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Ru-catalysed synthesis of fused heterocycle-pyridinones and -pyrones

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S. Ruiz,[a] C. Carrera,[a] P. Villuendas,[a] and E. P. Urriolabeitia*[a]

The synthesis of fused heterocycle-pyridinones has been achieved by oxidative coupling of N-unprotected primary heterocycle-amides with internal alkynes. The reaction, which is catalysed by Ru(II) and assisted by Cu(II), takes place through C–H and N–H bond activation of the heterocyclic unit. The scope of the reaction includes a variety of alkynes, electron-rich thiophenes, furan and pyrrole, and even electron-poor pyridines. The reaction is fully regioselective with respect to the position of the C–H bond activation due to the directing effect of the amide group. In the same way, the synthesis of fused heterocycle-pyrones (isocoumarins) has been developed by Ru-catalysed oxidative coupling of heterocyclic carboxylic acids and internal alkynes. The reaction involves C–H and O–H bond activation. This reaction also has a broad scope, from electron-rich thiophenes, furans and pyrroles to electron-deficient pyridines and quinolines.

Introduction

Heterocyclic compounds that contain pyridinone or pyrone units fused with another heterocycle (Figure 1a) are of great interest due to their biological and pharmacological activities.[1,2] The strong and diverse activity of these compounds prompted the development of a variety of synthetic methods and the intensive search for new pathways continues today. The synthesis of fused heterocycle-pyridinones can be achieved by general classical methods, such as those used for isoquinolones and isoquinolines (Pomeranz–Fritsch, Bischler–Napieralski and Pictet–Spengler), which involve two disconnections between the carbonyl carbon and either the N atom or the aromatic ring (Figure 1b).[3] There are also specific methods (Figure 1c) and these include a Curtius rearrangement followed by cyclisation,[4c] the condensation of 3-aminothiophene derivatives with isatines and Meldrum's acid,[4f] cyclisation of dehydroamino acids,[4g] domino reactions of dimethylaminopropenoyl-cyclopropanes with Lawesson's reagent,[4b] or the cyclisation of ortho-methylbenzamide by lithiation and reaction with DMF,[4h] amongst others. Developments in this area also include the use of transition metal catalysts.[4] Similarly, the synthesis of isocoumarins has been carried out using many different methods, including those promoted by transition metals.[5,6] Most of these methods, however, share a common structural starting point, which is a benzene ring with a β-functionalized alkyl chain and a C_1 group *ortho* to the alkyl chain: for instance, the condensation of homophthalic acids or the intramolecular cyclisations of *o*-alkynylbenzoates.[5,6]

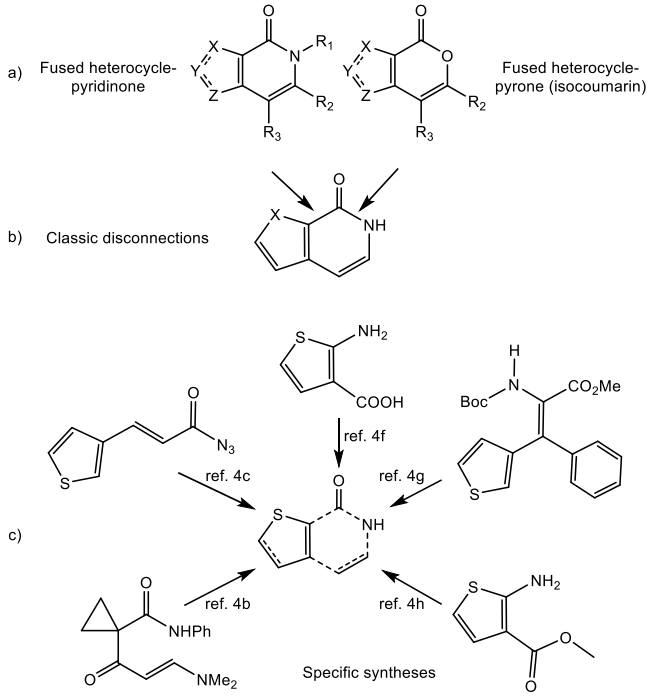

Figure 1. General molecular skeletons of fused heterocycle-pyridinones and -pyrones, and some classical methods for their synthesis

Despite their general character, these syntheses suffer from some disadvantages: (a) they take place under harsh conditions; (b) the substrates must be highly prefunctionalized to achieve high reactivity and selectivity, even in the presence of transition metal catalysts; (c) the reactions are multi-step and generate considerable waste; (d) most of the reagents are not commercially available and usually have complex syntheses, they are highly toxic or difficult to handle (e.g., phosgene). For these reasons – and given the general interest in this type of compound – other synthetic methods have been explored.

[a] Instituto de Síntesis Química y Catálisis Homogénea, CSIC-Universidad de Zaragoza, Pedro Cerbuna 12, E-50009 Zaragoza (Spain).

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The most successful alternative synthesis of pyridinones and isocoumarins has probably been the directed functionalization of C–H bonds catalysed by transition metals, because this approach allows non-classical disconnections under relatively mild conditions. The use of catalytically directed C–H bond activation processes is a well-established procedure in organic synthesis.[7] The synthesis of pyridinones and isocoumarins has been achieved through N–H/C–H or O–H/C–H oxidative coupling between, respectively, amides or acids and internal alkynes (Figure 2).[8-14]

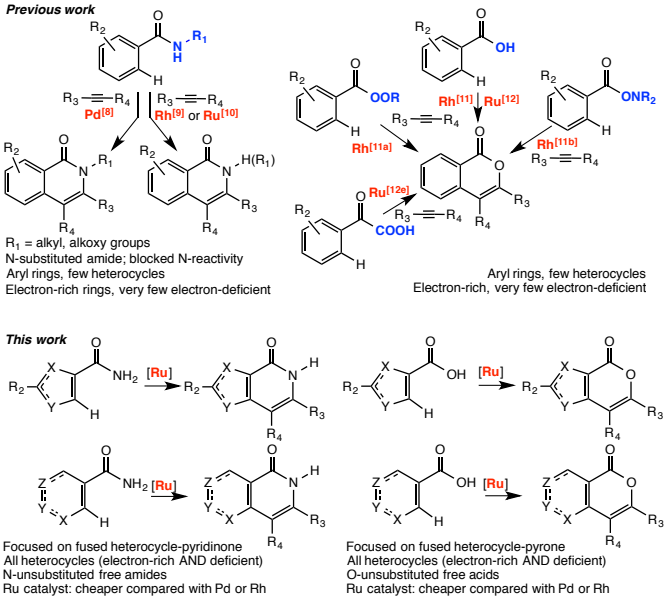


Figure 2. Previous work on the synthesis of isoquinolones and isocoumarins, and relationship with the study reported here.

Previous work on the synthesis of pyridinones and isoquinolones has shown that Pd,[8] Rh,[9] and Ru[10] are the most efficient metals to promote this coupling. As for the synthesis of isoquinolones, the mono-insertion and subsequent coupling only takes place when the N atom of the amide is protected. Attempts to use primary amides resulted in no reaction or in the formation of polycyclic compounds. In addition, a few examples of fused pyridinones have been found. The synthesis of isocoumarins by metal-catalysed C–H bond activation has been performed mainly with rhodium[11] and ruthenium[12] catalysts. The use of other metals such as palladium[13] or iridium[14] for this type of C–H/O–H coupling has hardly been reported. However, once again the synthesis of heterocycles fused with the 2-pyrone ring is poorly represented despite several specific contributions.[11f,12a]

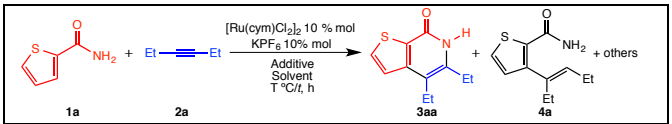
We propose here a general method for the synthesis of fused heterocycle-pyridinones and -pyrones (isocoumarins) based on the oxidative coupling of primary heterocycle-amides and heterocyclic acids with internal alkynes. The process is catalysed by $[RuCl_2(\eta^6\text{-cymene})]_2$, assisted by $Cu(OAc)_2$ and NaOAc, and takes place in toluene. The use of ruthenium is an optimal choice[15] because it combines high activity and selectivity with low cost.[16] The method also has two clear advantages. The main advantage is that it is general for a large number of heterocycles, from electron-rich (thiophenes, furans or pyrroles) to electron-poor (pyridines or isoquinolines), despite the known reluctance of electron-deficient heterocycles to undergo functionalization.[17] The second advantage is that the synthesis of fused heterocycles is achieved directly from the corresponding unprotected precursors, which are usually commercially available or easily prepared, thus reducing the number of synthetic steps and minimizing the production of waste.

Results and discussion

1. Catalytic synthesis of fused heterocycle-pyridinones.

The first step was to optimize the reaction conditions on a model system, for which the coupling between thiophene-2-carboxamide **1a** and 3-hexyne **2a** (Table 1) was selected. The conditions employed were those optimized for related precursors, such as benzylamines and naphthylamines: 1 mmol of substrate, 2 mmol of alkyne, $[Ru(cymene)Cl_2]_2$ (10% mol) as catalyst, KPF_6 (10% mol) and $Cu(OAc)_2$ (1 equiv.) as additives, methanol as solvent and 100 °C as the reaction temperature.[18] After 24 hours under these conditions an equimolar mixture of **1a** and 4,5-diethylthieno[2,3-*c*]pyridin-7(6*H*)-one **3aa** was obtained following the workup procedure described in the Experimental Section (entry 1).

Table 1. Optimization of the conditions for the coupling reaction between **1a** and **2a**[a]



Entry	Solvent	Oxidant / additive	T °C	NMR ratio[b] (%) **1a**/**3aa**/**4a**/others[c]
1	MeOH	$Cu(OAc)_2$	100	50/50/-/-
2	^{t}AmOH	$Cu(OAc)_2$	100	46/36/18/-
3	HFIP	$Cu(OAc)_2$	100	83/17/-/-
4	^{t}AmOH	$Cu(OAc)_2$[d]	100	61/39/-/-
5	^{t}AmOH	$Cu(OAc)_2$	120	25/50/25/-
6	^{t}AmOH	$Cu(OAc)_2$	140	33/47/20/-
7	toluene	$Cu(OAc)_2$	120	-/60/40/-
8	toluene	$Cu(OAc)_2$[d]	120	-/70/20/10
9	toluene	$Cu(OAc)_2$ + K_2CO_3	120	-/78/9/13
10	toluene	$PhI(OAc)_2$ + K_2CO_3	120	32/68/-/-
11	toluene	$Cu(OAc)_2$ + 2 NaOAc	120	-/87/6/7

[a] **1a** (1 mmol), **2a** (2 mmol), $[Ru(cymene)Cl_2]_2$ (0.1 mmol), KPF_6 (0.1 mmol), $Cu(OAc)_2$ (1 mmol), additive (1 equiv.), solvent (3 mL), temp, 24 h. [b]NMR ratio determined on the crude reaction mixture after removal of Cu(II). [c]Other hydroarylation isomers. [d]2 mmol.

In an effort to increase the conversion of **1a** a short screening of solvents and temperatures was performed. When the reaction was carried out in *tert*-amyl alcohol (entry 2) a similar conversion was achieved but in addition to **3aa** the hydroarylation product **4a** was obtained. The use of hexafluoroisopropanol as solvent (HFIP, entry 3) led to a further

decrease in the conversion and only 17% of **3aa** was obtained. The influence of other reaction parameters was investigated with ^{t}AmOH used as the solvent. An increase in the amount of $Cu(OAc)_2$ to 2 equivalents led to a lower conversion (39% of **3aa**, entry 4). However, a slight increase in the reaction temperature (120 °C, entry 5) gave a notable increase in the conversion to afford a mixture of **3aa** (50%) and **4a** (25%). A further increase in temperature (140 °C, entry 6) did not improve these results.

Since the appropriate choice of solvent in this type of reaction seems to be critical, we expanded the range of solvents studied. The use of toluene led to a marked change in the reaction outcome as full conversion was obtained on using $Cu(OAc)_2$ (1 equiv.) at 120 °C for 24 hours to afford 60% of **3aa** and 40% **4a** (entry 7). This is a remarkable result because toluene is not a typical solvent for this class of C–H functionalization.[18]

Once full conversion had been achieved, we attempted to minimize the formation of **4a**, which probably occurs by protodemetallation of the vinyl derivative formed after migratory insertion of the alkyne. Therefore, the removal of H^+ from the reaction medium by addition of an external base should, in principle, decrease the amount of **4a** and favour the formation of **3aa**. In good agreement with our hypothesis, an increase in the $Cu(OAc)_2$ concentration to 2 equivalents (entry 8) increased the amount of **3aa** (70%) *versus* **4a** (20%) along with other hydroarylation compounds in minor quantities (10%). Even better results were obtained by replacing 1 equivalent of $Cu(OAc)_2$ by K_2CO_3 (entry 9, 78% **3aa**), while the best base proved to be NaOAc (entry 11, 87% **3aa**). The presence of $Cu(OAc)_2$ as a source of acetates and oxidant is mandatory, because attempts to replace this oxidant by others led to failure (entry 10). Once the reaction conditions had been optimized we investigated the scope of the reaction using different heterocycles **1a–1l** and alkynes **2a–2e** (see Figure 3).

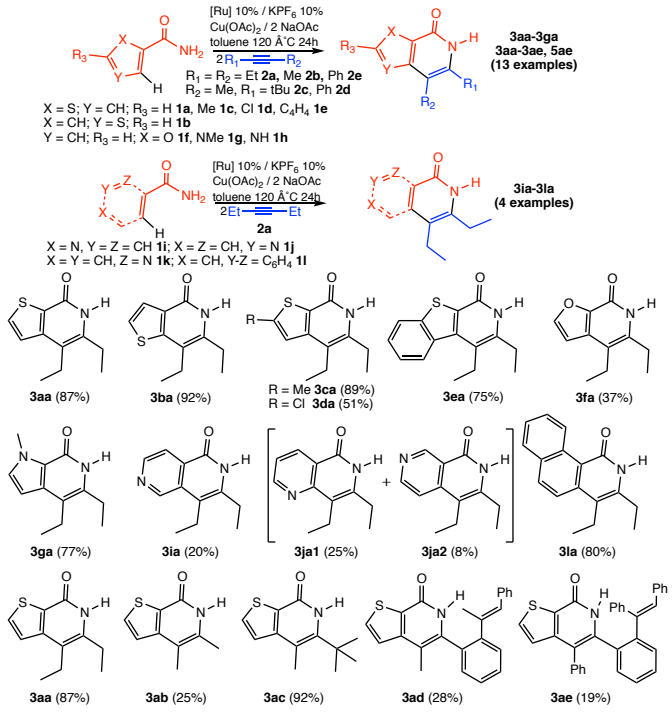


Figure 3. Scope of the synthesis of fused heterocycle-pyridinones **3**.

The results show that this method is general for a variety of substrates. For example, electron-rich heterocycles such as thiophenes (**3aa–3da**), benzothiophene (**3ea**), furan (**3fa**) and *N*-methylpyrrole (**3ga**) gave the corresponding fused pyridines in moderate to good yields. The slightly lower yield of the benzannulated derivative **3ea** is consistent with previous results, as is the lower reactivity shown by the furan ring **3fa** compared with that of thiophene or pyrrole.[18a,19] In addition, the method tolerates the presence of electron-donating (**3ca**) and electron-withdrawing (**3da**) substituents at the 5-position of the thiophene ring, although the reaction works better for the electron-donating group. The oxidative coupling is selective, with the C–H bond at the 3-position activated when the amide group is in the 2-position (**3aa**, **3ca–3ga**). This allows the synthesis of isomers that cannot be obtained by other routes, with this fact being especially challenging in the case of furan, where examples of this type of metallation are still scarce.[19,20] Clearly, when the directing group is in the 3-position (**3ba**) the reaction takes place at the very favourable 2-position.

The reactivity can be extended to the electron-poor pyridine heterocycles. This type of oxidative coupling is very rare in electron-deficient heterocycles[17] and usually gives alkyne poly-insertion[9e] or requires the prior modification of the heterocycle[9a] to give the best performance for the mono-insertion of the alkyne. In our case, isonicotinamide **1i** and nicotinamide **1j** reacted with 3-hexyne **2a** through C–H bond activation and alkyne mono-insertion to give the corresponding 3,4-diethyl-2,6-naphthyridin-1(2*H*)-one (**3ia**), as a single isomer, and the two isomeric compounds 7,8-diethyl-1,6-naphthyridin-5(6*H*)-one (**3ja1**) and 3,4-diethyl-2,7-naphthyridin-1(2*H*)-one (**3ja2**), which were separable by column chromatography, in low yields (20–33%). Despite the yields, it is remarkable that a weak coordinating group, such as the free amide, should be able to direct the reaction towards its adjacent position even in the presence of the strongly coordinating pyridine group. This preferential orientation could be based on the generation of an anion at the N atom by deprotonation in the initial stages of the reaction, followed by strong N-bonding of the resulting C(O)NH group to the Ru centre. This concept has been used recently by Yu and co-workers to overcome the restrictions imposed by certain strong bonding groups,[21] and it seems that it also applies in the case reported here. As expected, the carbocyclic 1-naphthylamide **1l** reacted cleanly with **2a** to give 3,4-diethylbenzo[*h*]isoquinolin-1(2*H*)-one (**3la**) in good yield.

We also studied the scope of the reaction by changing the alkyne. The reaction generally worked well with electron-rich alkynes (**3aa–3ac**) and full conversions were observed, although yields of pure **3ab** were low. Compounds **3aa–3ac** were obtained as single isomers. This behaviour is expected for symmetrical alkynes **2a** and **2b**, but means that the reaction takes place with total regioselectivity for 4,4-dimethyl-2-pentyne **2c**.[22] The results of NOESY-1D experiments (see ESI) show that irradiation of the methyl peak (2.37 ppm) promotes a strong NOE in the signals at 7.19 ppm (H_{thio}) and 1.38 ppm (*t*-Bu), which implies that the *t*-Bu group is in the 5-position, close to the N atom, while the Me group is in the 4-position. This

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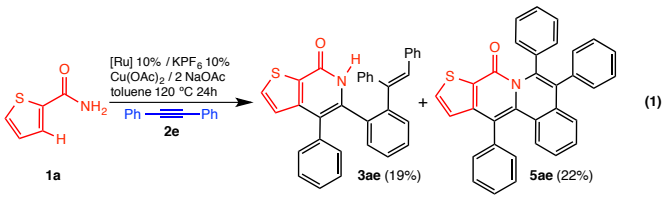
configuration is the same as that observed in related thienopyridines, isoquinolines or benzoisoquinolines.[18a,b] Aryl-containing alkynes also underwent the oxidative coupling process, but the outcome of the reaction was slightly different. The reaction with 1-phenyl-1-propyne **2d** gave **3ad** as a single regioisomer after two consecutive C–H activation-alkyne insertion cycles. This complete regioselectivity is remarkable considering that two insertions take place. The first insertion afforded the 4-methyl-5-phenylthieno[2,3-*c*]pyridin-7(6*H*)-one core. This intermediate can undergo a second C–H activation at the 5-phenyl ring, followed by alkyne insertion and protodemetallation to give the hydroarylated **3ad** with full regioselectivity considering the two steps. The olefinic fragment has an *E*-configuration, as inferred from the signal of the alkenyl methyl group at 1.81 ppm, which appears as a doublet (1.3 Hz) due to coupling with the *trans* H atom. On the other hand, the reaction of **1a** with diphenylacetylene **2e** gave the expected product of double insertion **3ae** (similar to **3ad**) and the tetracyclic derivative **5ae**. The two products were isolated in a roughly equimolar amount (see equation 1). Compounds **3ae** and **5ae** probably originate from a common mechanism. As explained for **3ad**, **1a** reacts with the first equivalent of alkyne **2e** to give the corresponding 4,5-diphenylthieno[2,3-*c*]pyridin-7(6*H*)-one, which can undergo a second ruthenation at the 2'-position of the 5-phenyl ring and a subsequent insertion of alkyne **2e**. From this common intermediate the protodemetallation would give the hydroarylation derivative **3ae** while reductive elimination by C–N bond coupling would afford the triphenylthieno[3',2':4,5]pyrido[2,1-*a*]isoquinolin-8-one **5ae**. The double alkyne insertion observed in compounds **3ad** and **3ae** has previously been observed in closely related substrates.[18a,b] However, this is a rare process, since monoinsertion usually takes place, and thus it expands the synthetic utility of the method.

Compounds **3aa**, **3ab**, **3ac** and **5ae** were characterized by X-ray diffraction. Full details of the crystallographic work are provided in the ESI.



(1)

2. Catalytic synthesis of fused heterocycle-pyrones (isocoumarins)

As explained in the Introduction, the synthesis of isocoumarins has been extensively developed, but there are very few examples of analogues from heterocycles.[5,6,8-14] Prompted by the excellent results obtained in the synthesis of fused heterocycle-pyridinones, we attempted the Ru-catalysed synthesis of fused heterocycle-pyrones by oxidative coupling of alkynes with the corresponding heterocyclic acids. Thiophene-2-carboxylic acid **6a** was selected as the initial substrate and the reaction conditions optimized for the amides were employed. Under these conditions (1 mmol **6a**, 2 mmol alkyne **2a**, Ru-catalyst 10% mol, KPF_6 10% mol, $Cu(OAc)_2$ 1 mmol, NaOAc 2 mmol, toluene, 120 °C, 24 h) the fused 4,5-diethyl-7*H*-thieno[2,3-*c*]pyran-7-one **7aa** was obtained in 59% isolated yield (Figure 4). A short screening of other reaction conditions (longer reaction times and other temperatures) did not show any improvement; therefore, we employed the same reaction conditions for the synthesis of pyridinones and pyranones. The incorporation of the alkyne onto the thiophene ring occurred through regioselective C–H bond activation at the 3-position of the thiophene, probably due to presence of the carboxylate as a directing group. Despite the harsh conditions, the integrity of the carboxylate moiety was maintained throughout the process, and decarboxylative side reactions were not observed, except in a single example (see below). Therefore, the same reaction conditions were used to explore the scope in terms of alkynes and heterocycles.

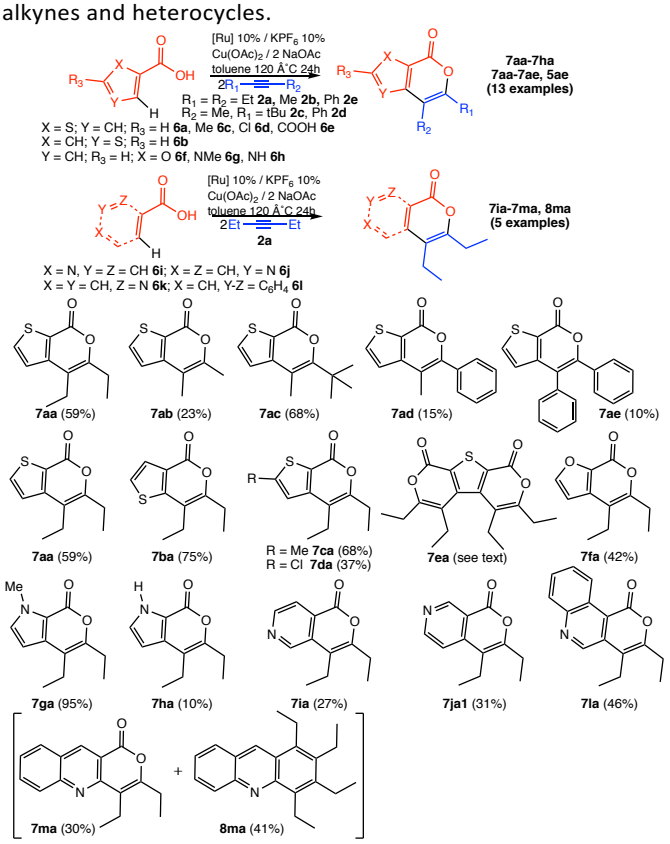


Figure 4. General scope of the synthesis of fused heterocycle-pyrones **7**.

The thiophene **6a** reacted with different internal alkynes **2a**–**2e** to afford the corresponding thieno[2,3-*c*]pyranones **7aa**–**7ae**, as shown in Figure 4. The reaction with 2-butyne **2b** afforded **7ab** in 23% yield. Even when complete conversion was observed, the need for repeated column chromatography to obtain a pure product led to a low yield. The reaction with 4,4-dimethyl-2-pentyne **2c** afforded two different products, **7ac** and **7ac2**, as shown in equation 2. When the reaction was carried out under the optimized conditions, i.e., using two equivalents of alkyne, the isolated yields were 50% and 20%, respectively. These two compounds could be separated by column chromatography. Compound **7ac** is the expected isocoumarin and is formed by selective C–H activation at the 3-position of the thiophene, followed by migratory insertion of the alkyne in

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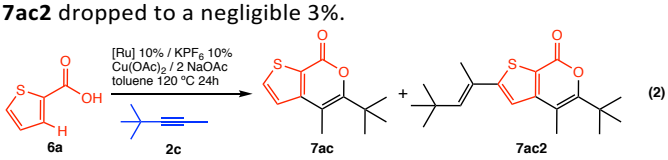
such a way that the ^{t}Bu group was in the position nearest to the O atom.[22] This arrangement was determined by 1D-NOESY experiments and is the same as that observed in the thieno-pyridinone **3ac**. On the other hand, characterization of **7ac2** showed that it is a product of the further reaction of **7ac**. More specifically, **7ac2** seems to be the result of the hydroarylation of alkyne **2c** using **7ac** as the aryl source, after C-H activation at the 7-position of the latter. The presence of **7ac2** together with **7ac** at the end of the reaction is related to the excess of alkyne **2c** used (2 mmol) with respect to thiophene **6a** (1 mmol). Therefore, when the starting molar ratio **6a:2a** was reduced to 1:1, the isolated yield of **7ac** increased to 68%, while that of **7ac2** dropped to a negligible 3%.



(2)

The reactivity with alkynes containing aryl groups (1-phenyl-1-propyne **2d** and diphenylacetylene **2e**) was also studied. In both cases, very complex mixtures of different products were obtained, from which the monoinsertion derivatives **7ad** and **7ae** were isolated in low yields (Figure 4). In the case of **7ad**, the insertion of the alkyne was fully regioselective because only one isomer was detected and isolated. In this compound, the phenyl ring is in the position adjacent to the oxygen, as shown by 1D-NOESY experiments. In contrast, bis-insertion products were not detected, as in the case of fused pyridinones. This fact is probably related to the lower bonding ability of the oxygen in isocoumarins **7** compared with the nitrogen in pyridinones **3**.

The reaction has a high versatility with respect to the use of different heterocycles. Thiophenes with electron-donating (Me) and electron-withdrawing (Cl) substituents in the 5-position afforded the corresponding isocoumarins **7ca** and **7da** in good to moderate yields (68% and 37%, respectively, Figure 4). The reaction with the thiophene-3-carboxylate **6b**, which can direct C–H activation to the 2- and 4-positions, took place with complete regioselectivity at the 2-position, as expected, to give **7ba** in a good isolated yield (75%). The dicarboxylic acid derivative **6e**, which bears the two substituents at the 2- and 5-positions, also reacted with 3-hexyne **2a** to give a complex mixture of compounds. The difunctionalised isocoumarin **7ea** was detected in the mixture, but only at a very low level and this was not sufficient to perform the isolation and purification. This fact highlights the difficulty in performing double C–H oxidative couplings on the same thiophene ring – a situation that is consistent with previous observations on thiophene-imine substrates.[19] Considering other electron-rich heterocycles such as furan or N-Me-pyrrole, their oxidative coupling with alkyne **2a** took place regioselectively to afford the expected 4,5-disubstituted 7*H*-furan[2,3-*c*]pyranone **7fa** and 1-methyl-pyrano[3,4-*b*]pyrrol-7(1*H*)-one **7ga** in moderate (42%) or excellent (95%) yields, respectively. Even the N-unprotected pyrrole-2-carboxylic acid reacted to give the corresponding product **7ha**, albeit in low yield (10%).

In addition, we attempted similar reactions starting from electron-deficient pyridine- and isoquinolinecarboxylic acids. The reaction of isonicotinic acid (pyridine-4-carboxylic acid) **6i** or nicotinic acid (pyridine-3-carboxylic acid) **6j** with alkyne **2a** afforded the pyrano-pyridinone derivatives **7ia** and **7ja** in yields of 27% and 44%, respectively. Compound **7ja** was obtained as a mixture of the two possible isomers, **7ja1** (31%) and **7ja2** (13%), due to activation at the 4- and 2-positions, respectively. Compound **7ja1** could be separated and purified by column chromatography, but **7ja2** proved difficult to purify. For this reason, only **7ja1** was fully characterized. As one would expect, 2-picolinic acid **6k** did not react with alkyne **2a**, probably due to the formation of an N,O-chelate with the Ru(II) centre and the subsequent deactivation of the catalyst. On the other hand, the reaction of quinolin-4-carboxylic acid **6l** with **2a** proceeded under the optimized conditions to give the pyrano-quinolinone **7la** in 46% isolated yield. The reaction showed full regioselectivity, with only the 3-position of **6l** activated, and afforded the species with three fused six-membered rings. Finally, reaction of the quinolin-3-carboxylic acid **6m** with **2a** gave a mixture of two products, i.e., the expected pyrano-quinoline **7ma** (30% isolated yield) due to regioselective activation at the 2-position of the starting material, and the substituted tetraethylacridine **8ma** (41% isolated yield). Products derived from activation of the 4-position were not observed. The acridine **8ma** could originate due to initial Ru-mediated C–H activation at the 2-position, directed by the 3-carboxylate group, migratory insertion of one equivalent of alkyne **2a**, decarboxylation to form a new five-membered ruthenacycle, subsequent migratory insertion of a second equivalent of alkyne **2a** and final C–C coupling by reductive elimination.

3. Mechanistic proposal

A mechanistic proposal can be made based on our previous work[18b] and on related studies found for similar substrates.[10,12] It is especially relevant that, for these heterocycles, the reaction gives better results in toluene (aprotic and non-polar solvent) than in alcohols (protic and polar).

We attempted to gain an insight into the reaction mechanism by performing control experiments. Reaction was not observed in the absence of Ru or Cu salts, so both of these species are necessary. Furthermore, reaction was not observed on heating $Cu(OAc)_2$ with **6a** in toluene, with the blue color remaining unaltered after 24 hours under reflux in toluene. However, a rapid reaction was observed when [Ru(*p*-cymene)Cl_2]$_2$, $Cu(OAc)_2$ and **6a** were heated in toluene for several minutes. This finding suggests that the ruthenium dimer probably reacts with $Cu(OAc)_2$ in the first steps of the reaction to give $Ru(OAc)_2$(*p*-cymene), as reported previously.[15a,23] Beyond this point it was not possible to follow the reaction since, due to the presence of paramagnetic Cu(II), only broad resonances were observed in the NMR spectra. Starting from $Ru(OAc)_2$(p-cymene) we propose N–H/O–H deprotonation of the heterocyclic substrate in a first step to give the neutral species **A** (Figure 5), which undergoes C–H bond activation to give the cycloruthenated complex **B**. Species **B** could react with internal alkynes **2** to give intermediate **C** by migratory insertion, which would produce Ru(0) derivative **D** by reductive elimination and

formation of the corresponding C–N or C–O bonds. Final oxidation with $Cu(OAc)_2$ would liberate the fused heterocycle and regenerate the catalyst. All species throughout the cycle are neutral.

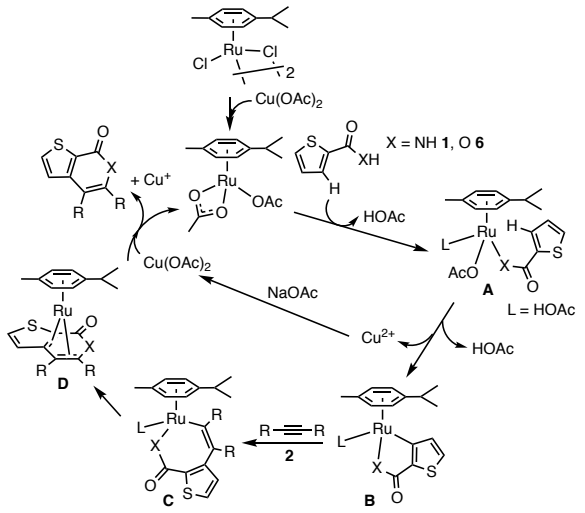


Figure 5. Mechanistic proposal for the catalytic synthesis of fused heterocycle-pyridinones **3** and -pyrones **7**.

Experimental

General methods

Solvents were used as received from commercial sources. The solvents were not distilled or subjected to additional purification. All reactions were carried out without an inert atmosphere. Column liquid chromatography was performed on aluminium oxide 90 neutral (50–200 µm) or silica gel (70–230 µm). ^{1}H and ^{13}C NMR spectra were recorded on $CDCl_3$ or DMSO-d_6 solutions at 25 °C on Bruker AV300, ARX300 or AV400 spectrometers (δ in ppm and J in Hz) at a ^{1}H NMR operating frequency of 300.13 or 400.13 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced using the solvent signal as an internal standard. The full assignment of ^{1}H NMR peaks was performed through standard 2D ^{1}H-COSY (2K points in t2 using a spectral width of 10 ppm; 128 t1 experiments were recorded and zero-filled to 1K; for each t1 value four scans were signal-averaged using a recycle delay of 1 s) and selective 1D ^{1}H-NOESY experiments. Typical mixing times in the case of selective 1D-NOESY experiments were 800 ms or 1 s, as a function of the irradiated signal. These values of optimized mixing times were set equal to the longitudinal relaxation time T1, which in turn was determined using the inversion-recovery sequence. Once the ^{1}H NMR signals were fully assigned, the corresponding ^{13}C NMR peaks were identified using standard ^{1}H-^{13}C edited-HSQC and ^{1}H-^{13}C HMBC 2D-experiments. In both cases 4K points in t2 using spectral widths of 10 ppm (^{1}H) and 200 ppm (^{13}C) were used, with averaged values of the coupling constants $^1J_{CH}$ = 145 Hz and long-range $^nJ_{CH}$ = 8 Hz. Typically, 256 t1 experiments were recorded and zero-filled to 2K. For each t1 value 16 scans were signal-averaged using a recycle delay of 2 s. HRMS and ESI (ESI^+) mass spectra were recorded using a MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 m/z and mass resolution 15000 (FWHM). Infrared spectra (4000–380 cm^{-1}) were recorded on a Perkin-Elmer Spectrum One IR spectrophotometer.

X-ray crystallography: data collection and structure solution and refinement

Crystals of compounds **3aa**, **3ab**, **3ac** and **5ae** were obtained by slow evaporation at room temperature of solutions of the corresponding compounds in ethyl acetate. X-ray data collections were performed at room temperature on an Oxford Diffraction Xcalibur2 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). In each case, a single crystal was mounted at the end of a quartz fibre in a random orientation and covered with epoxy resin. In all cases, a hemisphere of data was collected based on ω- or ϕ-scan runs. The diffraction frames were integrated using the program or CrysAlis RED,[24] and the integrated intensities were corrected for absorption with SADABS.[25] The structures were solved and developed by Patterson and Fourier methods.[26] All non-H atoms were refined with anisotropic displacement parameters. The H atoms were placed at idealized positions and treated as riding atoms. Each H atom was assigned an isotropic displacement parameter equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of its parent atom. The structures were refined to F_o^2, and all reflections were used in the least-squares calculations.[27] CCDC 1523072 (**3aa**), CCDC 1523073 (**3ac**), CCDC 1523074 (**5ae**) and CCDC 1523075 (**3ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of the ruthenium catalyst and other precursors

The syntheses of the ruthenium catalyst [Ru(*p*-cymene)(µ-Cl)Cl]$_2$,[28] and amides **1b**,[29] **1c**,[29a] **1d**,[29b,30] and **1g**,[29a,31] were carried out following published procedures. The spectroscopic data were compared with the literature data to confirm their structures. Other starting heterocyclic amides, acids and alkynes were purchased from commercial sources and used as received.

General procedure for the catalytic synthesis of fused hetarylpyridinones 3 or isocoumarins (hetarylpyranones) 7

The corresponding amide **1a**–**l** or acid **6a**–**l** (1 mmol) and alkyne **2a**–**e** (2 mmol) were added to a suspension of [Ru(*p*-cymene)$Cl_2]_2$ (0.061 g, 0.1 mmol), [$Cu(OAc)_2$] (0.181 g, 1.0 mmol), NaOAc (0.164 g, 2 mmol) and K[PF_6] (18.7 mg, 0.1 mmol) in toluene (3 mL) into a Young flask. The solution was heated at 120 °C for 24 h. After the reaction time the solvent was evaporated to dryness. The resulting solid residue was extracted with CH_2Cl_2 (3 × 10 mL), and the solid phase was separated each time by centrifugation at 3400 rpm for 10 min. The resulting solution was concentrated to a small volume (≈ 2 mL) and filtered over neutral alumina, eluting with a mixture of CH_2Cl_2/MeOH (95:5, 50 mL) to remove completely any residual Cu(II). The resulting brown solution was evaporated to dryness.

The residue was further purified by column chromatography on silica gel eluting with mixtures of hexane/ethyl acetate (**3aa** to **5ae**) or hexane/diethyl ether (compounds **7aa** to **7ae**) unless stated otherwise.

Characterization of compounds

Only one representative compound of each family is described here as an example. The full characterization of all prepared compounds is given as ESI.

4,5-Diethylthieno[2,3-*c*]pyridin-7(6*H*)-one 3aa

White solid (179 mg, 87%). Column chromatography: elution with hexane/ethyl acetate (90/10) gave compound **4aa**. After exhaustive washing with this mixture compound **3aa** remained on the column. Therefore, elution was carried out with a mixture hexane/ethyl acetate (50/50), which gave pure **3aa**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H, NH), 7.65 (d, 1H, H_{thio}, $^3J_{HH}$ = 5.2 Hz), 7.22 (d, 1H, H_{thio} $^3J_{HH}$ = 5.2 Hz), 2.65 (m, 4H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3, $^3J_{HH}$ = 7.6 Hz), 1.14 (t, 3H, CH_2CH_3, $^3J_{HH}$ = 7.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.1 (C), 140.7 (C), 133.3 (CH), 127.2 (C), 122.9 (CH), 114.6 (C), 23.6 (CH2), 21.4 (CH2), 15.3 (CH3), 14.4 (CH3). The carbonyl C was not observed despite long accumulation trials, changes in the relaxation delay, or attempts to inverse detection through ^{1}H-^{13}C HMBC. IR (ν, cm^{-1}): 1632 (vs, CO). HRMS (ESI-TOF) m/z: $[M + H]^+$ calc. $C_{11}H_{14}NOS$ 208.0791, found 208.0786.

4,5-Diethyl-7*H*-thieno[2,3-*c*]pyran-7-one 7aa

White solid (123 mg, 59%). Column chromatography: elution with hexane/diethyl ether (50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, CH_{thio}, $^3J_{HH}$ = 5.2 Hz), 7.13 (d, 1H, CH_{thio}, $^3J_{HH}$ = 5.2 Hz), 2.53 (m, 4H, CH_2CH_3), 1.21 (t, 3H, CH_2CH_3, $^3J_{HH}$ = 7.5 Hz), 1.13 (t, 3H, CH_2CH_3, $^3J_{HH}$ = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1 (C), 157.3 (C), 149.0 (C), 136.3 (CH), 122.9 (CH), 122.6 (C), 113.4 (C), 23.5 (CH_2), 21.1 (CH_2), 14.7 (CH_3), 12.8 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calc. $C_{11}H_{12}NaO_2S$ 231.0450, found 231.0451.

Conclusions

The N-unprotected heteroarylamides **1** and the heteroaryl carboxylic acids **6** react with internal alkynes **2** to give the corresponding fused heterocycle-pyridinones **3** and heterocycle-pyrones (isocoumarins) **7**. This process is very general, because both electron-rich (pyrrole, thiophene, furan) and electron-poor (pyridine, quinoline) heterocycles can be functionalized. The process has a high atom economy and minimizes the synthetic steps, avoids the need for the protection and deprotection of functional groups, and is a viable alternative to classical methods for the synthesis of this class of compounds. The reaction takes place through C–H/X–H (X = N, O) oxidative coupling and it is catalysed by the Ru(II) complex $[Ru(p\text{-cymene})Cl_2]_2$ and assisted by $Cu(OAc)_2$. The C–H activation reaction takes place with full regioselectivity at the position adjacent to the amide or the acid, which behave as directing groups.

Conflicts of interest

There are not conflicts to declare

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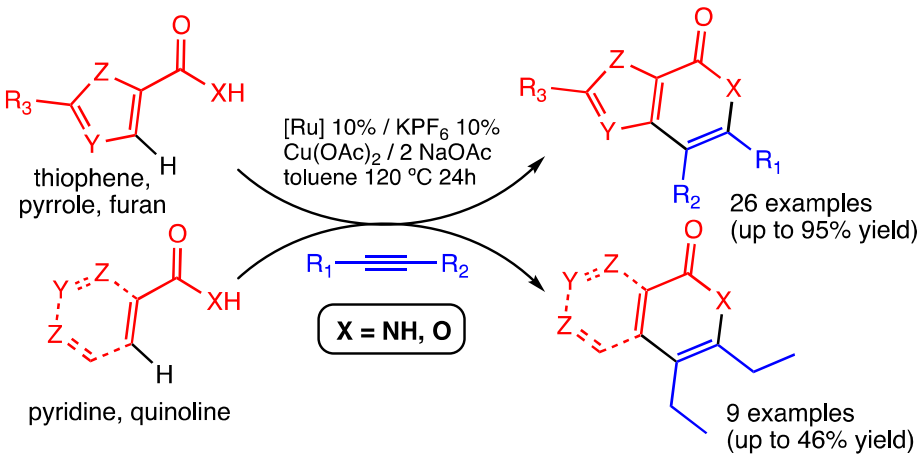

Heterocycle-pyridinones and heterocycle-pyranones have been prepared by Ru-catalysed oxidative coupling of N-unprotected primary heterocycle-amides and heterocycle-carboxylic acid with internal alkynes