Selective Demethylation of 3-Phenoxyquinoxalin-2(1h)-one Acetate Derivatives

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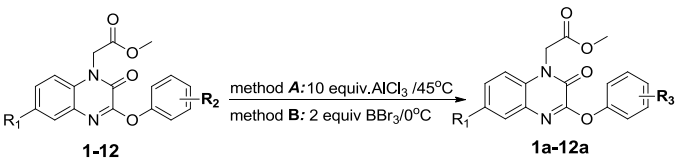
ABSTRACT: Using the previously reported novel quinoxaline scaffold, we synthesised the precursor compounds **1-12**. According to the synthetic methodology, we described the discovery of a novel selective demethylation of quinoxaline derivatives with $AlCl_3$ and BBr_3, proposed a high selectivity demethylation approach. And this approach will provide a opportunity for developing new antioxidant base on phenolic hydroxyl.
KEYWORD: demethylation; diabetes; quinoxaline

1 INTRODUCTION

Diabetes mellitus is a metabolic disorder in which the body's ability to regulate blood glucose levels goes awry, either from defects in the secretion or in the activity of the hormone insulin.[1] Several hypotheses have been proposed to explain the pathogenic mechanism leading to diabetic complications and the prominent theory suggests that the activation of aldose reductase causes significant portion of the glucose enter into polyol pathway under hyperglycemia leading to the accumulation of sorbitol, which results in diabetic complications. High level in free radicals of reactive oxygen species (ROS) and in turn the oxidative stress under hyperglycemia is also ascribed to a major cause of the diabetic complications.

In order to develop new drugs for the therapy of the diabetic complications, we have designed and synthesized a series of quinoxaline derivatives as aldose reductase inhibitors (ARIs).[2] Recently, we further designed a group of 3-phenoxyquinoxalin-2(1h)-one acetate derivatives as ARI candidate which may have radical scavenging capability.[2] During the synthesis of the compounds, phenolic methoxyl and methyl ester were present at the same time in the intermediate and therefore the selective demethylation of the phenolic methoxyl was a key step. Herein, we discuss about the demethylation method and its selectivity.

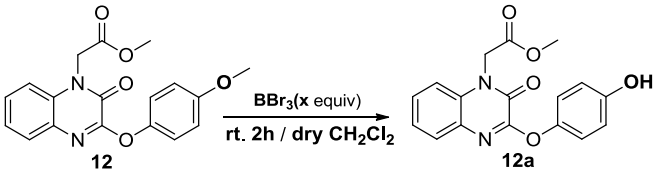
Table 1. Optimization of conditions for the demethylation of $AlCl_3$ and BBr_3



NO.	R	R_2	R_3	$Y1^{[a]}$	$Y_2^{[b]}$
1	F	3,5-$(CH_3O)_2$	3,5-$(OH)_2$	82%	30%
2	F	3,4-$(CH_3O)_2$	3,4-$(OH)_2$	no reaction	25%
3	F	4-CH_3O	4-OH	no reaction	37%
4	C	3,5-$(CH_3O)_2$	3,5-$(OH)_2$	86%	20%
5	C	3,4-$(CH_3O)_2$	3,4-$(OH)_2$	no reaction	38%
6	C	4-CH_3O	4-OH	no reaction	27%
7	B	3,5-$(CH_3O)_2$	3,5-$(OH)_2$	88%	*28%*
8	B	3,4-$(CH_3O)_2$	3,4-$(OH)_2$	no reaction	34%
9	B	4-CH_3O	4-OH	no reaction	19%
10	H	3,5-$(CH_3O)_2$	3,5-$(OH)_2$	85%	31%
11	H	3,4-$(CH_3O)_2$	3,4-$(OH)_2$	no reaction	25%
12	H	4-CH_3O	4-OH	no reaction	23%

[a] Y_1 represent the isolated **1a-12a** yield of method A
[b] Y_2 represent the isolated **1a-12a** yield of method B

Table2. Optimization of conditions for the demethylation of **12** with BBr_3



entry	BBr_3(x equiv)	Yield[a]
1	0.5	40%
2	1	84%
3	1.5	53%
4	2	27%
5	2.5	13%
6	3	trace
7	3.5	trace

[a] Isolated yield based on **12**

2 RESULTS AND DISCUSSION

The preparation of compounds **1-12** was based on the reported method.[2] An extensive literature research revealed that various lewis acids such as aluminum trihalides or boron trihalides have been used as mild demethylation agents, and in particular $AlCl_3$ and BBr_3 can be used to selectively remove the methyl of aromatic methoxy groups.[3] Thus, $AlCl_3$ and BBr_3 were used as demethylation reagents in the present study. Compounds **1-12** were treated with excess of $AlCl_3$ (method A) at 45℃ or BBr_3 (method B) at room temperature as shown in Table1. [4,5]

By the method A, the reaction of compounds **1**, **4**, **7**, and **10** were observed with $AlCl_3$ in high yields of 82%, 86%, 88%, and 85%, respectively, while no reaction was found for the remained compounds. However, by method B the reaction with BBr_3 was observed for all substrates **1-12**, but it only gave low yield of 19% to 38%. Therefore, the reaction condition was further optimized for the method B with **12** as a sample of the substrates, and the product **12a** was obtained in good yield of 84% using one equivalent of BBr_3 (Table 2). Less or more equiv BBr_3 all resulted in trace product or in low yield of 13%. These results suggest that the mount of BBr_3 could greatly affect the yield.

3 CONCLUSION

The present study found that the lewis acid $AlCl_3$ as demethylation agent was specific for the demethylation of meta-methoxyl of aromatic ring of quinoxaline derivatives in high yield. However, BBr_3 could be used for the demethylations of all substrates and lead to good yields using a suitable mount of the demethylation agent.

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