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Selective nitrogen protection of hydroxyalkylbenzimidazoles using 2,2,2-trichloroethylchloroformate

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Abstract—A method for selective N-protection of hydroxyalkylbenzimidazoles using 2,2,2-trichloroethylchloroformate (Troc-Cl) applicable to various alkyl chain lengths has been developed. In the specific case of 5-(1-[2,2,2-trichloroethyl formyl]-benzimidazol-2-yl)-propan-1-ol, migration of Troc from the benzimidazole to the primary alcohol occurs in the presence of triethylamine, allowing the choice of selective N-Troc or O-Troc protection.

The commercialization of polymer electrolyte membrane fuel cells (PEMFCs) is becoming an increasingly important goal as the demand for clean, efficient, and portable energy rises. The polymer membrane in the cell acts as an electronic barrier and as the proton conduction medium between the anode and cathode. Presently, membranes require the addition of small molecules such as water, phosphoric acid, and heterocycles to facilitate proton conduction. Polymers containing covalently bound imidazole and benzimidazole as protogenic moieties have been investigated by several research groups,[1–3] and both show proton conduction at operating temperatures from 120 to 200 °C, however, a full range of polymeric materials has not been investigated. We are interested in preparing polymer electrolyte membranes from well-defined homo and block copolymers that contain immobilized heterocyclic side chains. In preparing benzimidazole functional acrylate monomers **1** and **2** (Fig. 1), a novel selective protection/deprotection scheme of the benzimidazole amine was identified.

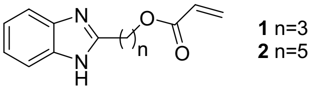

Figure 1. Benzimidazole functional acrylate monomers.

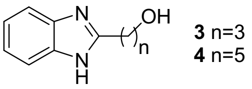

Figure 2. Hydroxyalkylbenzimidazole precursors.

The acrylate synthesis proceeds from the corresponding hydroxyalkylbenzimidazoles **3** and **4** (Fig. 2), prepared by reaction of 1,2-phenylene diamine with γ-butyrolactone or ε-caprolactone, respectively, in the presence of a catalytic amount of *p*-toluenesulfonic acid at 200 °C for two hours. The resulting materials contain two nucleophiles, a primary alcohol, and the 2° amine in the benzimidazole ring. Selective synthesis of **1** and **2** requires protection of the amine, however, the di-nucleophilic nature of hydroxyalkylbenzimidazoles complicates protection schemes. Competing reactions can result in a mixture of N-, O-, and doubly protected materials; therefore, a selective protection scheme must be identified.

Selective N-protection of **3** with benzyl bromide was reported by Indusegaram et al.,[4] subsequently, we prepared *N*-benzyl **4** according to the reported method. However, N-debenzylation by common hydrogenolysis methods failed,[5] consistent with the literature reports for *N*-benzyl aromatic heterocycles. Several alternate N-debenzylation methods have been reported, however, these reaction conditions are either incompatible or experimentally inconvenient. Haddach et al. report the use of potassium *tert*-butoxide/DMSO and oxygen to afford clean N-debenzylation of aromatic

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Keywords: 2,2,2-Trichloroethylchloroformate; Troc; Benzimidazole; Selective N-protection.

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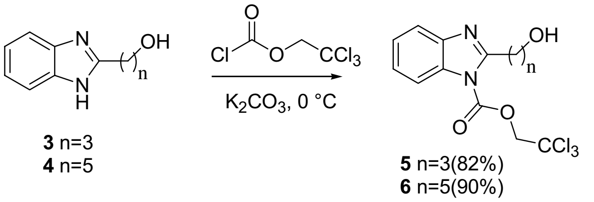
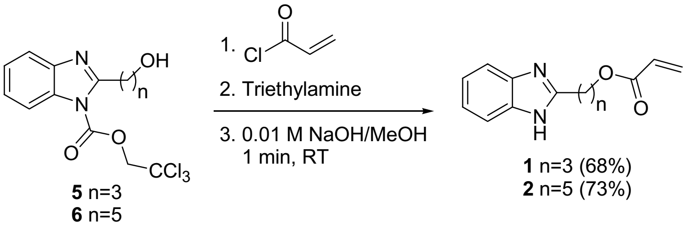
heterocycles.[6] The method is tolerant to many functional groups, but not esters, making this method impractical in our case. Rao and Pandey reported a mild N-debenzylation procedure using sodium in liquid ammonia with *t*-BuOH at −78 °C that is tolerant to ester functionality,[7] however, use of liquid ammonia for synthesis on a 5–10 g scale is not attractive. Finally, there are reports of substituting a more labile protecting group for the *N*-benzyl.[8,9] Rawal et al. report displacing the *N*-benzyl with 2,2,2-trichloroethoxycarbonyl (Troc) and deprotecting with Zn/acetic acid, and Campbell et al. report substituting with β-trimethylsilylethyl chloroformate (Teoc) then deprotecting with tetra-*n*-butylammonium fluoride in THF.

Rather than performing a two-step debenzylation, we decided to investigate a direct route to N-Troc hydroxyalkylbenzimidazoles. The Troc group can be removed under relatively mild conditions and is stable to acidic environments.[10] Additionally, it has been reported that Troc can be used to selectively protect primary alcohols in the presence of secondary alcohols,[11] exploiting the nucleophilicity difference of the two alcohols. Following this vein, we were able to prepare N-Troc protected hydroxyalkylbenzimidazoles **5** and **6** in good yield by reacting **3** and **4** directly with 2,2,2-trichloroethylchloroformate (Troc-Cl) at 0 °C in the presence of potassium carbonate as an acid scavenger (Scheme 1). The more nucleophilic benzimidazole amine reacts preferentially, resulting in the N-troc protected material when the stoichiometric ratio of Troc-Cl to amine is close to 1:1 and the Troc-Cl concentration is kept at a minimum during the reaction. An excess of Troc-Cl greater than 2–3 mol % can result in formation of some doubly protected material, and addition of Troc-Cl too quickly results in a mixture of N-, O-, and doubly protected materials.

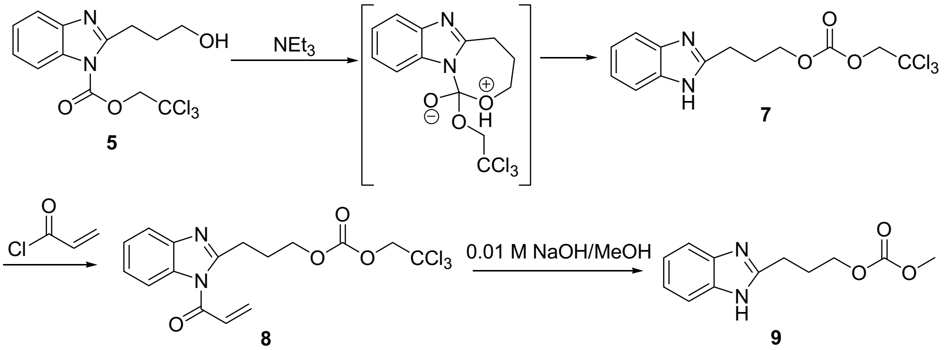


Scheme 1. Selective nitrogen protection of hydroxyalkylbenzimidazoles.

The benzimidazole acrylate **1** was prepared by reaction of **5** with acryloyl chloride in dichloromethane, followed by neutralization with triethylamine. After removal of the reaction solvent under reduced pressure, the N-troc was rapidly removed in the presence of basic methanol (Scheme 2). Whereas, benzimidazole acrylate **2** was prepared by reacting **6** with acryloyl chloride in the presence of triethylamine in dichloromethane, followed by troc removal. Under basic conditions, **5** undergoes an internal rearrangement from N-troc to O-troc **7** presumably through a seven-membered cyclic intermediate. Subsequent addition of acryloyl chloride forms the benzimidazole acrylamide **8**. Upon addition of basic methanol, the acrylamide is cleaved and the O-troc is transformed into the methyl carbonate **9** (Scheme 3). This type of rearrangement is not observed for **6**, most likely due to the five methylene spacer between the benzimidazole and the alcohol resulting in a nine-membered cyclic intermediate which is not as favorable as the seven-membered intermediate. This rearrangement



Scheme 2. Preparation of benzimidazole functional acrylate monomers.



Scheme 3. Transformation of N-Troc hydroxypropylbenzimidazole to 5-(1*H*-benzimidazol-2-yl)-propylmethyl carbonate.

expands the utility of the protection scheme by allowing selective protection of either the benzimidazole amine or the alcohol in hydroxypropylbenzimidazoles through an intramolecular rearrangement. O-Troc is not cleaved to the parent alcohol by basic methanol, but there are several methods reported that demonstrate clean removal of troc-protected alcohols.[10] Additionally, the N-Troc to O-Troc rearrangement was found to occur catalytically with triethylamine and dimethylaminopyridine, and with an equimolar amount of potassium carbonate, however, only minimal conversion was observed in the presence of pyridine.

In summary, we have identified a selective N-protection method for hydroxyalkylbenzimidazoles using 2,2,2-trichloroethylchloroformate. The scheme allows for the one-step protection of the benzimidazole nitrogen in the presence of a primary alcohol, exploiting the difference in nucleophilicity of the two groups. Once protected, a variety of functional groups can be selectively attached at the hydroxyl site, followed by rapid N-troc removal under mild basic conditions. Further, Troc-Cl can also be used to selectively protect the alcohol in hydroxypropylbenzimidazoles by performing a base catalyzed internal rearrangement of **5** in the presence of triethylamine.

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Supplementary data

An experimental section with procedural details and characterization information is included in a supplementary data file. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.037.

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