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Short Note

4-Amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one

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Abstract: The new 4-amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one was successfully prepared through the Au/TiO_2-catalyzed $NaBH_4$ activation and chemoselective reduction of the new 4-nitro-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one. The latter was synthesized by the one-pot tandem reactions of 6-hydroxy-5,7-dinitrocoumarin with *p*-tolylmethanol under Au/TiO_2 catalysis. The dinitrocoumarin was obtained by the nitration of 6-hydroxycoumarin with cerium ammonium nitrate (CAN). The structure of the synthesized compounds was confirmed by FT-IR, HR-MS, ^{1}H-NMR and ^{13}C-NMR analysis. Preliminary biological tests show low anti-lipid peroxidation activity for the title compound.

Keywords: Au-nanoparticles; $NaBH_4$; amino-substituted fused oxazolocoumarin; fused oxazolocoumarins; chemoselective reduction; *o*-hydroxynitrocoumarins

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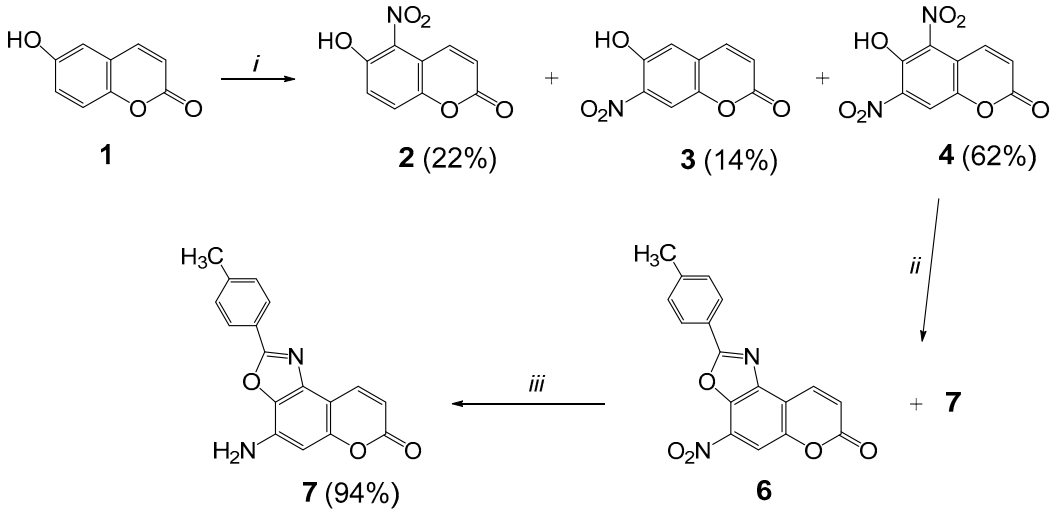
1. Introduction

Coumarin derivatives are widely distributed in nature, presenting interesting biological properties such as anticoagulant, anti-inflammatory, antivirus, anticancer, antioxidant or antidiabetic [1–7]. Fused coumarins also exhibit biological activity. Especially, fused oxazolocoumarins have been tested for their antioxidant [8], antimicrobial [9], anti-inflammatory [10], photosensitizing [11] or photoreleasing of aminolevulinic acid [12] activities. There are several methodologies for the synthesis of fused oxazolocoumarins. The condensation of *o*-aminohydroxycoumarins with aldehydes [9,13–15], acids [14], anhydrides [13,15]; or of *o*-amidohydroxycoumarins with anhydrides [16], $POCl_3$ [17] or P_2O_5 [18] led to those products. Furthermore, substituted fused oxazolocoumarins were synthesized by the reduction of 4-hydroxy-3-nitrosocoumarin in acetic anhydride in the presence of Pd/C [19], or of 6-hydroxy-4-methyl-5-nitrocoumarin acetate in acetic acid with iron powder [20], or of 3-hydroxy-3-nitrocoumarins in liquid carboxylic acids in the presence of Pd/C or PPh_3 and P_2O_5 [8]. Recently, we prepared oxazolocoumarins by one-pot tandem reactions of *o*-hydroxynitrocoumarins with benzyl alcohol in toluene under catalytical conditions using gold nanoparticles supported on TiO_2, by $FeCl_3$ or by silver nanoparticles supported on TiO_2 [21].

Aminocoumarins are valuable building blocks for the synthesis of fused pyridocoumarins presenting significant biological activities such as antibacterial [22], antifungal [23], antimalarial [24], antioxidant [25] and wound-healing [26]. Pyridocoumarins are prepared from aminocoumarins through the one-pot Povarov reactions with aromatic aldehydes and cyclic enol ethers [27], the reactions with vinyl ketones [28], or under Vilsmeier conditions [29] or with phenylacetylene and benzaldehydes under catalysis by I_2 [30] or by other Lewis acids [25,31]. The cycloisomerization of propargylaminocoumarins, prepared from aminocoumarins, followed by oxidation, led also to pyridocoumarins under catalysis by $AgSbF_6$ [32] or $BF_3.Et_2O$ [33] or Au/nanoparticles [34].

The need for the synthesis of new compounds, to probe novel biological activity containing a heterocyclic ring fused to the pyridocoumarin moiety, led us to the synthesis of amino-substituted fused oxazolocoumarins. In continuation of our interest on fused oxazolocoumarin [8,22] and pyridocoumarin [25,33,34] derivatives, we would like to report here the synthesis of novel amine **7**, through a selective reduction procedure, and the biological evaluation of the products. The reactions studied and the synthesized products are depicted in Scheme 1.



Scheme 1. Reagents and Conditions: (i) CAN (1 equiv.), CH_3CN, r.t. 30 min; (ii) p-tolylmethanol (**5**) (3 equiv.), Au/TiO_2 (4 mol%), toluene, sealed tube, 150 °C, 54 h; (iii) Au/TiO_2 (1 mol%), $NaBH_4$ (4 equiv.), MeOH, r.t. 1 h.

2. Results and Discussion

2.1. Synthesis

The starting material for this procedure was the 6-hydroxy-5,7-dinitrocoumarin (**4**), which was synthesized in 62% yield along with 6-hydroxy-5-nitrocoumarin (**2**) (22% yield) and 6-hydroxy-7-nitrocoumarin (**3**) (14% yield) by nitration of 6-hydroxycoumarin (**1**) with cerium ammonium nitrate (CAN) in CH_3CN at r.t., according to the literature [35]. In this paper, the authors obtained **3** in 50% yield using 1 equiv. of CAN, while by using 2 equiv. of CAN they isolated compound **3** in 74% yield along with compound **2** (12%). No evidence for the presence of the dinitro-derivative **4** was noticed. When we performed the above reaction with 0.5 equiv. of CAN, only compound **2** [36] (10 %) was isolated along with 85% of the starting compound **1**. The spectral data of compound **4** resemble well with that given in the literature [37], where the preparation was achieved by using nitric/acetic acids.

The reaction of **4** with *p*-tolylmethanol (**5**) in a sealed tube in toluene in the presence of Au/TiO_2 (4 mol%) at 150 °C led to 4-nitro-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one (**6**) (45% yield) accompanied by 4-amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one (**7**) (13%). This reaction was performed in analogy to our recent work on the synthesis of fused oxazolocoumarins by the treatment of *o*-hydroxynitrocoumarins with benzyl alcohol catalyzed by Au/TiO_2 or Ag/TiO_2 or $FeCl_3$ [21]. During this process, a simultaneous reduction of nitro- to amine-group and oxidation of benzyl alcohol to benzaldehyde occurred, followed by imine formation from the amine and benzaldehyde, cyclization by addition of hydroxy-group to imine and oxidation of the intermediate oxazoline to oxazole. The selective reduction of the 5-nitro group of coumarin in comparison to the 7-nitro group by the intermediate gold-hydride [21] could be attributed to a possible complexation of gold to the 3,4-double bond of coumarin. In the ^{1}H-NMR spectrum of **6**, there are two doublets at 6.42 (1 H, J = 9.6 Hz) and 8.28 (1 H, J = 9.6 Hz) for the 3-H and 4-H, respectively, and one singlet at 8.30 (1 H) for the 8-H. The chemical shift of 4-H (8.28 ppm) is downfield in comparison to 4-H (7.69 ppm) of compound **4** due possibly to de-shielding from the

oxazole-ring. The p-tolyl-group gave rise to the two doublets at 7.35 (1 H, *J* = 7.9 Hz) and 8.15 (1 H, *J* = 7.9 Hz) and one singlet at 2.43 (3 H). The HR-MS is *m/z* $[M + H]^+$ calcd for $C_{17}H_{11}N_2O_5$: 323.2789, found: 323.2791.

The reduction of nitro-derivative **6** with $NaBH_4$ as hydride ion donor, in the presence of the catalyst Au/TiO_2, according to a recent publication for the use of Au-NPs in the reduction of nitroarenes to anilines [38], resulted to the chemoselective preparation of 4-amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one (**7**) in 94% yield. This is a new compound with absorptions in FT-IR at 3446, 3356 cm^{-1} for the NH_2 group. There are two doublets at 6.29 (1 H, *J* = 9.6 Hz) and 8.26 (1 H, *J* = 9.6 Hz) for the 3-H and 4-H, respectively, in the ^{1}H-NMR spectrum of **7**, a broad singlet at 4.50 ppm for the NH_2 protons and one singlet at 6.61 (1 H) for the 8-H, see Supplementary Materials. This upfield shift is consistent with the structure of **7** with the oxazole-ring fused at the 5,6-position and the NH_2 group at the 7-position of the coumarin moiety. If the oxazole ring is at the 6,7-position and the amine group at the 5-position of the coumarin (in a structure isomeric to **7**), the 8-H would be expected to be above 7.0 ppm. In the case of 2-phenyl-6H-chromeno[6,7-d][1,3]oxazol-6-one the 8-H is at 7.54 ppm [21]. The p-tolyl group gives rise to two doublets at 7.36 (1 H, *J* = 7.9 Hz) and 8.15 (1 H, *J* = 7.9 Hz) and one singlet at 2.46 (3 H). In the ^{13}C-NMR, there is the upfield peak for the 8-C of the coumarin moiety at 98.1 ppm in comparison to the carbons of nitro-compound **6,** see Supplementary Materials. This peak is consistent with the analogous peak (98.9 ppm) for 7-aminocoumarin [39]. The HR-MS is *m/z* $[M + Na]^+$ calcd for $C_{17}H_{12}NaN_2O_3$: 315.2778, found: 315.2784.

2.2. Biology

Preliminary biological experiments were performed in vitro. Compounds **6** and **7** were tested as possible antioxidant agents and inhibitors of soybean lipoxygenase according to our previous published assays [10,25]. They did not present any interaction with DPPH at 100 μM after 20 and 60 min under the reported experimental conditions. The anti-lipid peroxidation activity was very low at 100 μM (less than 1% for compound **6** and 23% for compound **7**), as tested by the 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) protocol. No inhibition of soybean lipoxygenase was observed.

3. Materials and Methods

3.1. Materials

All the chemicals were procured from either Sigma–Aldrich Co. or Merck & Co., Inc. (St. Louis, MO, USA) Melting points were determined with a Kofler hotstage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer Spectrum BX spectrophotometer as KBr pellets. NMR spectra were recorded with an Agilent 500/54 (DD2) (Santa Clara, CA, USA) (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively) using $CDCl_3$ as solvent and TMS as an internal standard. *J* values are reported in Hz. Mass spectra were determined with a LCMS-2010 EV Instrument (Shimadzu, Kyoto, Japan) under electrospray ionization (ESI) conditions. HRMS (ESI-MS) were recorded with a ThermoFisher Scientific model LTQ Orbitrap Discovery MS. Silica gel No. 60, Merck A.G. was used for column chromatography.

3.2. Synthesis of 6-Hydroxy-5,7-dinitrocoumarin (**4**)

Cerium ammonium nitrate (CAN) (1.69 g, 3.08 mmol) in acetonitrile (10 mL) was added in three portions over a period of 15 min to a solution of 6-hydroxycoumarin (**1**) (0.5 g, 3.08 mmol) in acetonitrile (10 mL) under stirring. The reaction mixture was then stirred for 30 min (TLC-monitored) and then quenched by pouring over ice (~50 g). It was then repeatedly extracted with ethyl acetate (3 × 10 mL). The combined extracts washed successively with sodium bisulfite solution, brine and water, and dried (Na_2SO_4). After evaporation, the residue was subjected to column chromatography [silica gel, hexane: ethyl acetate (1:1)] to give **2** and **3** as a mixture followed by the 6-hydroxy-5,7-dinitrocoumarin (**4**) (0.48 g, 62 % yield). The mixture of **2** and **3** were subjected to a second column chro-

matography [silica gel, dichloromethane] to give 6-hydroxy-5-nitrocoumarin (**2**) (0.14 g, 22 % yield) and 6-hydroxy-7-nitrocoumarin (**3**) (89 mg, 14% yield).

6-Hydroxy-5,7-Dinitrocoumarin (**4**): Red solid, m.p. 153–155 °C (dec) (EtOH), (lit. [37]: 155–157 °C).

6-Hydroxy-5-nitrocoumarin (**2**): Yellow solid, m.p. 159–161 °C (EtOH), (lit. [36]: 158–160 °C).

6-Hydroxy-7-nitrocoumarin (**3**): Yellow solid, m.p. 231–233 °C (EtOH), (lit. [36]: 232 °C).

3.3. Synthesis of 4-Nitro-2-(p-tolyl)-7H-chromeno[5,6-d]oxazol-7-one (**6**)

The 6-hydroxy-5,7-dinitrocoumarin (**4**) (100 mg, 0.40 mmol), *p*-tolylmethanol (**5**) (145.4 mg, 1.19 mmol), 1 % Au/TiO_2 [156.2 mg (1.56 mg Au, 0.00793 mmol, 2 mol%)] and toluene (4 mL) were added in a sealed tube. The resulted mixture was stirred at 150 °C for 54 h. After cooling, the catalyst was removed by filtration and the solvent was concentrated under reduced pressure. The residue was subjected to column chromatography [silica gel, hexane: ethyl acetate (2:1)] to give compound **6** (57 mg, 45 % yield) followed by the 4-amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one (**7**) (15.2 mg, 13 % yield) and unreacted compound **4** (40 mg, 40 %).

4-Nitro-2-(p-tolyl)-7H-chromeno[5,6-*d*]oxazol-7-one (**6**): Light yellow solid, m.p. 90–92 °C (MeOH). IR (KBr): 3052, 2924, 2853, 1716 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3), 6.42 (d, 1H, *J* = 9.6 Hz), 7.35 (d, 2H, *J* = 7.9 Hz), 8.15 (d, 2H, *J* = 7.9 Hz), 8.28 (d, 1H, *J* = 9.6 Hz), 8.30 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.9, 111.1, 116.5, 117.5, 127.4, 127.67, 127.7, 129.9, 132.2, 136.8, 145.8, 146.0, 155.5, 160.6, 164.0. LC-MS (ESI): 320 $[M - H]^-$. HR-MS (ESI), (M.W.: 322): *m/z* $[M + H]^+$ calcd for $C_{17}H_{11}N_2O_5$: 323.2789, found: 323.2791.

3.4. Synthesis of 4-Amino-2-(p-tolyl)-7H-chromeno[5,6-d]oxazol-7-one (**7**)

The catalyst, 1% Au/TiO_2 [12.2 mg (0.12 mg Au, 0.0006 mmol, 1 mol%)], was placed in a 5 mL flask, followed by the addition of methanol (2 mL), nitro compound **6** (20 mg, 0.062 mmol) and $NaBH_4$ (gradual addition because of hydrogen release (9.4 mg, 0.25 mmol)). The reaction mixture was then stirred at room temperature for 1 h. After the completion of the reaction (TLC-monitored), the slurry was filtered under reduced pressure to remove the catalyst and washed with methanol (~5 mL). The filtrate was evaporated under vacuum to afford the corresponding 4-amino-2-(*p*-tolyl)-7*H*-chromeno[5,6-*d*]oxazol-7-one, (**7**) (17 mg, 94 % yield): Light yellow solid, m.p. 177–179 °C (hexane/ethyl acetate). IR (KBr): 3446, 3356, 2924, 2852, 1725, 1634 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.46 (s, 3H, CH_3), 4.50 (brs, 2H), 6.29 (d, 1H, *J* = 9.6 Hz), 6.61 (s, 1H), 7.36 (d, 2H, *J* = 7.9 Hz), 8.15 (d, 2H, *J* = 7.9 Hz), 8.26 (d, 1H, *J* = 9.6 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 31.0, 98.1, 111.4, 116.5, 117.4, 127.3, 127.7, 129.8, 129.9, 139.2 146.1, 146.7, 148.9, 156.1, 160.0, 164.7. LC-MS (ESI): 315 $[M + Na]^+$, 347 $[M + Na + MeOH]^+$. HR-MS (ESI), (M.W.: 292): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{12}NaN_2O_3$: 315.2778, found: 315.2784.

3.5. Biological Experiments: In Vitro Assays

The compounds were dissolved in DMSO.

- Antilipid peroxidation: the AAPH protocol was followed [25].
- Lipoxygenase inhibition: according to our previous protocol [25].
- Antioxidant activity: interaction with the stable free radical DPPH (final concentration 0.05 mM) in ethanol absolute (final concentration of the tested compounds 0.1 mM) [25].

4. Conclusions

We demonstrated an efficient and chemoselective method for the synthesis of amino-substituted fused oxazolocoumarins using Au-NPs catalysis in the presence of $NaBH_4$ for the reduction of the corresponding nitro-substituted fused oxazolocoumarins. The

preliminary biological assays pointed that compound **7** presents low anti-lipid peroxidation activity.

Supplementary Materials: The following are available online, NMR and LC-MS (ESI) spectra of compound **7**.

Author Contributions: Conceptualization, writing—original draft preparation, supervision, K.E.L.; performed the biological tests, review and editing the manuscript, D.J.H.-L.; performed the experiments, E.-E.N.V.; performed experiments, editing, in part, the manuscript, T.D.B. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in this article.

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Conflicts of Interest: The authors declare no conflict of interest.

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