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Pyridinium hydrobromide perbromide induces *ipso* bromodeformylation in *o*-hydroxy and *o*-methoxy substituted aromatic aldehydes†

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Abstract—The reaction of *o*-hydroxy and *o*-methoxy substituted aromatic aldehydes with PHPB in pyridine gives aromatic bromination products including those arising from *ipso* bromodeformylation.

Pyridinium hydrobromide perbromide (PHPB[1]) has been extensively used in synthetic organic chemistry as a halogenating[2] and oxidizing[3] reagent among other uses.[4] Less frequently, this compound has also been employed as a reagent for aromatic bromination.[5]

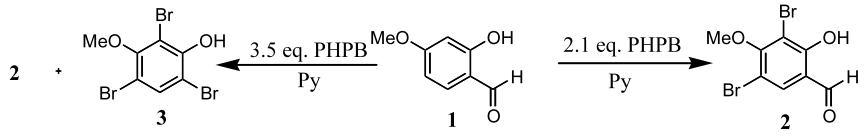
In this context, the bromination of 2-hydroxy-4-methoxybenzaldehyde **1** using PHPB (2.1 equiv., pyridine) has been reported to give the expected 3,5-dibromo-2-hydroxy-4-methoxybenzaldehyde **2** in 83% isolated yield[6] (Scheme 1). In our hand this experiment was well reproduced (80% isolated yield of **2**). However, we have observed that the use of 3.5 equiv. of PHPB affords, under the same reaction conditions, a mixture of **2** and 2,4,6-tribromo-4-methoxyphenol **3** in a ratio 3:2 = 93:7 (evaluated by GC/MS) and 65% overall yield. As a result we deduce that an *ipso* substitution of the formyl group took place after aromatic bromination.

Considering that, to the best of our knowledge, this *ipso* formyl substitution induced by PHPB has not been previously reported,[7] we have studied some aspects of this reaction. Our results are described in the present report.

Benzaldehyde, 1- and 2-naphtaldehyde did not react with PHPB under a range of conditions: we recovered quantitatively the starting aromatic compound. In sharp contrast with these results, substituted *o*-methoxy or *o*-hydroxybenzaldehydes (with the exception of *o*-methoxybenzaldehyde itself[8]) undergo reaction with PHPB to give mixtures of aromatic bromination products with concomitant *ipso* substitution of the formyl group. These results are quoted in Table 1.

Regarding the features of this reaction, two aspects should be indicated. First, the presence of an hydroxy or methoxy group *ortho* to the formyl group appears to be necessary in order to achieve the *ipso* substitution. Furthermore the reaction of 3,5-dimethoxybenzaldehyde with PHPB (4 equiv.) affords a mixture of 2-bromo-3,5-dimethoxybenzaldehyde **4** and 2,6-dibromo-3,5-dimethoxybenzaldehyde **5** in a ratio 4:5 = 7:1 and 51% overall yield. No trace of *ipso* substitution product was observed (Scheme 2).

On the other hand, it is known that substituted benzaldehydes are oxidized by the action of PHPB in acetic acid.[10] In order to determine whether the related carboxylic acid is an intermediate of the *ipso* substitution



Scheme 1.

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† Dedicated to Dr. Manfred Stud. *'In memoriam'*.

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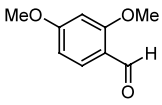
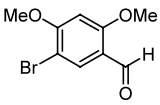
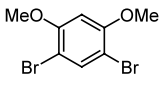
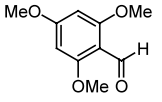
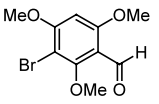
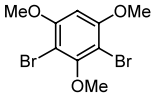
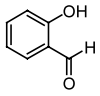
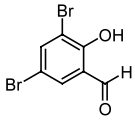
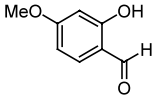
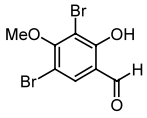
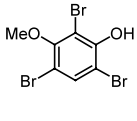
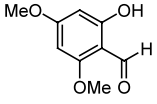
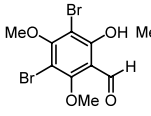
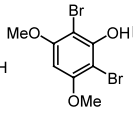
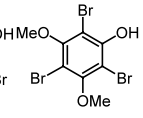
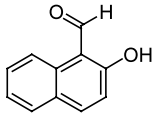
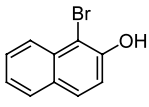
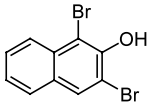
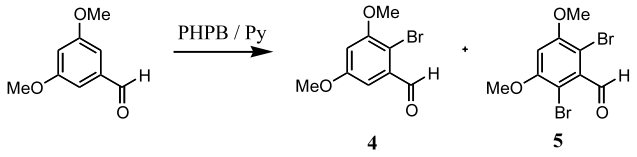
Table 1. Reaction of some substituted aromatic aldehydes with PHPB[9]

Entry	Aldehyde	Overall yield [b]	Product distribution [a]	Eq.of PHPB
			 	
1		91	95 : 5	3.0
2		82	62 : 38	5.0
			 	
3		93	64 : 36	3.0
4		64	34 : 66	5.0
			 	
5		36	76 : 24	3.0
6		70	29 : 71	4.0
			 	
7		80	100 : 0	2.1
8		65	7 : 93	3.5
			  	
9		70	9 : 11 : 80	4.0
			 	
10		31	61 : 39	3.0
11		68	100 : 0	1.1

a) Determined by GC/MS. Conditions: Capillary column 95% dimethyl 5% diphenylpolysiloxane. Gradient of temperature 45º-290ºC. Mass spectrometer, HP 5890.
b) Purified mixture of products.

reaction, salicylic acid was subjected to the reaction with PHPB in pyridine (3 equiv.). As a result 52% of 2,4,6-tribromophenol was obtained. Thus, if the carboxylic acid is an intermediate of the reaction, the need of an hydroxy or methoxy group in *ortho* position to the formyl (or carboxylic) group can be justified by the formation of a complex PHPB-aromatic compound, as indicated in Fig. 1, analogous to the proposed for the decarboxylation of formic and oxalic acid by reaction with PHPB in acetic acid solution[11] (Fig. 1).



Scheme 2.

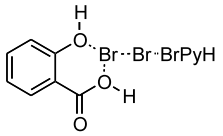


Figure 1.

In summary, a new reaction of *ipso* bromodeformylation induced by PHPB in pyridine has been described. This reaction competes with the expected aromatic bromination when activated *o*-hydroxy or *o*-methoxybenzaldehyde were subjected to it. In the case of less activated aromatic aldehydes (2-hydroxy-1-naphtaldehyde) the *ipso* bromodeformylation was the only process observed.

Acknowledgements

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8. It has been reported that in the reaction of *o*-methoxybenzaldehyde with PHPB in a mixture of H_2O:AcOH:Et_2O (10:40:50), 8% of a 'monobromination product' was obtained. See Ref. 5d. When we carried out the reaction of this aldehyde with PHPB in pyridine the starting material was quantitatively recovered.
9. **Experimental procedure**: A solution of pyridinium hydrobromide perbromide in pyridine (1 mL/mmol) was added dropwise to a solution of the aldehyde in pyridine (2 mL/mmol) at 50°C. The reaction was stirred for 2 h at 50°C and then hydrolyzed with ice-water (100 mL/g aldehyde). After filtration of the precipitate, this was purified by column chromatography (AcOEt:hexane = 1:2 v/v). All isolated products were characterized by IR, ^{1}H, ^{13}C NMR, and MS.
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