



# A synthetic approach towards novel alkyl 4,5-dibromo-2-methylbenzoate derivatives

Gabriela Alejandra Gauna<sup>a</sup>, Diego Cobice<sup>b</sup>, Josefina Awruch<sup>a,\*</sup>

<sup>a</sup>Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 1113 Buenos Aires, Argentina

<sup>b</sup>Boehringer Ingelheim S.A., R&D—Development Center, Av. del Libertador 7208, 1429 Buenos Aires, Argentina

## ARTICLE INFO

### Article history:

Received 31 March 2008

Received in revised form 8 May 2008

Accepted 16 May 2008

Available online 21 May 2008

### Keywords:

Arenes

Ethers

Esters

Oxidation

N-Bromosuccinimide

## ABSTRACT

Alkyl 4,5-dibromo-2-methylbenzoate derivatives **16–18** were synthesized from 1,2-dibromo-4-alkoxy-methyl-5-methylbenzene **2–4** in the presence of catalytic amounts of NBS as a radical initiator. Only primary ether derivatives rendered the corresponding esters.

© 2008 Elsevier Ltd. All rights reserved.

## 1. Introduction

Benzyl ethers react with NBS in carbon tetrachloride under free radical conditions to give favorable yields of the corresponding benzaldehydes.<sup>1,2</sup> When benzylic trimethylsilyl ethers are allowed to react with NBS in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile in boiling carbon tetrachloride, the corresponding aldehydes are obtained in good yields.<sup>3</sup> However, aliphatic primary trimethylsilyl ethers give esters directly formed from two molecular equivalents of the starting trimethylsilyl ethers rather than the expected aliphatic aldehydes.<sup>4</sup> In addition, alcohols were found to be oxidized to the corresponding carboxylic acid in the presence of catalytic NBS in an oxygen atmosphere at room temperature and irradiation with a 400 W high-pressure mercury lamp. Among the solvents examined, ethyl acetate and acetonitrile were found to be the most effective to afford the corresponding carboxylic acid. Additionally, 4-substituted electron-donating or electron-withdrawing benzyl alcohols afforded the corresponding benzoic acids in good yields.<sup>5,6</sup>

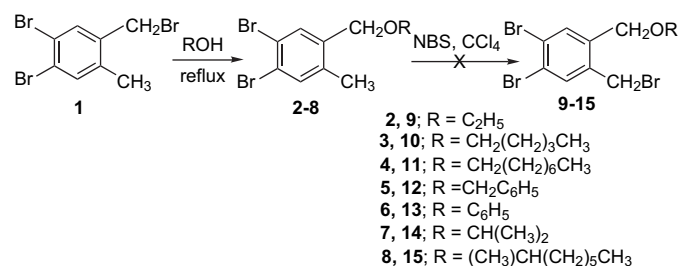
Methyl bromination of 1,2-dibromo-4-alkoxymethyl-5-methylbenzene (**2–8**) could be a possible route to prepare precursors for different degrees of lipophilic derivatives by replacing the bromine atom. However, the reaction of **2–8** (1 equiv) with NBS (1 equiv) to obtain desired compounds **9–15** gave unexpected results.

## 2. Results and discussion

### 2.1. Synthesis and characterization

Attempts to obtain compounds **9–15** by reaction of **2–8** (1 equiv) and NBS (1 equiv) under reflux in carbon tetrachloride failed. As shown in Scheme 1, the starting material was 1,2-dibromo-4-bromomethyl-5-methylbenzene (**1**) synthesized from 1,2-dibromo-4,5-dimethylbenzene (1 equiv) and NBS (1 equiv) in boiling carbon tetrachloride. This reaction was achieved without a radical initiator since there was no difference whatever with or without benzoyl peroxide, used as an initiator; results were practically the same.<sup>7</sup> The reaction of **1** with sodium alkoxide gave 1,2-dibromo-4-alkoxymethyl-5-methylbenzenes **2–8**.

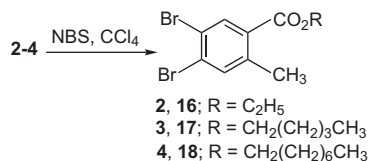
When a mixture of **2–4** (1 equiv) and NBS (1 equiv) was heated overnight under reflux in carbon tetrachloride esters **16–18** were



Scheme 1. Obtention of ethers **2–8** from compound **1**.

\* Corresponding author. Tel.: +54 11 4964 8252; fax: +54 11 4508 3645.  
E-mail address: jawruch@ffyb.uba.ar (J. Awruch).

obtained in good yields (Scheme 2),<sup>8</sup> while benzylic (5) and phenol (6) ethers, as well as secondary alcohol ethers (7, 8) yielded 4,5-dibromo-2-methylbenzoic acid (19), in fair to good yields.



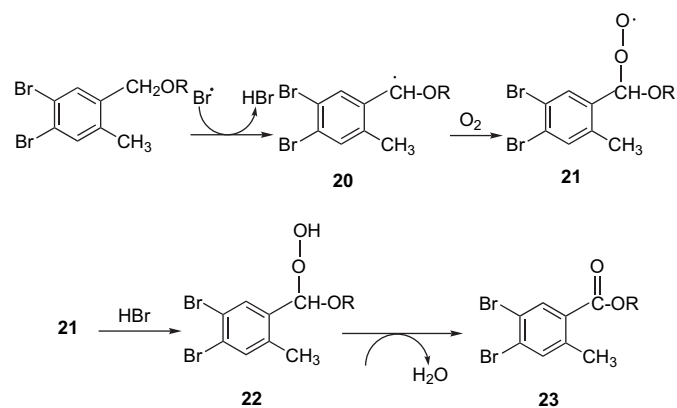
Scheme 2. Conversion of ethers 2–4 to esters 16–18.

Based on these results, further studies have been initiated to investigate the reaction of 2–8 with catalytic amounts of NBS. Therefore, 2–4 (1 equiv) and NBS (0.02 equiv) were reacted in boiling carbon tetrachloride. Different reaction times were analyzed, showing 40% yield during the first 2 h of the reaction and reaching 71, 63 and 87% yield after 4 h reaction for compounds 16, 17 and 18, respectively. The reaction of 5–8 with NBS (0.02 equiv) carried out in boiling carbon tetrachloride afforded 19 after a 2 h reaction, Figure 1. The reaction of 2–8 with NBS (0.02 equiv) in the presence of benzoyl peroxide (0.02 equiv) as initiator in carbon tetrachloride at reflux temperature, under the above conditions, rendered the same products and yields obtained without any radical initiator. These results are consistent with those obtained by our group some years ago.<sup>7</sup>

The formation of acid 19 can be understood taking into account that secondary alcohol derivatives, as well as benzylic alcohol and phenol esters, are capable of giving a stable carbonium ion in the acidic medium after protonation and S<sub>N</sub>1 hydrolysis thus allowing us to obtain 4,5-dibromo-2-methylbenzoic acid (19). On account of the instability of the corresponding carbocation, ester derivatives of the primary alcohols are unable to follow the proposed mechanism, hence esters 16–18 are obtained as the main product.

On the other hand, an attempt to purify 1,2-dibromo-4-*tert*-butoxymethyl-5-methylbenzene by filtering through a silica gel column failed to afford it. 1,2-Dibromo-4-hydroxymethyl-5-methylbenzene was obtained in good yields due to hydrolysis.

Formation of the esters can be rationalized as outlined in Scheme 3. A radical species 20 is generated by the abstraction of a hydrogen radical with a bromo radical. The radical species traps molecular oxygen to afford peroxy radical 21, which subsequently turns into ester 23 via hydroperoxide 22. This mechanism is similar to that reported by Kuwabara and Itoh<sup>5</sup> who described the oxidation of benzyl alcohols to acids by means of *N*-bromosuccinimide, oxygen and light at room temperature. Traces of 4,5-dibromo-2-methylbenzoic acid (19) were obtained as an additional evidence of the proposed mechanism. Besides, the obtention of esters 16–18 in the presence of catalytic amount of NBS is a further evidence of the proposed path.



Scheme 3. Mechanism of ether oxidation.

Substrate	Product	Yield (%)
		71
		63
		87
		50
		41
		71
		68

Figure 1. Reaction products of 1,2-dibromo-4-alkoxymethyl-5-methylbenzene with catalytic amounts of NBS.

Download English Version:

<https://daneshyari.com/en/article/5228170>

Download Persian Version:

<https://daneshyari.com/article/5228170>

[Daneshyari.com](https://daneshyari.com)