Synthesis of Fused Oxazolocoumarins from *o*-Hydroxynitrocoumarins and Benzyl Alcohol Under Gold Nanoparticles or $FeCl_3$ Catalysis[†]

Evangelia-Eirini N. Vlachou,[a] Gerasimos S. Armatas,[b] and Konstantinos E. Litinas[a]*

[a]Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

[b]Department of Materials Science and Technology, University of Crete, Vassilika Vouton, Heraklion 71003, Greece

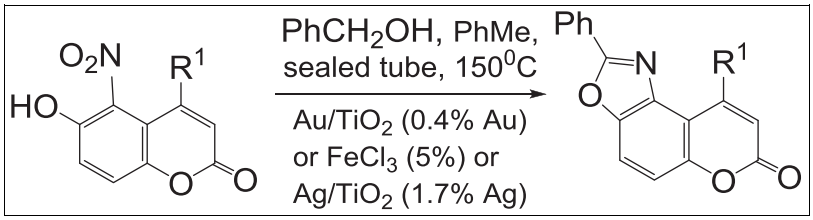
*E-mail: klitinas@chem.auth.gr

[†]Preliminary communications presented at the 12th Chemistry Congress of Greece-Cyprus, Thessaloniki, Greece, May 2015, CD Abstrs., slides, pdf 73; IXth Joint Meeting in Medicinal Chemistry, Athens, Greece, June 2015, Abstrs. P51.

Received May 12, 2016

DOI 10.1002/jhet.2842

Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



Synthesis of fused oxazolocoumarins has been achieved from the one-pot tandem reactions of *o*-hydroxynitrocoumarins with benzyl alcohol in toluene under catalysis in a sealed tube at 150°C. The catalysis was performed by gold nanoparticles supported on TiO_2 (0.4 mol% Au) or $FeCl_3$ (5%) or silver nanoparticles supported on TiO_2 (1.7 mol% Ag).

J. Heterocyclic Chem., **00,** 00 (2017).

INTRODUCTION

Coumarin derivatives, natural or synthetic, represent a class of compounds with important biological activities [1–5], such as anticoagulant, antibiotic, antiiflammatory, antivirus, or anticancer. Fused coumarin derivatives possess also a wide range of biological effects. Especially, furocoumarins are used as photochemotherapeutics [6,7]. Fused oxazolocoumarins have been studied for photosensitizing [8], antibacterial [9], anti-inflammatory [9,10], and antimicrobial [11] activities or as agonists/antagonists of the benzodiazepine receptor [12].

There are few synthetic methods for the preparation of fused oxazolocoumarins starting from the heating on a steam bath of a mixture of 6-hydroxy-4-methyl-5-nitrocoumarin acetate with iron powder, CH_3COONa, and $(CH_3CO)_2O$ in acetic acid [13]. The reactions of *o*-aminohydroxycoumarins with acids [12,14], anhydrides [9], or aromatic aldehydes [9,11,12,14] led also to oxazolocoumarins. The condensations of 7-methoxyimino-4-methylchromen-2,8-dione with methylarenes, arylacetic esters, benzylchloride, or phosphorus ylides gave the corresponding title compounds [15]. Another procedure was by anodic oxidation of 7-hydroxycoumarin in a solution of MeCN and $LiClO_4$ [16].

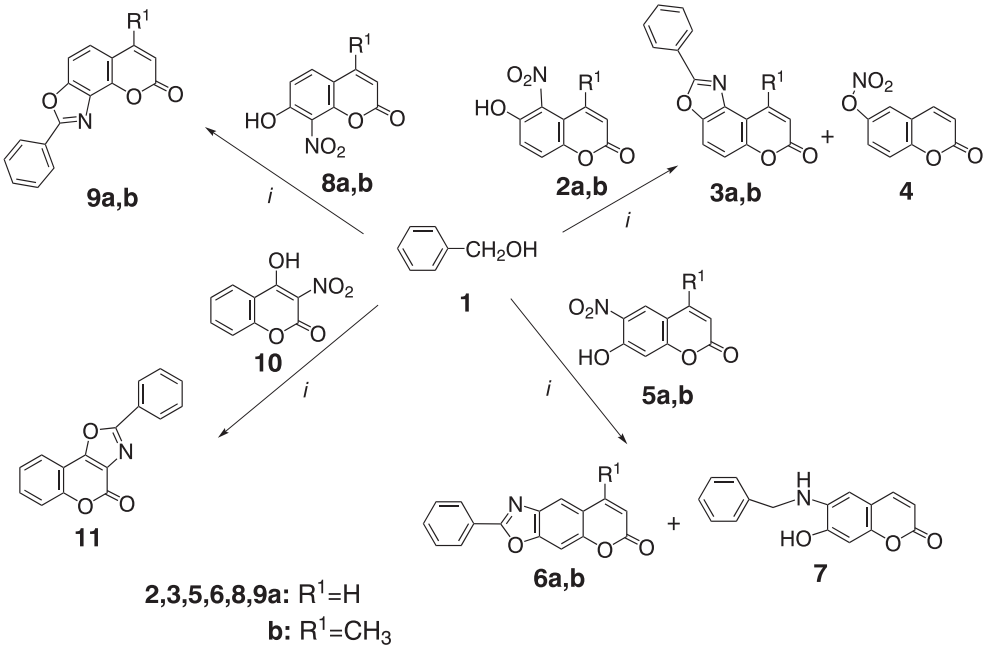
Among the conventional methods for the synthesis of benzoxazoles, there are usually two approaches. One is the use of *o*-haloanilides by intramolecular cyclization with CuO nanoparticles (NPs) [17] or $FeCl_3$ [18] catalyzed cross coupling or base-mediated in DMSO [19] at 140°C. The other is the condensation of *o*-aminophenols with either carboxylic acids in the presence of Lawesson's reagent under microwaves [20] or the condensation of aromatic aldehydes under 2-Iodoxybenzoic acid (IBX) oxidation [21] or under Ir-catalyzed hydrogen transfer reactions [22]. Very recently [23] the Ag/TiO_2 NPs were applied for an analogous synthesis from aldehydes and carboxylic acids derivatives in water. Recently 2-arylbenzoxazoles were synthesized in a one-pot tandem procedure from *o*-nitrophenols and benzyl alcohols under dppf catalysis [24] or catalysis by gold NPs supported on titanium oxide [25].

In continuation to our interest in this field [3,15,26,27], we wish to apply the catalysis [26] with NPs Au/TiO_2 or with $FeCl_3$ [27], as well as the catalysis with NPs Ag/TiO_2 for the first time in the synthesis of fused oxazolocoumarins in a one-pot tandem procedure using the *o*-hydroxynitrocoumarins as starting materials along with benzyl alcohol. The reactions studied and the products obtained are depicted in Scheme 1.

RESULTS AND DISCUSSION

The reaction of 6-hydroxy-5-nitrocoumarin (**2a**) [28] with excess of benzyl alcohol (**1**) in the presence of catalytic amount (0.4 mol% Au) of 1% Au/TiO_2 NPs (Method A, Table 1, entry 1) in refluxing toluene for 8 days resulted to the corresponding 2-phenyl-7 *H*-chromeno[5,6-*d*][1,3]oxazol-7-one (**3a**) in 55% yield,

Scheme 1. Reagents and conditions: (i) Method A: (0.4 mol% Au) of 1% Au/TiO_2 NPs, (Ar atmosphere, toluene, reflux) or (sealed tube, 150°C); Method B: 5% $FeCl_3$ (Ar atmosphere, toluene, reflux) or (sealed tube, 150°C); Method C**:** (1.7 mol% Ag) 4% Ag/TiO_2 NPs (Ar atmosphere, toluene, reflux) or (sealed tube, 150 °C); **4** (from Method B, MW, 120°C); **7** (from Method C).



while 13% of the starting coumarin recovered. The MS spectrum of the new compound **3a** gave the expected molecular ion at *m/z* 264 $[M + H]^+$ In the ^1H–NMR spectrum, there is a doublet at 8.42 ppm (d, 1H, J = 9.6 Hz) for the 4-H of the coumarin moiety, deprotected from the fused oxazole ring, and a peak at 8.28 ppm (dd, 2H, J_1 = 2.0 Hz, J_2 = 7.6 Hz) for the *o*-H of phenyl ring, while in the ^{13}C–NMR spectrum, there are only aromatic and *C* = O carbons. We investigated next the suitable conditions for the synthesis of fused oxazolocoumarins by using the aforementioned coumarin **2a** as the representative reactant. Different catalysts and solvents were screened under different temperatures (Table 1). The analogous reaction between **2a** and **1** in the presence of 5% $FeCl_3$ (Method B, Table 1, entry 2) as the catalyst led to the oxazolocoumarin **3a** in 46% yield with 25% unreacted coumarin **2a.** The use of 4% Ag/TiO_2 NPs (Method C, Table 1, entry 3) in this reaction for the first time as a catalyst (1.7 mol% Ag) in analogous reactions, according to our knowledge, gave only 18% of **3a**. A blank experiment without the use of any catalyst had no results (Method D, Table 1, entry 4).

When the reaction of **2a** and **1** was performed in toluene in a sealed tube at 150°C for 24 h under Method A, the

Table 1

Optimization for the conditions of the synthesis of 2-phenyl-7*H*-chromeno[5,6-d][1,3]oxazol-7-one (**3a**) from 6-hydroxy-5-nitrocoumarin (**2a**) with benzyl alcohol (**1**)**.**

Entry	Method	Conditions	Products (yield %)
1	A: Au/TiO_2 (0.4 mol% Au)	Toluene, Ar, reflux, 8 days	**3a** (55), **2a** (13)
2	B: $FeCl_3$ (5%)	Toluene, Ar, reflux, 2 days	**3a** (46), **2a** (25)
3	C: Ag/TiO_2 (1.7 mol% Ag)	Toluene, Ar, reflux, 9 days	**3a** (18), **2a** (49)
4	D: No catalyst	Toluene, Ar, reflux, 24 h	**2a** (100)
5	A	Toluene, sealed tube, 150°C, 24 h	**3a** (95)
6	B	Toluene, sealed tube, 150°C, 2 days	**3a** (93)
7	C	Toluene, sealed tube, 150°C, 3 days	**3a** (48), **2a** (24)
8	A	Toluene, MW, 110°C, 4 min	**3a** (5), **2a** (70)
9	B	Toluene, MW, 120°C, 4 min	**3a** (24), **4** (40), **2a** (35)
10	C	Toluene, MW, 110°C, 4 min	**2a** (100)
11	A	H_2O, Ar, reflux, 7 days	**2a** (100)
12	A	DCE, Ar, reflux, 6 days	**3a** (traces), **2a** (95)
13	E**:** CF_3SO_3Ag	Toluene, Ar, reflux, 5 days	**2a** (100)

yield of the product **3a** was increased to 95% (Table 1, entry 5). The similar reaction under Method B resulted to 93% of **3a** (Table 1, entry 6), while under Ag/TiO_2 NPs (Method C) led to 48% of **3a** (Table 1, entry 7). The reaction of **2a** and **1** under Method A and microwave (MW) irradiation gave only 5% of the product **3a** (Table 1, entry 8), while under Method B and MW irradiation, the **3a** was received in 24% yield along with the unexpected nitrate **4** (40%) (Table 1, entry 9). The analogous reaction under Method C in microwaves was unsuccessful (Table 1, entry 10). By changing the solvent to H_2O or 1,2-dichloroethane (DCE) (Method A), the starting coumarin **2a** was almost recovered (Table 1, entries 11,12). The use of CF_3SO_3Ag in the place of silver NPs had not any outcome for the reaction (Method E, Table 1, entry 13).

After the examination of suitable reaction conditions, different *o*-nitrohydroxycoumarins were reacted with benzyl alcohol in the presence of the aforementioned catalysts (Table 2). The reactions of 6-hydroxy-4-methyl-5-nitrocoumarin (**2b**) [13] with excess of benzyl alcohol (**1**) in a sealed tube at 150°C in the presence of Au/TiO_2 NPs (Method A) or $FeCl_3$ (Method B) or Ag/TiO_2 NPs (Method C) resulted to oxazolocoumarin **3b** [14] in 55%, 49%, or 33% yield, respectively (Table 2, entries 1–3). The yields are lower than in the case of **3a** (Table 1, entries 5–7) possibly because of steric reasons from the 4-CH_3 group.

The analogous reactions of 7-hydroxy-6-nitrocoumarin (**5a**) [28,29] with benzyl alcohol (**1**) under all the referred catalysts earlier led to the oxazolocoumarin **6a** in moderate yields (Table 2, entries 4–6). In the case of Method C, the 6-benzylamino-7-hydroxycoumarin (7) was also isolated. The 7-hydroxy-4-methyl-6-nitrocoumarin (**5b**) [28] reacted also with **1** (Scheme 1) and gave the oxazolocoumarin **6b** [30] in good enough yields (Methods A,B) (Table 2, entries 7–9). In the cases of the reactions of **1** with the 7-hydroxy-8-nitrocoumarins **8a,b** [9,28], the products **9a,b** received in better yields under Method B (Table 2, entries 10–16). Furthermore, the reaction of 4-hydroxy-3-nitrocoumarin (**10**) [31] resulted to oxazolocoumarin **11** [12] in lower yields (Table 2, entries 16–18).

In the proposed mechanism for these reactions under the use of gold or silver NPs (Scheme 2), in analogy to previous reports [23–25], benzaldehyde (**A**) is formed by oxidation of benzyl alcohol (**1**), while metal-hydride species [32–36] are generated. The study for the oxidation of **1** by Au NPs is well established [34,37], while with Ag NPs is limited [35,36]. *o*-Nitrohydroxycoumarin **5a** is reduced next *in situ* from the metal-hydride species to the *o*-aminohydroxycoumarin **B** in a hydrogen transfer process. Hydrogenations of nitrobenzenes have been studied for both Au [38] and Ag [39] NPs. The next step is the reaction of **A** and **B** to give the imine **C**. The imine **C** is cyclized to the dihydrooxazolocoumarin **D**, which is oxidized to the final product, the oxazolocoumarin **6a**. This oxidation could be attributed to the M-NPs especially in the cases of refluxing toluene under Ar atmosphere (Table 1, entries 1–3). In the cases of sealed tubes, the yields were better possibly because of the amount of air presented in the tubes (Table 1, entries 5–7). When Ag NPs were used, a reduction in the imine **C** led to benzylaminocoumarin **7**. This event could be explain by the lower yields of Method C (Tables 1 and 2).

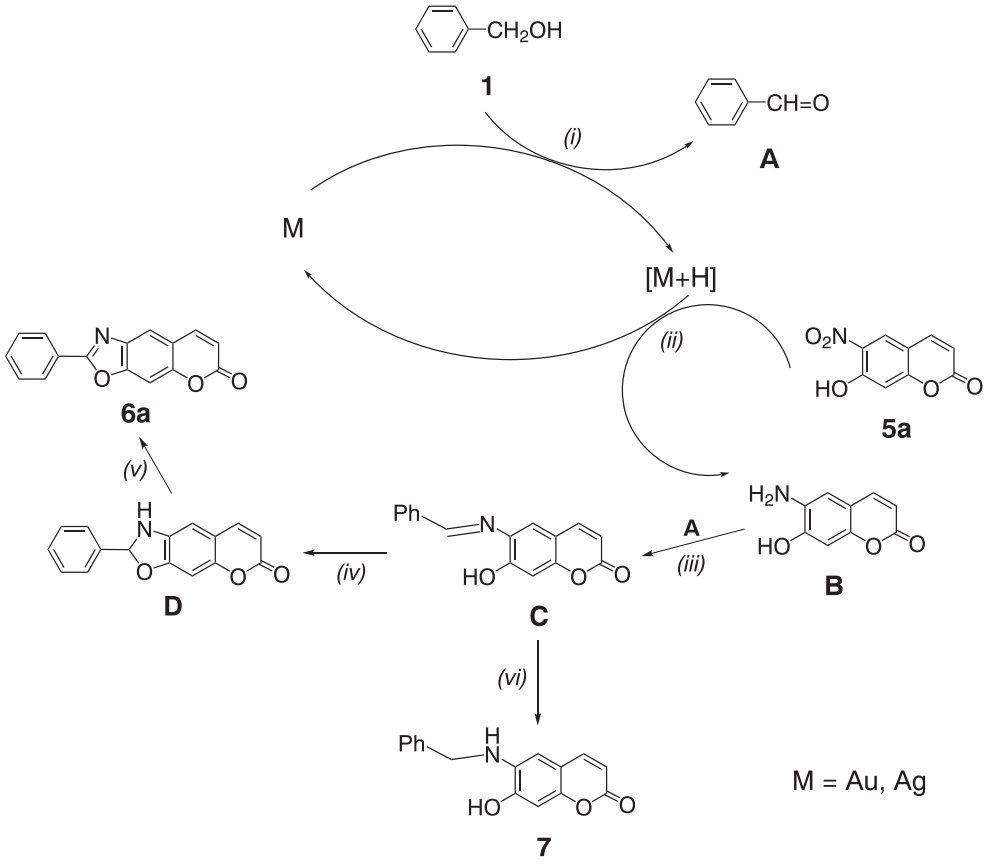
A similar plausible mechanism could be followed in the case of $FeCl_3$ catalysis in analogy to the Fe–catalyzed synthesis of benzoxazoles [24].

Table 2

Reactions of *o*-nitrohydroxycoumarins with benzyl alcohol (**1**) in toluene in a sealed tube at 150°C.

Entry	*o*-Nitrohydroxycoumarin	Conditions	Products (yield %)
1	**2b**	Method A, 7 days	**3b** [14] (55), **2b** (15)
2	**2b**	Method B, 6 days	**3b** (49), **2b** (22)
3	**2b**	Method C, 9 days	**3b** (33), **2b** (35)
4	**5a**	Method A, 6 days	**6a** (30), **5a** (33)
5	**5a**	Method B, 44 h	**6a** (40), **5a** (27)
6	**5a**	Method C, 7 days	**6a** (26), **5a** (42), **7** (5)
7	**5b**	Method A, 3 days	**6b** [30] (71)
8	**5b**	Method B, 3 days	**6b** (57), **5b** (16)
9	**5b**	Method C, 6 days	**6b** (25), **5b** (43)
10	**8a**	Method A, 2 days	**9a** (45), **8a** (26)
11	**8a**	Method B, 3 days	**9a** (48), **8a** (22)
12	**8a**	Method C, 6 days	**9a** (36), **8a** (29)
13	**8b**	Method A, 2 days	**9b** [11] (38), **8b** (34)
14	**8b**	Method B, 3 days	**9b** (60)
16	**8b**	Method C, 9 days	**9b** (31), **8b** (29)
17	**10**	Method A, 24 h	**11** [12] (33), **10** (31)
18	**10**	Method B, 24 h	**11** (25), **10** (46)
19	**10**	Method C, 48 h	**11** (25), **10** (35)

Scheme 2. Conditions: (i) Oxidation (dehydrogenation) of **1**; (ii) reduction (hydrogen transfer; (iii) imine formation (condensation); (iv) cyclisation; and (v) oxidation (dehydrogenation).



In conclusion, the one-pot tandem catalyzed synthesis of fused oxazolocoumarins from *o*-hydroxynitrocoumarins and benzyl alcohol is herein reported. The catalysis is performed with gold or silver NPs supported on TiO_2 or with $FeCl_3$. The catalysis with Ag/TiO_2 NPs is the first ever reported for the synthesis of the benzoxazole moiety from an *o*-hydroxynitrobenzene and alcohol. The synthesis of coumarinyl nitrates in the presence of $FeCl_3$ is under further investigation.

EXPERIMENTAL

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 1310 spectrophotometer as KBr pellets. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz for ^1H and ^{13}C, respectively) or an Agilent (Varian) 500/54 (500 MHz and 125 MHz for ^1H 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 on an LCMS-2010 EV Instrument (Shimadzu) under electrospray ionization (ESI) conditions. Microanalyses were performed on a Perkin-Elmer 2400-II Element analyzer. Silica gel N°60, Merck A.G., was used for column chromatography. The MW experiments were performed in a Biotage (Initiator 2.0) scientific MW oven.

General Procedure. Nitration of 6-hydroxycoumarin by the nitrating agent. A solution of 6-hydroxycoumarin (0.5 g, 3.1 mmol) in concentrated H_2SO_4 (4.16 mL) was cooled in an ice-bath at 0°C. A cooled at 0°C solution of concentrated H_2SO_4 (0.63 mL) and concentrated HNO_3 (0.2 mL) was then added dropwise maintaining the temperature at 0°C. The stirring was continued for 1 h at 0°C till the consumption of the starting compound. The mixture was poured on ice (~50 g). The precipitate was filtered, washed with H_2O, and dried under vacuum to give **2a** (0.56 g, 89% yield).

6-Hydroxy-5-nitrocoumarin (2a). Yellow solid, mp 159–161°C (EtOH) (lit. [28] mp 158–160°C).

6-Hydroxy-4-methyl-5-nitrocoumarin (2b). (96% yield), yellow solid, mp 215–217°C (EtOH) (lit. [13] mp 208–215°C).

7-Hydroxy-8-nitrocoumarin (8a). (94% yield), yellow solid, mp 220 °C (dec) (EtOH) [lit. [28] mp 218°C (dec)].

7-Hydroxy-4-methyl-6-nitrocoumarin (5b). (42% yield from 7-hydroxy-4-methylcoumarin) yellow solid, mp 248–250°C (EtOH) (lit. [28] mp 252–254°C).

7-Hydroxy-4-methyl-8-nitrocoumarin (8b). (51% yield from 7-hydroxy-4-methylcoumarin) pale orange solid, mp 253–255°C (EtOH) (lit. [9] mp 255–256°C).

General procedure for the catalyzed reactions of *o*-nitrohydroxycoumarins with benzyl alcohol.

a Method A.

i Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 ml, 0.784 g, 7.26 mmol), 1% Au/TiO_2 [19 mg (0.19 mg Au, 0.00096 mmol)], and toluene (1 mL) were added in a sealed tube. The resulted mixture was stirred at 150°C for 24 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 **3a** (60 mg, 95% yield).

ii The earlier procedure was repeated under reflux in Ar atmosphere for 8 d and led to **3a** (35 mg, 55% yield).

iii Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol), 1% Au/TiO_2 [19 mg (0.19 mg Au, 0.00096 mmol)], and toluene (1 mL) were added in a vial for MW oven and irradiated under microwaves at 110°C for 4 min (monitoring by TLC). 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 **3a** (3 mg, 5% yield), followed coumarin **2a** (35 mg, 70%).

iv The same procedure in H_2O (1 mL) under reflux for 7 days left unchanged the coumarin **2a**, while the reflux in DCE (1 mL) for 6 days gave only traces of **3a**.

b Method B.

i Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol), $FeCl_3$ (2 mg, 0.012 mmol), and toluene (1 mL) were added in a sealed tube. The resulted mixture was stirred at 150°C for 2 days. After cooling, the catalyst was removed by filtration, and the solvent was concentrated under reduced pressure. The residue was separated by column chromatography [silica gel, hexane : ethyl acetate (2:1)] to give **3a** (59 mg, 94% yield).

ii The earlier procedure was repeated under reflux in Ar atmosphere for 2 days (monitoring by TLC) and gave the **3a** (29 mg, 46% yield).

iii Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 ml, 0.784 g, 7.26 mmol), $FeCl_3$ (2 mg, 0.012 mmol), and toluene (1 mL) were added in a vial for MW oven and irradiated under MW at 120°C for 4 min (monitoring by TLC). 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 **3a** (15 mg, 24% yield), followed by the nitrate **4** (20 mg, 40%) and coumarin **2a** (17.5 mg, 35%).

c Method C.

i Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol), 4% Ag/TiO_2 [11 mg (0.44 mg Ag, 0.00407 mmol)], and toluene (1 mL) were added in a sealed tube. The resulted mixture was stirred at 150°C for 3 days. 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 **3a** (30 mg, 48% yield), followed by coumarin **2a** (12 mg, 24%).

ii **3a** was received in only 18% yield (11 mg), when the aforementioned procedure was repeated under reflux in Ar atmosphere for 9 days.

iii Coumarin **2a** (50 mg, 0.24 mmol), benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol), 4% Ag/TiO_2 [11 mg (0.44 mg Ag, 0.00407 mmol)], and toluene (1 mL) were added in a vial for MW oven and irradiated under MW at 110°C for 4 min. TLC examination indicated only unchanged starting coumarin **2a**.

d Method D. A solution of coumarin **2a** (50 mg, 0.24 mmol) and benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol) in toluene (1 mL) was refluxed for 24 h. TLC examination indicated only unreacted coumarin **2a**.

e Method E. CF_3SO_3Ag (11 mg, 0.043 mmol) was added to the solution of coumarin **2a** (50 mg, 0.24 mmol) and benzyl alcohol (**1**) (0.75 mL, 0.784 g, 7.26 mmol) in toluene (1 mL), and the resulted mixture was heated under reflux for 5 days. TLC examination indicated only the starting coumarin **2a**.

2-Phenyl-7H-chromeno[5,6-d][1,3]oxazol-7-one (3a). Light yellow solid, mp 214–216°C (MeOH), IR (KBr): 3071, 1729, 1619, 1602, 1547, 1477 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 6.57 (d, 1H, J = 9.6 Hz), 7.32 (d, 1H, J = 8.9 Hz), 7.53–7.59 (m, 3H), 7.70 (d, 1H, J = 8.9 Hz), 8.28 (dd, 2H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 8.42 (d, 1H, J = 9.6 Hz); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 111.1, 113.3, 113.7, 117.0, 126.6, 127.7, 129.1, 132.2, 138.5, 139.0, 146.9, 151.6, 160.8, 165.3; MS (ESI): *m/z* 264 $[M + H]^{+\cdot}$, 318 $[M + Na + MeOH]^+$ *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.92; H, 3.60; N, 5.29.

2-Oxo-2H-chromen-6-yl nitrate (4). Yellow oil, IR (KBr): 3015, 1717, 1613 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 500 MHz) δ 6.28 (d, 1H, J = 9.4 Hz), 7.05 (dd, 2H, J_1 = 1.9 Hz, J_2 = 8.6 Hz), 7.32 (d, 1H, J = 1.9 Hz), 7.36 (d, 1H, J = 8.6 Hz), 7.64 (d, 1H, J = 9.4 Hz); ^{13}C–NMR ($CDCl_3$, 125 MHz) δ 107.1, 113.5, 113.8,

117.1, 128.2, 143.4, 153.3, 159.1, 161.2; MS (ESI): *m/z* 208 $[M + H]^{+\cdot}$, 206 $[M-H]^-$. *Anal.* Calcd for $C_9H_5NO_5$: C, 52.19; H, 2.43; N, 6.76. Found: C, 52.11; H, 2.49; N, 6.68.

9-Methyl-2-phenyl-7H-chromeno[5,6-d][1,3]oxazol-7-one (3b). [55% yield (Method A), 49% yield (Method B), and 33% yield (Method C)] light yellow solid, mp 208–210°C (MeOH) (lit. [14] mp 211–212°C).

2-Phenyl-6H-chromeno[6,7-d][1,3]oxazol-6-one (6a). (19 mg, 30% yield, Method A; 25 mg, 40% yield, Method B; 16.5 mg, 26% yield, Method C), yellow solid, mp 207–209°C (MeOH), IR (KBr): 3053, 1720, 1610, 1575 cm^{-1}; ^1H–NMR ($CDCl_3$, 300 MHz) δ 6.43 (d, 1H, J = 9.6 Hz), 7.54 (s, 1H), 7.55–7.57 (m, 3H), 7.82 (s, 1H), 7.83 (d, 1H, J = 9.6 Hz), 8.25 (dd, 2H, J_1 = 1.9 Hz, J_2 = 7.6 Hz); ^{13}C–NMR ($CDCl_3$, 75 MHz) δ 99.5, 115.3, 116.5, 118.1, 126.3, 127.8, 129.1, 132.3, 139.2, 143.9, 152.3, 152.6, 160.5, 164.8; MS (ESI): *m/z* 264 $[M + H]^{+\cdot}$, 302 $[M + K]^+$, 318 $[M + Na + MeOH]^+$ *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 73.07; H, 3.53; N, 5.39.

6-(Benzylamino)-7-hydroxy-2H-chromen-2-one (7). (3 mg, 5% yield, Method C), light yellow solid, mp 180–182°C (MeOH), IR (KBr): 3424, 3212, 3057, 2924, 2848, 1724, 1606, 1562 cm^{-1}; ^1H–NMR ($CDCl_3$, 300 MHz) δ 5.04 (s, 2H), 6.37 (d, 1H, J = 9.6 Hz), 6.79 (s, 1H), 7.36–738 (m, 6H), 7.60 (d, 1H, J = 9.6 Hz); ^{13}C–NMR ($CDCl_3$, 75 MHz) δ 46.5, 112.5, 115.4, 115.7, 117.6, 127.9, 129.2, 132.3, 140.9, 143.0, 143.7, 155.9, 160.2, 161.6; MS (ESI): *m/z* 268 $[M + H]^+$ *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.42. Found: C, 71.85; H, 4.79; N, 5.34.

8-Methyl-2-phenyl-6H-chromeno[6,7-d][1,3]oxazol-6-one (6b). [71% yield (Method A), 57% yield (Method B) and 25% yield (Method C)] light yellow solid, mp 231–232 °C (MeOH) (lit. [30] mp 232–233°C).

2-Phenyl-8H-chromeno[8,7-d][1,3]oxazol-8-one (9a). (28 mg, 45% yield, Method A; 30 mg, 48% yield, Method B; 22 mg, 36% yield, Method C), light yellow solid, mp 197–199°C (MeOH), IR (KBr): 3071, 1729, 1657 cm^{-1}; ^1H–NMR ($CDCl_3$, 300 MHz) δ 6.45 (d, 1H, J = 9.6 Hz), 7.49 (d, 1H, J = 8.5 Hz), 7.54–7.58 (m, 3H), 7.82 (d, 1H, J = 8.5 Hz), 7.86 (d, 1H, J = 9.6 Hz), 8.29 (dd, 2H, J_1 = 1.7 Hz, J_2 = 7.6 Hz); ^{13}C–NMR ($CDCl_3$, 75 MHz) δ 99.5, 107.4, 115.4, 118.1, 126.6, 128.1, 129.1, 132.2, 139.2, 139.7, 143.9, 150.8, 160.5, 164.6; MS (ESI): *m/z* 264 $[M + H]^{+\cdot}$, 296 $[M + H + MeOH]^{+\cdot}$, 318 $[M + Na + MeOH]^+$ *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.87; H, 3.51; N, 5.22.

6-Methyl-2-phenyl-8H-chromeno[8,7-d][1,3]oxazol-8-one (9b). [38% yield (Method A), 60% yield (Method B), and 31% yield (Method C)] light yellow solid, mp 232–234°C (MeOH) (lit. [11] mp 232–234°C).

2-Phenyl-4H-chromeno[3,4-d][1,3]oxazol-4-one (11). (20.5 mg, 33% yield, Method A; 16 mg, 25% yield, Method B; 16 mg, 25% yield, Method C), light yellow solid, mp 191–193°C (MeOH) (lit. [12] mp 189–190°C).

REFERENCES AND NOTES

[1] Murray, D. H.; Mendez, J.; Brown, S. A. In The Natural Coumarins: Occurrence, Chemistry and Biochemistry; John Wiley & Sons: New York, 1982; p 1.

[2] O'Kennedy, R.; Thornes, R. D. Coumarins: Biology, Applications and Mode of Action; John Wiley & Sons: Chichester, 1997; p 1.

[3] Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. Curr Pharm Des 2004, 10, 3813.

[4] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. Curr Med Chem 2005, 12, 887.

[5] Kostova, I.; Raleva, S.; Genova, P.; Argirova, R. Bioinorg Chem Appl 2006. DOI: 10.1155/BCA/2006/68274.

[6] Dall'Acqua, F.; Vedaldi, D. In CRC Handbook of Organic Photochemistry and Photobiology; Horspool, W. M.; Song, P. S. Eds.; CRC Press: Boca Raton, FL, 1995; pp 1341–1350.

[7] Kitamura, N.; Kohtani, S.; Nakagaki, R. J Photochem Photobiol C Photchem Rev 2005, 6, 168.

[8] Pathak, M. A.; Fellman, J. H.; Kaufman, K. D. J Invest Dermatol 1960, 35, 165.

[9] Sahoo, S. S.; Shukla, S.; Nandy, S.; Sahoo, H. B. Eur J Exp Biol 2012, 2, 899.

[10] Kontogiorgis, C.; Hadjipavlou-Litina, D. J. Enz Inh Med Chem 2003, 18, 63.

[11] Prasanna, B.; Sandeep, A.; Revathi, T. World J Pharm Pharm Sci 2014, 3, 404.

[12] Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. Il Farmaco 1998, 53, 375.

[13] Kaufman, K. D.; McBride, D. W.; Eaton, D. C. J Org Chem 1965, 30, 4344.

[14] Reddy, S. J Indian Chem Soc 1981, 58, 599.

[15] Bezergiannidou-Balouctsi, C.; Litinas, K. E.; Malamidou-Xenikaki, E.; Nicolaides, D. N.; Mentzafos, D.; Terzis, A. Tetrahedron 1993, 49, 9127.

[16] Abdelghani, S.; Abd El-Aal, A.; Shehab, W.; El-Mobayed, M. Synthesis 2003 1373.

[17] Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. J Org Chem 2009, 74, 8719.

[18] Bonnamour, J.; Bolm, C. Org Lett 2008, 10, 2665.

[19] Peng, J.; Zong, C.; Ye, M.; Chen, T.; Gao, D.; Wang, Y.; Chen, C. Org Biomol Chem 2011, 9, 1225.

[20] Sejas, J.; Vazquez-Tato, M.; Carballido-Reboredo, M.; Crecente-Campo, J.; Romar-Lopez, L. Synlett 2007, 313.

[21] Chen, F.; Shen, C.; Yang, D. Tetrahedron Lett 2011, 52, 2128.

[22] Blacker, A. J.; Farah, M. M.; Hall, M. I.; Mrsden, S. P.; Saidi, O.; Williams, J. M. J. Org Lett 2009, 11, 2039.

[23] Maleki, B.; Baghayeri, M.; Vahdat, S. M.; Mohammadzadeh, A.; Akhoondi, S. RSC Adv 2015, 5, 46545.

[24] Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G.-J. Org Lett 2012, 14, 2722.

[25] Tang, L.; Guo, X.; Yang, Y.; Zha, Z.; Wang, Z. Chem Commun 2014, 50, 6145.

[26] Symeonidis, T. S.; Lykakis, I. N.; Litinas, K. E. Tetrahedron 2013, 69, 4612.

[27] Symeonidis, T. S.; Hadjipavlou-Litina, D. J.; Litinas, K. E. J Heterocyclic Chem 2014, 51, 642.

[28] Lei, L.; Yang, D.; Liu, Z.; Wu, L. Synth Commun 2004, 34, 985.

[29] Lin, S.-T.; Yang, F.-M.; Yang, H.-J.; Huang, K.-F. J Chem Research (S) 1995, 372.

[30] Cires, L.; Ofenberg, H.; Craita, C. Org Prep Proc Int 2001, 33, 361.

[31] Iaroshenko, V. O.; Mkrtchyan, S.; Gevorgyan, A.; Vilches-Herrera, M.; Sevenand, D. V.; Villinger, A.; Ghochikyan, T. V.;

Saghiyan, A.; Sosnovskikh, V. Y.; Langer, P. Tetrahedron 2012, 68, 2532.

[32] Cui, X.; Zhang, C.; Shi, F.; Deng, Y. Chem Commun 2012, 48, 9391.

[33] Tang, C. H.; He, L.; Liu, Y. M.; Cao, Y.; He, H. Y.; Fan, K. N. Chem-Eur J 2011, 17, 7172.

[34] Abad, A.; Conception, P.; Corma, A.; Garcia, H. Angew Chem Int Ed 2005, 44, 4066.

[35] Mitsudome, T.; Mikami, Y.; Funai, H.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. Angew Chem Int Ed 2008, 47, 138.

[36] Bayat, A.; Shakourian-Fard, M.; Ehyaei, N.; Hashemi, M. M. RSC Adv 2015, 5, 22503.

[37] Davis, S. E.; Ide, M. S.; Davis, R. J. Green Chem 2013, 15, 17.

[38] Liu, X.; He, L.; Liu, Y.-M.; Cao, Y. Acc Chem Res 2014, 47, 793.

[39] Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. Chem Commun 2005, 5298.