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THE PHOTOCHEMICAL SYNTHESIS OF α,α,α-BROMODIFLUOROTOLUENE AND α,α,α-CHLORODIFLUOROTOLUENE

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Abstract: The syntheses of α, α, α -chlorodifluorotoluene and α, α, α -bromodifluorotoluene from α, α -difluorotoluene and *N*-chlorosuccinimide and *N*-bromosuccinimide, respectively, were achieved photochemically using sunlight and/or sunlamp irradiation. These methods gave high product yields and very little by-product formation.

The introduction of fluorine into organic molecules, especially at a specific site, can exert a profound effect on the physical, chemical or biological properties which cannot be achieved by incorporating any other functional group. Fluorocarbon compounds do not often occur in nature so their existence depends on synthesis.¹ In this paper we report the high yield syntheses of α, α, α -bromodifluorotoluene, **1**, and α, α, α -chlorodifluorotoluene, **2**. Surprisingly, the synthesis of **1** has never been reported, despite its extremely simple structure and its many potential uses as starting material. The first report of **2** was in a 1937French patent where α, α, α -trichlorotolu¹ene was treated with SbF₃/2NaF.²

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From 1937 to 1967 no further reports of this compound appeared until Olah described its synthesis by the azobisisobutyronitile-initinated chlorination of α, α -difluorotoluene with chlorine.³ Olah used **2** as a precursor for the generation of PhCF₂⁺ in super acid media.³ However, the experimental details for the synthesis **2** were not given. In 1992, Yoshida's group reported the low yield preparation of **2** by thermal decomposition of bis(chlorodifluoroacetyl) peroxide in benzene.^{4,5} This route employed chlorodifluoroacetic anhydride to make the peroxide which subsequently reacted with benzene in a sealed ampoule to give **2**. Despite several attempts, we could not repeat Yoshida's synthesis. We describe, herein, an easy, high yield method to make **1** and **2** via sunlight- or sunlamp-initiated halogenation of α, α -difluorotoluene with *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS), respectively (see Table 1, Entries1 and 2).

$$\bigcirc CF_2H + \bigcirc N - X \xrightarrow{sunlight/} CCL_4 \bigcirc CF_2X \\ 0 \qquad 1 X = Br \\ 2 X = Cl$$

 α,α -Difluorotoluene was prepared by fluorination of benzaldehyde using SF₄⁶ and purified by distillation (bp: 139.9°C). α,α -Difluorotoluene (6.7g, 51.8mmol) and NBS (20.0g, 111mmol) were dissolved in carbon tetrachloride (100 mL). The mixture was degassed by two freeze-pump-thaw procedures and under nitrogen. The magnetically stirred mixture was exposed to sunlight during the daytime and a sunlamp at night. After 50 h of irradiation a 97% yield (GC) of

1 was formed with less than 1% by-products (GC). Succinimide was easily filtered due to its low solubility in CCl₄ (0.006M). The product (10.03g, 95% purity by GC) was purified by fractional distillation at either 38-42°C (10 to 15 torr) or 144-146°C (1 atm) and collected in 83.5% isolated yield.⁷ Synthesis of **2** was achieved by chlorination of PhCF₂H (0.2g, 1.56mmol) with NCS (0.4g, 2.0mmol) in an identical manner. PhCF₂Cl, **2**, was formed in 96-98% GC yield after 50 h with only 1.8% of by-products (GC area percent). Purification by distillation (140°C, 760 Torr) gave 0.24g of **2** (95% isolated yield). Compounds **1** and **2** were readily identified by NMR spectroscopy and both EI and CI modes of mass spectrometry (GC/MS). The benzylic carbon of **1** appeared at δ =118.4 ppm as a triplet (*J*_{C-F} = 304 Hz) while the benzylic fluorines appeared at 119.3 ppm downfield from C₆F₆ (43.7 ppm upfield from CFCl₃).

Many other classic methods for benzylic halogenation failed to give 1 or 2. Using Br₂ (Br₂:C₆H₅CF₂H = 2:1, Entry 3) and sunlight/sunlamp irradiation as described above gave a constant product distribution (23%, 1, GC) after 24 h. This remained unchanged through 50 h. Within the other 73% of the reaction mixture, 52% is the starting material and more than fifteen different by-products were formed. Bromination with *t*-BuOBr (*t*-BuOBr:C₆H₅CF₂H = 2:1 Entry 4) in sunlight also gave a constant product distribution after 24 h with only 20% of 1 present (GC, 24-50h) with many by-products. Chlorinations with *t*-BuOC1 (*t*-BuOC1:C₆H₅CF₂H = 2:1) reached a constant product distribution after 24 h. No further changes occurred within 50 h. The yield of C₆H₅CF₂Cl based on GC area percent was only about 26%. Many other by-products had been formed (entry 5,

Entr	Reagent	Solvent	Method	Time	Yield
1	NBS	CCl ₄	Sunlight/sunlamp	50	97 (1)
2	NCS	CCl ₄	Sunlight/sunlamp	50	99 (2)
3	Br ₂	CCl ₄	Sunlight/sunlamp	50	23 (1)
4	t-BuOBr	CCl_4	Sunlight/sunlamp	50	20 (1)
5	t-BuOCl	CCl ₄	Sunlight/sunlamp	50	26 (2)
6	Br ₂	CCl ₄	UV mercury lamp /quartz	48	0(1)
7	Br ₂	CCl ₄	Rayonet UV (50-70°C)	24	0(1)
8	NBS	CCl₄	Δ , Bz ₂ O ₂ (reflux 77°C)	24	0(1)
9	PCl ₅	CCl ₄	Δ , (reflux 77°C)	10	0 (2)
10	PCl ₅	neat	Δ, (80-110°C)	3	0(1)
11	Br ₂	AcOH	Δ, (20-25°C)	16	0(1)

Table 1. Halogenation of α, α -difluorotoluene. Preparation of α, α, α -bromodifluorotoluene, 1, and α, α, α -chlorodifluorotoluene, 2.

Table 1). This result resembled that obtained in the *t*-BuOBr bromination of $C_6H_5CF_2H$.

The reaction mixtures of Entry 3-5 were not worked up due to the low yields of 1 and 2 and the complexity of the product distributions. These reactions never gave higher yields of 1 and 2 even when excess halogenating reagent was present or when long reaction times were used.

Surprisingly, no production of 1 was observed in the bromination of $C_6H_5CF_2H$ with Br_2 in CCl₄ using a mercury vapor UV lamp as the light source in a quartz vessel. Even after 48 h no new products were detected by GC analysis

(Entry 6). Apparently, 1 was formed but it readily photolyzed under UV irradiation to regenerate $C_6H_5CF_2H$. The success of reactions 1 and 2 (Table 1) occurs because both 1 and 2 are not readily photolyzed by sunlight in contrast to their rapid photolyses when exposed to the UV output of both mercury vapor and Rayonet UV lamps.

The radical-initiated bromination of $C_6H_5CF_2H$ with NBS upon heating (77°C) with benzoylperoxide in either CCl₄ for 24 h was attempted. However, no new products were formed and only $C_6H_5CF_2H$ was recovered (Entry 8). Also, thermal chlorinations with PCl₅ (Entries 9 and 10) did not generate **2**.

Why did the sunlight-initiated NBS bromination give high yield of 1 while Br_2 bromination did not? The traditional mechanism for the bromination with NBS in CCl₄ holds that bromine atoms act as the chain carrier.^{8,9,10} The successful synthesis of 1 provides new evidence concerning when this traditional mechanism may operate. Here we propose that the chain carrier in the photo-initiated NBS bromination is the succinimidyl radical.¹¹ The succinimidyl radical is a stronger hydrogen abstractor than bromine.^{11,12} The bond dissociation energy (BDE) of C₆H₅CH₂-H is 88 kcal/mol.¹³ The BDE of C₆H₅CF₂-H has not been reported but it is likely to be significantly higher than 88 kcal/mole. Therefore, the succinimidyl radical would be favored relative to Br[•] as the chain carrier (Scheme 1). Our results clearly showed that the bromination of C₆H₅CF₂H with Br₂ and NBS are quite different. Furthermore, no bromine was observed visually during the NBS bromination reaction (the reaction mixture remained clear during the reaction) further suggesting the succinimidyl radical must be the chain carrier.



Scheme 1

The succinimidyl radical will be increasingly favored as the chain carrier (relative to Br[•]) as the C-H bond dissociation energy increases.

The NCS chlorination (Entry 2 in Table 1) gave a very high yield the high selectivity similar to that observed for the NBS bromination in entry 1. It is likely that the NCS chlorination follows the same mechanism as the NBS bromination where the succinimidyl radical is the chain carrier.

In summary, we have developed a convenient method that can directly convert $C_6H_5CF_2H$ to either $C_6H_5CF_2Br$ or $C_6H_5CF_2Cl$ in high yield with an easy work up. Abstraction of the benzylic hydrogen in $C_6H_5CF_2H$ by Br[•] and BzO[•] proved difficult. This work highlights differences between the chemical behavior of the benzylic hydrogens of toluene and α, α -difluorotoluene.

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- 1, ¹H NMR (CDCl₃, 300 MHz): δ = 7.60-7.65 (m, 2H, H (C-2, C-6)), 7.45-7. 7.50 (m, 3H, H (C-3, 4, 5)). ¹⁹F NMR (C₆D₆, 400 MHz): δ = 119.3ppm, downfield of C₆F₆ (s, 2F, -CF₂H). ¹³C NMR (CD₃Cl, 300 MHz): 118.40 (t, $_{\rm F}$ = 303.98 Hz) 124.24, 124.31, 124.37, 128.63, 131.25, 138.16 (t, $^{2}J_{\rm C}$ $_{\rm F} = 23.45$ Hz). GC-MS (EI) m/z: 189 (M - F)⁺, 127 (M - Br)⁺, 77 (C₆H₅)⁺. GC-MS (CI) m/z: 235 (C₆H₅CF₂⁷⁹Br + C₂H₅)⁺, 237 (C₆H₅CF₂⁸¹Br + C₂H₅)⁺, 206 $(C_6H_5CF_2^{81}Br)^+$, $(C_6H_5CF^{79}Br)^+$. $(C_6H_5CF_2^{79}Br)^+$ 187 208 189 $(C_6H_5CF^{81}Br)^+$, 127 $(C_6H_5CF_2)^+$: **2**, ¹H NMR (CDCl₃, 300 MHz): $\delta = 7.62$ -7.66 (m, 2H, H (C-2, 6)), 7.46-7.52 (m, 3H, H (C-3, 4, 5)). ¹⁹F, (C₆D₆, 400 MHz NMR): $\delta = 114$ ppm, downfield of C₆H₆ (s, 2F, -CF₂Cl). GC-MS (EI)

m/z: 164 (C₆H₅CF₂³⁷Cl)⁺, 162 (C₆H₅CF₂³⁵Cl)⁺, 127 (C₆H₅CF₂⁺), 77 (C₆H₅⁺). GC MS (CI) m/z: 191 (C₆H₅CF₂³⁵Cl + C₂H₅)⁺, 193 (C₆H₅CF₂³⁷Cl + C₂H₅)⁺, 165 (C₆H₅CF₂³⁷Cl + H)⁺, 164 (C₆H₅CF₂³⁷Cl)⁺, 163 (C₆H₅CF₂³⁵Cl + H)⁺, 145 (C₆H₅CF³⁷Cl)⁺, 143 (C₆H₅CF³⁵Cl)⁺, 127 (C₆H₅CF₂⁺).

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