Journal of Organometallic Chemistry, 175 (1979) 11—19

PREPARATION AND CONDENSATIONS OF 1-LITHIOMETHYL-3-METHYLISOQUINOLINE AND ITS 6,7-DIMETHOXY DERIVATIVE

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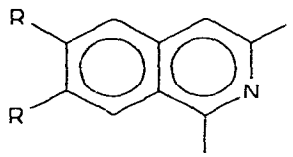
(Received March 13th, 1979)

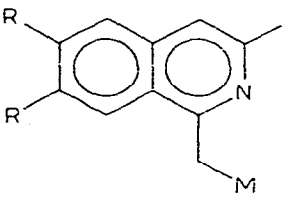
Summary

1,3-Dimethylisoquinoline and 6,7-dimethoxy-1,3-dimethylisoquinoline have been conveniently metalated by n-butyllithium and lithium diisopropylamide in ethers/hexane and by sodium amide in liquid ammonia to afford only the 1-alkalimethyl derivatives. Although the isomeric 3-alkalimethyl-1-methylisoquinolines could not be obtained by metallation of the parent dimethylisoquinolines, 3-lithiomethyl-1-methylisoquinoline was prepared by reduction of 3-methoxymethyl-1-methylisoquinoline with lithium metal. The 1-alkalimethylisoquinoline derivatives were condensed with a variety of electrophiles to give alcohols, enols, enamines, and alkyl compounds in good to excellent yields. Isomerizations between 1-lithiomethyl-3-methylisoquinoline and 3-lithiomethyl-1-methylisoquinoline were not observed.

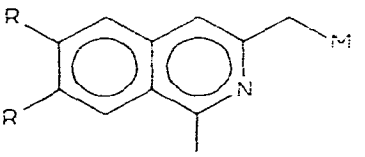
Certain previous studies in this laboratory have been directed towards the chemistry of 1-lithiomethylisoquinoline [1], 3-lithiomethylisoquinoline [2], and the isomeric 2-lithiomethyl-4-methyl- and 4-lithiomethyl-2-methylquinolines [3]. The latter reagents were prepared by treatment of 2,4-dimethylquinoline with n-butyllithium in ethyl ether and in THF, respectively, where thermodynamic versus kinetic control was found to operate as a function of the solvent and time of reaction. The size of the base in such reactions was also shown to be important [4]. Because of the above, it was deemed of interest to determine if 1,3-dimethylisoquinoline (I) could be conveniently converted to lithio derivatives II and III by varying the solvent, reaction time, and size of base in their preparations. Moreover, neither II nor III or the corresponding 6,7-dimethoxy derivatives V and VI have been described previously despite the fact that they could serve as useful synthetic intermediates in the preparation of isoquinoline derivatives.



(I, R = H;
IV, R = OCH_3)

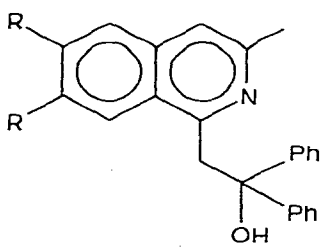


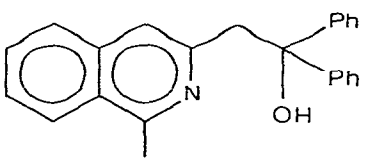
(II, R = H;
V, R = OCH_3)



(III, R = H;
VI, R = OCH_3)

Surprisingly, despite the above described regioselective metalations of 2,4-dimethylquinoline, treatment of I with either n-butyllithium or lithium diisopropylamide (LDIPA) in THF/hexane or ether/hexane at a variety of temperatures (—78 to +25°C) or with sodium amide in liquid ammonia afforded only organoalkali reagent II as evidenced by condensation with benzophenone to give VII. None of the isomeric alcohol VIII was observed in any case. That even the sterically hindered LDIPA on I afforded II was unexpected because of peri-hydrogen interaction which should have subjected the 1-methyl group to steric retardation of metalation. The structure of alcohol VII was confirmed by elemental analysis and X-ray crystallography [5]. The latter technique had to be employed because ^1H and ^{13}C NMR ambiguously suggested the presence of VII and VIII, respectively.



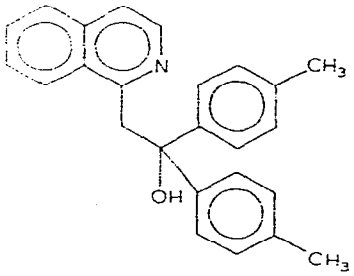


(VIII)

(VII, R = H;
XVI, R = OCH_3)

Reagent II, prepared from I and n-butyllithium in THF at 25°C, then was condensed with a variety of electrophiles in addition to benzophenone. Thus, II and 4,4′-dimethylbenzophenone, benzaldehyde, and veratraldehyde gave alcohols IX, X, and XI, respectively. Reagent II was also acylated by methyl benzoate and methyl 4-chlorobenzoate to yield enols XII and XIII, respectively. Finally, II was condensed with benzonitrile and benzyl chloride to afford enamine XIV and alkyl derivative XV, respectively.

Similarly, 6,7-dimethoxy-1-lithiomethyl-3-methylisoquinoline (V) was prepared from IV and n-butyllithium in THF at 25°C. This reagent was then combined with appropriate electrophiles to afford alcohols XVI and XVII, enol XVIII, and enamine XIX. The structures of all the above products were demonstrated by elemental analysis and by IR and NMR spectroscopy. Condensations of II and V with α,β-unsaturated ketones will be described in a later publication [6].



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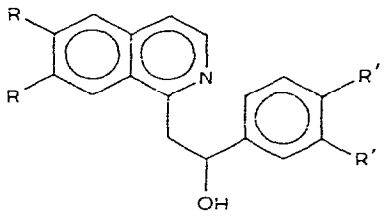
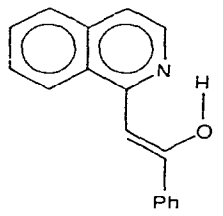
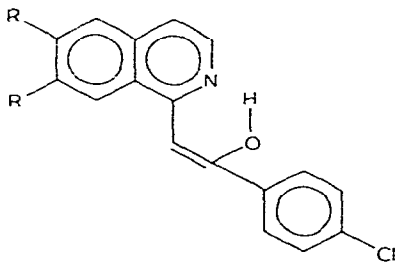


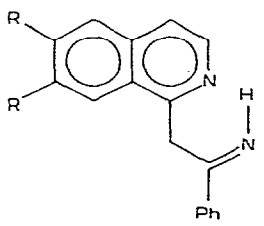
(X, R = R′ = H;
XI, R = H, R′ = OCH_3;
XVII, R = OCH_3, R′ = H)



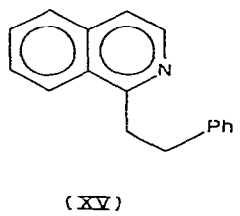
(XII)



(XIII, R = H;
XVIII, R = OCH_3)



(XIV, R = H;
XIX, R = OCH_3)



(XV)

A brief note about the regiointegrity of carbanions II and III seems in order. Thus, lithio derivative III was prepared unequivocally by reduction of 3-methoxymethyl-1-methylisoquinoline using lithium metal dispersed in THF. After quenching with deuterium oxide, NMR analysis of the product surprisingly showed that deuterium had been incorporated only at the 3-methyl position. A blank experiment involving I, n-butyllithium, and deuterium oxide in THF gave product containing deuterium only in the 1-methyl position. To determine if intermolecular transmetalation were possible, 1-methylisoquinoline was added to a previously prepared solution of 3-lithiomethylisoquinoline. After an appropriate time, treatment of the reaction mixture with benzophenone failed to afford the alcohol arising from 1-lithiomethylisoquinoline.

It may be concluded that, in contrast to the equilibrating monolithio salts of 2,4-dimethylquinoline, carbanions II and III, and presumably V and VI, are stable with respect to isomerization both by inter- or intra-molecular processes. Apparently, in the current study, metalation of I and IV is dependent only upon the relative acidities of the 1- versus the 3-methyl groups. Previous workers have demonstrated that the methyl group of 1-methylisoquinoline is more reactive than that of 3-methylisoquinoline towards reagents that are purported to proceed via carbanions [7].

The condensations of II and V described above would seem to be general and should be capable of extension to many other electrophiles.

Experimental

Melting points were taken in capillary tubes on a Thomas Hoover Uni-melt 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, a Varian T-60, or a Varian EM-360 spectrometer using tetramethylsilane as an internal standard. n-Butyllithium was purchased from Apache Chemicals of Rockford, Illinois. Unless otherwise indicated, organic chemicals were purchased from Aldrich Chemical Co. or Eastman Organic Chemicals. Tetrahydrofuran was distilled from a solution containing calcium hydride. Thin layer chromatography was accomplished with Eastman Chromatogram Sheets with fluorescent indicator. Alumina was purchased from Merck and Co., silicar from Mallinckrodt Chemical Works, and silica gel from Davidson Chemical.

Preparation of 1-lithiomethyl-3-methylisoquinoline using n-butyllithium; condensation with benzophenone

To a 100 ml three-necked flask equipped with a septum, reflux condenser, and stirrer were added under an argon atmosphere at room temperature 25 ml of dry THF, 1.00 g (0.0064 mol) of 1,3-dimethylisoquinoline, and 4.1 ml. (0.0064 mol) of 15% n-butyllithium in hexane. After stirring for 30 min, the red-brown solution was assumed to contain 0.0064 mol of 1-lithiomethyl-3-methylisoquinoline (II). To this solution was added 1.15 g (0.0064 mol) of benzophenone in 25 ml of THF and the solution was stirred for one hour. The reaction mixture was then quenched with water, filtered, and concentrated under vacuum to give a yellow semi-solid. This material was dissolved in 30 ml of ether to give, upon standing, 1.61 g (75%) of 1,1-diphenyl-2-(3-methyl-1-isoquinolyl)ethanol (VII). Further recrystallizations from ether yielded colorless crystals, m.p. 149—151°C; IR (Nujol) 3100 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 3.90 (s, 2, CH_2), 6.85—7.15 (m, 7, ArH, OH). 7.25—7.50 (m, 7, ArH), 7.75—8.10 (m, 2, ArH) ppm. Anal. Found: C, 85.06; H, 6.10. $C_{24}H_{21}NO$ calcd.: C, 84.92; H, 6.24%.

The addition of benzophenone to II was also effected at several different temperatures in THF/hexane or ethyl/hexane. The specifics follow where the percent yield refers to the amount of VII obtained: THF/hexane: —78°C, 62%; 0°C, 65%. Ether/hexane: —78°C, 60%. 0°C, 62%.

Preparation of 1-lithiomethyl-3-methylisoquinoline using LDIPA; condensation with benzophenone

To a 100-ml three-necked flask equipped as above were added 25 ml of dry solvent, 0.9 ml (0.0064 mol) of diisopropylamine, and 4.1 ml (0.0064 mol) of 15% n-butyllithium in hexane. The light yellow solution was stirred for 30 min. At the end of this time, the desired temperature was reached and the solution was treated with 1.00 g (0.0064 mol) of 1,3-dimethylisoquinoline in 25 ml of dry solvent. After stirring for 30 min, the red-brown solution was assumed to contain 0.0064 mol of 1-lithiomethyl-3-methylisoquinoline. To this solution was added 1.15 g (0.0064 mol) of benzophenone in 25 ml of dry solvent and the solution was stirred for 1 h. The reaction mixture was then quenched with water, filtered, and concentrated under vacuum to give a yellow semi-solid. The material was dissolved in 30 ml of ether to give, upon standing, 1,1-diphenyl-2-(3-methyl-1-isoquinolyl)ethanol (VII). Further recrystallizations from ether

yielded colorless prisms, m.p. 149—151°C. Specifics follow: THF/hexane: —78°C, 57%; 0°C, 69%. Ether/hexane: —78°C, 68%; 0°C, 63%.

Preparation of 3-methyl-1-sodiomethylisoquinoline using sodium amide; condensation with benzophenone

A 250-ml, three-necked flask, equipped with a mechanical stirrer, dry-ice condenser, and addition funnel was charged with 125 ml of commercial anhydrous liquid ammonia. To this was added a sodium pellet followed by a catalytic amount of ferric nitrate, then additional sodium pellets until 0.30 g (0.013 g-atom) of the metal had been added. The mixture was then stirred until conversion to sodium amide was complete (approx. 30 min). To this mixture was added during a 5 min period 2.0 g (0.013 mol) of 1,3-dimethylisoquinoline in 25 ml of dry ether. After stirring for an additional 5 min, the solution was assumed to contain 0.013 mol of 3-methyl-1-sodiomethylisoquinoline. To this mixture was added 2.30 g (0.013 mol) of benzophenone in 25 ml of dry ether. This solution was stirred for 5 min and then added to 5.0 g of ammonium chloride in ammonia. After evaporation of the ammonia, the residue was treated with 100 ml of water and the organic portion was extracted with 100 ml of ether. The ether layer was dried over sodium sulfate, and concentrated under vacuum to give a yellow semi-solid. The material was dissolved in 50 ml of ether to give 0.91 g (42%) of 1,1-diphenyl-2-(3-methyl-1-isoquinolyl)ethanol (VII), m.p. 148—150°C, mixed m.p. 147—150°C.

Condensation of 1-lithiomethyl-3-methylisoquinoline with other electrophiles

To a 100-ml three-necked flask equipped with a septum, reflux condenser, and stirrer were added under an argon atmosphere 1.0 g (0.0064 mol) of 1,3-dimethylisoquinoline, 25 ml of the dry solvent, and 4.1 ml (0.0064 mol) of 15% n-butyllithium in hexane. After stirring for 30 min at the appropriate temperature, the resulting red-brown solution was assumed to contain 0.0064 mol of 1-lithiomethyl-3-methylisoquinoline and was treated with a solution of 0.0064 mol of the electrophile in 25 ml of dry THF added during 5 min. After 60 min, the mixture was quenched with water, filtered, and concentrated under vacuum to give crude product which was recrystallized as outlined below.

A. 4,4'-Dimethylbenzophenone. This ketone (1.35 g) afforded 1.93 g (82%) of 1,1-bis(4-methylphenyl)-2-(3-methyl-1-isoquinolyl)ethanol (IX) m.p. 149—151°C (ether); IR (Nujol) 3100 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.35 (s, 6, $ArCH_3$), 1.55 (s, 3, CH_3), 3.25 (s, 2, CH_2), 6.10 (s, 1, OH), 6.20 (s, 4, Ar-H), 6.55—6.80 (m, 7, ArH), 7.15—7.50 (m, 1, ArH) ppm. Anal.: Found: C, 85.11; H, 6.194. $C_{26}H_{25}NO$ calc.: C, 84.98; H, 6.186%.

B. Benzaldehyde. This aldehyde (0.65 g) yieled 1.06 g (64%) of 2-(3-methyl-1-isoquinolyl)-1-phenylethanol (X), m.p. 93—94°C (petroleum ether B); IR (Nujol) 3100 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.70 (s, 3, CH_3), 3.10—3.90 (m, 10, ArH) ppm. Anal. Found: C, 82.02; H, 6.59. $C_{18}H_{17}NO$ calcd.: C, 82.10; H, 6.59%.

C. Veratraldehyde. This aldehyde (1.07 g) gave 0.97 g (47%) of 1-(3,4-dimethoxyphenyl)-2-(3-methylisoquinolyl)ethanol (XI), m.p. 138—140°C (ether); IR (Nujol) 3300 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.70 (s, 3, CH_3), 3.40—3.65 (m, 2, CH_2), 3.95 (s, 6, OCH_3), 5.30—5.55 (m, 1, CH), 6.50—6.70 (s, 1,

OH), 6.90—8.30 (m, 7, ArH) ppm. Anal. Found: C, 74.32; H, 6.64. $C_{20}H_{21}NO_3$ calcd.: C, 74.28; H, 6.55%.

D. Methyl benzoate. This ester (0.87 g) afforded 1.12 g (67%) of 3-methyl-1-(2-hydroxy-2-phenylethenyl)isoquinoline (XII), m.p. 145—147°C (petroleum ether B); IR (Nujol) 3200 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 6.70 (s, 1, OH), 6.80 (s, 1, =CH), 7.40—8.40 (m, 9, ArH) ppm. Anal. Found: C, 82.90; H, 5.88. $C_{18}H_{18}NO$ calcd.: C, 82.73; H, 5.79%.

E. Methyl p-chlorobenzoate. This ester (1.09 g) yielded 1.17 g (62%) of 3-methyl-1-[2-(4-chlorophenyl)-2-hydroxyethenyl]isoquinoline (XIII), m.p. 141—143°C (95% ethanol); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 6.70 (s, 1, OH), 6.80 (s, 1, =CH), 7.40—7.80 (m, 5, ArH), 8.00—8.40 (m, 4, ArH) ppm. Anal. Found: C, 73.02; H, 4.82. $C_{18}H_{14}ClNO$ calcd.: C, 73.09; H, 4.73%.

F. Benzonitrile. This nitrile (0.66 g) gave 1.15 g (69%) of 1-(2-amino-2-phenylethenyl)-3-methylisoquinoline (XIV), m.p. 142—144°C (petroleum ether B); IR (Nujol) 3450 cm^{-1} (NH); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 6.25 (s, 1, NH), 6.90 (s, 1, =CH), 7.15—7.75 (m, 9, ArH and NH), 8.15—8.30 (m, 1, ArH).Anal. Found: 82.83; H, 6.13. $C_{18}H_{16}N_2$ calcd.: C, 83.04; H, 6.20%.

G. Benzyl chloride. This alkyl halide (0.81 g) afforded 1.17 g (74%) of 3-methyl-1-(2-phenylethyl)isoquinoline (XV), m.p. 60—61°C (petroleum ether B); NMR ($CDCl_3$) δ 2.65 (s, 3, CH_3), 2.95—3.30 (m, 2, CH_2), 3.40—3.80 (m, 2, CH_2), 7.20—7.50 (m, 6, ArH), 7.50—7.75 (m, 3, ArH), 7.95—8.20 (m, 1, ArH) ppm. Anal. Found: C, 87.14; H, 7.01. $C_{18}H_{17}N$ calcd.: C, 87.41; H, 6.93%.

Preparation and condensations of 6,7-dimethoxy-3-methyl-1-lithiomethylisoquinoline

To a 100-ml three-necked flask equipped with a septum, reflux condenser, and stirrer were added at room temperature under an argon atmosphere 25 ml of dry THF, 1.09 g (0.005 mol) of 6,7-dimethoxy-1,3-dimethylisoquinoline, and 3.2 ml (0.005 mol) of 15% n-butyllithium in hexane. After stirring for 30 min, the dark purple solution was assumed to contain 0.005 mol of 6,7-dimethoxy-1-lithiomethyl-3-methylisoquinoline and was treated with a 0.005 mol solution of the electrophile in 25 ml of dry THF added during 5 min. After stirring for 60 min, the reaction mixture was quenched with water, filtered, and concentrated under vacuum to afford crude product which was recrystallized from the solvent indicated.

A. Benzophenone. This ketone (0.91 g) gave 1.25 g (63%) of 1,1-diphenyl-2-[(6,7-dimethoxy-3-methyl)-1-isoquinolyl]ethanol (XVI), m.p. 185—186°C (benzene/petroleum ether B); IR (Nujol) 3200 cm^{-1} (OH), NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 3.90 (s, 2, CH_3), 3.95 (d, 6, OCH_3), 6.85—7.15 (m, 8, ArH, OH), 7.20—7.70 (m, 6, ArH) ppm. Anal. Found: C, 77.86; H, 6.18. $C_{26}H_{27}NO_3$ calcd.: C, 78.17; H, 6.31%.

B. Benzaldehyde. This aldehyde (0.53 g) yielded 0.95 g (59%) of 2-[(6,7-dimethoxy-3-methyl)-1-isoquinolyl]-1-phenylethanol (XVII), m.p. 125—127°C (benzene/petroleum ether B); IR (Nujol) 3200 cm^{-1} (OH), NMR ($CDCl_3$) δ 2.65 (s, 3, $ArCH_3$), 3.35—3.75 (m, 2, $ArCH_2$), 3.95 (d, 6, OCH_3), 5.35—5.55 (m, 1, ArCH), 6.95 (s, 1, ArH), 7.20—7.70 (m, 6, ArH) ppm. Anal. Found: C, 74.13; H, 6.43. $C_{20}H_{23}NO_3$ calcd.: C, 74.28; H, 6.55%.

C. Methyl p-chlorobenzoate. This ester (0.86 g) afforded 1.30 g (67%) of 6,7-dimethoxy-3-methyl-1-[2-(4-chlorophenyl)-2-hydroxyethenyl]isoquinoline (XVIII), m.p. 247—248.5°C (acetone); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 4.00 (d, 6, OCH_3), 6.30 (s, 1, =CH), 6.50 (s, 1, OH), 6.70 (s, 1, ArH), 7.10—7.50 (m, 4, ArH), 7.70—7.90 (d, 2, ArH) ppm. Anal. Found: C, 67.46; H, 5.12. $C_{20}H_{20}ClNO_3$ calcd.: C, 67.51; H, 5.10%.

D. Benzonitrile. This nitrile (0.52 g) yielded 1.05 g (65%) of 1-(2-amino-2-phenylethenyl)-6,7-dimethoxy-3-methylisoquinoline (XIX), m.p. 190—192°C (acetone); IR (Nujol) 3475 cm^{-1} (NH); NMR ($CDCl_3$) δ 2.50 (s, 3, CH_3), 3.90 (d, 6, OCH_3), 5.95 (s, 1, =CH), 7.70—7.80 (d, 2, NH_2), 7.00—7.70 (m, 8, ArH) ppm. Anal. Found: C, 74.68; H, 6.21. $C_{20}H_{22}N_2O_2$ calcd.: C, 74.97; H, 6.29%.

Preparation of 1-(methoxymethyl)-2-phenylethanamine

To a 1-l three-necked flask equipped with an addition funnel, stirrer, and reflux condenser was added 51.0 g (0.34 mol) of 2-amino-3-phenyl-1-propanol in 500 ml of dry benzene. To this stirred solution was added 7.75 g (0.34 g-atom) of sodium wire in portions and stirring was continued until hydrogen evolution ceased. At this time, the excess sodium was removed, and the mixture was heated with 48.2 g (0.34 mol) of methyl iodide in 100 ml of dry benzene. After refluxing for 30 min, the solid which formed upon cooling was dissolved in 250 ml of water and the benzene layer was separated. The benzene layer was dried over sodium sulfate, filtered, concentrated under vacuum, and the residual oil was vacuum distilled at 68—69°C/1—2 mmHg to give 29.1 g (52%) of 1-(methoxymethyl)-2-phenylethanamine. An analytical sample was prepared from the hydrochloride which was recrystallized twice from acetone to yield colorless needles, m.p. 121—123°C; NMR ($CDCl_3$) δ 3.00—4.10 (m, 5, CH and CH_2), 3.50 (s, 3, OCH_3), 7.30 (s, 5, ArH), 8.45—8.85 (s, 3, NH_3^+) ppm. Anal. Found: C, 59.70; H, 8.01. $C_{10}H_{16}ClNO$ calcd.: C, 59.55; H, 7.99%.

Preparation of N-[1-(methoxymethyl)-2-phenylethyl]ethanamide

To a 250-ml round-bottomed flask was added 28.0 g (0.17 mol) of 1-(methoxymethyl)-2-phenylethanamine followed by 100 ml of freshly distilled acetic anhydride and the mixture warmed on a steam bath for 30 min. The excess acetic anhydride was removed under vacuum and the residual oil vacuum distilled at 120—122°C/1—2 mmHg to give a viscous, colorless oil. The oil was dissolved in a minimum amount of ethyl ether which yielded, upon scratching, 30.6 g (87%) of *N*-[1-(methoxymethyl)-2-phenylethyl]ethanamide. An analytical sample was obtained by two further recrystallizations to give colorless needles, m.p. 63—65°C; IR (Nujol) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.45 (s, 3, $ArCH_3$), 3.90—4.00 (d, 8, $ArCH_2$ and OCH_3), 6.80 (s, 1, ArH), 7.00—7.55 (m, 12, ArH), 8.10—8.90 (s, 1, OH) ppm. Anal. Found: C, 69.56; H, 8.40. $C_{12}H_{17}NO_2$ calcd.: C, 69.54; H, 8.27%.

Preparation of 3,4-dihydro-3-methoxymethyl-1-methylisoquinoline

To a 1-l round-bottomed flask were added 30.0 g (0.145 mol) of *N*-[1-(methoxymethyl)-2-phenylethyl]ethanamide and 400 ml of dry xylene. To this refluxing solution was added portionwise, over a period of 30 min, 35.0 g (0.25 mol) of phosphorus pentoxide. Reflux was maintained for another 30 min.

After cooling, the xylene was decanted from the dark brown solid, which was then treated with 400 ml of water. The mixture was shaken until all solid had dissolved. The aqueous solution was extracted with two 100-ml portions of ethyl ether, made basic with 10% sodium hydroxide, and the mixture extracted with four 100-ml portions of ethyl ether. The final four ether extracts were combined, dried over sodium sulfate, filtered, concentrated under vacuum, and the residual oil was vacuum distilled at 85—87°C/1—2 mmHg to give 14.5 g (53%) of 3,4-dihydro-3-methoxymethyl-1-methylisoquinoline; NMR (neat) δ 2.20 (s, 3, CH_3), 2.10—2.90 (m, 3, CH_2 and CH), 3.20 (s, 3, OCH_3), 3.10—4.00 (m, 2, CH_2O), 6.80—7.20 (m, 4, ArH) ppm. An analytical sample was obtained as the picrate which was recrystallized twice from 95% ethanol to give yellow needles, m.p. 167—168°C. Anal. Found: C, 51.82; H, 4.43. $C_{18}H_{18}N_4O_8$ calcd.: C, 51.67; H, 4.34%.

Preparation of 3-methoxymethyl-1-methylisoquinoline

To a 300-ml round-bottomed flask were added 14.0 g (0.074 mol) of 3,4-dihydro-3-methoxymethyl-1-methylisoquinoline, 100 ml of dry decalin, and 0.5 g of 5% palladium on activated carbon. After refluxing for 24 h, the mixture was filtered while hot through a fiberglass filter. The decalin was removed under vacuum and the residual oil was vacuum distilled at 105—108°C/1—2 mmHg to give 11.3 g (82%) of 3-methoxymethyl-1-methylisoquinoline; NMR (neat) δ 2.70 (s, 3, CH_3), 3.35 (s, 3, OCH_3), 4.50 (s, 2, CH_2), 6.80—7.65 (m, 5, ArH) ppm. An analytical sample was obtained as the picrate which was recrystallized from 95% ethanol to yield yellow needles, m.p. 154—156°C. Anal. Found: C, 52.01; H, 3.91. $C_{18}H_{16}N_4O_8$ calcd.: C, 51.92; H, 3.87%.

Preparation of 3-(lithiomethyl)-1-methylisoquinoline

A 100-ml three-necked flask equipped with dropping funnel, reflux condenser, and stirrer was charged with 0.75 g (0.011 g-atom) of a lithium dispersion in 25 ml of dry THF, and cooled to 0°C. To this stirred suspension was added dropwise under an argon atmosphere a solution of 2.00 g (0.011 mol) of 3-methoxymethyl-1-methylisoquinoline in 10 ml of dry THF and the resulting light brown solution stirred at 0°C for 60 min. The reaction mixture was then quenched with D_2O, filtered, and concentrated under vacuum to give a light yellow oil. The oil was vacuum distilled at 82—84°C/1.0 mmHg to give 1.05 g (71%) of 3-deuteriomethyl-1-methylisoquinoline; NMR ($CDCl_3$) δ 2.60 (s, 3, CH_3), 2.70 (s, 2, CH_2), 6.75—7.85 (m, 5, ArH) ppm.

Preparation of 1-deuteriomethyl-3-methylisoquinoline

A 0.0064 mol solution of 1-(lithiomethyl)-3-methylisoquinoline, prepared as above, was quenched with D_2O, filtered, and concentrated under vacuum to give a light yellow oil. This oil was vacuum distilled at 82—84°C/1.0 mmHg to give 0.85 g (84%) of 1-deuteriomethyl-3-methylisoquinoline; NMR ($CDCl_3$) δ 2.60 (s, 2, CH_2), 2.70 (s, 3, CH_3), 6.75—7.85 (m, 5, ArH) ppm.

Attempted metalation of 1-methylisoquinoline with 3-(lithiomethyl)isoquinoline

To a 200-ml, three-necked flask equipped with a septum, reflux condenser,

and stirrer were added under an argon atmosphere 30 ml of dry THF, 1.35 g (0.0134 mol) of diisopropylamine, and 7.0 ml (0.011 mol) of 15% n-butyllithium in hexane and the bright yellow solution was stirred for 30 min. To this solution of LDIPA was added a solution of 25 ml of dry THF and 1.43 g (0.010 mol) of 3-methylisoquinoline and the resulting deep red solution was stirred under reflux for 60 min. To this solution was added 1.43 g (0.010 mol) of 1-methylisoquinoline in 10 ml of dry THF and the mixture was stirred for an additional 30 min. At this time, the mixture was treated with 1.82 g (0.010 mol) of benzophenone in 10 ml of dry THF. After refluxing for 30 min, the reaction mixture was quenched with water, filtered, and concentrated under vacuum to give a yellow oil. TLC indicated this oil contained only starting materials. Although alcohol derived from 1-lithiomethylisoquinoline would have been obtained if this carbanion were present [1], the reaction conditions are insufficient to effect condensation between 3-lithiomethylisoquinoline and benzophanone.

Acknowledgement

This research was supported by the National Institute of General Medical Sciences, National Institutes of Health by grant GM21500.

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