A concise route to functionalized benzofurans directly from gem-dibromoalkenes and phenols

Maddali L. N. Rao,* and Priyabrata Dasgupta

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India
maddali@iitk.ac.in

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1. Preparation of (2,2-dibromovinyl)benzene:

To a round bottom flask, benzaldehyde (1 g, 9.42 mmol, 1 equiv) in 30 mL DCM and cooled at 0 °C under nitrogen atmosphere. Then, CBr₄ (6.2 g, 18.84 mmol, 2 equiv) and PPh₃ (9.9 g, 37.68 mmol, 4 equiv) were added successively in portions and stirred for 1 h under N₂. After that, the reaction mixture was quenched with hexane, filtered and the eluted part was concentrated for further purification by column chromatography (100-200 mesh silica-gel) using hexane as eluent. The desired product was obtained as pale yellow liquid (2.3 g, 93%) and is consistent with literature data.


2. Preparation of 1c:

![Chemical structure](image)

An oven-dried Schlenk tube under N₂ atmosphere was charged with 1-(2,2-dibromovinyl)-4-methylbenzene 1a (0.104 g, 0.375 mmol, 1 equiv), p-nitrophenol 1b (0.52 g, 0.375 mmol, 1equiv), Cs₂CO₃ (0.611 g, 1.875 mmol, 5 equiv) and NMP (3 mL) respectively. The reaction mixture was stirred at 110 °C in an oil bath for 8 h under N₂. The mixture was cooled to r.t. and followed by work-up using ethylacetate (50 mL). The organic extract was washed with water (10 mL), brine (10 mL), dried over anhydrous MgSO₄ and concentrated. The crude was purified by silica-gel column chromatography using 2% EtOAc in hexane as eluent. Product 1c was isolated as yellow viscous liquid (0.109 g, 87%). This procedure was also followed for the preparation of intermediate 3c with (E)-(4,4-dibromobuta-1,3-dienyl)benzene and p-cyanophenol.
3. Gram scale reaction (2.26):

![Chemical Reaction Diagram]

An oven-dried 100 mL Schlenk tube equipped with a magnetic pellet under N₂ atmosphere, added 1-(2,2-dibromovinyl)-4-methylbenzene 1a (1 g, 3.62 mmol, 1 equiv), methyl 4-hydroxybenzoate (0.55 g, 3.62 mmol, 1 equiv), Cs₂CO₃ (5.9 g, 18.1 mmol, 5 equiv) and NMP (35 mL) respectively. The reaction mixture was stirred at 110 °C in an oil bath for 8 h under N₂. Then the mixture was cooled to r.t and added Pd(OAc)₂ (0.041 g, 0.181 mmol, 0.05 equiv) under N₂ and continued at 130 °C for 6 h. After cooling to r.t, the reaction mixture was transferred to a round-bottom flask to distill out NMP under reduced pressure. The obtained crude was diluted with ethyl acetate, passed through a column of silica-gel with repeated washings. The combined organic extract was concentrated to lowered volume and washed with water and brine. The ethyl acetate was concentrated and the crude was purified by using silica-gel column chromatography with 1% EtOAc in hexane to obtain 2.26 as a brown solid (0.405 g, 42%).
4. Spectral data of intermediates 4c and 5c:

4c. Pale yellow viscous liquid (0.095 g, 50%, as isomeric mixtures); $R_f = 0.64$ (EtOAc-hexane 1:9). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (d, 0.8H, $J = 8.72$ Hz, Ar-H), 7.28-7.25 (m, 6H, Ar-H), 7.16-7.13 (d, 0.4H, $J = 8.72$ Hz, Ar-H), 7.07-6.99 (m, 7H, Ar-H), 6.62 (m, 1H, Ar-H), 6.57-6.54 (m, 3H, Ar-H), 6.47-6.45 (m, 0.5H, Ar-H), 6.40 (d, 0.6H, $J = 6.4$ Hz, Ar-H), 6.36 (s, 2H, $-\text{CH}_2\text{olefin}$), 6.30 (s, 0.2H, $-\text{CH}_3$), 2.30 (s, 8H, $-\text{CH}_2\text{olefin}$), 2.28 (s, 1H, $-\text{CH}_3$). $^{13}$C (100 MHz, CDCl$_3$): $\delta$ 157.0, 153.3 139.2, 130.6, 130.0, 129.4, 128.8, 125.8, 110.2, 105.2, 94.2, 21.3. IR (film): 3165, 2862, 1543, 1026, 667 cm$^{-1}$. HRMS (EI) calcd for C$_{24}$H$_{20}$Br$_2$O$_2$ [M$^+$] 497.9830; found 497.9839. The intermediate 4c is susceptible for decomposition on standing at room temperature.

5c. Yellow viscous liquid (0.084 g, 38%, as isomeric mixtures); $R_f = 0.20$ (EtOAc-hexane 1:9). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 (d, 0.4H, $J = 9.16$ Hz, Ar-H), 7.30-7.21 (m, 6H, Ar-H), 6.78-6.75 (m, 5H, Ar-H), 6.34 (s, 0.2H, $-\text{CH}_2\text{olefin}$), 6.32 (s, 2H, $-\text{CH}_2\text{olefin}$), 3.82 (s, 3H, $-\text{CO}_2\text{CH}_3$), 3.77 (s, 6H, $-\text{CH}_3$). $^{13}$C (100 MHz, CDCl$_3$): $\delta$ 166.0, 160.4 156.9, 152.7, 132.5, 131.0, 127.3, 125.5, 114.2, 113.7, 112.2, 111.9, 111.4, 109.8, 109.3, 93.6, 93.4, 55.3, 52.3. IR (film): 3165, 2824, 1703, 1643, 1496, 1138, 1057, 733 cm$^{-1}$. HRMS (EI) calcd for C$_{26}$H$_{22}$Br$_2$O$_6$ [M$^+$] 587.9783; found 587.9788.
5. $^1$H, $^{13}$C and HRMS spectra of intermediate 1c:

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 1c

![NMR Spectrum](image)
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 1c
EI (HRMS) spectrum of 1c

[M+] calcd 333.0001
6. $^1$H, $^{13}$C and HRMS spectra of intermediate 3c:

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 3c
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 3c
EI (HRMS) spectrum of 3c

[M⁺] calcd 325.0102
7. $^1$H, $^{13}$C and HRMS spectra of benzofuran products (2.1-3.4):

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.1
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.1
ESI (HRMS) spectrum of 2.1

[MH⁺] calcd 254.0817

S13
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.2

S14
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.2
EI (HRMS) spectrum of 2.2

$[M^+] \text{ calcld } 233.0841$
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.3
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.3
EI (HRMS) spectrum of 2.3

[\text{M}^+] \text{calc} \ 226.0794
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.4
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.4
EI (HRMS) spectrum of 2.4

[M⁺] calcd 242.0498
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.5
\[ ^{13}C \text{NMR (125 MHz, CDCl}_3 \text{) spectrum of 2.5} \]
EI (HRMS) spectrum of 2.5

[Diagram of molecule with labels]
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.6
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.6
EI (HRMS) spectrum of 2.6
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.7
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.7
EI (HRMS) spectrum of 2.7

[Image of the spectrum with annotations: 
- H3C
- O
- C
- CH3

2.7

[M+] calcd 222.1045]
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.8
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.8
EI (HRMS) spectrum of 2.8

[M⁺] calcd 236.1201
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.9
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.9
EI (HRMS) spectrum of 2.9

[M⁺] calcd 236.1201
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.10
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) spectrum of 2.10
EI (HRMS) spectrum of 2.10

[2.10]

$[M^+] \text{ calcd } 208.0888$
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of 2.11
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.11
ESI (HRMS) spectrum of 2.11

[MH$^+$] calc 220.0762
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.12
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.12
EI (HRMS) spectrum of 2.12

$[M^+] \text{ calcd } 228.0342$
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.13
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.13
EI (HRMS) spectrum of 2.13
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.14
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.14
EI (HRMS) spectrum of 2.14

[$\text{[M$^+$]}$] \text{calcd 244.0888}$
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of 2.15
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.15
EI (HRMS) spectrum of \textbf{2.15}

\[ [M^+] \text{ calcd} \ 253.0294 \]
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of **2.16**
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.16
EI (HRMS) spectrum of 2.16

$\text{O}_2\text{N}$

$\text{[M$^+$ calcd 273.0193}$
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.17
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.17
EI (HRMS) spectrum of 2.17

2.17

$[M^+] \text{ calcd } 261.9952$
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of 2.18
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.18
EI (HRMS) spectrum of 2.18

2.18

[M⁺] calcd 295.9562
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.19
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.19
EI (HRMS) spectrum of 2.19

2.19

[M⁺] calcd 256.0655
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.20
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of **2.20**
EI (HRMS) spectrum of 2.20

[M+'] calcd 274.0994
\(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum of 2.21
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.21
EI (HRMS) spectrum of 2.21

[\text{M}^+] \text{ calc} \ 258.0448
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 2.22
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 2.22
EI (HRMS) spectrum of 2.22
\(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum of 2.23
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.23
EI (HRMS) spectrum of 2.23

[\[M^+\]] \text{calcd} 242.0498
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.24
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.24
EI (HRMS) spectrum of 2.24

[M⁺] calcd 242.0498
$^{1}$H NMR (400 MHz, CDCl$_3$) spectrum of 2.25
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.25
EI (HRMS) spectrum of 2.25

$[M^+]$ calcd 253.0739
$\text{H}_2\text{C}_2\text{O}_2\text{C}$

H NMR (400 MHz, CDCl$_3$) spectrum of $\text{2.26}$
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.26
EI (HRMS) spectrum of 2.26

[M⁺] calcd 266.0943
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.27
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.27
EI (HRMS) spectrum of 2.27

$[\text{M}^+]$ calcd 286.0397
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2.28
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 2.28
EI (HRMS) spectrum of 2.28

$[M^+] \text{ calcd } 270.0692$
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of 3.1
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 3.1
EI (HRMS) spectrum of 3.1
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 3.2
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 3.2
EI (HRMS) spectrum of 3.2

[M⁺] calcd 270.1045
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 3.3
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 3.3
EI (HRMS) spectrum of 3.3

[3.3] M⁺ calcd 284.1201
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 3.4
$^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 3.4
EI (HRMS) spectrum of 3.4

[M⁺] calcd 295.0845
8. $^1$H, $^{13}$C and HRMS spectra of intermediates 4c and 5c:

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4c
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 4c
EI (HRMS) spectrum of 4c
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 5c
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 5c
EI (HRMS) spectrum of 5c
9. $^1\text{H}, ^{13}\text{C}$ and HRMS spectra of benzodifurans 4.1 and 5.1:

$^1\text{H}$ NMR (400 MHz, CDCl$_3$) spectrum of 4.1
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 4.1
EI (HRMS) spectrum of 4.1

$[M^+]$ calcd 338.1307
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of 5.1
$^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of 5.1
EI (HRMS) spectrum of 5.1

5.1

\([M^+]\) calcd 428.1260
10. Crystal structure of benzodifuran 4.1:

The single crystal X-ray was recorded in Bruker SMART APEX-II CCD diffractometer. Data was collected at 273 K using graphite-monochromated MoKα radiation (λ = 0.71073 Å). The crystal structure was solved by direct methods and was refined by full matrix least squares on $F^2$ using SHELXL-97 and SHELXTL. All hydrogen atoms were included in idealized positions using a riding model. Anisotropic displacement parameters were used for refining non-hydrogen atoms.

Ref: (a) G. M. Sheldrick, SHELXL-97, Program for Crystal Structure Solution and Refinement; University of Göttingen, Göttingen, Germany, 1997; (b) G. M. Sheldrick, Acta Cryst., 2008, A64, 112.

Crystal data for compound 4.1: C$_{48}$H$_{36}$O$_4$, $M = 676.77$, Monoclinic, $a = 18.012(2)$ Å, $b = 6.5373(8)$ Å, $c = 14.3077(19)$ Å, $α = 90.00°$, $β = 98.302(4)°$, $γ = 90.00°$, $V = 1667.1(4)$ Å$^3$, $T = 273(2)$ K, space group Cc, $Z = 2$, $μ$(MoKα) = 0.085 mm$^{-1}$, 6737 reflections measured, 3191 independent reflections ($R_{int} = 0.0642$). The final $R_f$ values were 0.0978 ($I>2σ(I)$). The final $wR(F^2)$ values were 0.2589 ($I>2σ(I)$). The final $R_f$ values were 0.1541 (all data). The final $wR(F^2)$ values were 0.3025 (all data). The goodness of fit on $F^2$ was 1.065. CCDC number CCDC 1406195.

Fig. X-ray structure of 4.1