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Deoxygenation of Furanmethanols with ZnI_2-$NaCNBH_3$. An Efficient Protocol for the Preparation of 2- and 3-alkylfuran Compounds

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Uma nova e eficiente metodologia para a desoxigenação de 2- ou 3-furanometanóis é apresentada. O processo baseia-se nas condições especiais de redução do $NaCNBH_3$ combinado com ZnI_2, que mostrou-se compatível com a presença de ligações duplas ou outros grupos facilmente redutíveis por outras metodologias empregadas para desoxigenação de furanometanóis. Vários alquilfuranometanóis foram preparados e submetidos a desoxigenação fornecendo os alquilfuranos correspondentes em rendimentos que variaram de bons a excelentes.

A new and effective methodology for deoxygenation of 2- or 3-furanmethanols is presented. This protocol is based on the unique characteristics of $NaCNBH_3$ combined with ZnI_2, which is compatible with the presence of double bonds and other easily reduced functional groups. A number of furanmethanol derivatives were prepared and submitted to these deoxygenation conditions to afford the corresponding 2- or 3-alkyl furans in good to excellent yields.

Keywords: *furanmethanol, deoxygenation, alkylfuran, sodium cyanoborohydride*

Introduction

Alkylfurans are valuable intermediates in organic synthesis mainly for their characteristics as "multi-masked functional groups", that is, they can be efficiently transformed into several other functional groups, e.g. cyclopentenones.[1] Besides this well-recognized feature, alkylfuran systems are also part of an increasing number of interesting naturally occurring compounds, such as: dehydroambliol **1**[2], lasiosperman **2**[3], and the pseudopterolide kallolide B **3**[4], a potential cell division inhibitor and anti-inflammatory agent.

Alkylfuran compounds are usually obtained by alkylation of furanylmetallo intermediates, with alkyl halides in yields that vary from good to poor[5]. The yields are highly dependent on several factors: (i) the nature of the organometallic intermediate, (ii) the structure of the alkyl halide, whether primary, secondary or branched, and (iii) the reaction conditions[6]. A straightforward route to alkylfurans involves the deoxygenation of furanmethanols. However, this approach has few precedents in the literature; in fact, there is a lack of general and selective methodology for efficient deoxygenation of furanmethanols[7]. Of the methods surveyed in the literature, the most common procedures for achieving deoxygenation of furanmethanols

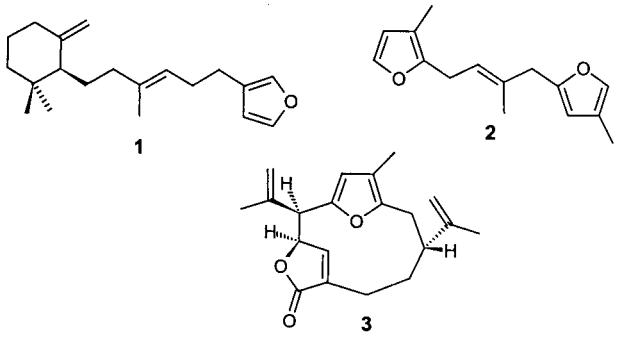


Figure 1. Some examples of alkylfuran natural products.

involve reduction with Li-NH_3[8] or catalytic hydrogenation[9]. Deoxygenation employing Li-NH_3 requires well-controlled reaction conditions, and for synthetically valuable results the furanmethanol substrates have to be derivatized (such as an acetate, for example) because the free alcohol is usually rather unreactive[8]. On the other hand, catalytic hydrogenation may also lead to furan ring reduction, an easy and synthetically useful reaction, especially when Rh is used as the active catalyst[10]. A major drawback of catalytic hydrogenation is its poor chemoselectivity when other reducible functional groups, such as double bonds, are present.

Here we describe a practical and effective procedure for obtaining alkylfurans from furanmethanols in high yields and under mild conditions. This process employs the reductive system ZnI_2-$NaCNBH_3$ in an extension of Lau's procedure developed to reduce α-aromatic carbonyls to the corresponding methylene compounds[11].

Experimental Details

Typical procedure for the preparation of furanmethanols (preparation of **7***)*

To a dry THF solution of 2-methylfuran (5.0 g, 61 mmoles in 90 mL of THF) at -78 °C under nitrogen and magnetic stirring n-BuLi (24.4 mL of a 2.5 M solution in hexanes, 1 equiv.) was slowly added. After the addition of n-BuLi the cooling dry-ice bath was removed and the reaction warmed up to room temperature within a 4 h period. The resulting dark-colored mixture was then cooled to 0 °C and a THF solution of 3,3-dimethyl-4-pentenal (5.8 g, 52.6 mmoles in 10 mL of THF) was slowly added to the reaction mixture. The cooling bath was removed and the reaction mixture stirred at room temperature for another 3 h. Next, the reaction was quenched by the addition of H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and rotaevaporated in vacuum to give a brown oil, which was distilled under reduced pressure (110-116 °C, 30 Torr) to provide a faint yellow oil (7.6 g, 75% yield) corresponding to furanmethanol **7**. This material was shown to be homogeneous by TLC.

Spectroscopic data for **7**

IR (film): ν = 3390, 2960, 1640, 1570, 1390, 1370 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.06 (d, J = 2.6 Hz, 1 H), 5.91 (dd, J = 18.0, 10.7 Hz, 1H), 5.87 (d, J = 2.6 Hz, 1H), 5.0 (dd, J = 18.0, 1.1 Hz, 1H), 4.98 (dd, J = 10.7, 1.1 Hz, 1H), 4.71 (m, 1H), 2.27 (s, 3H), 2.0 (bs, 1H), 1.88 (m, 2H), 1.1 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, DEPT): δ = 147.9 (CH), 110.8 (CH_2), 106.1 (CH), 105.7 (CH), 65.2 (CH), 47.2 (CH_2), 27.7 (CH_3), 26.0 (CH_3), 13.3 (CH_3).

MS (70 eV): m/z (%) = 194 (10), 176 (13), 161 (20), 124 (82), 111(100), 55 (40).

Typical procedure for the deoxygenation of furanmethanols (preparation of ***10****)*

To a solution of furanmethanol 5 (467 mg, 3.0 mmoles) in 1,2-dichloroethane (15 mL) was added, ZnI_2 (1.45 g, 4.56 mmoles) and $NaCNBH_3$ (1.42 g, 22.6 mmoles). The resulting mixture was then stirred at room temperature for 15 min, when TLC indicated complete consumption of starting material. The reaction mixture was filtered through a short Celite column (7 g) using hexane as eluent (~ 50 mL). The collected fractions were combined and rotaevaporated to afford a pale-yellow liquid (335 mg, 80% yield) corresponding to 2-methyl-5-isobutyl-furan **10**. This material was shown to be homogeneous by TLC and further purification was not necessary.

Spectroscopic data for ***10***

IR (film): ν = 2945, 1560, 1465, 1385, 1365 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.85 (d, J = 3.0 Hz, 1 H), 5.75 (d, J = 3.0 Hz, 1H), 2.25 (s, 3H), 2.65-1.80 (m, 3H), 0.95 (d, J = 7.0 Hz, 6H).

Selected spectroscopic data

13: IR (film): ν = 2950, 1617, 1570, 1375, 1360, 1215 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 5.85 (m, 3 H), 4.95 (m, 2 H), 2.5 (m, 2 H), 1.0 (s, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 154.8, 149.8, 147.6, 110.7, 105.6, 104.6, 40.4, 36.3, 26.4, 23.4 and 13.3.

MS (70 eV): m/z (%) = 178 ($M^{+\bullet}$, 16), 109 (26), 108 (90), 95 (100).

16: IR (film): ν = 3400, 2960, 2860, 1500, 1460, 1160, 1020, 870 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): = 7.35 (m, 2 H), 6.35 (d, 1 H), 4.55 (t, J = 7.1 Hz, 1 H), 2.80 (br s, 1 H), 1.65 (m, 2 H), 1.30 (m, 4 H), 0.88 (t, J = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 143.7, 139.5, 129.8, 109.1, 67.4, 38.1, 28.3, 23.1 and 14.5.

MS (70 eV): m/z (%) = 156 ($M^{+\bullet}$, 16), 97 (100), 84 (10), 69 (27).

17: IR (film): ν = 2950, 2920, 2845, 1500, 1160, 1030, 870 cm^{-1}.

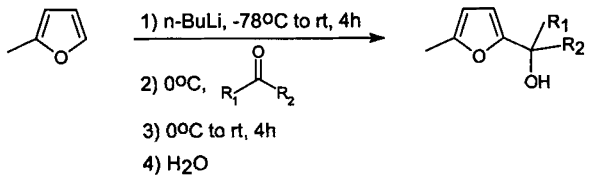
^1H NMR ($CDCl_3$, 200 MHz): δ = 7.38 (br s, 1 H), 7.20 (br s, 1 H), 6.28 (br s, 1 H), 2.42 (t, J = 7.2 Hz, 2 H), 1.70-1.48 (m, 2 H), 1.46-1.25 (m, 4 H), 0.90 (t, J = 7.0 Hz, 3 H).

MS (70 eV): m/z (%) = 138 ($M^{+\bullet}$, 2), 95 (15), 82 (100), 81 (60), 77 (4), 67 (10), 53 (29).

Results

The furanmethanols **4**, **5**, **6**, **7**, **8** and **9** were prepared by slight modifications of the standard procedures described

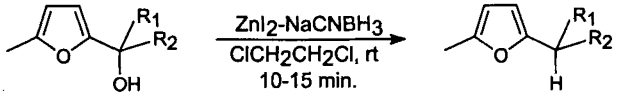
in the literature[12], i.e., the 5-methyl-2-furanyllithium was generated *in situ* from 2-methylfuran and n-butyllithium at low temperature, and condensed with an aldehyde or a ketone to provide the furanmethanol in good yield after purification, as indicated in Scheme 1.



4; R_1= H, R_2 = i-C_3H_7 (74%)
5; R_1= H, R_2 = n-C_3H_7 (80%)
6; R_1= H, R_2 = $C(CH_3)_2CH_2CHCH_2$ (70%)
7; R_1= H, R_2 = $CH_2C(CH_3)_2CHCH_2$ (75%)
8; R_1= C_2H_5, R_2 = C_5H_{11}(76%)
9; R_1= CH_3, R_2 = C_6H_{13} (78%)

Scheme 1.

Each of the above furanmethanols **4-9**[13] were then submitted to deoxygenation conditions using ZnI_2-$NaCNBH_3$ in 1,2-dichloroethane to give the corresponding alkylfurans **10-15** in good yields, regardless of structural variations, as shown in Scheme 2. The experiments involving alkenylfuran compounds **12** and **13**, which have a terminal double bond, were important to demonstrate the compatibility between the deoxygenation conditions and the presence of a double bond. It is also worth mentioning that contrary to the deoxygenation of tertiary alcohols described by Lau under similar conditions[11], deoxygenation of furanmethanols is a very fast reaction, with total consumption of starting material occurring in less than ten min at room temperature. Reaction mixtures are very clean, and normally a pure product is obtained after flash chromatography.



4 - 9

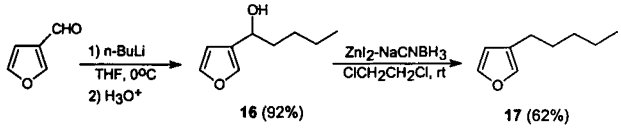
10; R_1= H, R_2 = i-C_3H_7 (80%)
11; R_1= H, R_2 = n-C_3H_7 (92%)
12; R_1= H, R_2 = $C(CH_3)_2CH_2CHCH_2$ (88%)
13; R_1= H, R_2 = $CH_2C(CH_3)_2CHCH_2$ (80%)
14; R_1= C_2H_5, R_2 = C_5H_{11}(76%)
15; R_1= CH_3, R_2 = C_6H_{13} (89%)

Scheme 2.

The mechanism for deoxygenation is not clear yet, although a single electron transfer (SET) mechanism is suggested for reactions occurring under the conditions described above[11]. A strong evidence for an operating SET mechanism is the presence of dimers, however in no instance were dimers observed during our work. Since our main objectives were on the synthetic utility of the process no experiments concerning the mechanistic aspects of this reaction were designed or pursued.

It is known from the literature that 3-furanmethanols show some differences in reactivity when compared to 2-furanmethanols[14]. Thus, they may not necessarily follow the same reaction path to provide the expected 3-alkylfurans. For this reason, we decided to carry out the deoxygenation of a 3-alkylfuranmethanol to investigate the generality of the process, which would be interesting from the synthetic point of view.

To test this point, 3-butyl furanmethanol **16** was prepared by adding n-butyllithium to 3-furaldehyde in THF in 92% isolated yield and then submitted to deoxygenation. Deoxygenation under the standard conditions described above provided the corresponding 3-n-pentyl furan **17** in a reasonable isolated yield of 62% (Scheme 3). This result clearly demonstrated the generality of the deoxygenation process, indicating that it is equally applicable to either 2- or 3-alkylfuranmethanols.



Scheme 3.

Despite the mildness of the deoxygenation process, it requires an excess of the Lewis acid ZnI_2 (usually 50% excess) and a large excess of the reducing agent $NaCNBH_3$ (6-7 fold excess) to drive the reaction to completion at a reasonable rate. Attempts to use stoichiometric amounts of ZnI_2 and $NaCNBH_3$ resulted in incomplete deoxygenation even after an extended period of 24 h.

Conclusion

The deoxygenation of 2- or 3-furanmethanol derivatives employing the ZnI_2-$NaCNBH_3$ protocol is a good alternative to the traditional methodologies described in the literature. The process is a general one and it is also compatible with the presence of easily reduced functional groups, such as double bonds and alkylfurans. The reaction is practical and very simple to carry out, and the yields of the corresponding alkylfurans are usually very good.

Acknowledgments

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13. All new products were fully characterized by spectroscopic methods (^1H and ^{13}C NMR, IR, and mass spectrometry) as homogeneous materials (TLC). The aldehydes and ketones used in this work are commercially available compounds, except the aldehydes 3,3-dimethyl-4-pentenal and 2,2-dimethyl-4-pentenal. 3,3-Dimethyl-4-pentenal was prepared in 48% yield in a single step (allyl vinyl ether, dimethylallyl alcohol, mercuric acetate (cat.), 110 °C, 72 h, sealed tube; followed by distillation (135-140 °C) of the crude mixture). The literature reports a two-step procedure for the preparation of this compound in 50% overall yield [P. Cresson, *Bull. Soc. Chim.* 2618 (1964), and W.H. Watanabe and L.E. Colon, *J. Am. Chem. Soc.* **79**, 2828 (1957)]. 2,2-dimethyl-4-pentenal was prepared according to literature [P.D. Magnus and M.S. Nobbs, *Synth. Commun.* **10**, 273 (1980)].
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