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Preparation of 1,2- and 1,4-dihydro derivatives of 6,7-dimethyl-2,3-diphenylquinoxaline *via* its dianion formed by reductive metallation

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Abstract Treatment of 6,7-dimethyl-2,3-diphenylquinoxaline with sodium in tetrahydrofuran formed a monomeric dianion. The chemical behavior of this dianion was investigated by a variety of reagents. As the result, alkylation reactions gave 1,2-dihydro derivatives, while acylation reactions occured at 1,4-positions. Annulation of the pyrazine ring system was accomplished by treating the dianion with oligomethylene dichlorides, $Cl(CH_2)_nCl$, $n = 2$–4.

Keywords Heterocycles; Reductions; Nucleophilic substitutions; Annulation; Nitrogen anions.

Introduction

The dianions formed by the reductive metallation of unsaturated heterocyclic systems are very useful intermediates in the synthesis of nonaromatic dihydro derivatives of heteroaromatic compounds. Moreover, these dianions are interesting due to their vicinal anionic centers. Although the formation of some heterocyclic dianions has been investigated by NMR [1], their chemical behavior has not been researched widely. So, our research group has studied on the alkylation and acylation reactions of the dianions of fused heterocyclic compounds recently [2–4].

In this report, the reductive metallation of 6,7-dimethyl-2,3-diphenylquinoxaline (**1**) having a conjugative arrangement with electron donating phenyl groups and nitrogen atoms, is investigated.

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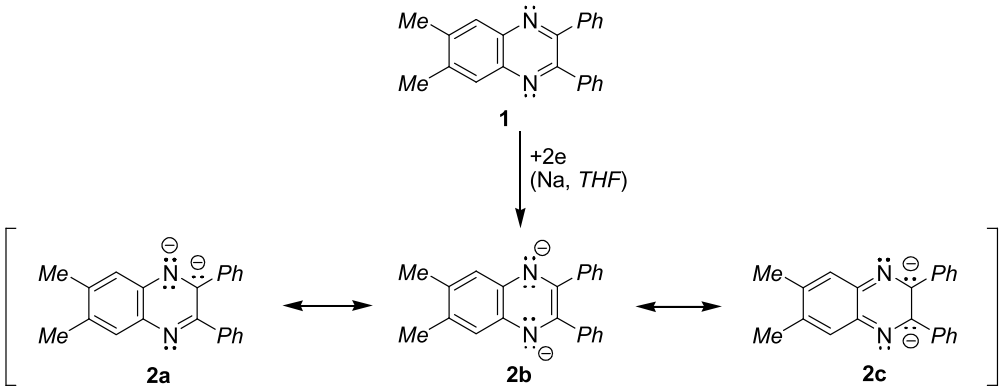
Results and discussion

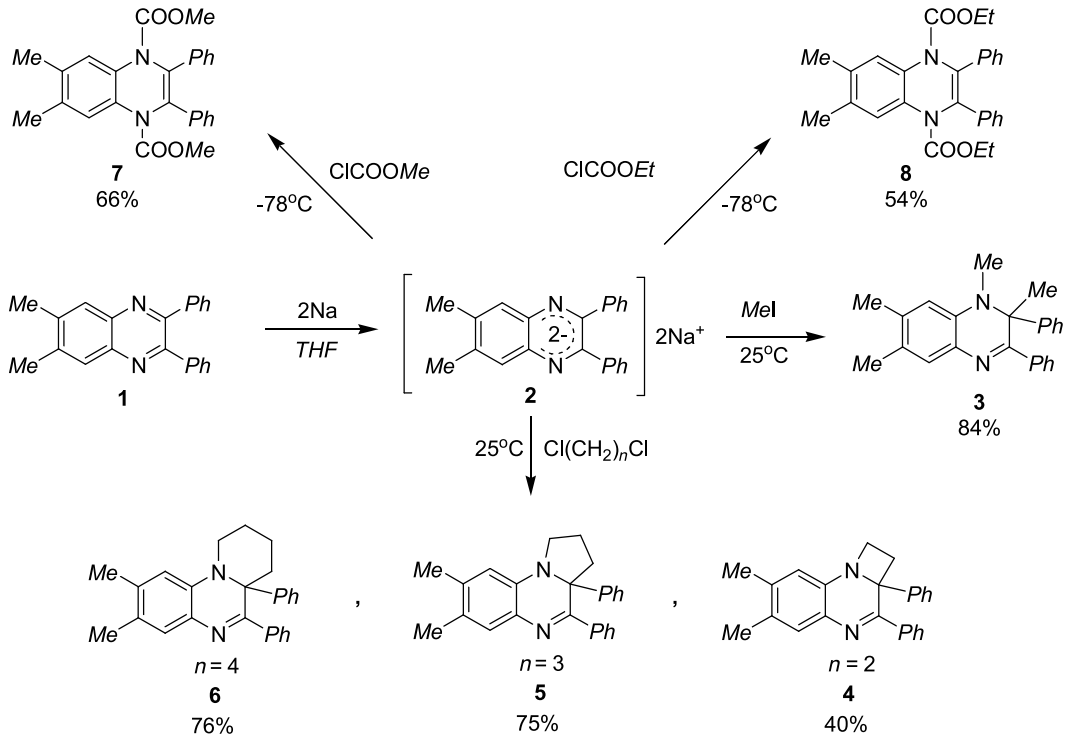
Treatment of **1** with excess sodium metal in tetrahydrofuran under an inert atmosphere gave a deep purple colored solution of dianion **2**. Under these conditions **1** was converted to a monomeric dianion **2** which resonance structures can be thought as **2a**, **2b**, and **2c** (Scheme 1).

However, in our opinion, the most probable resonance structures are **2a** and **2b** in comparison with **2c**. For determination of this expectation, the chemical behavior of the dianion with several reagents were investigated. To carry out these reactions, unreacted sodium was removed from the dianion solution and the reagents were injected to alkylating agents through a septum under argon atmosphere. The reaction mixtures were stirred for 5–8 h. The products **3**–**8** isolated from these reactions were purified by chromatographic methods and characterized by IR, NMR, and MS data and their purity was established by means of elemental analysis (Scheme 2).

From the alkylation reactions of **2**, performed at 25°C, 1,2-dialkylation products were isolated as main products, while small amounts of these products formed at −78°C. 1,2-Di-hydro-1,2,6,7-tetramethyl-2,3-diphenylquinoxaline (**3**) was obtained by the reaction with methyl iodide. ^{1}H NMR spectra of



Scheme 1



Scheme 2

3 showed four singlets belonging to 1-, 2-, 6-, and 7-methyl groups at $\delta = 2.46$, 1.81, 2.21, and 2.28 ppm. This methylation showed that the alkylation of **2** proceeded stepwise, the first alkyl group being introduced at the benzylic carbon followed by the second at nitrogen.

Annulation to four-, five-, and six-membered ring systems at 1,2-positions of **2** were accomplished by the alkylation reactions with a series of oligomethylene dichlorides, $Cl(CH_2)_nCl$ ($n = 2$–4). These azetidino- (**4**), pyrrolidino- (**5**), and piperidino- (**6**) systems were performed through intramolecular *exo-tet* ring closure in accordance with *Baldwin*'s *rules* [5].

The ^{1}H NMR spectra of **4**–**6** showed N–CH_3 signals at 3.48–4.10 ppm and the other signals at 3.03–3.61, 2.01–2.86, and 1.53–2.95 ppm as multiplets.

Acylation of **2** with methyl and ethyl chloroformate was executed at −78°C. These reactions occured on the negatively charged nitrogen atoms with the formation of 1,4-dihydro derivatives **7** and **8** of **1**. These structures were confirmed by ^{13}C NMR spectra of **7** in which C=O group was observed at 155.35 ppm.

The mass fragmentation and elemental analysis results of all compounds supported the suggested structures. In all experiments, some **1** was recovered, probably because of only partial reduction of **1** to **2**, or conversion of **2** to **1** by traces of the oxygen introduced into the system during the handling of the reaction reagents.

Experimental

Melting points were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. IR spectra were recorded on a Philips PU 9714 and Mattson 1000 FTIR spectrometer in KBr pellets. The NMR spectra were determined on a Varian 200 MHz Gemini in $CDCl_3$ with *TMS* as internal standart. UV spectra were recorded with Philips PU 8700 UV/VIS spectrometer using chloroform. Mass spectra were obtained with Shimadzu GC/MS QP 2000 A. Elemental analyses (C, H, and N) were carried out using *Perkin-Elmer* 240 B microanalyzer; their results were in favourable agreement with the calculated values. Column chromatography was performed with silica gel 60 (70–230 mesh) purchased from *E. Merck*. Thin-layer chromatography (*TLC*) was effected with Eastman Kodak Chromagram 13181 silica gel sheets with fluorescent indicator. Tetrahydrofuran was purified by refluxing for at least 8 h over $LiAlH_4$ under N_2, and when needed the solvent was refluxed for 2 h and the required amount was redistilled immediately before use. All reactions involving alkali-metal compounds were conducted in an atmosphere of purified and dried *Ar*. For determining of completion time of reduction, the reductive metallation of **1** on a preparative scale was performed. Removal of weighed aliquots of the solution during the reaction between **1** and sodium in tetrahydrofuran, quenching the aliquots in 1:1 = water:methanol, and titrating with standardized HCl, demonstrated that formation of deep purple solution of the dianion **2** was completed after 18 h.

6,7-Dimethyl-2,3-diphenylquinoxaline (**1**) was prepared from 4,5-dimethyl-1,2-phenylenediamine and 1,2-diphenylethanedione. Physical properties of **1** are comparable with the data given in literature, *e.g.*, mp 177°C (Ref. [7] 173–175°C and [8] 172°C); IR and NMR spectra were also found to be similar to those of published in Refs. [7, 8].

General procedure

rac-1,2-Dihydro-1,2,6,7-tetramethyl-2,3-diphenylquinoxaline (**3**, $C_{24}H_{24}N_2$)

Compound **1** (0.310 g, 1.0 mmol) was placed in a specially designed flask [6] equipped with a stirring bar and a septum, the flask was evacuated and filled *Ar*. Then 100 cm^3 of *THF* was destilled and freshly cut sodium (*ca.* 1 g) was added. Under an *Ar* atmosphere, the mixture was stirred about 18 h and the excess sodium was removed from the solution of **2**. Methyl iodide (0.284 g, 2.0 mmol) was injected through the septum. This mixture was stirred for 5 h. The color of reaction mixture changed from deep purple to deep brown. After injection of 1 cm^3 of methanol, the color changed to yellow and the solution was extracted with diethyl ether (3×100 cm^3). The combined extracts were dried over sodium sulfate and evaporated. The crude reaction product was chromatographed on silica gel. Elution of column with toluene gave yellow fluorescent crystals. Recrystallization from 40 to 60°C petroleum ether afforded 0.286 g (84%) **3**. Mp 176°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.81$ (s, 2-CH_3), 2.21 (s, 7-CH_3), 2.28 (s, 6-CH_3), 2.46 (s, 1-CH_3), 6.39–7.53 (m, 12H, aromatic) ppm; IR (KBr): $\bar{\nu} = 3080$, 2970, 2850, 2740, 1625, 1497, 1446, 1344 cm^{-1}; UV (chloroform): $\lambda_{max} = 233$, 258 nm; MS (70 eV): m/z (%) = 341 (M + 1, 20), 340 (M^+, 47), 325 (100), 263 (48), 236 (24), 118 (31), 103 (24), 77 (28).

rac-6,7-Dimethyl-2a,3-diphenylazetidino[1,2-a]quinoxaline (**4**, $C_{24}H_{22}N_2$)

1,2-Dichloroethane (0.194 g, 2.0 mmol) was added to the dianion solution prepared by the procedure described for compound **3**, after 8 h stirring, the color of this resulting solution was yellow. The crude reaction product was isolated and chromatographed on silica gel. Elution with toluene gave yellow fluorescent oily product, 0.138 g (40%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.17$ (s, 7-CH_3), 2.23 (s, 6-CH_3), 3.10 (m, 2-CHa), 3.54 (m, 2-CHb), 3.92 (m, 1-CHa), 4.06 (m, 1-CHb), 6.56–7.80 (m, 12H, aromatic) ppm; IR (KBr): $\bar{\nu} = 3080$, 2980, 2850, 2770, 1610, 1590, 1480, 1440, 1312 cm^{-1}; UV (chloroform): $\lambda_{max} = 268$, 328 nm; MS (70 eV): m/z (%) = 339 (M + 1, 44), 338 (M^+, 100), 337 (M − 1, 87), 323 (43), 310 (89), 309 (85), 261 (92), 234 (84), 206 (37), 103 (38), 77 (23).

rac-7,8-Dimethyl-3a,4-diphenylpyrrolidino[1,2-a]-quinoxaline (**5**,$C_{25}H_{24}N_2$)

The reaction described above was repeated with 1,3-dichloropropane (0.225 g, 2.0 mmol) for 6 h. Chromatography (silica/toluene) of crude product provides yellow needles, 0.266 g (75%). Mp 169°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.01$–2.12 (m, 2-CH_2), 2.18 (s, 8-CH_3), 2.21 (s, 7-CH_3), 2.43 (m, 3-CHa), 2.80 (m, 3-CHb), 3.48–3.69 (m, 1-CH_2), 6.36–7.66 (m, 12H, aromatic) ppm; IR (KBr): $\bar{\nu} = 3120$, 2980, 2850, 2815, 1600, 1497, 1370, 1290 cm^{-1}; UV (chloroform): $\lambda_{max} = 257$, 326 nm; MS (70 eV): m/z (%) = 353 (M + 1, 35), 352 (M^+, 81), 337 (22), 323 (26), 276 (100), 275 (64), 249 (38), 248 (96), 176 (38), 103 (35), 77 (41).

rac-8,9-Dimethyl-4a,5-diphenylpiperidino[1,2-a]quinoxaline (**6**, $C_{26}H_{26}N_2$)

The same reaction with compound **3** was performed with 1,4-dichlorobutane (0.254 g, 2.0 mmol). Stirring was continued for 5 h. The crude product was chromatographed (silica/toluene) and yellow fluorescent oil (0.280 g, 76%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.53$–1.78 (m, 3-CH_2), 2.17 (s, 9-CH_3), 2.25 (s, 8-CH_3), 2.35 (t, 4-CH_2), 2.83–2.95 (m, 2-CH_2), 3.58 (m, 1-CH_2), 6.55–7.46 (m, 12H, aromatic) ppm; IR (KBr): $\bar{\nu} = 3120$, 2980, 2850, 2780, 1625, 1497, 1446, 1344 cm^{-1}; UV (chloroform): $\lambda_{max} = 254$ nm; MS (70 eV): m/z (%) = 367 (M + 1, 51), 366 (M^+, 100), 365 (M − 1, 26), 310 (31), 309 (34), 290 (98), 289 (57), 263 (38), 262 (94), 247 (31), 234 (37), 207 (34), 183 (43), 103 (34), 77 (26).

Dimethyl 1,4-dihydro-6,7-dimethyl-2,3-diphenylquinoxaline-1,4-dicarboxylate (**7**, $C_{26}H_{24}O_4N_2$)

The solution of dianion **2** was cooled −78°C and methyl chloroformate (0.189 g, 2 mmol) was injected. The reaction mixture was stirred for 4.5 h, and then allowed warming to room temperature. The crude product obtained after 1 h stirring as described for **3** was chromatographed on silica gel. After elution of **1** with toluene, **7** was obtained by elution of the column with chloroform as colorless bright small plates, 0.285 g (66%). Mp 195°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.33$ (s, 6-CH_3, 7-CH_3), 3.62 (s, 1-CO_2CH_3, 4-CO_2CH_3), 7.15–7.47 (m, 12H, aromatic) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.71$ (CH_3), 54.92 ($COOCH_3$), 126.23–137.27 (C=C, aromatic 18C), 155.35 ($COOCH_3$) ppm; IR (KBr): $\bar{\nu} = 3110$, 3010, 2970, 2830, 1727, 1497, 1446, 1344 cm^{-1}; UV (chloroform): $\lambda_{max} = 250$ nm; MS (70 eV): m/z (%) = 429 (M + 1, 100), 428 (M^+, 51), 427 (M − 1, 47), 370 (92), 310 (59), 309 (99), 233 (54), 207 (33), 103 (48), 77 (26).

Diethyl 1,4-dihydro-6,7-dimethyl-2,3-diphenylquinoxaline-1,4-dicarboxylate (**8**, $C_{28}H_{28}O_4N_2$)

The procedure described for **7** was repeated with ethyl chloroformate (0.217 g, 2.0 mmol). The reaction mixture was stirred at −78°C for 3.5 h, and then at room temperature for 2 h. Chromatographic separation on silica gel with toluene followed by chloroform gave colorless crystals, 0.245 g (54%). Mp 206–207°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 1.03 (t, 1-$CO_2CH_2CH_3$, 4-$CO_2CH_2CH_3$), 2.32 (s, 6-CH_3, 7-CH_3), 4.05 (q, 1-$CO_2CH_2CH_3$, 4-$CO_2CH_2CH_3$), 7.14–7.52 (m, 12H, aromatic) ppm; IR (KBr): $\bar{\nu} = 3110$, 3005, 2970, 2830, 1730, 1510, 1464, 1371, 1336 cm^{-1}; UV (chloroform): $\lambda_{max} = 243$ nm; MS (70 eV): m/z (%) = 457 (M + 1, 82), 456 (M^+, 68), 455 (M − 1, 34), 383 (57), 339 (82), 310 (55), 309 (100), 233 (64), 207 (36), 192 (31), 104 (49), 77 (33).

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