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REACTIONS OF 1,2-BIS(TRIFLUOROACETYL)BENZENE WITH NUCLEOPHILES LEADING TO HETEROCYCLIC COMPOUNDS

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SUMMARY

The reaction of 1,2-bis(trifluoroacetyl)benzene (II) with ammonia, hydrazine, hydroxylamine and L-alanine has been investigated and the resulting heterocyclic compounds fully characterized on the basis of spectral data. The reaction of II with o-aminophenol and o-phenylenediamine led to the formation of tetracyclic compounds XI and XII respectively. The structure of compound XII has been further supported by single crystal X-ray crystallography. Our studies reveal the potential of the diketone II as a valuable synthon for the synthesis of a variety of heterocyclic systems with trifluoromethyl substituents.

INTRODUCTION

The chemistry of fluorinated carbonyl compounds has been extensively studied and documented. [1-3] The presence of an electron-withdrawing perfluoroalkyl group leads to a change in typical carbonyl group reactivity by enhancing the electrophilic properties of the carbonyl group. This results in new reactions not normally observed with non-fluorinated ketones.

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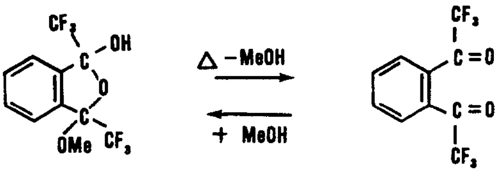
The initial carbonyl addition products are often very stable and in some cases even distillable.

Though hexafluoroacetone is the most extensively studied fluorinated ketone, other fluorinated mono- and diketones have been prepared and in some cases their reaction investigated. These include α,α,α-trifluoroacetophenone [4,5], perfluorobiacetyl [6] and 1,4-bis(trifluoroacetyl)benzene [7]. Our recent studies [8] leading to a high yield synthesis of 1,2-bis(trifluoroacetyl)benzene (II) prompted us to investigate some of its reactions. The nonfluorinated analog of II, 1,2-bisacetylbenzene gives 1,4-dimethylphthalazine on reaction with hydrazine hydrate or semicarbazide hydrochloride and sodium acetate in water [9]. Similarly 1,2-bisbenzoylbenzene reacts with hydrazine hydrate in ethanol to yield 1,4-diphenylphthalazine [10]. With hydroxylamine hydrochloride and sodium acetate in ethanol, only a dioxime is formed from 1,2-bisacetylbenzene.

The reaction of II with nucleophiles such as ammonia, hydrazine, hydroxylamine, L-alanine, o-aminophenol and o-phenylenediamine was investigated. The results of our investigation are reported in this paper.

RESULTS AND DISCUSSION

1,2-Bis(trifluoroacetyl)benzene (II) was prepared by the thermal decomposition of 3-methoxy-1,3-bis(trifluoromethyl)-1-phthalanol (I). The phthalanol I as reported previously [8] was prepared from o-dibromobenzene via sequential lithium-bromine exchange and treatment with methyltrifluoroacetate.

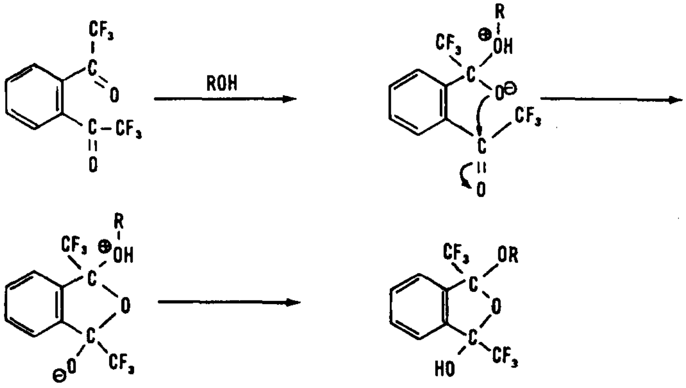


I

II

The diketone II reacts very readily with MeOH to give the starting phthalanol I, and with water gives the dihydroxy compound III [8].

The reaction with water and MeOH can be rationalized as indicated in Scheme 1.



I, R = Me

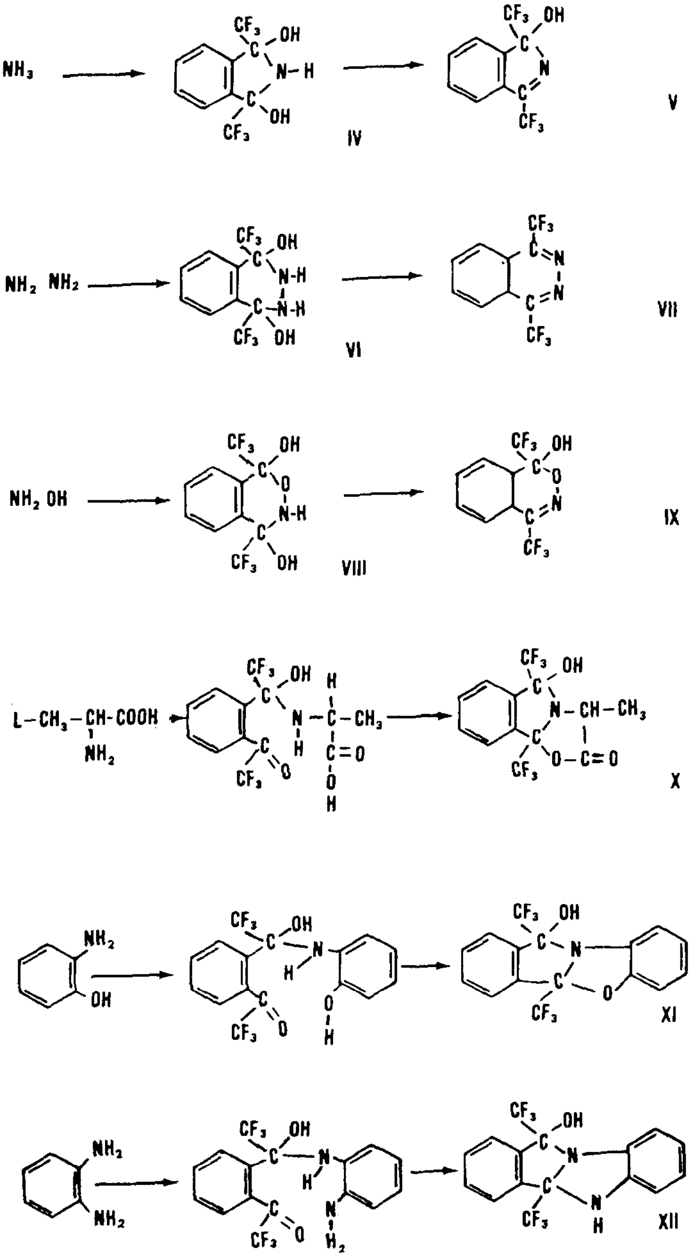
III, R = H

SCHEME 1

Thus in the addition of H_2O and MeOH the proximity of the two carbonyl groups leads to the formation of cyclic ethers via internal nucleophilic attack of the initial intermediates on the adjacent carbonyl carbon as proposed Scheme 1). These extremely facile additions led us to investigate the reactions of the diketone II with various nucleophiles in order to prepare other perfluoroalkyl substituted heterocyclic compounds. The results of our studies are summarized in Table I.

Reaction of the diketone II with dry ammonia at room temperature, in petroleum ether gave a white solid.

The NMR data suggested a <u>cis-trans</u> isomeric mixture of the expected initial adduct IV and dehydration product V (see Scheme 2). This mixture could readily be dehydrated to V by azeotropic distillation with toluene. When II



SCHEME 2

Reactions of II with various nucleophiles was heated with hydrazine dihydrochloride or hydroxylamine hydrochloride in pyridine, the initial adducts which could be VI and VIII respectively, were not obtained. Instead, the products isolated were VII and IX formed apparently by dehydration of VII and VIII. Alternate structures possible were considered and ruled out on the basis of spectral data.

Reaction of L-alanine with the diketone II in refluxing toluene gave a fused heterocyclic compound X with a bridgehead nitrogen. The same product X could also be obtained though in lower yields by heating together I and L-alanine. Since this reaction could be brought about at a temperature (135°C) much lower than that required for the conversion of I to II (280°C) it might suggest that the free diketone II is not formed during this reaction. Though the reactions with other amino acids were not studied, the method would be suitable to prepare similar amino acid derivatives. Reaction of II with o-aminophenol and o-phenylenediamine in the absence of any solvents gave compounds with bridgehead nitrogen, XI and XII respectively, in good yields. In these cases other possible alternate structures were considered before assigning the proposed structures.

For the product from o-phenylenediamine, structure XII was assigned on the basis of NMR data (see Table I) though its IR spectrum indicated the presence of NH_2, NH and OH groups. Therefore X-ray data were obtained which confirmed structure XII. An ORTEP diagram of XII is given in Figure 1. It may be remarked that we are unable, at the present time, to explain the presence of all the 4 different absorptions observed between 3500 and 3300 cm^{-1} in its IR spectrum, though only one -NH and one -OH group is present in structure XII.

It can be readily seen from the above examples that a large variety of novel heterocyclic systems could be derived from the diketone II and appropriate nucleophiles.

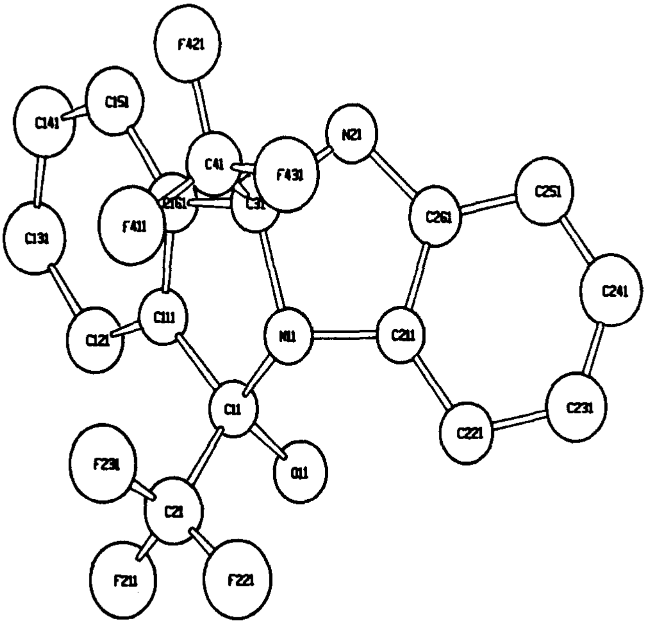


Fig. 1. An ORTEP drawing of compound XII

EXPERIMENTAL

All reactions were carried out under an atmosphere of dry nitrogen. All melting points are uncorrected. Gas chromatographic analyses were performed on a Perkin-Elmer Sigma 1 or Sigma 2B instrument using 6 ft stainless steel columns (1/4" od) packed with 10% SE-30 on Chromosorb W or 3% OV-1 on Supelcoport. TMS was used as the internal standard for ^{1}H and ^{13}C NMR spectra. $CFCl_3$ was used as the internal standard for ^{19}F NMR spectra. Mass spectral analyses were carried out on a DuPont 21-491B mass spectrometer fitted with a Finnigan INCOS Data System. IR spectra were obtained on a Perkin-Elmer Model 683 Grating Spectrophotometer.

Synthesis of V (nc)

Dry ammonia was bubbled through a solution of II (2.3 g; 8.5 mmol) in dry petroleum ether. A white solid separated. This was filtered, washed several times with petroleum ether and dried (2.3 g) m.p. 90.5-94.0°C. This solid (1.0 g) was refluxed in dry toluene (20 h) under azeotropic conditions. Most of the toluene was removed by distillation and pentane was added to the residue. The precipitated solid was filtered, washed with pentane and dried (0.72 g). This was crystallized from CH_2Cl_2-pentane to obtain a colorless crystalline solid (0.55 g; yield 55%), m.p. 153-5°C; MS(CI) *m/e* 270 (M^++1); (EI) *m/e* 269 (M^+), 200 (M^+-CF_3); IR (KBr) 3200 (br, OH), 1620, 1580, 1465, 1400-1050 (C-F), 870-670 cm^{-1}; NMR, ^1H ($CDCl_3$) _ 7.5-8.0 (m, Ar-H), 5.2 (br s, OH); 19F(Me_2CO-d_6) δ -69.1 (s, CF_3-C=N), -79.9 (s, CF_3- C-N); ^{13}C(Me_2CO-d_6) δ 166.9 (q, *J*=37.4 Hz, CF_3-C=N), 147.9, 134.2 (ArC), 132.8, 132.3, 125.9, 123.5 (ArCH), 124.1 (q, *J*=285 Hz, CF_3), 120.3 (q, *J*=275 Hz, CF_3), 100.6 (q, *J*=31.3 Hz, C(OH)CF_3). Anal. Calcd. for $C_{10}H_5F_6NO$: C, 44.61; H, 1.86; N, 5.20. Found: C, 44.64; H, 1.76; N, 5.09.

Synthesis of 1,4-bis(trifluoromethyl)phthalazine VII (nc)

A mixture of *ortho*-diketone II (1.23 g, 4.6 mmol) and hydrazine dihydrochloride (0.48 g, 4.6 mmol) in dry pyridine (5 ml) was heated (bath 85-90°C) for 26 h. After cooling to room temperature, the reaction mixture was poured into water (150 ml). The solid that separated was filtered, washed with water and dried (1.1 g). This was crystallized from CH_2Cl_2-petroleum ether (b.p. 37-58°C) using charcoal to give a crystalline solid (0.876 g, 73%), mp 185-186°C; MS(EI) *m/e* 266 (M^+), 247 (M^+-F); MS(CI) *m/e* 267 (M^++1); IR (KBr) 3100-3000, 1540, 1500, 1400-1050 cm^{-1} (C-F); NMR, (CD_2Cl_2) ^1H δ 8.1-8.4 (complex multiplet, ring H); ^{19}F δ -63.3 (d, *J*=1.91 Hz, CF_3); ^{13}C δ 150.4 (q, *J*=33 Hz, C-CF_3), 135.3 (s, Ar-CH), 124.9 (s, Ar-CH), 124.4 (s, ArC), 122.0 (q, *J*=277 Hz, CF_3). Anal. Calcd. for $C_{10}H_4F_6N_2$: C, 45.11; H, 1.50. Found: C, 44.98; H, 1.56.

1,4 Bis(trifluoromethyl)-1-hydroxy[2,3,1] benzoxazine IX (nc)

A mixture of *ortho*-diketone II (2 g, 7.4 mmol) hydroxylamine hydrochloride (0.52 g, 7.5 mmol) and dry pyridine (5 ml) was heated to reflux. Refluxing was continued for 20 h. The reaction mixture was then cooled to room temperature and poured into water (150 ml). It was extracted with Et_2O, the Et_2O extract was washed with water (twice) and then dried over anhydrous $MgSO_4$. Removal of the solvent gave a viscous residue which solidified on standing (2 g). This was crystallized from hot CH_2Cl_2 using charcoal to give a pale yellow solid (1.22 g), which was subsequently sublimed under reduced pressure (70-75°C (bath temp)/ 3.2 mm) to give a colorless crystalline solid (1.19 g, 56%), mp 88-90°C; MS(EI) *m/e* 286 (M+1), 268 (M^+-OH), 266 (M^+-F), 254 (M^+-NOH) 216 (M^+-CF_3), 196; IR(KBr) 3500-3200 (bonded OH), 1610-1570, 1400-1050 cm^{-1} (C-F); NMR, (CD_2Cl_2) ^1H δ 4.5 (br, OH), 7.6-7.8 (m, Ar-H); ^{19}F δ -65.4 (s, CF_3-C=N), -83.4 (s, CF_3-C-O-) ^{13}C δ 95.0 (q, J=33 Hz, $CF_3\underline{C}$-O-), 119.0, 125.7 (ArC), 120.8 (q, *J*=276 Hz, CF_3) 122.3 (q, *J*=288 Hz, CF_3), 124.7, 126.4, 132.2, 135.1 (ArCH), 147.1 (q, *J*=33 Hz, $CF_3\underline{C}$=N). Anal. Calcd. for $C_{10}H_5O_2F_6N$: C, 42.1; H, 1.75; N, 4.91. Found: C, 42.33; H, 1.85; N. 4.93.

Preparation of X (nc)

The diketone II (2.0 g; 7.4 mmole), L-alanine (0.7 g, 7.8 mmole), and dry toluene (10 ml) were mixed and refluxed in a round bottom flask using a Dean-stark receiver to remove the water formed during condensation. The reaction was stopped after 6 h. The red liquid obtained was cooled, diluted with Et_2O and washed thoroughly with water to remove any unreacted L-alanine. The solvents were removed from the organic layer in a rotary vacuum evaporator to obtain a viscous brown liquid which solidified on cooling. The solid was recrystallized from hexane to yield pale yellow crystals (1.40 g, yield 56%). An analytical sample was obtained by vacuum sublimation. Colorless needles m.p. 136-7°C; MS(EI) *m/e* 342 (M^++1), 324

(M^+-OH), 297 (M^+-CO_2), 272 (M^+-CF_3); IR(KBr) 3430 (bonded OH), 3100-3000, 2940, 1780 (C=O), 1600, 1400-1050 cm^{-1} (C-F). NMR (Me_2CO-d_6); ^{1}H, δ 7.77 (broad, Ar H), 4.73 (q, *J*=7.2 Hz, CH), 2.04 (Distorted pentet; solvent and OH), 1.56 (d, *J*=7.2 Hz, CH_3); ^{19}F, δ -81.04 (q, *J*=3.8 Hz, CF_3), -81.95 (q, *J*=3.8 Hz, CF_3); ^{13}C, δ 139.72, 133.15 (ArC), 133.84, 133.00, 125.65, 125.35 (Ar-CH), 124.5 (q, *J*= 283 Hz, CF_3), 123.6 (q, *J*=283 Hz, CF_3), 118.4 (q, *J*=30 Hz, *C*-CF_3), 95.0 (q, *J*=30 Hz, *C*-CF_3) 50.9 (CH), 17.8 (CH_3). Anal. Calcd. for $C_{13}H_9F_6NO_3$: C, 45.75; H, 2.64; N, 4.10. Found: C, 45.89; H, 2.63; N, 4.04.

Preparation of X from I and L-alanine

Compound I (0.5 g; 1.66 mmol) and L-alanine (0.15 g; 1.7 mmol) were dissolved in diglyme (5 ml) in a 100 ml flask and heated at about 135°C for 2 days. After cooling, the reaction mixture was poured into water, extracted with Et_2O and the solvent removed to yield a brown solid. G.C. analysis of the solid showed it to be mainly the product X; but unlike the product from the free diketone, there were some impurities present. The product was sublimed to obtain colorless needles (yield 32%) which were identical in all respects with the product obtained from the free ketone II.

A similar reaction carried out without solvent by heating together I and L-alanine at 140°C for 3 h gave 45% yield of X as estimated by GC area %. A longer reaction time would perhaps lead to higher yields.

Preparation of XI (nc)

The diketone II (2.7 g, 10 mmole) and *o*-aminophenol (1.15 g, 10.5 mmole) were mixed in a 100 ml flask, heated to 130°C and maintained at that temperature for 4 h, using an air condenser. At the end of this period GC analysis of an aliquot sample showed that the ketone II had reacted completely giving essentially one product. The reaction flask was cooled and the solid obtained (3.53 g) was sublimed under vacuum to yield colorless needles (2.82 g, yield 78%). The sublimate was recrystallized once from hexane for analysis. M.P. 155°C; MS(EI) m/e 361 (M^+), 292 (M^+-CF_3); IR(KBr) 3490 (-OH), 3100-3000, 1600, 1400-1050 cm^{-1} (C-F); NMR (Me_2CO-d_6); ^1H, δ 7.73 (broad, unresolved, ArH), 7.2-6.5 (complex multiplet, ArH); ^{19}F, δ -81.6 (q, J=4.4 Hz, CF_3), -82.8 (q, J=4.4 Hz, CF_3); ^{13}C, δ 154.20, 139.79, 134.21, 132.75 (Ar-C), 133.28, 132.93, 126.03, 125.73, 125.08, 122.71, 119.62, 109.38 (Ar-CH), 124.4 (q, J=283 Hz, CF_3), 123.8 (q, J=286 Hz, CF_3), 105.5 (q, J=33 Hz, $\underline{C}-CF_3$), 95.0 (q, J=33, $\underline{C}-CF_3$). Anal. Calcd. for $C_{16}H_9F_6NO_2$: C, 53.18; H, 2.49; N, 3.88. Found: C, 53.26; H, 2.53; N, 3.75.

Preparation of XII (nc)

In a 100 ml flask, the diketone II (1.92 g, 7.1 mmol) and o-phenylenediamine (0.78 g, 7.2 mmol) were mixed under a nitrogen atmosphere and heated to about 130°C for 3 h using an air condenser. On cooling, the yellow liquid solidified. It was recrystallized from hexane to obtain pale yellow needles (2.21 g, yield 86%). A second crystallization gave the analytical sample melting at 130-131°C. MS(EI) m/e 360 (M^+), 341 (M^+-F), 291 (M^+-CF_3); IR(KBr) 3500, 3425 (NH_2?), 3450 (OH), 3300 (NH), 1600, 1400-1050 cm^{-1} (C-F); NMR (Me_2CO-d_6); ^1H, δ 7.6 (m, ArH), 6.7 (complex multiplet, ArH+OH), 6.1 (brs, NH); ^{19}F, δ -81.1 (q, J=5.4 Hz, CF_3), -83.2 (q, J=5.4 Hz, CF_3); ^{13}C, δ 144.41, 140.14, 137.55, 134.95 (Ar-C), 132.27, 131.52, 125.93, 124.61, 124.05, 120.33, 118.75, 110.48 (Ar-CH), 125.36 (q, J=286 Hz, CF_3), 124.62 (q, J=283 Hz, CF_3), 94.9 (q, J=33 Hz, $\underline{C}-CF_3$), 91.28 (q, J=32 Hz, $\underline{C}-CF_3$). Anal. Calcd. for $C_{16}H_{10}F_6N_2O$: C, 53.33; H, 2.78; N, 7.78. Found: C, 53.25; H, 2.81; N, 7.70.

Collection of the X-ray data and solution of the structure of XII

Colorless crystals were grown by evaporation of a hexane solution. $C_{16}H_{10}N_2OF_6$; space group P_2 1c; a=12.296 (2), b=15.659 (3), c=15.802 (4) Å, β=98.80 (2)°, Z=8. The crystal dimensions were 0.125 x 0.30 x 0.375 mm.

X-ray examination of the crystal and data collection were carried out at room temperature on an Enraf-Nonuis CAD4 diffractometer employing graphite-monochromated MoKα radiation (λ=0.71073 Å). The cell parameter and standard deviations were determined by least-squares fitting of the angular settings of 24 reflections lying in the range $25^{\circ} < 2\theta < 30^{\circ}$. Intensity data were collected by the w-2θ scan mode with 2θ lying between 4° and 50°. A total of 5775 reflections were measured, yielding 2248 independent reflection having $I > 3\sigma(I)$. Absorption corrections were considered to be negligible and were not applied. The structure was solved via a combination of MULTAN and difference Fourier syntheses. Subsequent full-matrix least squares refinement with isotropic thermal parameters for all non-hydrogen atoms gave an unweighted R index of 0.109. Hydrogen atoms were excluded in the structure refinement. The two crystallographically independent molecules in the asymmetric unit have identical geometries.

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