Regiospecific Synthesis of Aromatic Compounds via Organometallic Intermediates. 4.[1] Synthesis of Ortho-Disubstituted Benzenes

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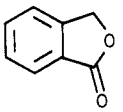
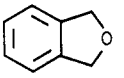
Phthalides **1** and phthalans **2** with substituents in the heterocyclic ring have been prepared starting from *o*-dibromobenzene via sequential metal–halogen exchange reactions and treatment with appropriate electrophiles. Low temperatures are essential for the stability of the intermediates involved in these reactions. The free diketone **23** obtained from the phthalan **19** has potential application in the synthesis of a variety of heterocyclic systems.

Aromatic organolithium compounds can be conveniently made by the metal–halogen exchange reaction[2,3] and are useful intermediates in the synthesis of a variety of compounds containing functional or nonfunctional substituents. Sequential metal–halogen exchange reactions have been used to introduce similar or dissimilar substituents in the aromatic ring.[1] In the present study, we have investigated the sequential lithium–bromine exchange reaction using *o*-dibromobenzene. It has previously been shown that *o*-bromophenyllithium can be prepared in excellent yields at −110 °C and reacts with electrophiles to give a variety of ortho-substituted bromobenzenes in good yields.[4] The first electrophile used in our present study was methyl trifluoroacetate since the trifluoromethyl group has a pronounced effect on providing stability to the lithium hemiketal intermediate.[5] Subsequent metal–halogen exchange reaction followed by treatment with a second functional electrophile has provided heterocyclic compounds such as phthalides **1** and phthalans **2** with



phthalide (1)



phthalan (2)

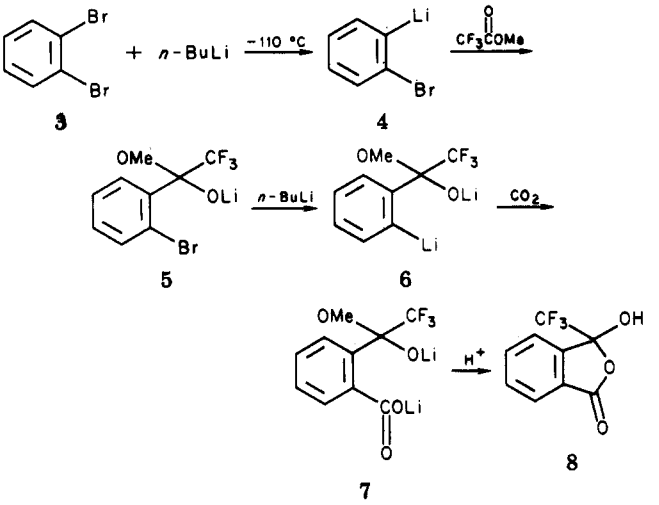
substituents in the heterocyclic ring. Phthalides have been synthesized earlier from substrates in which one functional group is present prior to the metal–halogen exchange step.[6] Sequential metal–halogen exchange followed by derivatization has also been applied to ortho-disubstituted thiophenes[7] and benzothiophenes.[8] The method developed in our present study has potential application in the synthesis of a variety of heterocyclic systems which are currently under investigation and will be discussed in a future publication.

Results and Discussion

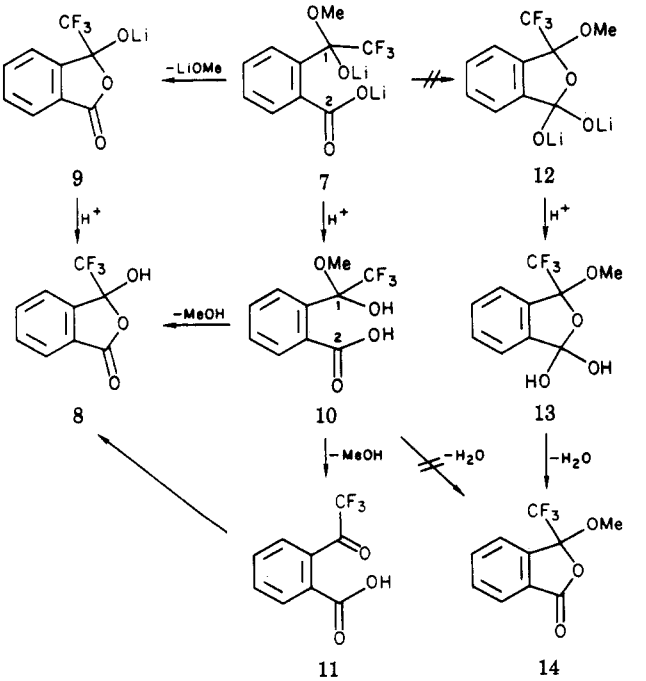
The reaction steps leading to a substituted phthalide are shown in Scheme I. The synthetic utility of this reaction would depend on the stability and reactivity of the intermediates **4**, **5**, **6**, and **7**. We have observed that these intermediates have sufficient stability in ether–THF (1:6, v/v) at −110 °C and yet have enough reactivity to give a high yield of the final product. The phthalide **8**, for example, has been isolated in 83% yield.

Different pathways can be conceived for the conversion of **7** to **8** (see Scheme II). Cyclization might occur before acidification by an internal nucleophilic attack in **7** either on the saturated carbon (C-1) or the carbonyl carbon (C-2). The former route leading to **9** and on acidification to **8**

Scheme I



Scheme II



appears to be the major pathway involved in this reaction, since the isolated product is **8** and not **14**. An alternate

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(1) For previous publications of this series, see, part III: Eapen, K. C.; Dua, S. S.; Tamborski, C. *J. Org. Chem.* **1984**, *49*, 478. Part II: Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1983**, *251*, 149. Part I: Chen, L. S.; Chen, G. J.; Tamborski, C. *Ibid.* **1983**, *251*, 139.

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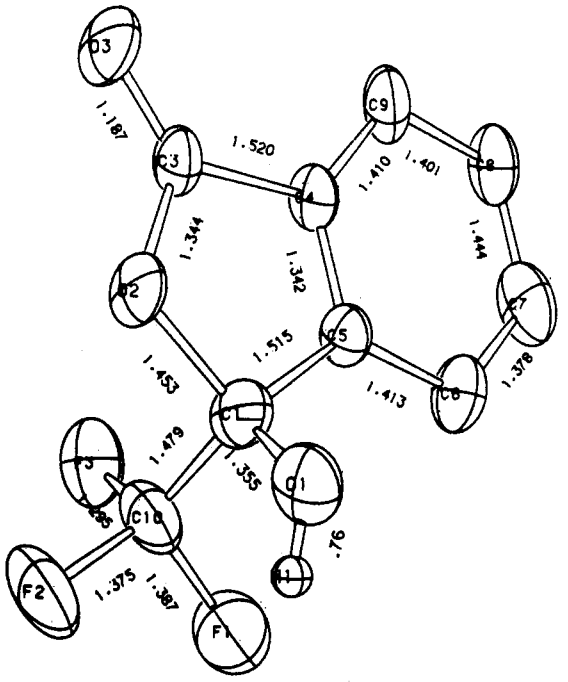
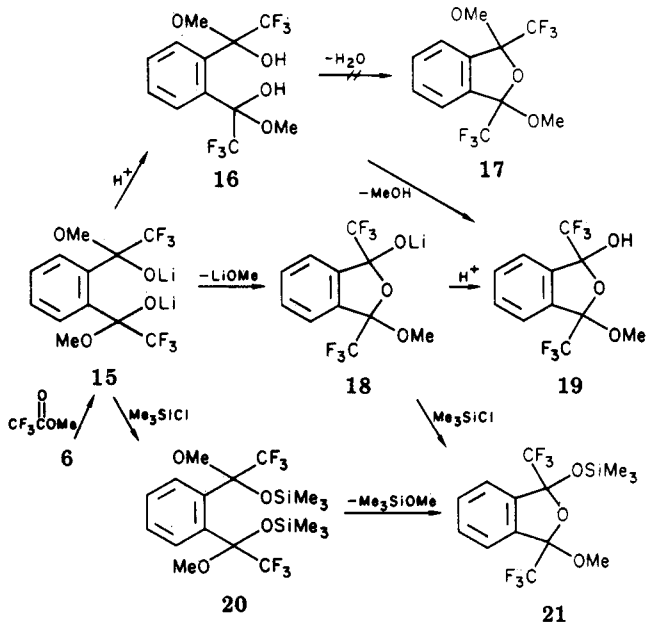


Figure 1. ORTEP drawing of phthalide 8.

Scheme III

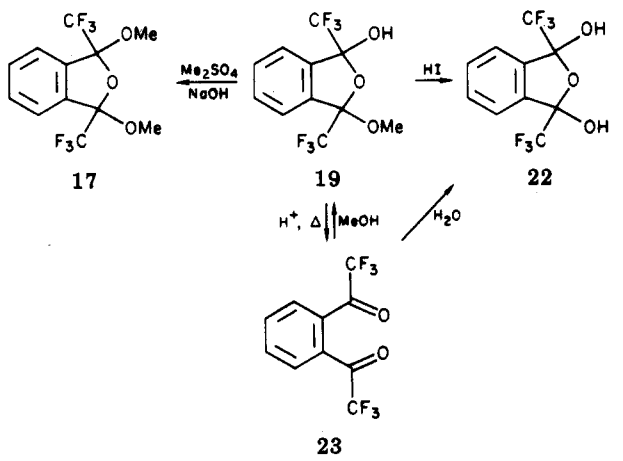


route has to be considered where cyclization occurs after acidification. Acid-catalyzed elimination of water or methanol can take place in **10**. Dehydration is not clearly involved as it would give **14**, which is not the observed product. Elimination of methanol from C-1 and C-2 would lead directly to the observed product. Alternately elimination of methanol from C-1 may give rise to keto acid **11** which then tautomerizes to **8**. Though it is difficult to understand why elimination of methanol from **10** would be more favorable than dehydration, the possibility of **8** being formed via this pathway cannot be completely ruled out. The structure **8** for the final product has been confirmed from spectral data (see Experimental Section) and X-ray studies. An ORTEP drawing of **8** is shown in Figure 1. It may be noted that the hydroxyl hydrogen in **8** is equidistant from two of the fluorine atoms of the trifluoromethyl group.

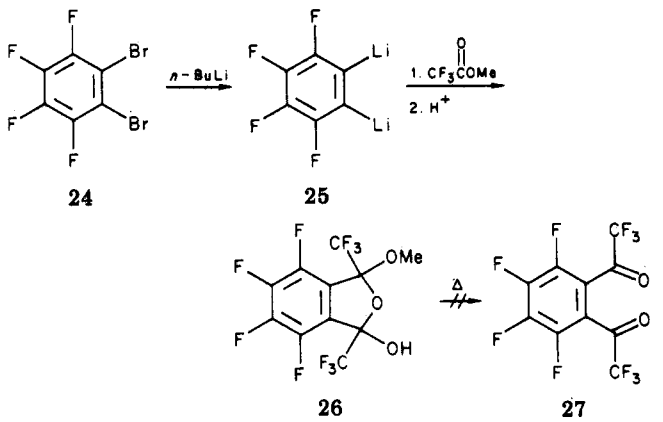
When instead of CO_2 methyl trifluoroacetate was used as the second electrophile in the reaction with **6**, the product isolated was a cis–trans mixture of substituted phthalan **19** as indicated in Scheme III. Arguments similar to those advanced earlier explain the formation of the product **19** via intermediates **16** and/or **18**. In an attempt to identify the intermediate lithium salt as either **15** or **18**, separate experiments were performed whereby $(CH_3)_3SiCl$ was added to the lithium salt intermediate. It was expected that a trimethylsiloxy derivative of either structure may be formed and identified. If compound **20** would be isolated, it would suggest **15** as the lithium salt intermediate, and if **21** was formed, compound **18** would be suggested as the probable intermediate. Since compound **21** was isolated from these experiments, it is strongly suggested that the lithium salt intermediate was **18**. Since there is the possibility that **20** may have been formed initially and subsequently eliminated $(CH_3)_3SiOCH_3$, compound **21** could be formed by this alternate route. Because of these possibilities it is still uncertain as to the actual structure of the intermediate lithium salt.

Some reactions of the phthalan **19** were investigated. These are shown in Scheme IV. Treatment of **19** with $NaOH–Me_2SO_4$ yielded the dimethoxy derivative **17** as an isomeric mixture (ratio 9:1). Reaction of **19** with hydriodic

Scheme IV



Scheme V



(2) Jones, R. G.; Gilman, H. "Organic Reactions"; Wiley: New York; 1942, Vol. 6, p 340.
(3) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York; 1974, p 136.
(4) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283.
(5) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1981**, *18*, 117.
(6) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1982**, *48*, 2356 and references therein.
(7) Gronowitz, S.; Michael, U. *Acta Chem. Scand.* **1968**, *22*, 1353.
(8) Di Menna, W. S. *Tetrahedron Lett.* **1980**, *21*, 2129.

acid yielded the dihydroxy compound **22** as a mixture of isomers. Heating **19** with a few drops of trifluoroacetic acid under an inert atmosphere gave a high yield of the ortho diketone **23**. Addition of water to **23** gave a cis–trans mixture of **22**. Addition of methanol similarly gave an isomeric mixture of **19**. This is not surprising because fluorinated ketones are known to react very readily with nucleophilic reagents.[9] In the case of the diketone **23**, the proximity of the two carbonyl groups leads to the formation of cyclic structures. Addition of other nucleophiles to give heterocyclic compounds is under investigation.

We have also prepared the fluorinated analogue of **19**. The reaction sequence is indicated in Scheme V. In this case, sequential metalation was not required as the perfluorodilithio compound **25** is stable at −78 °C.[10] Subsequent reaction of **25** with methyl trifluoroacetate followed by acidification yielded **26** in 46% yield. Attempted conversion of **26** to **27** under conditions similar to those used for the synthesis of **23** so far has not been successful, indicating a more thermally stable structure.

Experimental Section

Reactions involving *n*-BuLi were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Commercial anhydrous Et_2O was freshly distilled from $LiAlH_4$ prior to use. THF was freshly distilled from sodium benzophenone ketyl. All melting and boiling points are uncorrected. Gas chromatographic analyses were performed on Perkin-Elmer Sigma 1 or Sigma 2B instruments using 6-ft stainless steel columns ($^1/_4$ in. o.d.) packed with 10% SE-30 on Chromosorb W or 3% OV-1 on Supelcoport. Me_4Si was used as internal standard for ^1H and ^{13}C NMR spectra. $CFCl_3$ was used as internal standard for ^{19}F NMR spectra. Mass spectra were taken on a DuPont 21-491B instrument fitted with a Finnigan INCOS data system.

Synthesis of 3-Hydroxy-3-(trifluoromethyl)phthalide (8). To a stirred solution of *o*-dibromobenzene (9.44 g, 40 mmol) in a mixture of Et_2O–THF (30:180 mL) at −118 °C was added an *n*-BuLi solution (28 mL of 1.44 M in hexane, 40 mmol) over a period of 25 min. The reaction temperature was maintained below −110 °C during addition. Methyl trifluoroacetate (5.6 g, 44 mmol) was added dropwise during 25 min, and the reaction mixture was stirred for 20 min. A solution of *n*-BuLi (34 mL of 1.44 M solution in hexane, 49 mmol) was then added during 25 min. The reaction mixture was stirred for an additional 2.25 h during which time a white solid appeared. Dry CO_2 was admitted during 2 h into the reaction mixture at −110 °C. The white solid dissolved and a slightly exothermic reaction was noted. The reaction mixture was stirred, gradually allowed to warm up overnight, and hydrolyzed by pouring into ice-cold dilute aqueous HCl (500 mL, ~2 M). The organic layer was separated, the aqueous layer was extracted twice with Et_2O, and the Et_2O fractions were combined. The combined organic layer was dried over anhydrous $MgSO_4$, and removal of solvent yielded a yellow viscous liquid (12.5 g). Trituration with petroleum ether (40–60 °C) yielded a colorless crystalline solid (5.45 g). An additional 1.8 g of solid was obtained from the mother liquor by trituration with petroleum ether, thus yielding a total of 7.25 g (83.1%) of the product. An analytical sample was prepared from CH_2Cl_2–petroleum ether: mp 98–100 °C; MS (CI), *m/e* 218 (M^+), 201 ($M^+ - OH$), 149 ($M^+ - CF_3$); IR (KBr) 3300 (OH), 3100 (ArCH), 1765 (C=O), 1605 (Ar C=C), 1400–1100 cm^{-1} (C—F); ^1H NMR ($CDCl_3$) δ 4.9 (br s, 1 H, OH), 7.6–7.9 (m, 4 H, Ar H); ^{19}F NMR ($CDCl_3$) δ −83.3 (s, CF_3); ^{13}C NMR ($CDCl_3$) δ 100.2 (q, J = 36 Hz, CCF_3), 121.39 (q, J = 285 Hz, CF_3), 124.0, 126.0, 126.6, 132.4, 135.5, 141.9 (Ar carbons), 167.4 (C=O). Anal. Calcd for $C_9H_5F_3O_3$: C, 49.54; H, 2.29; F, 26.15. Found: C, 49.41; H, 2.05; F, 26.25.

Synthesis of 3-Methoxy-1,3-bis(trifluoromethyl)-1-phthalanol (19). To a well-cooled (−118 °C) solution of *o*-dibromobenzene (28.3 g, 120 mmol) in Et_2O–THF (60–360 mL) was added a solution of *n*-BuLi (52.2 mL of 2.3 M solution in hexane, 120 mmol) dropwise during 1 h. A solution of methyl trifluoroacetate (16.8 g, 132 mmol) in THF (15 mL) was added dropwise (1 h). The reaction mixture was stirred for an additional 20 min followed by dropwise addition (1 h) of a solution of *n*-BuLi (52.2 mL of 2.3 M solution in hexane, 120 mmol). After stirring for 2.5 h, methyl trifluoroacetate (16.8 g, 132 mmol) in THF (15 mL) was added dropwise (1 h). The temperature was kept below −110 °C during all these additions and at least for 4 h after the final addition. The reaction mixture was stirred overnight (16 h). During this time the temperature rose to −60 °C. The contents were then hydrolyzed by the addition of 3 M aqueous HCl. The organic layer was separated. The aqueous layer was saturated with NaCl and extracted (2 × 100 mL) with Et_2O. This was combined with the original organic layer. After drying over anhydrous $MgSO_4$, solvent was removed to give a residue (35.7 g). On stirring with petroleum ether and cooling in the freezer overnight, some solid separated. This was filtered, washed with petroleum ether, and dried (24.4 g). The solid was then crystallized from CH_2Cl_2–petroleum ether by using charcoal. An almost colorless solid (20.2 g, 56%) was thus obtained, mp 59–61 °C. Ratio of cis–trans isomers from NMR was 5.5:4.5. MS (CI), *m/e* 285 ($M^+ - OH$), 271 ($M^+ - OMe$), 233 ($M^+ - CF_3$), 201 [$M^+ - (CF_3 + MeOH)$]; IR (KBr) 3480 (OH), 3060 (Ar CH), 2960 (aliphatic CH), 1400–1000 cm^{-1} (CF); ^1H NMR ($CDCl_3$) δ 3.18 (s), 3.26 (s) and a broad underlying peak (OH and OMe) 7.62 (m, Ar H); ^{19}F NMR ($CDCl_3$) δ −81.9 (q, J = 6.0 Hz, CF_3 in cis isomer), −82.4 (s, CF_3 in trans isomer), −82.8 (s, CF_3 in trans isomer), −83.2 (q, J = 6.0 Hz, CF_3 in cis isomer); ^{13}C NMR ($CDCl_3$) δ 51.57 (s, OMe), 51.76 (s, OMe), 103.15 (q, J = 35.2 Hz, CCF_3), 103.24 (q, J = 34.8 Hz, CCF_3), 108.45 (q, J = 34.2 Hz, CCF_3), 108.61 (q, J = 34.3 Hz, CCF_3), 121.21 (q, J = 287 Hz, CF_3), 121.69 (q, J = 284 Hz, CF_3), 123.59, 123.96, 124.27, 124.28, 132.02, 132.08, 132.27, 132.45, 133.14, 133.24, 136.68, 137.16 (Ar carbons). Anal. Calcd for $C_{11}H_8F_6O_3$: C, 43.7; H, 2.65. Found: C, 43.3; H, 2.6.

Preparation of 17. Compound **19** (400 mg, 1 mmol) was dissolved in the minimum amount of 1 N aqueous NaOH. Dimethyl sulfate (740 mg, 5.9 mmol) was then added, and the reaction mixture was stirred and heated at 60–65 °C for 48 h. The solid that separated was filtered and washed once with dilute NaOH and then with water to give 150 mg (59.7%) of the product. GC analysis showed this to be a mixture of two isomers in the ratio 9:1. The major isomer was obtained in a pure form by one recrystallization from Et_2O to give a colorless crystalline solid: mp 91–93 °C; MS (EI), *m/e* 297 ($M^+ - CF_3$), 285 ($M^+ - OMe$), 247 ($M^+ - CF_3$); IR (KBr) 3060–3000 (Ar CH), 2980, 2930, 2870 (aliphatic C–H), 1400–1100 (C–F); ^1H NMR ($CDCl_3$) δ 3.42 (s, 6 H, OMe), 7.5–7.7 (m, 4 H, Ar H); ^{19}F NMR ($CDCl_3$) δ −79.17 (s, CF_3); ^{13}C ($CDCl_3$) δ 52.32 (s, OMe), 123.65, 123.76, 131.8, 135.11 (Ar carbons). Anal. Calcd for $C_{12}H_{10}F_6O_3$: C, 45.57; H, 3.16. Found: C, 45.52; H, 3.31.

Synthesis of 21. The reaction was carried out as described for the preparation of **19**. Before the acidification step, most of the solvent was evaporated by bubbling nitrogen through the reaction mixture at room temperature. The sticky yellow solid residue was dried under vacuum. Chlorotrimethylsilane (3.05 g, 28 mmol) was added to a solution of the above salt (4.6 g) in THF (20 mL), and the reaction mixture was stirred and refluxed gently under nitrogen atmosphere for 24 h. The reaction mixture was evaporated to dryness, and the residue was stirred with petroleum ether and filtered. The filtrate was evaporated to dryness to give a pale yellow liquid (2.84 g). GC analysis indicated this to contain 66% (GC area %) of the desired product. A pure sample of the silyl ether **21** was obtained by purification on a silica gel column eluting with petroleum ether–CH_2Cl_2 (85:15, v/v). The product **21** eluted first and was obtained as a colorless liquid. Micro boiling point for the product was 242 °C. NMR (^1H) showed the product to be a mixture of cis (55%) and trans (45%) isomers. MS (EI), *m/e* 359 ($M^+ - Me$), 355 ($M^+ - F$), 343 ($M^+ - OMe$), 285 ($M^+ - OSiMe_3$); IR (neat) 3080–3050 (Ar CH), 2960, 2910, 2850 (aliphatic CH), 1400–1100 (CF), 880–840 cm^{-1} (SiMe); ^1H NMR ($CDCl_3$) δ 0.17 (s, $SiMe_3$), 0.20 (s, $SiMe_3$), 3.20 (s, OMe), 3.30 (s, OMe), 7.5–8.0 (m, Ar H); ^{19}F NMR ($CDCl_3$) δ −80.9 (q, J = 6.6 Hz, CF_3 in cis), −81.1 (s, CF_3 in trans), −81.2 (q, J = 6.6 Hz, CF_3 in cis), −81.4 (s, CF_3 in trans). Anal. Calcd for $C_{14}H_{16}O_3F_6Si$: C, 44.92; H, 4.28; F, 30.48. Found: C, 45.06; H, 4.28; F, 29.47.

(9) Gambaryan, N. P.; Rokhlin, E. M.; Zeifman, Y. V.; Ching-Yun, C.; Knunyants, I. L. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 947.
(10) Tamborski, C.; Soloski, E. J. *J. Organomet. Chem.* **1969**, *20*, 245.

Synthesis of 22. A mixture of compound **19** (0.81 g, 2.7 mmol) and hydriodic acid (8 mL) was refluxed for 11 h. After being cooled to room temperature, the reaction mixture was extracted with Et_2O. The aqueous layer was saturated with NaCl and extracted again with Et_2O. The Et_2O extracts were combined and washed with a saturated solution of aqueous sodium thiosulfate. The Et_2O extract was then dried over anhydrous $MgSO_4$. Removal of Et_2O gave a sticky residue which on treatment with CH_2Cl_2–hexane yielded an almost colorless solid. Recrystallization was done from Et_2O–hexane to give the product (0.34 g, 44%) as an isomeric mixture (ratio 2:3): mp 87–91 °C; MS (EI), *m/e* 219 ($M^+ - CF_3$), 201 [$M^+ - (CF_3 + H_2O)$]; IR (KBr) 3500–3000 (br, hydrogen-bonded OH), 1400–1100 cm^{-1} (CF); ^1H NMR ($CDCl_3$) δ 2.0–2.5 (br, OH), 7.64 (m, Ar H); ^{19}F NMR ($CDCl_3$) δ −83.26 (s, CF_3), −84.12 (s, CF_3). Anal. Calcd for $C_{10}H_6F_6O_3$: C, 41.67; H, 2.08. Found: C, 41.22; H, 2.23.

Preparation of Ortho Diketone 23. The phthalanol **19** (8.00 g) was heated at 280 °C (bath) with a few drops of trifluoroacetic acid under an atmosphere of nitrogen. The compound was analyzed periodically on GC to check conversion to free ketone. The conversion to free ketone was essentially complete in 5–6 h. It was then distilled under reduced pressure to give the free ketone **23** as a colorless liquid (5.8 g, 81%), bp 74 °C (2.8 mm). After several days of standing under an inert atmosphere at room temperature, the ketone solidified to large colorless crystals which were extremely hygroscopic and low melting. No attempt was made to obtain a melting point. MS (EI), *m/e* 201 ($M^+ - CF_3$), 151 (201 − CF_2), 123 (151 − CO); IR (neat) 3080 (Ar CH), 1755, 1725 (C=O), 1400–1100 cm^{-1} (CF). Anal. Calcd for $C_{10}H_4F_6O_2$: C, 44.44; H, 1.48. Found: C, 44.65; H, 1.27. The free ketone **23** on exposure to the atmosphere readily absorbs moisture to give a colorless solid, mp 87–92 °C. GC, TLC, MS, and NMR (including isomer ratio) of this solid compare with that of compound **22**. Similarly, the free ketone **23** adds dry methanol to give a colorless crystalline solid whose GC, TLC, MS, and NMR (including isomer ratio) are similar to that of compound **19**.

Preparation of 26. This reaction was carried out at −78 °C. *o*-Dibromotetrafluorobenzene (36.96 g, 120 mmol) was dissolved in freshly distilled dry Et_2O (500 mL). A solution of *n*-BuLi (131 mL of 2.2 M solution in hexane, 288 mmol) was added dropwise at such a rate that the reaction temperature did not rise above −75 °C. After the addition of *n*-BuLi was over, the reaction mixture was stirred for 1/2 h. A solution of methyl trifluoroacetate (41.5 g, 324 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred overnight (16 h) during which the temperature rose to −32 °C. The reaction mixture was acidified with 3 M aqueous HCl. The layers were separated, and the aqueous layer was saturated with NaCl and extracted with Et_2O. This extract was combined with the original Et_2O layer. After drying over $MgSO_4$ and removing solvent, a viscous liquid residue was obtained. This was distilled under reduced pressure by using a Vigreux column (100 × 15 cm). The distillation was repeated on the major fraction of the distillate to yield a colorless viscous liquid (20.6 g, 46%), bp 68–73 °C (1.4 mm); two isomers in the ratio 1:1, MS (EI), *m/e* 357 (M^+ − OH), 343 (M^+ − OMe), 305 ($M^+ - CF_3$); IR (neat) 3580 (free OH), 3440 (bonded OH), 2850 (CH), 1640, 1510 (Ar), 1400–1050 cm^{-1} (CF); ^1H NMR (CD_3COCD_3) δ 3.37 (s, OMe), 3.44 (s, OMe) 8.25 (b, OH); ^{19}F NMR (CD_3COCD_3) δ −81.0 (m, CF_3), −138.0 (m, Ar CF), −148.0 (m, Ar CF); ^{13}C NMR (CD_3COCD_3) δ 52.68 (s, OMe), 53.05 (s, OMe), 104.7 (q, *J* = 35.0 Hz, CCF_3), 109.3 (q, *J* = 35.8 Hz, d, *J* = 8.5 Hz, CCF_3), 118.1 (d, *J* = 15.6 Hz), 122.0 (m), 142.0–147.0 (series d, Ar carbons), 123.0 (q, *J* = 285 Hz, CF_3). Anal. Calcd for $C_{11}H_4O_3F_{10}$: C, 35.29; H, 1.07. Found: C, 35.00; H, 1.13.

Collection of the X-ray Data and Solution of the Structure for Compound 8. Crystals were grown by evaporation of a dichloromethane–petroleum ether solution: $C_9H_5O_3F_3$ space group $P2_12_12-D^4$; *a* = 6.942 (19) Å; *b* = 8.047 (2) Å; *c* = 16.196 (56) Å; *Z* = 4. The crystal volume was 0.0028 mm^3. Lattice constants and intensity data were measured by using Nb-filtered Mo Kα radiation on a Picher FACS I diffractometer. A total of 1244 reflections were measured by using the θ–2θ scan method with a scan speed of 2°/min to 2θ − 55°. Upon irradiation, the crystal suffered an 80% decrease in intensity over a period of 48 h, presumably due to a degradation in the lattice. The structure was solved by MULTAN80 and refined to final *R* value of 0.164. The rather high *R* value reflects the poor quality of the crystal data.

Acknowledgment. We thank Dr. Wallace S. Brey, Jr., of University of Florida for NMR data, Dr. Costandy Saba of University of Dayton Research Institute for mass spectral analyses, and Dr. Albert Fratini of the University of Dayton for the X-ray analysis.

Registry No. **3**, 583-53-9; **6**, 90719-12-3; **8**, 76284-63-4; *cis*-**17**, 90719-13-4; *trans*-**17**, 90719-14-5; **18**, 90740-87-7; *trans*-**19**, 90719-15-6; *cis*-**19**, 90719-16-7; *cis*-**21**, 90719-17-8; *trans*-**21**, 90719-18-9; *cis*-**22**, 90719-19-0; *trans*-**22**, 90719-20-3; **23**, 90719-21-4; **24**, 827-08-7; *cis*-**26**, 90719-22-5; *trans*-**26**, 90719-23-6; MeO_2CCF_3, 431-47-0; $MeSiCl_3$, 75-79-6.

Tests of a Piperidino Mask for the Protection of Functionalized Carbon Sites in Multistep Syntheses

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Primary alkyl chlorides (R–Cl) are easily isolated in excellent yield after treatment of the appropriate *N*-alkylpiperidines (R–NC_5H_{10}) with α-chloroethyl chloroformate. The method is exemplified by the conversion of a variety of alkylpiperidines, including systems with other sensitive functionalities, to the respective chlorides in yields varying from 90 to 97%. The potential significance of this process in drug congener preparation and in total synthesis is outlined. Similar fragmentations of *N-sec*-alkylpiperidines are described.

α-(chloroethyl chloroformate (ACE–Cl) recently has been introduced[1] as a clean and economical[2] reagent for the selective N-dealkylation of tertiary amines. High yield applications to the preparation of the prescription pharmaceuticals, nalbuphine and naltrexone, have been described.[1] Dealkylation is effected by heating the tertiary amine with ACE–Cl in 1,2-dichloroethane to give the intermediate **2** which is de*ACE*ylated just by warming in methanol. Ordinarily, the yields of **3** are nearly quanti-

$$R_3N \xrightarrow{\text{ACE-Cl}} \underset{\mathbf{1}}{[R_3\overset{+}{N}\text{–ACE Cl}^-]} \rightarrow \underset{\mathbf{2}}{R_2NC(=O)OCHClCH_3} + RCl$$

$$\mathbf{2} + MeOH \xrightarrow{\text{warm}} \underset{\mathbf{3}}{R_2NH\cdot HCl} + CO_2 + CH_3CH(OMe)_2$$

(1) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(2) Reaction of a 1:1.1 neat mixture of MeCHO and $COCl_2$ in the presence of a reusable $PhCH_2N^+(n\text{-}Bu)_3\ Cl^-$ catalyst affords ACE–Cl in 96% vacuum distilled yield. See footnote 4 in ref 1.

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