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Steric effects on forming different by-products in the formylation reaction of 2,4-dialkylphenol (dialkyl = *t*-Bu/*t*-Bu, *t*-Bu/Me and Me/Me) proved by their structural and spectral characterizations

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Abstract

In the formylation reaction of 2,4-dialkylphenol (2,4-di-*tert*-butylphenol, 2-*tert*-butyl-4-methylphenol and 2,4-dimethylphenol) in the presence of hexamethylenetetramine, steric effects of alkyl groups play important roles in forming different types of by-products, namely 2,4-di-*tert*-butyl-6-[(6,8-di-*tert*-butyl-2*H*-1,3-benzoxazin-3(4*H*)-yl)methyl]phenol (**1**), 2-*tert*-butyl-4-methyl-6-[(6-*tert*-butyl-8-methyl-2*H*-1,3-benzoxazin-3(4*H*)-yl)methyl]phenol (**2**) and tris(2-hydroxy-3,5-dimethylbenzyl)amine hydrochlorate (**3**). These three compounds are fully characterized and single-crystal structures of **1** and **3** are further elucidated.

Keywords: Formylation reaction; Steric effects; Crystal structures; Hydrogen bonding interactions

1. Introduction

Nitrogen-containing benzoheterocycles and their derivatives are important intermediates for organic synthesis and useful candidates for the studies on biochemistry and medicinal chemistry [1–3]. Tris(2-hydroxy-3,5-dialkyl)amines [4] are typical tripodal ligands and there have been many related reports in the literature. For instance, Holmes et al. reported the structures and dynamic NMR behavior of new classes of silatranes and phosphatranes derived from the tripodal ligand tris(2-hydroxy-3,5-dialkyl)amine [5]. Gallium(III) and Indium(III) complexes of tris(2-mercaptobenzyl)amine and tris(2-hydroxybenzyl)amine [6] and dimethoxy-(tris(2-oxy-3,5-dimethylbenzyl)amine) tantalum(IV) salts [7] have also been documented. With regard to tris(2-hydroxy-3,5-dimethylbenzyl)amine [8], its phenylphosphinate [9] and 2,2′-thiobis(4-methyl-6-*tert*-butylphenyl)phosphonate [10] as well as its Fe(III) complex have been structurally reported previously [11].

In addition to the conventional preparation methods, our experimental results show that 2,4-di-*tert*-butyl-6-[(6,8-di-*tert*-butyl-2*H*-1,3-benzoxazin-3(4*H*)-yl)methyl]phenol (**1**), 2-*tert*-butyl-4-methyl-6-[(6-*tert*-butyl-8-methyl-2*H*-1,3-benzoxazin-3(4*H*)-yl)methyl]phenol (**2**) and tris(2-hydroxy-3,5-dimethylbenzyl)amine hydrochlorate (**3**) can also be yielded as the main by-products in the process of Duff reaction [12] of 2,4-dialkylphenol and hexamethylenetetramine (HMT). However, different by-products can be obtained in different yields due to the use of different dialkyl ring substituents (dialkyl = *t*-Bu/*t*-Bu, *t*-Bu/Me and Me/Me), as can be seen in Scheme 1. In addition, we present herein the single-crystal structures of **1** and **3**.

2. Experimental

2.1. Materials and measurements

Melting points were measured without correction in this work. 2,4-Di-*tert*-butylphenol, 2-*tert*-butyl-4-methylphenol

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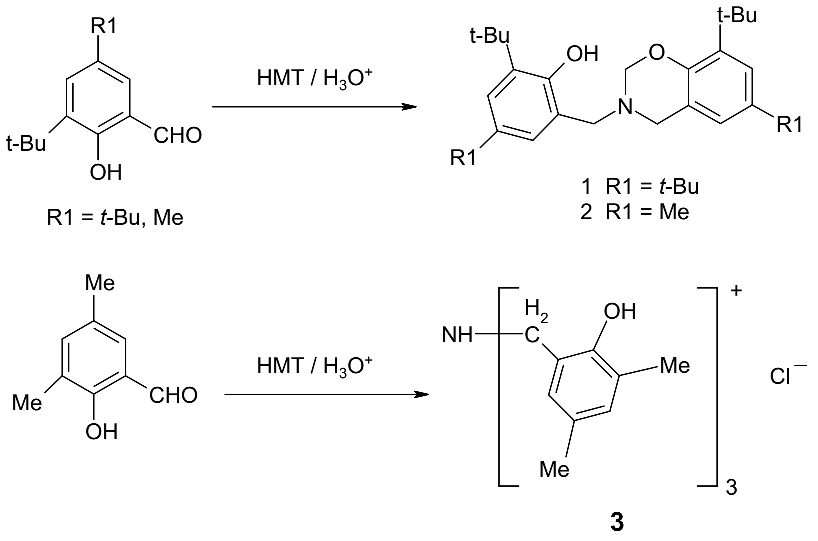

Scheme 1. Synthetic routes for compounds **1**–**3**.

and 2,4-dimethylphenol were purchased as commercial chemicals from Aldrich. All other solvents and reagents were of analytical grade and used without further purification. Analyses for carbon, hydrogen and nitrogen were performed on a Perkin-Elmer 1400C analyzer. Infrared spectra (4000–400 cm^{-1}) were recorded with a Nicolet FT-IR 170X spectrophotometer on KBr disks. ^1H NMR spectra were obtained in a Bruker 500 MHz NMR spectrometer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Finnigan MAT SSQ 710 mass spectrometer in a scan range of 100–1200 amu. The samples were determined by injecting the diluted methanol solutions using 1:1 methanol/water solvent as the mobile phase. The spray voltage and capillary temperature were set at 4.5 kV and 200 °C, respectively.

*2.2. Synthesis of 2,4-di-tert-butyl-6-[(6,8-di-tert-butyl-2H-1,3-benzoxazin-3(4H)-yl)methyl]phenol (**1**)*

The preparation method of **1** is the same as that of 3,5-di-*tert*-2-hydroxybenzaldehyde reported by Larrow et al. [13]. The crude product (mainly a mixture of 3,5-di-*tert*-2-hydroxybenzaldehyde and **1**) was suspended in a warm (55 °C) methanol solution and a white powder was separated by vacuum filtration which afforded compound **1** in a yield of ~35%. 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde could be separated from the filtrate by cooling to 0 °C and subsequent sucking in a yield of ~45%. Mp 167–168 °C. Anal. Calcd for $C_{31}H_{47}NO_2$: C, 79.95; H, 10.17; N, 3.01%. Found: C, 79.79; H, 9.96; N, 2.82%. IR (KBr disk, cm^{-1}): 3300 (OH), 2960, 2904, 2869 and 1390 (*t*-Bu), 1231 (C—O). ^1H NMR (500 MHz, $CDCl_3$, 298 K, TMS): δ 1.28 (s, 9H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.36 (s, 9H, *t*-Bu), 1.57 (s, 9H, *t*-Bu), 4.10 (s, 4H, N—CH_2—Ar), 4.87 (s, 2H, Ar—O—CH_2—N), 6.84 (s, 1H, Ar—OH), 7.23–7.32 (m, 4H, Ar—H). ESI-MS: *m*/*z* 466.3 $[C_{31}H_{47}NO_2+H]^+$ (100%). Single crystals suitable for X-ray analysis were grown from ethanol by slow evaporation at room temperature in air.

*2.3. Synthesis of 2-tert-butyl-4-methyl-6-[(6-tert-butyl-8-methyl-2H-1,3-benzoxazin-3(4H)-yl)methyl]phenol (**2**)*

The synthesis of 3-*tert*-butyl-5-methyl-2-hydroxybenzaldehyde is the same as 3,5-di-*tert*-2-hydroxybenzaldehyde in a yield of ~35% except that CH_3COOH was used to replace CF_3COOH. Compound **2** is not isolated because of the synthetic difficulties (<10% yield) but an ESI-MS peak at 382.1 corresponding to the cation of $[C_{25}H_{35}NO_2+H]^+$ (100%) verifies the presence of **2** in the residue.

*2.4. Synthesis of tris(2-hydroxy-3,5-dimethylbenzyl)amine hydrochlorate (**3**)*

The synthesis of 3,5-dimethyl-2-hydroxybenzaldehyde is the same as above-mentioned two aldehydes. Hydrochlorate **3** was obtained as precipitate from the water/ether mixture. The precipitate was collected and recrystallized by ethanol/water in a yield of ~40%. Mp 210–211 °C. Anal. Calcd for $C_{27}H_{34}ClNO_3$: C, 71.11; H, 7.51; N, 3.07%. Found: C, 71.03; H, 7.38; N, 2.97%. IR (KBr disk, cm^{-1}): 3241 (N—H), 3111, 3011, 2970, 2916, 2862, 1492, 1443, 1422, 1387 (CH_3), 1249, 1195 (C—O). ^1H NMR (500 MHz, $CDCl_3$, 298 K, TMS): δ 2.24 (s, 18H, CH_3), 4.08 (s, 6H, CH_2), 6.79 (s, 3H, Ar—OH), 7.03 (s, 3H, Ar—H), 7.29 (s, 3H, Ar—H), 9.28 (s, 1H, N—H). ESI-MS: *m*/*z* 420.2 $[C_{27}H_{34}ClNO_3-Cl]^+$ (100%). Single crystals suitable for X-ray analysis were grown from a mixture of ethanol and water in a 2:1 (v/v) ratio by slow evaporation at room temperature in air.