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Bulky alkylaminophenol chelates with high potential for functionalization

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ABSTRACT

Aminophenols are an important class of N,O-ligands, particularly for the coordination of first-row transition metals. While their structural and electronic character and the additional possibility of bioactivation are well appreciated in coordination chemistry, particularly of responsive systems, the synthesis of the more branched and structurally demanding models is still a challenge. Therefore, the synthesis of bulky bis(hydroxybenzyl)-*N*'-(aminopyridyl)propanamines is described here. It consists of the Mannich reaction of 2,4-disubstituted phenols with 3-aminopropan-1-ol and paraformaldehyde to *N*,*N*-bis(2-hydroxybenzyl)-3-aminopropan-1-ol. Substitution of the hydroxyl group with chlorine followed by amination with 2-(aminomethyl)pyridine results in bulky pentadentate N,O-ligands with a free site on the nitrogen atom for further functionalization. The method features good yields and high selectivity, and the products are well identified by spectroscopic methods.

1. Introduction

Alkylaminophenols constitute a principle group of N,O-ligands [1]. They are vastly applied for coordination of first row transition complexes, serving, for example, as catalysts in oxidation [2–5], polymerization processes [6], or organic carbonate synthesis from CO_2 [7–9]. Their benefits come from the tripod geometry of the alkylamine skeleton that allows for the formation of a chelating structure [10,11]. The amine nitrogen atom opens up the possibility of symmetry control [12]. Additionally, the electronic character of the nitrogen electron pair could be tuned and therefore fitted to many hard acids, such as high-valent d-block metals [13]. On the other hand, the presence of a phenol moiety in close vicinity of the nitrogen atoms secures the systems' high affinity to transition metals [14]. These features have attracted the attention of coordination chemists, who often impose additional factors on these ligands. One such structural factor is bulkiness of the substituents which allows for selective interactions (or even their elimination) with other molecules. Moreover, the recent enthusiasm in the idea of responsive molecules has launched the quest for systems which may be capable of covalent bond formation and cleavage within the molecule upon activation by an external stimulus [15]. This concept has already been investigated among bioresponsive contrast agents that belong to rapidly developed molecular probes [16,17]. Alkylaminophenols perfectly fit the basic elements of responsive molecules delivering a very tunable skeleton with both electronic and structural features, as has been demonstrated for magnetic resonance imaging contrast agents based on iron complexes [18–20]. Despite these benefits which are well appreciated due to the above-mentioned applications and despite some efficient methods such as the one published by Kerton et al that was carried out “on water” [21], synthetic approaches are still often a barrier to obtaining systems with the most desired features. For this reason, we present our study on branched, bulky *N*,*N*-bis(hydroxybenzyl)-*N*'-

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(pyridylmethyl)propanediamines **3** with one free nitrogen site for further substitution. This is an extended system of simpler *N*,*N*-bis(hydroxybenzyl)-*N*-ethan-*N*'-(pyridylmethyl)diamines which has already gained reasonable attention and has achieved most of the properties in groups of magnetic resonance imaging contrast agents [18].

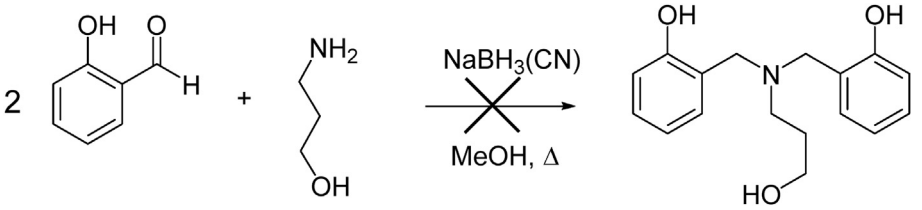
2. Results and discussion

The approach to the synthesis of *N*,*N*-bis(hydroxybenzyl)-*N*'-(pyridylmethyl)propanediamines was initially launched by a method our group published for their *N*-ethyl counterparts [18] (Scheme 1). However, the major product separated for the post-reaction mixture was reduced salicylaldehyde. A plausible explanation for this reaction's failure was lower nucleophilicity of 3-aminopropan-1-ol due to internal H-bonding as compared to 2-aminoethanol.

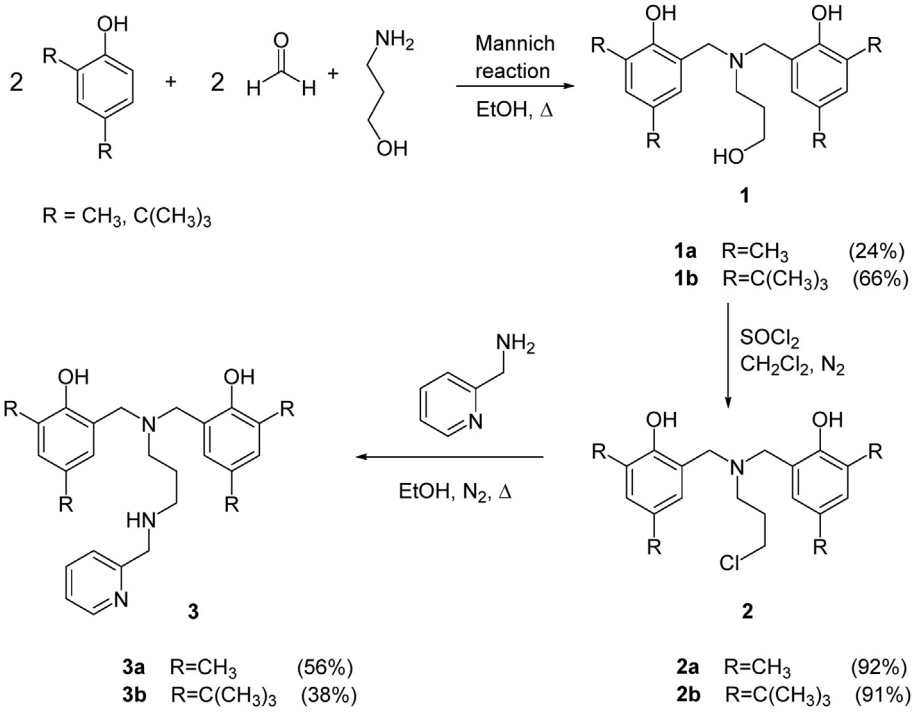
The alternative approach to the *N*,*N*-bis(hydroxybenzyl)-*N*-propane skeleton is via the Mannich reaction, analogous to ethyl derivatives [22]. There, due to the low regioselectivity of the benzene ring substitution in phenols, it is favored to block one of the *ortho* and the only *para* position with alkyl substituents. This was additionally beneficial to our idea of constructing a molecule with bulky substituents, thus, we used 2,4-dialkylphenols in the Mannich reaction (Scheme 2).

We were surprised to note that the yields (up to 66% for **1b**), although generally not high, were much more elevated than in our previous reductive amination approach (34% [18]). The final yields refer to the pure product of an apparently five-molecular, multistep, two-stage Mannich reaction. Byproducts were easily separated from the post-reaction mixture and identified as structures with a single phenyl fragment (Scheme 3).

The next step consisted chlorination of hydroxyl groups with thionyl chloride. The reaction proceeded through a multiphase reaction mixture of *N*- and *O*-sulfonation intermediates and their salts. However, the final workup by hydrolysis in aqueous bicarbonate led to crude product **2**, which is usually of sufficient quality for further transformations. The stability of the 3-chloropropan-1-amine



Scheme 1. Synthesis of *N*,*N*-bis(hydroxybenzyl)-*N*-propanamines via reductive amination.



Scheme 2. The Mannich reaction of 2,4-disubstituted phenols to *N*,*N*-bis(hydroxybenzyl)-*N*-propanamines. Yields of pure products are given in parentheses.

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