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# Concentration-Dependent Reactions of Deoxofluor with Arylglyoxal Hydrates: A New Route to Polyfluoro Ethers

**Rajendra P. Singh and Jean'ne M. Shreeve***

*Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343*

*jshreeve@uidaho.edu*

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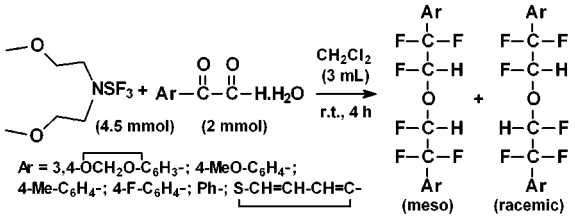
## ABSTRACT




**In concentrated solutions ($CH_2Cl_2$) at 25 °C, arylglyoxal hydrates, ArCOCHO·$H_2O$ (Ar = 3,4-$OCH_2O$-$C_6H_3$-, 4-MeO-$C_6H_4$-, 4-Me-$C_6H_4$-, 4-F-$C_6H_4$-, Ph-, S-CH=CH-CH=C-) (2a–f) with Deoxofluor gave fluorinated ethers, $ArCF_2CHFOCHFCF_2Ar$, (3a–f) in >90% yields as meso/racemic mixtures (∼1:1). Under very dilute conditions, mixtures of $ArCF_2CHO$ (major) (4a–f) and $ArCF_2CF_2H$ (6a–f) (minor) were obtained. The structures of 3b (racemic) and 4a (meso) have been confirmed by single-crystal X-ray analysis.**

Fluorine or a fluorinated group is a highly important substituent in the field of organic chemistry, most often bringing about some remarkable changes in the physical, chemical, and biological properties of new compounds/materials that make them suitable for diverse applications in the areas of materials science, agrochemistry, and industry.[1−4] Although a wide variety of methods have been developed for introducing one or more fluorine atoms into organic compounds,[5] the use of Deoxofluor as a nucleophilic fluorinating reagent is gaining in popularity.[6−8] Utilization of Deoxofluor in the conversion of a simple system such as an aldehyde or a ketone into the corresponding difluoro derivative is well explored,[7] but this methodology has not been extended to polycarbonyl compounds. In our continuing efforts to introduce fluorine into organic compounds nucleophilically,[8] we discovered a new route to aryl polyfluorinated ethers by the reactions of arylglyoxal hydrates with Deoxofluor.

Treatment of **2a** (2 mmol) with Deoxofluor (**1**) (4.5 mmol) in dichloromethane (3 mL) at room temperature for 4 h afforded **3a** and **4a** as a meso and racemic mixture (∼1:1)

* Tel: 208-885-6215. Fax: 208-885-9146.

(1) For the general applications of organofluorine compounds, see: *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.

(2) For the use of organofluorine compounds in medicinal and biomedical chemistry, see: (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) *Organic Chemistry in Medicinal Chemistry and Biomedical Applications*; Filler, R., Ed.; Elsevier: Amsterdam, 1993. (c) Welch, J. T.; Eswaraksrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991. (d) Filler, R.; Kirk, K. Biological Properties of Fluorinated Compounds. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1011−1022. (e) Elliot, A. J. Fluorinated Pharmaceuticals. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1119−1125. (f) Sholoshonok, V. A., Ed. *Enantiocontrolled Synthesis of Organo-Fluorine Compounds: Stereochemical Challenge and Biomedical Targets*; John Wiley and Sons: New York, 1999.

(3) For the use of of organofluorine compounds in agrosciences, see: (a) Cartwright, D. Recent Developments in Fluorine-Containing Agrochemicals. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 237−257. (b) Lang, R. W. Fluorinated Agrochemicals. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 1143−1148.

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in 91% isolated yield. Under similar reaction conditions, various arylglyoxal hydrates (**2b**−**f**) were also converted into aryl polyfluoro ethers (**3b**−**f** and **4b**−**f**) in >90% isolated yields. (Scheme 1). Both the meso (**3a**−**f**) and racemic (**4a**−**f**) compounds were separated by flash chromatography using a methylene chloride and pentane mixture (1:2) as an eluting solvent. Each of the meso compounds gave two sets of signals in the $^{19}F$ NMR spectra centered at about −110 ppm ($CF_2$) (ABX pattern) and −138 ppm (CHF) as a doublet of multiplets. In the racemic products, the signals due to $CF_2$ were essentially identical to those for the meso cases, but the signal due to CHF was observed at about −146 ppm as a doublet of multiplets. In the $^{13}C$ NMR spectra of meso and racemic products, a characteristic shift was observed due to the CHF carbon, i.e., in meso compounds as a doublet of triplets at about 107 ppm with $J = 238$ Hz and in the racemic species as a doublet of triplets at about 103 ppm with the same $J$ value as in the case of meso. Finally, the structures of **3b** and **4a** have been confirmed by single-crystal X-ray analysis.

When the reactions described in Scheme 1 were carried out under very dilute conditions, aryl polyfluoro ethers were not formed, but rather difluoro aldehydes or tetrafluoro derivatives were formed. For example, the reaction of **2a** (1 mmol) with Deoxofluor (**1**) (2.5 mmol) in methylene chloride (200 mL) at 25 °C for 4 h afforded a mixture of **5a** (75%) and **6a** (25%). Under similar reaction conditions, various arylglyoxal hydrates (**2b**−**f**) also gave a mixture of **5b**−**f** as major and **6b**−**f** as minor (Scheme 2). Reaction of concentrated solutions of nonhydrated aryl glyoxals (**7g**−**i**) in methylene chloride with Deoxofluor produced the tetrafluoro derivatives (**8g**−**i**) in excellent isolated yields, whereas only trace amounts of difluoro products (**9g**−**i**) were found (Scheme 2).

The reaction mechanism for the formation of difluoro or tetrafluoro products is similar to that of the reaction between simple aldehydes and ketones[6b,7] with Deoxofluor. The mechanism for the formation of fluorinated ethers is tentatively described in Scheme 3. Fluorination of the carbonyl group α to the phenyl or substituted phenyl group likely occurs first to give **A**. It is known that Deoxofluor fluorinates alcohols, ROH, to produce the corresponding fluorinated derivative, R−F. When the hydrated arylglyoxal (**A**) reacts, the formation of a fluorinated alcohol (**B**) is expected. Fluorine-containing alcohols with fluorine on the α-carbon are unstable with respect to loss of HF or can react with HF under highly concentrated conditions to give an unstable

**Scheme 1**

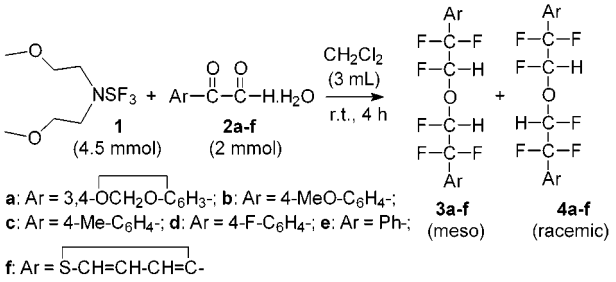
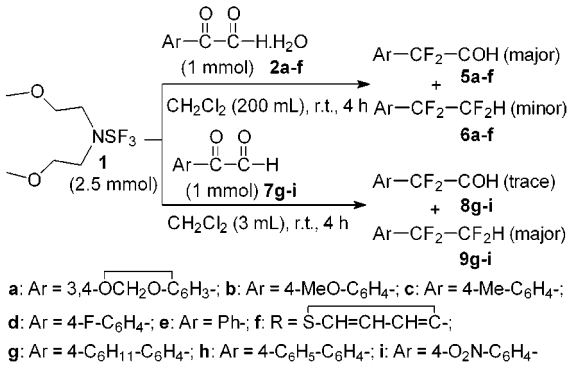



**Table 1.** Reaction of Aryglyoxal Hydrates[a] with Deoxofluor at Room Temperature

| substrate (as hydrate) | products[b] (% yield[c]) meso | racemic |
|---|---|---|
| **1a** | **3a** (47) | **4a** (44) |
| **1b** | **3b** (48) | **4b** (45) |
| **1c** | **3c** (47) | **4c** (46) |
| **1d** | **3d** (45) | **4d** (45) |
| **1e** | **3e** (46) | **4e** (44) |
| **1f** | **3f** (47) | **4f** (46) |

[a] All reactions were carried out with 2 mmol of substrate and 4.5 mmol of Deoxofluor in 3 mL of dichloromethane. [b] Meso and racemic products were separated by flash chromatography and characterized by spectroscopic analysis. [c] Isolated.

**Scheme 2**




(4) The ability of fluorine to change the properties of organic molecules has been discussed extensively elsewhere. For example, see: Smart, B. E. Characteristics of C−F systems. In *Organofluorine Chemistry*: *Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 57−82.

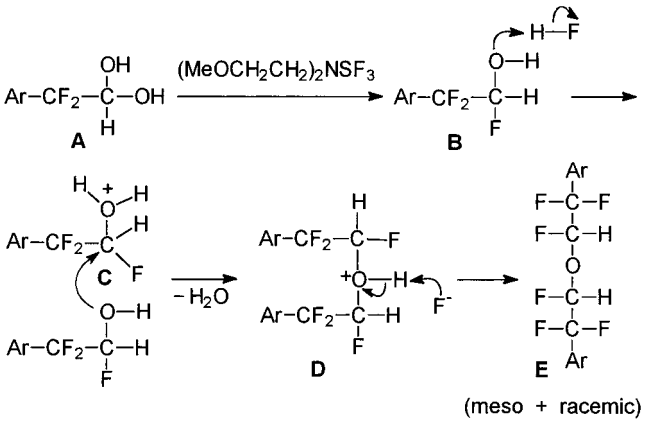
(5) For general discussion on the synthesis of organofluorine compounds, see: (a) Olah, G. A.; Prakash, G. K. S.; Chambers, R. D. *Synthetic Fluorine Chemistry*; Wiley and Sons: New York, 1992. (b) Furin, G. G. *Synthetic Aspects of the Fluorination of Organic Compounds*; Harwood Academic Publisher: London, 1991. (c) Furin, G. G. Introduction of Fluorine by N−F Compounds. In *Methods of Organic Chemistry (Houben-Weyl) Organo-Fluorine Compounds*; Georg Thieme Verlag: Stuttgart, New York, 1999; pp 432−499. (d) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431−12477. (e) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (f) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717−1736. (g) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505−519. (h) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2081. (i) Rozen, S.; Mishani, E.; Bar-haim, A. *J. Org. Chem.* **1994**, *59*, 2918. (j) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883−2887. (k) Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753−4758.

(6) (a) Lal, G. S.; Pez. G. P. U.S. Patent 6,080,886, 2000. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Projonic, F. M.; Chen, H. *J. Org. Chem.* **1999**, *64*, 7048−7054. (c) Lal, G. S.; Labach, E.; Evans, A. *J. Org. Chem.* **2000**, *65*, 4830−4832.

(7) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Projonic, M. *J. Chem. Soc., Chem. Commun.* **1999**, 215−216.

(8) (a) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7633 and references therein. (b) Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, in press. (c) Singh, R. P.; Chakraborty, D.; Shreeve, J. M. *J. Fluorine Chem.* **2001**, in press.

**Scheme 3**




intermediate **C**. A second molecule of the fluorinated alcohol (**B**) attacks at the highly nucleophilic carbon of **C**, which results in the formation of an intermediate **D**. Under acidic conditions (HF), the formation of ether **E** is not surprising (Scheme 3). As a result of the presence of Deoxofluor, fluorination of the carbonyl group α to the phenyl or substituted phenyl group could also occur later in the process. Under very dilute conditions, if appropriate nucleophiles are not available, the intermediates **B**, **C**, and **D** easily decompose. It should be noted that nonhydrated aryl glyoxals do not form polyfluoro ethers even when water is present in the reaction mixture.

In summary, a new application of Deoxofluor to give polyfluoro ethers is reported. Depending on the concentration of the reaction solution and the degree of hydration of the arylglyoxal, fluorinated ethers or tetrafluoro and difluoro derivatives are selectively produced. Further studies of Deoxofluor with other substrates are continuing.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **3a**−**f, 4a**−**f**, **9g**−**i**; crystal data and structure refinements, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and ORTEP drawings for **3b** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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