

Ruthenium(II) catalysed synthesis of pyrrole and indole fused isocoumarins via C-H bond activation in DMF and water[†]

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Abstract: Pyrrole and indole fused isocoumarins constitute an important structure unit in natural products and pharmacophores, although direct selective bifunctionalisations of pyrrole and indole remain a challenge. Here we report a one pot synthesis of pyrrole and indole fused isocoumarins from simple 1-methyl pyrrole-2-carboxylic acid and 1-methylindole-3-carboxylic acid via annulation with alkyne in the presence ruthenium(II) catalyst based on [RuCl₂(*p*-cymene)]₂ and Cu(OAc)₂·H₂O as oxidant in DMF. This ruthenium(II) catalysed transformation is shown to be profitably performed in water as solvent. The reaction which involves the carboxylate coordination, activation of heterocycle sp² C-H bond and insertion of alkyne is regioselective, leading to good yields of isocoumarins.

Isocoumarins and their derivatives constitute a class of bioactive compounds and are found in many natural products. They exhibit significant biological activities such as anti-allergenic, antimicrobial,^[1] antifungal,^[2] anti-inflammatory,^[3] antimalarial,^[4] and anti-HIV^[5]. Owing to their wide biological properties, isocoumarins constitute an important synthetic target and several reports have explored their synthesis,^[6,7] however, a straightforward synthesis of these valuable compounds is still a challenging task. Among several synthetic methods developed in recent years, transition metal catalysed syntheses of isocoumarins are the most attractive and environmentally benign.^[6] Recently, catalyst derivatives of Cu,^[8] Pd,^[9] Ru^[6c,d,10] and Rh^[11] have been employed for the synthesis of isocoumarin derivatives through annulation reaction involving initial functionalization of arene sp² C-H bonds. It is noteworthy that regioselective functionalisations promoted by metal catalysed sp²-C-H bond activation offer efficient routes for a fast access to various

functional molecules.^[12] Initially palladium catalysts were used for the direct C-H functionalization of heterocycles,^[13,14] however tremendous progress has been made, in terms of synthesis efficiency, atom economy and process cost, with the less expensive ruthenium(0)^[15] and especially the more stable, even in water, ruthenium(II) catalysts^[16--17] for cross C-C bond formation from sp² C-H bonds. A wide range of N-containing heterocycles^[18] and even weakly coordinating functional groups such as carboxylic acids^[19], ketones,^[20] or amides^[21] can now direct regioselective ruthenium(II)-catalysed C-H bond functionalisations.^[18-22]

Recently, ruthenium(II)-catalysed annulations involving C-H/N-H and C-H/O-H bond cleavage leading to isocoumarins have been reported by several groups.^[6c,d, 23] Especially Jeganmohan^[6c] and Ackermann^[23b] have performed ruthenium(II)-catalysed annulations of aromatic carboxylic acids with alkynes involving the activation of arene sp² C-H bonds in the presence of copper(II) as oxidant but with an additive such as AgSbF₆ or KPF₆. An efficient ruthenium(II) catalysed annulation of aromatic carboxylic acids with alkyne, using molecular oxygen as sole oxidant, has just been reported.^[24]

Herein, we wish to report an efficient and regioselective annulation of N-methylpyrrole-2-carboxylic acid and N-methylindole-3-carboxylic acid with substituted alkynes, and the direct synthesis of isocoumarin derivatives, promoted by the simple ruthenium(II) catalyst [RuCl₂(*p*-cymene)]₂ with Cu(OAc)₂·H₂O as oxidant in DMF, without the use of other additive and in one step with atom economy. It will be shown that this catalytic annulation can be successfully performed in water.

Results and Discussion

The annulation reaction of N-methylpyrrole-2-carboxylic acid **2** with disubstituted alkynes was attempted with the catalyst [RuCl₂(*p*-cymene)]₂ **1** in the presence of Cu(OAc)₂·H₂O in DMF and then in water. In order to select optimized conditions, the reaction was first carried out using [RuCl₂(*p*-cymene)]₂ (5 mol%), KOAc (10 mol%), substrate (0.5 mmol), diphenylacetylene (1.2 equiv.), and

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[†] Supporting information for this article is given via a link at the end of the document.

Cu(OAc)₂·H₂O (1.5 equiv.) in DMF under air, at only 80 °C, and it afforded the annulation product, 1-methyl-4,5-diphenylpyrano[3,4-b]pyrrol-7(1H)-one **4a** in 87% isolated yield (Table 1, entry 1). When the reaction was carried out under nitrogen atmosphere, **4a** was obtained in almost identical yield. The isolated yield was surprisingly further increased to 91% when the reaction was carried out without KOAc which was shown before to accelerate the C-H bond cleavage by deprotonation of functional arenes^[25] (Table 1, entry 2). This observation indicates that the required carboxylate partner of the Ru(II) catalyst arises from Cu(OAc)₂. However, decreasing catalyst loading to 2.5 mol% gave only 30% of **4a** (Table 1, entry 3).^[26] The reaction of **2** with diphenylacetylene and 20 mol% of KOAc in the presence of oxygen and without Cu(OAc)₂·H₂O at 80°C, under conditions closely related to those of the annulation of aromatic carboxylic acids,^[24] led to the isolation of only 18% of **4a**, thus showing that for the heterocycle **2** the action of Cu(II) is required for efficient annulation.

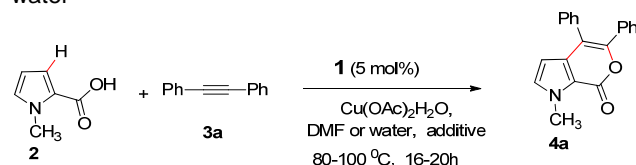
It was shown that water allowed the ruthenium(II)-catalysed C-H bond functionalisation, sometimes with improved catalyst activity^[17b,27] and that ruthenium(II) catalysed alkenylation could also be performed in water.^[19b,27c] We have thus explored the catalytic efficiency of [RuCl₂(*p*-cymene)]₂ **1** catalyst in water for annulation of heterocycle **2**. First the annulation reaction was carried out using the catalyst **1** (5 mol%), pyrrole-2-carboxylic acid **2** (0.5 mmol), alkyne (1.2 equiv.), Cu(OAc)₂·H₂O (2 equiv.) in water (2 mL) under air for 20 h and the desired product **4a** was isolated only in 53% yield (Table 1, entry 4). Employing additive such as PivOH, KOPiv or KPF₆ (20 mol%) did not give any significant change in the product yield, but performing reaction under nitrogen atmosphere led to slight improvement (Table 1, entry 5-9). However, the use of 2 equiv. of alkyne leads to a strong increase of the desired product **4a** isolated yield, up to 82%, (Table 1, entry 10-11), thus showing that this catalytic annulation can be profitably performed in water.

Employing 10 mol% of catalyst under nitrogen could even further enhanced the yield to 90% (entry 12). Limited examples of ruthenium(II)-catalysed annulations of heterocycles can take place in water, as from aromatic carboxylic acids^[23a] or enamines.^[23b] By contrast, an efficient ruthenium-catalysed isoquinolone synthesis by annulation in

water of benzamides was performed in the presence of KO₂CMe additive.^[28]

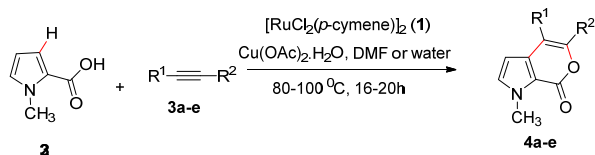
With these optimized reaction conditions, we have evaluated the ruthenium(II)-catalysed annulation of N-methylpyrrole-2-carboxylic acid **2** (Scheme 1) and of N-methylindole-3-carboxylic acid **5** (Scheme 2) with various alkynes first in DMF (Table 2) then in water (Table 3).

Table 1. Optimization of ruthenium(II)-catalysed annulation of heteroaromatic acid **2** with diphenylacetylene in DMF and water^[a]

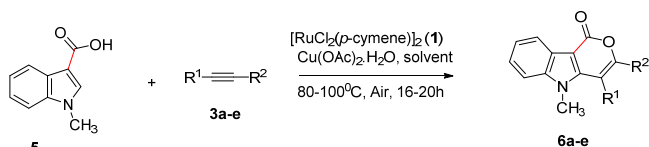


Entry	Ruthenium Catalyst	Additive (20 mol%)	Solvent	Yield (%) ^[b]
[1]	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	KOAc	DMF	87
[2]	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	DMF	91
[3] ^c	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	DMF	30
[4]	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	H ₂ O	53
[5]	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	PivOH	H ₂ O	54
[6] ^d	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	KOPiv	H ₂ O	59
[7] ^d	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	H ₂ O	60
[8] ^d	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	KPF ₆	H ₂ O	69
[9] ^{d,e}	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	KOAc	H ₂ O	18
[10] ^{d,f}	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	H ₂ O	55
[11] ^{d,g}	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	H ₂ O	82
[12] ^{d,h}	[RuCl ₂ (<i>p</i> -cymene)] ₂ (1)	—	H ₂ O	90

^[a]Reaction conditions: Substrate **2** (0.5 mmol), catalyst **1** (0.025 mmol), diphenylacetylene (0.65 mmol, 1.2 equiv.), Cu(OAc)₂·H₂O (1.5 or 2.0 equiv.), Additive (0.1 mmol), Solvent (2 mL), Temp. 80°C/16 h (DMF) and 100°C/20 h (water), under air. ^[b]Isolated yield after column chromatography. ^[c]Reaction performed using 2.5 mol% of catalyst **1**. ^[d]Reaction performed under N₂ atmosphere. ^[e]Reaction performed with 2 equiv. of diphenylacetylene but without Cu(OAc)₂·H₂O; ^[f] 0.5 equiv. of Cu(OAc)₂·H₂O was used; ^[g] 2 equiv. of diphenylacetylene was used; ^[h] Reaction performed with 10 mol% catalyst.

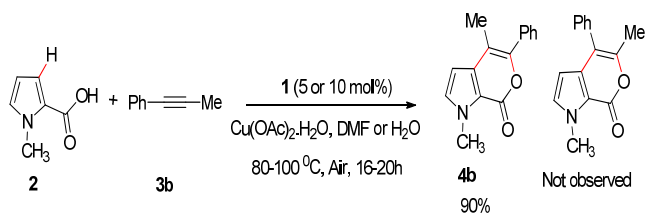


Scheme 1. Annulation of **2** with substituted alkynes into isocoumarins **4a-e**.



Scheme 2. Annulation of 1-Methylindole-3-carboxylic acid **5** with alkynes.

The annulation of N-methylpyrrole-2-carboxylic acid **2** with 4-octyne, 3-hexyne and 2-butyne, performed in DMF with catalyst **1** as for diphenylacetylene (Table 2, entry 1), gave the desired products **4c**, **4d** and **4e** isolated in 62%, 78% and 57% respectively (entries 4-6). The reaction of **2** with 1-phenylpropyne is highly *regioselective* as it leads to **4b** as the only product in 84% isolated yield Scheme 3, (Table 2, entry 2). The use of additional 20 mol% of KOAc has beneficial influence as the isolated yield of **4b** was obtained up to 90% with catalyst **1** (Table 2, entries 2, 3).



Scheme 3. Annulation of 1-methylindole-2-carboxylic acid **2** with 1-phenylpropyne

Table 2. Ruthenium(II) catalyzed annulations of N-methyl-2-Pyrrolecarboxylic acid **2** and N-Methylindole-3-carboxylic acid **5** in DMF^[a]

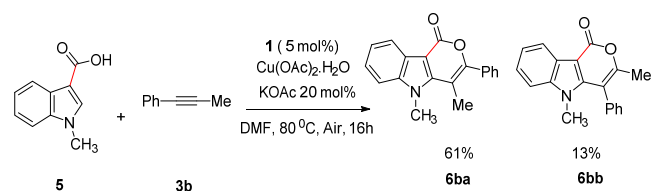
Entry	Substrates 2 and 5	Alkynes	Products	Isolated Yield (%) ^[b]
1	2	$R^1 \equiv R^2$ 3a-3e Ph—Ph	4a-e $R^1 = R^2 =$ Ph (4a)	91
2	2	Ph—CH ₃	$R^1 = \text{Me}; R^2 =$ Ph (4b)	84
3 ^[c]	2	Ph—CH ₃	$R^1 = \text{Me}; R^2 =$ Ph (4b)	90
4	2	H ₃ C—CH ₂ —C≡C—CH ₂ —CH ₃	$R^1 = R^2 =$ (CH ₂) ₂ CH ₃ (4c)	62
5	2	H ₃ C—CH ₂ —C≡C—CH ₃	$R^1 = R^2 =$ CH ₂ CH ₃ (4d)	78
6	2	H ₃ C—C≡C—CH ₃	$R^1 = R^2 =$ CH ₃ (4e)	57
7	5	$R^1 \equiv R^2$ 3a-3e Ph—Ph	6a-e $R^1 = R^2 =$ Ph (6a)	77
8	5	Ph—CH ₃	$R^1 = \text{Me}; R^2 =$ Ph (6ba) 8 $R^1 = \text{Ph}, R^2 =$ Me (6bb)	42
9 ^[c]	5	Ph—CH ₃	$R^1 = \text{Me}; R^2 =$ Ph (6ba) 13 $R^1 = \text{Ph}, R^2 =$ Me (6bb)	61
10	5	H ₃ C—CH ₂ —C≡C—CH ₂ —CH ₃	$R^1 = R^2 =$ (CH ₂) ₂ CH ₃ (6c)	64
11	5	H ₃ C—CH ₂ —C≡C—CH ₃	$R^1 = R^2 =$ CH ₂ CH ₃ (6d)	70
12	5	H ₃ C—C≡C—CH ₃	$R^1 = R^2 =$ Me (6e)	25

^[a]Reaction conditions: Substrate (0.5 mmol), Catalyst **1** (0.025 mmol), alkynes (0.65 mmol, 1.2 equiv.), Cu(OAc)₂·H₂O (1.5 equiv.), DMF (2 mL), Temp. 80 °C, Time 16h; ^[b]Isolated yield after column chromatography; ^[c]Reaction performed in the presence of KOAc (20 mol%).

The annulation of 1-methylindole-3-carboxylic acid **5** with diphenylacetylene has been carried out with catalyst **1** (5mol%) alkyne (1.2 mmol) in DMF in the presence of 1.5 equiv Cu(OAc)₂·H₂O (Table 2). It led to the annulation product **6a** in 77% yield (Table 2, entry 7). Analogously, the annulation of **5** with 4-octyne, 3-hexyne and 2-butyne led to isocoumarins **6c**, **6d** and **6e** in 64%, 70% and 25%, respectively (Table 2, entries 10, 11, 12). Unlike for **2**, the annulation of **5** with 1-phenylpropyne, under similar conditions, afforded two products **6ba** and **6bb** in 42% and 8% (Table 2, entry 8). However, for this particular alkyne, the addition of KOAc (20 mol%) is beneficial, affording the products **6ba** and **6bb** in 61% and 13% isolated yields, respectively (Scheme 4, Table 2, entry 9).^[29]

Ruthenium(II) catalysts often tolerate water and water as solvent can increase the Ru(II) catalyst activity in the presence of carboxylate as cocatalyst.^[17b,27] Thus the annulation of heterocycle **2** was attempted with Ru(II) catalyst **1** in water (Table 3). The annulation reaction of **2** in water performed with 10 mol% of catalyst using 2 equivalents of alkyne and of Cu(OAc)₂·H₂O was found to give the best results. Thus, annulation of **2** with diphenylacetylene could lead to the formation of 90% of isocoumarin **4a** after 20 h at 100 °C (Table 3, entries 1-3).

Annulation reaction of **2** with 4-octyne led to the isolation of **4c** in 52% yield. These results show that the annulation of **2** is not quite as productive as in DMF. The annulation reaction of **2** with the unsymmetrical alkyne, 1-phenylpropyne was carried out in water. This reaction is highly regioselective giving a good yield of the desired product **4b** in 69% or 75% yield with 5 or 10 mol% of catalyst **1** (Table 3, entries 4, 5). The annulation of **2** with 1-phenylpropyne gave only a single isomer irrespective of the solvent used either DMF or water with compatible yields (Scheme 3).



Scheme 4. Annulation of 1-methyl indole-3-carboxylic acid **5** with 1-phenylpropyne

The annulation reaction of **5** in water was also carried out employing three alkynes: diphenylacetylene, 1-phenylpropyne and octyne. The reaction of **5** with diphenylacetylene using 5 mol% of [RuCl₂(*p*-cymene)]₂ leads to 42% of **6a** (Table 3, entry 7).

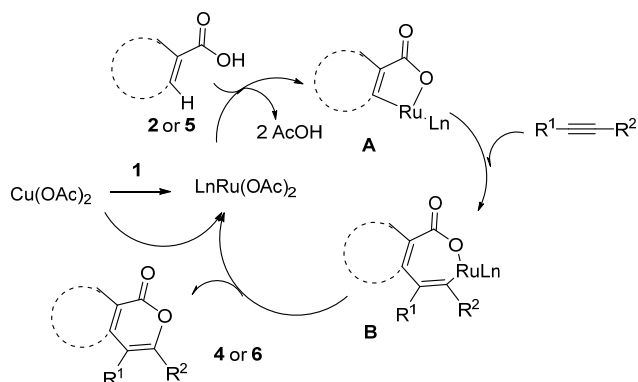
Table 3. Ruthenium(II) Catalysed annulations of N-methyl-2-Pyrrole carboxylic acid **2** and N-Methylindole-3-carboxylic acid **5** in water^[a]

Entry	Substrates 2&5	Alkynes	Products	Isolated Yield (%) ^[b]
		$R^1-C\equiv C-R^2$ 3a-c		
1 ^[c]	2	Ph—C≡C—Ph	R ¹ = R ² = Ph (4a)	59
2 ^[d]	2	Ph—C≡C—Ph	R ¹ = R ² = Ph (4a)	82
3	2	Ph—C≡C—Ph	R ¹ = R ² = Ph (4a)	90
4 ^[d]	2	Ph—C≡C—CH ₃	R ¹ = Me; R ² = Ph (4b)	69
5	2	Ph—C≡C—CH ₃	R ¹ = Me; R ² = Ph (4b)	75
6	2		R ¹ = R ² = (CH ₂) ₂ CH ₃ (4c)	52
		$R^1-C\equiv C-R^2$ 3a-c		
7 ^[c]	5	Ph—C≡C—Ph	R ¹ = R ² = Ph (6a)	42
8	5	Ph—C≡C—Ph	R ¹ = R ² = Ph (6a)	77
9	5	Ph—C≡C—CH ₃	R ¹ = Me, R ² = Ph (6ba)	35
			R ¹ = Ph, R ² = Me (6bb)	30
10 ^[e]	5		R ¹ = R ² = (CH ₂) ₂ CH ₃ (6d)	87

^[a]Reaction conditions: Substrate **2**, **5** (0.5 mmol), catalyst [RuCl₂(*p*-cymene)]₂ (**1**) (0.05 mmol), alkynes (1 mmol, 2 equiv.), Cu(OAc)₂·H₂O (2 equiv.), Water (2 mL), under N₂ atmosphere, Temp. 100 °C, Time 20h; ^[b]Isolated yield after column chromatography; ^[c]0.025 mmol of catalyst **1** and alkyne (1.2 equiv.) were used; ^[d]0.025 mmol of catalyst **1** and 2 equiv. of alkyne were used. ^[e]10 mol% of **1**.

However, using 10 mol% of catalyst and 2 equiv. of diphenylacetylene the isolated yield of the desired product was increased to 77% (Table 3, entry 8). The annulation of **5** with 1-phenylpropyne in water also gave two products **6ba** and **6bb** in 35% and 30% respectively, indicating that the reaction of **5** with 1-phenylpropyne afforded two products irrespective of solvent water or DMF (Table 3, entry 9). Among the alkynes evaluated, 4-octyne reacted with **5** and could lead to **6d** with excellent yields of 87% in water (entry 10).

The annulation reaction is expected to proceed first by coordination of the carboxylate to the ruthenium(II) site, followed by activation of the *ortho* C-H bond via C-H deprotonation with acetate arising from $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ ^[25] to form the cyclometallate **A**. The coordinative insertion of the alkyne into the Ru(II)-C bond of **A** should give the intermediate **B** followed by reductive elimination leading to derivatives **4** and **6**. The second role of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ is then to reoxidize the produced ruthenium(0) species into the active ruthenium(II) catalyst (Scheme 5).



Scheme 5. Proposed mechanism for the formation of **4** or **6**

In conclusion, an efficient catalytic annulation of pyrrole-2-carboxylic acid and indole-3-carboxylic acid with alkynes into isocoumarins promoted by the ruthenium(II) catalyst $[\text{RuCl}_2(p\text{-cymene})]_2$ without other additive than the provider of acetate and the oxidant $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ has been performed. The reaction was carried out in DMF giving good to excellent yields of the theisocoumarins **4** and **6** depending on the alkyne. The catalytic annulation easily proceeds in water as safe and renewable solvent. It is less effective than in DMF, but it is competitive for several alkynes such as diphenylacetylene, 1-phenylpropyne and 4-octyne. The

reaction is highly regioselective only for the annulation of **2** with 1-phenylpropyne which forms exclusively **4b** irrespective of solvent.

Experimental Section

General procedure for ruthenium(II) catalysed annulation of pyrrole and indole carboxylic acid in DMF

A dried Schlenck tube was loaded with $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.0153g, 0.025 mmol, 5 mol%), heterocyclic acid (**2** or **5**) (0.5 mmol), alkyne (0.65 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.149g, 0.75 mmol) and DMF (2 ml). The reaction mixture was stirred in DMF at 80°C for 16 h under air. After which the solvent was evaporated. The residue was purified via filtration over silica gel column using petroleum ether and ethyl acetate as eluants, to eliminate excess of alkyne and ruthenium residue, to give the compounds **4** and **6**.

General procedure for ruthenium(II) catalysed annulation of pyrrole and indole carboxylic acid in water

A dried Schlenck tube was loaded with $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.03 g, 0.05 mmol), heterocyclic acid **2** or **5** (0.5 mmol), alkyne (1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.199g, 1.0 mmol). The reaction mixture was stirred in water (2 ml) at 100°C for 20 h under nitrogen. The reaction mixture was extracted with ethyl acetate (2x20 mL). The solution was dried with sodium sulphate and evaporated. The residue was purified via filtration over silica gel column using petroleum ether and ethyl acetate as eluants to give the compounds **4** and **6**.

Acknowledgements

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Keywords: Indole, pyrrole, Bioactive natural product, Annulation reaction, Ruthenium(II) catalyst, C-H bond activation, Isocoumarin synthesis.

Supporting Information: Experimental procedures for the preparation and spectroscopic characterization of **4a-e** and

6a-e (¹H, ¹³C & ESI-MS). Copies of ¹H and ¹³C NMR spectra

of 4a-e and 6a-e.

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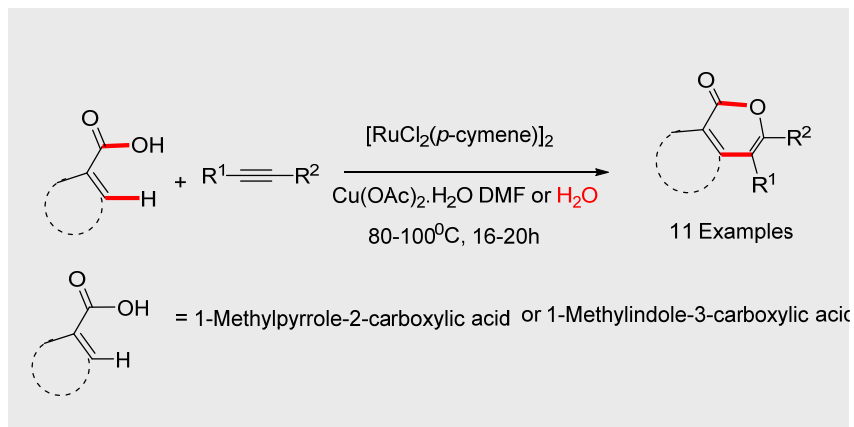
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Entry for the Table of Contents

COMMUNICATION



Keisham S. Singh*, Sneha G. Sawant, Pierre H. Dixneuf *

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Ruthenium(II) catalysed synthesis of pyrrole and indole fused isocoumarins via C-H bond activation in DMF and water

1-methylpyrrole-2-carboxylic acid and 1-methylindole-3-carboxylic acid are efficiently annulated with alkynes, by non expensive and stable to water ruthenium(II) catalyst $[RuCl_2(p\text{-cymene})]_2$ and with acetate provider and oxidant $Cu(OAc)_2 \cdot H_2O$, via C-H and O-H bond activation, to give their respective pyrrole and indole fused isocoumarin derivatives. These catalytic reactions can be performed in DMF and competitively in water.