Study of the ortho-methoxy substituent group effect in selective demethylation reactions of methoxybenzoic acids.

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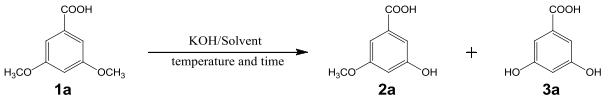
INTRODUCTION

The methylation of the hydroxyl group is largely used in synthesis due to high stability of the methoxy group to several reaction conditions. However, the procedures for *O*-demethylation of aryl methyl ethers involves the use of costly reagents or elaborated methods, requiring anhydrous conditions or difficult to carry out. In most cases the simplest methods of *O*-demethylation are not selective, resulting in complete demethylation products[1,2]. In order to prepare demethylated 3,5-dimethoxybenzoic derivatives, this work presents a new selective methodology for demethylation of phenolic methoxyl group using simple and inexpensive reagents. The methodology was adjusted to 3,5-dimethoxybenzoic acid and is summarized in the reaction of aryl methyl ether with ethylene glycol, KOH, at 120 °C or 180 °C.

RESULTS AND DISCUSSION

Initial testing were carried out with 3,5-dimethoxybenzoic acid, we have determined that the entry 7 has been the best condition found for the highest yield of the desired product (Table 1). This methodology was also applied to 2,3-, 2,4- and 2,6-dimethoxybenzoic acids; 4-methoxybenzoic and 4-bromo-3,5-dimethoxybenzoic acids. In such cases it was possible to observe that the reaction has proceeded best at 180 °C and in the *ortho* or *para*-methoxyl substrates was observed the formation of decarboxylation products (Table 2).

Table 1. Monodemethylation reaction conditions for 3,5-dimethoxybenzoic acid using ethylene glycol or diethylene glycol and KOH.

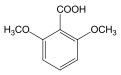
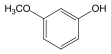
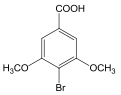
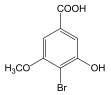


1a 2a 3a

entry	KOH (equiv)	solv.	Temp. (°C)	Time (h)	**2a** yield (%)	**3a** yield (%)
1	3,7	DEG	220	16	30,9	8,4
2	5	DEG	220	16	38,5	22,7
3	5	DEG	180	16	---	---
4	23	DEG	220	16	10,8	35,9
5	23	DEG	180	16	75,8	4,5
6	23	DEG	220	4	54,7	13,9
7	23	EG	180	4	99,2	---

DEG= Diethylene glycol EG= Ethylene glycol

Table 2. *O*-demethylation of aryl methyl ethers using ethylene glycol and KOH.

entry	diethers	KOH (equiv)	Temp (°C)	Time (h)	Product	yield (%)
1	 **1b**	23	180	4	 **2b**	100
2	 **1c**	23	180	4	 **2c**	99
3	 **1d**	23	180	4	 **2d**	92
4	 **1e**	23	180	4	 **2e**	99
5	 **1f**	23	180	4	 **2f**	96
6	 **1g**	10	180	4	 **2g**	89

CONCLUSION

This methodology resulted in the selective demethylation of aryl methyl ethers and the desired products were obtained in good yields. However, in substrates with a methoxy group at the *ortho* position products of decarboxylation were produced too.

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