

## 2,3-dihydrobenzo[b][1,4]dioxine N-alkylation using various proton catalysts

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### Abstract.

The majority of the compounds that are created using 2,3-dihydrobenzo[b][1,4]dioxine have pharmacological qualities and are employed as synthesis intermediates to create a variety of medications and medicinal substances that are used to treat different illnesses that affect the human body. Thus, the N-alkylation reaction between 2-(2-hydroxyethyl)isoindoline-1,3-dione and 2,3-dihydrobenzo[b][1,4]dioxine was examined in this study. It was investigated how different proton catalysts affected the N-alkylation process. The resulting compound's structure was examined by the application of physico-chemical study methods.

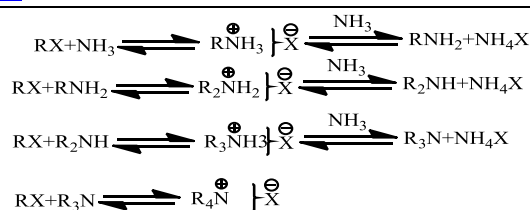
**Key words:** proton catalyst, N-alkylation, Gabriel synthesis, amidoalkylation, spectrum analysis, 2-(2-hydroxyethyl)isoindoline-1,3-dione, 2,3-dihydrobenzo[b][1,4]dioxine.

### Introduction

The compounds with the phthalimide group and BDO derivative have a broad range of applications and strong biological activity, according to the literature. They are employed, for instance, in medicine and agriculture as a useful and significant organic substance with high activity and tasteful organic synthesis [1-5].

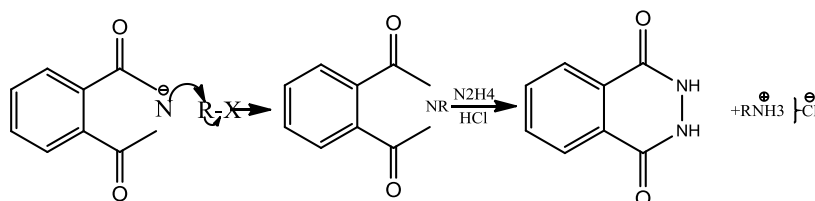
The N-alkylation (Gabriel synthesis, amidoalkylation) reactions of 2-(2-hydroxyethyl)isoindoline-1,3-dione with 2,3-dihydrobenzo[b][1,4]dioxine are the subject of this article [6,-10].

The process of creating primary amines by reacting alkyl halides with ammonia under pressure is covered in this passage. The concept is predicated on the breaking down of carbon-nitrogen (C-N) bonds, which produces amide anion synthons and carbocations. Primary amine production is the desired result. In actuality, though, the yield is poor as the reaction yields some quaternary ammonium salt in addition to a mixture of primary, secondary, and tertiary amines. This undesirable result is explained by the successively produced compounds' enhanced sensitivity to further alkylation [6].

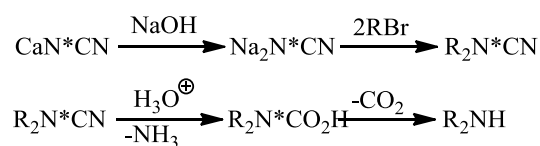


The passage indicates that ammonolysis of alcohols, facilitated by specific metallic oxide catalysts, is a widely employed method on a large scale for producing various types of amines.

The potassium salt of phthalimide is proposed in the passage as an alternate reagent equivalent for the amide anion synthon. N-alkylphthalimide is the product of this reagent's reaction with a single molecular part of alkyl halide. The Gabriel synthesis is the procedure by which the N-alkylphthalimide is cleaved to yield the target primary amine. The chapter describes a different way to make potassium phthalimide that entails heating the compound with a halide when potassium carbonate is anhydrous. By doing this, the first potassium phthalimide preparation is avoided. After reacting with hydrazine hydrate and heating the mixture with hydrochloric acid, N-substituted phthalimide is cleaved. The amine hydrochloride remains in solution after the resultant insoluble phthalylhydrazide is filtered out. After that, the amine may be released and separated using the proper techniques[7].



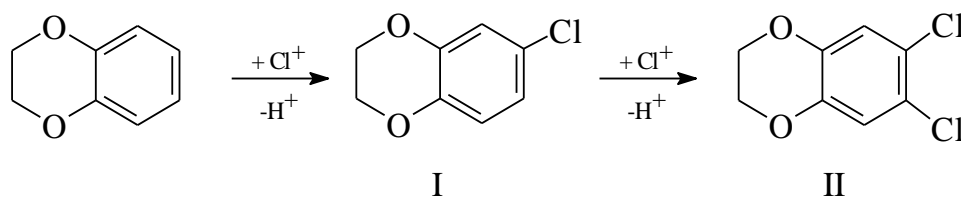
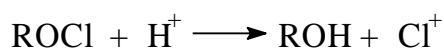
It is straightforward to prepare pure symmetrical secondary amines by hydrolyzing dialkylcyanamides with diluted sulfuric acid. By treating sodium cyanamide, which is itself made from calcium cyanamide and an aqueous sodium hydroxide solution, with an alkyl halide, the proper dialkyl cyanamide is created. The reagent  $[\text{:N-C=N}]^2$  in this instance can be thought of as a disguised NH group [8].



The electrophilic exchange reactions of aromatic ethers in the presence of proton catalysts were investigated by Zorin A.V. [6]. In these processes, catalysts such as acetic acid or trifluoroacetic acid were used. The effect of  $\text{H}_2\text{SO}_4$  in catalytic proportions on the course of these reactions in the presence of trifluoroacetic and acetic acids was investigated. Sulfuric acid is used, which slows down the process.

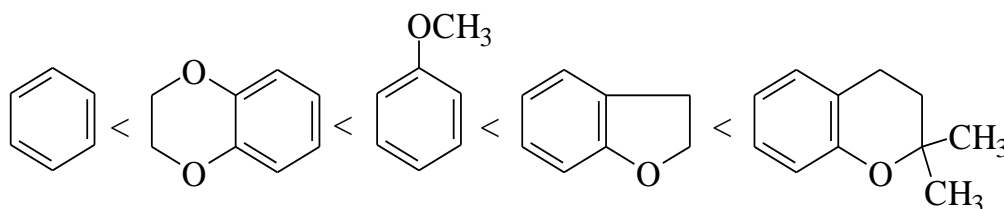
High yields of the corresponding compounds were produced when BDO was chlorinated with n-alkyl hypochlorite in mixes including acetic acid, carbon tetrachloride, trifluoroacetic acid, or acetic acid and sulfuric

acid [6]. This is due to the fact that the acid produces an active chlorine cation through a reaction with the alkyl hypochlorite, which then interacts with the aromatic ring. The following is the overall structure of the reaction:



When  $\text{R}=\text{C}_4\text{H}_9\text{OCl}$  is conducted in a combination of  $\text{CH}_3\text{COOH}$  and  $\text{H}_2\text{SO}_4$  for 1 hour at  $20\text{--}25^\circ\text{C}$ , I 75%, II 12%, and I yield of  $\text{R}=\text{C}_2\text{H}_5\text{OCl}$  were produced with 9% I and 67% II of 6-chloro- and 6,7-dichlorobenzo-1,4-dioxane (II).

Different aromatic ethers have also been used to study the aforementioned reactions. The reactivity of aromatic ethers and the rate of electrophilic exchange processes grow in the following sequence because the ether group in aromatic ethers donates electrons:



### Materials and Methods (optional)

To ascertain the composition of the reaction products, Silufol-254 plates were subjected to thin layer chromatography (TLC). In the mobile phase system of benzene and ethyl ether of acetone (3:1), TLC was used to assess the reaction's development and the purity of the compounds that were produced during the process. Aluminum plates with a silica gel coating (silica gel 60 F254) purchased from MERCK in India were used for the TLC stationary phase. UV light was used to see how compounds were distributed on TLC plates. Column chromatography was used to clean the reaction mixture, and the yield of the chemical reaction that resulted from isolation was determined. After separation by column chromatography, the reaction mixture was confirmed by TLC using benzene and ethyl acetone (3:1) as the mobile phase. The reaction was subsequently completed, and the liquid was poured into ice-cold water. The solid material that had crystallized was filtered and dried. The FT-IR spectra of the goods were obtained on a Carl Sies (Germany) Specord IR-71 spectrophotometer using the KBr pellet method. TMS was used as the internal standard for the  $^1\text{H}$  NMR recordings, and chemical shift values were expressed in ppm scale using a Bruker (Germany) 400 MHz NMR apparatus. Using a Mvtec melting point equipment and the open capillary approach, the uncorrected melting points of the produced compounds were determined [11].

**2,3-dihydrobenzo[b][1,4]dioxine amidoalkylation using 2-(2-hydroxyethyl)isoindoline-1,3-dione in the presence of  $\text{H}_2\text{SO}_4$ .** 1.91 g (0.01 mol) of 2-(2-hydroxyethyl)isoindoline-1,3-dione and 4.08 g (0.03 mol) of 2,3-

*dihydrobenzo[b][1,4]dioxine* were heated in a sand bath within a 3-neck flask that had a reflux condenser and a mechanical stirrer. Over the course of 20 minutes, 0.3 g (0.003 mol) of H<sub>2</sub>SO<sub>4</sub> was gradually added as the reaction temperature hit 120°C. For four hours, the reaction was conducted between 140 and 160°C. The benzene was extracted in a water combination following the cooling of the reaction mixture. There was an easy way to remove the benzene once the layer had been cured with CaCl<sub>2</sub>. *2,3-dihydrobenzo[b][1,4]dioxine* that had not yet reacted was extracted from the residue by driving at 135°C (40 mmHg) under vacuum. Alcohol was used to dissolve the residue, which was then allowed to cool. After being filtered out, the precipitate was dried. The material crystallized again in acetic acid. The 6-phthalimidoethylbenzodioxane-1,4 that was obtained had a mass of 1.7 g (55%). Melting point 146-148°C.

**6-β Phthalimidoethylbenzodioxan-1,4**-white crystalline substance. Melting point: 146-148°C, (C<sub>2</sub>H<sub>5</sub>OH). R<sub>f</sub>=0,59 (silufol, benzene: acetone 3:1).

Specific absorption frequencies in the IR spectrum (sm<sup>-1</sup>); the CH<sub>2</sub> group vibrates symmetrically at 2853 and asymmetrically at 2962; vibrations of the CH<sub>2</sub> group deformation linked to nitrogen at 1430; valence vibrations of the C=O group bonded to nitrogen, 1713, 1773; vibrations of the CH bond in the 1,2-disubstituted aromatic ring at 721; Deformation vibrations of the CH bond in the 1,2,4-trivalent aromatic ring; and vibrations of the C=C bond in the aromatic ring at 1580, 1614.

Sinhala language in the PMR range (C<sub>5</sub>D<sub>5</sub>, δ, m.) 3,9-4,1 (2H, O-CH<sub>2</sub>), 4,4-4,65 m (2H, -CH<sub>2</sub> ba 2H, CH<sub>2</sub>), 7,2-7,55 m (1',2',4'-C<sub>6</sub>H<sub>3</sub>), 7,6-7,85 m (4H, 1,2-C<sub>6</sub>H<sub>4</sub>).

**2,3-dihydrobenzo[b][1,4]dioxine amidoalkylation using 2-(2-hydroxyethyl)isoindoline-1,3-dione in the presence of ZnCl<sub>2</sub>.** A sand bath was used to heat 4.08 g (0.03 mol) of 2,3-dihydrobenzo[b][1,4]dioxine and 2.54 g (0.01 mol) of 2-(2-hydroxyethyl)isoindoline-1,3-dione in a three-necked flask fitted with a reflux condenser and a mechanical stirrer. Following the achievement of 100°C in the reaction, 0.1 g (7.5·10<sup>-4</sup> mol) of ZnCl<sub>2</sub> was introduced. For four hours, the reaction was conducted at 150–160°C. The reaction mixture was cooled, then water was added and benzene was used to extract the mixture. There was an easy way to remove the benzene once the layer had been cured with CaCl<sub>2</sub>. The remaining 2,3-dihydrobenzo[b][1,4]dioxine was separated from the unreacted portion by vacuum-driving 122°C (38 mm.sm.). Alcohol was used to dissolve the residue, which was then allowed to cool. The precipitate was removed by filtering. Alcohol was used to recrystallize the substance to purify it. 1.85 g (60% ) of 6-(α-Phthalimidoethyl)benzodioxane-1,4 was obtained. R<sub>f</sub>=0.67 (silufol, benzene:acetone: 3:1), Melting point 54-56°C.

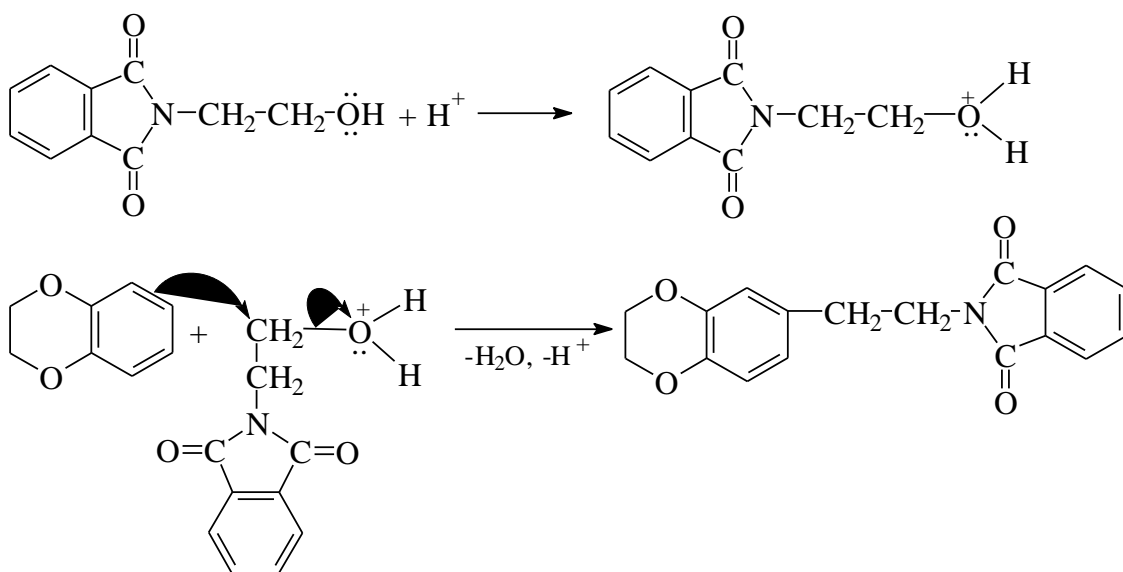
**6-(α-Phthalimidoethyl)benzodioxane-1,4** - white crystalline substance. Melting point 54-56°C. (C<sub>2</sub>H<sub>5</sub>OH). R<sub>f</sub>=0,67 (silufol, benzene:acetone 3:1).

Sinhala language in the PMR range (C<sub>5</sub>D<sub>5</sub>, δ, m.) 1,85 c (3H, CH<sub>3</sub>), 3,8-4,2 m (1H, CH), 7,4-7,6 m (1,2,4-C<sub>6</sub>H<sub>3</sub>), 7,6-7,85 m (4H, 1,2-C<sub>6</sub>H<sub>4</sub>).

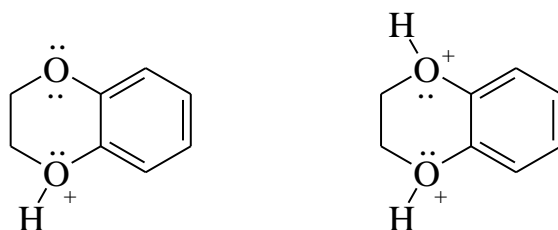
## Results and Discussion

By adjusting the reaction conditions, we conducted reactions to produce an amidoalkyl product. Through the reduction of catalyst in the process, 6-phthalimidoethylbenzo-zodioxan-1,4 was extracted with a 13% yield

using the reagents 2,3-dihydrobenzo[b][1,4]dioxine: 2-(2-hydroxyethyl)isoindoline-1,3-dione:H<sub>2</sub>SO<sub>4</sub> 1:1:0.5 mol ratio at 140–160°C for 4 hours. Under the given circumstances, a 55% yield of 6-phthalimidoethylbenzodioxan-1,4 was produced by reacting the reagents 2,3-dihydrobenzo[b][1,4]dioxine: 2-(2-hydroxyethyl)isoindoline-1,3-dione:H<sub>2</sub>SO<sub>4</sub> 1:1:0.3. This reaction scheme is how 6-phthalimidoethylbenzodioxan-1,4 is formed:



The decreased capacity of the substrate to participate in electrophilic exchange events due to the protonation of oxygen atoms in the heteroring might account for the reduced productivity of 2,3-dihydrobenzo[b][1,4]dioxine amidoalkylation reactions in the presence of protonic acids.

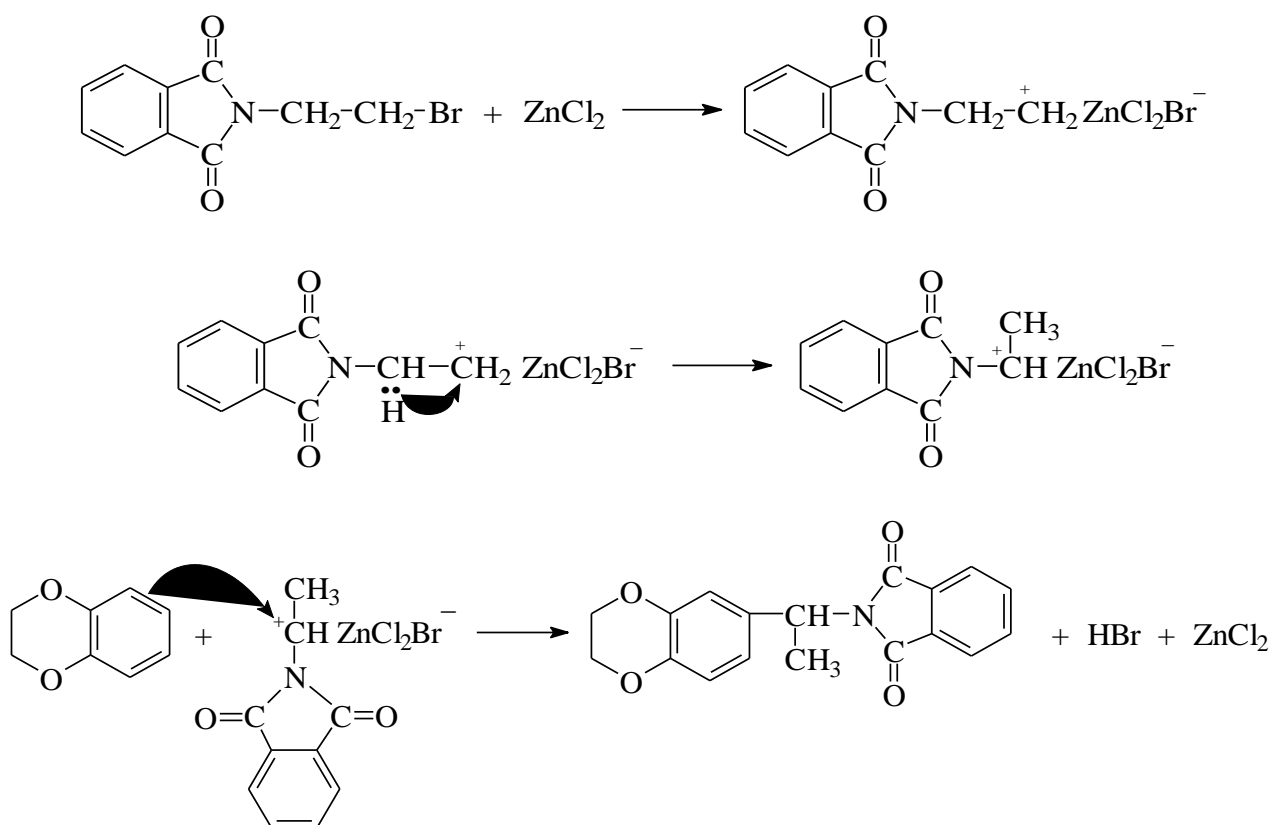


As a result, the degree of protonation of the 2,3-dihydrobenzo[b][1,4]dioxine molecule determines the resultant yield in reactions involving protonic acids. A similar circumstance was previously seen during the 2,3-dihydrobenzo[b][1,4]dioxine chloromethylation procedure [12]. The 2,3-dihydrobenzo[b][1,4]dioxine ring's reactivity is comparatively strong when the quantity of protonic acids is low because the heteroring's oxygen atoms reduce protonation. The reactions performed above, using the reagents 2,3-dihydrobenzo[b][1,4]dioxine: 2-(2-hydroxyethyl)isoindoline-1,3-dione:H<sub>2</sub>SO<sub>4</sub> in a ratio of 1:1:0.3, at 140–160°C for 4 hours, validated this.

Investigating the impact of reagent addition order on amidoalkylation reaction product yield yielded the following experimental results. When sulfuric acid was added to the combination of 2,3-dihydrobenzo[b][1,4]dioxine and 2-(2-hydroxyethyl)isoindoline-1,3-dione, the reaction mixture totally darkened at 40–100°C. The reagents were taken in the ratio of 2,3-dihydrobenzo[b][1,4]dioxine: 2-(2-hydroxyethyl)isoindoline-1,3-dione:H<sub>2</sub>SO<sub>4</sub> 1:1:3. The reaction mixture does not darken and an amidoalkyl product is generated when 0.3 mol of sulfuric acid is added to the combination of 2,3-dihydrobenzo[b][1,4]dioxine and 2-(2-hydroxyethyl)isoindoline-1,3-dione at 120–130°C.

The amidoalkylation reaction of 2,3-dihydrobenzo[b][1,4]dioxine with  $\beta$ -bromomethylphthalimide in the presence of  $ZnCl_2$  was conducted in order to investigate the structure of the amidoalkyl product generated by amidoalkylation of 2,3-dihydrobenzo[b][1,4]dioxine with 2-(2-hydroxyethyl)isoindoline-1,3-dione in the presence of  $H_2SO_4$ . After 4 hours at 150–160°C in the reaction mixture of reagents 2,3-dihydrobenzo[b][1,4]dioxine:  $\beta$ -bromomethylphthalimide: $ZnCl_2$  1:1:7.5·10<sup>-4</sup> mol, the amidoalkyl product was extracted with a yield of 60%.

The following provides an explanation for how this material formed:  $\beta$ -Bromoethylphthalimide and Lewis acid— $ZnCl_2$ —form a dense ion pair (I). The displacement of the hydride ion in this dense ion pair results in the formation of a reasonably stable (II) dense ion pair. This dense ion pair reacts with 2,3-dihydrobenzo[b][1,4]dioxine to produce 6-( $\alpha$ -phthalimidoethyl)-benzodioxane-1,4.



The deformation vibrations of the  $CH_3$  group are located between 1325 and 1360  $cm^{-1}$  in the IR-spectrum of the starting materials and the produced products; The  $CH_2$  bond exhibits both symmetric and asymmetric vibrations at 2848, 2853, 2872, and 2886  $cm^{-1}$ . The OH group's valence vibrations are at 3471  $cm^{-1}$ . The  $C=O$  group attached to nitrogen exhibits deformation vibrations at 1696, 1706-1715, 1726, 1767-1768, 1773-1776  $cm^{-1}$ . The  $OCH_2$  group exhibits deformation vibrations at 1364, 1392, 1397, 1403  $cm^{-1}$ . The  $C-C$  bond in the aromatic ring exhibits symmetric and asymmetric vibrations at 1578, 1580, 1599, 1608, 1612, 1614, and 1685  $cm^{-1}$ . The  $CH$  bond in the 1,2-disubstituted aromatic ring is observed at 721, 722, 725  $cm^{-1}$ . The  $CH$  bond in the 1,2,4-trisubstituted aromatic ring was observed at 857, 880  $cm^{-1}$  [47].

The PMR spectra of the starting materials and synthesized products showed the following signals: 1.85, 1.7-1.9 m. multiplet and singlet signals of protons in the  $CH_3$  group; 3.75, 4.2, 4.5 4.4-4.6 m. triplet signals of protons in

the CH<sub>2</sub> group bound to nitrogen in; 3.75, 3.8, 3.9, 4.0 m. singlet and triplet signals of protons in the CH<sub>2</sub> group bound to oxygen in; 3.8-4.2 m. multiplet signals of the CH group protons; 3.9-4.1 m. of protons of the CH<sub>2</sub> group attached to the aromatic ring. Triplet signals of 1,2-substituted aromatic ring protons were seen at 7.75, 7.5-7.6, and 7.85 m. Multiplet signals of 1,2,4-trivalent aromatic ring protons were observed at 7.2-7.85 and 7.4-7.6 m.

### Conclusions

One of the proton catalysts we utilized was the amidoalkylation reaction of 2,3-dihydrobenzo[b][1,4]dioxine with 2-(2-hydroxyethyl)isoindoline-1,3-dione, which we exclusively conducted in the presence of H<sub>2</sub>SO<sub>4</sub> and in the following ratio of reagents 2,3-dihydrobenzo[b][1,4]dioxine: 2-(2-hydroxyethyl)isoindoline-1,3-dione:H<sub>2</sub>SO<sub>4</sub> 1:1:0.3, 6-phthalimidoethyl-benzodioxane-1,4 can be obtained by heating it to 140–160°C for four hours. One can create the isomeric amidoalkyl product 6-( $\alpha$ -phthalimidoethyl)-benzodioxane-1,4 by reacting 2,3-dihydrobenzo[b][1,4]dioxine with  $\beta$ -bromomethylphthalimide at 150–160°C while using a ZnCl<sub>2</sub> catalyst.

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