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Dithionite-mediated perfluoroalkylation of furan derivatives with dimerization[†]

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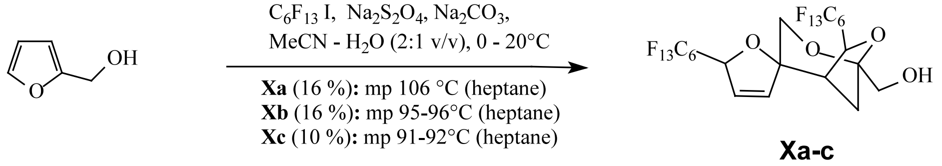
Abstract—2,5-Dimethylfuran (**1**) and 2-pivaloyloxymethylfuran (**4**) were alkylated with 1-iodo-perfluorohexane using sodium dithionite as radical initiator. Perfluorohexylation in the 2-position accompanied with dimerization was observed forming the products **2**, **3** and **5**, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

Biological activity and/or transport properties of organic compounds are influenced by fluorine and fluorinated moieties, respectively.[1,2] Two alternative strategies are applied to introduce fluorine atoms into organic compounds, direct fluorination methods and 'building-block' methods.[3–6] An excellent review about the synthesis of fluoroheterocycles with five-membered rings was published by K. Burger.[7]

Thermally or photochemically initiated trifluoromethylations of furan were firstly reported by Naumann et al[8] using iodo-trifluoromethane. The authors applied relatively drastic thermal conditions (240 h at 120 and 160°C), which only resulted in small yields of 2-trifluoromethylfuran (9.5 and 19.1%). A moderate yield of 39.6% was only achieved by UV-irradiation with an external high-pressure mercury vapor radiator for 168 h. In all cases polymeric by-products were observed. Chen[9] reported about fluoroalkylations of various azaheteroaromatics initiated by UV-irradiation (reaction time: 4–12 h). As a rule monomeric trifluoromethyl or perfluoroalkyl derivatives were obtained. Merely, 2,5-dimethylpyrrole and CF_2I_2 gave after UV-irradiation for 11 h a trifluoromethylated dimer. Recently, Huang and Wu[10] summarized their results about dithionite-mediated additions of 1-halo-perfluoroalkanes to double bonds.[11] In this paper also perfluoroalkylations of electron rich heterocycles were mentioned, however, experimental details or references were not given by the authors. The general statement is that furan, thiophene and pyrrole could be perfluoroalkylated in 2-position.

Because the reaction conditions of dithionite-mediated perfluoroalkylations are generally very mild and experience has shown that the method works well, we investigated perfluorohexylations of selected furan derivatives to obtain 'building blocks' for special liquid crystals. The reactions led to unexpected results. Furfurol yielded using the usual reaction conditions of dithionite-mediated perfluoroalkylations a mixture of three diastereomeric solid dimers (Scheme 1). An exact structural assignment of the individual isomers separated by column chromatography was not successful.[12]

The furans **1** and **4**, alkylated with 1-iodo-perfluorohexane under analogous reaction conditions, gave the perfluoroalkylated dimers **2**, **3**, and **5**, respectively



Xa-c

Scheme 1. Dithionite-mediated perfluorohexylation of furfurol yielding three diastereomeric dimers of type **X** [12].

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[†] Dedicated to Professor Dieter Naumann on the occasion of his 60th birthday.

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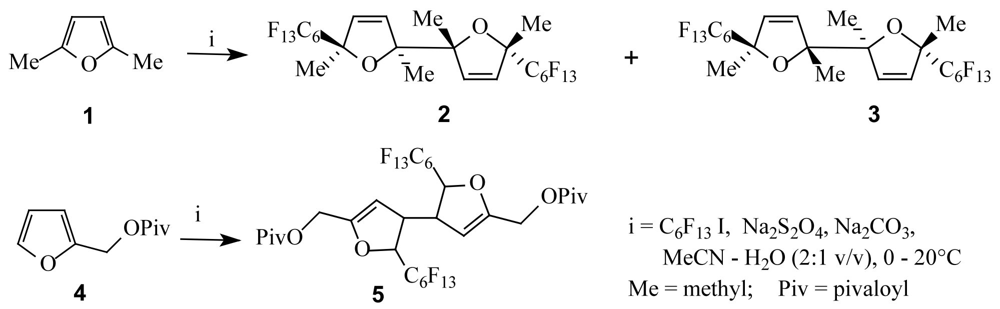
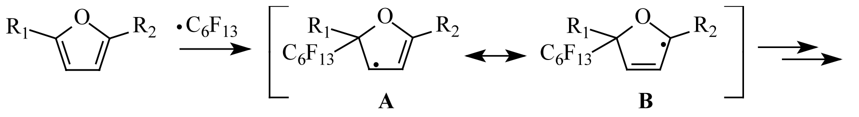


$i = C_6F_{13}I$, $Na_2S_2O_4$, Na_2CO_3,
MeCN - H_2O (2:1 v/v), 0 - 20°C
Me = methyl; Piv = pivaloyl

Scheme 2.



Scheme 3. Mesomeric stabilized radical (resonance forms A and B) formed by attack of a perfluorohexyl radical on a furan derivative.

(overall yields 38–45%). The compounds were isolated in pure form by column chromatography (Scheme 2).[13] Additionally, higher molecular by-products were detected (TLC), however, these compounds were not separated. It is noteworthy that monomeric products were only formed in traces. We assume that the mild reaction conditions of dithionite-mediated perfluoroalkylations (0–20°C) favor dimerizations compared to the more drastic conditions of the Naumann-procedure mentioned above.

As shown in Scheme 2, the perfluorohexyl moieties are only introduced into an α-position of the furans; the attack on a non-substituted α-position is preferred. Key intermediate is an allylic radical (Scheme 3). To give an explanation for the preferred formation of the products **2** and **3** is a risk. Perhaps, resonance form **B** allows a thermodynamically controlled course of reaction (distance to the strong electron withdrawing group). However, also the steric discrimination of the substituents R_1 and R_2 may control the following reaction step. If R_2 is relatively large (pivaloyloxymethyl group of compound **4**), the corresponding resonance form **A** dimerizes to product **5**.

The structures of the products **2**, **3** and **5** are supported by their MS and NMR spectra; selected data of **2**, **3** and **5** see Ref. 14. Because of the C_2 symmetry of the diastereomers **2** and **3** some protons and C-atoms are homotopic and therefore their signals have the same chemical shift. Consequently, the corresponding spectra are simplified, i.e. the ^1H spectra show only four signals. The *cis* arrangement of the two methyl groups in **2** was confirmed by NOESY-experiments.

2-Pivaloyloxymethylfuran (**4**) gave only one diastereomeric dimer (MS (CI); $m/z = 1001.7$). The ^1H NMR spectrum of diastereomer **5** shows only five signals indicating the high symmetry of the molecule. The vicinal HF-coupling ($J_{F,H\text{-}2} = 20.2$ Hz) and the chemical shift of H-3 ($\delta = 3.48$ ppm) indicates a saturated partial structure. By the ^{13}C-^1H-correlation spectrum the 3/3′-connection of the two rings was confirmed. Consequently, the steric hindrance by the pivaloyloxymethyl group was obviously sufficient to prevent a connection of two rings based on resonance form **B**.

Acknowledgements

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13. (2*S*,5*R*,2′*R*,5′*S*)-2,5,2′,5′-Tetramethyl-5,5′-diperfluorohexyl-2,5,2′,5′-tetrahydro-[2,2′]-bisfuryl (**2**) and (2*R*,5*R*,2′*S*,5′*S*)-2,5,2′,5′-tetramethyl-5,5′-diperfluorohexyl-2,5,2′,5′-tetrahydro-[2,2′]-bisfuryl (**3**). To a stirred mixture of 2,5-dimethylfuran (**1**) (2.5 mL, 23.5 mmol), $NaHCO_3$ (5.0 g, 60 mmol) and 1-iodo-perfluorohexane (6.8 mL, 31 mmol) in acetonitrile/water (100 mL, 2:1 v/v) sodium dithionite (5.0 g, 28 mmol) was added in portions at 0°C within 1 h (argon atmosphere). Then the mixture was allowed to warm up to rt and stirring was continued for 2 h. After extraction with diethyl ether (100 mL), the organic phase was washed with water (3×60 mL), dried (Na_2SO_4) and concentrated. Column chromatographic separation (heptane/ethyl acetate = 50/1 v/v) gave the colourless crystalline products **2** (R_f 0.61), 645 mg (33%), mp 97°C (heptane), $[\alpha]_D^{25} = \pm 0$ and **3** (R_f 0.48), 235 mg (12%), mp 65°C (heptane), $[\alpha]_D^{25} = \pm 0$.

    2,2′-Diperfluorohexyl-5,5′-dipivaloyloxymethyl-2,3,2′,3′-tetrahydro-[3,3′]bisfuryl (**5**). 2-Pivaloyloxymethyl furan (**4**) (1.04 g, 5.7 mmol), $NaHCO_3$ (1.1 g, 13 mmol), 1-iodo-perfluorohexane (2.5 mL, 11.5 mmol) and sodium dithionite (2.0 g, 11.5 mmol) in acetonitrile/water (30 mL, 2:1 v/v) were treated and worked-up as described for **2**/**3**. Column chromatographic purification (R_f 0.35, heptane/ethyl acetate 6:1 v/v) gave 2.17 g (38%) of the crystalline product **5**, mp 137°C (heptane).
14. **2**: ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.99 (d, 2H, H-4, H-4′, $^3J_{3,4} = 6.1$ Hz); 5.69 (d, 2H, H-3, H-3′, $^3J_{3,4} = 6.1$ Hz); 1,51 (s, 6H, 2×CH_3); 1.38 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.8 (s, C-3); 126.1 (s, C-4); 96.1 (s, C-2); 91.3 (t, C-5); 21.6 (s, CH_3); 21.3 (s, CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ (ppm) = −85.7 (CF_3); −122.7 (CCF_2); −123.9 (CF_2); −126.9 (CF_2); −127.7 (CF_2); −131.1 (CF_2). Anal. calcd for $C_{24}H_{16}F_{26}O_2$ (830.34): C, 34.70; H, 1.90; found: C, 34.85; H, 1.84. MS (CI): molpeak 830.7.

    3: ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.91 (d, 2H, H-4, H-4′, $^3J_{3,4} = 5.9$ Hz); 5.73 (d, 2H, H-3, H-3′, $^3J_{3,4} = 5.9$ Hz); 1.49 (s, 6H, 2×CH_3); 1.35 (s, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 135.6 (s, C-3); 127.2 (s, C-4); 96.3 (s, C-2); 91.1 (t, C-5); 21.8 (s, CH_3); 20.7 (s, CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ (ppm) = −80.7 (CF_3); −116.7 (CCF_2); −117.9 (CF_2); −119.4 (CF_2); −121.7 (CF_2); −125.9 (CF_2). Anal. calcd for $C_{24}H_{16}F_{26}O_2$ (830.34): C, 34.70; H, 1.90. Found: C, 35.08; H, 1.86; MS (CI): molpeak 830.6.

    5: ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 4.96 (s, 2H, H-4); 4.68 (d, 2H, CH-CF_2, $^3J = 20.2$ Hz); 4.61 (s, 4H, O-CH_2); 3.48 (s, 2H, H-3); 1.19 (s, 18H, 6×CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 177.7 (s, C=O); 155.3 (s, C-2), 99.6 (s, C-3), 79.6, 79.2, 79.1, 78.7 (4s, C-5); 57.5 (s, CH_2); 47.1 (s, C-4); 38.7 (s, C); 26.9 (s, 3×CH_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ (ppm) = −85.7 (s, CF_3); −126.9 (s, CCF_2); −127.8 (s, CF_2); −131.1 (s, CF_2); −134.1 (s, CF_2); −135.3 (s, CF_2); Anal. calcd for $C_{32}H_{28}F_{26}O_6$ (1002.5): C, 38.34; H, 2.82. Found: C, 38.66; H, 2.66; MS (CI): molpeak 1001.7.