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A remarkable case of pterin specific oxidative coupling: unequivocal synthesis of 6,7-alkoxypterins and 1,4-dioxanopterin with ceric ammonium nitrate

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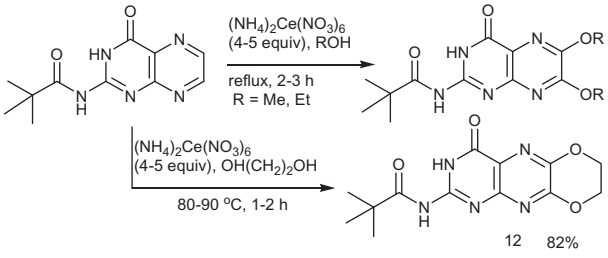
ABSTRACT

A facile and efficient synthesis of a series of methoxy and ethoxy substituted pterins (characterized by single crystal X-ray structures of 6,7-dimethoxy and diethoxy-pterins) along with 1,4-dioxanopterin is reported along with a possible mechanism for their formation by treatment of pterins with ceric ammonium nitrate in methanol, ethanol, and ethylene glycol respectively. This unequivocal alkoxylation is unique only with pterin (and 5-deaza-pterin) and is unsuccessful with quinoxaline.

Introduction

Pterins are among the more important substructures in heterocycles, and their versatile properties make them more interesting than other heterocycles such as quinoxalines, pyridines, pyrimidines etc.[1] It is also known that the derivatives of pterin mainly include pterins and folates. Pterins are those compounds that contain the basic pterin core [2-aminopteridin-4(3*H*)-one] with additional functional groups attached to the pyrazine sub-ring and the trivial name pteridine (from Greek word 'pteron') was first introduced by Wieland for the condensed pyrazino[2,3-*d*]pyrimidine ring system. The first investigations and major study of natural monomeric chromophore pterins were performed by Gowland Hopkins in 1895, who carefully isolated white, yellow, and red pigments from different European butterfly wings (Lepidoptera).[2] Now, pteridine natural products such as folic acid (vitamin B9), biopterin, and neopterin, as well as the synthetic anticancer drug methotrexate, which contains different substituents universally at the C-6 position of the pteridine ring,[3] are also very familiar. Scientists have also shown that the deficiency of folate contributes to physiological disorders (e.g., anemia) and creates defects in the neural tube of pregnant women.[4] More recently, it has been shown that the fully reduced form of biopterin[5] (H_4biopterin isolated from animals) acts as an essential cofactor for nitric oxide synthase (NOS).[6] Pterin is also an important moiety in the molybdenum cofactor essential for humans.[6b,c] Therefore, pterins and substituted pterins have a major role in the human life system. Synthesis of pterins substituted at the 6 (mainly) and 7 positions can be conducted in two ways: the first one starts with substituted pyrazine and then forms the pyrimidine ring, and the other is condensation of 5,6-pyrimidine diamines with compounds containing 1,2-dicarbonyl with different substituents. Literature reports indicate that there are rare examples to prepare 6,7 substituted pterins by direct insertion of substituents at 6,7 positions applying any method only on pterin. At first, Caronna and recently Anslyn et al. have shown the direct



Scheme 1. General synthetic route of alkoxylation of pteridine.

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insertion of an acyl group at the specific 7 position by the generation of an acyl radical in the presence of H_2SO_4-$FeSO_4$/tBuOOH-H_2O.[7] Taylor reported an elegant regiospecific synthesis of 6-chloropterin from pterin 8-oxide via rearrangement by treatment with trifluoroacetic acid and acetyl chloride at room temperature.[8]

In our continued effort in the synthesis of pterin-derived molecules, including molybdenum cofactor,[3,8i,j] we report a facile and direct addition of methoxy and ethoxy groups at the 6 and/or 7 positions of pterin with the treatment of methanol and ethanol, respectively, in the presence of ceric ammonium nitrate (CAN) (Scheme 1 and Tables 1 and 2). Alkoxy pteridines and *N*-alkyl pteridinones[9] do not necessarily need to be made by alkylation of the parent tautomeric pteridinones. Alkoxypteridines and *N*-alkylpteridinones may be treated as tautomeric pteridinones that are fixed by *O*- or *N*-alkylation. Alkoxy groups either in the pyrimidine moiety or pyrazine moiety are either synthesized starting from alkoxy pyrimidine diamine followed by pyrazine annulation or alkoxy pyrazine followed by pyrimidine annulation.[10]

From details of experiments on pterins in the presence of alcohols and ceric ammonium nitrate, we have observed that only the free positions (6 and/or 7) of pterin are substituted by methoxy or ethoxy groups under refluxing conditions. Now it is clear that the methoxy and ethoxy groups have come from methanol and ethanol, respectively, which also act as a solvent in the reaction medium.

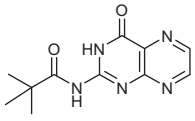
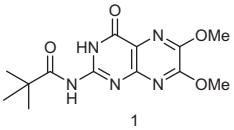
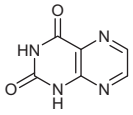
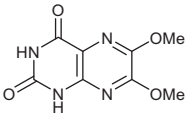
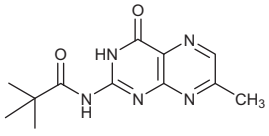
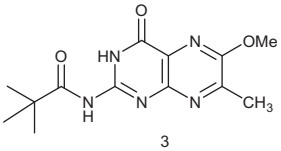
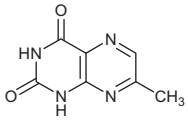
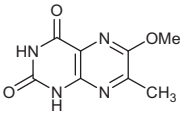
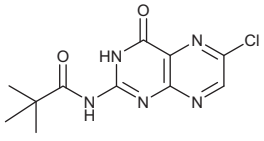
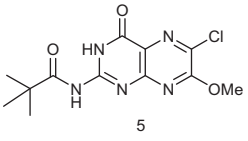
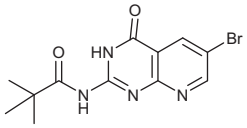
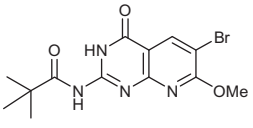
Ceric(IV) ammonium nitrate is a common oxidizing agent, but also its applications in carbon-heteroatom bond formation in organic synthesis is notable.[11] Carbon-heteroatom bond formation mediated by CAN include C–Br, C–I, C–S, C–N, and C–Se bonds. However, in this reaction, we have used ceric(IV) ammonium nitrate (CAN) as a key oxidizing agent using 4–5 equiv.

In our study, we also use different types of pterin derivatives (synthesized in the laboratory following reported procedures), for example, 7-methylpterin,[8g,h] 6-chloropterin,[8a] and 6-bromo-deazapterin. Notably, there is neither oxidation of the methyl group nor displacement of halide groups of pterins by the action of ceric ammonium nitrate. To increase the solubility of pterins 2-amino group of synthesized pterins are first converted into the 2-*N*-pivaloyl derivatives, which were used as precursors for alkoxy pterins. The results are summarized in Tables 1 and 2. The synthesis of 1,4-dioxano-pterin is easily achieved with 2-*N*-pivaloylpterin and ethylene glycol in the presence of ceric ammonium nitrate (80–90 °C, 2 h).

The tentative mechanistic pathway is depicted in Scheme 2 on the basis of the literature precedents. In this mechanism, the pterin forms a cationic radical species in the presence of Ce(IV).[12] This cationic radical species undergoes nucleophilic substitution by an alcohol as follows.

Additionally, this specific oxidative alkoxylation reaction with CAN was unsuccessful to give any isolable product in case of quinoxaline as well as 6,7-disubstituted pteridine system [Table 2: (vi) & (vii)]. Such a unique property of pterin with CAN may be due to the presence of 4-oxopyrimidine (assisting the reaction) instead of benzene in quinoxazoline. This method is applicable only to pterin systems containing no substituent at either or both the 6

Table 1
Methoxylation of pterins derivatives at the 6,7 positions using methanol

Entry	Reactant	Reagent & conditions	Product	Yield
(i)		$(NH_4)_2Ce(NO_3)_6$ (4–5 equiv), MeOH reflux, 2–3 h	 1	86
(ii)		"	 2	74
(iii)		"	 3	78
(iv)		"	 4	70
(v)		"	 5	75
(vi)		"	 6	84