Tetrahedron Letters 53 (2012) 11-14

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Selective methoxy ether cleavage of 2,6-dimethoxyphenol followed by a selective acylation

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ARTICLE INFO

Article history: Received 9 July 2011 Revised 25 October 2011 Accepted 26 October 2011 Available online 31 October 2011

Keywords: Friedel-Crafts Fries rearrangement Selective methoxy cleavage Selective acylation Ethacrynic acid Substituted catechols

ABSTRACT

A Friedel–Crafts reaction of 2,6-dimethoxyphenol in the presence of aluminum chloride and propanoyl or butanoyl chloride, respectively, lead, at elevated temperatures, to a selective cleavage of one of the methoxy groups followed by a selective acylation of the *meta* position with respect to the phenolic hydroxyl group. Under the same reaction conditions 2-methoxyphenol does not get demethylated; a mechanism to account for these findings is proposed. This reaction gives access to a variety of *ortho*-acylated catechols. Substituted catechols are widely used in supramolecular chemistry and are precursors of pesticides, flavors, and fragrances. Additionally, catechol moieties are found in various natural products.

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The Friedel–Crafts alkylation and acylation of aromatic systems, commonly known as the Friedel–Crafts reaction, was developed by Friedel and Craft in 1877.¹ This reaction is still a very important tool in synthetic organic chemistry. In our laboratory, we are using this reaction to synthesize analogs of ethacrynic acid (EA) (Fig. 1). Ethacrynic acid is a loop diuretic which is used to treat high blood pressure and edema.^{2,3} Some of our analogs possess a significant potency to inhibit the migration of several cancer cell lines.^{4,5}

As the starting materials for the syntheses of the EA analogs, we used various substituted phenols or phenol itself. In the first step, these compounds were acylated by a Friedel–Crafts reaction in the presence of aluminum chloride (AlCl₃) as the Lewis acid catalyst and the corresponding acyl chloride in carbon disulfide (CS₂) as the solvent. If the reaction was carried out below room temperature, the major products obtained from the acylation reaction were esters, formed via O-acylation of the phenolic oxygen of the phenol derivatives. In order to obtain the C-acylated products (*ortho* or *para* to the hydroxyl group), the reaction has to be carried out at higher temperatures. At these elevated temperatures, the Fries rearrangement takes place in which the phenyl ester rearranges to the hydro-xy aryl ketone.^{6,7} This protocol worked very well for all of the phenol derivatives we used, except for 2,6-dimethoxyphenol **1** (Scheme 1). To our surprise, the Friedel–Crafts acylation with this

compound did not yield the expected *para*-acylated hydroxy aryl ketone. Instead, it lead to a selective cleavage of one of the methoxy groups with a subsequent acylation of the position meta to the hydroxyl group, to form 1-(2,3-dihydroxy-4-methoxyphenyl)propan-1-one 6 or 1-(2,3-dihydroxy-4-methoxy-phenyl)butan-1-one 7, respectively, as the major product (Scheme 1). In order to further investigate the product formation, we performed the reaction at various temperatures. When the reaction was carried out at 0 °C for 12 h, the major product obtained from the reaction was 2,6dimethoxyphenyl propionate 2 or 2,6-dimethoxyphenyl butyrate 3, respectively (Scheme 1). Carrying out the reaction at room temperature for 12 h, mainly lead to the formation of the para-acylated products 1-(4-hydroxy-3,5-dimethoxyphenyl)propan-1-one 4 and 1-(4-hydroxy-3,5-dimethoxyphenyl)butan-1-one **5**, respectively. However, if the reaction was performed at elevated temperatures (approximately 46 °C), a selective cleavage of one of the methoxy groups followed by a selective acylation of the meta position occurred to form 1-(2,3-dihydroxy-4-methoxyphenyl)propan-1-one



Figure 1. Structure of ethacrynic acid (EA).







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Scheme 1. Friedel-Crafts reaction of 2,6-dimethoxyphenol 1 with an acyl chloride at different temperatures and the corresponding yields.







Scheme 3. Proposed mechanism for the reaction of 2,6-dimethoxyphenol **1** with propanoyl or butanoyl chloride, respectively.

6 or 1-(2,3-dihydroxy-4-methoxyphenyl)butan-1-one **7**, respectively (Scheme 1).

To investigate the selective cleavage of one of the methoxy groups more in-depth, we wanted to determine whether aluminum chloride ($AlCl_3$) or the respective acyl chloride or a combination of both is responsible for the ether cleavage. Thus, we refluxed



Scheme 4. Proposed mechanism for the reaction of 2-methoxyphenol **8** with propanoyl or butanoyl chloride, respectively.



2,6-dimethoxyphenol **1** in CS_2 in the presence of 3 equiv of $AlCl_3$ but in the absence of acyl chloride. After 24 h, the only compound we could isolate was the starting material (Scheme 2). Additionally, we performed the reaction in the presence of 3 equiv of butanoyl chloride or 3 equiv of propanoyl chloride, respectively, but in the absence of $AlCl_3$. After 24 h of reflux in CS_2 , we obtained the same result; only the starting material could be isolated. An early conclusion is that the selective cleavage only occurs in the presence of both $AlCl_3$ and the respective acyl chloride.

Additional investigations were carried out with 2-methoxyphenol $\mathbf{8}$ and 3-methoxyphenol, respectively. Both phenol derivatives were reacted with propanoyl chloride and butanoyl chloride under the same reaction conditions as described above and for both compounds no ether cleavage was obtained. These results were insofar surprising since due to the structural similarity of 2-methoxyphenol **8** and 2,6-dimethoxyphenol **1**, it was expected that 2-methoxyphenol **8** will also be demethylated in the Friedel–Crafts acylation reaction.

An extensive literature search revealed that various Lewis acids such as aluminum trihalides or boron trihalides have been used as ether-cleaving agents,^{8–11} in particular AlCl₃¹² and BCl₃¹³ can be used to selectively cleave aromatic methoxy groups adjacent to a carbonyl function without affecting other methoxy groups present in the molecule. Haraldsson et al. have reported the selective cleavage of aromatic benzyl ethers with magnesium bromide via a neighboring group effect.¹⁴ In 1979, Paul et al. reported the selective cleavage of 2,3,4,6-tetramethoxybenzaldehyde with aluminum chloride at position 2 (*ortho* to the carbonyl function).¹⁵ To the best of our knowledge, there has been no report on the selective ether cleavage of *ortho* methoxy phenols with additional acylation of the position *para* to the hydroxyl group of the substituted phenol.

In the following, we propose a mechanism for the reaction of 2,6-dimethoxyphenol **1** with propanoyl or butanoyl chloride, respectively (Scheme 3). This mechanism shall account for our findings that one of the methoxy groups of 2,6-dimethoxyphenol **1** gets demethylated in these reactions, whereas this cannot be observed for 2-methoxyphenol **8** (Scheme 4).

The first step of the proposed mechanism is the formation of an ester via O-acylation of the hydroxyl group of the phenol derivative (not shown in Scheme 3). The next step includes a complexation of aluminum chloride to the carbonyl oxygen of the ester and to the oxygen of the methoxy group as shown in Scheme 3; additionally a second molecule of aluminum chloride chelates into the other side between the phenolic oxygen and the oxygen of the methoxy group, to form complex **A**. The loss of a chloride anion from the aluminum chloride forms complex **B** and produces a nucleophile (Cl⁻), which, even if poor, is capable of attacking the carbon of the methoxy group, thereby cleaving the ether. We believe that this cleavage is possible due to the double complexation of 2.6-dimethoxyphenol 1 to aluminum chloride which makes this compound highly electron deficient and thus very reactive toward the Cl⁻ attack on the carbon of the methoxy group. On the other hand, this activation through a 'double complex' is not possible for 2-methoxyphenol 8 (Scheme 4). Simultaneously, the ester is cleaved (similar to the Fries rearrangement) to generate an acylium carbocation which is coordinated to the aluminum (complex C). Due to the possible free rotation about the O-Al single bond, complex **D** is formed simply by rotating about the O-Al bond and now the acylium carbocation can attack the carbon of the phenyl ring *meta* to the phenolic oxygen atom to form complex **E**. Due to the coordination of the acylium carbocation to the aluminum, this electrophilic attack leads, due to sterical reasons, exclusively to the *meta*-acylated phenol derivatives **6** or **7**, respectively, which can be obtained after an aqueous work-up (Scheme 3).

The first step of the proposed mechanism of the reaction of 2methoxyphenol **8** with an acyl chloride is also the formation of an ester via O-acylation of the hydroxyl group of the phenol derivative (not shown in Scheme 4). The next step includes a complexation of aluminum chloride to the carbonyl oxygen of the ester and to the oxygen of the methoxy group, as shown in Scheme 4, to form complex **F**. This complex undergoes an intramolecular Fries rearrangement and the free acylium carbocation attacks either the *ortho-* or *para*-position with respect to the phenolic oxygen of 2methoxyphenol **8** to form the *ortho-* or the *para*-product, respectively (Scheme 4).

The above proposed mechanism for the formation of compounds 6 and 7 (Scheme 3) explains why 2,6-dimethoxyphenol 1 undergoes a selective methoxy cleavage, whereas this is not observed for 2-methoxyphenol 8. Another feasible mechanism to account for our findings is that aluminum chloride only binds to the carbonyl oxygen of the ester and to the oxygen of the methoxy group of both compounds, 2,6-dimethoxyphenol **1** and 2-methoxyphenol 8. In this case, the open side ortho to the phenolic oxygen of 2methoxyphenol 8 would make the carbonyl carbon of the ester, compared to 2,6-dimethoxyphenol 1, more sterically accessible (Fig. 2). Therefore, we propose that immediately after the activation of the corresponding compound (complexation) with AlCl₃, aluminum chloride migrates to the phenolic oxygen atom (Scheme 4), thereby generating a free acylium carbocation. This rearrangement is much faster than the loss of a Cl⁻, therefore, no demethylation is observed for 2-methoxyphenol 8. Since the ortho side of 2,6-dimethoxyphenol **1** is blocked, the migration of aluminum chloride is slow compared to the abstraction of a Cl⁻ and its subsequent attack on the carbon of the methoxy group which would lead to the observed demethylation of 2,6-dimethoxyphenol 1.

In order to underpin our proposed mechanism, we performed the Friedel–Crafts acylation with 3,5-dimethoxyphenol **9** under the same reaction conditions as described above (Scheme 5). We carried out the reaction at 0 °C, at room temperature, and at elevated temperatures. The results are shown in Scheme 5.

At 0 °C and at room temperature the formation of the ester **10** or **11**, respectively, predominates and at higher temperatures the *para*-acylated product (1-(4-hydroxy-2,6-dimethoxyphenyl)propan-1-one **12**, or 1-(4-hydroxy-2,6-dimethoxyphenyl)butan-1-one) **13**



Scheme 5. Friedel-Crafts reaction of 3,5-dimethoxyphenol 9 with an acyl chloride at different temperatures and the corresponding yields.

was formed as the major product. No product from a selective cleavage of one of the methoxy groups was obtained which is not surprising since an activation of 3,5-dimethoxyphenol 9 by AlCl₃ is not possible in the way it is described above for 2,6-dimethoxyphenol 1.

In summary, the work presented here demonstrates that in the presence of an acyl chloride (e.g., propanoyl chloride or butanoyl chloride, respectively), and a Lewis acid catalyst (AlCl₃), 2,6-dimethoxyphenol **1** undergoes a selective methoxy cleavage with a subsequent acylation of the position *meta* to the phenolic oxygen atom. A mechanism to account for the observed results has been proposed and underpinned by various experiments. Further investigations with other methoxy substituted phenols are currently underway in our laboratory.

General procedure: ¹⁶ 2,6-dimethoxyphenol **1** (154 mg, 1.0 mmol, 1.0 equiv) was added to carbon disulfide at room temperature. Powdered aluminum chloride (267 mg, 2.0 mmol, 2.0 equiv) was added in batches. The mixture was allowed to stir for 10 min at room temperature before the corresponding acyl chloride (1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was refluxed for 12 h and after cooling to room temperature, carbon disulfide was decanted. The residue was added to a mixture of ice (10.0 g) and concentrated hydrochloric acid (approximately 1 mL to obtain pH 1) which yielded an oily fraction. The fraction was extracted three times with ether (10 mL) and the combined organic layers were washed with 5% sodium bicarbonate solution (10 mL) and dried over sodium sulfate. The obtained yellow liquid was purified through column chromatography using ethyl acetate/hexane (1:5) as the eluent.

Acknowledgments

The financial support of the US National Institutes of Health (P20 RR016480) under the INBRE program of the National Center for Research Resources (NCRR) is greatly appreciated.

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