane (0.127 g, 1 mmol) instead of 1,3-dichloropropane. The crude reaction product was chromatographed to give **7b** (0.306 g, 82%) as bright colorless crystals (m.p.: 140°C).

IR (KBr): $\nu = 3280$, 3040, 2920, 1580, 1460, 1290, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 0.84–0.92 (2H, t), 1.22–1.64 (2H, m), 2.26–2.37 (2H, m), 3.28–3.35 (2H, t), 6.64–7.68 (15H, m, aromatic and NH (exchangeable with D_2O)) ppm; MS: $m/z = 374$ (M^+,85), 283 (M^+-$CH_2CH_2CH_2CH_2Cl$, 88), 220 (M^+-2Ph, 52).

1-Carbomethoxy-1,4-dihydro-3,4-diphenylcinnoline (**8**; $C_{22}H_{18}N_2O_2$)

The general procedure applied to **2** using methyl chloroformate (0.189 g, 2 mmol) as the reagent gave N-acylated products. **8** was obtained from the column as first eluent (0.130 g, 38%) as bright colorless crystals (m.p.: 140°C)

IR (KBr): $\nu = 3040$, 2930, 1700, 1580, 1480, 1425, 1220, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 4.01 (3H, s, CO_2CH_3), 5.37 (1H, s, CH), 7.17–8.19 (14H, m, aromatic) ppm; MS: $m/z = 342$ (M^+, 97), 311 (M^+-OCH_3, 7), 283 (M^+-$COOCH_3$, 62), 265 (M^+-Ph, 97), 239 (M^+-PhC=N, 35).

1,4-Dicarbomethoxy-1,4-dihydro-3,4-diphenylcinnoline (**9**; $C_{24}H_{20}N_2O_4$)

The second eluent from the above chromatography was diacylated product **9** (0.228 g, 57%, bright colorless crystals, m.p.: 205°C).

IR (KBr): $\nu = 3040$, 2940, 1710, 1470, 1430, 1220, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz) 3.60 (3H, s, C-CO_2CH_3), 3.98 (3H, s, N-CO_2CH_3), 7.11–7.66 (14H, m, aromatic); MS: $m/z = 400$ (M^+, 78), 341 (M^+-$COOCH_3$, 27), 297 (M^+-PhC=N, 29), 282 (M^+-2$COOCH_3$, 57), 252 (97).

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