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The Synthesis of 3-(2'-Hydroxybutyl) isobenzofuran-1 (3H)-one

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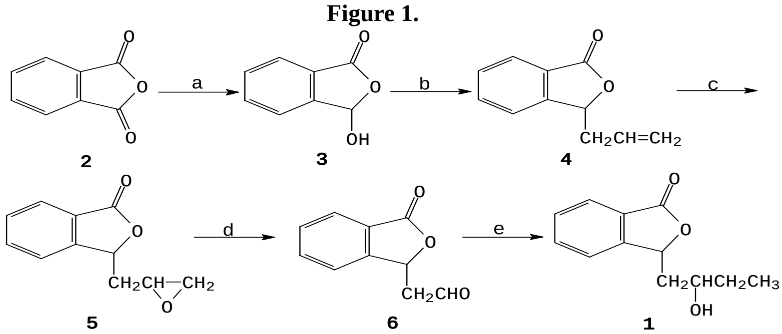
Abstract: The synthesis of 3-(2'-hydroxybutyl) isobenzofuran-1 (3H)-one **1** from phthalic anhydride *via* the intermediate 3-(2'-oxoethyl) isobenzofuran-1 (3H)-one **6** was described.

Keywords: Synthesis, 3-(2'-hydroxybutyl) isobenzofuran-1 (3H)-one.

1 (3H)-Isobenzofurans (phthalides) were reported to exhibit a wide range of biological activities. For example, 3-n-butylphthalide (NBP) exhibits antiasthmatic[1], anticonvulsant[2] activities. Peng and Zhou have studied on the metabolism of NBP in rats[3]. They found that 3-(3'-hydroxybuty l)-isobenzofuran-1 (3H)-one, 3-(2'-hydroxybutyl) isobenzofuran-1 (3H)-one **1** and 3-hydroxy-3-butylisobenzofuran-1 (3H)-one were the main the metabolites of NBP. The research of their pharmacology is helpful to search for the drugs against cerebral ischemia. Now, we report a route to 3-(2'-hydroxybutyl) isobenzofuran-1 (3H)-one **1** (**Figure 1**).

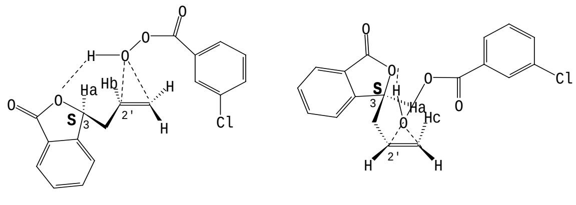
Figure 1.



Reagents and conditions: a: 1) $NaBH_4$/DMF, 0℃; 2) NBS/ $(PhCO_2)_2O$, CCl_4; 3) H_2SO_4/THF/H_2O; b: $BrCH_2CH=CH_2$, Sn, THF, 35℃; c:m-$ClC_6H_4CO_3H$/CH_2Cl_2, 0℃; d:H_5IO_6/H_2O, 45℃; e: 1) $(C_2H_5)_2Zn$/Et_2O, R.T.; 2) NH_4Cl

Many methods of the synthesis of **3** have been reported. We synthesized **3** according to Ref.4. Reaction of **3** with allyl bromide in THF at 35℃in the presence of activated Sn afforded the 3-allylisobenzofuran-1 (3H)-one **4** [5] as a pale yellow oil. Compared with Grignard reaction, this reaction did not require anhydrous conditions and under nitrogen protection and the yield was excellent (95%). **4** was epoxidized with m-chloroperoxyb-enzoic acid (mCPBA) in CH_2Cl_2 to afford 3-(2', 3'-epoxypropyl) isobenzofuran-1 (3H)-one **5** as white powder (melted at 64-66℃) in 90% yield after silica gel chromatography. **5** consists of two diastereoisomers in a ratio of about 3:2 based on ^{1}HNMR. We propose that the intermolecular hydrogen bonding between **4** and mCPBA results in the diastere-ioselectivity of reaction (**Figure 2)**. Molecular models suggest that the hindrance between Ha and Hc is stronger than that between Ha and Hb.

Figure 2.



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Reaction of **5** with periodic acid in water at 45℃afforded 3-(2’-oxoethyl) isobenzo-furan-1 (3H)-one **6** as a yellow oil in 90% yield after silica gel chromatography[7].

We attempted to synthesize **1** *via* reaction of **6** with C_2H_5MgBr in Et_2O at-78℃, but the products were complicated and the yield of **1** was poor. Finally, we used $(C_2H_5)_2Zn$ instead of C_2H_5MgBr. Reaction of **6** with $(C_2H_5)_2Zn$ in Et_2O at room temperature proceeded smoothly and afforded the desired 3-(2’-hydroxybutyl) isobenzofuran-1 (3H)-one **1** as a yellow oil in 80% yield after silica gel chromatography. **1** consists of two diastereoisomers in a ratio of about 1:1 based on ^{1}HNMR spectrum[8]. TLC was carried out with different solvent systems, but two diastereoisomers could not be separated by silica gel chromatography. The synthesis of the optical isomers of **1** was.

References and Notes

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5. The spectra of **4**: IR (film, cm^{-1}):1767 (C=O), 1645 (C=C); ^{1}HNMR (500MHz, $CDCl_3$) δ: 2.61-2.65 (1H, m, H1’), 2.71-2.75 (1H, m, H1’), 5.10-5.18 (2H, m, H3’), 5.50 (1H, t, J=6.0, H3), 5.69-5.76 (1H, m, H2’), 7.46 (1H, t, J=6.7, H4), 7.51 (1H, t, J=6.6, H6), 7.65 (1H, J=6.5, H5), 7.86 (1H, d, J=6.7, H7); m/z (EI): 174 (M^+, 2), 133 (M^+-41, 100).
6. The spectra of **5**: IR (KBr, cm^{-1}): 1759 (COO), 1065 (COC); ^{1}HNMR (300MHz, $CDCl_3$) δ: 2.06 (1H, m, H1’), 2.30 (1H, m, H1’), 2.59, 2.73 (1H, m, H3’), 2.80, 2.89 (1H, m, H3’), 3.04, 3.29 (1H, m, H2’), 5.58 (t, J=6.6, H3), 5.68 (t, J=5.6, H3), 7.48 (1H, t, J=6.6, H4), 7.53 (1H, t, J=6.9, H6), 7.71 (1H, m, H5), 7.92 (1H, d, J=6.9, H7); m/z (EI): 191 (M^++1, 4), 173 (M^+-OH, 4), 160 (M^+-CH_2OH+1, 25), 133 (M^+-CH_2CHOCH_2, 100).
7. The spectra of **6**: IR (film, cm^{-1}): 1761 (COO), 1726 (CHO); ^{1}HNMR (500MHz, $CDCl_3$) δ: 3.10 (2H, m, H1’), 5.97 (1H, t, J=6.3, H3), 7.49 (1H, d, J=7.8, H4), 7.54 (1H, t, J=7.5, H6), 7.69 (1H, t, J=7.8, H5), 7.91 (1H, d, J=7.8, H7), 9.87 (1H, s, H2’); m/z (EI): 176 (M^+, 22), 147 (M^+-CHO, 55), 133 (M^+-CH_2CHO, 100).
8. The spectra of **1**: IR (film, cm^{-1}): 3460 (OH), 1751 (COO); ^{1}HNMR (500MHz, $CDCl_3$) δ: 0.98 (3H, m, H4’), 1.53-1.73 (2H, m, H3’), 1.95 (1H, m, H1’), 2.15 (1H, m, H1’), 3.95 (0.5H, m, H2’), 4.04 (0.5H, m, H2’), 5.65 (0.5H, dd, J=4.4, 8.5, H3), 5.78 (0.5H, d,, J=9.8, H3), 7.45-7.56 (2H, m, H4, H6), 7.68 (1H, m, H5), 7.91 (1H, d, J=7.5, H7); m/z (EI):207 (M^++1, 2), 188 (M^+-H_2O, 15), 177 (M^+-CH_3CH_2, 8), 159 (M^+-CH_3CH_2-H_2O, 32), 146 (M^+-CH_3CH_2CH (OH)-1, 25), 133 (M^+-CH_3CH_2CH (OH) CH_2, 100).

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