Tetrahedron Letters 51 (2010) 5322–5324

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A different route to 3-aryl-4-hydroxycoumarins

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ARTICLE INFO

Article history:
Received 1 July 2010
Revised 23 July 2010
Accepted 2 August 2010
Available online 9 August 2010

Keywords:
4-Hydroxucoumarin
Aryl halides
Radical nucleophilic substitution
C_3-Arylation

ABSTRACT

We herein report the simple and direct arylation of 4-hydroxycoumarins by photoinduced reaction with aryl halides (iodobenzene, iodonaphthalene, 4-iodoanisole, 2-iodoanisole). Good yields of 3,4-disubstituted coumarins were obtained in these reactions (>60%). Extension of the procedure to the reaction with *o*-dihalobenzenes leads to the synthesis of ring closure products which bear a tetracyclic aromatic-condensed ring system, although in lower overall yields (≈45%).

4-Hydroxycoumarins constitute an important class of benzopyrones. Many of them display pharmacological effects[1] and are key intermediates for different products.[2] To date numerous compounds have been isolated from natural products[3] and synthetic analogues have been prepared.[4]

The simplest synthetic route to 3-aryl-4-hydroxycoumarins is via direct arylation at C3 of the coumarin ring. Different reactants are used, for example aryldiazonium chloride,[5] arylbismuth^{V} reagents,[6] and aryllead^{V} triacetates.[7]

In recent years, it has been informed that the palladium-catalyzed coupling reaction obtained this type of compounds. However, most of these approaches are focused on 3,4-disubstituted coumarins.[8] Only limited reactions for the synthesis of 3-substitued 4-hydroxycoumarins have been reported. For example, phenyliodonium zwitterion reacts with aryl boronic acids to give products with good yield.[9] The main limitations of these methodologies lie in the difficulty found in the preparation of reactants or the toxicity of these.

The radical nucleophilic substitution can be considered as an alternative route for the formation of carbon–carbon bonds.[10] This type of reactions finds increasing application in the synthesis of complex organic molecules,[11,12] particularly, since such reactions are generally carried out under mild conditions and the substrates tolerate many functional groups. It is well known that in an $S_{RN}1$ reaction, a nucleophile is combined with an aryl radical to provide the corresponding coupling product (Scheme 1).[10] These nucleophilic substitutions involve electron transfer steps (ET) and the intermediacy of radical and radical anions. Traditionally, aryl halide substrates give the aryl radical in the photoelectron transfer reaction from the nucleophile (Eqs. 1 and 2). The radicals thus formed can react with the nucleophile to give the radical anion of the substitution product (Eq. 3), responsible for continuing the propagation chain of the mechanism proposed (Eq. 4) (Scheme 1).

$$
\begin{array}{rcll}
\mathrm{ArX} + \mathrm{Nu}^{-} & \xrightarrow{h\nu} & \mathrm{ArX}^{\bullet -} + \mathrm{Nu}^{\bullet} & (1)\\
\mathrm{ArX}^{\bullet -} & \longrightarrow & \mathrm{Ar}^{\bullet} + \mathrm{X}^{-} & (2)\\
\mathrm{Ar}^{\bullet} + \mathrm{Nu}^{-} & \longrightarrow & \mathrm{ArNu}^{\bullet -} & (3)\\
\mathrm{ArNu}^{\bullet -} + \mathrm{ArX} & \longrightarrow & \mathrm{ArNu} + \mathrm{ArX}^{\bullet -} & (4)\\
\hline
\mathrm{ArX} + \mathrm{Nu}^{-} & \longrightarrow & \mathrm{ArNu} + \mathrm{X}^{-} &
\end{array}
$$

Scheme 1.

Continuous efforts toward the coumarin synthesis have been reported due to the importance of these molecules. In this Letter we propose a selective arylation approach, based on the radical nucleophilic substitution mechanism, for the generation of 3-aryl-4-hydroxycoumarins from commercially available reactants. Finally, the methodology we report herein can be extended to obtaining a tetracyclic aromatic ring structure by the reaction of either anion with *o*-dihalobenzenes.

The results of the photoinitiated reactions of the anion of 4-hydroxycoumarin (**1**) with different aryl halides (**2**) (Scheme 2) are shown in Table 1.

The general procedure for the above-mentioned reactions is as follows: to a solution of anion **1**, obtained by deprotonation of 4-hydroxycoumarin with potassium *tert*-butoxide (KBuO-*t*) in DMSO, was added the substrate.[13] Following this approach, the 4-hydroxycumarin anion (**1**), as an electron donor, was unreactive toward **2a** under photostimulation and afforded only 32% yield of

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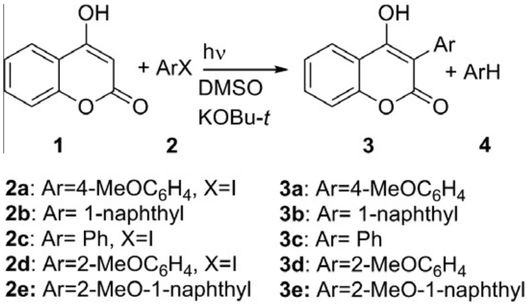
doi:10.1016/j.tetlet.2010.08.013



Scheme 2.

Table 1
Photoinduced reactions of aryl halides with the anion of 4-hydroxycoumarin (**1**) in DMSO[a]

Exp.	**1**	Substrate	Base	Products[b] (% yields)	
	$M \times 10^3$	$M \times 10^3$	$M \times 10^3$	ArH	Substitution
1[c]	77	**2a**, 27	80	11	**3a**, traces
2	308	**2a**, 52	458	44	**3a**, 27
3	508	**2a**, 50	654	21	**3a**, 64
4[d,e]	156	**2a**, 52	298	—	—
5[e,f]	152	**2a**, 54	298	—	—
6	304	**2b**, 58	476	35	**3b**, 62
7	501	**2b**, 50	604	17	**3b**, 79
8	508	**2c**, 52	650	nq[g]	**3c**, 75
9	500	**2d**, 49	650	40	**3d**, 54
10	300	**2e**, 53	476	80	—
11	2000	**2e**, 200	2600	96	—
12	508	**5**, 52	650	nq	**6**, 75
13[c]	77	**2a**, 27	80	11	**3a**, traces

[a] Photoinitiated reactions (unless indicated), carried out under nitrogen. Reaction time (180 min). X^- (%) >90% determined potentiometrically on the basis of ArX concentration.
[b] Determined by GLC and the internal standard method on the basis of ArX concentration.
[c] Reaction time = 300 min, X^- (%) = 32%.
[d] *p*-Dinitrobenzene (30 mmol %).
[e] X^- (%) <7%.
[f] Reaction carried out in the dark.
[g] nq = not quantified.

iodide ions, anisole (11%), and traces of the substitution product (Table 1, entry 1). However, in the presence of an excess of KBuO-*t* (KBuO-*t*/nucleophile/substrate ratio = 9:6:1) and under irradiation (entrainment conditions)[14] affording the product corresponding to substitution at C_3 of the coumarin cycle **3a** (27%), and anisole **4a** (44%) after quenching with NH_4NO_3 (Table 1, entry 2).

The percentage of **3a** increases to 64% with a nucleophile/substrate ratio of 10 (Table 1, entry 3). This photoinduced reaction is completely suppressed by the addition of a good electron-acceptor such as *p*-dinitrobenzene (*p*-DNB) (Table 1, entry 4). This result, the absence of reaction in the dark after 3 h (Table 1, entry 5) and the presence of anisole, can be regarded as indicative of the $S_{RN}1$ mechanism.[10] In the initiation step a photoinduced ET from KOBu-*t* to **2** takes place (Eq. 1).[10] The radical originated by dissociation of aryl halide radical anion (Eq. 2) can couple with the nucleophile to form the radical anion of the substitution product (Eq. 3) or can be reduced by hydrogen atom abstraction from the solvent to afford compound **4**.[15] It is important to mention that the *O*-arylated product of **1**[16] or of KOBu-*t*[10] is not formed in any of these reactions.

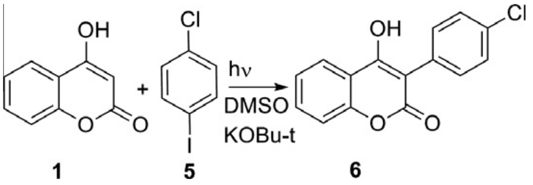
By employing this protocol, the reaction of the anion of **1** was examined with the aryl halides (**2b**–**e**).

Similar results to those obtained in the reaction of **2a** with **1** were observed when we used 1-iodonaphthalene (**2b**); the C_3-arylation compound (**3b**) was the main product formed (79% after 3 h irradiation) accompanied by the reduction product naphthalene (17%) (Table 1, entries 6 and 7). High yields of C_3-arylation were also obtained by the reaction with iodobenzene (**2c**) (75%) (Table 1, entry 8). 2-Iodoanisole (**2d**) reacts with anion of **1** to afford **3d** and anisole in 54% and 40% yields, respectively (Table 1, entry 9).

Unfortunately, 1-iodo-2-methoxynaphthalene (**2e**) failed to afford the arylation of the nucleophile, the main reaction being its reduction to 2-methoxynaphthalene (>80%) (Table 1, entries 10 and 11). A similar behavior was found when this substrate reacted with other nucleophiles.[12,15] These results show that the coupling reaction of the anion of **1** is sensitive to the high steric hindrance of the aryl radical.

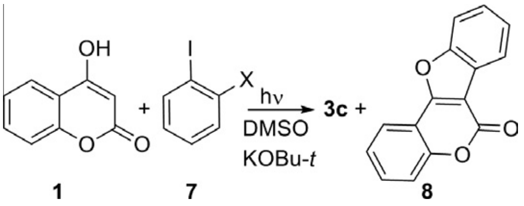
The relative reactivity of the anion of **1** was determined in competition experiments and estimated according to the approximation previously reported.[17] We could determine that 4-hydroxycumarin ion is 4 times less reactive than 2-naphthoxide ion, the latter being a hydroxy anion more reactive in this mechanism.[10,15]

On the basis of the promising results obtained with the aryl halides tested, the photoinduced methodology has been extended to the reaction of **1** with dihalobenzenes. The 1-chloro-4-iodobenzene gives the substitution product with retention of chloride (**6**) in 65% of yield (Table 2, entry 1). This product can then be modified by different chemical reactions.



(5)

We investigated the reaction of anion **1** with *o*-dihalobenzenes as an alternative procedure to the synthesis of the tetracyclic ring systems **8** by biaryl coupling followed by intramolecular heterocyclization.[11] *o*-Diiodobenzene **7a** reacts with the anion of **1** to afford the reduced-substituted product **3c** and the substituted-cyclized compound **8** in 60% and 39% yields, respectively (Table 2, exp. 1). On the other hand, compounds **3c** and **8** were obtained by reaction of the anion of **1** with *o*-bromoiodobenzene **7b** (40% and 28% yields, respectively, Table 1, exp. 2).



(6)

However, *o*-chloroiodobenzene affords **3c** and **8** (14% and 26%, respectively). In this case we find the monosubstituted compound with retention of halide, 4-hydroxy-3-(2-chlorophenyl)coumarin (**9**). Further studies are in progress in order to replace the chlorine atom of **6** and **9**.

Table 2
Photoinduced reactions of *o*-dihalobenzene with the anion of 4-hydroxycoumarin (**1**) in DMSO[a]

Exp.	**1**	**7**	Base	Products[b] (% yields)			
	$M \times 10^3$	$M \times 10^3$	$M \times 10^3$	ArH	**3c**	**8**	**9**
1	635	**7a**, 50	810	2	60	39	—
2	630	**7b**, 52	820	18	40	28	—
3	508	**7c**, 50	743	37	14	26	23

[a] Photoinitiated reactions (unless indicated), carried out under nitrogen. Reaction time (180 min).
[b] Determined by GLC and the internal standard method on the basis of ArX concentration.

In summary, we have described an efficient and facile route for the synthesis of 3-aryl-4-substituted coumarins from commercially available, easily handled, and inexpensive reactants via photoinduced radical nucleophilic substitution under mild conditions with good yields. The substrates tolerate many functional groups. Moreover, the reaction provides an alternative access to the tetracyclic system **8** in moderate yields.

Acknowledgments

This work was supported by Agencia Córdoba Ciencia (ACC), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and Secretaría de Ciencia y Tecnología (SECyT), Universidad Nacional de Córdoba (UNC), Argentina. S.A.R. thanks CONICET for the award of a fellowship.

Supplementary data

Supplementary data (general methods and materials. ^{1}H NMR and ^{13}C NMR spectra and MS of compounds **3a**, **3b**, **3c**, **3d**, **6**, **8** and **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.013.

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13. The reactions were carried out in a 50 mL three-neck round-bottomed flask equipped with a nitrogen inlet and a magnetic stirrer. To 20 mL of dry and degassed DMSO under nitrogen were added potassium *tert*-butoxide (1.456 g, 13 mmol) and then 4-hydroxycoumarin (1.620 g, 10 mmol). After 15 min 4-iodoanisole (234 mg, 1.0 mmol) was added and the reaction mixture was irradiated for 180 min. The reaction was quenched with an excess of ammonium nitrate and water (30 mL). The mixture was extracted three times with methylene chloride (20 mL); the organic extract was washed twice with water, dried ($MgSO_4$), the reduction products (ArH) were quantified by GC in this extract and compared with authentic commercial samples; the remaining aqueous phase was acidified with nitric acid 65% P/V to pH 3–4, the precipitate was filtered with low pressure and redissolved with acetone. Products were isolated by column or radial chromatography [hexane/ethyl acetate (1:1 or 1.5:1)] and characterized by ^{1}H NMR and ^{13}C NNR and mass spectrometry. All products are known and exhibited physical properties identical to those reported in the literature.
14. Entrainment is useful when Nu_1^- is rather unreactive at initiation (Eq. 1), but quite reactive at coupling (Eq. 3). Under these conditions the other Nu_2^- (KBuO-*t*), more reactive at initiation but not reactive in the coupling reaction, is added. Nu_2^- increases the generation of radical intermediates which are coupled with the more reactive nucleophile Nu_1^-.
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16. For regioselectivity of the coupling between aryl radicals and arylhydroxy anions, see: Baumgartner, M. T.; Blanco, G. A.; Pierini, A. B. *New J. Chem.* **2008**, *32*, 464–471.
17. The equation used in the relative reactivity determination of pairs of nucleophiles versus a radical is as follows:

$$\frac{k_1}{k_2} = \frac{\ln([\mathrm{Nu}_1]_0/[\mathrm{Nu}_1]t)}{\ln([\mathrm{Nu}_2]_0/[\mathrm{Nu}_2]_t)}$$

where $[\mathrm{Nu}_1]_0$ and $[\mathrm{Nu}_2]_0$ are initial concentrations and $[\mathrm{Nu}_1]_t$ and $[\mathrm{Nu}_2]_t$ are concentrations at time t of both nucleophiles. This equation is based on a first-order reaction of both anions with the phenyl radicals, see: Bunnett, J. F. In *Investigation of Rates and Mechanisms of Reactions*, 3rd ed.; Lewis, E. S., Ed.; Wiley-Interscience: New York, 1974, part 1, p 159.