Practical Synthesis of 9-Chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine

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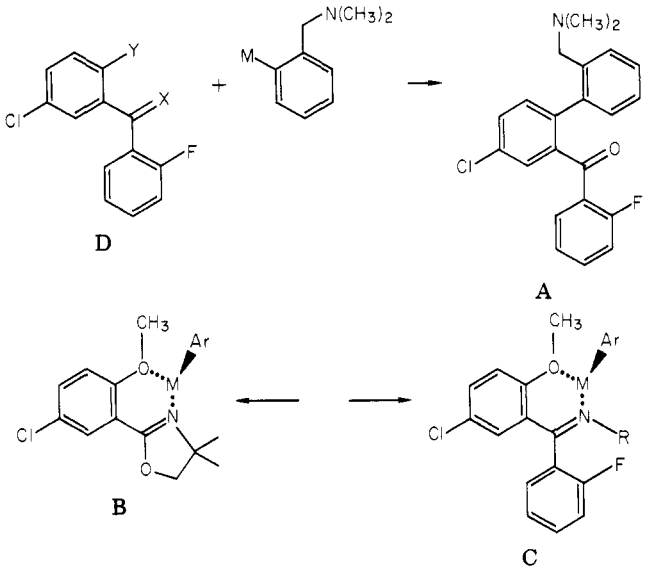
A short and efficient synthesis of the title compound 1 is described. The key step is a highly chemoselective nucleophilic aromatic substitution between the Grignard reagent 6 and the benzophenone imine 5. The successful application of this new reaction extends the scope of such methodology beyond (*o*-fluoroaryl)- and (*o*-methoxyaryl)oxazolines to include appropriately substituted benzophenone imines.

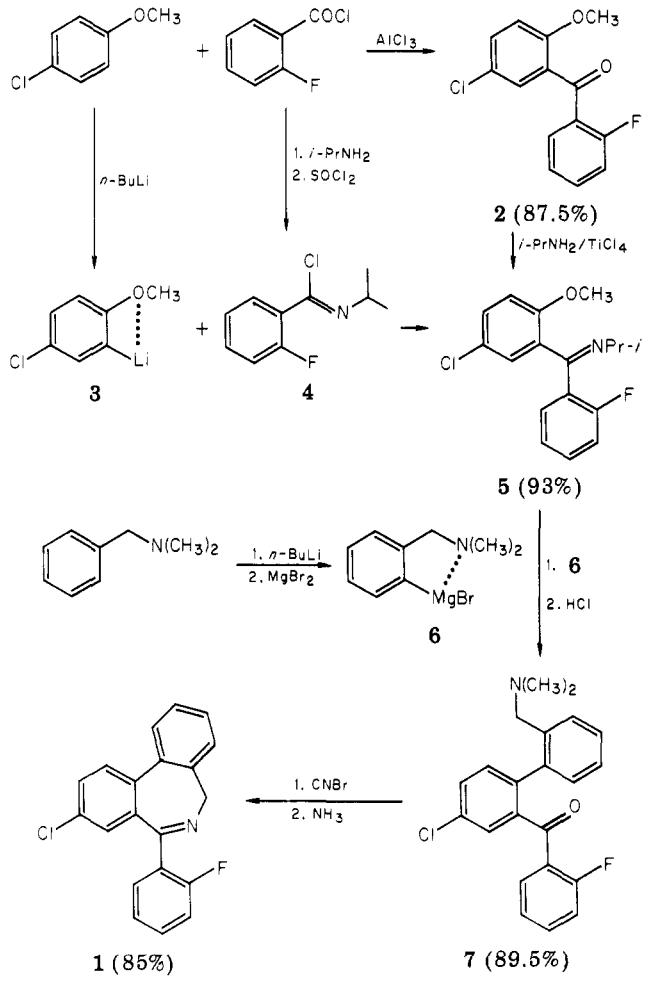
The preceding account[1] describes two syntheses of the title compound 1. Both sequences involve ten and eight steps, respectively, and proceed with an overall yield of approximately 22%. The relative complexity of both approaches coupled with their dependence on (*o*-fluorophenyl)lithium, stable only at temperatures below −50 °C, made them unsuitable for substantial scale-up. Here we report a five-step synthesis of 1 proceeding with an overall yield of greater than 60%.

The retrosynthetic analysis discussed in the preceding paper[1] referred to the benzophenone D as a potential precursor for A. If a scheme based on such a starting



material could be devised, the need for (*o*-fluorophenyl)lithium could be circumvented, since D could be accessible via a Lewis acid catalyzed acylation. The key to the success of such a scheme was clearly the formation of the crucial aryl–aryl bond. It was felt essential to develop methodology which would permit a nucleophilic displacement of Y in a benzophenone, D, with an appropriate organometallic derivative of *N*,*N*-dimethylbenzylamine. Specifically, it appeared both intriguing and appealing to effect such a transformation based on the mechanistic principles (B) operative in Meyers' nucleophilic aromatic substitution.[2] Accordingly, Y and X in benzophenone D would have to serve as donor atoms in a bidentate ligand which could serve to coordinate with the metal of the nucleophile. A logical choice for Y was the methoxy group since it not only meets the coordination criteria but also could facilitate a regiospecific preparation of the appropriate benzophenone. The other pivot X of the bidentate

Scheme I



ligand was chosen to be an alkyl imine with donor properties resembling those of the oxazoline nitrogen. In addition, the imine also was to serve as a carbonyl protecting group. While the choice of R may not be that critical, an isopropyl residue was preferred over methyl in order to avoid or suppress a potential α deprotonation, which has been obbserved with *N*-methylbenzophenone imine.[3,4] Of more fundamental importance for a successful outcome of the desired reaction, however, was the role that both the methoxy and fluoro substituents would play with respect to coordinating ability and leaving group character in a

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competitive environment. Fortuitously, the substrate C has both of these groups in an ortho position. Since both F and CH_3O are readily displaced from their ortho positions in aryloxazolines,[2,5] it was difficult to assess what factors, such as the stereochemistry of the imine, might influence the course of the reaction.

Scheme I outlines the synthetic sequence leading to 1. The imine 5 was initially prepared by reacting 4-chloro-2-lithioanisole (3)[6] with the imine chloride 4, obtained as a distillable oil in 89% yield from the corresponding isopropyl amide upon treatment with thionyl chloride. More practical access to 5 proceeds via the benzophenone 2, available in 87% yield from a Friedel–Crafts reaction between p-chloroanisole and o-fluorobenzoyl chloride. Condensation of benzophenone 2 with isopropylamine and titanium tetrachloride[7] produced a 93% yield of a mixture of isomeric imines 5. Both isomers were isolated in crystalline form (mp 93–95 and 72–74 °C), but no conclusive assignments could be made regarding their syn/anti configurations.

The nature of the configuration of 5 was of some concern. It was assumed that only the anti configuration (anti of CH_3O–aryl and the i-Pr group) would allow for the coordination necessary for the chemospecific displacement of the methoxyl group. Temperature-dependent NMR studies, however, indicated that both configurational isomers underwent thermal equilibration at ca. 60 °C, resulting in a 50:50 mixture (C_6D_6 solvent). Thus, in view of the fact that the nucleophilic displacement reaction had to be carried out at elevated temperatures (refluxing tetrahydrofuran), the configurational integrity of the starting imine 5 was no longer considered to be a factor. The Grignard reagent 6 was prepared from N,N-dimethylbenzylamine via lithiation with n-butyllithium and transmetalation with anhydrous magnesium bromide. In a one-pot operation the Grignard 6 (1.5 equiv) was directly reacted with the imine 5 (refluxing 48 h) and then hydrolyzed with aqueous hydrochloric acid to produce the amino ketone 7 in 89.5% yield as a crystalline compound. Under the described conditions, the nucleophilic aromatic substitution thus proceeds with a gratifyingly high degree of chemoselectivity with a marked preference of OCH_3 over F as the coordinating ligand for magnesium. A careful analysis of the mother liquors of 7 did not reveal any detectable amounts of the alternate product arising from displacement of fluorine. Cleavage of the benzylic amine with cyanogen bromide followed by treatment with ethanolic ammonia produced the benzazepine 1, isolated as its methanesulfonate salt, in 85% yield.

In summary then, a practical synthesis of 1 has been developed which is both short and efficient. The key step is a chemospecific nucleophilic aromatic substitution on 5. The successful utilization of this reaction thus extends the scope of such methodology beyond (o-fluoroaryl)- and (o-methoxyaryl)oxazolines to include appropriately substituted benzophenone imines.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 with Me_4Si as an internal standard. The following abbreviations are used: br, broad; w, weak; ex, exhangeable with D_2O; s, singlet; t, triplet; q, quartet; m, multiplet.

(3-Chloro-6-methoxyphenyl)(2-fluorophenyl)methanone (2). To a cold slurry (−10 °C) of p-chloroanisole (313.75 g, 2.2 mol) and aluminum trichloride (266.7 g, 2 mol) in methylene chloride (750 mL) was added dropwise (1.5 h) a solution of o-fluorobenzoyl chloride (317.2 g, 2.22 mol) in methylene chloride (100 mL). The reaction mixture was stirred at −10 to −5 °C (maximum) for 48 h and then quenched by slowly adding the above mixture to an ice/water mixture (1000 g/500 mL) while maintaining a temperature of 0 °C or colder. (Note that there is a violent release of HCl gas during the quenching process.) The methylene chloride layer was separated and the aqueous layer extracted with fresh methylene chloride (500 mL). The combined organic layers were washed with 1 N potassium carbonate solution (500 mL), dried over anhydrous sodium sulfate (100 g), and concentrated to a volume of 500 mL. The concentrate was cooled (0 °C), and to this was added heptane (~200 mL) so as to precipitate the product. The first crop yielded 315 g (60% theory) of product while concentration of the mother liquors led to the isolation of an additional second crop, resulting in an overall yield of 87.5% of 2: mp 77–79 °C; NMR ($CDCl_3$) δ 7.9–6.7 (m, 7 H), 3.6 (s, 3 H); IR (Nujol) 1653, 1612 cm^{-1}.

4-Chloro-[o-fluoro-α-(isopropylimino)benzyl]-2-methoxybenzene (5). To a cold (0 °C) solution of ketone 2 (212 g, 0.8 mol) and isopropylamine (472 g, 8.0 mol) in 750 mL of dry toluene was added dropwise (30–45 min) a solution of titanium(IV) chloride (80 g, 0.8 mol) in 120 mL of toluene. The reaction mixture was gradually warmed to room temperature and stirred an additional 30–40 h, during which time a copious precipitate (TiO_2) was formed. The reaction mixture was filtered, the filter cake washed with toluene (100 mL), and the combined filtrate washed twice with water (400 mL). The toluene layer was concentrated under vacuum to ~250 mL and cooled to 10–17 °C, and the product was precipitated by slowly adding hexane (~400 mL). The product was filtered, washed with hexane, and dried to yield ~195 g (93%) of product: mp 93–95 °C (for the high-melting isomer); NMR ($CDCl_3$) δ 7.9–6.7 (m, 7 H), 3.72 (s, 3 H, high-melting isomer), 3.50 (s, 3 H, low melting isomer), 3.1–3.8 (m, 1 H), 1.15 (d, J = 5.5 Hz, 6 H); IR (Nujol) 1633 cm^{-1}.

Compound 5 was prepared by the following alternative method. To a cold (0 °C) solution of p-chloroanisole (392 g, 2.75 mol) in 2.75 L of anhydrous ether was added dropwise (1.5 h) 1.25 L of a 2.4 M solution of n-butyllithium (3 mol) in hexane. The reaction mixture was stirred at 0 °C for 25 h to complete lithiation. The above solution was added dropwise (1.5 h) to a cold (−20 °C) solution of imino chloride 4 (499 g, 2.5 mol) in 3 L of anhydrous ether, while the reaction mixture was kept between −12 and −5 °C. The reaction mixture was stirred an additional 20 h and was then quenched by adding it to a solution of 240 mL of 50% sodium hydroxide in 1 L of crushed ice, followed by the addition of 1 L of cold water. The organic layer was separated, washed with saturated salt solution, dried over sodium sulfate, and concentrated. The residue was dissolved in hexane, treated with charcoal, filtered, and cooled to initiate crystallization: yield 422 g (55.3%) of product 5 consisting mostly of the lower melting isomer, mp 72–74 °C. Anal. Calcd for $C_{17}H_{17}ClFNO$: C, 66.77; H, 5.60; N, 4.58. Found: C, 66.74; H, 5.54; N, 4.46.

1-[Chloro(isopropylimino)methyl]-2-fluorobenzene (4). A mixture of o-fluoro-N-isopropylbenzamide (575 g, 3.17 mol) and thionyl chloride (290 mL, 484 g, 4.07 mol) was warmed on a steam bath until all of the solid dissolved and then refluxed for an additional 45 min. The excess thionyl chloride was distilled off and the residue distilled in vacuo to yield 568.9 g (~89%) of product 4 [bp 72 °C (2 mm)] as a colorless liquid. This product was used directly to make compound 5.

5-Chloro-2-[o-[(dimethylamino)methyl]phenyl]-2′-fluorobenzophenone (7). To a solution of N,N-dimethylbenzylamine (101.4 g, 0.75 mol) in 750 mL heptane was added with stirring a 2.3 M hexane solution of n-butyllithium (326 mL, 0.75 mol) over a period of 1.5 h. The reaction mixture was refluxed for 40 h, during which time a copious white precipitate was formed. The solvent was removed (atmospheric distillation followed by vacuum distillation), and the resulting ortho-lithiated derivative, cooled (10 °C) under a nitrogen atmosphere, was slurried in tetrahydrofuran (600 mL). This mixture was warmed to 30 °C to afford an amber solution which was added to a cold (10 °C) suspension of magnesium bromide (152 g, 0.83 mol) in tetra-

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hydrofuran (300 mL). The reaction mixture was heated to reflux for 1 h to assure transmetalation and then cooled to 5 °C, followed by the addition of a solution of compound **5** in tetrahydrofuran (200 mL) over a 10-min period. The reaction mixture was refluxed an additional 48 h, cooled (10 °C), and hydrolyzed by adding 150 g of ice followed by the slow addition of 1 L of 5 N HCl. The tetrahydrofuran was distilled off, and the resulting aqueous solution was refluxed for 4 h, cooled, and extracted with toluene (500 mL). The aqueous layer was basified to pH 8 with 50% sodium hydroxide solution and the product extracted into toluene (1 L). The toluene layer was treated with carbon, dried, and concentrated under vacuum to yield a residue which was dissolved in heptane (500 mL) and cooled to yield 164.5 g (89.5%) of product **7**: mp 95–96 °C; NMR ($CDCl_3$) δ 7.7–6.7 (m, 11 H), 3.2 (s, 2 H), 2.1 (s, 6 H); IR (Nujol) 1662, 1651, 1601 cm^{-1}. Anal. Calcd for $C_{22}H_{19}ClFNO$: C, 71.83; H, 5.21; N, 3.81. Found: C, 72.13; H, 5.19; N, 3.71.

Methanesulfonate of 9-Chloro-7-(*o*-fluorophenyl)-5*H*-dibenz[*c*,*e*]azepine (1). To a cold (−5 °C) solution of compound **7** (36.7 g, 0.1 mol) in methylene chloride (200 mL) was added dropwise a solution of cyanogen bromide (13 g, 0.12 mol) in methylene chloride (50 mL). When the addition was complete, the reaction mixture was stirred for 2 h (0–5 °C) and then concentrated in vacuo. The white solid residue was dissolved in tetrahydrofuran (400 mL) and added slowly (30 min) to a cold (−5 °C) solution of anhydrous ammonia (~50 g) in anhydrous ethanol (600 mL). The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo to a residue which was dissolved in toluene (200 mL). The toluene solution was washed with saturated sodium carbonate solution (50 mL) and water (150 mL) and concentrated to an oil which was then dissolved in ethanol (60 mL). To the ethanol solution was added slowly with cooling methanesulfonic acid (10.7 g, 0.11 mol), and after continued cooling (−10 °C) the product crystallized to yield 35 g (~85% yield) of compound **1** as its methanesulfonate salt: mp 186.6–187.6 °C; NMR ($CDCl_3$) δ 8.1–7.0 (m, 11 H), 5.6 (d, J = 12.6 Hz, 1 H), 4.2 (d, J = 12.6 Hz, 1 H), 2.78 (s, 3 H). Anal. Calcd for $C_{20}H_{13}ClFN{\cdot}CH_3SO_3H$: C, 60.31; H, 4.10; N, 3.35. Found: C, 60.35; H, 4.39; N, 3.22.

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Registry No. **1**, 81537-93-1; **1** $MeSO_3H$, 82374-05-8; **2**, 82374-06-9; **4**, 82374-07-0; **5** (isomer 1), 82374-08-1; **5** (isomer 2), 82374-09-2; **7**, 81537-96-4; *p*-chloroanisole, 623-12-1; *o*-fluorobenzoyl chloride, 393-52-2; isopropylamine, 75-31-0; *o*-fluoro-*N*-isopropylbenzamide, 64141-89-5; *N*,*N*-dimethylbenzylamine, 103-83-3; *o*-lithium-*N*,*N*-dimethylbenzylamine, 27171-81-9.

Oxygen-17 Nuclear Magnetic Resonance Spectroscopy of Sulfoxides and Sulfones. Alkyl Substituent Induced Chemical Shift Effects

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Oxygen-17 NMR chemical shifts have been determined for a number of cyclic and acyclic as well as aliphatic, olefinic, and aryl sulfoxides and sulfones. The ^{17}O NMR chemical shifts for the acyclic, aliphatic, and aromatic sulfoxides reported here absorb in the narrow range between δ −20 and +20, while the cyclic, aliphatic sulfoxides absorb between δ −13 and +66 relative to external (but naturally abundant) $H_2{}^{17}O$. The sulfonyl oxygens are deshielded relative to the sulfinyl oxygens, exhibiting chemical shifts for acyclic and cyclic sulfonyl oxygens between δ 120 and 183 for the sulfones reported here. Diastereotopic sulfonyl oxygens exhibit chemical shift nonequivalence. Substituent-induced chemical shift effects by a methyl or methylene group on the sulfinyl and sulfonyl oxygens are discussed.

Introduction

Oxygen-17 NMR spectroscopy is rapidly becoming a useful and potentially powerful tool for the elucidation of bonding and structural features of oxygen-containing organic molecules in spite of the extremely low natural abundance (0.037%) and sensitivity (2.91×10^{-2} times that for ^1H at constant field) as well as the quadrupole moment of the ^{17}O nucleus.[1] Oxygen-17 nuclear shieldings in sulfoxides and sulfones may be best understood from the results of semiempirical calculations which indicate that while "local" diamagnetic[2] and paramagnetic contributions are important, ^{17}O NMR shifts are largely dominated by the paramagnetic term[1,3] (eq 1). In this equation, ΔE is

$$\sigma_P{}^O = -\frac{e^2\hbar^2}{2m^2c^2\Delta E}\langle r^{-3}\rangle_{2p_O}\sum Q_{SO} \qquad (1)$$

referred to as the "average energy" approximation and can be expressed as $\sum_i \Delta E_i^{-1}$ where ΔE_i is the excitation energy from the ground electronic state to the various excited states of increasing higher energy. However, the first state (lowest energy) is often approximated to ΔE (i.e., $\Delta E_1 \approx \Delta E$).[1d] The expectation value of the inverse cube of the mean radius of the atomic 2p orbital of oxygen is symbolized by $\langle r^{-3}\rangle_{2p_O}$. Q_{SO} describes the elements of charge density on oxygen and the extent of multiple bond contributions between sulfinyl/sulfonyl sulfur and oxygen. While all of these terms appear to be mutually dependent, some contribute to the paramagnetic shielding term more heavily than others.

Our interest in the ^{17}O NMR spectral properties of simple sulfoxides and sulfones was prompted by (i) the fact that few systematic investigations have been performed

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