A Convenient Synthesis of 9*H*-Dibenz[*c*,*f*]imidazo[1,2-*a*]azepin-9-ones

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A convenient three step synthesis of 9*H*-dibenz[*c*,*f*]imidazo[1,2-*a*]azepin-9-ones from readily available 2-phenylimidazoline and a methyl benzoate is described.

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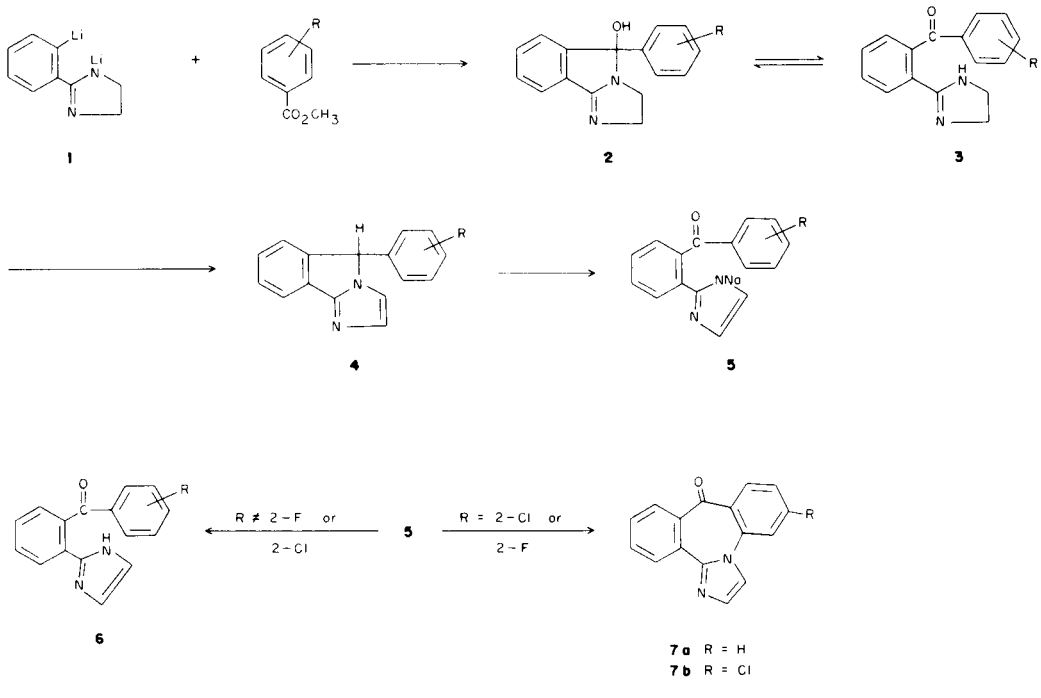
It has been reported (1) that the air oxidation of the anion generated from a 5-aryl-5*H*-imidazo[1,2-*a*]isoindole (**4**) and sodium hydride in DMF resulted in the formation of a 2-(2-imidazoyl-2yl)benzophenone (**6**). Since the reaction most likely proceeds through the sodium salt **5** a benzoyl group containing an ortho halogen (X = F, Cl) could undergo an internal nucleophilic displacement by the imidazoyl anion to form a 9*H*-dibenz[*c*,*f*]imidazo[1,2-*a*]-azepin-9-one **7**. In the present work we demonstrate this reaction by preparing **7** in three steps from readily available starting materials.

Reaction (2) of the dilithio salt of 2-phenylimidazoline (1) with a 2-halogenated methyl benzoate gave the 5-aryl-2,3-dihydro-5*H*-imidazo[2,1*a*]isoindol-5-ols **2**. The ultraviolet spectrum of these compounds are in agreement with the tricyclic form **2** rather than that of the benzophenone tautomer **3**. This finding is consistent with the tautomeric equilibrium found with derivatives of **2** that do not contain a halogen atom in the ortho position of the phenyl group (3).

Dehydration of **2** in refluxing acetic acid gave **4** in good yields. Conversion of the 2'-fluorophenyl derivative **4a** to its sodium salt by sodium hydride in DMF followed by oxygenation (air) for about 48 hours at room temperature resulted in the formation of 9*H*-dibenz[*c*,*f*]imidazo[1,2-*a*]-azepin-9-one (4) (**7a**)in 76% yield (Scheme I). The structure of **7a** was confirmed mainly by ir and mass spectral data. When the 2'-chlorophenyl analog **5b** was oxygenated under the same condition a 42% yield of **7a** was isolated. Extension of the reaction to the 2',4'-dichlorophenyl

Scheme I



For **2,3,4,5**: **a** = 2-F; **b** = 2-Cl; **c** = 2,4-Cl_2

derivative **4b** gave the 2-chloro derivative **7b** in 70% yield.

Treatment of the salt formed from **2a** and sodium hydride in DMF with air for up to 120 hours resulted in recovery of starting material and none of the 2,3-dihydro analog of **7a**. Failure of **2a** to undergo a cyclization similar to **5a** is probably due to the tautomeric equilibrium of the salt existing exclusively in the tricyclic form (OH in **2** equals ONa).

EXPERIMENTAL

Infrared (ir) spectra were recorded on Perkin-Elmer 257 and 457 grating infrared spectrometers and ^{1}H nuclear magnetic resonance (nmr) spectra were recorded using either a Varian T-60 or A-60A spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS; coupling constants (J) are given in Hz. ^{13}C-nmr spectra were obtained at 25.2 MHz on a Varian XL-100-12 spectrometer system equipped with a 602/L 16K computer in the Fourier transform mode with sample concentration of *ca* 0.5*M* when possible. Chemical shifts are relative to TMS as an internal standard and those assignments marked with an (*) may be interchanged. The uv spectra were obtained in 95% ethanol on a Cary Model 15 spectrometer and the mass spectra on a LKB 900 mass spectrometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Except where noted solvents were reagent grade and used as received. The organolithium reagents were obtained from Foote Mineral Co., and Lithium Corporation of America, and used without further purification. The tetrahydrofuran was dried by storage over 3 Å molecular sieves. Analytical thin layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of Silica Gel G with fluorescent indicator.

5-Aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (2).

To a stirred solution of 18.2 g (0.125 mole) of 2-phenylimidazoline in 125 ml of dry THF (nitrogen atmosphere) there was added dropwise 160 ml (0.375 mole of *n*-BuLi) of 1.6*M* *n*-BuLi in hexane at such a rate that the internal temperature did not exceed 30°. The suspension was heated at 50° for *ca*.3 hours and then treated dropwise with a solution of 41.0 g (0.26 mole) of methyl *o*-fluorobenzoate (bp 94-97° at 12 mm) in 50 ml of THF while maintaining the temperature below 60°. After standing overnight at room temperature the mixture was cooled in an icebath and treated dropwise with 63 ml of saturated ammonium chloride solution. After an additional 1 hour the resultant solid (17.7 g) was filtered off, washed with water and then recrystallized from 2-propanol to give 15.4 g (46%) of **2a**, mp 168° dec, Rf 0.15 (chloroform-methanol 90:10); ir (potassium bromide): broad salt-like bands 3.0-4.0 μ, 6.04 (C=N); uv: λ max 263 (ϵ 4,790), 269 (5,005), 275 (4,805); ^{1}H nmr (DMSO-d_6): δ 4.05 (4H, octet, CH_2CH_2), 6.95-8.25 (8H, m, **2** C_6H_4), 9.10 (1H, broad s, OH).

Anal. Calcd. for $C_{16}H_{13}FN_2O$: C, 71.6; H, 4.9; N, 10.4. Found: C, 71.7; H, 5.2; N, 10.6.

From 25.8 g (0.18 mole) of phenylimidazoline, 224 ml of 1.6*M* *n*-BuLi in hexane and 61.8 g (0.34 mole) of methyl *o*-chlorobenzoate (bp 110-112° at 12 mm) reacted as above there was obtained 16.6 g (32%) of **2b**, mp 187° dec, Rf 0.20 (chloroform methanol 80:20): ir (potassium bromide): broad salt-like bands 3.0-4.0 μ, 6.05 (C=N); uv λ max 266 (ϵ 4,800), 278 (4,850); ^{13}C-nmr (DMSO-d_6): 167.3 (C-9b), 153.5 (C-5a), 136.9 C-1'), 132.0 (C-5a), 131.7 (C-9a), 131.3 (C-7), 130.2, 127.3 (C-3' to C-6'), 128.9 (C-8), 123.4 (C-9), 122.0 (C-6), 59.9 (C-2), 40.9 (C-3).

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.5; H, 4.6; Cl, 12.4; N, 9.8. Found: C, 67.7: H, 4.8, Cl, 12.7; N, 9.5.

From 34.6 g (0.28 mole) of 2-phenylimidazoline, 320 ml of 1.6*M* *n*-BuLi and 102.1 g (0.50 mole) of methyl 2,4-dichlorobenzoate reacted as above, there was obtained 15.5 g (27%) of **2c**, mp 173° dec, Rf 0.2 (chloroform-methanol 80:20); ir (potassium bromide) broad salt-like bands from 3.0-4.0 μ, 6.05 (C=N); uv: λ max 270 (ϵ 4,165), 276 (4,265).

*Anal.*Calcd. for $C_{16}H_{12}Cl_2N_2O$: C, 60.2, H, 3.8; Cl, 22.2; N, 8.8. Found: C, 60.1; H, 4.1; Cl, 22.5; N, 8.7.

5-Aryl-5*H*-imidazo[2,1-*a*]isoindoles **4**.

A solution containing 11.0 g of **2a** in 110 ml of glacial acetic acid was stirred and refluxed for *ca.* 8 hours under a nitrogen atmosphere. The mixture was concentrated *in vacuo* and the residue treated with 25 ml of 2*N* sodium hydroxide and then 150 ml of toluene. The toluene layer was separated, dried with anhydrous magnesium sulfate, filtered and then concentrated *in vacuo* to an oil that crystallized from ether-pentane to give 8.8 g (84%) of **4a**, mp 85-87°, Rf 0.4 (chloroform); ^{1}H nmr (deuteriochloroform): δ 6.48 (1H, s, ≡CH); 6.60-8.05 (10 H, m, HC=CH, 2 C_6H_4).

Anal. Calcd. for $C_{16}H_{13}FN_2$: C, 76.2; H, 5.2; N, 11.1. Found: C, 76.5; H, 4.8; N, 11.2.

Compound **4b**.

In similar manner there was obtained **4b** (70%), mp 91-93° (methylene chloride pentane); Rf 0.50 (chloroform-methanol 90:10) ^{1}H nmr (deuteriochloroform): δ 6.60 (1H, s, ≡CH), 7.06 (1H d, J = 2, H-2), 7.08-7.90 (8H, m, H-3, C_6H_3, C_6H_4), 7.95 (1H, d of d, J = 9, J' = 2, H-9).

Anal. Calcd. for $C_{16}H_{13}ClN_2$: C, 71.5; H, 4.9; Cl, 13.2; N, 10.4. Found: C, 71.2; H, 4.6; Cl, 13.5; N, 10.3.

Compound **4c**.

Compound **4c** was obtained in a yield of 65%, mp 128-130° (ethanol-pentane, Rf 0.5 (chloroform-methanol 90:10); ^{1}H nmr (deuteriochloroform): δ 6.50 (1H, s, ≡CH), 7.02 (1H, d, J = 2, H-2), 7.08-7.61 (7H, m, H-3, **2** C_6H_3), 7.90 (1H, d of d, J = 8, J' = 2, H-9).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2$: C, 63.4; H, 4.0; N, 9.2. Found: C, 63.7; H, 3.7; N, 9.2.

9*H*-Dibenz[*c,f*]imidazo[1,2-*a*]azepinones **7a** and **7b**.

To a flask equipped with a gas inlet tube and a calcium chloride drying tube there was added 200 ml of dry DMF, 1.1 g (0.023 mole) of sodium hydride as a 53% dispersion in mineral oil and 5.5 g (0.022 mole) of **4a**. The pale yellow solution was stirred and dry air was bubbled into the mixture at room temperature for *ca.* 48 hours. The resultant solid (2.7 g) was filtered off and the filtrate concentrated *in vacuo* to a solid. The combined solids were recrystallized from methanol-pentane to give 4.1 g (76%) of **7a**, mp 219-221° (lit (5) mp 218-220°) Rf 0.4 (Chloroform-methanol 95:5); ir (potassium bromide): 6.02 μ (C=O); uv: λ max 238 (ϵ 20,073), 259 (21,400), 335 (2,215); ms: 246 (M^+), 218 (M^+-CO).

In similar manner 5.7 g (0.021 mole) of **4b**, 1.1g (0.022 mole) of 53% sodium hydride and 200 ml of dry DMF gave 2.2 g (42%) of **7a**, mp 218-220°.

Compound **7b**.

From 5.3 g (0.017 mole) of **4c**, 0.90 g (0.0164 mole) of 53% sodium hydride and 180 ml of dry DMF processed as in the preparation of **7a** there was obtained 3.3 g (70%) of **7b**, mp 202° (ethanol-pentane), Rf 0.6 (chloroform-methanol 90:10); ir (potassium bromide): 6.01 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 7.21-7.95 (8H, m), 8.35 (1H, d of d, J = 7, J' = 2).

Anal. Calcd. for $C_{16}H_9ClN_2O$: C, 68.5; H, 3.2, Cl, 12.6; N, 10.0. Found: C, 68.4; H, 3.2; Cl, 12.4; N, 9.8.

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