

Oxidative Removal of Heterocyclic Alkyl or Sugar Side Chain by Microwave: A Simple Step to Xanthopterin, 6-Formylpterin, and 3-Hydroxymethyl-2(1H)-quinoxalinone

Shyamaprosad Goswami* and Annada C. Maity

Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah-711 103, India

(Received June 11, 2007; CL-070628; E-mail: spgoswamical@yahoo.com)

One-step microwave-assisted oxidative removal of 3-methyl and 3-sugar side chain in 2(1H)-quinoxalinone system by selenium dioxide and sodium periodate respectively resulting 2(1H)-quinoxalinone has been reported. Similarly xanthopterin (as acetyl derivative **11**) was isolated from selenium dioxide oxidation of 7-methylxanthopterin. In the absence of adjacent lactam moiety, sodium periodate efficiently oxidizes 2-acetylaminopterins **7** and **8** to 2-acetylamin-6-formylpterin (**16**) and the quinoxaline tetrols **9** and **10** respectively to quinoxaline aldehyde **17**. However, all the compounds remained unchanged on refluxing with selenium dioxide. The new quinoxalone compounds **15** and **18** were simply synthesized by manganese dioxide oxidation of the completely unprotected 3-substituted sugar of 2(1H)-quinoxalinone **5** and quinoxaline **10** respectively under microwave condition.

Oxidative removal of alkyl or hydroxyalkyl side chain in aromatic and heterocyclic system is an important organic reaction to establish their structures and this is also a very useful synthetic reaction to produce the unsubstituted aromatic or heterocyclic system at the desired position. Thus, development of environmentally mild oxidative degradation reaction in the side chain of heterocyclic molecules is an important challenge. Microwave technology has recently been proven to be very effective, mild, and an efficient tool in accelerating organic transformations and has been widely employed in parallel synthesis and also in drug discovery process.^{1,2}

To our knowledge selenium dioxide or sodium periodate-mediated oxidative removal of methyl group in a heterocyclic system is unprecedented in literature specially under microwave condition. Previously, we have reported a new convenient and straightforward route to the synthesis³ and selenium dioxide oxidation⁴ of 2-substituted quinoxalines using microwave. However, selenium dioxide as well as sodium periodate oxidation of xanthopterin derivatives and 3-substituted 2(1H)-quinoxalinone as heterocyclic compounds in solvent-free condition remain unexplored. Here, a useful, straightforward, economic and efficient method⁵ for the new synthesis of a xanthopterin e.g. 2-acetylamin-4,6(3H,5H)-pteridinedione (**11**) and 2(1H)-quinoxalinones **12**, **13**, and **14** (Entry 1–6) in good yield under microwave condition by one-step oxidative decarboxylation reaction (Table 1) has been reported. However, all the compounds remained unchanged on refluxing with selenium dioxide.

Benzylic oxidation by manganese dioxide is also a very important and mild reaction in neutral condition, and it is thus an economic procedure for achieving selective oxidation.⁶ However, under microwave condition, the completely unprotected 3-substituted sugar of 2(1H)-quinoxalinone **5** and quinoxaline **10** gave the new compounds 3-hydroxymethyl-2(1H)-quinoxalinone (**15**) and 2-hydroxy-1-quinoxalin-2-ylethanone (**18**) as

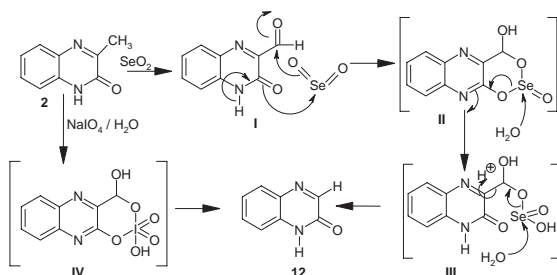
the oxidative degradation products. Thus, selective benzylic cleavage of the 3-substituted sugar of 2(1H)-quinoxalinone **5** by MnO₂ did not seem to be straightforward.

The starting materials used in the Table 1 from the Entries 1 to 10 were prepared in our laboratory by reported literature procedures. The starting compound, the protected acetyl derivative **1** was obtained⁷ from 2-amino-7-methyl-4,6(3H,5H)-pteridinedione which was synthesised by condensation of 2,5,6-triamino-4(3H)-pyrimidinone with pyruvic acid. The starting materials

Table 1. Oxidative removal of methyl or polyhydroxyalkyl-substituted heterocyclic compounds (**1–10**)

Entry	Starting Material	Reagents and Condition ^{a,b}	Yield ^c /%	Product
1		SeO ₂ , 450 W, 20 min	62	
2		SeO ₂ , 450 W, 18 min NaIO ₄ , 450 W, 20 min MnO ₂ , 450 W, 25 min	73 63 59	
3		SeO ₂ , 450 W, 25 min	61	
4		SeO ₂ , 450 W, 23 min	64	
5		SeO ₂ NaIO ₄ , 300 W, 4 min MnO ₂ , 300 W, 6 min	no reaction 53 40	
6		NaIO ₄ , 450 W, 5 min	52	
7		NaIO ₄ , 450 W, 6 min	34	
8		NaIO ₄ , 450 W, 8 min	32	
9		NaIO ₄ , 300 W, 3 min MnO ₂ , 80 W, 2 min	56 14 + 45	
10		NaIO ₄ , 300 W, 5 min MnO ₂ , 80 W, 4 min	50 10 + 42	

^aReactions were monitored by TLC analysis. ^bA domestic BPL Microwave Oven (800G) was used. ^cYields refer to the isolated pure products after column chromatography.



Scheme 1. Plausible mechanism for the formation of **12** from **2** by SeO_2 or NaIO_4 .

pyrido[2,3-*b*]pyrazinone derivatives **3** and **4** respectively were made by condensing corresponding diaminopyridine with pyruvic acid.⁸ 2-Acetylamino-7-methyl-4,6(3*H*,5*H*)-pteridinedione (**1**), 3-methyl-2(1*H*)-quinoxalinone⁹ (**2**) and 3-substituted sugar of 2(1*H*)-quinoxalinone¹⁰ **5** were subjected to selenium dioxide and sodium periodate oxidations respectively affording **11** from **1** and **12** from **2** and **5**, respectively. However, selenium dioxide could not produce compound **12** from the starting material **5** which remained almost unreacted. The yield was better with selenium dioxide compared to sodium periodate oxidation in case of 3-methyl-2(1*H*)-quinoxalinone as the starting substrate. Interestingly, manganese dioxide produced only the new 3-hydroxymethyl-2(1*H*)-quinoxalinone (**15**) from **5** under microwave condition. All the compounds made here were well characterized by spectroscopic studies as well as by comparison with authentic samples. The reaction conditions and yields are summarized in Table 1.

A plausible mechanism for the formation of compound **12** from **2** by sodium periodate as well as by selenium dioxide oxidation is shown in Scheme 1. The presence of lactam moiety in the compounds (Entry 1–6) seems to play a key role in the above such oxidative total carbon chain loss with simple substitution by hydrogen. In the cases of compounds (Entry 7–10) where lactam carbonyl moiety is absent, only the corresponding aldehydes were obtained with sodium periodate oxidation.

Thus, we have succeeded in achieving a facile oxidative and degradative one-step synthesis of 2-acetylamino-6-formylpterin (**16**) (Entry 7 and 8) and quinoxaline aldehyde **17** (Entry 9 and 10) by using simple sodium periodate as an oxidant. However, selenium dioxide oxidation failed to give the desired aldehydes. 6-Formylpterin is a precursor of the pteridine substrate of dihydropterolate biosynthesis.¹¹ We are interested in synthetic studies¹² on compound Z of molybdenum cofactor¹³ which has a C-6-substituted pterin ring system. *N*-Acetylaminotetrol **7** when oxidized by sodium periodate gave the acetyl protected 6-formylpterin¹⁴ **16** in 30–35% yield which thus constitutes a new synthesis of 6-formylpterin.

Further, quinoxaline tetrols⁷ **9** and **10** provide a convenient route to the synthesis of quinoxaline aldehyde **17** in 50–60% yield by simple periodate oxidation from inexpensive starting materials. The partial oxidative degradation of quinoxaline tetrols **9** and **10** by manganese dioxide presumably occurred by the facile oxidative benzylic bond cleavage¹⁵ and gave the major product quinoxaline aldehyde **17** (56%) and also 2-hydroxy-1-quinoxalin-2-ylethanone (**18**) in a low yield (14%).

In conclusion, we have developed this new method which is simple, mild, efficient and inexpensive for the synthesis of xanthopterin, 6-formylpterin, 2(1*H*)-quinoxalinone, pyrido[2,3-*b*]pyrazinone derivatives, 3-hydroxymethyl-2(1*H*)-quinoxalinone, 2-hydroxy-1-quinoxalin-2-ylethanone, and quinoxaline aldehyde from the corresponding methyl or sugar derivatives under microwave oxidative degradation.

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