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Original article

Selective amination of the mucohalic acid derivatives

Tian-Cai Li [a], Cou-Xi Chen [a], Xue-Qiang Li [a,b,*], Xiao-Hui Gao [a]

[a] School of Chemistry and Chemical Engineering, Ningxia University, Yinchuan 750021, China
[b] Ningxia Development Center of Natural Products and Medication, Ningxia University, Yinchuan 750021, China

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ABSTRACT

An efficient synthesis of 4,5-diamino-3-halofuran-2(5*H*)-ones has been developed based on a sequential acylation and bisamination of mucohalic acids. The β- and γ-amination products have also been prepared with high regioselectivity. This reaction shows some advantages in terms of its simple operation and readily available but highly functionalized starting material. All products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and HRMS.

1. Introduction

Butenolides [2(5*H*)-furanones] are an important class of compounds, because the butenolide motifs are found in many complex natural products and pharmaceutical intermediates [1]. For example, 5-hydroxyfuran-2(5*H*)-ones have shown activity as antimutagen, bactericides, antitumor agents, allergy inhibitors, stimulatory agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, *etc.* [2]. Despite these achievements, the development of efficient and convenient methods for the synthesis of highly functionalized butenolides for further elaboration is still of current interest.

Recently, 3,4-dihalo-5-hydroxy-2(5*H*)-furanones (mucohalic acids) have attracted considerable attention due to their unique disposition of various functionalities [3]. According to the literature, those inexpensive, commercially available materials can be easily transformed to various substituted butenolides in the presence of different nucleophilic reagents *via* three different pathways (Scheme 1): (a) *via* a Michael addition-elimination process at the vinylogous position to afford compound **2**. (b) *via* an S_N2 process at the allyl position to give the γ-substituted product **3**. (c) *via* an S_N2' process to form compound **4**.

However, only one molecular nucleophile participated in those reactions described above. There are no reports on such a process occurring at both the vinylogous and allyl positions to furnish β, γ-disubstituted product **5A**. Herein, we wish to report a successful diamination process of mucohalic acid derivatives to afford 4, 5-diamino-3-halofuran-2(5*H*)-ones (Scheme 2).

2. Experimental

A represent procedure for the amination of the mucohalic acid derivatives with amines is presented as following:

To a stirred solution of 5-acetoxy-3,4-dihalo-5*H*-furan-2-one **1** (1 mmol) in toluene (20 mL) was added excess of amine **6** at 20–30 °C. After an additional 1.5 h (monitored by TLC), The resulting mixture was poured into ice water (10 mL) and toluene (20 mL), the organic layers were dried over anhydrous Mg_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether–EtOAc (4:1) to give the target product **5k**: Light-yellow solid, mp 116–118 °C, yield 46%.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.14 (s, 3H), 3.84 (m, 2H), 4.67 (m, 2H), 5.49 (s, 1H), 7.17–7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.46, 158.66, 136.80, 136.01, 127.29–129.23, 91.21, 87.90, 74.25, 55.59, 38.62 29.70; IR (KBr, cm^{-1}): ν_{max}: 2935, 1731, 1614, 1456, 1319, 1114, 732. ESI-TOFMS *m/z*: 401. 0865 $[M+H]^+$, calcd. for $C_{20}H_{22}BrN_2O_2$: 401.0865.

3. Results and discussion

Recently, Zhang *et al.* [4] reported an efficient amination process of mucohalic acids **1**, but only γ-substituted product (*via* an S_N2 process) was formed even an excess amount of amine was used. It is very interesting that a favorable Michael addition-elimination process did not occur. We believed that the two processes are competitive in this reaction and envisioned that the

* Corresponding author.
E-mail address: lixq@nxu.edu.cn (X.-Q. Li).

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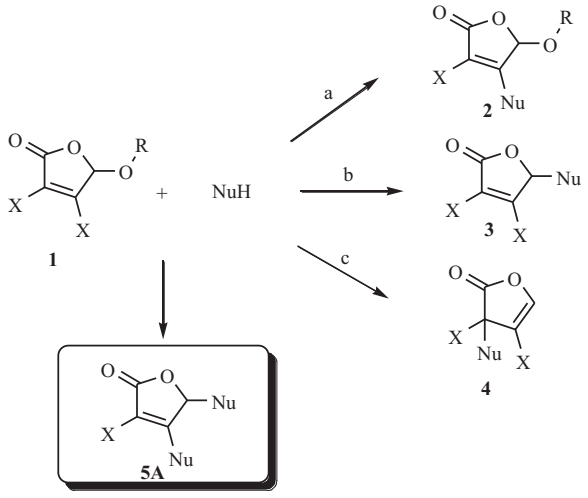
Table 1
Bisamination of mucohalic acids **1**.

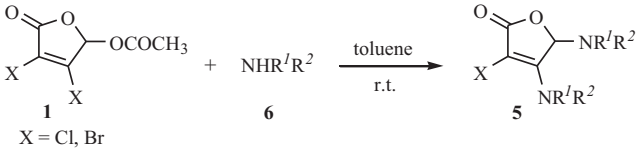
Entry	1	6		T (h)	5	Yield (%)[a]
	X	R^1	R^2			
1	Br	H	Me	4	**5a**	59
2	Br	H	Et	4	**5b**	58
3	Br	H	*n*-Pr	1.5	**5c**	60
4	Br	H	*n*-Bu	1.5	**5d**	60
5	Br	H	Bn	1.5	**5e**	48
6	Cl	H	Me	4.5	**5f**	55
7	Cl	H	Et	4	**5g**	55
8	Cl	H	*n*-Pr	1.5	**5h**	58
9	Cl	H	*n*-Bu	1.5	**5i**	59
10	Br	Me	Me	1	**5j**	53
11	Br	Me	Bn	1.5	**5k**	46
12	Cl	Me	Me	1	**5l**	50

[a] Isolated yields.

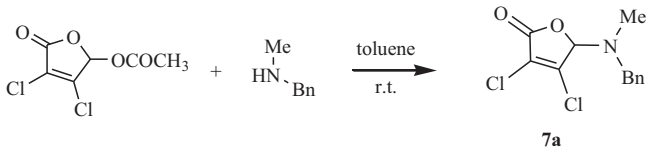
bisamination product could form by a careful choice of amines and conditions. The starting material **1** was prepared readily by the acylation of the hydroxy group in mucohalic acid in the presence of a solid acid catalyst [5]. To our delight, mucohalic acid acetates **1** reacted with some selected amines in toluene at room temperature affording a series of β, γ-disubstitution products **5** in moderate to good yields (Table 1). Treatment mucobromo or mucochloric esters with selected primary amines gave the corresponding β, γ-bisamination products **5** in good yields (entries 1–9). The mucobromo acid acetate reacted with benzylamine gave β, γ-diamination product **5e** in 48% yield in a short period of time, which is different from Zhang's report (entry 5) [4]. For less hindered dimethylamine, both mucobromo and mucochloric acid acetates can be converted to β, γ-diamino products **5** in moderate yields (entry 10 and 12). When *N*-methylbenzylamine was used, the mucobromo acid acetate gave β, γ-diamination product **5k** in 46% yield, while the mucochloric acid acetate only afforded γ-amination product **7a** in 68% yield. (entry 11 and Scheme 3).



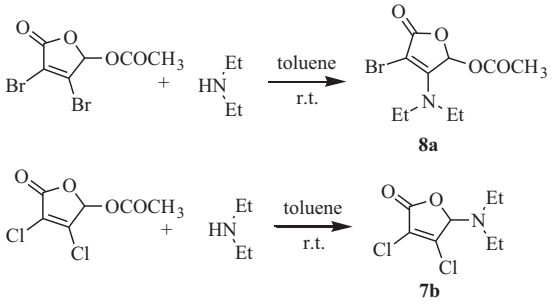
Scheme 1. Reactions of the mucohalic acid derivatives with nucleophilic reagents.



Scheme 2. Amination of the mucohalic acid derivatives.



Scheme 3. γ-Amination of mucochloric ester with secondary benzyl amine.



Scheme 4. Different regioselectivities of the aminations of mucobromo ester and mucochloric ester.

Presumably these differences were caused by nucleophilic reagents steric effects.To compare the difference between mucobromo and mucochloric acid acetate in reactivity, they were both treated with diethylamine. Surprisingly, the mucochloric derivative gave the γ-amination product **7b** in 70% yield. However, the mucobromo acid acetate afforded the β-amination product **8a** in 75% yield (Scheme 4). We thought this is due to the difference of the C–X bond energy. The results indicated that the regioselectivity of the substitution reaction could be more easily controlled by choosing the suitable mucohalo acid derivatives and amine by comparison with Klaus's report [6].

4. Conclusion

In conclusion, we have reported an efficient synthesis of various 4,5-diamino-3-halofuran-2(5*H*)-ones, and disclosed an interesting way to control the regioselectivity of amination of the mucohalo acid derivatives. Further investigations on the mechanistic study and extension of the scope of these reactions are under way in our group.

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