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SHORT COMMUNICATION

SYNTHESIS OF AZIDO DERIVATIVES OF MUCOBROMIC ACID

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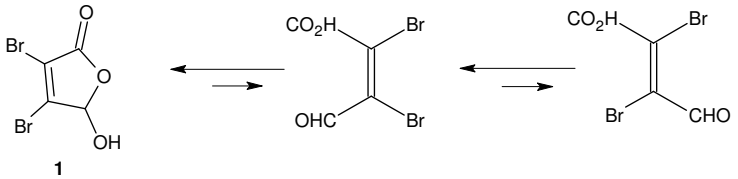
ABSTRACT. Mucobromic acid is a highly reactive multicentered molecule. It was converted to its corresponding but unstable diazido derivative by reaction with two equivalents of sodium azide. The resultant 3,4-diazido-5-hydroxyfuran-2(5H)-one was obtained in moderate yield (42%) but decomposed readily even at low temperatures. Its more stable analogue 3,4-diazido-5-methoxyfuran-2(5H)-one was obtained in excellent yield after reacting 5-methoxy-3,4-dibromofuranone with two equivalents of sodium azide. The 4,5-dibromopyridazinones which are in effect masked mucobromic acid derivatives, underwent nucleophilic substitution reactions with various nucleophiles, including azides and afforded corresponding azidopyridazinones in good yields. The synthesized azido-furanone and pyridazinone derivatives are earmarked for click reactions.

KEY WORDS: 3,4-Diazido-5-hydroxyfuran-2(5H)-one, 3,4-diazido-5-methoxyfuran-2(5H)-one, 4,5-Diazidopyridazinones, Mucobromic acid

INTRODUCTION

Fossil-based chemical raw materials are becoming increasingly scarce and expensive and it is therefore important to look for alternative sources of chemical products [1, 2]. The use of bio-based renewable sources of raw materials for chemical production is at the centre of our research initiatives. One such raw material, furfural derived from biomass, is a cheap and readily available substrate for the synthesis of an array of chemical compounds. Recently, we became interested in mucobromic acid as a precursor for the syntheses of azidofuranone and azidopyridazinone derivatives that are a subject of this work. Mucobromic acid **1** is readily available from the reaction of furfural with bromine in aqueous media [3]. It exists in the cis isomer, stabilized by the internal reaction between the aldehyde and carboxylic acid groups. The aldehyde group is thus transformed into a hemiacetal function similar to the anomeric center found in the cyclic forms of carbohydrates. This is evidenced by the absence of an aldehyde proton in the ^{1}H-NMR spectrum around 10 ppm and the appearance of what looks like an anomeric proton at 6.22 ppm. Although the ^{13}C-NMR shows all four carbon atoms, an aldehyde carbon is conspicuously absent, confirming the cyclic form of this molecule as shown in Scheme 1.



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Scheme 1

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Although mucobromic acid has four reactive sites most transformations reported thus far made use of only the aldehyde function except those that involved the Heck-type reactions [4]. Allylation of aldehydes is a fundamental transformation in organic chemistry and the metal-mediated Barbier-type allylation reaction is considered to be a useful and effective approach to the formation of carbon-carbon bonds. For example, mucobromic acid is employed as an aldehyde in an indium-mediated Barbier-type allylation reaction to generate a wide range of γ-allylic, α,β-unsaturated-γ-butyrolactones [5]. A vast number of biologically active natural products contain substituted γ-allylic, α,β-unsaturated-γ-butyrolactones, such as the antifungal metabolites from the marine sponge *Pachastrissa sp.*, bipinnata, palinurin and palinurine A and B, novel cytotoxic sesterterpenes from the sponge *Sarcotragus sp.*, and so on [5, 6]. Mucobromic acid has also been shown to cross-link gelatine [7] and undergo a Friedel-Crafts acylation reaction affording substituted γ-aryl- γ-butenolides [8].

The high reactivity of mucohalic acids in general can be further exemplified by their known mutagenic activity that results from their reaction with nucleotides, affording etheno, oxaloetheno and halopropenal derivatives [9].

In addition, mucohalic acids' high reactivity has been exploited for the preparation of stereodefined acyclic unsaturated dihalogenated derivatives and sulphur- or nitrogen-containing heterocycles including precursors of agrochemicals [10].

In this work, we decided to take advantage of the enhanced reactivity of mucobromic acid and its versatility to synthesise corresponding azido derivatives of furan-2(5H)-one and also azido derivatives of pyridazinones with the future aim of exploring their reactivity in click reactions [11].

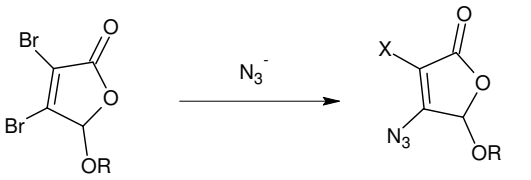
Mucobromic acid has previously been used in the synthesis of pyridazinones reported to exhibit a broad array of biological activities [7, 8]. In an attempt to modulate this bioactivity and due to the antitumor action of the acetylene unit in many compounds, Lemière and his group studied the introduction acetylene groups into the pyridazinone structure via a Sonogashira as well as a Suzuki coupling [12].

RESULTS AND DISCUSSION

We started this work by assessing the reactivity of mucobromic acid by reacting it with various carbon centered nucleophiles, such as cyanide, methyl nitroacetate, methyl azidoacetate, and nitromethane. In all these cases, the products formed decomposed almost instantly and could not be isolated, purified and characterized. However, the reaction of mucobromic acid with two equivalents of sodium azide was a fast reaction, which after half an hour afforded 3,4-diazido-5-hydroxyfuran-2(5H)-one **1b**. The ^{1}H-NMR spectrum recorded in $DMSO_{D6}$, showed only two protons as expected at δ (300 MHz) 6.64 (s, 1H), and 8.96 (bs, 1H), whilst the ^{13}C-NMR comprised of the four carbon atoms at δ (75 MHz, $DMSO_{D6}$): 93.87, 116.94, 157.31 and 164.15. The IR spectrum shows the characteristic absorption of the N_3 groups at 2128 cm^{-1}. Unfortunately, this compound proved to be unstable and decomposed on standing even at low temperature. 5-Methoxy-3,4-dibromofuranone **2a** on the other hand, reacted with two equivalents of sodium azide and formed 3,4-diazido-5-methoxyfuran-2(5H)-one **2b** in an excellent yield of 95% (Table 1). No evidence of product decomposition was observed. Although we did not encounter any major problems with the azido compounds, extreme care is nevertheless advised when working with them since they are high energy compounds capable of detonation. Careful literature study has revealed that the instability of azido furanones is a common feature [13, 14]. We then reasoned that this instability could be brought under control by simultaneously blocking the aldehyde and carboxylic acid groups of mucobromic acid by reacting them with hydrazines forming corresponding pyridazinones as described by Zhang and co-workers [6]. The pyridazinones reacted readily with nucleophiles and formed stable azides in

good yields (Table 2). Particularly noteworthy is the stability exhibited by diazopyridazinones; they could be stored at room temperature for a long time without any noticeable decomposition. The IR absorption of the N_3 groups appeared distinctly at 2104 and 2126 cm^{-1}. The reaction of dibromopyridazinones with one equivalent of sodium azide led to the selective substitution of only one bromine atom. The second bromine atom could be substituted by a different nucleophile and such selectivity attests to the synthetic utility of mucobromic acid.

Table 1. Synthesis of azidofuranones

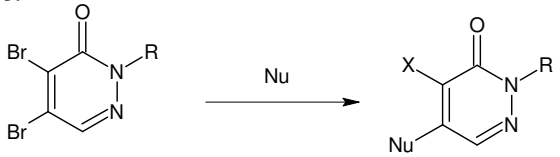


1: R = H
2: R = CH_3

1b: R = H
2b: R = CH_3

R	X	Product	% Yield
H	N_3	**1b**	42
CH_3	N_3	**2b**	95

Table 2. Synthesis of pyridazinones



3 **4**

R	Nu	X	Product	% Yield
Ph	CN	Br	**4a**	86
Ph	N_3	N_3	**4b**	87
Ph	N_3	Br	**4c**	94
H	N_3	Br	**4d**	41
H	N_3	N_3	**4e**	70

EXPERIMENTAL

General procedure for the synthesis of 4,5-diazido-2-phenylpyridazinone. In a 25 mL round-bottomed flask fitted with a reflux condenser, a magnetic stirring bar and a calcium chloride drying tube was placed dry finely ground sodium azide (0.21 g, 3.33 mmol). A solution of 4,5-dibromo-2-phenylpyridazinone (0.5 g, 1.5 mmol) in 15 mL of acetone was added to the finely ground sodium azide and the mixture was stirred and refluxed for 4 hours. The reaction mixture was allowed to cool, filtered and the filtrate evaporated to give a crude solid product that was recrystallized by slow evaporation from a mixture of acetone and hexane to afford a light brownish solid; 0.336 g (87%); m.p. 92-94 ^oC, δ_H (300 MHz, $CDCl_3$): 7.39-7.58 (m, 5H), 7.76 (s, 1H); δ_C (75 MHz, $CDCl_3$): 114.95, 125.58, 129.09, 129.23, 129.70, 141.40, 141.99 and 157.36; IR (CH_2Cl_2) cm^{-1}: 2104 and 2126. The other pyridazinones as well as 3,4-diazido-5-methoxyfuran-2(5H)-one were synthesized by a method analogous to the above general

procedure, whereas 3,4-dibromo-5-methoxyfuran-2(5H)-one was obtained according to reference 13.

CONCLUSION

3,4-Diazido-5-hydroxyfuran-2(5H)-one was successfully synthesized and analyzed. However, due to its high chemical instability its more stable pyridazinone derivatives were prepared. The stable 3,4-diazido-5-methoxyfuran-2(5H)-one coupled with the pyridazinone derivatives will be investigated as target molecules for click reactions, the subject of our subsequent investigations. Nevertheless, pyridazinone derivatives have shown interesting biological activities including COX-2 inhibition [15]. The compounds may be subjected to biological screening tests in other laboratories.

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