Communication

Synthesis and Spectroscopic Characterization of Furan-2-Carbaldehyde-\textsuperscript{d}

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Abstract: Here, we present a protocol for the one-step synthesis of the title compound in quantitative yield using adapted Vilsmeier conditions. The product was characterized by \textsuperscript{1}H-, \textsuperscript{2}H-, \textsuperscript{13}C-NMR-, as well as IR and Raman spectroscopy. Spectral data are given in detail.

Keywords: 2H; formylation; D-label; isotope-shift; NMR; Raman; IR

1. Introduction

Furfural is an important starting material for a large number of reactions. It plays an indispensable role in many synthetic pathways, e.g., for the synthesis of pharmaceuticals, dyes, or polymeric materials [1–3]. Since furfural can be obtained from renewable resources, the heterocycle has attracted reasonable interest in terms of green chemistry [4–6]. Isotope labeling is a key concept in modern organic chemistry to track compounds, understand metabolisms, or clarify reaction mechanisms [7–9]. Because of the stronger deuterium–carbon bond, deuterated drug molecules can alter the metabolism and help to improve pharmacokinetic or toxicological properties. Hence, deuteration is an important research issue in medicinal chemistry as well [10,11]. In addition, \textsuperscript{2}H-, and even \textsuperscript{14}C- and \textsuperscript{18}O-isotope derivatives of furfural, especially of the aldehyde group, have been synthesized before [10,12]. As early as 1973, D.J. Chadwick et al. pioneered the synthesis of all single D-labeled furfural isomers [13,14].

Besides the complete deuteration of a molecule, it is of interest to mark a specific position with an isotope label in order to track its path during a chemical transformation. Scheme 1 summarizes the known literature methods for the synthesis of furan-2-aldehyde-\textsuperscript{d} (1), starting either from furfural (2), furan (3), difuran-2-yl)ethanedione (4), or 2-(furan-2-yl)-2-oxoacetic acid (5). The different synthetic strategies can be summarized as follows: (1): Starting from 2, the aldehyde is protected as a thioacetal, subsequent deprotonation by a lithium base, and quenching with D\textsubscript{2}O, followed by the mercury-catalyzed removal of the protecting group [15,16]; (2): Vilsmeier reaction from 3 using DMF/POCl\textsubscript{3} [13]; (3): cleavage of 4 by cyanide in D\textsubscript{2}O as solvent [13]; and (4): the decarboxylation of 5 using PPh\textsubscript{3}/NEt\textsubscript{3} in deuterated water [17]. Upon closer inspection, all the described methods suffer from demanding multiple steps, expensive starting materials, and/or a poor yield in relation to expensive materials. For the direct exchange of the aldehyde proton in 2 by deuterium to 1, no reactions were found. More recently, two methods for the direct H/D exchange via a photo-redox reaction or an N-heterocyclic carbene (NHC) catalyzed reaction were described. The scope of these methods includes a wide range of aldehyde substrates, but furfural (2) is missing in both cases [18,19]. Shinada et al. summarized methods for the formation of deuterated aldehydes [20], but they did not mention a straightforward synthesis for 1. However, some reactions using furfural-\textsuperscript{d} (1) for the synthesis of deuterated compounds have been described before [17,21–23].
In this report, we describe the optimized formylation of furan (3) using DMF-d7 under adapted Vilsmeier conditions to yield 1 quantitatively. Comprehensive 1H-, 13C-, 2H-NMR, EI-MS, as well as vibrational spectra (IR/Raman) are presented in detail.

2. Results and Discussion

To improve the accessibility of furan-2-carbaldehyde-d (1), we optimized the Vilsmeier protocol to obtain deuterated furfural in a quantitative yield starting from furan (3). Therefore, we choose DMF-d7 as the source of formyl. However, DMF-d1 is commercially available as well, but for a higher price than DMF-d7. Utilized DMF-d7 had a degree of deuteration of 99.6%, determined by 1H-NMR spectroscopy. For the reaction, stoichiometry DMF-d7 was calculated as the limiting reactant, and all other components were used in excess. As a result, a gram-scale synthesis method was developed (see Section 3.2). Compared to the earlier-described Vilsmeier protocol [13], the atom economy of the used DMF-d7 was maximized as proven by the quantitative yield (99%). The applied extraction/evaporation workup yielded a product purity of about 97% (1H-NMR). Hence, the received product can be used for subsequent reactions without further distillation purification. Overall, the new synthetic procedure increases the yield by 15%, while also accelerating the reaction protocol by avoiding a time-demanding purification procedure which was necessary in previous reports. The increase in the yield is especially important as the deuterated starting material is expensive.

2.1. NMR Analysis Details

The recorded 1H- as well as 13C-spectra are shown in Figure 1. The observed 1H-NMR signals are in good agreement with earlier published data [15,24]. The low abundance of byproducts (<3%) proves the excellent reaction and workup selectivity. A degree of deuteration of about 99.6% was determined by the residual aldehyde 1H-resonance at 9.64 ppm (see Figure 1, inlay). In the proton decoupled 13C-NMR spectrum, expected 13C/2H multiplicity was observed. Coupling constants of 1J(13C(1)-D) = 27.3 Hz and 2J(13C(2)-D) = 4.5 Hz were found. Comparison between the 13C-NMR resonances of furfural (2) and furfural-d (1) indicates a deuterium isotope shift of Δδ(C(1)) = 20.6 Hz and Δδ(C(2)) = 2.4 Hz. Comprehensive 13C-Spectra were recorded from a mixture of furfural (2) and furfural-d (1) (see Figure 2). A 2H-NMR spectrum was recorded on a 20 mg/mL DMSO solution with 1% DMSO-d6 as an internal reference. 2H resonance of 1 was observed at 9.35 ppm with a FWHM of 23 Hz.
Fural (2) and furfural-d (1) (see Figure 2). A 2H-NMR spectrum was recorded on a 20 mg/mL DMSO solution with 1% DMSO-d6 as an internal reference. 2H resonance of 1 was observed at 9.35 ppm with a FWHM of 23 Hz.

Figure 1. Assigned 1H- and 13C-NMR spectra of the received product 1.

Δδ 13C(1)-(H/D) = 20.6 Hz  Δδ 13C(2)-(H/D) = 2.4 Hz

Figure 2. Comparison of the 13C-NMR resonances of fural (2) and furfural-d (1) (20 mg/mL 1 in CDCl3 solution spiked with 20 mg 2). An isotope shift for the 13C(1)-D/H signal of about 20.6 Hz and 2.4 Hz for the 13C(2)-D/H signal was observed. (13C-Resonances of 1 are marked by *).
2.2. Comprehensive EI-MS Spectra Analysis

The comparison of the EI-MS spectra is shown in Figure 3. The degree of deuteration of the analyzed sample of compound 1 was 99.6% (1H-NMR). The expected 1 Dalton difference between 1 and 2 was observed for the mole peaks [M+]. The fragmentation loss of the aldehyde H- or D-atom formed a furanyl–acylium ion fragment with m/z = 95 in both cases. A mass difference of 2 Dalton between the mole peak (97 m/z) and the furanyl–acylium fragment (95 m/z) was found in the case of 1. The fragmentation loss of a formyl-ion yields a fragment of m/z = 29 in the case of 2 and m/z = 30 in the case of 1. Both effects substantiate the location of the D on the carbonyl group of 1. A comparison of other fragments (int. > 20%) shows comparable patterns (m/z = 67, 51, 39) for both molecules. Only the masses of m/z = 39/40 differ and may be assigned to different H/D fragments.

2.3. Comprehensive IR Spectra Analysis

In Figure 4, the ATR-IR spectra are shown. As expected, the characteristic ν(O=C-H) bands of furfural (2) were observed between 2847 and 2715 cm⁻¹. For the deuterated furfural 1, ν(O=C-D) bands were found between 2139 and 2080 cm⁻¹. The exchange of H to D caused a shift of about 700 cm⁻¹ for 1. The sp²-CH bands were found at similar frequencies in both cases. The comparison of the fingerprint regions of both compounds reveals clear differences too (see Figure 5). For furfural (2), the bands at, e.g., 1687/1668 as well as 1472/1463 were previously assigned as vibrational modes of OO-cis- and OO-trans-furfural conformers [25]. For 1, these bands were not observed. Hence, we speculate that the rotational barrier along the C(1)-C(2) axis prevents isomerization and favors one isomer in neat material at an ambient temperature.

The comparison of the fingerprint regions reveals only small differences. The furfural-d (1) misses the earlier-mentioned double bands at 1651 cm⁻¹ and 1462 cm⁻¹ and instead only shows a single band at these positions. In addition, in the case of 1, the band at 1366 cm⁻¹ is missed. Characteristic bands for 1 were instead found at 1047 cm⁻¹ and 712 cm⁻¹ (see Figure 5).

2.4. Comprehensive Raman Spectra Analysis

Raman spectra were recorded using neat materials. In Figure 6, the received Raman spectra of furfural (2) and furfural-d (1) are shown. Characteristic C=O-H bands were found at 3125, 2855, and 2719 cm⁻¹. By the H/D-exchange, C=O-D bands were found at 2144, 2120, and 2084 cm⁻¹ and are in good agreement with the expected shift of about 700 cm⁻¹ also seen in the IR spectra. Other CH bands were unaffected by the deuteration, and thus bands were observed at the same wavenumbers for both molecules. A comparison of fingerprint bands revealed very similar spectra (see Figure 7). In the case of 2, deformation vibrations for C-H bonds were found at 1473 and 1466 cm⁻¹. Even here, the OO-cis/OO-
trans conformation effect can be seen. For the bands at 1367 cm$^{-1}$, no equivalent band was found in the spectra for the deuterated compound 1. Hence, the Raman bands behave similarly to the IR absorption bands.

Figure 4. Comprehensive ATR-FTIR spectra of furfural (2) and furfural-d (1).

Figure 5. Comprehensive ATR-FTIR spectra of the fingerprint region highlighting differences between 1 and 2.
Figure 6. RAMAN spectra of furfural (2) and furfural-\textsubscript{d} (1).

Figure 7. Comprehensive Raman spectra of the fingerprint region.
3. Materials and Methods
3.1. Materials

Furan (CAS: 110-00-9), furfural (CAS: 98-01-1), oxalyl chloride (CAS: 79-37-8), and methylenechlorid (CAS: 75-09-2) were received from Sigma-Aldrich Chemie GmbH, 82024 Taufkirchen, Germany, ordered at the highest quality and used as received. DMF-d7 (CAS: 7789-20-0) was received from DEUTERO GmbH, 56288 Kastellaun, Germany, at 99.5% deuteration quality and used as received.

3.2. Method of Synthesis

In total, 2.1 g (28.4 mmol, 2.04 mL, 1.0 eq.) of DMF-d7, 14.5 g (213 mmol, 15.4 mL, 7.5 eq.) of furan, and dichloromethane (DCM, 20 mL) were added into a 250 mL flask equipped with a magnetic stirring bar and a dropping funnel under inert conditions (N2). The flask was placed in an ice bath for 10 min before 3.9 g of (31.2 mmol, 2.65 mL, 1.1 eq.) (COCl)2 in 20 mL DCM was added dropwise within 10 min. A white precipitate formed during the addition. The batch was stirred in the ice bath and allowed to warm up overnight. After 12 h, a clear, slightly reddish solution formed. The flask was cooled again within an ice bath before 50 mL of saturated Na2CO3 solution was added in small portions. After the gas development ended, the reaction mixture was stirred for 10 min in the ice bath before the phases were separated and the aqueous phase was extracted 3x with 30 mL of DCM. The combined organic phases were washed 3x with about 30 mL of saturated NH4Cl solution and 3x with about 30 mL of brine. The organic phase was dried with 15 g of MgSO4 and subsequently evaporated under a reduced pressure to produce 2.7 g (yield: 99%) of a slightly reddish liquid.

1H-NMR analyses showed a purity better than 97% (see Figure 1) and a deuteration degree of 99.6%. Depending on the subsequent reaction steps, this product can be used without further purification. Bulb-to-bulb distillation was at 80 °C, 20 mbar, and ice cooling yielded about 2.55 g (26.3 mmol, 93%) of furan-2-carbaldehyde-d (1). The product was stored under inert gas and cooled conditions to prevent discoloration and decomposition. 1H NMR (300 MHz, CDCl3) δ(ppm): 7.68 (dt, J = 1.6, 0.7 Hz, 1H, C5-H), 7.25 (dt, J = 3.6, 0.7 Hz, 1H, C3-H), 6.59 (ddd, J = 3.6, 1.7, 0.5 Hz, 1H, C4-H). 13C NMR (75 MHz, CDCl3) δ: 177.9 (C1D), 177.59 (C1D), 177.2 (C1D), 177.2 (C1D), 152.9 (C2), 152.9 (C2), 152.8 (C2), 148.1 (C5), 121.1 (C3), 112.6 (C4). 2H NMR (46 MHz, CDCl3) δ(ppm): 8.35.

3.3. Instrumental Analytics

NMR spectra were recorded using a 300 MHz Avance I (Bruker, Germany) with a QNP probe head at 25 °C using standard pulse sequences. All compounds were analyzed as a 40 mg/mL CDCl3 solution. The 2H-NMR probe was analyzed as 20 mg/mL DMSO-d6 solution with 1% DMSO as the internal reference. Data were analyzed using the software MestReNova V.14.3.1 (Mestrelab Research, S.L. 15706 Santiago de Compostela, Spain). For the comprehensive 13C-Spectra, a 20 mg/20 mg mixture of 1 and 2 was analyzed (see Figure 2). The Raman spectra of the neat materials were recorded on a JASCO FT/IR-6300 Spectrometer equipped with an RFT-6000 Raman unit. The Raman spectra obtained 1064 nm laser excitation. The ATR-IR spectra of the neat materials were recorded using a JASCO FT/IR-6300 spectrometer equipped with a PIKE Technologies MIRacle Single Reflection ATR-Unit. ATR-correction was applied for all the spectra. IR- and RAMAN data were analyzed using Peak Spectroscopy Software V.4.00 (Operant LLC, Monona, WI 53716, USA).

4. Conclusions

We presented a protocol for the quantitative synthesis of furan-2-carbaldehyde-d (1) starting with furan using DMF-d7 and (COCl)2. The desired product was obtained in quantitative yield (99%). The 1H-NMR spectra revealed a deuteration degree of >99% and a purity of the product of >96%. 13C-NMR-, ATR-IR, and Raman spectra were recorded and discussed in detail.
Supplementary Materials: The supporting information can be downloaded online.

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References


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