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An improved method for the synthesis of γ-lactones using sodium bromate and sodium hydrogen sulfite

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Abstract—*o*-Alkylbenzenecarboxylic acids are treated with a sodium bromate and sodium hydrogen sulfite reagent under a two-phase system using ethyl acetate as solvent, under mild conditions to give the corresponding cyclized phthalides in moderate to satisfactory yield. Intermediately the α-brominated alkylbenzenecarboxylic acids are formed by the in situ generated hypobromous acid. These α-brominated acids undergo an intramolecular nucleophilic substitution reaction to afford the corresponding γ-lactones. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Many natural products have γ-lactone skeletons,[1] most of which display a wide variety of significant biological activity.[2] They have also been employed as key intermediates for the synthesis of natural products.[3] A number of papers[4–6] and reviews[7] have been published on the synthesis of phthalides. This reveals that the direct preparation of γ-lactones from the corresponding *o*-alkyl aromatic carboxylic acid is very useful and important. Thus, there have been extensive studies on the preparation of such skeletons. Previously, $Na_2S_2O_8$, $AgNO_3$ and CuX_2 at 80°C,[8] oxidative cyclization with [bis(trifluoroacetoxy)iodo]benzene and iodine via aromatic carboxyloxy radicals[9,10] and lactonization with organohypervalent iodine compounds in the Suarez system[11] are reported for direct conversion of *o*-alkylbenzenecarboxylic acids to γ-lactones.

In this communication we describe the conversion of *o*-alkyl aromatic carboxylic acids into its corresponding γ-lactones by using the $NaBrO_3/NaHSO_3$ reagent at room temperature under a two-phase system.

The chemistry of the $NaBrO_3/NaHSO_3$ reagent has been widely studied because it can serve as an effective bromohydroxylation reagent of olefins,[12] alkynes, allylic alcohols.[13] The oxidation of primary alcohols,[14] diols, ethers[15] and α-bromination of alkyl benzenes[16] was also reported. In the course of our study to extend the scope of the $NaBrO_3/NaHSO_3$ reagent in organic synthesis, we have found that *o*-alkyl aromatic carboxylic acids are converted directly in a two-phase system using ethyl acetate/water and ambient conditions to the corresponding γ-lactones (Scheme 1).

2. Results and discussions

$NaBrO_3/NaHSO_3$ and most of the *o*-alkyl aromatic carboxylic acids **1a**–**1e** are commercially available (Merck, Fluka, Aldrich). The required starting material 2-benzylbenzoic acid (**1g**) was prepared using literature procedures[17,18] whereas 2-ethylbenzoic acid (**1f**), 2-*n*-propylbenzoic acid (**1h**) and 2-*n*-butylbenzoic acid (**1i**) were prepared by the lithiation–alkylation of *o*-methylbenzoic acid.[19,20] In a typical experiment, to a two-phase system comprised of a solution of *o*-methylbenzoic acid (**1a**) in ethyl acetate and aqueous $NaBrO_3$ (3 equiv.) aqueous $NaHSO_3$ (3 equiv.) was added over a period of about 15 min and stirred at room temperature for 40 h. The phthalide **2a** was obtained in 63% yield which is higher in comparison to when using other oxidation agents.[9,10] The yields using

Keywords: sodium bromate; sodium hydrogen sulfite; hypobromous acid; intramolecular nucleophilic substitution; phthalide and derivatives.

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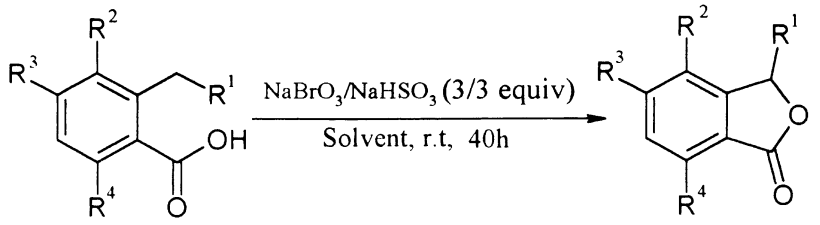

1

1a: $R^1=R^2=R^3=R^4=H$
1b: $R^1=R^2=R^4=H$, $R^3=Br$
1c: $R^1=R^3=R^4=H$, $R^2=NO_2$
1d: $R^1=R^2=R^3=H$, $R^4=NH_2$
1e: $R^1=R^2=R^4=H$, $R^3=CH_3$

1f: $R^2=R^3=R^4=H$, $R^1=CH_3$
1g: $R^2=R^3=R^4=H$, $R^1=C_6H_5$
1h: $R^2=R^3=R^4=H$, $R^1=C_2H_5$
1i: $R^2=R^3=R^4=H$, $R^1=C_3H_7$

2

2a: $R^1=R^2=R^3=R^4=H$
2b: $R^1=R^2=R^4=H$, $R^3=Br$
2c: $R^1=R^3=R^4=H$, $R^2=NO_2$
2d: $R^1=R^2=R^3=H$, $R^4=NH_2$
2e-I: $R^1=R^2=R^4=H$, $R^3=CH_3$
2e-II: $R^1=R^2=R^4=H$, $R^3=CH_2Br$
2f: $R^2=R^3=R^4=H$, $R^1=CH_3$
2g: $R^2=R^3=R^4=H$, $R^1=C_6H_5$
2h: $R^2=R^3=R^4=H$, $R^1=C_2H_5$
2i: $R^2=R^3=R^4=H$, $R^1=C_3H_7$

Scheme 1.

Table 1. Synthesis of γ-lactones from *o*-alkylbenzenecarboxylic acids

Substrate	Lactone	Yield (%)
1a	**2a**	63
1b	**2b**	60
1c	**2c**	58
1d	**2d**	17
1e	**2e-I/2e-II**	50/19
1f	**2f**	53
1g	**2g**	68
1h	**2h**	51
1i	**2i**	49

this two-phase system are gradually higher than in a homogeneous solution in acetonitrile, where **2a** is obtained only in a yield of 41%. Using the above procedure, the γ-lactones shown in Table 1 were prepared.

Only 2-amino-6-methylbenzoic acid (**1d**) which is not sufficiently soluble in ethyl acetate gave under these conditions, the γ-lactone in lower yields 8%. However, when this reaction was carried out under homogeneous conditions using CH_3CN as a solvent, the corresponding γ-lactone was obtained in 17% yield. The results are given in Table 1.

We have found a one-step conversion of *o*-alkyl aromatic carboxylic acids **1** to the corresponding γ-lactones **2** by using the $NaBrO_3/NaHSO_3$. This reagent generates HOBr which delivers a Br-radical in the aqueous solution.[16] The radical moves to the ethyl acetate phase where **1** is dissolved, brominates the benzyl group and subsequently by intramolecular nucleophilic attack forms the γ-lactones **2**.[21,22]

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21. A: To a solution of **1** (3 mmol) in AcOEt (6 ml) and $NaBrO_3$ (9 mmol) in H_2O (4.5 ml) was added $NaHSO_3$ (9 mmol) in H_2O (9 ml) during a period of 15 min, and the mixture was stirred at room temperature for 40 hours. The mixture was extracted with diethyl ether (50×3). Then the combined organic layer was washed with aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo to leave crude materials. B: To a solution of **1** (3 mmol) in CH_3CN (12 ml) and $NaBrO_3$ (9 mmol) in the H_2O (9 ml) was added $NaHSO_3$ (9 mmol) in H_2O (18 ml) during a period of 15 min at ambient temp. The product was worked up as described above.
22. All compounds were isolated by column chromatography (silica gel, hexane:ethyl acetate = 10:1) and were characterized by IR, EIMS, FDMS and NMR spectral data and compared with available spectral data of the literature quoted in Refs. 5, 9, 11.