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An efficient modification of ellipticine synthesis and preparation of 13-hydroxyellipticine

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Abstract—A simple modification of a previously published ellipticine synthesis is reported, which decreases the reaction time and increases the yield and purity of the product. Benzylic oxidations of 1,4-dimethylcarbazole and ellipticine derivatives were studied and 13-hydroxyellipticine was prepared.

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, **2a**), an alkaloid isolated from Apocyanaceae plants and several of its derivatives exhibits promising results in the treatment of osteolytic breast cancer metastases, kidney sarcoma, brain tumors and myeloblastic leukemia.[1] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects and complete lack of hematological toxicity.[2] The antineoplastic property of ellipticine was considered to be based mainly on DNA intercalation and/or inhibition of topoisomerase II.[3–7] Recently, it was demonstrated that ellipticine covalently binds to DNA in vitro and in vivo after being enzymatically activated with cytochrome P450 or peroxidases.[1,8–11] Deoxyguanosine was identified as the target base to which the two ellipticine metabolites, 13-hydroxyellipticine and 12-hydroxyellipticine are bound,[9] forming two major ellipticine-derived DNA adducts.[9–11] It was suggested that 13-hydroxyellipticine might, depending on the environment, decompose spontaneously to the reactive carbenium ion ellipticine-13-ylium, which reacts with one of the nucleophilic centers in the deoxyguanosine residue in DNA (i.e., the exocyclic $-NH_2$ group of guanine).[8,9,12]

Many synthetic pathways for the preparation of ellipticine have been proposed.[13] The most convenient synthesis starts from indole requiring five reaction steps to afford *para*-toluenesulfonamide **1a**, which cyclizes in boiling dioxane containing HCl to give ellipticine **2a** in 70% yield.[14] The major problem in all the syntheses of ellipticine is the low solubility of the alkaloid in polar as well as non-polar solvents, which makes chromatographic purification inconvenient. Two syntheses of 13-hydroxyellipticine have been published,[15,16] in both cases the synthesis was rather complicated and the overall yields were low. Several unsuccessful synthetic approaches to ellipticines with a substituent at C-13 have also been reported.[17]

We found that a simple modification of the previously published synthesis[14] of ellipticine increases the yield and purity of the product dramatically. When *para*-toluenesulfonamide **1a** was replaced with benzenesulfonamide **1b**, the cyclization reaction to ellipticine (**2a**) was much faster (100% conversion in 20 min compared to 6 h with *para*-toluenesulfonamide **1a**) and the yield was better (97%); ellipticine crystallizes directly from the reaction mixture and no further purification was necessary. 9-Methoxyellipticine (**2b**) was also prepared from the appropriate benzenesulfonamide **1d** and the reaction rate and yield were also better than in the case of *para*-toluenesulfonamide **1c** (Scheme 1). The mechanism of the reaction probably involves ring closure and then solvolysis of sulfonamide. The *para*-toluenesulfonamide with a closed 1,2-dihydropyridine ring was also isolated from the reaction of compound **1a**.[14] Electronic effects of the substituent at the *para* position of the sulfonamides probably influence the stability of sul-

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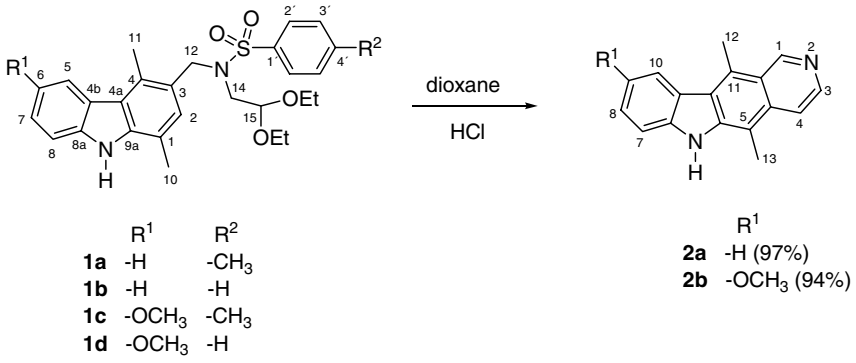


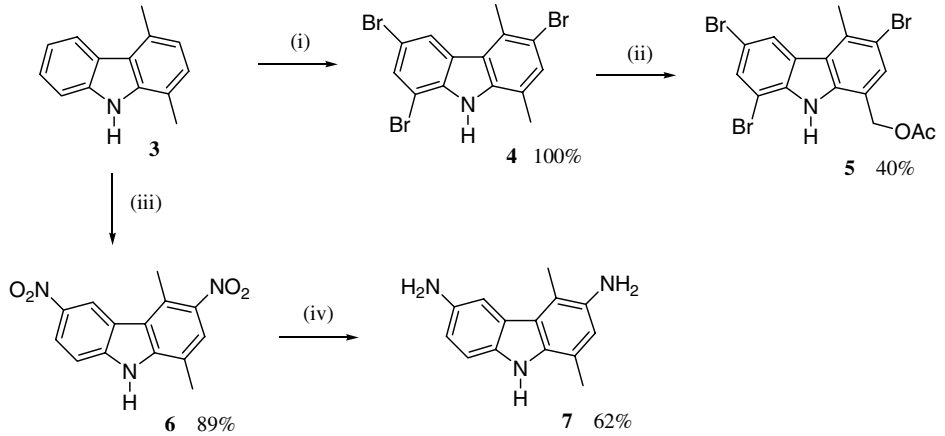
Scheme 1.

fonamides against solvolysis dramatically. Electron donating groups such as methyl make sulfonamide more stable and consequently, solvolysis is slower.

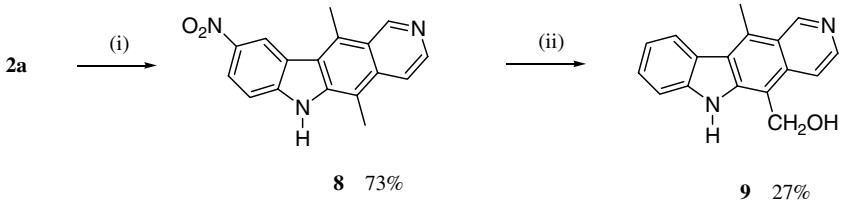
We wanted to explore the possibility of the preparation of 13-hydroxyellipticine by oxidation of the benzylic methyl groups. 1,4-Dimethylcarbazole (**3**) was used as a model compound for studying the benzylic oxidation with various oxidation agents. When $K_2S_2O_8$–$Cu(OAc)_2$ in acetic acid[18] was used, the reaction mixture polymerized. Polymerization also occurred when the Étard reaction[19] was applied to 1,4-dimethylcarbazole (**3**). Oxidation with CrO_3 led to a complex mixture, which showed no evidence of oxidation products in the ^{1}H NMR. The reaction of **3** with bromine did not lead to oxidation of benzylic positions, however aromatic substitution took place and 3,6,8-tribromo-1,4-dimethylcarbazole (**4**) was the reaction product. The tribromo derivative was further oxidized with $K_2S_2O_8$ to yield 4-acetoxymethyl-3,6,8-tribromo-1-methylcarbazole (**5**) as the major product. Hence, in this case benzylic oxidation took place and the resulting hydroxy derivative was acetylated with acetic acid present as the solvent. *N*-Bromoacetamide in the presence of dibenzoylperoxide was used as another oxidation reagent, but as in the case of bromine, no benzylic oxidation took place. The result of this reaction was a mixture of three products (probably monobromo derivatives); when an excess of *N*-bromoacetamide was added and the reaction time was prolonged, tribromo derivative **4** was the only product of the reaction.

Dinitroderivative **6** was prepared by oxidation of 1,4-dimethylcarbazole and was then oxidized with $K_2S_2O_8$. The reaction gave a mixture, which was not separated, but according to the ^{1}H NMR spectrum, the benzylic methyls had been oxidized. The signals for the CH_3 groups at 2.4 and 2.8 ppm were missing and new signals at 5.4 and 5.8 ppm were apparent indicating the presence of acetoxy groups at the benzylic positions. A signal at 2 ppm was due to the acetate methyl group. The dinitro derivative was reduced with $SnCl_2$ and the resulting 3,6-diamino-1,4-dimethylcarbazole (**7**) oxidized with $K_2S_2O_8$, however, the reaction mixture polymerized (Scheme 2).

It is clear from the experiments described above that 1,4-dimethylcarbazole is very sensitive to oxidizing agents. The benzylic oxidation conditions led to aromatic substitution or to polymerization (probably by a radical mechanism). When electron accepting substituents (which in addition block the positions of possible aromatic substitution) were introduced into the molecule, benzylic oxidation can take place preferably at the methyl group at position 1. This is probably due to the greater steric hindrance of the methyl group at position 4 and also the higher stability of the intermediate benzyl radical.



Scheme 2. Reagents and conditions: (i) Br_2, $CHCl_3$ 20 min, rt; (ii) $K_2S_2O_8$, $CuSO_4$, AcONa, AcOH, 2 h, reflux, 30 min, 100 °C; (iii) HNO_3, AcOH; (iv) $SnCl_2$, HCl, 1 h, 100 °C.



Scheme 3. Reagents and conditions: (i) HNO_3, AcOH, 0 °C, 45 min; (ii) (1) $K_2S_2O_8$, $CuSO_4$, AcONa, AcOH, 2 h, reflux; (2) $SnCl_2$, HCl, 1 h, 100 °C; (3) $NaNO_2$, 10 min, 5 °C; (4) EtOH.

The information obtained from these experiments was utilized to prepare 13-hydroxyellipticine. Firstly, 9-nitroellipticine (**8**) was prepared by nitration of ellipticine. Next, nitro compound **8** was oxidized with $K_2S_2O_8$ and the nitro group of the product was reduced without isolation with $SnCl_2$. The resulting amino derivative was diazotized and reduced with ethanol to give 13-hydroxyellipticine (**9**). The overall yield of this reaction sequence was 27% after purification by preparative HPLC (Scheme 3). Ellipticine could not be oxidized directly at the benzylic position as it, as well as 1,4-dimethylcarbazole (**3**), are very sensitive to oxidation and polymerization or electrophilic substitution often occurs.

Supplementary data

Supplementary data (experimental procedures and characterization of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.160.

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