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A CONVENIENT METHOD FOR THE PREPARATION OF SUBSTITUTED NAPHTHO[2,3-b]-1,4-DIOXIN BY THE DIELS-ALDER REACTION.

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Abstract. The naphtho-fused systems **3** and **4** were synthesized from the hydroxy-acetal **1** through deacetylation, formation of unstable diene **2** and Diels-Alder cycloaddition with the appropriate dienophile in acidic media.

The generation of reactive dienes (quinodimethanes and their cyclic analogues isobenzofurans) from aromatic systems and their subsequent Diels-Alder intermolecular or intramolecular cycloadditions, has been shown to be a interesting method for the rapid preparation of a variety of polycyclic systems.[1-4]

The Diels-Alder reactivity of these substances with benzyne, 3,4-pyridyne, dimethyl acetylenedicarboxylate and others dienophiles has been investigated in detail.[5-7] The isobenzofurans with a single substituent do not seem to be stable enough for routine isolation.[8]

Here, we wish to report a fast and efficient method for the synthesis of the naphtho-fused systems from ortho-disubstituted benzenoid analogues in only one step. The route is depicted in scheme 1.

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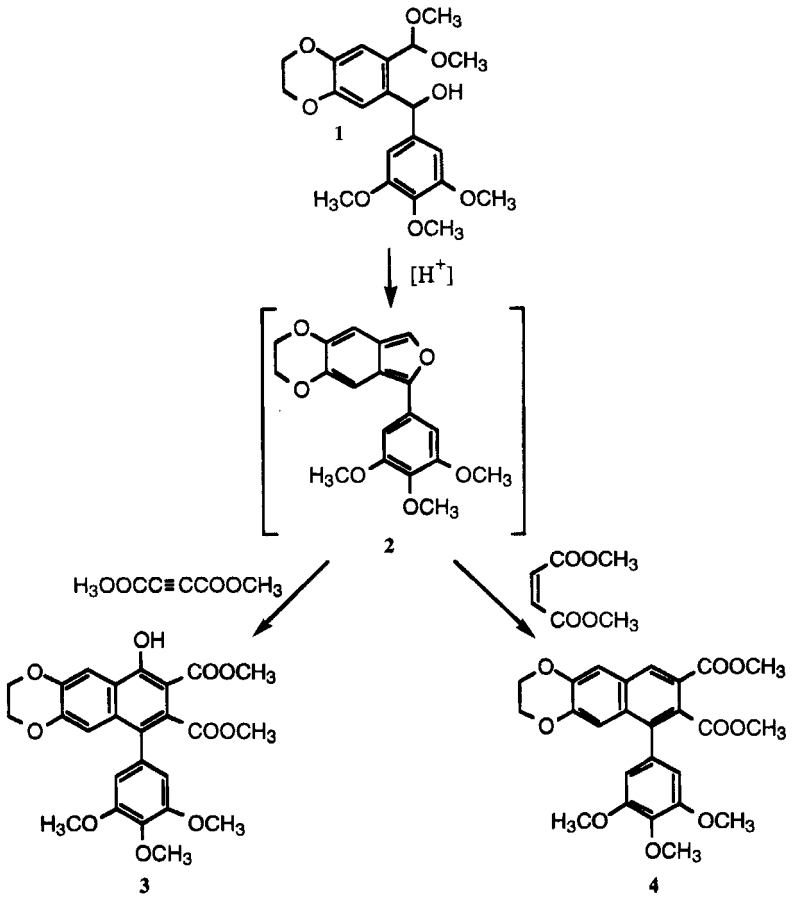


Scheme 1

The hydroxy-acetal **1** was converted to the naphtho[2,3-b]dioxin system (**3** or **4**) by treatment with *p*-toluenesulfonic acid or acetic acid and, the monosubstituted isobenzofuran formed *in situ* must be intercepted by a suitable dienophile. Attempts to isolate the oxabicyclo adducts with triply bonded dienophiles (DMAD) or with olefinic dienophiles (dimethyl maleate) were not successful due to fast aromatization.

Table 1. Transformation of **1** to **3** in acidic media.

Entry	Dienophile	Solvent	Acid	Temp(°C)	Time	Yield(%)[a]
1	DMAD	Toluene	*p*-TSOH	100°C	1h	77
2	DMAD	Acetic A.	Acetic A.	80°C	7h	61
3	DMAD	DMAD	*p*-TSOH	r.t.	1h 30m.	34[b]
4	DMAD	Ether	*p*-TSOH	Reflux	7h	26
5	DMAD	Acetic A.	Acetic A.	80°C	30 m.	30
6	DMAD	Acetic A.	Acetic A.	r.t.	1h 30m.	[c]
7	DMAD	Benzene	*p*-TSOH	110°C	1h	26
8	DMAD	Toluene	Acetic A.	Reflux	3h	9
9	DMM	Toluene	*p*-TSOH	100°C	5h	23

[a] Yields refered to pure isolated products. [b] Under hydrogen with Pd-C. [c] The starting material was recovered. DMAD=Dimethyl acetylenedicarboxylate. DMM=Dimethyl maleate.

The aromatization of these heterocyclic systems, may have happened because of the acidic media of the reaction mixture, favoring the cleavage of the ether and tautomerization (**3**) or cleavage and dehydration (**4**).

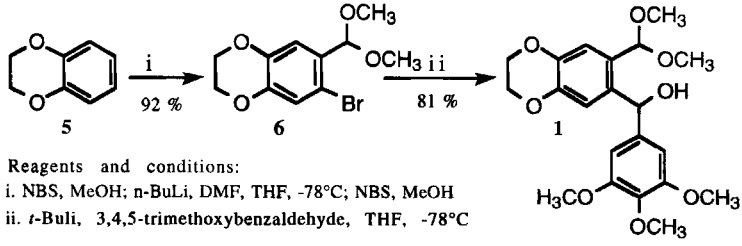
The methods reported in literature for the synthesis of analogues compounds are less satisfactory.[9-11]

We now report all conditions studied for the formation of isobenzofuran, cycloaddition and aromatization in table 1. The initial attempts at room temperature with (entry 6) or without (entry 3) solvent give the desired compoud **3** in low yield. The reducing conditions are unfavored for this reaction, thus the conversion of **1** to **3** with *p*-toluenesulfonic acid at room temperature under a hydrogenation catalyst give the aromatic compound in 34 % yield (entry 3) and others hydrogenated products. When ether were used as a solvent

at reflux after 7 h the product **3** was obtained in only 26% (entry 4). Good yields could be obtained (comparing entry 2 with 8) when a large excess of acetic acid was used and long time of reaction (comparing entry 2 with 5) was employed. The best conditions were obtained when *p*-toluenesulfonic acid in catalyst amount and toluene as solvent were used at 100°C for 1 h (entry 1).

The hydroxy-acetals as **1** are the versatile building blocks for the synthesis of many compounds in organic chemistry[1,2]. In this work, **1** was synthesized conveniently from the commercial 2,3-dihydro-1,4-benzodioxin (Scheme 2) by selective bromination followed of formylation. In the following bromination and acetalation step with N.B.S. in methanol give the bromo-acetal **6** in quantitative yield. In this case, the succinimide formed *in situ* lead to formation of acetal function.

Treatment of **6** with *t*-butyllithium in THF at -78°C and condensation with the 3,4,5-trimethoxybenzaldehyde give the acetal **1** in reasonable yield.



Scheme 2

It is noteworthy that the one-pot conversion involves several unstable intermediates due to the acidic environment, but of great interest in organic synthesis.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp apparatus and are uncorrected. The NMR H^1 and C^{13} spectra were recorded on Varian Gemini 200 or 300 spectrometer with tetramethylsylane as internal standard and using $CDCl_3$ as the solvent; chemical shifts are in δ (ppm).The mass spectra were recorded on a Hewlett-Packard 5988-A Microanalyses were determined on a Carlo ERBA-1106 analyser; analytical values obtained were within ±0,4 % of the calculated values. All reagents were of commercial quality or were purified before use.Organic solvents were purified by standard procedures. THF are distilled under an inert atmosphere from purple solutions of sodium-benzophenone.

7-Dimethoxymethyl-6-(3,4,5-trimethoxyphenyl-1-hydroxy methyl)-2,3-dihydro-1,4-benzodioxin (**1**).

Compound **6** (2,032 g, 7,02 mmol) was dissolved in dry THF (10 ml) under argon and the solution then cooled to -78°C. A solution (1,7 M) of *t*-butyllithium in hexane (8,26 ml, 14,05 mmol) was then added and the mixture was stired for 2 h. A solution of 3,4,5-trimethoxybenzaldehyde (2,75 g, 14,05 mmol) in dry THF (10 ml) was added with stirring over 20 min. and the stirring continued untill to reach an room temperature. Solution of NH_4Cl (10 ml) was added and the organic layer was separated. The water layer was extracted with ether (3x25 ml). The combined organic solutions were dried (Na_2SO_4) and evaporated to give the crude product. The product was purified by column chromatography (silica gel, Hexane/EtOAc), giving 2,31 g of **1** (81% yield).

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3,32 (s, CH_3); 3,39 (s, CH_3); 3,84 (s, CH_3); 3,86 (s,CH_3); 4,24 (s, 4H,

CH_2-O); 5,44 (s, CH-O); 6,06 (ba, 1H, OH); 6,66 (s 2H, Ar); 6,70 (s, 1H, Ar); 7,10 (s, 1H, Ar).

^{13}C NMR (50,4MHz, $CDCl_3$) δ (ppm): 53,1 (CH_3); 53,7 (CH_3); 56,0 (CH_3); 61,0 (CH_3); 64,3 (CH_2, CH_2-O); 71,4 (CH, CH-O); 102,1 (CH, $CH(OCH_3)_2$); 103,6 (CH, CH Arom.); 116,6 (CH, CH Arom); 117,9 (CH, CH Arom); 128,9 (C); 135,7 (C); 138,9 (C); 141,5 (C); 142,9 (C); 152,5 (C).

6-Hydroxy-7,8-bis(methoxycarbonyl)-9-(3,4,5-trimethoxyphenyl)-2,3-dihydronaphtho[2,3-b]-1,4-dioxin. (**3**).

Method A:

0,16 ml (0,13 mmol) of DMAD and *p*-toluenesulfonic acid (15 mg) were added to a solution of 175 mg (0,043 mmol) of the acetal **1** in dry toluene (5 ml). After the solution stirred for 1h at 100°C, the toluene was removed in vacuo. The crude was purified by chromatography on silica gel (Hexane/EtOAc 7/3) giving 162 mg of **3** as a white solid (77% yield). m.p. 227-228°C.

The compound **3** has also been prepared from 4 g. of **1** under the same conditions described above with approximate yield. The difficulty is in the preparation of the starting material **1** from **5** in four steps.

Method B:

0,5 ml (4,6 mmol) of DMAD was added dropwise to a stirred solution of 500 mg (1,23 mmol) of the acetal **1** in acetic acid (4 ml). After stirring the reaction mixture 7h at 80°C the temperature was allowed to rise slowly to room temperature. The acetic acid was removed, and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated, and the mixture was purified by chromatography on silica gel (Hexane/EtOAc 7/3),

giving 369 mg of **3** as a white solid m.p. 227-228°C. (61% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3,58 (s, 3H, CH_3); 3,88 (s, 6H, CH_3); 3,92 (s, 6H, CH_3); 4,34 (s, 4H, CH_2-O); 6,51 (s 2H, $H_{2'}$ and $H_{6'}$); 6,95 (s, 1H, H_5); 7,90 (s, 1H, H_{10}); 12,3 (s, 1H, OH).

^{13}C NMR (50,4 MHz, $CDCl_3$) δ (ppm): 52,5 (CH_3); 53,3 (CH_3); 56,6 (CH_3, $2CH_3$); 61,5 (CH_3); 64,8 and 65,1 (CH_2, CH_2-O); 101,5 (C); 108,3 (CH, $C_{2'}$ and $C_{6'}$) 110,8 (CH, C_{10}); 113,2 (CH, C_5); 120,9 (C); 128,4 and 128,6 (C); 132,4 and 132,8 (C); 137,8 (C); 144,9; 147,7; 153,2; 160,7 (C); 169,8 and 170,9 (C, CO).

m/z:484

6-(3,4,5-trimethoxyphenyl)-7,8-bis(methoxycarbonyl)-2,3-dihydronaphtho[2,3-b]-1,4-dioxin. (**4**).

To a solution of **1** (250 mg, 0,621 mmol) in dry toluene (4 ml) are added dimethyl maleate (0,466 ml, 3,72 mmol) and acetic acid (0,5 ml). The mixture was stirred at 100°C for 5 h. K_2CO_3 solution was added, filtered and the solvent removed in vacuo. The residue was purified by column chromatography (Hexane/EtOAc) on silica gel, giving 64 mg (23% yield) of the compound **4** as a white solid m.p. 175-176°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3,66 (s, 3H, CH_3); 3,82 (s, 3H, CH_3); 3,86 (s, 3H, CH_3); 3,93 (s, CH_3, $2CH_3$); 4,35 (s, 4H, CH_2-O); 6,56 (s, 2H, $H_{2'}$, $H_{6'}$); 7,07 (s, 1H, H_5); 7,39 (s, 1H, H_{10}); 8,42 (s, 1H, H_9).

^{13}C NMR (50,4 MHz, $CDCl_3$) δ (ppm): 52,1 (CH_3); 52,4 (CH_3); 56,0 ($2CH_3$); 60,8 (CH_3); 64,2 and 64,3 (CH_2, CH_2-O); 107,3 (CH, $C_{2'}$,$C_{6'}$); 112,3

(CH); 114,4 (CH); 122,6 (C); 128,4 (C); 129,3 (C); 130,0 (C); 130,4 (C); 132,2 (C); 136,9 (C); 137,3 (C); 145,1 (C); 146,4 (C); 152,7 (C); 166,3 and 169,5 (C, CO).

m/z: 468

7-Bromo-6-(dimethoxymethyl)-2,3-dihydro-1,4-benzodioxin. (**6**)

To a solution of the 6-formil-2,3-dihydro-1,4-benzodioxin (900 mg, 5,48 mmol) in methanol (25 ml) cooled in an ice-salt bath, is added dropwise the NBS (985 mg, 5,53 mmol). The mixture are stirred for 30 min. at this temperature and then was allowed to room temperature and the stirring continued for a further 6 h.
The reaction was quenched by addition of aqueous 2N NaOH untill pH= 8. The methanol was removed in vacuo, water was added, and the organic material extracted with CH_2Cl_2 (3x25 ml). The extracts were dried (Na_2SO_4), and after removal of the solvent, the residue obtained 1,46 g (92% yield) was sufficient pure for use in the next step.

^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3,51 (s, 6H, CH_3-O); 4,23 (s, 4H, CH_2-O-); 5,43 (s, $CH(OCH_3)_2$); 7,06 (s, 1H, Arom); 7,11 (s, 1H, Arom).

^{13}C NMR (50,4 MHz, $CDCl_3$) δ (ppm): 53,7 (CH_3, CH_3-O-); 64,2 (CH_2, CH_2-O-); 64,3 (CH_2, CH_2-O-); 102,5 (CH, CH Arom); 112,9 (C); 116,8 (CH, CH Arom); 120,9 (CH, CH Arom); 129,7 (C); 142,7 (C); 144,2 (C).

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