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# First Acid-Catalyzed Entry to *O*-Alkylated Hydroximides from Benzylic Alcohols

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A facile method for the synthesis of *O*-alkylated hydroximides through the acid-catalyzed alkylation of hydroximides by using benzylic alcohols as alkylating agents is described for the first time. The obtained *O*-propargylated products offered easy access to 2,5- and 4,5-dihydroisoxazoles.

## Introduction

*O*-Alkylated hydroximides (hydroxyphthalimides) represent a versatile class of useful synthons for the synthesis of several heterocyclic compounds such as dihydroisoxazoles,[1,2] polysubstituted pyridine *N*-oxides,[3] and α-aminoxy acids,[4] as well as other potentially bioactive compounds[5] through *O*-alkyl hydroxylamine (Figure 1). Generally, these compounds are obtained by *O*-alkylation of hydroximide by using alkyl halides in the presence of a stoichiometric amount of base[5a,6] or with alcohols under Mitsunobu conditions.[1–4,7] The latter method is the most frequently used method, but it suffers from the generation of phosphane oxide and hydrazine dicarboxylate as byproducts, which often makes the isolation of pure product in good yield difficult.[1,8] In addition, a single literature precedence is available on the *O*-alkylation of *N*-hydroxyphthalimide by using aliphatic tertiary alcohols in the presence of stoichiometric $BF_3{\cdot}OEt_2$.[9] Alternatively, *O*-alkylated hydroximides are achieved from hydrocarbons through Cu-catalyzed benzylic and allylic C–H activation[10] or from carbonates by transition-metal-catalyzed C–O bond formation.[11] Hence, the development of efficient new methods for *O*-alkylation of hydroxamides by using alcohols as alkylating agents is an attractive objective.

In recent years, π-activated alcohols have received considerable attention as alkylating agents towards green and atom-economic practices, as they generate only water as a byproduct in the reaction.[12] Among these, benzylic alcohols are gaining prominence due to the moderate stability and high reactivity of benzylic carbocations generated in the presence of a Lewis or Brønsted acid.[13] The efficacy of π-activated alcohols in direct nucleophilic $S_N1$-type reactions has been covered by Cozzi and co-workers in a recent review.[14] Our work on the utility of benzylic alcohols as carbon electrophiles by treatment with various carbon, oxygen, and nitrogen nucleophiles[15] has encouraged us to further explore the scope of benzylic alcohols as alkylating agents. Herein, we report the first acid-catalyzed *O*-alkylation of hydroxamides by using benzylic alcohols (Scheme 1).

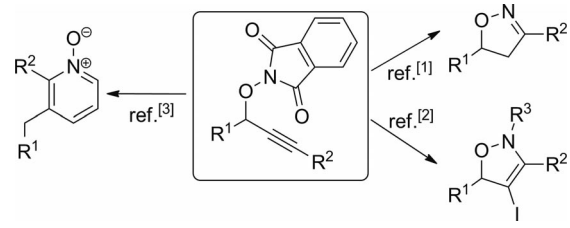
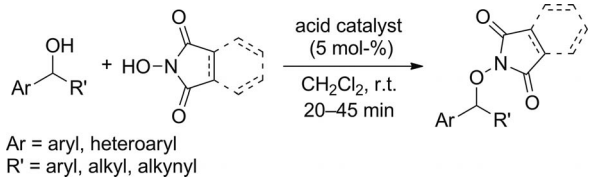



Figure 1. Synthesis of N,O-heterocycles from *O*-propargylated hydroxyphthalimide.




Scheme 1. Acid-catalyzed access to *O*-alkylated hydroximides.

## Results and Discussion

Diphenylmethanol (**1a**) was selected as a model alkylating agent for the acid-catalyzed *O*-alkylation of *N*-hydroxyphthalimide (**2a**). To optimize the reaction conditions,

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we examined different acid catalysts, and the results are summarized in Table 1. At first, the *O*-alkylation of **2a** with **1a** was tested by using $BF_3{\cdot}OEt_2$ (5 mol-%) as the catalyst in $CH_2Cl_2$ at room temperature. To our delight, the starting material was consumed in 30 min and desired *O*-alkylated product **3a** was obtained in 78% yield (Table 1, Entry 1). Next, the same reaction was examined with different acid catalysts (5 mol-%) in $CH_2Cl_2$ as solvent to identify the best catalyst for the *O*-alkylation of hydroximides. Among the catalysts used, *p*-toluenesulfonic acid provided good yield (86%) of product **3a** in 30 min with a clean reaction profile (based on TLC; Table 1, Entry 3).

Table 1. Optimization of the reaction conditions for the acid-catalyzed *O*-alkylation of *N*-hydroxyphthalimide (**2a**) with benzylic alcohol (**1a**).

| Entry | Acid | Conditions | Time [min] | Yield [%][a] |
|---|---|---|---|---|
| 1 | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$, r.t. | 30 | 78 |
| 2 | $ZnCl_2$ | $CH_2Cl_2$, r.t. | 40 | 80 |
| 3 | *p*-TSA | $CH_2Cl_2$, r.t. | 30 | 86 |
| 4 | $B(C_6F_5)_3$ | $CH_2Cl_2$, r.t. | 30 | 82 |
| 5 | – | $CH_2Cl_2$, reflux | 2880 | 0[b] |

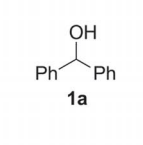
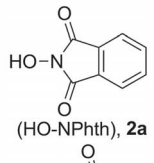
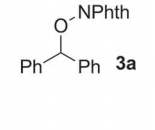
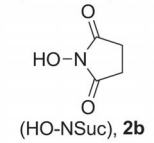
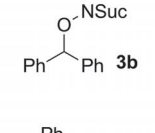
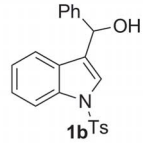
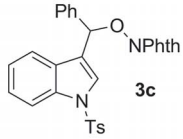
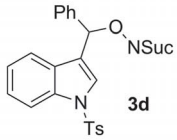
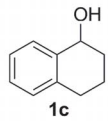
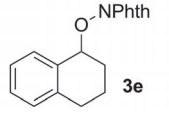
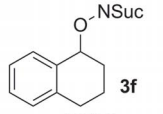
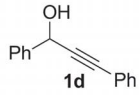
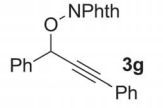
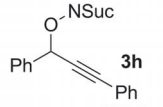
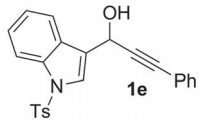
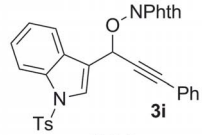
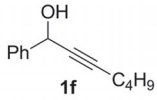
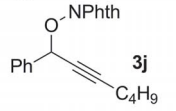
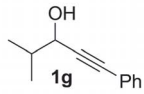
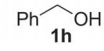
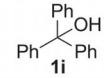
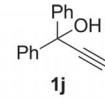
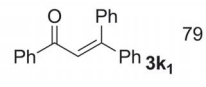
[a] Isolated yield after purification. [b] No reaction.

$ZnCl_2$ and $B(C_6F_5)_3$ also furnished the product in 80 and 82% yield, respectively (Table 1, Entries 2 and 4). It was observed that there was no reaction in the absence of a catalyst (Table 1, Entry 5). On the basis of the above results, *p*-TSA was chosen for further studies, which was also successfully utilized earlier by Sanz et al. and others for the direct nucleophilic substitution of various benzylic alcohols.[16,17]

To explore the generality of the reaction, a range of alcohols were studied for the *O*-alkylation of *N*-hydroxyphthalimide (**2a**) and *N*-hydroxysuccinimide (**2b**) under the optimized conditions (Table 2). This method is efficient for the alkylation of **2b** with **1a** to give **3b** in 84% yield (Table 2, Entry 2). Benzylic alcohols **1b** and **1c** were treated with both **2a** and **2b** under the present reaction conditions to provide the corresponding *O*-alkylated products **3c** to **3f** in good yields (Table 2, Entries 3 to 6). Next, we sought to extent the method by using propargylic alcohols as alkylating agents to obtain *O*-propargylated hydroxylamines, which are useful synthons for the preparation of 2,5- and 4,5-dihydroisoxazole derivatives.

Thus, the reaction of propargylic alcohol **1d** with **2a** and **2b** in the presence of p-TSA (5 mol-%) gave the corresponding products **3g** and **3h** in 82 and 78% yield, respectively (Table 2, Entries 7 and 8). Similarly, propargylic substrates **1e** and **1f** were also successful in smooth *O*-alkylation of **2a** (Table 2, Entries 9 and 10). However, the reaction of propargylic alcohol **1g** with *N*-hydroxyphthalimide failed to give the desired *O*-propargylated product even after 2 h at room temperature (Table 2, Entry 11). The results from the above reactions clearly demonstrate that the *O*-alkylation was successful only in the case of propargylic alcohols, ob-

Table 2. *p*-TSA-catalyzed *O*-alkylation of hydroximides with benzylic alcohols.

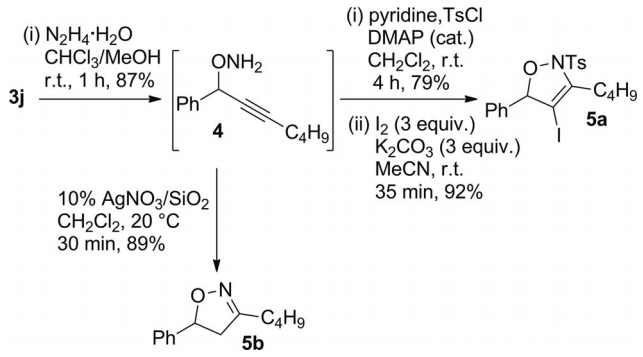
| Entry | Alcohol | Hydroxamide | Time [min] | Product[a] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 |  **1a** |  (HO-NPhth), **2a** | 30 |  **3a** | 86 |
| 2 | **1a** |  (HO-NSuc), **2b** | 40 |  **3b** | 84 |
| 3 |  **1b** | **2a** | 70 |  **3c** | 74 |
| 4 | **1b** | **2b** | 60 |  **3d** | 73 |
| 5 |  **1c** | **2a** | 30 |  **3e** | 79 |
| 6 | **1c** | **2b** | 60 |  **3f** | 77 |
| 7 |  **1d** | **2a** | 45 |  **3g** | 82 |
| 8 | **1d** | **2b** | 40 |  **3h** | 78 |
| 9 |  **1e** | **2a** | 60 |  **3i** | 69 |
| 10 |  **1f** | **2a** | 45 |  **3j** | 78 |
| 11 |  **1g** | **2a** | 120 | – | – |
| 12 |  **1h** | **2a** | 120 | – | – |
| 13 |  **1i** | **2a** | 200 | – | – |
| 14 |  **1j** | **2a** | 120 |  **3k$_1$** | 79 |

[a] All the products were characterized by $^1H$ and $^{13}C$ NMR spectroscopy and mass spectrometry. [b] Isolated yield.

tained from aromatic aldehydes and not with the propargylic alcohols generated from aliphatic aldehydes. This may be due to the formation of more reactive benzylic carbocation from the former alcohols. The reaction of **2a** with primary benzylic alcohol **1h** and tertiary benzylic alcohol **1i** also failed to give the product (Table 2, Entries 12 and 13), which demonstrates that the alkylation was successful only with secondary benzylic alcohols. On the other hand, 1,1,3-triphenylpropargyl alcohol (**1j**) did not react with **2a** under the present reaction conditions, instead it isomerized into β-phenyl chalcone **3k$_1$** (Meyer–Schuster rearrangement).[17a,18]

Furthermore, we have demonstrated the utility of *O*-propargylated hydroximides in the synthesis of 2,5- and 4,5-dihydroisoxazole derivatives (Scheme 2).[1] Hence, compound **3j** was treated with hydrazine hydrate in $CHCl_3$/MeOH (1:1) to remove the phthalimide group to obtain hydroxylamine **4** in 87% yield. *N*-Tosylation of **4** with tosyl chloride in the presence of pyridine followed by reaction with $I_2/K_2CO_3$ in $CH_3CN$ provided 4-iodo-2,5-dihydroisoxazole **5a** in 72% yield (over 2 steps), whereas the reaction of **4** with 10% $AgNO_3/SiO_2$ in $CH_2Cl_2$ afforded 4,5-dihydroisoxazole **5b** in 89% yield.




Scheme 2. Synthesis of dihydroisoxazoles from **3j**.

## Conclusions

In summary, we have developed the first acid-catalyzed *O*-alkylation of hydroximides by using secondary benzylic alcohols as alkylating agents, which is an attractive, green approach. The reaction conditions are metal-free, mild, and efficient to obtain the *O*-alkylated hydroximides in good yields. The applicability of *O*-propargylated hydroximide has also been successfully demonstrated for the synthesis of 2,5- and 4,5-dihydroisoxazole compounds. The present method may find broader utility in the synthesis of various N,O-heterocycles.

## Experimental Section

**Typical Experimental Procedure for the *p*-TSA-Catalyzed *O*-Alkylation of Hydroximides:** To a solution of secondary benzylic alcohol **1a**–**f** (1 mmol) in dichloromethane (5 mL) was added hydroximide **2a**,**b** (1.2 mmol) and *p*-TSA (0.05 mmol) at room temperature, and the mixture was stirred for the given time (see Table 2). After completion of the reaction (monitored by TLC), the mixture was quenched by the addition of saturated aq. solution of sodium hydrogen carbonate (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layer was dried with anhydrous $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexanes) to afford *O*-alkylated hydroximides **3a**–**j**. The products obtained were characterized by IR, $^1$H, and $^{13}$C NMR spectroscopy and mass spectrometry.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and characterization data of the prepared compounds.

## Acknowledgments

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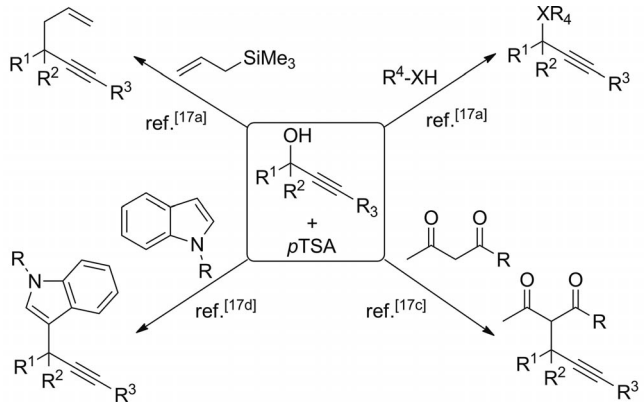


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