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SYNTHESIS OF A NEW TRIPROTONATED LIGAND AND SELECTIVE O-DEMETHYLATION OF METHYL ARYL ETHER BY BORON TRIBROMIDE

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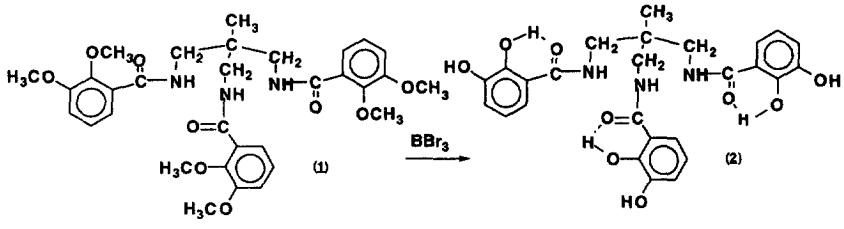
Abstract: Selective O-demethylation of the ortho methyl catecholate of *N,N',N"*-tris-(2,3-dimethoxybenzoyl)-1,1,1-tris-(L-methioninemehyl)-ethane (7) has been accomplished by boron tribromide. The intramolecular nucleophilic attack of divalent sulphur on methyl enhance this cleavage, favours this selctivity and consequently afford the triprotonated ligand *N,N',N"*-tris-(2-hydroxy-3-methoxybenzoyl)-1,1,1-tris-(L-methioninemethyl)-ethane (8) in a good yield.

Keywords: Catechol, Boron tribromide, Dealkylation

It was been reported very recently that ferric enterobactin undergoes a series of sequential protonation reactions that eventually result in a neutral triprotonated Fe^{3+} enterobactin complex as a salicylate mode of binding. This configuration facilitates the iron release by a biological reductant [1]. To confirm this hypothesis the first model was synthesised in many steps [2]. One of the salient steps in the preparation of such a compound is to protect the ortho- and meta-catechol with two different protecting groups. After building the siderophore backbone, selective O-dealkylation of the ortho-catechol lead to the formation of a ligand which was able to form a neutral triprotonated Fe^{3+}. However, this selectivity is not easily always obtained and depends on the nature of the different functions handled by the ligand. Thus, the choice of reagent capable of cleaving the alkyl aryl ether bound is very important. Many agents of O-dealkylation of ethers mostly in the homogenous phase have been reported. They are classified as Brönsted acid [3] such as hydrogen halogen, pyridin, amine salts (pyridinium chlorydrate and bromhydrate) or as Lewis acids [3-5] such as AlX_3 and BX_3. However, due to their nucleophilic character, bases [3] are also used as O-demethylating agents such as organo-alkali-metals. Recently, we reported the preparation of a new tris-catecholamide 1,1,1-tris-(2,3-dihydroxy)-ethane (2) analogue of enterobactin in which the O-demethylation is obtained both in position 2 and 3 on treatment of 1,1,1-tris-(2,3-dimethoxybenzoyl)ethane (1) by boron tribromide. This operation needs one or more equivalents of BBr_3 per catechol. This ligand was obtained in a good yield and considered as the smallest synthetic tris-catecholamide siderophore [8] (**Schema 1**).



Schema 1

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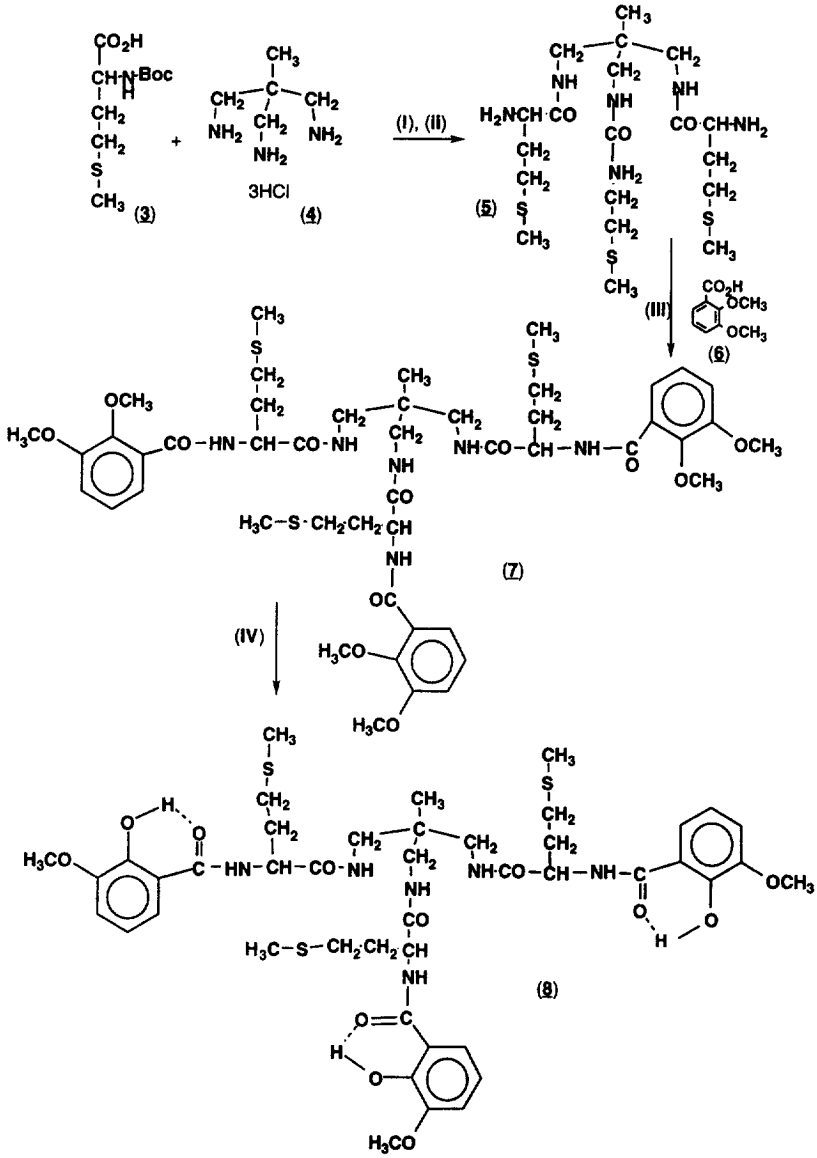
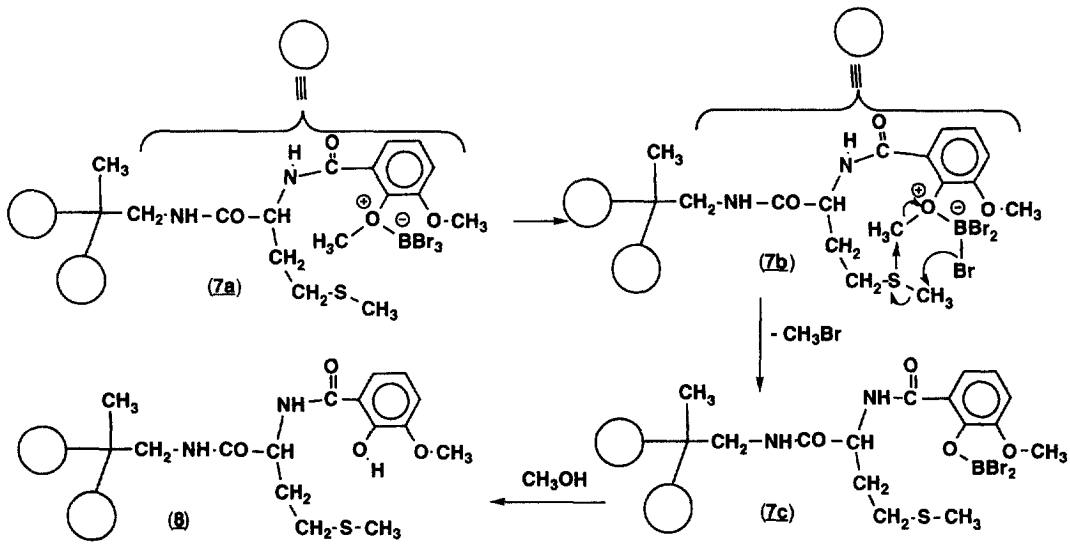
In connection with our interest in synthetic siderophore models, we report the preparation of a new triprotonated analogue of enterobactin (8) in this paper. This model was synthesised in three steps. The triamine or 1,1,1-tris-(aminomethyl)-ethane (4) was synthesised as reported elsewhere [8, 9]. The second step was the preparation of the activated form of Boc-L-methionine (3) using carbonyldiimidazole (CDI). No attempt was made to isolate the intermediate which was directly treated with 3 equivalents of triethylamine and one equivalent of triamine (4) in dichloromethane to give 1,1,1-tris-(Boc-L-methioninemethyl)-ethane in 75 % yield after chromatography. Removal of the Boc groups using CF_3CO_2H followed by evaporation under reduced pressure gave the 1,1,1-tris-(L-methioninemethyl)-ethane (5) [10] (100 %).



Scheme 2: Reagents and conditions: i, CDI, CH_2Cl_2, ii, CF_3CO_2H, iii, CDI, CH_2Cl_2, iv, BBr_3.

Finally the *N,N',N''*-tris-(2,3-dimethoxybenzoyl)-1,1,1-tris-(L-methioninemethyl)-ethane (7) [11] was obtained in a good yield by coupling 2,3-dimethoxy benzoïc acid (6) with triamine (5) using CDI. Due to the presence of six amide functions , basic O-demethylating agents were avoided and this operation succeeded only with good yield selectively for position 2 rather than position 3 in acidic conditions even using more than two equivalents of BBr_3 per catechol. This intriguing result is due to the presence of divalent sulphur on the molecule which contributes to this selective O-demethylation. In general, acidic reagents give rise to the formation of oxonium intermediates by transfer of proton (Brönsted acid) to oxygen , or by creation of dative bound O-metal (Lewis acid). Like most varieties of Lewis acids, the bore halides [13] were first implicated in the creation of a dative bound between oxygen atom of the ether and the bore atom of the Lewis acid to form oxonium species (7a). The reaction is therefore considered to proceed simultaneously via nucleophilic attack of both divalent sulphur and Br^- on the more electron-deficient carbon atom as shown in **scheme 3**. This intramolecular mechanism is in agreement with those reported elsewhere [14-16] for the cleavage of methylether of primary and secondary alcohols by the combination of a hard acid boron trifluoride and soft nucleophile thiols. To our knowledge this is the first example in which an intramolecular nucleophilic attack of divalent sulphur favours this selective O-demethylation. The nmr spectra of (8) shows a large downfield shift of the ortho-catechol hydrogen (12.09 ppm). However an excess of BBr_3 leads to an undesired cleavage of the S-CH_3 function and, consequently, the destruction of the ligand.



Scheme 3

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References and notes

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10. 1,1,1-tris-(L-methioninemethyl)-ethane (**5**) ^{1}H-NMR (250 MHz) δ_H (D_2O), 0.65 (s, 3H, CH_3); 1.87 (s, 9H, 3-S-CH_3); 1.95 (m, 6H, 3 -CH_2, J = 6.8 Hz); 2.39 (t, 6H, 3 -CH_2, J = 6.8 Hz); 2.93 (d, 6H, 3 -CH_2, J = 3.2 Hz); 3.90 (t, 3H, 3 -CH, J = 6.8 Hz); ^{13}C-NMR (250 MHz) δ_C 14.42 (s, S-$\underline{C}H_3$); 18.44 (s, $\underline{C}H_3$); 28.31 (s, $\underline{C}H_2$-S-); 30.98 (m, -$\underline{C}H_2$-CH_2); 40.92 (s, $\underline{C}H_2$-NH); 43.38 (s, $\underline{C}$-quat); 51.76 (m, $\underline{C}$H); 168.84 (s, $\underline{C}$=O); IC-MS (NH_4^+): *m/z* = 811 (M^++1).
11. *N,N',N''*-tris-(2,3-dimethoxybenzoyl)-1,1,1-tris-(L-methioninemethyl)-ethane (**7**) ^{1}H-NMR (200 MHz) δ_H ($CDCl_3$) 0.8 (s, 3H, CH_3) ; 2.10 (s, 9H, 3 -S-CH_3) ; 2.19 (m, 6H, 3 -CH_2) ; 2.55 (t, 6H, 3 -CH_2, J = 7.5 Hz) ; 3.01 (d, 6H, 3 -CH_2, J = 6.4 Hz) ; 3.89 (s, 9H, 3 -OCH_3) ; 3.94 (s, 9H, 3-OCH_3) ; 4.73 (m, 3H, CH) ; 5.31 (d, 3H, 3 -NH, J = 7.2 Hz); 7.17 (m, 6H, Aroma-H) ; 7.63 (dd, 3H, Aroma-H) ; 8.60 (m, 3H, 3 NH); ^{13}C-NMR (200 MHz) δ_C ($CDCl_3$) 15.33 (s, 3C, C-$\underline{C}H_3$) ; 19.48 (s, 1C, $\underline{C}H_3$) ; 30.04 (s, 3C, $\underline{C}H_2$-S) ; 31.84 (s, 3C, $\underline{C}H_2$-CH_2-S) ; 41.42 (s,1C, C-quater); 42.99 (s, 3C, $\underline{C}H_2$-NH) ; 53.20 (s, 3C, $\underline{C}$H) ; 61.45 (s, 3C, O$\underline{C}H_3$) ; 61.91 (s, 3C, O$\underline{C}H_3$) ; 115.65 (s, 3C, C-Aroma) ; 122.95 (s, 3C, C-Aroma) ; 124.24 (s, 3C, C-Aroma) ; 125.87 (s, 3C, C-Aroma) ; 147.73 (s, 3C, C-Aroma) ; 152.53 (s, 3C, C-Aroma) ; 165.33 (s, 3C, C=O); 172.21 (s, 3C, C=O), ESI *m/z*= 1003 ($(M+1)^+$, 100).
12. *N,N',N''*-tris-(2-hydroxy-3-methoxybenzoyl)-1,1,1-tris-(L-methioninemethyl)-ethane (**8**) ^{1}H-NMR (200 MHz) δ_H (DMSO-d_6) 0.66 (s, 3H, CH_3) ; 1.89 (m, 6H, CH_2) ; 2.01 (s, 9H, 3 S-CH_3) ; 2.86 (s, 6H, 2 CH_2) ; 3.15 (t, 6H, 2 CH_2) ; 3.76 (s, 9H, 3 OCH_3) ; 4.46 (m, 3H, 3 CH) ; 6.79 (t, 3H, Aroma-H, J = 7.6 Hz) ; 7.31 (d, 3H, Aroma-H, J = 7 Hz) ; 7.48 (d, 3H, Aroma-H, J = 7 Hz) ; 8.11 (t, 3H, 3 NH); 8.89 (d, 3H, 3 NH) ; 12.09 (s, 3H, 3 OH); ^{13}C-NMR (200 MHz) δ_C (DMSO-d_6) 15.28 (s, 3C, S-CH_3) ; 19.67 (s, 1C, CH_3) ; 31.27 (s, 3C, $\underline{C}H_2$-S-CH_3) ; 32.18 (s, 3C, $\underline{C}H_2$-CH_2-S-); 43.02 (s,3C, -$\underline{C}H_2$-) ; 43.92 (s,1C, C-quater) ; 54.79 (s, 3C, $\underline{C}$H) ; 56.65 (s, 3C, O$\underline{C}H_3$) ; 114.32 (s, 3C, C-Aroma) ; 116.01 (s, 3C, C-Aroma); 119.53 (s, 3C, C-Aroma) ; 122.02 (s, 3C, C-Aroma) ; 149.54 (s, 3C, C-Aroma); 153.27 (s, 3C, C-Aroma) ; 170.36 (s, 3C, C=O) ; 174.57 (s, 3C, C=O). ESI *m/z* = 961 ($(M + 1)^+$, 13.63) ; 983 ($(M + 23)^+$, 30.99), IC/NH_4^+ *m/z* = 961 ($(M + 1)^+$, 11.44).
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