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NEW SYNTHESIS OF 4,4'-DIMETHOXYTRITYL CHLORIDE USING ZINC HALIDES

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Abstract:
A new method for Friedel-Crafts alkylation is developed using zinc halides in excellent yield. This is an effective method for a large scale preparation of DMT-Cl from anisole and benzotrichloride. Zinc-catalyzed reactions are environmentally safe in comparison with aluminium trichloride-induced processes.

Keywords: Friedel-Crafts alkylation, Zinc halides, and Chlorination

Introduction:

In organic and medicinal chemistry, 4,4'-Dimethoxytrityl chloride (DMT-Cl) is an essential reagent, especially for the synthesis of oligonucleotides. In oligonucleotide synthesis, DMT-Cl is frequently used for the protection of hydroxyl group. In order to ensure selective reactivity during stepwise DNA and RNA synthesis, this transient protection is essential. It is extremely significant in pharmaceutical and biomedical applications due to its distinct protective and removable characteristics.[1] An environmentally safe and scalable process is always a great surge of interest to synthetic chemist across the world.[2] The synthesis of 4,4'-dimethoxytrityl chloride involves the Friedel-Crafts alkylation of anisole with benzotrichloride in the presence of a Lewis acid catalyst such as aluminium chloride ($AlCl_3$). This method allows for the regioselective introduction of the trityl group onto the aromatic ring, driven by the electron-donating effect of the methoxy group, which activate the para and ortho positions. The Friedel-Crafts reaction proceeds via carbocation electrophilic substitution, forming the desired DMT-Cl product with high selectivity. [3, 4, 5]

We have investigated an efficient and environmentally safe reaction condition for synthesis of 4,4'-dimethoxytrityl chloride using zinc-mediated Lewis acid and the results are given below.

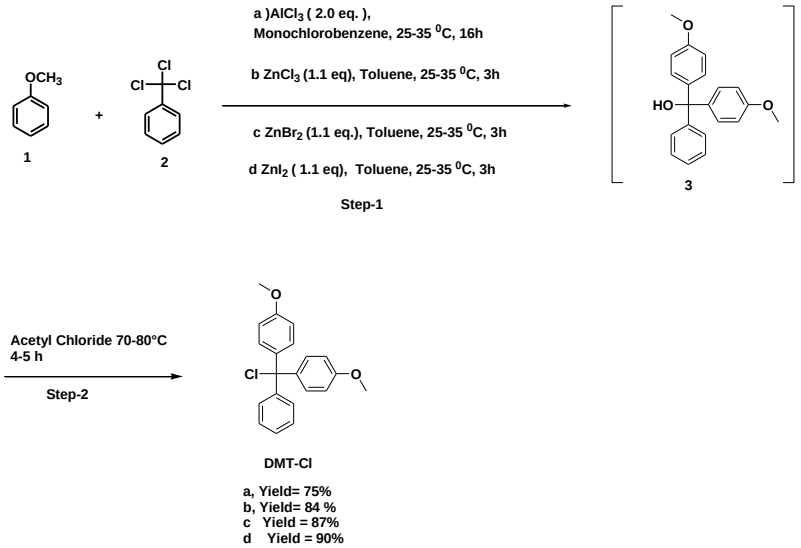
Results and Discussion:

Traditionally, the synthesis of DMT-Cl follows a Friedel-Crafts alkylation mechanism where benzotrichloride reacts with anisole in the presence of a strong Lewis acid catalyst, such as aluminium chloride. While $AlCl_3$ effectively facilitates electrophilic aromatic substitution, it poses significant environmental and safety concerns, including corrosiveness, waste generation, and stringent handling requirements. [6,7, 8]

Anisole was reacted with benzotrichloride in the presence of a Lewis acid using a chlorinated solvent as the reaction medium. The reaction was carried out at a temperature range of 0°C to 30°C for 6–8 h, resulting in the formation of desired product.[9, 10]The molar ratio of anisole to benzotrichloride in step-1 was in the range of 2.0 to 1.0. The molar ratio of the Lewis acid to benzotrichloride in step-1 was maintained within the range of 1.0 to 1.1.

As part of the ongoing efforts to develop greener and more sustainable synthetic methodologies, alternative catalysts with comparable or superior efficiency are highly desirable. Zinc halides ($ZnBr_2$, $ZnCl_2$, and ZnI_2) have emerged as promising substitutes due to their lower toxicity, water solubility, and reduced environmental impact. Unlike $AlCl_3$, which requires extensive neutralization and generates large amounts of waste, $ZnBr_2$ and ZnI_2 offer a more environmentally benign and easily removable catalytic system. Using zinc halides ($ZnBr_2$, $ZnCl_2$ and ZnI_2) as Lewis acid catalysts, 4,4'-dimethoxytrityl chloride (DMT-Cl) was effectively synthesized from anisole and benzotrichloride as an alternative to conventional aluminium chloride ($AlCl_3$)-catalyzed techniques. Compared to $AlCl_3$, the use of zinc halides offered a number of benefits, such as reduced corrosiveness, enhanced environmental compatibility, and ease of handling. Additionally, a reduced output of acidic byproducts simplified the reaction workup, facilitating more effective product isolation and purification. Overall, this enhanced synthetic strategy utilizing zinc halides provides a more viable and sustainable way to produce DMT-Cl, which enables it for extensive industrial uses in organic synthesis[11], medicinal chemistry, and oligonucleotide synthesis. Future research may explore green solvents, solvent-free techniques, or alternative catalysts to further enhance the efficiency and sustainability of the process.

Scheme-1



Conclusions:

It has been demonstrated that the Friedel-Crafts alkylation for the synthesis of 4,4'-dimethoxytrityl chloride (DMT-Cl) using Lewis acid, zinc halides as an alternative to conventional aluminium chloride-catalyzed reaction. Compared to aluminium chloride the use of zinc halides offered a number of benefits, such as reduced corrosiveness, enhanced environmental compatibility, and ease of handling on manufacturing process.

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11. **Synthesis of 4,4'-Dimethoxytrityl chloride:** A) To a solution of toluene (10 L) and anisole (2.43 kg, 22.48 mol), zinc bromide (2.53 kg 11.24 mol) was added at 2 to 5°C. To this reaction mixture a solution of benzotrichloride (2 kg, 10.23 mol) in toluene (2 L) was slowly added. After addition, temperature of reaction mixture was rise up to 25 to 35°C. The reaction mixture was allowed to continuous stirring for 3-4 h. The conversion of reaction is monitored by TLC. After complete conversion of benzotrichloride, un-dissolved solid was filtered and the filtrate was collected and washed with water. The toluene layer was further treated with acetyl chloride (0.9 kg, 11.46 mol) at 70 to 75°C and continue maintained at 70 to 75°C temperature for 5-6 h. Distillation of toluene was carried out under vacuum below 70°C. After the distillation completed, n-hexane (10 L) was added and cool it to 25 to 35°C for 2 h. The isolation of product was done by filtration, isolated solid dried under vacuum (650-700 mm/Hg) for 6-8 h to get 2.94 kg of crystalline solid in 87% yield. The compound showed ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 7.20-780 (*m*, 9H), 6.20 (*s*, 1H), 3.8 (*s*, 6H). ESI-MS: for $C_{21}H_{19}ClO_2$ [M+H]/z: 339.19.

B) To a solution of toluene (10 L) and anisole (3 kg, 27.7 mol), zinc iodide (3.12 kg, 9.78 mol) was added at 2 to 5°C. To this reaction mixture a solution of benzotrichloride (2.46 kg, 12.59 mol) in toluene (2 L) was slowly added. After addition, temperature of reaction mixture was rise upto 25 to 35°C. The reaction mixture was allowed to continuous stirring for 3-4h. The conversion of reaction is monitored by TLC. After complete conversion of benzotrichloride, undissolved solid was filtered and filtrate was collected and washed with water. The toluene part was treated with acetyl chloride (1.1 kg, 18.18 mol) at 70 to 75°C for 5-6 h. Distillation of toluene was carried out under vacuum below 70°C. After the distillation completed, n-hexane (10 L) was added and cooled it to 25 to 35°C for 2 h. The isolation of product was done by filtration, isolated solid dried under vacuum (650-700 mm/Hg) for 6-8 h to get 3.05 kg of crystalline solid in 90% yield. ESI-MS: for $C_{21}H_{19}ClO_2$ [M+H]/z: 339.19.

C) To a solution of toluene (10 L) and anisole (2.75 kg, 25.4 mol), zinc chloride (2.86 kg, 20.97mol) was added at 2 to 5°C. To this reaction mixture a solution of benzo trichloride (2.26 kg, 11.56 mol) in toluene (2 L) was slowly added. After addition, temperature of reaction mixture was rise up to 25 to 35°C. The reaction mixture was allowed to continuous stirring for 3-4h. The conversion of reaction is monitored by TLC. After complete conversion of benzotrichloride, solid was filtered and filtrate was collected and washed with water. The toluene layer was treated with acetyl chloride (1.01 kg, 16.7 mol) at 70 to 75°C and maintained at 70 to 75°C temperature for 5-6 h. Distillation of toluene was carried out under vacuum below 70°C. After the distillation completed, n-hexane (10 L) was added and cooled it to 25 to 35°C for 2 h. The isolation of product was done by filtration, isolated solid dried under vacuum (650-700 mm/Hg) for 6-8 h to get 2.85 kg of crystalline solid in 84% yield; ESI-MS: for $C_{21}H_{19}ClO_2$ [M+H]/z: 339.19.

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