SYNTHESIS OF AMINO-SUBSTITUTED FUSED OXAZOLOCOUMARINS *VIA* Au/TiO_2-CATALYZED SELECTIVE REDUCTION OF THE CORRESPONDING NITRO-DERIVATIVES IN THE PRESENCE OF $NaBH_4$

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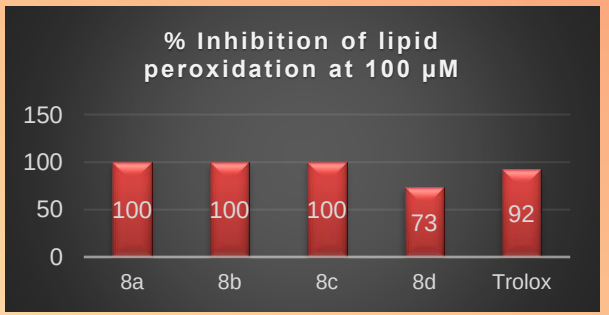
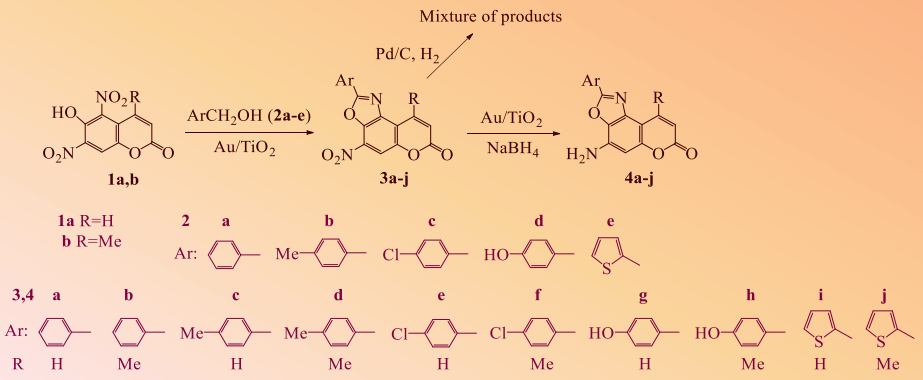
INTRODUCTION

Fused coumarin derivatives present interesting biological activities. Especially, fused oxazolocoumarins have been tested for their antioxidant [1], or photoreleasing of aminolevulinic acid [2] activities. Fused pyridocoumarins poccess biological activities as antimalarial [3], antioxidant [4], and wound-healing [5]. Pyridocoumarins are prepared from aminocoumarins through the one-pot Povarov reactions with aromatic aldehydes [6], the reactions with phenylacetylene and benzaldehydes under catalysis by Lewis acids [4,7]. The cyclo-isomerization of propargylaminocoumarins, prepared from amino-coumarins, followed by oxidation led also to pyridocoumarins under catalysis by $AgSbF_6$ [8] or Au/nanoparticles [9]. In continuation of our interest on fused oxazolocoumarin [1,10] and pyridocoumarin [4,9] derivatives we would like to report here the synthesis of novel amino-substituted fused oxazolocoumarins through a selective reduction procedure, as a preliminary step for the synthesis of fused oxazole ring to fused pyranoquinolinones, and the biological evaluation of the products.





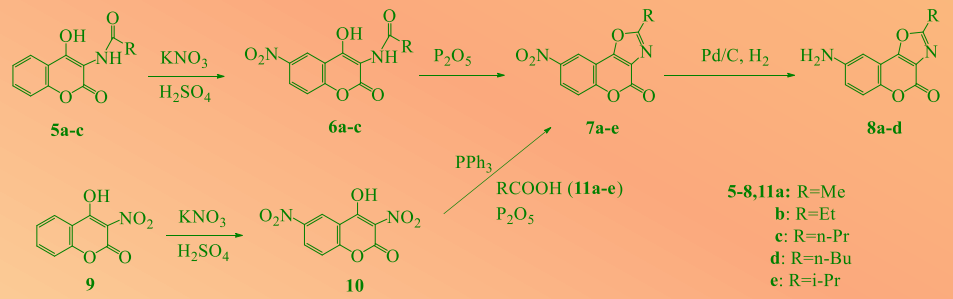
Scheme 1

CHEMISTRY

The reactions studied and the products obtained are depicted in Schemes 1-2. The reactions of 5,7-dinitro-6-hydroxycoumarins **1a,b** with the p-substituted benzyl alcohols **2a-e** catalyzed by Au/TiO_2 under heating in a sealed tube, in analogy to our former work [10], resulted to the 7-nitro-substituted fused oxazolocoumarins **3a-j** in low yields (20-45%). The efforts for reduction of nitro-group of **3a,c,e** with Pd/C under H_2 resulted to mixture of products with reduction of both nitro and aryl group. Following a recent publication for the reduction of nitroarenes to anilines with Au-NPs[11], we obtained the selective reduction of nitro-group by Au/TiO_2 in the presence of $NaBH_4$, as an H donor, to the amino-substituted derivatives **4a-j** in excellent yields (94-99%) (Scheme 1).

Next, we tried the direct nitration of 2-methyl-4*H*-chromen[3,4-d]oxazol-4-one [1] with HNO_3/H_2SO_4 or with $Cu(NO_3)_2.3H_2O/H_2SO_4$. In both cases the expected **7a** was received in only ~20% yield, while compound **6a** was isolated in ~64% yield upon hydrolysis. So, we prepared the compounds **7** by two different ways (Scheme 2). Nitration of 3-alkyl-amino-4-hydroxycoumarins **5a-c** [1] with KNO_3/H_2SO_4 led to the nitro-compound **6a-c.** The cyclization/dehydration of the later with P_2O_5 in toluene under microwave irradiation, in analogy to our former work [1], resulted to the 8-nitro-substituted fused oxazolocoumarins **7a-c**. Nitration of 4-hydroxy-3-nitrocoumarin (**9**) [1] with KNO_3/H_2SO_4 gave 4-hydroxy-3,6-dinitrocoumarin (**10**). The one-pot reaction of the later in the presence of PPh_3, acids **11a-e** and P_2O_5 under microwave irradiation led to **7a-e**. The selective reduction of those compounds by Pd/C under H_2 atmosphere gave the amino-substituted compounds **8a-e** (Scheme 2). All the above referred reactions were performed in excellent yields in every step.

The experiments for the formation of pyridine ring from the amino-derivatives **4a-j** and **8a-d** are in progress.



Scheme 2

BIOLOGICAL EVALUATION

Experiments *in vitro*

Inhibition of linoleic acid lipid peroxidation

Production of conjugated diene hydroperoxide by oxidation of sodium linoleate in an aqueous dispersion is monitored at 234 nm. 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) is used as a free radical initiator and the experimental procedure follows ref.[1,4,13]

The compounds **4b**, **4e**, **4g** and **4i** present similar anti-lipid peroxidation activity, whereas **4f** and **4j** did not exhibit any antioxidant activity. **4a**, the simpler analogue is the most potent. The combination of 7-amino coumarin with the condensed oxazolyl phenyl substitution consist the biological active scaffold. Donors or acceptor groups as phenyl substituents did not increase the biological results. There are minimum steric requirements for the antioxidant activity.

All the derivatives **8a-c** highly and equally inhibit the lipid peroxidation. A decrease is observed by compound **8d**. The butyl substituent for steric reasons might induce this decrease. The common structural characteristics favor this potency.

Soybean lipoxygenase inhibition study

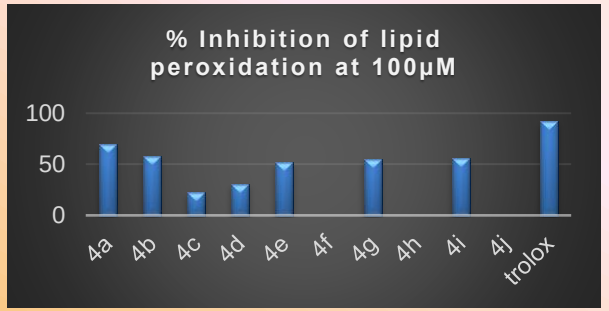
The compounds are tested according to our previously reported method.[1,4,13]

Noone of the derivatives **4a-j** is lipogygenase inhibitor.

Compound **8a** is the only lipoxygenase inhibitor with an IC_{50} value 55.5 μM. The other compounds were found inactive under the reported conditions.

CONCLUSION

It seems that compounds **8a-d** are more biologically interesting molecules and compound **8a** could be used as a lead compound.



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