

## Novel Hydroperoxides of 1-Imino-3,3-Disubstituted-1,3-Dihydro Isobenzofuran

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**Abstract:** Some 1-imino-3,3-disubstituted-1,3-dihydro isobenzofuran and 2-(1,1-disubstituted hydroxymethyl) benzamide derivatives have been obtained by the aminolysis of phthalide in the presence of triethylamine/aluminum chloride. 1-Benzylimino-3,3-disubstituted-1,3-dihydro isobenzofuran can be peroxidized to the corresponding hydroperoxides on exposure to the air for a long period. The structure was characterized by single crystal X-ray diffraction and the possible mechanism was suggested.

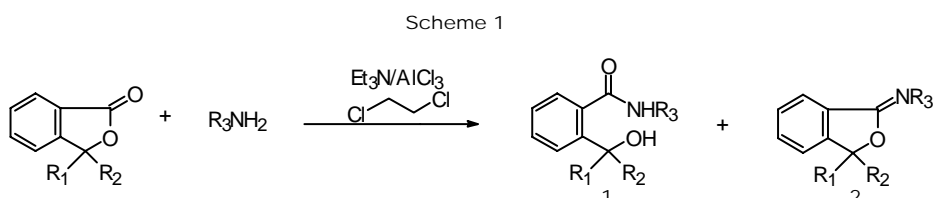
**Keywords:** Phthalide, hydroperoxide, aminolysis.

Taking advantage of the feasibility of phthalides to lactonize, we use phthalides as chemical delivery system to attempt masking polar groups such as carboxyl and amine groups in drug molecule to design prodrugs<sup>1-4</sup>. As a preliminary model reaction, a series of 3,3-disubstituted phthalides as template react with benzylamine and the resulting 2-(1,1-disubstituted hydroxymethyl) benzoic benzylamides were used as "postulated prodrug" to investigate the release rate of benzylamine. The template compounds include 3,3-dimethyl, 3,3-diethyl, 3,3-tetramethylene and pentamethylene phthalides. Surprisingly, in the aminolysis of the phthalide for preparing the hydroxymethyl benzamide a considerable amount of 1-benzylimino-3,3-disubstituted-1,3-dihydro isobenzofuran was produced, which on exposure to the air is peroxidized to hydroperoxides.

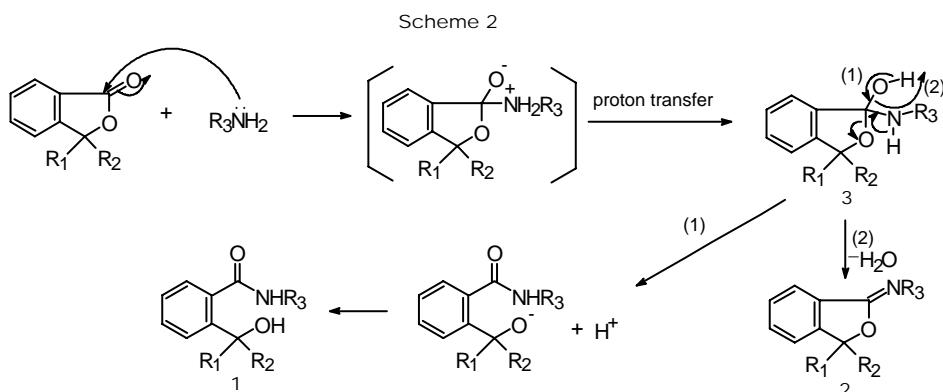
For preparing the 2-(1,1-disubstituted hydroxymethyl) benzamide derivatives, the aminolysis of 3,3-disubstituted phthalide in the presence of triethylamine/aluminum chloride<sup>5</sup> was carried out.

When the substrate is phthalides with 3,3-tetra or penta methylene groups( $R_1$  and  $R_2$ ) the expected products **1** are predominantly obtained, while  $R_1$  and  $R_2$  being diethyl or dimethyl the unexpected products **2** are produced. This indicated that the rigidity of the groups at 3-position may affect the reaction direction and the formation of products **1** and **2** are competitive. At r.t. **1** are solids, but **2** exist as yellowish oils. When the reaction was conducted under reflux, all the phthalides are able to give rise to the unexpected **2** with

comparatively low yield, without producing **1**.



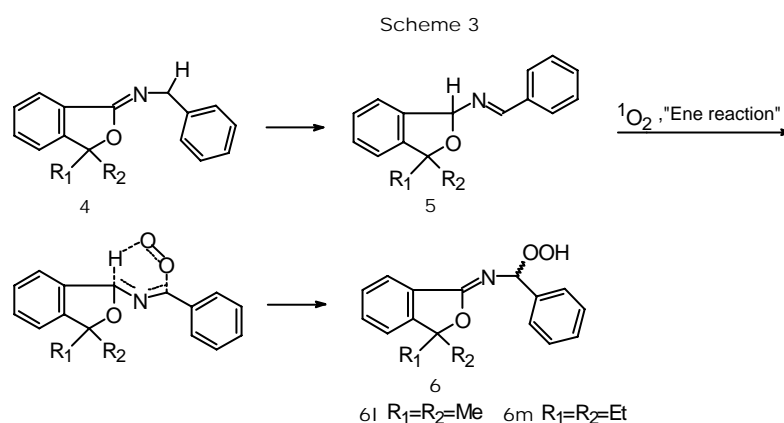
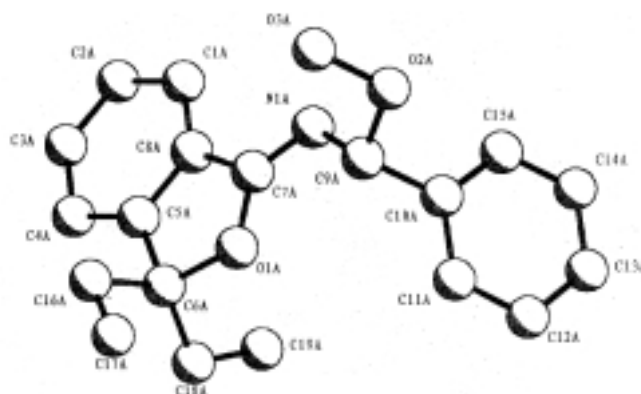
As shown in **Scheme 2**, compound **2** may be formed through the elimination of the water from the tetrahedral intermediate **3**.



It is very interesting that 1-benzylimino-3,3-disubstituted-1,3-dihydro isobenzofuran possesses a tendency to be oxidized on exposure to the air for a long period. An oxygen molecule is added to the benzylimine, giving rise to the corresponding hydroperoxides, the structures of which were identified by chemical analysis and spectroscopy. The presence of a peroxide linkage of **6m** was proved by the consumption of PPh<sub>3</sub> in toluene. The structure of **6m** was chemically identified by the formation of benzaldehyde 2,4-dinitrophenylhydrazone which was formed through decomposition of the hetero-peroxy-acetal moiety in **6m**. Some spectral data are listed as follows: FAB-MS, [M+H]=312.1; <sup>1</sup>H NMR(300MHz, DMSO-d<sub>6</sub>) δ 0.17(t, J=7.2Hz, 3H, CH<sub>3</sub>), 0.57(t, J=7.2Hz, 3H, CH<sub>3</sub>), 1.80(m, J=7.2Hz, 2H, 1/2CH<sub>2</sub>+1/2CH<sub>2</sub>), 1.94(m, J=7.2Hz, 2H, 1/2CH<sub>2</sub>+1/2CH<sub>2</sub>), 6.34(s, 1H, PhCHOH), 7.25-7.45(m, 7H, ArH), 7.62(t, 1H, ArH), 7.74(d, 1H, ArH), 11.76(s, 1H, OOH); <sup>13</sup>C NMR and DEPT (75MHz, DMSO-d<sub>6</sub>) δ 7.03(CH<sub>3</sub>), 7.49(CH<sub>3</sub>), 31.25(CH<sub>2</sub>), 31.52(CH<sub>2</sub>), 92.81(CH), 93.16(C), 121.39(CH), 122.92(CH), 127.39(CH), 128.04(CH), 128.37(CH), 128.69(CH), 130.66(C), 132.19(CH), 138.71(C), 147.92(C), 158.97(C); Anal. Calcd for C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>: C, 73.29; H, 6.80; N, 4.50; Found: C, 73.58; H, 6.93; N, 4.82. The peroxidation creates a chiral center in α-position of benzyl group. The chirality confers different environments to the two methyl groups of **6m**, in which the <sup>1</sup>H NMR methyl signals were split into two

distinct triplets. The structure also characterized by single crystal X-ray diffraction. As outlined in **Figure 1**, the X-ray structure of **6m** clearly indicated that the oxygen atom of the isobenzofuran and benzyl groups are in *cis* to each other, and the imine's configuration is just the same as it. The possible process is suggested in **scheme 3**. The  $\alpha$ -hydrogen of 1-benzylimino-3,3-disubstituted-1,3-dihydro isobenzofuran **4** is transferred to allylic position and intermediate **5** is attached by  $^1\text{O}_2$  through "Ene reaction", leading to the hydroperoxide **6**.

**Figure 1** X-ray structure of **6m**



In conclusion, some novel hydroperoxides of 1-benzylimino-3,3-disubstituted-1,3-dihydro isobenzofuran have been obtained unexpectedly. The structures were characterized by X-ray crystallography and other spectroscopy.

**Acknowledgment**

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