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Preparation of 3′-Bromodiphenyl Ethers from 3′-Carboxydiphenyl Ethers Using Free Radical Methodology

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Abstract:

The ability to convert commercial 3′-carboxydiphenyl ether herbicides to 3′-alkoxydiphenyl ether herbicides could allow more cost efficient preparation of the 3′-alkoxydiphenyl ethers. The free radical brominative decarboxylation of 3′-carboxydiphenyl ethers was explored and optimized. Yields of 50% were obtained, which are not high enough for commercialization. The intermediate 3′-bromodiphenyl ethers can, however, be used in the synthesis of other diphenyl ether analogues.

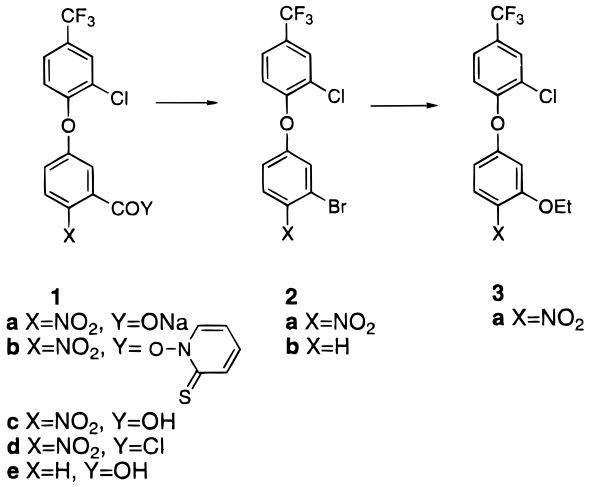
Introduction

Substituted diphenyl ethers constitute a large class of commercial herbicides. Among the commercial materials are some with very similar structures. For example, acifluorfen-sodium (Blazer, **1a**) and oxyfluorfen (Goal, **3a**) vary only in the 3′-substituent (Scheme 1). Preparation of one commercial herbicide from the other could result in substantial cost savings due to economy of scale. This paper describes exploratory process work to convert **1a** to **3a** via the intermediacy of the 3′-bromo compound, **2a**.

Other researchers have explored the possibility of converting 3′-carboxydiphenyl ethers to 3′-bromodiphenyl ethers and ultimately to the 3′-alkoxy compounds. Free radical halogenation has been achieved using excesses of bromine and peroxide, in the presence of heat and light.[1] Yields were low (30−40%), and mixtures of 3′-carboxy and 3′-bromodiphenyl ethers were obtained. Brominative decarboxylation of 3′-carboxydiphenyl ethers has also been performed using mercuric oxide, bromine, and light.[2] Neither of these routes is acceptable for commercial scale synthesis, due to the excesses of peroxide and bromine required in the first case and the use of mercury in the second.

Barton, Crich and co-workers have described the use of thiohydroxamic acid esters formed from carboxylic acids or their salts as general precursors to free radicals.[3−5] The free radicals can be trapped by a variety of reagents, including a source of bromine radical, to result in an efficient brominative decarboxylation.[6−8] Aliphatic acids undergo brominative decarboxylation rapidly and in high yield, but the reactions of aromatic acids are more problematic, as formation of the aryl radical is orders of magnitude slower than for aliphatic systems. Nevertheless, we chose to explore the possibility of using this technology to convert the 3′-carboxydiphenyl ethers to 3′-bromodiphenyl ethers.

Scheme 1



Discussion

We have successfully formed the thiohydroxamic acid ester, **1b**, of the 3′-carboxydiphenyl ether **1a** and optimized conditions for the brominative decarboxylation to form **2a**. The 3′-bromodiphenyl ethers can be converted to the 3′-alkoxydiphenyl ethers, **3**, in good isolated yields.[9] The 3′-bromodiphenyl ethers can also be reacted with other nucleophiles, besides alkoxide, to generate new 3′-substituted diphenyl ether analogues.

It was found that the thiohydroxamic acid ester intermediate, **1b**, can be formed either from the carboxydiphenyl ether, **1c**, and 2-oxo-1-oxa-3-thiaindolizinium chloride or by conversion of the 3′-carboxydiphenyl ether to the acid chloride **1d** and reaction with the sodium salt of 2-mercaptopyridine *N*-oxide. Best yields and purities were obtained via **1d** (50% vs 45% yield). Higher yields of **2a** (50% yield) were found

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(1) Lange, B. C.; Szapacs, E. M. Process for the Preparation of 3′-Halodiphenyl Ethers. U.S. Patent 4,588,487, 1986.
(2) Patterson, D. R. Process for Preparing 3′-Halodiphenyl Ethers. U.S. Patent 4,594,133, 1986.
(3) Barton, D. H. R.; Crich, D.; Motherwell, W. B. New and Improved Method for the Radical Decarboxylation of Acids. *J. Chem. Soc., Chem. Commun.* **1983**, 939−941.
(4) Barton, D. H. R.; Crich, D.; Motherwell, W. B. Photolytic Process for the Formation of Carbon-Containing Free Radicals and its Applications to Free Radical Polymerization in Particular. U.S. Patent 4,668,356, 1987.
(5) Crich, D.; Quintero, L. Radical Chemistry Associated with the Thiocarbonyl Group. *Chem. Rev.* **1989**, *89*, 1413−1432.
(6) Barton, D. H. R.; Crich, D.; Motherwell, W. B. A Practical Alternative to the Hunsdiecker Reaction. *Tetrahedron Lett.* **1983**, *24*, 4979−4982.
(7) Barton, D. H. R.; Lacher, B.; Zard, S. Z. Radical Decarboxylative Bromination of Aromatic Acids. *Tetrahedron Lett.* **1985**, *26*, 5939−5942.
(8) Barton, D. H. R.; Crich, D.; Motherwell, W. B. The Invention of New Radical Chain Reactions. Part VIII. Radical Chemistry of Thiohydroxamic Esters: A New Method for the Generation of Carbon Radicals from Carboxylic Acids. *Tetrahedron* **1085**, *41*, 3901−3924.
(9) Bayer, H. O.; Swithenbank, C.; Yih, R. Y. Herbicidal 4-Trifluoromethyl-4-Nitrodiphenyl Ethers. U.S. Patent 4,093,446, 1978.

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when **1d** was formed at 0 °C in the reaction solvent to be used in the brominative decarboxylation, bromotrichloromethane. Higher yields of **2a** were obtained when **1d** was formed with oxalyl chloride (50% yield) rather than thionyl chloride (40% yield).

The bromotrichloromethane solution of **1d** was reacted with the sodium salt of 2-mercaptopyridine *N*-oxide to form **1b**, which can in principle be decomposed to the carbon radical by heat, light, or radical initiators. With the diphenyl ether substrates, the best conditions for radical generation proved to be a combination of light and heat. The literature reports that AIBN improves the yield of brominative decarboxylation for aromatic substrates.[7] Addition of AIBN as a radical initiator with or without irradiation lowered yields (30−40% yield) and decreased the purity of **2a** obtained. The 3′-radical is trapped by bromotrichloromethane to form **2a**. In all cases, an equal amount of 2-[(trichloromethyl)-thio]pyridine byproduct is formed and must be separated from **2** by chromatography, extraction, or crystallization. No other identifiable byproducts formed during the conversion of **1a** to **2a**. Yields were calculated by isolation following chromatography, and purity was assessed by GC/MS and proton NMR.

On the basis of speculation that the 4′-nitro group could be interfering with the radical reaction, the same reaction sequence was repeated on the desnitro analogue, **1e**. No improvement in the yield of **2b** was observed.

Bromotrichloromethane, which is probably not a commercially useful solvent, was the only radical trap examined which resulted in the formation of a 3′-functionalized diphenyl ether. The use of carbon tetrachloride as solvent did not result in the formation of the 3′-chlorodiphenyl ether. Attempts were made to directly prepare the 3′-hydroxydiphenyl ether from **1** by reacting **1b** with *tert*-butanethiol, oxygen, DMAP, and trimethyl phosphite,[10] but no product corresponding to the 3′-hydroxydiphenyl ether product was observed by comparison to a known standard.[11,12]

The highest yield of **2** obtained following optimization was 50%, which is not high enough for economically viable commercial production of oxyfluorfen from acifluorfen-sodium. The free radical brominative decarboxylation based on the thiohydroxamic acid esters described in this paper represents an improvement over previous routes from **1** to **2** in that it makes use of no toxic metals[2] and higher yields were achieved relative to more conventional free radical procedures.[1]

Experimental Section

Preparation of 2-Chloro-4-(trifluoromethyl)-3′-bromo-4′-nitrodiphenyl Ether, 2a, Using Optimized Conditions. 2-Mercaptopyridine *N*-oxide (15 g, 0.12 mol) in THF (500 mL) was cooled to 0 °C under a nitrogen atmosphere and treated with sodium hydride (60% dispersion in mineral oil, 4.8 g, 0.12 mol) in portions. The slurry was stirred at room temperature for 16 h and then filtered. The solid was dried to yield 2-mercaptopyridine *N*-oxide, sodium salt (13.9 g, 79% yield), as a hygroscopic white solid, mp 256−260 °C.

A suspension of 2-chloro-4-(trifluoromethyl)-3′-carboxy-4′-nitrodiphenyl ether[11] (1.0 g, 2.8 mmol), **1c**, in bromotrichloromethane (20 mL) was cooled to 0 °C and treated with oxalyl chloride (0.26 mL, 3.0 mmol) and DMF (1 drop). The ice bath was removed and the mixture stirred for 1 h. The flask was placed under vacuum for about 5 min to remove hydrogen chloride and carbon dioxide.

A suspension of the sodium salt of 2-mercaptopyridine *N*-oxide (0.45 g, 3.0 mmol) and DMAP (34 mg, 0.3 mmol) in bromotrichloromethane (20 mL) was heated to reflux under a static nitrogen atmosphere. The acid chloride solution prepared above was placed in a dropping funnel above the hot salt suspension and added dropwise, while the refluxing mixture was irradiated with a 75 W incandescent bulb. After 3 h, the light source was removed and the reaction mixture was cooled to room temperature. The mixture was washed with water (3 × 25 mL) and dried through sodium sulfate. The solvent was removed *in vacuo* to yield a brown oil (1.9 g), which was placed on a 2.5 × 10 cm flash silica gel (230−400 mesh) column and eluted with 5% ethyl acetate in hexane. The higher R_f product, by TLC on silica gel eluted with 20% ethyl acetate in hexane, was **2a** (0.54 g, 50% yield) as a colorless oil, identical to a known standard.[1,12] ^{1}H NMR (200 MHz, $CDCl_3$, δ referenced to TMS): 8.0 (d, 1H), 7.8 (s, 1H), 7.65 (d, 1H), 7.3 (m, 2H), 7.0 (dd, 1H). The lower R_f product was 2-[(trichloromethyl)thio]pyridine[8] (0.23 g, 40% yield), as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ referenced to TMS): 8.8 (m, 1H), 8.0 (m, 2H), 7.5 (m, 1H).

Preparation of 2-Chloro-4-(trifluoromethyl)-3′-bromodiphenyl Ether, 2b. A suspension of **1e**[11] was treated as above to form **2b** (35% yield). ^{1}H NMR (200 MHz, acetone-d_6, δ referenced to TMS): 7.9 (d, 1H), 7.7 (dd, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 7.1 (m, 1H). Elemental anal. Calcd (obsd): C, 44.40 (44.08); H, 2.01 (2.36).

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(10) Barton, D. H. R.; Crich, D.; Motherwell, W. B. Conversion of Aliphatic and Alicyclic Carboxylic Acids into nor-Hydroperoxides, nor-Alcohols, and nor-Oxo Derivatives using Radical Chemistry. *J. Chem. Soc., Chem. Commun.* **1984**, 242−244.

(11) Johnson, W. O. Process for Preparing Phenoxybenzoic Acids. U.S. Patent 4,031,131, 1977.

(12) Comparison to known standard by TLC R_f (silica gel eluted with 10% ethyl acetate in hexane), GC t_R (Hewlett Packard 5890, 10 m DB-1 column, 100−250 °C, 20 °C/min ramp), mass spectroscopy (Hewlett Packard 5890 gas chromatograph, 15 m DB-5 column, Hewlett Packard 5970 mass selective detector, all GC/MS were recorded by Mr. Ron Ross), and ^{1}H NMR spectroscopy.

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