Communication

Catalytic Addition of Indole-2-Carboxylic Acid to 1-Hexyne

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Abstract: The synthesis of two novel enol esters, namely hex-1-en-2-yl indole-2-carboxylate and hex-1-en-2-yl 1-(hex-1-en-2-yl)-indole-2-carboxylate, is presented. Both compounds were generated by addition of indole-2-carboxylic acid to 1-hexyne employing $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ and $[AuCl(PPh_3)]/AgPF_6$, respectively, as catalysts.

1. Introduction

The catalytic addition of carboxylic acids to alkynes is the most straightforward and atom-economical method currently available to obtain enol esters, which are very useful intermediates for organic synthesis [1–7]. A large number of Groups 8–11 metal complexes able to promote the process have been reported in the literature, predominating those based on ruthenium and gold due to their exquisite regio- and stereo-selectivity [1–8]. In this context, some years ago we disclosed that the bis(allyl)-ruthenium(IV) derivative $[RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl; **1**) is an excellent catalyst for the selective Markovnikov addition of carboxylic acids to terminal alkynes [9]. As shown in Scheme 1, this complex is able to operate in aqueous medium and does not require acidic or basic additives. In a series of independent works we also demonstrated the wide substrate scope of complex **1**, which allows the addition of both aromatic, aliphatic and α,β-unsaturated carboxylic acids, not only to terminal alkynes, but also to 1,3-enynes and 1,n-diynes (n = 3, 4, 5) [9–11].
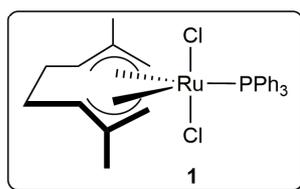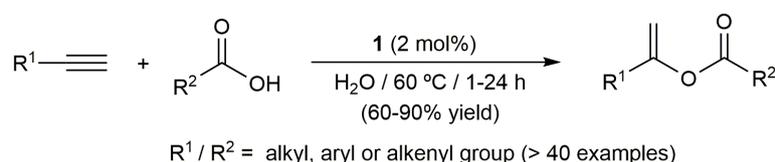
Scheme 1. Ruthenium(IV)-catalyzed Markovnikov addition of carboxylic acids to terminal alkynes.

An interesting result, not published previously, was found while studying the reactivity of indole-2-carboxylic acid (**2**) towards 1-hexyne (**3**) catalyzed by [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(PPh$_3$)] (**1**) since, in addition to the expected enol ester hex-1-en-2-yl indole-2-carboxylate (**4**), a second product is also formed, namely hex-1-en-2-yl 1-(hex-1-en-2-yl)-indole-2-carboxylate (**5**) (see Figure 1), which results from the addition of both the -CO$_2$H and NH units of **2** to 1-hexyne molecules. Details are herein presented, as well as characterization data are procedures to obtain enol esters **4** and **5** in high yield.
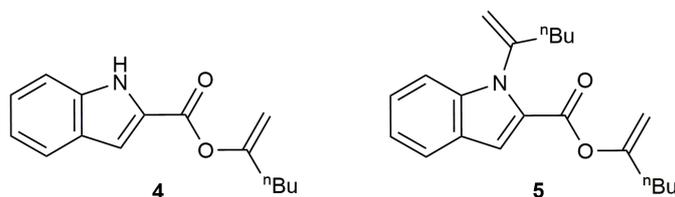
Figure 1. Structure of the novel enol esters **4** and **5**.

2. Results and Discussion

As shown in Table 1, when an equimolar amount of compounds **2** and **3** was heated at 60 °C in water with 2 mol% of the Ru(IV) complex **1** [9], a mixture of the novel enols esters **4** and **5** was formed in 4.9:1 ratio (entry 1). Under these conditions the conversion of the starting carboxylic acid **2** was only 68% after 9 h, while 1-hexyne (**3**) was completely consumed in the reaction. The selectivity towards the mono-addition product **4** could be significantly improved (**4**:**5** ratio = 11.0:1) by performing the reaction at 40 °C, but the conversion of **2** was lower (43%) even after 24 h of heating (entry 2). On the other hand, in order to orient the process towards the formation of **5**, a couple of experiments were carried out using a **2**:**3** ratio of 1:2 and metal loadings of 2 and 5 mol% (entries 3 and 4). The results obtained in such reactions were almost identical, showing the full conversion of **2** after 14 h and the generation of a mixture of **4** and **5**, with the mono-addition product **4** being again the major component (*ca.* 3:1 ratio).

Table 1. Addition of indole-2-carboxylic acid (**2**) to 1-hexyne (**3**) catalyzed by complex **1**. [1]
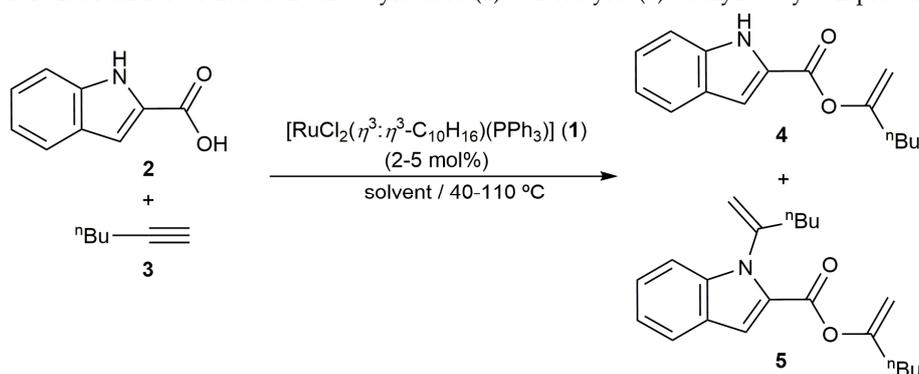
Entry	Catalyst Loading	Solvent	2:3 Ratio	T (°C)	Time (h)	Conv. (%) [2,3]	4:5 Ratio [3]
1	2 mol%	water	1:1	60	9	68	4.9:1
2	2 mol%	water	1:1	40	24	43	11.0:1
3	2 mol%	water	1:2	60	14	> 99	3.2:1
4	5 mol%	water	1:2	60	14	> 99	3.0:1
5	5 mol%	water	1:10	100	24	> 99	2.3:1
6	5 mol%	toluene	1:1	60	24	41	14.2:1
7	5 mol%	toluene	1:10	110	24	92	8.5:1

[1] Reactions were performed under N$_2$ atmosphere employing 1 mmol of indole-2-carboxylic acid (**2**) and 1 mL of the corresponding solvent. [2] Based on the quantity of acid **2** consumed. [3] Determined by ^{1}H NMR spectroscopy.

As shown in entry 5, the use of a large excess of 1-hexyne (10 equivalents) under refluxing conditions did not lead to a significant improvement in selectivity and **4** was again the major product formed (**4**:**5** ratio = 2.3:1). Additional experiments replacing water by toluene, under conditions that presumably could favor the formation of one or the other product, did not lead to the expected results (entries 6 and 7). It should be noted at this point that, in the absence of complex **1**, no reaction occurs between **2** and **3**.

Although enol esters **4** and **5** can be isolated in pure form after chromatographic work-up of the reaction mixtures commented above, the yields were poor, particularly for **5** (up to 12%). This fact prompted us to search for alternative catalysts that would allow the isolation of both compounds in high yield. In this sense, taking advantage of the known ability of arene-ruthenium(II) complexes of type $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PR_3)]$ to promote the Markovnikov addition of carboxylic acids to alkynes in organic media [12–14], we found that enol ester **4** can be selectively generated by performing the reaction between equimolar amounts of **2** and **3** in toluene at 80 °C employing $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ (5 mol%) as the catalyst (Scheme 2). Under these conditions, we were able to isolate **4** in 84% yield, with the ^{1}H NMR spectrum of the crude reaction mixture showing the presence of only trace amounts of **5** and other species probably derived from the competitive anti-Markovnikov addition of **2** to **3** [12–14]. The IR and NMR spectra recorded for the isolated compound **4** showed the characteristic signals of the NH ($v = 3340$ cm^{-1} and $\delta_H = 9.53$ ppm) and OC=CH$_2$ units [$\delta_C = 101.6$ (CH$_2$) and 160.6 (C) ppm and $\delta_H = 4.94$ and 5.00 ppm ($^2J_{HH} = 1.6$ Hz)]. These data, along with those obtained through MS accurate mass (HRMS) spectrometry, allowed to confirm its structure (see full details in the Materials and Methods section; copies of the IR and NMR spectra are provided as Supplementary Materials).
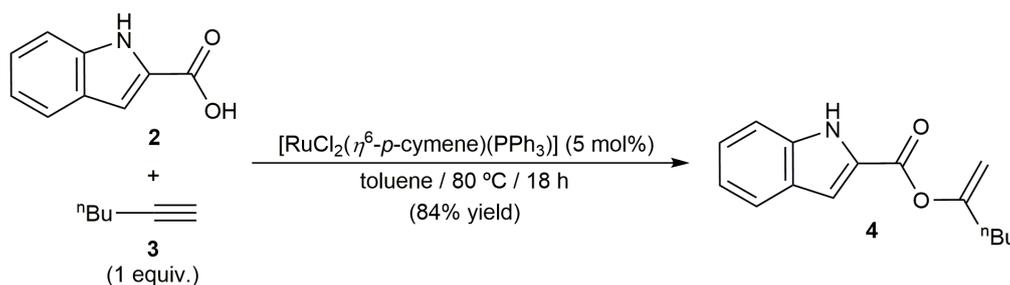
Scheme 2. Synthesis of the enol ester **4** using $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ as catalyst.

On the other hand, to synthesize the enol ester **5** in high yield we made use of the gold(I) cation $[Au(PPh_3)]^+$, whose utility as catalyst for both hydroamination [15,16] and hydro-oxycarbonylation [17–19] reactions of alkynes has been largely demonstrated. Thus, as shown in Scheme 3, when a mixture of indole-2-carboxylic acid (**2**) and 1-hexyne (**3**) in 1:3 molar ratio was treated with 5 mol% of $[Au(PPh_3)]^+$, generated in situ from $[AuCl(PPh_3)]$ and AgPF$_6$, in toluene at 100 °C for 14 h, compound **5** could be isolated in 71% yield. Inspection of the reaction crude by ^{1}H NMR spectroscopy showed the presence of a small amount of compound **4** (ca. 10%), which was easily separated by column chromatography. Concerning the spectroscopic data of **5**, the typical signals of the NH group were not further observed in the IR and ^{1}H NMR spectra. In addition, the latter confirmed the presence of two hex-1-en-2-yl units in the product by the appearance of four olefinic signals at 4.85/4.91 ($^2J_{HH} = 1.3$ Hz, O-C=CH$_2$) and 5.22/5.48 ppm ($^2J_{HH} = 1.1$ Hz, N-C=CH$_2$). The ^{13}C{^{1}H} NMR spectrum was also fully consistent with the proposed formulation, the most characteristic signals being those of the C=CH$_2$ unis, which resonate at $\delta_C = 101.3$ (O-C=CH$_2$), 112.8 (s, N-C=CH$_2$), 145.8 (s, N-C=CH$_2$) and 159.3 (s, O-C=CH$_2$) ppm (see full details in the Materials and Methods section).
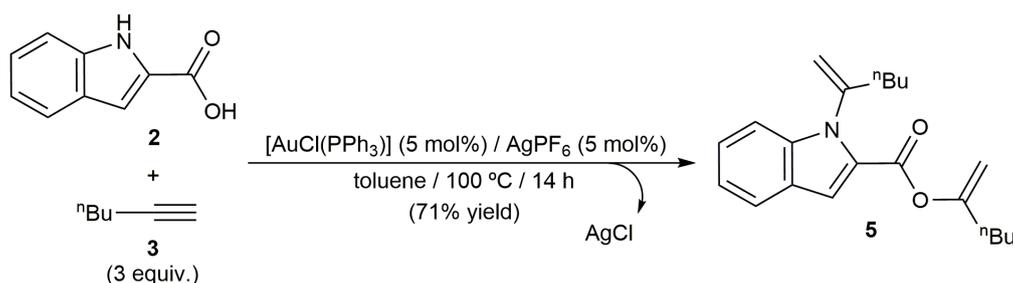
Scheme 3. Synthesis of the enol ester **5** using [AuCl(PPh₃)]/AgPF₆ as catalyst.

3. Materials and Methods

Experimental procedures were performed under an inert atmosphere of dry nitrogen employing vacuum-line and sealed-tube techniques. Organic solvents were dried and purified following standard procedures [20]. The metallic complexes [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(PPh$_3$)] (**1**) [9], [RuCl$_2$(η^6-*p*-cymene)(PPh$_3$)] [21] and [AuCl(PPh$_3$)] [22] were synthesized as described in the literature. A PerkinElmer 1720-XFT spectrometer (Waltham, MA, USA) was employed for IR measurements. NMR measurements were carried out at room temperature using a Bruker DPX-300 instrument (Billerica, MA, USA). The residual signal of the CDCl$_3$ solvent was employed as reference for the ^{13}C and ^{1}H NMR chemical shifts. HRMS data (QTOF Bruker Impact II mass spectrometer; Billerica, MA, USA) were provided by the General Services of the University of Oviedo. For the chromatographic work-up Merck silica gel 60 (230–400 mesh) was employed.

3.1. Synthesis of Hex-1-en-2-yl Indole-2-carboxylate (**4**)

Under nitrogen atmosphere, indole-2-carboxylic acid (**2**; 0.161 g, 1 mmol), 1-hexyne (**3**; 0.115 mL, 1 mmol), toluene (1 mL) and the ruthenium(II) complex [RuCl$_2$(η^6-*p*-cymene)(PPh$_3$)] (0.028 g; 0.05 mmol; 5 mol%) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 80 °C for 18 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using an ethyl acetate-*n*-hexane mixture (1:10 v/v) as the eluent. Yield: 0.204 g (84%). Yellow oil. IR (neat): ν = 3340 (s), 3060 (w), 2956 (s), 2930 (s), 2871 (m), 1703 (s), 1668 (m), 1620 (w), 1576 (w), 1526 (m), 1466 (w), 1429 (w), 1379 (m), 1341 (m), 1311 (m), 1247 (s), 1226 (s), 1187 (s), 1146 (s), 1108 (m), 977 (w) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.53 (s, 1H, NH), 7.78 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, CH$_{arom}$), 7.51–7.37 (m, 3H, =CH and CH$_{arom}$), 7.24–7.19 (m, 1H, CH$_{arom}$), 5.00 and 4.94 (d, 1H each, $^2J_{HH}$ = 1.6 Hz, =CH$_2$), 2.44 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH$_2$), 1.66–1.56 and 1.52–1.40 (m, 2H each, CH$_2$), 0.99 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH$_3$) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 160.6 (s, *C*=CH$_2$), 156.5 (s, *C*=O), 137.4 and 127.4 (s, C$_{arom}$), 126.8 (s, =C), 125.7, 122.7, 121.0 and 112.1 (s, CH$_{arom}$), 109.7 (s, =CH), 101.6 (s, =CH$_2$), 33.3, 28.7 and 22.2 (s, CH$_2$), 13.9 (s, CH$_3$) ppm. HRMS (ESI): *m/z* 266.11581, [M + Na$^+$] (calcd. for C$_{15}$H$_{17}$O$_2$NNa: 266.11570).

3.2. Synthesis of Hex-1-en-2-yl 1-(Hex-1-en-2-yl)-indole-2-carboxylate (**5**)

Under nitrogen atmosphere, indole-2-carboxylic acid (**2**; 0.161 g, 1 mmol), 1-hexyne (**3**; 0.345 mL, 3 mmol), toluene (1 mL), the gold(I) complex [AuCl(PPh$_3$)] (0.025 g; 0.05 mmol; 5 mol%) and AgPF$_6$ (0.013 g; 0.05 mmol; 5 mol%) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 100 °C for 14 h. After elimination of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography over silica gel using an ethyl acetate-*n*-hexane mixture (1:20 v/v) as the eluent. Yield: 0.231 g (71%). Yellow oil. IR (neat): ν = 3061 (w), 2957 (s), 2929 (s), 2872 (m), 1732 (s), 1656 (m), 1612 (w), 1570 (w), 1520 (m), 1477 (w), 1466 (w), 1446 (m), 1402 (w), 1390 (w), 1319 (w), 1267 (w), 1171 (s), 1147 (s), 1118 (m), 1094 (w), 1048 (m) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.70 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.0 Hz, CH$_{arom}$), 7.46–7.27 (m, 3H, =CH and CH$_{arom}$), 7.22–7.16 (m, 1H, CH$_{arom}$), 5.48 and 5.22 (d, 1H each, $^2J_{HH}$ = 1.1 Hz, N-C=CH$_2$),

4.91 and 4.85 (d, 1H each, $^2J_{HH}$ = 1.3 Hz, O-C=CH$_2$), 2.49 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH$_2$), 2.37 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH$_2$), 1.59–1.53 (m, 2H, CH$_2$), 1.45–1.36 (m, 6H, CH$_2$), 0.95 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH$_3$), 0.87 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH$_3$) ppm. ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ = 159.3 (s, O-*C*=CH$_2$), 156.5 (s, C=O), 145.8 (s, N-*C*=CH$_2$), 139.9 and 127.3 (s, C$_{arom}$), 126.0 (s, =C), 125.6, 122.4, 121.1 and 112.0 (s, CH$_{arom}$), 112.8 (s, N-C=*C*H$_2$), 111.6 (s, =CH), 101.3 (s, O-C=*C*H$_2$), 36.2, 33.2, 29.3, 28.7, 22.4 and 22.1 (s, CH$_2$), 13.8 (s, 2C, CH$_3$) ppm. HRMS (ESI): *m*/*z* 348.19401, [M + Na$^+$] (calcd. for C$_{21}$H$_{27}$O$_2$NNa: 348.19395).

4. Conclusions

In summary, two novel enol esters, namely hex-1-en-2-yl indole-2-carboxylate (**4**) and hex-1-en-2-yl 1-(hex-1-en-2-yl)-indole-2-carboxylate (**5**), have been synthesized by catalytic addition of indole-2-carboxylic acid to 1-hexyne and spectroscopically characterized.

Supplementary Materials: The following are available online, Figures S1–S4: ^{1}H, ^{13}C{^{1}H}, DEPT-135 NMR and IR spectra of compound **4**, Figures S5–S8: ^{1}H, ^{13}C{^{1}H}, DEPT-135 NMR and IR spectra of compound **5**.

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