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PREPARATION AND REACTIONS OF THE LITHIO AND DILITHIO SALTS OF 2,3-DIMETHYLQUINOXALINE

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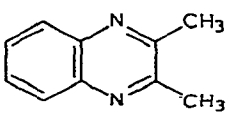
Summary

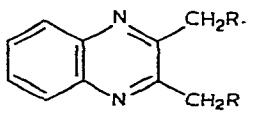
Metalation of 2,3-dimethylquinoxaline has been achieved by means of lithium diisopropylamide in THF/HMPA to afford either mono- or dicarbanions depending upon the stoichiometry of the metalating agents. The carbanions obtained have been condensed with representative electrophiles to give a variety of 2,3-disubstituted quinoxalines.

Introduction

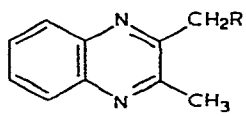
Though 2,3-disubstituted quinoxalines are normally prepared by condensation of appropriate *o*-phenylenediamines and α-diketones [1—3], an alternate method of synthesis involving organometallic reagents was discovered in 1931 which presumably has been employed only twice [4,5]. The method involved treatment of 2,3-dimethylquinoxaline (I) with two equivalents of potassium amide to give dianion II (R = K) [4] or with an excess of sodium amide to apparently afford the corresponding disodio salt [5]. The dipotassio salt has been reacted with ethyl bromide to give 2,3-di-n-propylquinoxaline (II, R = C_2H_5)



(I)



(II) R = M or D
(IV) R = $\overset{O}{\overset{\|}{C}}C_6H_5$
(XI) R = $C(OH)(C_6H_5)_2$
(XII) R = CH_3 or C_2H_5



(III) R = $\overset{O}{\overset{\|}{C}}C_6H_5$
(VI) R = $C(OH)(C_6H_5)_2$
(VII) R = $C(OH)C_6H_5$-α-$C_{10}H_8$
(VIII) R = CH_3 or C_2H_5
(IX) R = $\overset{NH}{\overset{\|}{C}}C_6H_5$

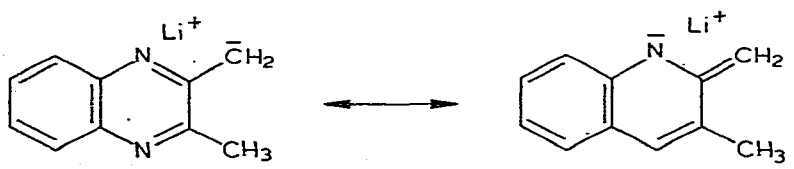
in a yield of 70% [4]. Similarly, the disodio salt has been condensed with ethyl benzoate to afford a mixture of III and presumably IV in low yields [5]. No other condensations of these salts appear to have been described.

As part of a general study of the chemistry of alkali derivatives of methylated heterocycles, * it was of interest to determine if both mono- and di-alkali derivatives of I could be prepared and, in turn, condensed with various electrophiles to give mono- and disubstituted products, respectively. This paper illustrates that such chemistry can be realized conveniently to provide a viable synthesis of substituted quinoxalines.

Results and discussions

Since the initially described metalations of I by alkali amides in ammonia required either inconvenient apparatus [4] or long reaction periods [5], it was deemed desirable to effect such reactions by stronger bases like alkyllithiums and lithium dialkylamides. Thus, treatment of I with two equivalents of n-butyllithium in THF or lithium diisopropylamide (LDIPA) in THF/HMPA followed by deuteration with deuterium oxide gave II (R = D) that contained one deuterium atom on each methyl group. Though the material balance of the former reaction was relatively low presumably due to addition of the base to the heterocycle, that of the latter reaction was quantitative. Thus, LDIPA was employed for the remainder of the study.

Attention was then directed towards the preparation of the monolithio salt (V) of 2,3-dimethylquinoxaline (I). Thus, treatment of I in THF with one equivalent of LDIPA in THF/HMPA afforded the desired carbanion since subsequent addition of benzophenone gave carbinol VI in a yield of 74%. Other condensations were realized with α-naphthyl phenyl ketone to give VII (62%), with methyl iodide and ethyl bromide to afford VIII (81%, 70%), with methyl benzoate to yield III (46%), and with benzonitrile to give IX (40%). Incidentally, though V is best pictured as a resonating system, only products arising from condensations at carbon were realized.

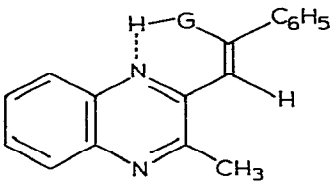


(V)

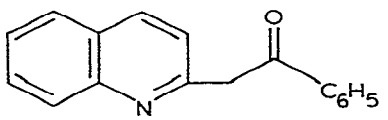
The structures of the condensation products were supported by elemental analysis and by IR and NMR spectroscopy. Interestingly, the IR spectrum of III exhibited only a weak absorption due to a carbonyl group. Moreover, the NMR spectra of both III and IX in chloroform-d_1 revealed the presence of a single vinylic type of proton; resonance due to protons on the 2-methylene group were absent. Upon addition of deuterium oxide to these solutions in the NMR spin

* For previous paper see ref. 6.

tubes, their NMR spectra gradually changed during a 24 hour period to indicate the absence of the vinylic proton. Clearly, III and IX exist in equilibrating systems between the enol and keto forms but mostly as the enols IIIb and IXb. These results explain why the previously described 2-phenacylquinoline (X) failed to exhibit reactions with hydroxylamine, phenylhydrazine, and aniline [5]. Parenthetically, X was prepared using the current method from 2-methylquinoline, LDIPA, and benzonitrile in a yield of 81%. Not surprisingly, the NMR spectrum of X was very similar to that of III and IX.



(IIIb) G = O
(IXb) G = NH



(X)

Next, attention was directed to the preparation of the dilithio salt II (R = Li) using the current method. Thus, treatment of I in THF with two equivalents of LDIPA in THF/HMPA conveniently gave the dicarbanion as evidenced by condensation with benzophenone to give XI in a yield of 49%. Other condensations of this species with methyl iodide and ethyl bromide gave XII (R = CH_3, 70% and R = C_2H_5, 60%); reaction with methyl benzoate, though, afforded a mixture of III (52%) and IV (6%). The NMR spectrum of IV suggested that it is better represented as a bis-enol similar to IXb.

Conclusion

The above described chemistry illustrates that either mono- or dilithio salts of 2,3-dimethylquinoxaline may be selectively prepared by means of lithium diisopropylamide. Subsequent condensations of these species with various electrophiles which are presumably general affords an attractive method of preparing substituted quinoxalines, many of which would be difficult to obtain by other procedures.

Experimental

Melting points were determined on a Thomas—Hoover Capillary Melting Point Apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee. Infrared spectra were recorded on a Perkin—Elmer 237B Spectrophotometer and NMR spectra were obtained at 60 MHz. on a Varian A-60 spectrophotometer using tetramethylsilane as an internal standard. Commercial anhydrous tetrahydrofuran and HMPA were distilled from solutions containing calcium hydride and stored in septum fitted bottles under a positive pressure of purified argon.

Preparation and reactions of 2-lithiomethyl-3-methylquinoxaline (V)

To a solution of 2.53 g (0.025 mol) of diisopropylamine in 10 ml of THF contained in a 300-ml, three-necked flask, equipped with a magnetic stirrer, constant pressure addition funnel, and a rubber septum, was added 16 ml (0.025 mol) of commercial 1.6 *M* n-butyllithium in hexane via a syringe. The resulting pale yellow solution was maintained at 0°C for 30 min, then treated with 4.5 g (0.025 mol) of HMPA via a syringe. The resulting bright yellow solution was stirred at 0°C for 15 min, then cooled to —78°C. This solution was then treated during 5 min with 3.9 g (0.025 mol) of 2,3-dimethylquinoxaline in 15 ml of THF. After 30 min, this mixture was reacted with electrophiles as follows.

A. Benzophenone. Addition of 4.6 g (0.025 mol) of benzophenone in 15 ml of THF to 0.025 mol of V gave a solution which was stirred for 1 h at 25°C and then inversely hydrolyzed with 100 ml of water. The layers were separated and the aqueous layer was extracted with three 20-ml portions of diethyl ether. The combined organic portions were washed with water, dried over calcium chloride, and concentrated to give a yellow gum which was recrystallized from aqueous ethanol to afford 6.4 g (74%) of 1,1-diphenyl-2-(3-methyl-2-quinoxalinyl)ethanol (VI): m.p. 144—145°C; NMR ($CDCl_3$) δ 2.65 (s, 3, CH_3), 3.92 (s, 2, CH_2), 7—8.13 (m, 14, ArH); IR (Nujol) 3225 cm^{-1} (OH).

Anal. found: C, 80.89; H, 5.72. $C_{23}H_{20}N_2O$ calcd.: C, 81.15; H, 5.92%.

B. α-Naphthyl phenyl ketone. Part A was repeated using 2.9 g (0.0125 mol) of the ketone and 0.0125 mol of V to afford 3.0 g (62%) of 1-α-naphthyl-1-phenyl-2-(3-methyl-2-quinoxalinyl)ethanol (VII): m.p. 184—185°C; NMR ($CDCl_3$) δ 2.5 (s, 3, CH_3), 4.0 (s, 2, CH_2), 6.9—8.1 (m, 16, ArH); IR (Nujol) 3320 cm^{-1} (OH).

Anal. found: C, 82.79; H, 5.59. $C_{27}H_{22}N_2O$ calcd.: C, 83.05; H, 5.68%.

C. Methyl iodide. Part B was repeated using 0.0125 mol of V and 3.55 g (0.025 mol) of methyl iodide to afford a yellow oil; distillation gave 1.74 g (81%) of 2-methyl-3-ethylquinoxaline (VIII, R = CH_3): m.p. 53.5—54.5°C; lit. [7] m.p. 53—54°C; picrate, m.p. 159—160°C; lit. [7] m.p. 159—160°C.

D. Ethyl bromide. Part B was repeated using 0.0125 mol of V and 2.7 g (0.025 mol) of ethyl bromide to afford a yellow oil; sublimation at 58°C (0.1 mmHg) gave 1.6 g (70%) of 2-methyl-3-propylquinoxaline (VIII, R = C_2H_5): m.p. 60—61.5°C; lit. [8] m.p. 60—61°C.

E. Benzonitrile. Part B was repeated using 0.0125 mol of V and 1.34 g (0.0125 mol) of benzonitrile to afford an orange solid; recrystallization from methanol gave 1.5 g (46%) of 1-phenyl-2-(3-methyl-2-quinoxalinyl)ethylidenimine (IX): m.p. 152—153°C; NMR ($CDCl_3$) δ 2.7 (s, 3, CH_3), 5.71 (s, 1, C = CH), 7.18—8.0 (m, 11, ArH); singlet at δ 5.71 disappears upon treatment with deuterium oxide for 24 h; IR (Nujol) 3315 and 3150 cm^{-1} (NH_2)..

Anal. found: C, 77.98; H, 5.88. $C_{17}H_{15}N_3$ calcd.: C, 78.13; H, 5.79%.

F. Methyl benzoate. Part B was repeated using 0.0125 mol of V and 1.70 g (0.0125 mol) of methyl benzoate to give an orange solid; recrystallization from aqueous ethanol yielded 1.30 g (40%) of 2-methyl-3-phenacylquinoxaline (III): m.p. 125—126°C; lit. [5] m.p. 125.6—126.5°C; NMR ($CDCl_3$) δ 2.55 (s, 3, CH_3), 6.15 (s, 1, C = C—H), 7.1—8.1 (m, 10, ArH); singlet at δ 6.15 disappears upon treatment with deuterium oxide for 24 h; IR (Nujol) 1650 cm^{-1} (C = O).

Preparation and reactions of the dilithio salt of 2,3-dimethylquinoxaline

The title compound was prepared as described above for the corresponding monoanion V using LDIPA and 2,3-dimethylquinoxaline (I) in a 2 : 1 ratio. Condensations were effected by adding the electrophile at —78°C during 5 min followed by stirring at 25°C for 1 h.

A. Benzophenone. Treatment of 0.025 mol of the dilithio salt (from 3.9 g of I) with 9.2 g (0.05 mol) of benzophenone in 20 ml of THF afforded a yellow solid that was recrystallized from ethanol to give 6.5 g (49%) of 2,3-bis(diphenylhydroxymethyl)methylquinoxaline (XI): m.p. 182—184°C; NMR ($CDCl_3$) δ 4.1 (s, 4, CH_2), 6.9—8.2 (m, 24, ArH); IR (Nujol) 3350 cm^{-1} (OH).

Anal. found: C, 82.50; H, 5.81. $C_{36}H_{30}N_2O_2$ calcd.: C, 82.73; H, 5.79%.

B. Methyl iodide. Part A was repeated using 1.03 g (0.0065 mol) of I, 0.0125 mol of LDIPA, and 2.75 g (0.019 mol) of methyl iodide to afford a yellow oil; distillation gave 0.85 g (70%) of 2,3-diethylquinoxaline (II, R = CH_3): m.p. 36—37°C; lit. [8] m.p. 35—37°C.

C. Ethyl bromide. Part B was repeated using 1.95 g (0.0125 mol) of I, 0.025 mol of LDIPA, and 4.1 g (0.037 mol) of ethyl bromide to afford a yellow oil that was distilled to give 1.60 g (60%) of 2,3-di-n-propylquinoxaline (II, R = C_2H_5): m.p. 42.5—44.5°C; lit. [8] m.p. 43—45°C.

D. Methyl benzoate. This reaction was effected using 1.95 g (0.0125 mol) of I and 0.025 mol each of LDIPA and methyl benzoate. Work-up afforded an orange solid that was recrystallized from 95% ethanol to give 0.2 g (6%) of 2,3-diphenacylquinoxaline (IV): m.p. 206—207°C; lit. [5] m.p. 204.5—205.2°C; NMR ($CDCl_3$) δ 6.43 (s, 2, C = C—H), 7.1 (s, 4, ArH), 7.3—8.15 (m, 12, ArH). The recrystallization liquor was cooled to yield 1.7 g (52%) of 2-methyl-3-phenacylquinoxaline (III): m.p. 125.5—126.5°C; lit. [5] m.p. 125.6—126.5°C.

References

1 S. Gabriel and A. Sonn, Chem. Ber., 40 (1907) 4850.
2 R.W. Bost and E.E. Towell, J. Amer. Chem. Soc., 70 (1948) 903.
3 E. Sawicki, B. Chastain, H. Bryant and A. Carr, J. Org. Chem., 22 (1957) 625.
4 R.A. Ogg and F.W. Bergstrom, J. Amer. Chem. Soc., 53 (1931) 1849.
5 F.W. Bergstrom and A. Moffat, J. Amer. Chem. Soc., 59 (1937) 1494.
6 E.M. Kaiser and P.L.A. Knutson, Tetrahedron Lett., (1975) 3583.
7 F. Asinger, M. Thiel and W. Schaefer, Ann. Chem., 637 (1960) 146.
8 J.K. Lanquist, G.J. Stacey and Imperial Chemicals Industries Ltd., British Patent 668 412 (Mar. 12, 1952); Chem. Abstr., 47 (1953) 5459b.