Tetrahedron Letters 49 (2008) 6234–6236

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Selective lithiation of bis(furan-2-yl)methane: an efficient protocol for novel *meso*-functionalised synthons

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ARTICLE INFO

Article history:
Received 18 June 2008
Revised 7 August 2008
Accepted 11 August 2008
Available online 14 August 2008

Dedicated to Professor Harjit Singh on the occasion of his 70th birthday

Keywords:
Lithiation
Bis(furan-2-yl)methane
Carbanion
Regioselectivity
meso-Functionalisation

ABSTRACT

Bis(furan-2-yl)methane can be lithiated at the inter-ring carbon atom (*meso*-position) to give carbanions which react with a variety of electrophiles to yield *meso*-elaborated derivatives in high yield and regioselectivity. This constitutes the first general approach to the title compounds.

1. Introduction

Functional elaboration of the *meso*-position of bis(heterocyclyl)methanes poses a challenge in view of non-availability of methods for obtaining potentially useful *meso*-elaborated derivatives.[1] *meso*-Elaboration of bis(furan-2-yl)methane **1** has not been reported, and the available routes for the synthesis of *meso*-substituted **1** generally rely on the acid-catalysed condensation of furan with functionalised aldehydes[2–4] or furfuryl alcohol,[4] which in addition to the limitation of their availability, often result in lower yields of the desired compounds. Further, the separation of **1** from the complex product mixture is often tedious which is dominated by the oligomers encompassing up to six furan units.[2,4] Alternatively, condensation of (2-furyl)lithium[5] with furfuraldehyde, followed by $NaBH_4$ reduction also furnishes **1** ($R^1 = R^2 = H$).[6] Indeed, a general route to obtain a number of *meso*-elaborated derivatives **1** has been elusive. *Meso*-elaboration of **1** is relevant in the context of natural and unnatural porphyrinoids[7,8] using biomimetic routes, which has led to the synthesis of fundamental porphyrin structural variants, such as dicationic tetraoxaporphyrins[8] as well as other categories of macrocycles such as calix[n]furans.[6] Compounds **1** are also useful as flavouring agents and find industrial application,[9] with some derivatives exhibiting interesting biological effects.[10] Recently, these were found to be good substrates for cycloaddition reactions with oxyallyl cations.[11]

Lithiation of five-membered heterocycles and their derivatives is well known.[12,13] Depending upon the reaction conditions and the nature of the electrophiles, incorporation of substituents occurs at a ring or benzylic position or in particular at *meso*-positions of bis(azol-1-yl)methanes. Recently, in case of bis(pyrrole-2-yl)methanes, we reported[14] exclusive substitution of the *meso*-position. We now report the metallation of bis(furan-2-yl)methane **1** ($R^1 = R^2 = H$) with a lithium base, with selective deprotonation of a *meso*-hydrogen, generating a carbanion.

2. Results and discussion

The *meso*-unsubstituted **1** was synthesised through condensation of furan with formaldehyde in an acid-catalysed reaction, following conditions of a reported protocol.[2] We initially examined the metallation of **1** with 1.0–1.2 equiv of *n*-BuLi (−78 °C to 0 °C) in anhydrous THF or diethyl ether and subsequent quenching with 1.0–2.0 equiv of benzaldehyde. Unreacted **1** (50–60%) along with polymeric material was obtained after quenching the reaction mixture with a saturated solution of ammonium chloride. Even the use of near equimolar or excess quantities of the high solvating TMEDA in combination with *n*-BuLi (−78 °C to 0 °C) did not improve the process. Treatment of **1** with *n*-BuLi (1.2 equiv) in THF in the presence of excess (1.5 equiv) of diisopropylamine (0 °C), which

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doi:10.1016/j.tetlet.2008.08.040

allowed successful metallation of the central methyl carbon in tris(2-thienyl)methane,[15] failed to metallate the *meso*-carbon of **1**. Even LDA (1.2 equiv) showed no reaction with **1**. To determine the optimal conditions for metallation at the *meso*-position, we sought to employ THF–DMSO as solvent with the hope of generating a more basic methylsulfinylmethyl (dimsyl) anion,[16] which being 'soft' should effect metallation of the relatively 'soft' *meso*-carbon of **1** as compared to the comparatively 'hard' C-5 position, as previous literature results suggest. Additionally, a comparison of the pK_a values of carbon acids: diphenylmethane (pK_a = 32.2), 2-benzylfuran (pK_a = 30.2) suggested that the *meso*-methylene of **1** should be more acidic (pK_a < 30.2) than C-5 position (pK_a of furan = 35).[17,18] Thus, **1** was expected to be metallated at the more acidic and 'soft' *meso*-position by the 'soft' dimsyl anion, generated in situ by the reaction of *n*-BuLi and DMSO (pK_a = 35), with the excess DMSO assisting in dispersing anion aggregates.[19] Moreover, the *meso*-position in **1** may draw activation for deprotonation as depicted in Figure 1. On the other hand, this type of activation shall impede the deprotonation and subsequent substitution of the furan (C-5) position, imparting regioselectivity to the process in favour of *meso*-substitution. The failure of the non-coordinative LDA to deprotonate either the *meso*- or C-5 positions further supports this hypothesis.

The following examples demonstrate the successful and occasionally nearly quantitative trapping of the *meso*-anionic species with a variety of electrophiles (Table 1).

Typically, treatment of **1** (Scheme 1) with 1.2 equiv of freshly prepared *n*-BuLi (2.1 N in hexane) in anhydrous THF/DMSO (7:3, v/v) solution at 0 °C (15 min), under a blanket of dry nitrogen gas, followed by stirring at ambient temperature for 15 min furnishes a turbid reddish brown anion solution. Addition of 1.5 equiv of benzaldehyde dissolved in THF (10 ml) at 0 °C, followed by stirring and monitoring the progress of the reaction (TLC), and quenching by saturated NH_4Cl solution furnished the *meso*-substituted product **3a** in 72% yield, after chromatographic purification.

The synthesis of various *meso*-substituted bis(furan-2-yl)methanes **3** is summarised in Table 1. The reactions proceeded smoothly with a range of electrophiles such as aldehydes (benzaldehyde, 4-chlorobenzaldehyde, 3,4-dimethoxybenzaldehyde and β-naphthaldehyde), ketones (acetone, acetophenone and 2-acetylthiophene), alkyl halides (ethyl bromide, *n*-propyl bromide, *n*-butyl bromide and benzyl bromide), isocyanates and isothiocyanates to furnish the corresponding *meso*-elaborated products. In the reactions of alkyl halides the isolation of the corresponding products **3h–j** (Table 1) was tedious owing to their low polarity and matching R_f (TLC) with the starting **1** and the isolated products were often accompanied by the starting **1**, as revealed from the ^{1}H NMR spectra of the 'purified' compounds obtained after column chromatography. In none of these reactions was the ring (C-5)-substituted product detected by ^{1}H NMR inspection of the crude reaction products. Only when the *meso*-position of **1** was blocked as dimethyl derivative **2,** does the lithiation-substitution occur at the C-5 position. Thus, deprotonation of **2** using *n*-BuLi (1.2 equiv) at −78 °C in anhydrous THF furnished a red coloured carbanion solution, which upon trapping with benzaldehyde and subsequent reaction with iodomethane furnished C-5 substituted ether **4a** in 68% isolated yield. Likewise, reaction of anion of **2** with 3,4-dimethoxybenzaldehyde followed by protection with iodomethane furnished corresponding product **4b** in 70% yield.

Table 1
Synthesis of *meso*-substituted bis(furan-2-yl)methane **3**/**4**

Entry	Substrate **1/2**	Electrophile	Product **3**	Yield[a] (%)
1	**1**	PhCHO	**3a**	72
2	**1**	4-Cl-C_6H_4CHO	**3b**	65
3	**1**	3,4-$(MeO)_2$-C_6H_3CHO	**3c**	70
4	**1**	β-$C_{10}H_7$CHO	**3d**	65
5	**1**	MeCOMe	**3e**	72
6	**1**	PhCOMe	**3f**	45
7	**1**	2-Acetylthiophene	**3g**	40
8	**1**	EtBr	**3h**	65[b]
9	**1**	*n*-PrBr	**3i**	56[b]
10	**1**	*n*-BuBr	**3j**	83[b]
11	**1**	$PhCH_2Br$	**3k**	69
12	**1**	PhNCO	**3l**	51
13	**1**	PhNCS	**3m**	30
14	**2**	PhCHO	**4a**	68
15	**2**	3,4-$(MeO)_2$-C_6H_3CHO	**4b**	70

[a] Isolated purified (column chromatography: silica gel 60–120 mesh, ethyl acetate/hexane as eluents) yields.
[b] Based on ^{1}H NMR (ureacted **1** in **3h**:35%; **3i**:44%; **3j**:17%).

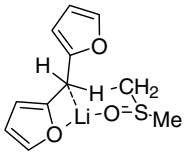
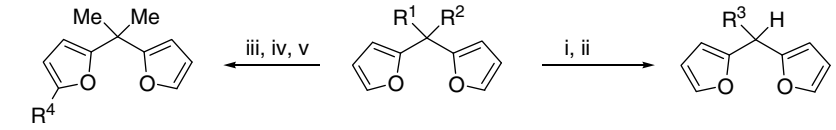


Figure 1. Proposed transition state in deprotonation of the *meso*-position of **1**.

In summary, we have shown that the *meso*-position of the bis-(furan-2-yl)methane **1** can be elaborated using a metallation-substitution sequence. The methodology is simple and furnishes the products in good to high yields. The *meso*-elaboration of **1** has not been reported earlier,[20] so our approach provides a route to



4a: R^4 = C(OMe)HPh
4b: R^4 = C(OMe)H-3,4-$(MeO)_2$-C_6H_3

1 : $R^1 = R^2$ = H
2 : $R^1 = R^2$ = Me

3a: R^3 = PhCH(OH); **3b**: R^3 = 4-ClC_6H_4CH(OH)
3c: R^3 = 3,4-$(MeO)_2$-C_6H_3CH(OH);
3d: R^3 = β-$C_{10}H_7$CH(OH);
3e: R^3 = MeCMe(OH); **3f**: R^3 = PhCMe(OH);
3g: R^3 = (2-thienyl)CMe(OH); **3h**: R^3 = Et;
3i: R^3 = *n*-Pr; **3j**: R^3 = *n*-Bu; **3k**: R^3 = CH_2Ph;
3l: R^3 = CONHPh; **3m**: R^3 = CSNHPh;

Scheme 1. Synthesis of *meso*-substituted bis(furan-2-yl)methanes. Reagents and conditions: (i) *n*-BuLi (1.2 equiv), THF/DMSO (7:3 v/v), 0 °C; (ii) electrophile (1.5 equiv), NH_4Cl quenching; (iii) *n*-BuLi (1.2 equiv), THF, −78 °C; (iv) electrophile (1.5 equiv) (v) KOBu^t (1.2 equiv), MeI (1.5 equiv), NH_4Cl quenching.

otherwise inaccessible *meso*-elaborated derivatives **3** with the possibility of further transformations at the newly incorporated *meso*-substituent.

3. Selected data

Compound **3a**: Yellow oil. R_f: 0.27 (10% ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 1H, OH, exchanged with D_2O), 4.41 (d, 1H, J = 7.2 Hz), 5.28 (d, 1H, J = 7.2 Hz), 6.11 (m, 1H), 6.22 (m, 1H), 6.29 (m, 1H), 6.35 (m, 1H), 7.24 (m, 5H), 7.22 (m, 1H), 7.40 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.76, 107.72, 108.21, 110.26, 110.45, 126.11, 127.70, 128.04, 141.58, 142.01, 151.82 ppm. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found C, 75.32; H, 5.24. MS: m/z, 276.8 (M^++23).

Compound **3e**: Viscous oil. R_f: 0.36 (10% ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 6H), 1.61 (s, 1H, OH, exchanged with D_2O), 4.19 (s, 1H), 6.26 (m, 2H), 6.34 (m, 2H), 7.38 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.66, 50.43, 108.23, 110.33, 141.60, 152.60 ppm. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found C, 69.62; H, 6.64. MS: m/z, 228.8 (M^++23).

Compound **3l**: White solid. R_f: 0.25 (15% ethyl acetate/hexane). Mp 78–80 °C (DCM/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 6.39 (m, 4H), 7.11 (m, 1H), 7.27 (m, 1H), 7.30 (m, 3H), 7.48 (m, 2H), 7.53 (s, 1H, NH, exchanged with D_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.43, 108.93, 110.87, 119.80, 124.65, 128.97, 142.86, 149.23 ppm. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found C, 71.65; H, 4.74; N, 5.35. MS: m/z, 289.8 (M^++23).

Compound **4a**: Yellow viscous oil. R_f: 0.70 (10% ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 6H), 3.55 (s, 3H), 5.21 (s, 1H), 5.89 (m, 1H), 5.96–5.97 (m, 2H), 6.24–6.25 (m, 2H), 7.22–7.38 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.29, 26.40, 37.52, 56.90, 78.90, 104.16, 104.74, 109.13, 109.96, 126.75, 127.24, 127.87, 128.32, 139.34, 141.13, 153.03, 159.97, 160.19 ppm. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found C, 76.85; H, 6.90. MS: m/z, 319.2 (M^++23).

Acknowledgements

We are thankful to CSIR, New Delhi, for the project 01(1960)/04/EMR-II and a senior research fellowship (F. No. 9/254(160)/2005-EMR-1) to A.S.

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