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

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Abstract: The new 4-amino-2-(p-tolyl)-7H-chromeno[5,6-d]oxazol-7-one was successfully prepared through the Au/TiO2-catalyzed NaBH4 activation and chemoselective reduction of the new 4-nitro-2-(p-tolyl)-7H-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/TiO2 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 and 13C-NMR analysis. Preliminary biological tests show low anti-lipid peroxidation activity for the title compound.

Keywords: Au-nanoparticles; NaBH4; amino-substituted fused oxazolocoumarin; fused oxazolocoumarins; chemoselective reduction; 3-hydroxynitrocoumarins

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 aminocoumarins through the one-pot Povarov reactions with aromatic aldehydes [9,13–15], acids [14], anhydrides [13,15]; or of α-amidohydroxycoumarins with anhydrides [16], POCl3 [17] or P2O5 [18] led to those products. Furthermore, substituted fused oxazolocoumarins were synthesized by the reduction of 4-hydroxy-3-nitrocoumarin 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 PPh3 and P2O5 [8]. Recently, we prepared oxazolocoumarins by one-pot tandem reactions of α-hydroxynitrocoumarins with benzyl alcohol in toluene under catalytical conditions using gold nanoparticles supported on TiO2, by FeCl3 or by silver nanoparticles supported on TiO2 [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 I2 [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 AgSbF6 [32] or BF3.Et2O [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$_3$CN, 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-hydroxyxocoumarin (1) with cerium ammonium nitrate (CAN) in CH$_3$CN 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-tolymethanol (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)-7H-chromeno[5,6-d]oxazol-7-one (6) (45% yield) accompanied by 4-amino-2-(p-tolyl)-7H-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 \( m/z \ [M + H]^+ \) calcld for \( \text{C}_{17}\text{H}_{11}\text{N}_{2}\text{O}_{5} \): 323.2789, found: 323.2791.

The reduction of nitro-derivative 6 with \( \text{NaBH}_4 \) as hydride ion donor, in the presence of the catalyst \( \text{Au/TiO}_2 \), according to a recent publication for the use of \( \text{Au-NPs} \) in the reduction of nitroarenes to anilines [38], resulted to the chemoselective preparation of 4-amino-2-(p-tolyl)-7\( \text{H} \)-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 \( ^1\text{H}-\text{NMR} \) 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-6\( \text{H} \)-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 \( ^{13}\text{C}-\text{NMR} \), 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 \( m/z \ [M + \text{Na}]^+ \) calcld for \( \text{C}_{17}\text{H}_{12}\text{NaN}_{2}\text{O}_{3} \): 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 \( \mu \text{M} \) after 20 and 60 min under the reported experimental conditions. The anti-lipid peroxidation activity was very low at 100 \( \mu \text{M} \) (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 \( ^1\text{H} \) and \( ^{13}\text{C} \), 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 \( \times \) 10 mL). The combined extracts washed successively with sodium bisulfite solution, brine and water, and dried (\( \text{Na}_2\text{SO}_4 \)). 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)-7H-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, 117.4, 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$_2$O$_5$: 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)-7H-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, 132.2, 136.8, 145.8, 146.0, 155.5, 160.6, 164.0. 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$_2$O$_3$: 325.2778, found: 325.2784.

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.

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

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