Tetrahedron Letters 49 (2008) 4189–4191

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: http://www.elsevier.com/locate/tetlet

Direct perfluoroalkylation of non-activated aromatic C–H bonds of phenols

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ARTICLE INFO

Article history:
Received 14 March 2008
Revised 3 April 2008
Accepted 7 April 2008
Available online 23 April 2008

ABSTRACT

A simple procedure for the perfluoroalkylation of the aromatic ring of phenols under mildly basic conditions is described. Treatment of a variety of phenols with perfluoroalkyl iodide in the presence of the radical initiator V-70L and Cs_2CO_3 provided the corresponding perfluoroalkylated products in moderate to good yields. Generally, the reaction proceeded smoothly at room temperature to yield regioselectively perfluoroalkylated products.

Perfluoroalkyl substituted compounds have been widely used as, among others, convenient materials for surfactants, lubricating oil, agricultural chemicals, drugs and polymers.[1] More recently, techniques for the separation of fluorous compounds from organic compounds have become increasingly popular[2] and many synthetic strategies based on fluorous chemistry have been reported.[3] In the field of transition metal catalyzed reactions, fluorous aromatics have been recognized as useful ligands for the design of several catalysts. The fluorophilic nature of these catalysts has enabled fluorous separation techniques to be used as a method of choice for the highly efficient purification of reaction mixtures and the recovery of the catalysts.[4] In order to capitalize upon the aforementioned applications, development of methods for the effective and easy introduction of a perfluoroalkyl group into aromatic molecules represents an important research endeavour. The direct perfluoroalkylation of a target molecule serves as one of the most powerful tools for synthesizing fluorinated aromatics. Existing methods developed to introduce perfluoroalkyl groups onto aromatic rings involve either the direct perfluoroalkylation of halogenated aromatics via coupling reactions or the use of electrophilic perfluoroalkylating agents.[5] However, except for a few free-radical reactions, there are few reports of the direct introduction of perfluoroalkyl groups into a non-activated C–H bond on aromatic rings.[6] Herein, we report a simple method for the direct perfluoroalkylation of phenols under mildly basic conditions. The novel perfluoroalkylation protocol described herein involves the use of a radical initiator V-70L (Fig. 1),[7] which allows the reaction to be carried out at room temperature,[8] and cesium carbonate as the mild base. The reaction furnishes regioselectively perfluoroalkylated phenol compounds in moderate to high yields.

A representative experiment is illustrated in Scheme 1 with salicylaldehyde **1a** as the substrate. To a solution of **1a** (300 mg, 2.46 mmol) and perfluorooctyl iodide (2.01 g, 3.68 mmol) in DMF (16 ml) were added V-70L (758 mg, 2.46 mmol) and cesium carbonate (6.41 g, 19.7 mmol) at room temperature. The mixture was stirred for 20 h at ambient temperature. After the addition of aq. HCl (1.0 M), the reaction mixture was extracted with diethylether. The organic layer was concentrated and the three regioisomers of perfluorooctylated compound **2a** (*ortho*; *para*; and *ortho*/*para dialkylated*) were purified by column chromatography over silica gel eluting with AcOEt/hexane 1/20 and obtained in 36%, 16%, and 25%, respectively.[9]

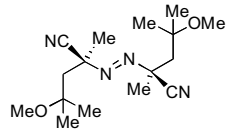
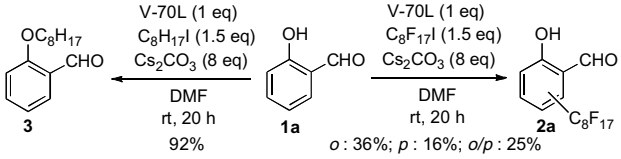


Figure 1.



Scheme 1. C-alkylation versus O-alkylation of salicylaldehyde **1a**.

It is noteworthy that no O-alkylated compound was observed in the ^1H NMR of the crude product. On the other hand, when octyl iodide (non-fluorous) was used instead of the corresponding perfluorooctyl iodide, the corresponding O-octylated compound **3**[10] was exclusively obtained as shown in Scheme 1 in 92% yield.

As part of our reaction optimization studies, we screened a variety of bases and found cesium carbonate to be the most effective base in terms of product yields. It was essential to use V-70L at

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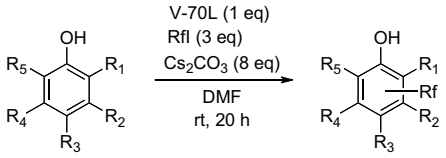
doi:10.1016/j.tetlet.2008.04.106

Table 1
Direct perfluoroalkylation of phenol derivatives



1a-g **2a-g**

Entry	Substrate	Rf	Orientation[a]	Yield[b] (%)
1	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_4F_9	*o*:*p*:*o*/*p* = 38:4:58	*o*:19; *o*/*p*:39
2	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_6F_{13}	*o*:*p*:*o*/*p* = 13:0:87	*o*:4; *o*/*p*:50
3	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_8F_{17}	*o*:*p*:*o*/*p* = 46:0:54	*o*:26; *o*/*p*:49
4	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	$C_{10}F_{21}$	—[c]	*o*:20; *o*/*p*:47
5	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_8F_{17}[d]	*o*:*p*:*o*/*p* = 49:22:29	*o*:36; *p*:16; *o*/*p*:25
6[e]	**1a:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_8F_{17}	*o*:*p*:*o*/*p* = 31:trace:69	*o*:23; p:4; *o*/*p*:44
7	**1b:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = OMe, R_5 = H	C_8F_{17}	*o*:*p*:*o*/*p* = 1:99:trace	*p*:50
8	**1c:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = OMe	C_8F_{17}	—	*p*:59
9	**1d:** R_1 = CHO, R_2 = H, R_3 = H, R_4 = H, R_5 = Me,	C_8F_{17}	—	*p*:37
10	**1e:** R_1 = CN, R_2 = H, R_3=H, R_4 = H, R_5 = H	C_8F_{17}	*o*:*p*:*o*/*p* = 0:0:100	*o*/*p*:76
11[f]	**1f:** R_1 = NO_2, R_2 = H, R_3 = H, R_4 = H, R_5 = H	C_8F_{17}	*o*:*p*:*o*/*p* = 51:16:33	*o*:42; *p*:13; *o*/*p*:16
12	**1g:** R_1 = H, R_2 = H, R_3 = NO_2, R_4 = H, R_5 = H	C_8F_{17}	*o*:*o*/*o* = trace:100	*o*/*o*:77

[a] Determined by crude ^{1}H NMR.
[b] Isolated yield after chromatography or crystallization.
[c] Orientation could not be determined due to the low solubility of the crude product.
[d] 1.5 equiv of **1a** was used.
[e] The condition without V-70L was used at 70 °C.
[f] The reaction was conducted for 10 h at 70 °C.

room temperature for the reaction to go to completion. When the reaction was conducted at temperatures higher than 70 °C, perfluoroalkylation proceeded without the initiator. However, a product mixture rich in an *o*/*p*-di-substituted adduct was obtained. (Table 1, entry 5). We also examined the effect of solvent on the reaction and found DMF to be the best. DMSO was also a suitable solvent for the reaction, but in general gave lower isolated yields of the desired adducts than DMF. We also found that electron withdrawing functionality such as formyl or nitro groups was required to achieve the successful perfluoroalkylation. When non-substituted phenol or alkyl phenols were used as substrates, a complex mixture of products was obtained. A summary of our reaction optimization and substrate scope for the perfluroalkylation experiments is summarized in Table 1.

The perfluoroalkyl groups were directly introduced onto the aromatic ring in either the *o*-orientation or the *p*-orientation with respect to the hydroxyl group. Notable observations are that when 3 equiv of perfluoroiodide is used with respect to the phenol, two alkylated products are obtained namely the *o*-mono perfluoroalkylated and *o*/*p*-di-substituted compounds (entries 1–4). On the other hand, three compounds, *o*-mono perfluoroalkylated, *p*-mono perfluoroalkylated and *o*/*p*-di-perfluoroalkylated, were obtained when the perfluoroalkyl iodide of 1.5 equiv was used (entry 5). Interestingly, the reaction using substrate **1b** provided the high *p*-selectivity in spite of using excess amounts of perfluorooctyl iodide (entry 7). When both *o*-positions of the hydroxyl group were occupied, the regioselective perfluoroalkylation occurred at the *p*-position (entries 8 and 9). When 2-cyanophenol was used as the substrate, both *o*-position and *p*-position were substituted in the same condition (entry 10). Although the presence of a nitro group on the aromatic ring attenuated its reactivity, moderate yields were still obtained under the standard conditions, and elevating the reaction temperature only showed a moderate improvement (entries 11 and 12).

In summary, a new method for the direct perfluoroalkylation of an aromatic sp^2 carbon in phenol derivatives has been developed. The reaction proceeds under mildly basic conditions at room temperature and does not require reagents that are typically needed for the oxidative coupling of aromatics. An investigation into the mechanism for this reaction is currently in progress and will be reported in due course.

Acknowledgements

We thank Professor Dennis P. Curran, University of Pittsburgh, for the useful discussion and Professor Shuji Akai, University of Shizuoka, for the elemental analysis of the fluorous compounds **2**. We also thank Wako Pure Chemical Industries Ltd for funding this work.

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7. 2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) is commercially available from Wako Pure Chemicals Ltd, Japan, and the abbreviation in brackets [V-70] is its trade name. This compound is a mixture of diastereomeric isomers whose melting points are 58 and 107 °C, and should be stored below −10 °C to prevent any decomposition. V-70L is the isomer, which shows low melting point. The typical procedure to separate the diastereomers is shown below: V-70 (5.0 g) in Et_2O (25 ml) was stirred at 10 °C for 30 min to precipitate only V-70H (1.8 g;

content of 100% from ^{1}H NMR). On the other hand, the filtrate, upon cooling to −10 °C for 2 days, gave crystallized V-70L (0.7 g; content of 100% from ^{1}H NMR); V-70L: mp ca. 58 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 12H), 1.64 (s, 12H), 2.26 (d, 2H, J = 11 Hz), 2.42 (d, 2H, J = 11 Hz), 3.21 (s, 6H).

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